Clinical Research Ethics
and Pediatric HIV Infection

John Gerard Twomey, Jr.
Wakefield, Rhode Island

B.S.N., Catholic University of America, 1972
M.S., Boston College, 1981

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Twomey, John Jr., G.
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Abstract

This research study investigates the views of a select group of people about the ethics involved in the conduct of clinical research that uses children with Human Immunodeficiency Virus as subjects. Physician and nurse researchers, Institutional Review Board members, and parents of children with HIV were interviewed using an open-ended interview structure. The sessions were audiotaped. Twenty-eight interviews were conducted at four clinical sites in the eastern United States.

Qualitative data analysis was done to determine the predominant issues that emerged from the interviews. The data analysis reveals five main themes, which include fourteen categories. Thirty-three subcategories with significant ethical implications for pediatric HIV clinical research are examined.

Several significant issues are identified in this study. Under the theme of Present vs Future Care, it became apparent that the dual imperatives faced by all of those involved in the care of children with HIV, to provide care while concommitantly doing research, is causing some ethical
concerns. Additionally, the theme regarding the Shift in the Research Ethics Paradigm: From Nonmaleficence to Beneficence illustrates that the application of traditional ethical norms to judge contemporary pediatric HIV clinical research practices may not be useful.

A conceptual finding of this study is that the traditional bioethical theoretical framework of justice-based principles may not be adequate to assess the contemporary moral practices in the domain studied. A newer framework that includes the ethics of context, entitled an ethic of care, may be more accurate in the ethical analysis of pediatric HIV research ethics. Several areas for further inquiry theoretically and empirically in these areas are suggested.
Acknowledgements

Many people have assisted me during the varied phases of this project. Several people deserve special thanks.

Sara Fry introduced me to the study of bioethics, particularly within the domain of nursing. She has continued to provide me with critical insights as I have attempted to increase my knowledge in this area. Mary Rorty is a philosopher who helped me greatly to continue searching for the nursing component of bioethics.

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The contributions to my studies at UVA made by my chair, Sara Arneson, go far beyond the extensive editing she did on my work. She consistently allowed me to be the owner
of my research, supporting me when I needed it and pointing out when I needed to go further in my efforts. Without her, I could not have completed this project.
Dedication

To Matt, who when not quite three years old, pulled himself into my lap and told Daddy that it was okay by him for me to go back to school;

To Stephen, who came along towards the end of this experience and provided the necessary perspective about where this project belonged in my life;

And to Ann, who never wavered in her trust and support throughout this journey, thank you for sharing yourselves with me. This process was meaningful only because you three were part of it.
# Table of Contents

Chapter I  
Introduction ............................................. 1

Chapter II  
Theoretical Framework and Literature Review ............ 10

Chapter III  
Research Design and Methods .................................. 50

Chapter IV  
Narrative Descriptions of Interviews......................... 66

Chapter V  
Data Analysis .................................................. 95

Chapter VI  
Discussion...................................................... 161

Chapter VII  
Summary and Conclusions ..................................... 182

References. .................................................... 201
Appendix A

Semi-structured Interview Questions .............. 217

Appendix B

Professional Information Sheet ................... 221

Appendix C

Parental Consent Format ......................... 222

Appendix D

List of Categories and Subcategories .............. 224

Appendix E

Description of Protocol 076 ...................... 229

Appendix F

Descriptive Statistics of Categories and Themes .... 236
Chapter I
Introduction

Children infected with the Human Immunodeficiency Virus (HIV) currently represent a meaningful number of the people afflicted by the Acquired Immunodeficiency Disease (AIDS) pandemic. The significance of the disease in the pediatric subpopulation in the United States will emerge from the pertinent factors that mark this group: a set of relatively poor, disadvantaged children who suffer from a new disease that is poorly understood and who require a large number of resources to treat their many resultant problems.

The problem of defining exactly what pediatric AIDS consists of has contributed to the difficulties in providing specific statistics for purposes of epidemiological study. Part of this problem stems from the fact that in many states, cases of HIV infection are only reportable for infectious disease epidemiological purposes when the patient is diagnosed with AIDS. In March, 1987, the Centers for Disease Control (CDC) had reports of 471 American (including Puerto Rican) children who met the criteria for AIDS (Plotkin, 1987). By July 1988, 1,095 cases of pediatric AIDS (children less than thirteen years of age) had been reported to the CDC (Falloon, Eddy, Wiener, & Pizzo, 1989). A year later, the number had risen to 1,681 (Pizzo, 1990). The CDC currently reports 3,898 children with AIDS in the United States (CDC, 1992). This rapid increase in the
prevalence of the disease only underscores the reality that the number of HIV seropositive children who are less ill are felt to be at least twice those of the AIDS figure. Projected figures approximate a figure of ten to twenty thousand symptomatically ill children with HIV in the 1990s (Oleske, 1987).

Developing the scanty knowledge base about the progression of pediatric HIV to AIDS is paramount. Early data from the National Institute of Allergy and Infectious Disease (NIAID) claimed that the one year survival rate from the date of diagnosis of children determined to have AIDS prior to one year of age was 70 percent; this rate only fell to 50 percent for those children diagnosed later in life (NIAID, 1988). More recent reports show that prognosis has improved for older seropositive children who show signs of AIDS while the younger infants with such symptoms still have higher mortality rates (Tovo et al., 1992).

Estimates of fiduciary costs of care of these children are difficult to make because of the complexity of their medical and accompanying problems. In one population, 25 percent of the infected children were already involved with local Child Protective Agencies and many were needing foster care. The majority had developmental delays and inpatient hospital visits averaged two to three per year (Boland, 1987).
Only three approved antiretroviral therapies currently exist for children with AIDS. Because Zidovudine (AZT), only limits the progression of some symptoms and has frequent side effects, and the other two antiretrovirals, Dideoxyinosine (ddI) and Dideoxycytidine (ddC) (AIDS Drug Approved, 1992), have been mostly studied only in adults and seriously ill children, their pediatric use, particularly in those who are asymptomatic, must be questioned. Further issues regarding HIV in children, including the natural history of the illness, its prevalence and epidemiology, and its costs suggest that further research into these topics is indicated.

Research using children presents many controversial problems, which include the basis of the investigation, adequacy of understanding of child and family, and the vulnerability of patients and families involved in the proposed trial (Fletcher, Van Eys, & Dorn, 1989). One study suggests that children with HIV may not receive the adequate protection necessary when they are clinical research subjects (Twomey, 1989b). Informed consent from ill or absent parents may be absent, risks and benefits of experiments may not be weighed adequately, and questions of whether ill children should bear the brunt of research have been raised.
Significance of the Issue to Nursing

Nurses are the group of health care professionals who arguably have been the most involved in the treatment of children with HIV. They have cared for pediatric AIDS patients in direct clinical care and in research efforts. Several issues have arisen from the relationship between nurses and children with HIV that have implications for the ethical care of these children whose status as research subjects needing protection cannot be separated from their condition as ill people needing care.

The first issue having a direct implication for nurses is the large number of abandoned HIV seropositive babies who live in hospitals with the nurses as their primary caretakers (McGuckin, 1992). Because many of these children will need drug therapy during their lives, nurses may have conflicting views on whether HIV seropositive children should or should not be entered into drug trials.

Secondly, pediatric nurses may not fully comprehend the clinical research process or realize that research trials do not place therapeutics for patients among their primary goals. Such knowledge deficits about the clinical research process persist despite the dictums of the American Nurses' Association Code which clearly states that nurses must focus on protecting the personhood of the patients who are subjects in clinical research (American Nurses' Association, 1985). In minor children, such protection must center
around the physical integrity of the child (Levine, 1989). Nurses need information about the objectives and issues of clinical research as their specific patients are affected by the research process (Diers, 1990).

Also the lack of knowledge about AIDS, particularly the pediatric version of the disease, can serve to hinder proper care of children with HIV. One study of 134 perinatal nurses showed many discrepancies between the nurses' knowledge level, attitudes toward their personal involvement in the care of children with HIV, and their perceived ethical obligations to provide nursing care to infected children (Prince, Beard, Ivey, and Lester, 1989). Clarification of the ethics of care may help nurses begin to understand more fully their therapeutic obligations while also protecting their patients who are enrolled in clinical research.
Statement of the Problem

Very little is known about the types of ethical problems inherent in using children with HIV infection as subjects in clinical drug trials.

Research Question

What are the ethical issues that arise when children with HIV infection are enrolled in clinical trials as identified by the clinicians and others, including their caretakers, involved in their care.

Definition of Terms

Theoretical

Child with HIV infection-child of either sex who is seropositive for the Human Immunodeficiency Virus on either the ELISA or Western Blot antibody test.

Clinical HIV research-systematic collection of data about the physiological responses resulting from administration of an active agent to individuals with HIV seropositivity.

Ethical issues concerning clinical research involving children with HIV infection-moral behaviors identified by the respondents that are expected of those participating in scientific experimentation as defined in the Belmont Report (National Commission, 1978). These behaviors have been identified as those that maintain the autonomy of the seropositive child, that consider both the beneficence and
the nonmaleficence of the HIV drug protocols enrolling seropositive children, and the justice of including seropositive children in the research.

Nurse and Physician Researcher—registered nurse or medical doctor who is involved in the conduct of clinical research with children with HIV.

Institutional Review Board (IRB) Member—a person who holds membership on a committee that is charged with reviewing prospective research studies for scientific suitability.

Parent of child with HIV—father or mother of a child with HIV infection who is enrolled in a clinical HIV drug trial.

Operational
Child with HIV infection—child from birth to three years of age who is seropositive for HIV who may be either symptomatic or asymptomatic for the signs of immunodeficiency disease, such as failure to thrive, neurodevelopmental delays, and opportunistic infections, and who is enrolled in a clinical HIV drug trial in an AIDS Clinical Trial Unit (ACTU) at a site included in this study.

Clinical HIV research—systematic collection of data from children with HIV infection who are three years and younger at an ACTU in formal clinical trials that are designed to study the physiological responses of these children to the administered drug that are related to their HIV status.
Ethical issues concerning clinical research involving children with HIV infection—moral behaviors expected of those involved in pediatric clinical HIV research as identified by the respondents in the semistructured interviews.

Nurse and Physician Researcher—a nurse or medical specialist who reports at least 50 percent of their professional duties is devoted to clinical research.

Institutional Review Board Member—a person who holds membership on a committee that is charged with reviewing prospective research studies for scientific suitability at an institution that conducts clinical research involving children with HIV and who reports reviewing at least one proposed protocol involving pediatric HIV drug trials.

Parent of child with HIV—legal parent or guardian of a child with HIV infection enrolled in a clinical HIV research trial at an ACTU.

Assumptions

1. Children with HIV infection represent a population that need special protection when involved in clinical HIV research.

2. Pediatric clinical HIV research does not present new ethical paradigmatic problems. Rather, such research provides new exemplars that challenge traditional research ethical analysis.
3. Recognition of the special ethical needs of children with HIV in clinical HIV research will contribute to the construction of protocols that will better respect the ethical status of such children and provide necessary knowledge about their medical needs.

4. Pediatric nurse and physician researchers, IRB members, and parents of children with HIV will have unique insights on the treatment of children with HIV who are subjects in clinical HIV research that have implications for the ethical analysis of such research in this population.
Chapter II

Theoretical Framework and Literature Review

This chapter contains the theoretical basis of the study which centers around the framework of research ethics and a contextually based ethic of care. The review of the literature includes the status of HIV infection in children, a discussion of the major issues in the ethical treatment of subjects in clinical research trials, particularly children with HIV, and assesses the construction of ethical protection for such subjects.

Theoretical Framework

Principle-Based Ethics

The moral foundation of clinical biomedical research is grounded in the classical bioethical framework that is accepted by most bioethical theorists (Levine, 1986). Many commentators (Beauchamp & Childress, 1989; Davis & Aroskar, 1983; Jameton, 1984; Veatch & Fry, 1987) describe this framework of rules that defines several specific moral principles as prima facie or primary when used to judge the ethical actions of individuals.

There has been general agreement that the construction of this framework, known as a principle-based ethical theory, which contrasts the deontological philosophy of Immanuel Kant with the utilitarian views of Jeremy Bentham and John Stuart Mill provides a sound basis for debate about
bioethical imperatives (Beauchamp & Childress, 1989). The essential ethical tension that results from these two philosophies arises because the deontological position gives more weight to the status of the individual in society while the utilitarian view mandates that the solitary human must occasionally sublimate personal rights for the collective good. Such a moral debate has obvious implications for research ethics when individuals are asked to give part of themselves in order to obtain good for the whole. However, such sacrifice can threaten their individual personhood and therefore place society in a position of being responsible for protecting them from unnecessary threats.

The prima facie principles that emerge from this classic bioethical system are the three principles of autonomy, beneficence/nonmaleficence, and justice. In brief, the principle of autonomy is based on the deontological views of Kant that state that the personhood of each individual is paramount and therefore respect for such personhood dictates that people are ends in themselves and cannot be used as a means to ends for others. The second principle includes beneficence, the belief that health care professionals must perform only those acts which will benefit their patients, and its counterpart principle, nonmaleficence, which says that such acts must actually do no harm to the patients. Justice, the third principle, while mandating that rights and responsibilities are
possessed by all actors in the health care domain, also
demands that the burdens and benefits of any aspect of the
biomedical system be distributed equitably. Such sharing
must be done with some sense of proportionality based on the
reality of the basic inequalities of daily life (Engelhardt,
1986).

The community of biomedical researchers has had a
standard bioethical framework prescribed for its activities
since the late 1970s. Formal guidelines were specifically
recommended for research involving children in the report of
the National Commission for the Protection of Human Subjects
of Biomedical and Behavioral Research (1978), entitled the
Belmont Report. In 1983, guidelines for researchers were
promulgated by the federal government (Department of Health
and Human Services, 1983a, March 8). The three general
bioethical principles form the basis of the Commission's
report which was ultimately used to shape the guidelines
that govern research with children today. Each principle
has specific interpretations that can influence the ethical
behavior of clinical pediatric HIV researchers.

Preservation of the autonomy of a research subject
involves maintaining the voluntariness of his or her
enrollment through informed consent to participate. Prior
to the enrollment of any child (under 18 years of age) in a
research trial, informed consent is solicited and obtained,
in almost all cases, from his or her parents. In the age
group that this study will focus on, it is accepted that parental consent is necessary prior to going forth with research and that parental dissent to a proposed clinical trial disqualifies the child from participation (Levine, 1983, 1989; McCartney, 1978).

Obtaining informed consent to participate in research from the parents of children with HIV raises some specific issues, particularly regarding their competence to consider their child's best interests. Because parents of children with HIV may be ill with HIV themselves and feel guilt over their role in the transmission of the virus, their judgement regarding their child's enrollment in research may be questioned (Twomey, 1989a). AIDS dementia may cloud their reasoning abilities. In addition, the abandonment of infants with HIV can completely preclude parental involvement in the informed consent process (Palacio & Weedy, 1991).

Part of the informed consent process involves telling the guardians of the child of the risks and benefits of being a research subject. The construction of a protocol with a favorable risk/benefit ratio means that the investigator has been successful in making a clinical application of the prima facie principles of nonmaleficence and beneficence. However, transforming this principle into actual research practice has proved to be one of the most elusive tasks of the ethical researcher.
Levine (1986) sketches a format of risk-to-benefit analysis that includes the variables of risks to individuals and to society that are incurred from research and the benefits that both parties might obtain. Risks can include physical, economic, and psychological burdens which should be judged on their "magnitude and expected duration" (p. 57). For children, such risks can include not only the threat of infection from frequent needle sticks but the possible injury to their psychological well-being from the trauma of frequent painful procedures. Can these risks be measured? If so, benefits might be appraised along similar lines.

The prime justice issue in research ethics is how to spread the risks of research so that the same subject groups are not continually being used in many different protocols, particularly if those subjects are ill (Levine, 1986). The National Commission (1978) viewed this issue as the central justice concept to be considered and urged special protection for what they termed "vulnerable subjects" (p.19). Heeding their words, the resultant federal regulations gave Institutional Review Boards the charge to disapprove protocols that did not provide special protection to certain vulnerable groups (Department of Health and Human Services, 1983a; 1983b), such as children, pregnant women, and minorities.
Children with HIV represent the type of population that the National Commission had in mind when defining a vulnerable population. The pool of seropositive children is small and it is expected that researchers will continually try to tap into this group as they develop new protocols. Increasingly, sick children may be entered into new experiments in attempts to find efficacious drugs. Overprotection of this select group of children with HIV may hinder scientific progress in pediatric HIV knowledge. Issues of justice that can arise include overexperimentation in attempts to study relatively minor drug effects, refusal of researchers to release potential therapies to children unless they are enrolled in studies, and restrictive protocol entrance requirements that may preclude some potential subjects from being included in drug testing.

Despite relative consensus about the theoretical framework of bioethics, difficulty exists in operationalizing this framework at the level of normative bioethics. This is the arena in which actual rules for bioethical conduct are debated and ultimately accepted and rejected by members of the health care community. Examination of the contrasting moral beliefs about research of those people caring for pediatric HIV patients may provide insight into how ethical decisions are made about the conduct of scientific inquiry with these children. In addition, it may be useful to examine theories that provide
alternatives to the classical principle-based ethical system.

(See Figure 1)

**Figure 1**

Comparative Aspects of the Moral Theories of the Principle-based Ethics and the Ethic of Care

<table>
<thead>
<tr>
<th>Philosophical Basis</th>
<th>Principled Ethics</th>
<th>Ethic of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locke, Rousseau</td>
<td>Hume</td>
<td></td>
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<tr>
<td>Rawls, Kant</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Ethical Theory</th>
<th>Rationalism, Contract theory</th>
<th>Anti-Rationalism, Virtue ethics</th>
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<table>
<thead>
<tr>
<th>Perspective of the individual</th>
<th>Autonomous</th>
<th>Inter-connected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principles of Emphasis</td>
<td>Individual</td>
<td>Individual's Responsibilities to others</td>
</tr>
<tr>
<td></td>
<td>Rights</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Role of Freedom</th>
<th>Individual freedom within society</th>
<th>Inter-connection of other responsibilities that limit freedom voluntarily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moral Judgements</td>
<td>which rights (principles) are predominant</td>
<td>what actions will produce the best results for all moral agents involved</td>
</tr>
</tbody>
</table>
An Ethic of Care

Principle-based ethics grounded in rules and principles has been accepted as appropriate theory to judge bioethical decision making, including moral issues in research ethics. Literature supports the richness of the intellectual debates that have led to principle-based ethics being the predominant mode of thinking in any bioethical analysis.

In recent years, a new theory has been developed that has implications for analysis of research ethics. Termed an ethic of care, this trend in knowledge development has a classical philosophical basis that is inimical to that which supports ethics based on principles. Instead of principles, it substitutes concepts such as perspectives. While most bioethicists who employ principle-based ethics would deny that their judgements contain prescriptions for the actions of involved moral agents, they do represent a striving to ascertain the predominant principles involved in the decision-making process. Moral dilemmas in principle-based ethics arise when no better or worse consequences will result from a decision based on one competing principle rather than the other. In an ethic of care, the goal of the decision-making process is similar to that of the system of principled ethics—to maximize the good of the actions of those people involved. However, pathways of reasoning and ultimate recommendations for actions can be vastly different.
Finally, it is recognized that the ethic of care has developed somewhat out of an intellectual backlash by female philosophers and other academics against what they perceive to be a bias against women in the principle-based ethical system (Cooper, 1989; Rorty, 1991). Current thought about the ethic of care reflects efforts to reconcile interpretations about how women perceive their moral existence in the world qua women (Card, 1991; Gilligan, 1982; Kittay and Meyers, 1987; Noddings, 1984) and the implications of such thinking for moral agents in a predominantly female profession—nursing (Benner and Wrubel, 1989; Bishop and Scudder, 1990).

Philosophically, principle-based ethics has drawn heavily on Kant's deontology, a theory that emphasizes a system of universal law that is arrived at through rational thought. Carol Gilligan's empirical research (1987) suggested that contemporary psychology of moral development has led to denigration of those who do not behave within this universal paradigm as morally immature (Kohlberg, 1984). A further extension of Kantian thought that is widely accepted in Western philosophy is Rawls's interpretation of the better society as one that accedes to a rational system of living that defines needs and virtues as universal (Rawls, 1971).

Baier (1987) argues that David Hume describes the human need to develop moral behaviors that are in accord with our
intuitions about what goods are derived from living in harmony with other people in a society. Hume's philosophy is more in accord with a feminist ethic that emphasizes individuality. He rejects conformity to a universal law as the highest form of character development. The concept that emerges from Hume's renunciation of rationalism forces a rethinking of how similar moral actions are judged.

Rather than a system of rationalism, an ethic of virtue emerges where the good can be recognized but not generalized (MacIntyre, 1984). The individual's perspective in the principled ethic is the autonomy of the individual that Kant zealously defended. In the caring ethic, there is an interconnectedness of the moral agent with society that implies an interdependence that affects every potential ethical action. The agent is never truly able to make a free autonomous decision because of the dependence of others on the moral agent (Noddings, 1990). Gilligan's (1982) example of the thoughts of the women contemplating abortion underscores the argument that an ethic of care cannot accommodate the truly autonomous individual.

What emerges out of the ethic of care is a lack of emphasis on individuals rights, but an accent on personal responsibilities--to self and others (Blum, 1988). While individuals do not possess the unconditional freedom to act that the principle of autonomy implies, in the caring ethic, true freedom exists because constraints on actions are
accepted voluntarily, such as in community settings as religious orders, marriage, or a vocational choice, like nursing (Sichel, 1991). Also, the focus of moral decision making switches from weighing of predominant principles or rules to determining which action will produce the best results for all moral agents involved in such decisions. This redefinition is not a reliance on classic utilitarian principles but represents a recognition of the relational ethic that emerges from ethics based on emotion and love rather than rules and hierarchy (Noddings, 1988).

A theory of the ethic of care could provide a valuable means of analysis when studying the ethics of clinical research. Whereas the use of the prima facie principles of the principle-based ethical theory has proven problematic in some research settings because of disagreements over the predominance of one principle over another, the ethic of care may, by emphasizing the needs and rights of the aggregate of those directly involved, prove useful in articulating ethical goods in some proposed research practices. Furthermore, because of the emphasis in the feminist and nursing literature about the ethics of caring, data collected from both female subjects and/or nurses in the study may be more accurately analyzed if this framework is included in this study (Rorty, 1992).
Review of the Literature

Status of the Problem of Pediatric HIV

The first cases of pediatric HIV infection in the United States were detected in children with symptoms of immunodeficiency disease who subsequently tested seropositive for the HIV antibody. In general, these children had a preexisting health problem for which they had received a blood transfusion during the early 1980s before the nation's blood supply was tested for HIV. In the initial trial of AZT in children, 13 of 21 subjects had been infected in this manner (Pizzo et al., 1988).

The demographics and ages of the children infected with the virus have changed since the initial studies were done. With cases of transfusion related HIV being reduced to almost none of newly reported cases, the evolving caseload consists almost totally of children under the age of three years of age who received the virus from their mothers perinatally, probably in utero. This is termed vertical transmission (Andiman & Modlin, 1991). Because of the nature of HIV in this population of children, defining the numbers of afflicted children, as well as addressing the problem of treatment, is a crucial problem (Oxtoby, 1991).

Pediatric AIDS is diagnosed on the basis of displayed symptoms, particularly serious bacterial infections and pneumonias and through the use of stricter lab criteria than in adults (Revision of the Case Definition, 1985;
Classification System for HIV, 1987). This is a revision of prior standards in which the diagnostic symptoms of AIDS in children were assumed to be identical to those in adults. Prior to this redefinition, there were few HIV seropositive children diagnosed as having AIDS because their symptoms were unlike those of adults with AIDS. It is now known that infected children have almost no cases of Kaposi's Sarcoma and their opportunistic infections are quite different from those of adults with AIDS.

The effect of this new definition has been twofold: it has eased the restrictions in the past definition that limited the numbers of children who are considered to have AIDS and has caused a concomitant increase in the diagnosed cases of pediatric AIDS (Pizzo, 1990). It also means that clinicians and researchers must deal with the questions of when and whom to treat, for the current definition of pediatric AIDS does not specify how a diagnosis of HIV seropositivity should be clinically managed. At this time, most children are treated symptomatically for their periodic illnesses. There is no agreement on when an asymptomatic, seropositive child should be started on drug therapy if his/her CD4 white cell count is not decreased (Hutman, 1990).

Probably the most confounding phenomena is that the natural progression of the disease is still so random in individual children that it makes predictive intervention
strategies somewhat presumptive. Approximately, 30%-50% of infants who are born to seropositive mothers are HIV antibody seropositive themselves upon initial testing (Boland, 1991). This is the result of the normal immunological function of the maternal-fetal dyad that provides the newborn with many protective maternal antibodies until the child's own immune system matures (Selekman, 1990).

Unfortunately, neonates who test HIV seropositive only show that the antibody exists in their serum but no current test can differentiate between infant and maternal antibodies. Current preliminary trials using polymerase chain reaction testing to mark HIV in neonatal serum indicate that this blood test may be useful to predict that those seropositive infants who are also symptomatic will later develop severe cases of AIDS (Rogers et al., 1989). However, it does not answer the question of which asymptomatic children with HIV will go on to develop AIDS. Because the normal immunological response of an infant to disease differs from that of the adult immune response, it cannot be assumed that a lack of the usual pediatric AIDS symptoms, such as delayed development and an increase in opportunistic infections, will guarantee that a seropositive child will not develop AIDS (Pizzo et al., 1988).

However, widespread treatment of neonates who are seropositive but demonstrate no symptoms of AIDS may not be
justified because of the many infants who will turn out to be HIV free upon subsequent testing. A study of 71 European children born to seropositive mothers found that 75% had lost the antibody by 12 months of age, but some remained in the infected group because of positive viral cultures (Mok et al., 1987). Furthermore, case histories continue to provide atypical situations such as the child who lost the assumed maternal antibody by the first birthday only to develop severe AIDS symptoms at the age of two years (Nicholas, Sondheimer, Willoughby, Yaffe, & Katz, 1989).

Current national surveillance studies show that 0.15% of newborns are HIV seropositive. This means that in the United States, 5,500–6,000 newly born babies, per year, will have HIV. In selected urban locations the rate of newborn infection is as high as 1.25% (Boland, 1991). Current estimates suggest that 25%–40% of infants with HIV will eventually develop AIDS (Nicholas et al., 1989).

For the purpose of clinical research ethics, the population of vertically infected children presents special reasons for close examination. From an ethical perspective, children who are research subjects are considered a special population because of their decreased competence to protect themselves. In pediatric HIV research, their traditional protectors, their parents, often may be unable to care or protect them. This population of patients and their parents generally comes from a poverty stricken culture that
exhibits two of the behaviors defined as placing people at high risk for HIV transmission: sharing of needles during intravenous drug use and unprotected sexual relations that involve exchange of body fluids (Hutchings, 1990). Women in this culture are infected by either their own drug use or having unprotected sex with a seropositive male. In one HIV surveillance study in a northeastern state, 25% of the infected women were diagnosed at inner city hospitals. The rate of HIV infection was more than three times higher in this group than women treated in any other part of the state (Hoff et al, 1988). From 1984 to 1989, the percentage of AIDS patients who were women grew from seven to ten percent while the percentage of this group who were minority women remained constant at 75% (Rogers et al., 1989). These statistics have remained steady through 1992 (CDC, 1992).

The needs of these families are great. They typically have inadequate or no health insurance, little family support to help care for infected children, and few resources to help them cope with the stress of a chronic and fatal disease (McGonigel, 1988). The combination of a population with a disease that requires a great deal of investigation and that is also socially disadvantaged provides a likely scenario for possible abuses in clinical research. Involvement in research can be the only access a poor family with an ill child has into the medical system, particularly if the needed care involves investigational
therapies. The analysis of the Belmont Report (National Commission, 1978) was that populations that are socially disadvantaged would likely need special protection if they were sampled for clinical research.

Many areas of research must be undertaken to fill the gaps in the pediatric HIV knowledge base. Not all needs will be met by simply following the model of adult HIV research. Needs include how to a) identify infants truly infected with HIV, b) determine at birth which seropositive children will later develop AIDS, and c) differentiate pediatric HIV from adult HIV (Novella, 1988).

Surveillance and diagnostic research will also provide necessary data about treatment. Currently, there are only two types of HIV drug therapies available, antiretroviral drugs and immunomodulator therapy. Antiretroviral agents such as AZT work directly against the virus, causing it to become less virulent in its effects (Balis & Poplack, 1991). However, studies using all of the currently approved drugs for use in pediatric HIV/AIDS indicate that not all children receive relief and further research is mandatory to discover what therapies will prove safe and efficacious. Such trials are referred to as Phase I and II trials. Phase III trials, in which therapies considered safe and useful for a disease are compared against each other to determine the best therapy will need to be done for many years.
Immunomodulating drugs, such as gammaglobulin, are being tested to see if drug support of the immune system will decrease pediatric opportunistic infections. Early studies indicate that such drugs may be useful against pediatric HIV, particularly in combination with antivirals. Many pediatric HIV clinical researchers and clinicians feel that future therapy will include combinations of drugs, similar to cancer therapy, and are constructing their studies utilizing multidrug treatments (Pizzo & Wilfert, 1991).

Major Ethical Issues in Pediatric Clinical Research

In his landmark text Ethics and Regulation of Clinical Research (1986), Levine lists five "ethical norms" (p. 19) that must be met by investigators in clinical research. These include good research design, competent investigators, informed consent of the subjects, a balance between harm and benefit, and equitable selection of subjects. Of these five norms, only the second addresses an area that has achieved consensus in its interpretation. Professional health care codes all include competency as an ethical imperative (American Nurses' Association, 1985). The rest of the list, however straightforward, contains topics so controversial in their interpretation that discussion of each must occur in order to appreciate more fully the task of studying applied
ethics in clinical research, particularly in regards to how HIV in children must be studied.

**Good Research Design**

If one accepts that competency in researchers is a given, than it logically follows that such competence must be exhibited by the construction and completion of "good research." However agreement on what typifies such a study, or more specifically how much variance an investigator is allowed in methodology from what is defined as the "best" methods is rarely found.

For achieving the most statistically correct results in the testing of drugs and other patient therapeutics, it is commonly agreed that the randomized controlled trial (RCT) is the purest methodology for attaining the most valid data. Levine (1986) describes the model as having four elements. First, the trial is controlled for bias by having at least two groups, one of which gets the experimental therapy and one group that receives another therapy. If this second or control group receives a therapy with no expected therapeutic value, the trial is referred to as a placebo controlled trial. Second, the results of the trial are analyzed statistically for usefulness in knowledge development. This requires that many trials have large numbers of subjects in order to meet the rigorous requirements of the statistical methods employed. Thirdly,
if possible, a double blind methodology is employed where neither the subject nor the administering investigator knows which patient is getting what therapy. This serves to limit the bias that either party might introduce into the observed results if the nature of the therapy was known. Fourth, the division of patients into therapy groups is randomized so that every patient has an equal chance of being entered into any of the groups. This is done to avoid bias.

The innate rigor of the RCT concomitantly preserves its status as the highest form of research methodology while exposing it to charges that its inflexibility may make it an unethical form of research practice in some instances. The first attack comes over the use of control groups. Those favoring controls say that it is imperative to preserve the integrity of the RCT's statistical superiority by insisting on controls. Chalmers (1981) and others (Chalmers, Block, & Lee, 1972; Shaw and Chalmers, 1970) have argued consistently that controls are absolutely necessary when efficacy of a drug is in question and to waive this requirement is in itself unethical. The issue is whether it is necessary to subject a group of ill patients who might respond to a nonvalidated therapy to the chances of being randomly assigned to the control group. Rosner (1987) points out that one may want to avoid the use of an RCT because it may not be possible to carry out the RCT properly if the conditions of the trial make it probable that it may not be
completed or not enough patients will be recruited to make it effective. A stronger argument that he presents is that referring clinicians may refuse to enroll their suffering patients in a trial that does not ensure benefits because of the possibility of randomization into the control group.

Feinstein (1983) elaborates on the basis for this concern when he says that the RCT option presents "inevitable conflicts" (p. 544) between those scientists who want to "preserve the pristine nature of the scientific process and those clinicians who want to engage in research while still putting subjects' interests first. He terms the first view "fastidious" and the latter "pragmatic" (p. 545). The fastidious group bases its beliefs on the consensus that scientific knowledge attainment is best when based in pure methodologies (Klerman, 1986). The pragmatic group feels, that philosophically, the practitioner is bound by the principle of beneficence to favor the treatment that will most probably benefit the patient. Gifford (1986) says that theoretically the conflict between fastidiousness and pragmatism is unresolvable. In practice, the clash between these groups causes extreme difficulty. Taylor, Margolese, and Soskolone (1984) cite concerns related to the therapeutic obligation of physicians for why some doctors did not refer patients to an RCT investigating breast cancer therapy options, ultimately "...threatening the...completion of the trial"(p.1363).
Chalmers (1990) has clarified his support for RCTs, stating that they are not indicated when one of the therapies to be tested is known to be effective in the identified patient population. This view supports the premise that placebo or nontreatment controls are unethical if this inhibits validated therapies from being available to ill patients (Makuch & Johnson, 1989).

However, there is less clarity when randomized tests are made up of two treatment groups, one which may be more efficacious than the other with neither treatment being considered a definitely accepted therapy for the disease being studied. This was one of the major questions in HIV clinical trials in which the promising drug, AZT, was forbidden for those involved in trials of other drugs (NICHD, 1988; NIAID, 1988), and highlights a dilemma that arises when investigators attempt to determine whether the research method is both scientifically and ethically sound. The question at hand was whether AZT had definite clinical value and, if so, whether it should be withheld to test the effects of another investigational therapy.

The issues of good design in pediatric research are not that different than when the subjects are adults. Neither minor children nor their parents may consent to the enrollment of children in research which is of no benefit to them but involves interventions that carry more than minimal risk. Therefore research design sometimes must be
compromised so that methods are less fastidious than desired. This can have an impact on the knowledge gained from pediatric research.

Another related topic is whether parents should consent to the use of placebos with their children (Fost, 1991). Consensus is that use of placebos must be fully explained to parents and that validity of results may be weakened if parents know to which group their children have been assigned.

**Informed Consent**

The debate over randomization brings into focus issues not only of research design but of patient autonomy. Because the majority of research abuses have been associated with subjects who were not aware that they were involved in experimentation or who were forcibly enrolled as subjects, requiring the investigator to attain informed consent from the subjects is a prime means of preserving the autonomy of patients/subjects (Levine, 1986). The Rules and Regulations of the Department of Health and Human Services (DHHS)(1983a) direct IRBs to require informed consent be part of each protocol that is submitted for approval. Section §46.116 of the Rules and Regulations is quite explicit about the need for potential subjects to be educated about the experimental nature of therapies, the risks and benefits, and if they are ill patients, that these therapies are not considered to be
of primary therapeutic value to them at this time. Waiver of the consent requirement or modification of the elements of consent are to be allowed, by the IRB, only under special circumstances in which "The research could not be practicably carried out without the waiver or alteration (of the consent requirement)" (§46.116.c.2).

Legal and ethical literature, while using separate languages, tend to agree on what constitutes informed consent. These elements of consent must be met:

a) all things that the consenting agent agrees to must be disclosed; b) the consenting agent must fully understand the agreement and what it means; c) the consent must be voluntary, without coercion; d) the consenting person must be competent, having the mental abilities to understand what the agreement means, including possible outcomes and negative results; and e) the consent must be enforceable, the agent must have the authority to consent, or if necessary to dissent and withdraw (Beauchamp & Childress, 1989). Informed consent is considered no different conceptually in clinical research than in any other area of medicine, however its practice tends to be much more formal and time consuming.

Macklin & Friedland (1986) succinctly summarize the problems of the autonomy issue in HIV clinical research.

Patients desperately seeking a cure, or even more limited benefits when no better alternatives exist, who
enter a study that offers the only hope, are hardly capable of granting informed consent in a fully voluntary manner. Even if they have been properly informed and understand well what they have been told, their desperation greatly influences their consent to enroll in a trial. This ethical problem is a built-in feature of the situation...(p. 279).

The concept of autonomy in pediatric research poses special problems of its own. Levine (1986) reports that the National Commission took the position that infants and young children have no true autonomy and that protection of their personhood is essentially physical protection from harm. The Commission considered the views of philosophers, such as Ramsey (1970), who claimed that the lack of autonomy does not detract from personhood but instead means that this inability to consent should disqualify young children from nontherapeutic research. Richard McCormick (1974) argued that actual consent from children can be implied from their membership in the human community which obliges them to participate in research, a truly paternalistic position. Along similar lines, Freedman (1975) solves the problem of allowing children to participate in nontherapeutic research programs by stating that their lack of autonomy means that they have no right of privacy (to refuse to participate) but only to protection.
The Commission, therefore, was faced with many arguments about the concept of pediatric autonomy and with the reality that to forbid research of either a therapeutic or nontherapeutic purpose would be to halt necessary inquiry into childhood health concerns. Children would be what Robert Levine terms "therapeutic orphans" (1986, p. 239), which refers to a population that suffers from true health problems that require inquiry but go uninvestigated. The effect of therapeutic orphan status, according to Shirkey (1968), means that children often are given drugs that have gone untested in pediatric samples, and therefore, are only informally investigated with already ill children in uncontrolled clinical settings.

In recommending that children be included in research supported by the federal government, the Commission accepted that such inquiry was essential. However, the key to involving children in any research, particularly research that is of no therapeutic worth to the individual, is protection of the child (National Commission, 1977).

Prior to the enrollment of any child (under 18 years of age) in an RCT, informed consent is solicited and obtained in almost all cases from his or her parents. Commentators have discussed whether obtaining parental consent should be the primary release for the pediatric investigator from charges of failure to consider the autonomy of the subject. Nonetheless, parental consent for children to participate in
research is necessary until they reach legal majority (Levine, 1983, 1989).

Such a position, supporting the role of the parent as the proper decision maker in this situation, derives from the traditional belief that parents are the best judges of their children's interests and that they should be given considerable latitude in how they raise their children within the framework of their cultural and moral beliefs about family life. With few exceptions, legal trends are to respect parents' judgements in matters of medical care, including research participation (Gaylin & Macklin, 1982).

Fletcher and colleagues specify that parental refusal of research participation should be honored. They state "...ethical guidance should be judged by the consequences of following it...(and) the consequences should be examined in terms of ethical principles widely accepted across cultural, philosophical, and religious lines" (Fletcher, van Eys, & Dorn, 1989, p. 309). This implies that such weight should be given to the parents less because of the legal rights of parenthood than their status as the only people who assume direct and total responsibility for the moral and physical health of their family.

**Autonomy and Pediatric HIV Research**

The moral framework of informed consent for children built around parental responsibility and rights has
weaknesses when applied to pediatric HIV research. Much of its frailties lie within the nature of the subject population. Because of the demographic background of pediatric HIV patients, parents are often absent, ill themselves, or simply assumed to be incompetent to give informed consent. The author conducted a pilot study (Twomey, 1989b) in which several instances were found where informed consent was an issue in enrollment in HIV protocols. In New York City, accession of eligible children who were in foster care into HIV therapy trials was forbidden by regulations intended to protect already disadvantaged children from being abused through frequent use as research subjects (New York City Health and Hospitals Corporation, 1976). The HIV pandemic has forced reconsideration of this policy.

In another venue, a research team, using child abuse law, successfully petitioned the local family court to remove a child with AIDS from the care of his family who had consented to participation of the child in an HIV therapy trial but failed to bring the child in for appointments, thereby endangering not only the child's health but the collection of valuable data. Part of the judge's ruling in placing the child in foster care was that participation in the drug trial should continue (Twomey, 1989b).

There is support in the literature for reassessment of the customary basis for awarding consent rights to parents.
Langham (1979) argues that because many people can claim "special" relationships with a child, the parental relationship confers more duties than rights and if those duties are unmet, those authorities with a more pertinent view of the child's needs may have a more ethical claim to a decision-making role.

Ackerman (1979) supports the notion of allowing those adults with special relationships with children to help guide a child's care but stops short of advocating the annulment of the parental assent or dissent. In a more recent article, he specifically states "...the welfare of particular child-subjects is well served by requiring the informed permission of parents or legal guardian prior to their participation in research" (Ackerman, 1990, p. 3). Furthermore, he supports parental ability to veto entry of a seropositive child into HIV drug trials even if it seems not to be in the best interest of the child and recommends discarding the parental decision only if it is certain to cause "serious and irreversible harm to the child" (p. 4).

Risk-Benefit Assessment

The construction of a protocol with a favorable risk/benefit ratio means that the investigator has been successful in making a clinical application of the prima facie principle of nonmaleficence and beneficence. However, transforming this principle into normative research
practices has proved to be perhaps the most elusive task of the ethical researcher.

Why is the assessment of risks and benefits so perplexing both philosophically and empirically? Partially because it involves predictions of outcomes based on data that cannot always be depended upon to be reliable. Furthermore, such predictions are constructed by one group of people (researchers) to be communicated to others (potential subjects). Such communication can be difficult because of the gap in languages spoken by the two groups. The first group speaks technically and quantitatively and the second wishes to know about the quality of the impact of research interventions upon them.

Levine (1986) sketches a format of risk-to-benefit analysis that includes the variables of risks to individuals and to society that are incurred from research and the benefits that both parties might obtain. Risks can include physical, economic, and psychological burdens which should be judged on their "magnitude and expected duration" (p. 57). Benefits should be appraised along similar lines.

Marshall (1986) claims that attempts to operationalize beneficence and nonmaleficence are counterproductive because the first concept is best applied as an aggregate good for the whole community while in research the individual good cannot be advertised. However, it is the individual who will bear the burden of any harms that occur from research.
In this analysis, a risk-to-benefit formula from the subject's perspective will always be a negative value. Spicker (1988) notes, also, the difficulty of accurately informing a subject of the risks and benefits of possible participation in an RCT when randomization makes prediction of risks even more uncertain.

Veatch (1987) traces operational definitions of risk and benefit to philosophical bases. He feels that it is unrewarding to try to measure one principle based on utilitarian principles (benefits) against one grounded in Kantian deontological thought (nonmaleficence). When determining the morality of research, he suggests a lexical ordering of other principles that include autonomy and justice, among others, and says that the haziness of risk-to-benefit analysis would lower its value in relationship to other principles. This is not the path that the National Commission nor the Federal Regulations chose to follow.

In regards to risks and benefits in pediatric research, Kopelman (1989) feels that because the National Commission was so divided over how to define risks to child subjects, its compromise solution was to make the benchmark concept in pediatric research that of minimal risk to subjects. This means that it is necessary to have a firm grip on what is defined as minimal risk. Because, at this time, IRBs can only approve pediatric protocols that involve nontherapeutic interventions that carry minimal risks, the
conceptualization of good research fails because of the inability to define what constitutes minimal risk. The DHHS defines minimal risk as

...the risks anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests (DHHS, §46.406).

Kopelman (1989) feels that pediatric research is able to continue despite the lack of consensus about what constitutes minimal risk because most pediatric protocols involve little risk. This begs the question of whether worthy questions that might involve more risk go uninvestigated--an issue which risky pediatric HIV research brings to the forefront. A further question that is germane to ethical research is whether we should expand the horizons of minimal risk only with sick children (Prentice, Antonson, Jameton, Graber, and Sears, 1989).

Risk-Benefit Assessment in Pediatric HIV Research

Because of the major morbidities seen in children with HIV, it would seem that a higher degree of risk would be justified in research with infected children. However, because of the ubiquitous nature of the organism in children under fifteen to eighteen months, it is difficult to know if administering experimental drugs when children are
seropositive but asymptomatic would put such children at more than minimal risk for no benefit. A recent work group on clinical research in HIV concluded that

Until there are reliable tests generally available to detect true HIV infection in seropositive but asymptomatic babies under 15 months, in general these children are not appropriate candidates for studies of drugs to treat HIV infection or AIDS (Levine, Dubler, & Levine, 1991, p. 14).

Nonetheless, the decision not to investigate in this age group when the diagnosis is unclear means that the significant number of asymptomatic children who go on to have AIDS and deteriorate quickly may suffer from lack of clinical drug and diagnostic knowledge.

Another controversial issue regarding risks and benefits has been the decision by some investigators to use placebo controls in trials with children with HIV (NICHD, 1988). Because these trials are phase III trials involving drugs that are believed to have some efficacy in the treatment of HIV, some commentators have claimed that administration of a placebo to symptomatic children places them at risk because of the withholding of a possibly therapeutic drug for the sake of fastidious methodology (Twomey, 1989b). Still, such methods are used and remain controversial (Nolan, 1989).
Equitable Selection of Subjects

The prime justice issue in research ethics is how to avoid the use of the same subject groups in many different protocols, particularly if those subjects are ill (Levine, 1986). The National Commission (1978) viewed this issue as the central justice point to be considered and urged special protection for what they termed "vulnerable subjects" (p.19). Heeding their words, the resultant federal regulations gave IRBs the charge to disapprove protocols that did not provide special protection to certain vulnerable groups (DHHS, 1983a; 1983b).

In pediatric research, the population is already defined as vulnerable because of the child's inability to fully protect himself or herself. The ethicist looking at potential pediatric research must balance the good of affirming inquiry into problems that afflict a sick population against the cumulative burden that a member of such a population incurs because of being both sick and a research subject. To add the factor of childhood to this moral equation is to make one quite hesitant to allow trials which continually recruit from the same populations.

Justice and Pediatric HIV

Because of the added burden of poverty and being from racial minority groups, most children with HIV are in need
of special protection when recruited into trials. Several specific justice issues have stood out in pediatric HIV trials.

One large trial included in its informed consent procedure the incentive that enrollment would guarantee that the subjects would receive better care from the clinician-investigators (NICHD, 1988). The implication is that non-enrollment will mean that resultant care would be suboptimal. Such a message can be powerfully coercive for poor parents seeking treatment for their child.

One criticism of the traditional NIH research program during the AIDS pandemic has been its inability to get possible therapeutic drugs to sick patients quickly and efficiently. At one time, AZT was the only approved antiviral drug for pediatric HIV. There are questions whether it is fair to tightly restrict entrance into trials in order to further enhance methodological rigor (Chalmers, 1990). Furthermore, it may be unfair to use the threat of termination of treatment with the resultant loss of access to experimental drug therapy when parents are reluctant to continue enrolling their children in consecutive trials that study the same drug.

Indeed, one question that has arisen has been of what moral claim a former research subject has to the fruits of his or her sacrifice if the drug tested is ultimately approved. Should it be made available freely to all former
subjects involved in its development and who should bear the costs of such a benefit (Twomey, 1989b)?

Involvement of IRBs in Protection of Research Subjects

Special considerations were given by the National Commission to the use of children in research. Prior discussion has focused on the primacy the Commission gave to the principle of children's autonomy and how the operational concept of this principle became protection of the child's physical being. There was controversy amongst the commissioners over how much protection could be waived in order to include children in nontherapeutic research that would involve exposure of the child to more than minimal risk (McCartney, 1978). Recommendation (5) of its Research Involving Children: Report and Recommendations (1977) states that such research can be conducted if the increased risk is no more than a minimal increase over minimal, if the research activity is similar to normal activities the subject incurs because of treatment of the underlying condition, and if the research can be considered to probably provide future benefits to children with similar conditions. Because this recommendation allows ill children to be put at some risk for research that will not directly benefit them, two of the commissioners considered this a violation of the principle of autonomy as manifested in the imperative to protect children subjects and refused to endorse the
recommendation. This was the only recommendation of the ten that was not adopted unanimously (National Commission, 1977).

One of the rationales for convening the National Commission was to use their recommendations in constructing protection for subjects in research funded by federal funds. This research is subject to regulations promulgated by the federal government in 1983. Regarding the issue of protection from risks, Levine (1983) feels that the final regulations followed the spirit of the Commission's recommendations.

Probably the most noticeable effect the final regulations has on present day research is that IRBs are statutorily given responsibility for monitoring and essentially approving all biomedical research in this country. Although some institutions had formed IRBs voluntarily as early as the 1960s to monitor their research, with the establishment of the federal regulations on biomedical research in 1983, IRBs were not optional if research was to take place (Mitchell & Steingrub, 1988). Though there is ongoing discussion about the particulars of what the details of the mission of an IRB should be at individual institutions, there is little dispute that their role is a legitimate part of the ethical mission of clinical research (Gray & Cooke, 1980). McNeill (1989) feels that IRBs contribute to an American system of research review
that is ",...far, far more elaborate, far more sophisticated, much more detailed than any other system around the world"
(p.4).

Because of the differences in personalities of IRB members, each committee is unique and provides different perspectives on research that is intended to reflect local community values. What one IRB may find allowable in research, another might not (Prentice, Antonson, Jameton, Graber, and Sears, 1989). Some concern has been voiced that local IRBs provide variable decisions on identical pediatric HIV protocols because of differing levels of reliance which each board has on the applying investigator (Twomey, 1989b).

Regulations demand that IRBs be a final consultant on the ethics of proposed research projects (Levine, 1989), and that their decisions often reflect the lack of consensus in the bioethical community over the morality of some protocols. Therefore part of inquiry into pediatric HIV clinical research ethics should include investigation of the views of IRB members on this topic.

Role of Nursing in Pediatric HIV Clinical Research

The role of nurses in pediatric HIV research is complex. While usually not the primary investigators in studies, they have many responsibilities that facilitate the
trials, such as recruitment, provision of care, and coordination of the protocols. Assumptions can be made that the ethical actions of nurses will be as complex as their roles. While trying to maintain the necessary numbers of subjects, they must also guard against violations of research ethics that would harm the personhood of the child. This suggests that while nurses may verbalize their ethical imperatives in principle-based ethical vocabulary (Jameton, 1984) their actions may be best understood in the framework of care. Analysis of the data must consider the influence of both ethical systems on research ethics.

Conclusion

The ethics of clinical research continue to be examined by contemporary bioethicists. Pediatric research has always presented those with an interest in the moral conduct of scientific investigators with special problems. Pediatric HIV poses so many new issues that challenge the analysis found in traditional pediatric research ethical thought that further study must be done to provide more dialogue in this area.

This discussion of the general applicable ethical theories in the area of pediatric HIV clinical research is intended to provide a broad area of focus for this exploratory study. Its focus clearly is to give a background to the preeminent contemporary bioethical
theories on the topic and therefore is not presented in a format that takes into account the many philosophical perspectives that shape basic bioethical conceptual frameworks about clinical research.
Chapter III
Research Design and Methods

This chapter contains an explanation and rationale for the chosen research design. It describes the sample chosen and methods of data collection. Data analysis procedures, including determinants of reliability and validity, are presented.

Research Design

The design of this study was a non-experimental field study. The purpose of such a design is to collect data about phenomena that occurred in the real settings where the subjects took part in clinical research. Its goal is to obtain data that reflects the personal perspective of the subjects sampled (Polit & Hungler, 1987). The analysis of the data was done using qualitative methods that allowed the investigator to interpret the data as it was collected and permitted multiple views of the issues that were captured in the collected data.

The phenomena investigated were the views of the subjects regarding the ethical treatment of child research subjects with HIV. The data were elicited from respondents at four clinical pediatric HIV research sites. The qualitative research design, with open-ended interview questions, and the subsequent method of data analysis was used because little empirical research existed on this
topic. This intellectual void supported the use of a methodology that allows for investigation of unanticipated topical areas that emerge from the collected data.

The data collection method addressed the research question by allowing subjects to share their perceptions of their clinical HIV research experiences with children. This methodology permitted the phenomena to be economically surveyed in such a way that the changing nature of the data could be captured without repeated data collections. The collection of these multiple individual experiences gave a more comprehensive view of the overall practices of clinical research ethics with children with HIV.

Population and Sample

The population for this study was all nurses and physicians who are involved in clinical pediatric HIV research, IRB members who review such research and the parents of HIV seropositive children age three years and younger who are enrolled in one or more clinical trials in the United States. The sample was drawn from four clinical sites and included a total of ten registered nurses, seven physicians, four Institutional Review Board (IRB) members, and seven parents of children with HIV. Several of the professional respondents had more than one role. This included one nurse who was also an IRB member, three IRB members who were physicians, and several of the physicians
who were ad hoc IRB members. However, for the purposes of
the study, each respondent was recruited to fill only one
respondent role, either as an IRB member, a nurse or a
physician.

Thirty-one sites drawn from a database compiled by the
United States Department of Health and Human Services,
Public Health Service of all clinical sites in the country
carrying out pediatric HIV clinical research were randomized
and five sites selected for inclusion in the study. Prior
to randomization, it was decided that the sample would be
restricted to sites in the New England and Mid-Atlantic
States, including Maryland and the District of Columbia.
This was done for the convenience of the researcher and
financial expedience.

Of the original five sites selected for investigation,
two were determined not to have the necessary number of
professionals to meet the study criteria and were excluded.
Three additional sites from the randomized list were
contacted before two suitable replacement institutions
agreed to participate. Late in the recruitment phase, one
site withdrew from the study, citing philosophical problems
with the methodology of the study. Recruitment of another
site was deemed unfeasible because of the time it took to
gain approval and access to a site. Therefore, the study
proceeded with the four sites already enrolled.
The 28 respondents were interviewed at four separate institutions that did pediatric HIV research. Two clinical sites were in the same Mid-Atlantic city on the east coast of the United States. The other two sites were in a New England state, with one being located in the largest city in the state and the other being in a large city located in a more rural area. Each site was certified as a pediatric AIDS Clinical Trial Unit (ACTU) by the National Institute of Allergy and Infectious Disease (NIAID) of the National Institutes of Health.

Because the research question explored the ethical views of health care professionals and parents of children with HIV, all subjects were directly involved in the research process. Therefore, each subject, other than IRB members and parents, was a nurse or physician who described spending at least 50 percent of his/her professional time in research with children. This requirement insured that the researchers were well versed in the issues surrounding research using children as subjects.

The specific sample at each site included the following:

1) At least two registered nurses who reported at least 50 percent of their research time to pediatric HIV care and research in inpatient and outpatient settings. At one site, two additional nurses who met the inclusion requirements were interviewed.
2) Two physicians who reported allocating at least 50 percent of their research time to pediatric HIV research and care in inpatient and outpatient settings. The lone exception occurred at one site where only one physician was available for interviewing when the data collection occurred.

The percentages of time that each subject devoted to pediatric HIV research and care was based on the researcher's past observations of the usual amount of time physicians and nurses devoted to this professional area. Typically, the pool of subjects eligible for inclusion in this study was drawn from those professionals working in pediatric subspecialties such as oncology and infectious disease. Because these professionals also worked with patients without HIV, it was rare that HIV care constituted the physicians' primary (more than 50 percent of time) duty. However, the sample at each site tended to be inclusive of the total number of physicians and nurses devoting the defined amount of professional time to the study topic.

3) One IRB member who had reviewed research protocols at his/her present institution that involved recruitment of children with HIV who are under three years of age.

4) Two parents or legal guardians of children under three years of age who had been recruited for participation in clinical HIV research. At one site, a
third parent was interviewed, while at another site, no parents were recruited because IRB permission to do so was not given before the site visit was made. Inclusion of the parent perspective was felt to be important, as anecdotal evidence in the literature reflects the fact that the goals of the subjects and families included in HIV research differ in many respects from the goals of the researchers (Chase, 1988; Gladwell, 1991).

**Instrument**

Open-ended interviews were used to elicit respondents' views on the ethical issues regarding research with children with HIV. This type of interview allowed the respondents to express their beliefs on the issues as they perceived them, while also preserving the interviewer's ability to focus the discussion on the desired topic.

Each interview was quite unique and different. The interview began with the researcher asking for the respondent's views about ethical issues in pediatric HIV clinical research. For some of the respondents, this request elicited much information and the discussion flowed easily. Occasionally, the interviewer asked for more elaboration from the subject or for the subject to share a personal story about an issue that was identified. However, in most of the interviews, some prompting of the respondent was necessary and was done by the interviewer asking
questions such as "Tell me how your group obtains its study subjects?" Additionally, as the data collection process proceeded with its concomitant data analysis, the interviewer developed a mental semi-structured interview schedule that emerged from the prior interviews and gave a general direction to pursue if the original open-ended exchange needed augmentation. (See Appendix A) Interviews ranged from fifteen to seventy-five minutes.

Open-ended interviews are considered an appropriate data collection instrument when investigating a topic in which there is little past knowledge available about the phenomena and the study is intended to be descriptive in nature (Lincoln & Guba, 1985). Qualitative scientists recognize that interviews often need some focusing by the interviewer and that with continued experience, the interviewer will become adept at knowing what topics to address and when to interject oneself to give the respondent some direction (May, 1991).

**Procedures**

**Data Collection**

At each site, the coordinator of the pediatric clinical trials was utilized as the contact person. This person was a nurse coordinator at three sites and a biologist coordinator at the fourth site. This person was used to gain access at each site and choose the respondents. The
selection of the respondents at each site was purposive for reasons of expediency. Often the interviewed professionals were the only available people who met the inclusion criteria and the IRB member was one that the contact person could reach during the time frame of the visit. The equally nonrandom selection of parent respondents occurred through review of patient charts by the contact person or study nurses to determine which patients were scheduled for a visit to the clinical site while the interviewer was there. Each parent was approached by the contact person or a designated nurse and asked if he or she was willing to participate in the study. The interviewer was not present at this time. If assent was given, the interviewer was introduced and obtained formal consent.

The physicians, nurses, and IRB members were recruited through announcements at staff meetings or direct approach by the contact person or researcher. The study proposal stated that if three or less subjects were accrued at a site, data from these subjects were to be included in the analysis and additional subjects to replace those not recruited would be sought from another site. If four or more subjects were accrued, no additional subjects were to be recruited. In addition, the minimal acceptable total percent of subjects in any group (physicians, nurses, IRB members, parents) was 60 percent of the planned total for that group. Therefore, the minimum number of physicians,
nurses, and parents would be six in each respective group and three IRB members. Based on the planned five sites, the lowest percentage of any group accrued was 70 percent, with overall accrual being 80 percent of the original total of 35 respondents.

All interviews were tape recorded except one in which the (IRB) respondent agreed to talk for a short amount of time and did not want the tape turned on. Field notes were taken, by the investigator, during and after all interviews. The use of interviews in naturalistic field study is widely accepted as a means of attaining data that is valid and robust enough to withstand challenges to its precision (Deatrick & Faux, 1991). Tape recording interviews allowed the researcher to be more interactive with the respondent during the interview, therefore permitting more spontaneity, eye contact, follow-up questions, and other acts that would have been omitted if the interviewer was focused on writing down all of the words spoken during the interview. Furthermore, less data are lost when it is captured on tape. Field notes taken during and after the interview allowed the investigator to enrich the data by noting nonverbal behaviors and other phenomena that affect data collection and analysis (Patton, 1980).
Data Analysis

Analysis of the data was done through the constant comparative analysis method (Glaser and Strauss, 1967; Lincoln and Guba, 1985). This use of constant comparative analysis included examining the data for eligibility for inclusion in categories and comparing the data in each category, integrating the categories and their properties, and looking for saturation of categories with data that would allow the researcher to conclude that the boundaries of the category were inclusive enough to be meaningful. Analysis was ongoing from the beginning of data collection and provided clues as to what issues might arise in subsequent interviews.

Data coding was done by transcribing the interviews and using a commercial data management software package (Ethnograph) to sort the data. That allowed separation of each piece of data into different categories. The basic element of analysis was a statement. Each statement was initially considered to be part of the phenomena if it reflected anything about pediatric HIV clinical research. A statement consisted of anything as short as a complete sentence to anything as long as a paragraph. As the number of significant statements grew, review of each statement was done to see if its topic could be narrowed into a category which would be supported by other similar statements from the same or different respondents (Strauss, 1987).
Data related to the research question, that of identifying ethical problems, were analyzed in the following manner:

1) All interview statements relevant to the topic of research ethics and pediatric HIV were identified,
2) all meaningful statements were grouped according to their similarities into categories,
3) all categories were reduced to specific themes by examining the existing relationships between categories, and
4) finally, the context from which the themes originated was presented and discussed.

**Ethical Considerations**

This study was approved by the University of Virginia Health Sciences Center Human Subjects Review Committee. During the enrollment stage of the study, it was ascertained that interviewing the non-parent respondents did not necessitate individual site IRB review and that the informed consent process could be verbal. To elicit consent from non-parents, each respondent was given an information sheet about the study (Appendix B) and verbal consent was obtained. At the three sites where parents were interviewed, IRB approval was obtained for the study and the informed consent process included verbal and written permission (Appendix C), except at one site where IRB
concern over parent anonymity was such that it mandated getting only verbal consent of parents to avoid having their names recorded.

**Trustworthiness of the Study**

In order to insure the rigor of the methodology of the study, the investigator used four criterion elements to establish the trustworthiness of the study. These consisted of credibility of the study, dependability and confirmability, and transferability of its findings. Establishing trustworthiness is a tenet of qualitative methodologies and incorporates the guarantee that qualitative research is reliable (Lincoln and Guba, 1985).

Credibility of the study assures that the findings of the study can be operationalized and was done by taking measures that showed that the conclusions of the study flow logically from the data collected. This was accomplished by the researcher immersing himself in the culture of the studied phenomena. Prior to the formalized site visits, the researcher engaged in activities such as pertinent literature review, background interviews with appropriate people with knowledge of the phenomena, and visits to sites with similar cultures (Twomey, 1989a; 1989b). During the study, researcher contact involved extensive communication with the study sites, on-site visitation with exposure to many different elements of the site, such as clinics where
the patient-researcher contact was made. Also, during site visits, the researcher spent up to two weeks in the geographic area of the institutions and used the facility like the respondents would have, for such activities as parking and eating. This experience helped to maximize the familiarity of the researcher with the culture of the research domain and how the parent subject viewed the site.

Dependability and confirmability of the data for the qualitative researcher replace the quantitative research concept of reliability (Lincoln & Guba, 1985). These concepts rely on showing that, for the former, the collection of data displays enough rigor so that it truly is capturing the phenomena of study as lived by the respondents, and for the latter, that the researcher can show how the data collected led to the conclusions.

In this study, dependability relied on the use of peer debriefing, which involved scheduled meetings with two separate peer researchers (doctoral students) experienced with the qualitative paradigm. In general, open-ended interviews limit the amount of bias that the interviewer introduces into the data collection procedures by allowing the respondents to present their own views on the topic discussed (Patton, 1988).

This strategy of data collection was tested by the researcher conducting three pilot interviews with one research nurse, one research physician, and one IRB member.
at an institution not included in the study prior to visiting the study sites. The topic of discussion was dependent on each pilot respondent's background and focused on general research ethics and/or research with children. After interview transcription, the pilot interviews were peer reviewed by a colleague, familiar with the qualitative paradigm, who examined each interview for signs that the phenomena of inquiry were being addressed and that the interview technique was collecting data without bias.

After the first three sites were visited, a second peer review session was held with a different peer reviewer who utilizes interview techniques when conducting research. At this point, the researcher felt some saturation of information on the topic was evident and that interviews may have become semi-structured, an occurrence not unknown in qualitative research. The second peer reviewer confirmed that the data being collected reflected the phenomena of inquiry and researcher bias did not seem to be influencing the data. The peer debriefers challenged the researcher to substantiate how interviews were conducted and pointed out any possible biases.

Confirmability in this study was assured by the researcher maintaining a system of empirical evidence that showed how the study was conducted and the results justified. This process is accomplished through an examination of an audit trail that allows judgements by a
third party that supports that the data and resultant conclusions are methodologically consistent and acceptable. Actions that the researcher employed to insure the study's credibility were to maintain field notes that reflected the context of the interviews and a log in which all steps of the study were written, such as the randomization process, the enrollment procedures, and phone conversations. Documents were retained that reflect institutional flavor and practices, such as IRB applications, protocol documents, and parent information sheets. Also, all data collection and analysis material were retained, such as original audiotapes, transcripts, data cards, and methodological notes. Additionally, the researcher consulted with a doctoral student, who conducts qualitative studies, during the coding and categorizing stage of analysis to audit the data prior to putting it into themes. This person selectively looked at statements to see if the chosen categories seemed logical and requested that the researcher explain the decision-making process used for categorization. Such preservation of archival data of the study allowed for an independent audit that could verify, as needed, the conduct of the study from beginning to end (Brink, 1991).

Transferability of the study's findings refers to the meaningfulness of the conclusions to similar ethical practice phenomena in clinical research with children subjects. Transferability of the findings to other settings
will be dependent on an individual's ability to compare the context in which the data was collected and determine its relevance to his/her own experience of the topic. These results are only an accurate portrait of the reality of the sites and subjects selected. However, these limited empirical findings will provide a basis for continued theorizing about the phenomena and could lead to further data collection on the topic, which underscores the meaningfulness of the study.
Chapter IV

This chapter presents narrative descriptions of each site and the interviewed individuals. This background narration provides the context in which the subsequent data can be understood and interpreted.

Pertinent phenomena that contribute to a comprehension of the data include the general geographic location of each site, its discrete location within that district, its physical plant and how the work is done at the site. The general patient population of each site is described, with special emphasis on its pediatric HIV seropositive subpopulation.

To protect the confidentiality of the respondents, the sites are identified by numbers indicating the order in which they were visited. For the same purpose of confidentiality, the names of the respondents and contact people have been changed in the descriptions in this chapter and are identified by codes that describe their respondent category and order of being interviewed in the data analysis chapter. (RN2 refers to the second nurse interviewed.) Also the pseudonyms used in this chapter are reflective of how the respondents were introduced and/or wished to be addressed during the interviews. For example, the IRB members and physicians are identified by professional titles and the nurses and parents all preferred the use of their first names.
**Site One**  The first site was visited in the early Spring in a New England city. The institution is a large teaching and research hospital whose mission for over a century has been provision of care to children. It is located in a dense urban area that houses several separate hospitals in an area of only a few city blocks. Site One is a tightly compacted set of discrete buildings connected by tunnels and pathways. One turns off the main street to enter its glass atrium and moves from the feeling of the constricted city avenues to an environment of openness and airiness created by the high ceilings and glass architecture. Immediately after entering through the revolving glass door, one sees a round information desk set in a large atrium. To the rear of the desk is a garden that is visible even in the worst weather because of the glass wall separating it from the atrium. Administrative areas are to the right through a small passageway. Children move with their parents on escalators and glass elevators past colorful structures and play areas on the left. On the second floor, there is a glassed-walled play area to the right of another information desk. Outside is a small circular garden with a fountain in it. Beyond the garden wall rise the walls of many other buildings so that one perceives the feeling of never being outside, even when between buildings.
Karen is the coordinator of the AIDS program at the hospital. She is about forty and has spent most of her career at this hospital. She explained that Site One does not provide primary care to seropositive children but accepts referrals from all over New England. Some families use the hospital's clinics for ambulatory care and the specialty clinics for specific problems, but there is no AIDS clinic. A child not on some type of protocol is not seen by Karen's program. Any seropositive or symptomatic child is hospitalized as needed whether or not they are on a study.

The geographic diversity of these patients was matched by their demographic variety. Many of the patients in the HIV programs were poor people of color from the inner city. Additionally, there were also a fair number of middle class children whose parents, according to the nurses, had engaged in high risk behaviors as younger people and now had passed the virus onto their progeny. Many of the parents had learned of their diagnosis close to the time that they discovered their child's viral status.

The research team headquarters was in cramped offices with many cubicles in a building that was much older than the clinical areas. This building was mostly a basic research building and all patient contact took place in the varied clinic areas.
MD Interview Number 1  Dr. Able's office is a small, 8x8 feet square space. He is a smallish 5'6"-5'7" man with thinning brown-grey hair combed across his head. He had on a white lab coat over a light blue shirt and patterned tie. He greeted me in a noncommittal way. He mentioned that he was concerned about the time commitment for the interview.

Dr. Able is a pediatric infectious disease specialist and is the director of this department at the hospital. His role includes medical resident teaching responsibilities, along with some involvement with the laboratory services and infection control measures that the hospital uses. Dr. Able says his entire medical practice has consisted of treating patients in a teaching institution. He has been doing infectious disease research for over 30 years. His involvement in HIV began in about 1985 when it was found that many of the children, who were routinely screened in the blood bank for the HIV antibody, were seropositive. Since his specialty was viral research, "...it was clear that I would be the person who was pretty much (responsible)..." Almost all of his research is now HIV-related.

RN Interview Number 1-Amy was waiting in the small conference room which was once a feeding area for research animals and now is a staff lounge. Amy is a small woman with dark curly hair who wears glasses with dark frames.
Amy has a masters degree in public health. She splits her time between her research position and providing clinical care for patients not on research protocols. She is the site coordinator for one pediatric HIV protocol. Amy has been in her position for about four years.

At first, Amy seemed uncomfortable but she definitely relaxed as the interview progressed. Part of this early discomfort may have been that she felt the need to give "correct" responses. She is also an IRB member and perhaps felt more pressure because of this position.

RN Interview Number 2  The second and third nurses worked in non-drug protocols with seropositive children. These protocols are called natural history or surveillance studies and enroll HIV-infected children to watch the progression of their illness. These protocols usually involve the same population that is receiving investigational drugs and are controversial because of the added stress they place on the families. IRB Respondents 1 and 3 noted that these type of studies have no direct benefit for the child except for increased contact with the medical/research team which may not be beneficial. These opinions may have developed because some of the surveillance measures result in pain and sedation. In fact, several of these measures have been challenged by IRBs.
The first interview was with Bea, a tall, angular woman with curly black hair, wearing a flowing blue dress and glasses with blue frames. Bea was the only respondent who believed that some of the ethical issues were of enough concern to her to make her rethink her role as a research coordinator. This is her first research experience and her first time working with physically ill children. She is a psychiatric nurse with considerable pediatric experience. In her role as coordinator of the Heart-Lung surveillance study, she is concerned about the stress on families and questions whether the benefits make up for these burdens.

Bea was unsure if she will continue in research beyond this job. Her decision will depend on whether she can reconcile her belief that research provides better care in the form of further knowledge for current and future patients with her concerns for the integrity of present families.

Parent Interview Number 1 The first parent, Coleen, was in the clinic with her child. She is a black woman of medium build who wears glasses with bluish tint on the frames.

Colleen had expressed nervousness about participation in the study which seemed to manifest itself in two ways. She tended to answer in short sentences, with little story telling and sometimes asked if her answers were okay. In the beginning of the interview, she didn't seem to
understand any of the details of her child's protocol.

She is a single mother with one daughter who is currently five years old. The child was discovered to be seropositive at age six months and has been involved in experimental protocols for about two years. Colleen assumes she contracted the virus from her husband who is now dead. She is asymptomatic herself, takes her AZT, and works full-time in an insurance agency.

After five minutes, it became apparent that she actually had considerable knowledge of her child's protocol, which involves AZT administration in combination with another antiretroviral or a placebo. The research team suggested her daughter start the protocol when she began having frequent ear infections and then contracted pneumonia. Coleen said that when the trial concludes, she will request that her daughter continue to take AZT.

Colleen stated she feels quite comfortable with the trial and the team caring for her child. She has private insurance and could receive her child's AZT without being involved in a study, but believes that the care would not be as good. Her child's lifestyle has only been minimally affected by the trial. Specifically she misses some school when she comes in for appointments.
RN Interview Number 3  Renee is a large woman who was wearing a loose flowing dress. She is infant coordinator of the Woman-Infant Surveillance Study. The investigators of this study enroll seropositive pregnant women and their infants and follow them for several years. Renee has a background as a research nurse in the private sector and her memories of that experience are dominated by the push to aggressively enroll subjects.

Renee was skeptical about research, stating she is unsure about the real benefits and she was outspoken about the potential harms that she believes are more than trivial.

Parent Interview Number 2  Gerry is a small woman, dressed in yellow slacks, tee shirt, and blue slippers. She had stayed overnight with her son.

Gerry has two children. The younger who is five years old is the afflicted boy. She described her son as being quite ill and said he currently is on his third trial, the first two drugs not being efficacious for him. He has a seizure disorder and frequent infections that have required hospitalizations, the current one for surgical debridement for mastoiditis. She has an older seronegative child. Gerry has a common law, seropositive, symptomatic husband about whom she says "He was the one who brought the virus in the family because he cheated on me and made me have it and it's taken him a long time to deal with it."
She stated she was not aware of her seropositive status until her son was diagnosed at age three months. "I only had two boyfriends and one of them is my husband now and he became positive." She takes AZT and is asymptomatic. According to her, her husband's role in the family's health care is minor because of his feelings of guilt.

Gerry, on the other hand, is quite assertive about health care. She claims German-American ancestry, though her fluent English has a slight accent that could be described as Spanish. She is Caucasian in appearance and states that her mother is from Puerto Rico, where Gerry trained as an LPN and medical assistant. She answered questions unflinchingly and the only clue of any nervousness was some clenching and unclenching of her hands. At one point she exclaimed "This is easier than interviewing with ten doctors!"

RN Interview Number 4  Nellie is a pleasant woman with short blonde hair, wearing dark slacks and a black sweater over her yellow shirt. She sat with her hands in her lap, occasionally raising one for slight emphasis. She maintained good eye contact and spoke spontaneously.

Nellie has been in her current position, which is her first research experience, for less than one year. Previously, she had been the AIDS educator for daycare providers. She described her current position as being "one
of the clinical research nurses." Her population of children has been largely asymptomatic except for blood count changes. She was not involved in HIV clinical trials when there were few alternatives to AZT. Nellie spoke of the research process as logical and largely beneficial to the children.

Institutional Review Board Interview Number 1 This interview was done at the home of Reverend Bob, which is attached to an old stone church in what is obviously an affluent area of town. Houses are large and driveways long. Reverend Bob was formal but friendly. He is in his fifties and was dressed in tweeds. He wears horn-rimmed glasses. His office is a book-lined rectangular room with a desk whose top is filled with papers. He pulled out a sheaf of papers and placed them on his lap. These papers are the files that he has accumulated over his term on the IRB. It represents research he has done in various libraries and materials he has collected. One of the documents is a risk/benefit worksheet which contains a formula that helps him to determine if a protocol is ethical. During the discussion he would hold, shake, or leaf through the pages.

Reverend Bob verbalized that he was quite serious about his role on the IRB. He believed he was randomly chosen to fill the spot on the IRB of another clergyman who was leaving. He says he brings his own "New England
Congregationalist, Calvinist humanist" background to a setting in which he views himself as a protector of disadvantaged people.

**Site Two** The contact person at this site is Helene, a woman in her late thirties. She is a nurse with a masters degree in public health and moved from California for this job. She stated that although this site has seen HIV seropositive children for about five years, it is only within the past year that this site has been involved in many pediatric trials and has become an ACTU.

Site Two is a modern hospital of recent construction that sits atop a hill overlooking a lake. In almost every way, it provides direct contrasts to Site One. Whereas Site One is in the middle of urban sprawl, Site Two is located in a rural area and serves a rural population. Site One is a referral, specialty center, whereas Site Two is a general teaching hospital with its own medical school.

Site Two was the only hospital easily accessible by automobile. The entire institution looks like it has been constructed within the past twenty years. The main doors open to admit patients into a waiting area with a gift shop on the left and the information desk on the right. By going directly down the corridor, one comes to an intersection which provides access to the entire hospital complex. To the right is the outpatient area; in the middle is the
elevator bank to the inpatient facilities; to the left is the medical school and research area.

RN Interview Number 5  Anne is a woman of medium height with grey brown short hair. She wore a blue print blouse and khaki pants. For the interview she took off her glasses. She has blue eyes that fixed on the interviewer as questions were asked but turned away as she responded.

Anne is a clinical nurse specialist who specializes in endocrine, rheumatology, and neurological pediatric nursing. She became involved in HIV about four years ago when seropositive children began being referred to her clinic. With the growth of the population and the implementation of clinical trials, she began assuming more care for HIV children. Because the model at her institution is primary care, she is the coordinator of all of her children's care, regardless of the primary diagnosis, or whether they are involved in research. She emphasized her role as a caregiver and sees herself as a hands-on provider. Anne estimated 50 percent of her caseload is HIV-related.

Parent Interview Number 3 and 4  The first parents at Site Two are Paula and Pete, foster parents of two seropositive brothers who are fourteen months apart. Pete is a man in his forties, with salt-and-pepper hair and beard. He wears glasses and a button down shirt and casual slacks. He began
talking even before Paula, a heavy woman with glasses and a loose blouse over pants, arrived.

Both parents seemed equally eager to talk and began almost immediately. They became involved in the boys' care two years ago when they took the children's mother in for care. She was a pregnant seropositive adolescent who was quite sick. Eventually the boys came to live with them. The mother had a miscarriage and apparently feeling overwhelmed, ran away, abandoning the boys. Pete and Paula spoke of her with a trace of remorse and resignation. The boys were officially put in their care soon thereafter. They have no other children. The younger of the two is about two years old and is the one on a drug trial. He has been on drug trials since he was two months old. His older brother has been relatively healthy and only on AZT until recently but is now starting to become symptomatic. The team is currently considering a protocol drug for him also. Pete and Paula are taking steps to adopt both boys.

Both parents were outspoken and neither had any problems responding. Paula tended to answer first and then Pete would follow. During the interview they focused on the frustrations of being the involved but relatively powerless guardians of the children.
MD Interview Number 2  Dr. Baker is a very articulate, thoughtful woman. She is in her early to mid thirties. Dr. Baker is a pediatric infectious disease specialist who described herself also as a specialist in HIV. She wore a black dress and has dark hair and eyes. She switches quickly from light chatter to intense discussion of issues.

She spoke mainly about the means of recruiting patients into protocols. Dr. Baker's essential philosophy is that all seropositive children should be in a trial. In her argument, there is an innate presumption of low risk in drug trials but not necessarily direct benefits to the child. Underlying her beliefs is the fact that there are relatively few seropositive children and for useful data to be found, all eligible children should be enrolled.

RN Interview Number 6  Stevie is a small woman, no taller than five feet. She described herself as approaching her fiftieth birthday. She is a cheery woman with short curly blond hair that frames her face and she wears clear-framed glasses. She wore a lab coat over a green skirt and pink blouse.

Stevie joined the pediatric HIV research team about eleven months ago and now carries a caseload of about twelve patients. She has 25 years of pediatric experience and is a clinical nurse specialist. Her volunteer work with children with HIV brought her to the research position. This is her
first research position.

She repeated the views of the professionals interviewed previously at Site Two that at this institution the patients' care needs were what drove the research experience. Stevie said that the children who were off study got the same surveillance services as children on study, because the research grants will underwrite these services if Medicaid does not. She sees a natural progression from the provider to the research role.

**Parent Interview Number 5** Bernice is a short, energetic looking woman, who wore a multicolored sweater over tights with thick colorful socks. Nina, her daughter, is a tall, dark skinned girl with a shy smile that shows one missing baby tooth.

Nina is one of four children that Bernice and her husband have adopted, though she says "But I do most of it [parenting]." Nina is the second oldest and the only seropositive child. Bernice has had Nina since she was two and the child has been enrolled in clinical trials since she was three.

Originally Bernice said that Nina's health was "fine," but she described Nina's symptoms as having worsened recently. At times Nina cannot tolerate the drugs and experiences limb pain that keeps her from walking. Finally, she confided "We didn't expect her to live this long."
IRB Interview Number 2  Dr. Braun is a quiet man but spoke freely. He wore gold-rimmed glasses and was dressed conservatively in a buttoned down, red striped Oxford shirt with tie. He clenched and unclenched his hands over his knees.

Dr. Braun has been on the IRB for three years. He is a specialist in pediatric gastroenterology and nutrition and does HIV research. He currently is the primary investigator on an intramural grant on the nutritional status of children with AIDS.

He identified several ethical issues that have arisen in pediatric HIV clinical research simply because adult and pediatric HIV disease is not identical. He saw the IRB's role as facilitating new research. Dr. Braun believed that joint discussion between the IRB and researchers prior to the submission of proposals was a good way of guaranteeing ethical research.

MD Interview Number 3  Dr. Duncan's specialty is pediatric infectious disease. He estimated that his involvement in pediatric HIV clinical research went back about three years. He stated "I can't think offhand of any specific ethical issues that have related to their (children's) trials themselves." He identified a few issues under directive questioning, but only in the abstract and did not feel that these problems had ever occurred at Site Two. He dismissed
the issue of competing trials as something that was troubling but not an ethical problem.

He almost recognized that keeping children in trials after the team had reported them as neglectful to DSS might produce an issue but downplayed this as not a problem at Site Two. Dr. Duncan responded only to directive questioning and seemed extremely pleased when the interview ended after 15 minutes.

Site Three Both Sites Three and Four are in the same large metropolitan city in the Mid-Atlantic region. They are on opposite sides of the city and their architecture, ambience, and surrounding neighborhoods are all quite different.

Site Three is located in a very poor part of the city. One could see where the demographic composition of the area has changed over time. Whereas the faces and the language of the people who received care at the site were multiethnic and multicultural, the care givers were almost all white. The hospital was an amalgamation of a number of old dirt-encrusted buildings, each of which seemed to have its own security system. One could not move freely from one clinical building to another.

Walking from the subway to the hospital, one must pass a large queue of people outside one of the buildings waiting to receive care at the ambulatory care clinic. Inside the building where the research offices are, the architecture is
like that of a large, older office building with lots of narrow corridors and few windows.

The pediatric HIV team had its own wing for its studies with women and children. The clinic site is an old patient ward, with the nurses' station serving as the secretaries' work station. The patient rooms, with their toilets and sink fixtures, serve as exam rooms and offices. Like Site One, Site Three is a referral center for HIV drug studies and in theory does not do primary care, except through its regular clinic system, where many of its protocol patients are seen.

RN Interview Number 7 Site Three only sees women and children in its protocols. Other patients go to different institutions. Besides Laurie, the contact person, there is one other nurse involved in the drug trials. The unit is quite busy with other people, because it provides space for nurses who are involved in several surveillance trials (similar to those described at Site One), social workers, and some physicians all on the same wing.

Laurie was the only one of the contact people who was interviewed. She is the coordinator of all the studies, but also carried her own caseload of HIV children. Laurie is 5'5"-5'6" with blond hair cut short and curly. She wore a black polo shirt with green scrub pants and white strapped clogs. Over her clothes she wore a white lab coat. She
tended to turn her hands in a washing motion while answering questions. Several times she asked for clarification of questions, then answered. On occasion, she gave examples of issues.

She had been in this job for two years. This was her first research experience but she had been caring for children with HIV since 1985, so she could claim as much experience with this group as anyone.

MD Interview Number 4 Dr. Sean's office is on the AIDS/HIV unit. He is a pediatric infectious disease specialist and was wearing a light shirt with a tie, dress pants and a lab coat. It became clear that he would not respond to any open-ended inquiry, only to direct questions. He essentially denied that there were any true ethical problems in pediatric clinical drug research nor anything of a pertinent ethical nature inherent in the research with children at Site Three. When some classical research issues such as informed consent and risk/benefit ratio were reviewed, he admitted they all could be "termed ethical." He basically only saw problems arising when there was interference with research protocols. Dr. Sean's attitude was that there were no problems that couldn't be fixed. His definition of a problem was if patients could not be enrolled in trials. However, he claimed that this has not occurred frequently at Site Three.
RN Interview Number 8  Lennie was interviewed in a small spartan room with one window. The furnishings consisted of a table and two chairs. This was apparently a popular room, for several people knocked on the door wanting to use it.

Lennie said she did not know too much about "ethics" but would be glad to talk. She was a scholarly appearing woman in her early thirties. She was an attractive Hispanic woman who has lived most of her life in the United States but still speaks with a noticeable accent. She wore glasses and tied up her black hair behind her head.

She did her best storytelling when asked to describe how "she feels" about her research role. This is her first research position, but she has six years inpatient pediatric experience. She has been in this job for a year and a half.

Parent Interview Number 6  Diane was a small, somewhat heavy, light skinned Hispanic woman who spoke English with only a hint of an accent. She and her husband had five children at home. Two were biologically her own and are seronegative. Three were foster children who were seropositive when they got them. The youngest, an infant, seroconverted to negative and has never needed any medications. The eldest two, age nine and five, were both on protocols. She and her husband, a maintenance worker, were finalizing details to adopt the five year older.
Diane strongly believed that she has much personal responsibility for the children in her care. Even though her legal role in the care of her two ill children is minimal, she is determined to be a firm advocate for them. They receive their care at different ACTUs in the city, and she says that she often compares the care each receives and would not hesitate to go to other centers if that became necessary to obtain proper care.

Institutional Review Board Interview Number Three Dr. Jones is an older woman with grey hair and blue plastic rimmed glasses. Sitting at her desk during the interview, she spoke softly, occasionally pausing for long periods while she considered a point. She seemed open to all questions and clearly considered her opinions as coming not just from her role as an IRB member but also as a primary investigator. Her IRB has her review all pediatric protocols, but she abstains from voting in the committee when she is the primary investigator (PI). Like many of the people involved in pediatric HIV research, her background is in infectious disease. She has been on the clinical staff and teaching faculty at Site Three for over twenty years. Her interests include maternal transmission of HIV as well as pure pediatrics. Contextually, the infectious disease people seem quite interested in maternal transmission for it provides a target for determining just when HIV is passed
and an opportunity to use drugs to prevent infection rather than what appears to be a futile attempt to hold back its progression.

**MD Interview Number 5** Dr. Gannoe is a petite, middle aged woman with brown hair containing a touch of gray. She wore a black outfit. She sat at a conference table outside her office and fixed her gaze directly ahead, looking away only when considering an answer.

Dr. Gannoe is a pediatric infectious disease specialist who has been a professor at the medical school at Site Three since 1985. She was the director of her department and the principal investigator of the pediatric AIDS clinical trial group.

Dr. Gannoe was involved in some of the early medical decisions regarding HIV drug trials and treatment in this country. These decisions directly affect research and treatment behavior today.

**Parent Interview Number 7** Penny was in the clinic to pick up her son's medication. He is a six year old with many HIV related diagnoses, including the nutritional/energy problem that prompted Penny to bring him in his stroller. He felt strong enough to take a trip around the clinic, where he greeted every caregiver in sight with a yell. He paid no attention to the nasogastric tube taped to his cheek and
shirt as he made his rounds. He even got busy Dr. Sean to come out of his office and talk. The ride seemed to invigorate him, for he eventually climbed out of his stroller.

Penny is a small, overweight black woman, dressed in blue jeans and a yellow top. She answered slowly but readily, referring to George's medical file to correctly list his medications. She mentioned but did not want to focus on her younger seropositive girl who "...is no longer with us." (She died at age three years old.) Penny is a single mother who gets help with George's care from her 25 year old son who is unemployed and lives at home. Penny's job is providing full time care. For example, today's visit from her fairly distant home was necessitated because George had run out of his over-the-counter antacid that the clinic would provide. She tried to purchase it herself, but the price was so high she had to come in to pick it up.

George has been on research protocols since he was eighteen months old. He has been on almost every drug for HIV related problems that has been available on and off protocol.

Site Four  Site Four was visited during a glorious spring week. This hospital is as much a shrine to philanthropy as to medicine. An affluent local businessman had taken the institution under his wing and, with a few of his friends,
essentially supported the entire place. The street on which Site Four is located was named for the philanthropist. The medical library holds many pictures of him and his wife, taken with luminaries such as U.S. Presidents. There are no east or north wings at this hospital. Instead, everything is named after donors.

In contrast to Site Three, this place looks as if funding problems do not exist for it. There was as much glass as concrete and large areas of empty space existed that made one feel as if one was in a museum. Site Four is located in a pleasant part of the city, with parks and museums adjacent and retail stores and housing nearby.

The research offices were in what appeared to be the oldest building on the block. The old brownstone had one entrance with a security guard inside the door. The ACTU was on the fourth floor.

Charlene is a doctorally prepared biologist who is on the faculty of the medical school. She is the contact person and has been with the project as coordinator for several years.

**RN Interview Number 9** Enid is a middle-aged woman with a soft Caribbean accent. She was dressed in a multicolored, purplish blouse over a blue skirt. She wore glasses.

Enid is a nurse with an obstetrical background and a masters degree in health education. Enid has been in her
position for about five months and currently carries five patients who are one single protocol at this time. At Site Four, the team members are responsible for the entire care of their subjects. Enid makes sure that any nonstudy medical needs are taken care of by one of the physicians, even if she must come into the emergency room to arrange the care. Her protocol was a randomized study which compared combinations of AZT, DDI, and/or placebo in seropositive, symptomatic patients.

MD Interview Number 6 Dr. Hope is about 5'7" with curly hair and a somewhat long beard. He was the only research physician interviewed who is not a pediatrician. He is an infectious disease doctor who described himself as one of the first physicians in the country to describe the HIV disease, in the early 1980s. Four years ago when Site 4 began doing studies with children, he was designated as the coordinator of all the Site Four protocols. This included being entitled the pediatric PI, although strictly as an administrator.

At first Dr. Hope fiddled with a pencil as he answered questions and then switched to a rubber band. He tended to glance toward the right wall as he talked, occasionally looking at the interviewer. He seemed less rushed as we went on, only looking at his watch once.
Because of his belief that essentially there were no ethical problems, probing about issues was needed. He actually spent some time on each question, though his basic premise was that every issue had a solution or proper path to follow.

RN Interview Number 10 William was the only male nurse that was interviewed. He works part-time at Site Four while completing his masters degree in community health education. He has been a pediatric nurse for twelve years and started his current position in 1989 when the pediatric research program was getting started. His plans are to leave the job in the fall after he completes his masters program and take a position in Europe with the World Health Organization doing HIV education programs.

William appeared to be in his early to mid thirties, with brown hair, a sharply dressed man, with a blue shirt and patterned tie and khaki pants. He was eating during the interview, spooning in yogurt between answers, which tended to be fairly long and with definite conclusions. He was quite firm with his responses and tended not to mull things over.

William was one of the researchers at Site Four who recruited children throughout the institution for participation in the early trials. During this experience, he found that he was also helping to set up a program of
primary care for them. To date, William has been involved in five trials and currently has about 30 enrolled patients.

MD Interview Number 7 Dr. Dunn is an older middle-aged man with short salt-and-pepper, curly hair. He wore glasses and had on a blue shirt and light tie under his lab coat. He sat at his desk with his back to a window with a breathtaking view of the river beyond.

He is a pediatric infectious disease specialist and has been seeing children with HIV for about ten years. His research has been conducted mostly in the past five years.

Dr. Dunn saw no ethical dilemmas in the area of pediatric HIV research, only some minor questions that are easily answered. According to him, the greatest goal was knowledge and the only alternative was to succumb to deadly disease.

He alluded that the ethical nature of the problems in pediatric HIV research continue to be solvable if one defines what is the knowledge needed, not the process one has to go through to attain it. The tenor of the interview was one of simple pragmatism as described by Dr. Dunn. He sees HIV as a deadly disease, good people are working on it, and things such as informed consent are relatively inconsequential because they could impede needed scientific progress.
Institutional Review Board Interview Number 4  Dr. Roberts is an internal medicine physician who spends the majority of her time doing renal cellular research. She is a bench scientist and does no research involving humans.

She has reviewed many HIV protocols, including pediatric studies. She admitted that the committee relies heavily on the PIs for information about what is being done. She said that she is very concerned about informed consent, feeling patients often do not understand the implications of being a subject.

Summary

During data collection for this study, four sites were visited and 28 subjects interviewed. Eight subjects were interviewed at Sites One and Two; seven subjects at Site Three; and five interviews were done at Site Four.

Four IRB members were interviewed. One IRB respondent was a clergyman. The other three were physicians who themselves conduct pediatric HIV clinical research. Three IRB members were men and one was a woman.

Seven respondents were interviewed in the role of MD respondent. One physician was interviewed at Site One and two physicians were interviewed at each of the other three sites. Six of the physicians' basic medical training was in pediatrics. All seven had subspecialty training in infectious disease. All seven either were members of or
reviewed and advised their institutional IRB on pediatric HIV protocols. Five of the physicians were men and two were women.

Ten nurses were interviewed. Eight coordinated pediatric HIV drug protocols while the other two coordinated pediatric HIV surveillance protocols. Four nurses were recruited at Site One while two each came from the other three sites. Nine nurses were women and one was a man. Three of the nurses had masters degrees in nursing and one had a masters in public health. All ten identified themselves as maternal-child nurses.

Seven parents were recruited at three sites. Three parents were interviewed at Site Two while two parents each were from Sites One and Three. Six parents were women and one was a man and he was the husband of one of the female subjects. Three of the women were natural parents and seropositive themselves. There were four foster parents. The mode of infection for all of the seropositive children belonging to the parents had been vertical transmission.
Chapter V
Data Analysis

In this chapter, findings are presented and the main categories are identified, including an explanation of how each category was developed. The themes that were identified from the examination of the multiple categories (Appendix D) are explicated, using examples of respondents' quotes and graphics (Wise, Plowfield, Kahn, & Steeves, in press). An exemplar case of the issues in pediatric HIV clinical research ethics that emerged from the study is presented and discussed.

Themes

Issues of Present Care vs Future Knowledge Development

The respondents spoke about the many factors that influence their participation in the research process. The motif that dominated the discussions that make up the four categories under this theme was the conflict between the need to balance proper care of the child today with the imperative to develop knowledge for the benefit of future patients.

Three of the categories involved concerns about pressures on three groups involved in pediatric HIV trials, the researchers, the parents of subject children, and the
Institutional Review Board. Conflicting strains on researchers to provide both care and do research were noted by the respondents. The stresses on parents who tried to get the best care for their children while worrying about what the future portended were described. Issues over how IRB members made decisions about protocols also arose. The fourth category consisted of statements about the effect of present and future knowledge needs regarding pediatric HIV on clinical research practice and ethics.

Physicians and nurses noted that while many of their intents can be termed virtuous, not all their research endeavors can be described as patient-centered. The parents recognized that their children needed help, but also understood that many research efforts would only produce future benefits for other children. IRB members talked about the different views expressed by members of their boards as they struggled with how to make decisions that allowed equitable and beneficial protocols to be performed. The underlying topics that make up the four categories in this theme are presented with illustrative quotes.

Concerns About Pressures on Researchers 21 of the 28 respondents reported that there was ethical significance in how pressures were applied to researchers who conducted pediatric HIV clinical research.
Pressure to produce results IRB respondents 1, 2, and 3 spoke about the effects of the pressure that is placed on the researchers that they have observed. IRB 1 noted that researchers are pushed to provide immediate results which are not judged by biologic data but by both the numbers of studies being done and the number of subjects who are enrolled. IRB 1 said:

If there was one problem, if you had to put it in a nutshell, the one problem is the relentless federal pressure to do things, either on a shorter term than we were able to or in ways that really (sic)... scientific merit was questionable but it was always the pressure, you know, "we've got these deadlines, you got to, please rush this one through."

IRB 1 went on to say that this pressure combined with the normal expectations of professional life can cause conflicts for researchers, "...the inside people have a very vested interest in terms of their own professional standards..." IRB 2 mirrored this concern, saying "There's also potential for conflict I guess."

In a series of statements MD 1 underscored the conflicts that researchers deal with on an ongoing basis. Money and careers are one of the things that drives academic physicians and nurses to do what they do...In other words, putting children into trials, we feel it's good for the children, we know it's good
for the money and we know it's good for the careers...Everything that we do depends on putting children onto protocols. So there's a lot of pressure to put...I mean I thought, that's so implicit in everything that we do and it bothers everybody. MD 4 also noted that the pediatric HIV clinical research program at his center felt the same pressures.

Three of the ten nurses described the pressure they felt to include children in trials. RN 3 stated this in the strongest terms, saying "We have X amount of time to get X number of children into X number of protocols and that there's a real push to get a child into a protocol."

Parent 1 was the only parent to make any conjectures about pressure on the researchers. She declared that "I know they're doing it for her. It's not for selfish reasons."

Pressure to provide care Six of the seven physicians stated that the primary impetus for enrolling children in research trials was the immediacy of needs of these afflicted children. Because of their background in infectious disease, they cited the importance of finding effective therapies and preventatives for HIV. They believed that the present system of research was appropriate to meet these tasks. MD 7's comments about the issue represent the views of the group.
The reason I got into clinical trials was because I thought we weren't providing adequate care to the patients who came here and inevitably being in the neighborhood we're in, we were going to get these children and it wouldn't be right not to provide the best of available care for them. I think the trials give us that.

MD 3 provided further rationale for using trials to deliver medicines to children rather than simply prescribing the drugs by saying this practice allowed the accumulation of a body of knowledge of the drugs' effects which would be beneficial in the future.

All ten nurses talked about conflicts they felt as research nurses to provide care to their patients. RN 7 said that pressure sometimes extended to enrolling or keeping children on protocols who probably were not good candidates for a particular study. She commented:

An example is one of the mothers that we approached... she just can't keep her appointments and she's not real smart ...I just didn't feel that she was going to be compliant and I couldn't understand what the benefit would be to science first of all and to herself.

Other nurses reflected similar pressures to the MDs and spoke of the need to offer the children something now. RN 4 expressed her feelings of exasperation when a child in foster care could not be entered into one of her trials
because the local child protective agency had not approved it. She stated "...we didn't have any other protocol at the time to offer asymptomatic children so that was another thing that was very frustrating." RN 1 reflected on her belief that the pressure can be double-edged, as she spoke of a child who needed therapy but was ineligible for a study because of elevated liver enzymes. She stated:

It was a real struggle for myself and I think especially for our PI to decide that, you know, this was a child that we weren't even going to approach about this DDI protocol. That we were just going to put him on another [non-protocol] regime. I mean, unfortunately our all, almost all of our money comes from the clinical trials group and so the more patients that we're able to enroll, the better off that we are money wise.

The conflicts that arise between the needs of research and the need to provide care were discussed by all of the nurses. Several noted that additional conflicts existed for them because they were pediatric nurses still involved in providing care for children. Five nurses specifically noted the tension between balancing research and care needs. RN 1 stated that "I would never recommend a study that I felt uncomfortable with but I'm always very caught between my idea...my ideals for pure science and my ideals for getting children the best possible care that's available."
Similarly, RN 5 noted:

I think that if you're dealing with a child that's your child and has been your child for a number of years, you can't be anything but an advocate for the way that the study will run. Also, I think you start with a research study and if your model is truly focused on the research and not on the kid, you feel as though it can't be flexible, it can't be broken, it can't be moved and adapted. And I think it's a very bad perspective to have...

These remarks of RN 1 and RN 5 reflect the conflict that endured for many of the providers between research and care.

Two of the nurses spoke of instances that led them to file reports of child neglect with local child protective agencies. RN 6 discussed the specific pressures that arise when a pediatric nurse has to address this issue. However, RN 2 addressed a different issue, that of confidentiality. She stated:

My feeling about it was I wanted to protect the child... Other people said "This is a research project, we have confidentiality issues here, we have assured the mother that we're going to maintain her confidentiality. We should not have filed."

Two nurses, RNs 5 and 6 specifically talked about the struggle between the present needs of patients' and the future oriented nature of research. RN 6 remarked:
We don't know a lot about any of the medications that we are using except the AZT and we don't have a lot of treatment for the kids and the only way we're going to learn is to have them involved in studies so that we can learn how the drug is affecting them, is it working on them? Without that I don't think we're going to have much of a future for the children coming up down the line.

RN 5 echoed this theme of reconciling the future with her present actions, noting that she encourages pediatricians to refer children to research protocols by telling them "The kid before you helps your kid."

In summary, the respondents discussed two topics in this category. The first was the pressure to produce results quickly. Three IRB respondents, two physicians, and three nurses discussed this topic. Specific points presented included the enrollment of as many subjects as possible, the need to keep them on protocols, and that without patients, funding sources would end the research protocols and therefore clients and researchers would suffer.

The second area of deliberation was the need to provide care. Six physicians and all ten nurses brought up this topic. However, the physicians spoke broadly of the imperative to defeat a dread disease whereas the nurses brought up the pressure of trying to enroll unsuitable
patients or conversely the frustration of not being able to enroll acceptable patients. They also noted issues such as confidentiality and the overall issue of how to balance the needs of present patients with concerns for the future cohort of ill children. The parents had little to add to this category, with only one making a contribution in her remarks.

**Concerns about Pressures on Parents** Twenty-three of the 28 respondents discussed ethical issues related to pressures on the parents of children in trials including their views on how trials are conducted and their goals for the trial.

**Concerns about the present** Three of the parents reflected that an important concern for them was a feeling of trust in the research team, specifically that the professionals would recognize any problems caused by the trial and take steps to protect their children. Despite this desire for a trusting relationship, six of the seven parents stated that they felt the team should share more information with the parents about the course of the trial, particularly how the medications were affecting their child. Parent 3 claimed "There is no one that can discuss anything about the protocol until it ends and then if it comes open and that can take a year or two after the protocol is over, even." Parent 1 mused about the trust that she must have despite lack of information, saying "And the thing that
bothers me is that you don't know what the either/or is that you're getting with it so, I don't know, I don't know, that's kind of tricky."

None of the IRB members or physicians recognized that parents needed to be able to discuss things with the research team or to receive feedback about their child's condition. In fact, IRB 2 said that in his experience, parents had little interest in the experimental ends of the protocol when he explained it to them, as they generally focused on possible benefits to their child. RN 3 noted that she saw the parents looking for a caring relationship and that trust in a significant caregiver could be a motivator to enroll a child in a trial.

Confidentiality emerged as an issue. Three of the nurses identified that some parents do not want their children to know that they are seropositive. RN 3 stated: "The moms will say, they'll tell you right up front, whether they've told them or not and they'll say 'Well, I haven't told them yet,' and then we talk about ways of getting that information to them."

Parental wishes for confidentiality become very important and can lead to conflict claimed four of the nurses. RN 3 felt confidentiality is such an important issue that she was compelled to withhold a child's seropositive status from other researchers. She emphasized her family's wishes by noting:
Some of the things that I end up dealing with [are] Moms' desires to not have anybody know that their child's at risk or a parent's desires that no one know their child's infected and the team saying "When can we talk to this person."

Only Parent 7 verbalized a loathing to discuss her child's condition with him, saying "I'm not too candid about his overall condition because he is very friendly and outgoing and he will, you know, tell a lot of people that might not accept it." No physicians or IRB members brought up parental concern about confidentiality as a factor in the researcher-family relationship.

IRB 2 and 3 spoke about what motivates parents to enroll their children in research studies. IRB 3 worried that lack of access to care may cause parents to enroll their seropositive children in trials without understanding the ramifications of participating in protocols. She noted "I suspect however that in this population they're so grateful to have somebody looking after them that they may not even realize what somebody else might consider a coercion."

Five of the nurses narrowed this claim, saying that parents want their children to have access to new medicines. RN 8 asserted:

They listen to the news, you know, the news is putting out DDI, DDC is better or maybe a combination with AZT
is better so that's what they want so they come here and say "No, no I heard about the combination study, that's what I want."

The physicians disagreed with the nurses and IRB members about what motivates parents. MDs 2 and 3 said they believed that parents have a need for knowledge about adult and pediatric HIV and that participating in trials can help provide such information. Both physicians feel that professionals should help parents better understand the disease and treatment. MD 3 described situations in which "We've had cases where they've been wary of it and once we've sat down with them and explained what it's about, they've gone along with it and have seen that it's the best option."

MDs 1, 2, 3, and 5 believed that parents enroll their children in trials partially because of their own illness. These four physician respondents stated that the seropositive status of the parents was an influencing motivator for parents to enroll their children. The parents' seropositive status, noted MDs 1 and 5, caused parental guilt, and played a factor in the parental consent to enrolling their children in a trial.

Five of the RNs recognized the presence of parental guilt as a motivator for participation in trials. In contrast, RN 1 identified the true emotional incentive to be fear, stating:
What I have found is that a lot of families, even when you give them the option to come off of clinical trial, they don't want to because they're afraid that if they change anything, something will happen and then it will be their fault and they'll feel guilty.

Other parents reject placing their child in a research trial. Claiming they may not like the research methodology, RN 4 said "...we've had parents who just really can't deal with the placebo part of it." She also believed:

The biggest thing that they really feel [is] like their child is in an experiment and that they're being a guinea pig and that they're not going to be getting treatment. You know, they don't consider the protocol medicine which is a treatment.

Future Concerns Three of the parents identified concern for other children. Discussing how this point affected her conclusions about whether to enroll her child in a trial, Parent 2 stated "Well, it meant an opportunity for him to get not cured but well, better and it meant for people to, you know, find out more about this disease to help other children." This statement shows how this parent is able to reconcile some of the turmoil she feels over her sick child undergoing the rigor of drug trials when his future survival is unknown.
Two of the nurses stated that some parents recognize that although research may not help their child, it may benefit future children. RN 4 described this by saying "I've had more than one parent say this to me, that you know, this may not help my son or my daughter but I'm hoping it's going to help someone else's along the way..."

No physicians or IRB members cited the enrollment of children in research for the future sake of others as a parental motivation. To recapitulate, the only area of agreement between parents and the other three groups of respondents was that some of the nurses recognized parental altruism as a motivation for enrollment decisions. Otherwise, while nurses, physicians, and IRB members looked at issues such as parental guilt, fear and desire for access to care and medications as concerns for parents, the six parent respondents did not raise these issues.

**Concerns about IRB Process** Eleven of the 28 respondents talked about how their respective IRB had made decisions about one or more pediatric HIV trials that had ethical connotations. All four IRB members, four MDs, and three nurses provided the comments.

**IRB Authority** This topic consisted of who was on the IRB and how each board carried out its responsibilities. Only the four IRB members provided any thoughts on this subject.
The membership of IRBs was discussed by two members as a source of conflict. IRB 3 and 4 both noted that IRB members share the burden of wanting to help research subjects while still promoting science. IRB 3 said: "I remember a couple of them [lay members] being more enthusiastic even than I about we've got to do something for these kids, these moms. Go for it basically." She went on to say that the professional members of the Board tended to get "stereotyped" by specialty and the rest of the members relied heavily on them for their expertise when it came to review protocols within their specialty.

All four respondents indicated that very few pediatric HIV protocols got turned down and these were usually accepted later after revisions had been made. However, variation in decision-making among the institutions existed. IRB 1 described the judging of pediatric protocols as following:

We went right to the Belmont report and were involved in that and who's going to receive the benefits and who bears the burdens...Slowly the IRB begins to develop a body of knowledge that they can refer back to and that's very helpful...There's a sense of, we have our law, we have our precedence, we do the best we can within the Federal regulations.

Conversely, IRB 2 admitted, "When you become a member of the IRB, you don't get any information about how you're supposed
to make your decisions or even how the IRB works."

**IRB Decisions** The four IRB members had comments about specific determinations that their boards had made and the effects of these conclusions. Respondents 2 and 3 noted that their committees had some disagreements over the issue of whether medications could be used with children solely on the basis of adult trials or if new protocols could be developed without the benefit of adult models. IRB 2 discussed the former issue saying "Compassionate use AZT had a little bit of difficulty since I was the institutional PI for that. I had a little bit of difficulty, persuading some members of the pediatric IRB that it was worth doing as on the basis of the adult trials." IRB 3 commented on the latter point by noting that approving the original HIV protocols for children at his institution concerned the IRB because "...all the members of the IRB had to sort of shift the way they were thinking about that in order to approve it because it has not been tried in adults."

Four of the seven MD respondents had comments about the IRB at their respective institution which tended to reflect conflict between the researchers and IRBs over the goals and conduct of pediatric HIV clinical research. MD 1 saw the IRB as very involved in whether protocols went forward or not and he expressed some dissatisfaction with this, saying "...the IRB actually disapproved our first protocol for using AZT in pregnant women." He went on to claim "I think
that the internal IRB has been more critical than our community advisory board and that has depended very much on the individual make-up of the IRB." He argued that "...they're supposed to be a review body, they're not really supposed to be a discourse body." MDs 2, 3, and 4 felt that their IRBs had few problems with trials. If objections arose from misunderstandings, they were cleared up by the investigator providing further information.

The four MDs saw IRBs as being focused on protection of subjects, sometimes to an extreme. MD 4 complained that: "They felt that we had the power to change the conditions of a nationwide collaborative trial..."

The four nurse respondents spoke of having little direct contact with the IRB. Only RN 4 was very upset about a protocol that the IRB had turned down, believing that the board did not understand that researchers were not trying to force people into trials but simply wanted to offer more choices. She contended "I think they [the IRB] get afraid that we're really experimenting too much, that we're doing too many protocols."

No parents brought up the IRB as an issue that affected their child's participation in trials, probably indicating that they did not know it existed. Whereas only the members themselves spoke of IRB process as an influence on pediatric HIV clinical research, nurses, physicians, and IRB members all saw some specific IRB decisions as contentious. The

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disagreements between researchers and IRB arose out of the differing groups' opinions on how to best serve the current ill population while looking toward the interests of future patients.

Knowledge Development Three of the four IRB members, all seven physicians, five of ten nurses, and three of the seven parents discussed how the evolution of pediatric knowledge development in HIV had produced ethical issues related to clinical research. The specific issues were about the nature of pediatric HIV and how this affects treatment decisions.

Current knowledge about pediatric HIV IRB 1, 2, and 3 described the knowledge problem in pediatric HIV clinical research. IRB 2 stated "...it's pretty clear that AIDS in children is not the same as AIDS in adults. The complications are different, the whole scenario is different so you need to have separate protocols." IRB 3 specifically noted "...that there was no way of knowing for sure at birth whether that baby was infected or not. MD 1 said "...the trials become so important that they do take on a certain urgency which is also somewhat unusual."

The parent respondents did not discuss conflicts in knowledge about HIV as much as the professionals did. Two of the three parent respondents identified current pediatric trials as necessary because adult research is not directly
useful in children. Parents 1, 3 and 6 noted that
information is needed for this disease. Parent 6 believed
"...I think the doctors don't know anymore than what they
can give them (sic). You know, that's the reason for the
study. For them to find out more, you know, and that's you
know, that's ok by me."

**Effects of knowledge problems on treatment of children**

IRB 3 highlighted the second knowledge conflict in pediatric
HIV clinical research, asserting "...at this point we have
no way of knowing whether anything in the way of treatment
is changing a baby from the fate of positive to negative..."
IRB 1 underscored the problem this presents for developing
pediatric protocols, saying "I can understand the fast track
would act for consenting adults but do we really want to do
this for children...?" IRB 2 concluded that the present
scenario is thus:

So that leaves the children out of, we don't know when
it's [drug treatment] safe in children. Many times
it's just sort of assumed that if it's ok in adults,
it's ok in kids and it's used any way but in AIDS
particularly, that's been a real crucial issue because
the time is of the essence I guess and children are
not, and if you go by the old standards, the children
are not going to get the benefit of any of the drugs
for years and years and years and that would be too
late for many of them.
All seven doctors commented on this topic of the effects of conflict in knowledge. MDs 1 and 2 claimed that one aspect of pediatric HIV clinical research is that it is progressing at a very fast pace—much faster than the norm in the research domain. The result of this he believes is that "...the data may be just sort of hot off the press and they go into children. So and that's true of a number of the newest drugs. That imperative for speed bothers a lot of people." MD 2 says some of this is inevitable because "...when we see these kids march through these drugs very quickly, (sic) so we're anxious to have new drugs available..."

Six of the physicians talked about the specific issues that called for this immediacy. These included when to start therapy in children, how quickly the knowledge base changes, how well drugs that seem to have some usefulness in pediatric HIV compare with each other, what dosages should be, and the reality that pediatric AIDS seems to be more virulent than the adult version. MD 7; ironically described how he views his position on the problem:

The short term effects of AZT are known, the long term effects of AZT are not known but that's true of every drug that has not had a 75 year history of supervised use and to say don't use AZT because you don't know the long term effects would effectively prevent the use of all drugs and put us at the mercy of disease.
MDs 2 and 3 said that these unknowns make them consider the development of protocols that are unorthodox from traditional ethical viewpoints. They would enroll nonsymptomatic seropositive infants in trials.

MD 2:

...these children are the children who will have the least amount of systemic disease and the smallest number, so that when, if you have side effects, you would be able to distinguish perhaps what's drug related and what's HIV related.

MD 3:

If a trial comes along in which children who are totally nonsymptomatic but are infected, comes along in a placebo control trial, that would make sense to me since we don't know the answer to whether a child who is 2 months old who is totally healthy but is infected should be on AZT at that point or whether they should be on AZT not until 2 or 3 years later when they develop symptoms.

Both physicians admitted that these views are quite controversial and demonstrate the disagreements of many researchers about how to proceed with ethical inquiry.

The five nurses who identified conflict in knowledge advancement agreed with the physicians that the fast pace of pediatric HIV clinical research was a problem. However, they differed in perspective. Essentially, their concerns
were not that drugs were being made available too quickly, but that once procurable, they were quickly being accepted by all participants as part of normal care. Even though AZT is almost a standard of care drug, it is still very new. RN 1 noted "In the scheme of research, the treatments are still quite experimental. I mean, they're approved very early on, much earlier than in any other disease and so in some ways, I think that that's really too bad."

The essence of these conflicts is that in order to provide care now, some time spent in collecting data about the disease and investigating drugs is suspended and that perhaps may result in harming, instead of benefitting, the children receiving the drugs. All four groups noted that issues about knowledge do exist but seem unanimous in the belief that this conflict is a burden to be accepted at this time.

Shift in the Research Ethic Paradigm

From Nonmaleficence to Beneficence

The review of literature detailed how, in the development of contemporary research ethics, emphasis has been placed on the personhood of the experimental subject. Whether such autonomy has been preserved through increased involvement of the adult subject in the consent process or through physical protection of the minor subject, the weight of most ethical action has rested on the side of minimizing
possible harm to the person participating in research. The data that are discussed in this theme reflect movement away from absolute protection of the subject to a position that allows the study population to absorb some risk in order to achieve possible benefits.

Four categories are presented that underlie this theme and include assessing risks and benefits, the effect of clinical research trials on the standard of health care for seropositive children, how entering research trials affects the access of the subjects to the health care system, and the ethical impact of specific research methods on the subjects. The four demonstrate different aspects of how the respondents viewed the reality that there is no risk-free pediatric HIV clinical research. The question remains how much benefit must be offered to offset these risks?

Risks and Benefits All 28 respondents identified the need to assess the ratio of risks to benefits to subjects as having ethical implications for pediatric HIV clinical research. The issues identified generally arose because of the difficulty in operationalizing theoretical risks and benefits in clinical settings and also because each risk to benefit determination had to reflect the potential harm or benefit for each individual.
Making generalizable risk to benefit assessments IRB respondents 1 and 3 spoke about the difficulties of making cogent risk to benefit ratio determinations when assessing protocols. IRB 1 spoke of using a tool that allowed determinations of the worth of a protocol looking at the measurable amounts of good and harm (such as extra phlebotomies) and comparing the theoretical good (such as decreased incidence of infection) and harm, but discovering that the unknowns outweighed the empirical data. As he said "You knew the probability that there was going to be harm and the magnitude you were not sure of, and the benefit you were not (sic) this was all for some kind of a benefit that was not clear." IRB 3 stated that his committee had decided to handle this issue by determining that "...if it has very much scientific merit, there's a lot of benefits to be gained from it and you may be willing to take more risks."

At the heart of such risk to benefit determinations must dwell some notion of the magnitude of the values and this is where disagreements between respondents occurred. IRB 1 said that investigators at his institution initially used to try to emphasize how much benefit a protocol provided. However, upon questioning, these benefits seemed ephemeral and such claims decreased. He stated

So we got down to "You've got to say what the benefit is." So they were very good at that and they never gilded the lily on that, in fact, if there was a
question about the risks, you would ask them about the benefits, they never ever made wild promises at all. IRB 2 declared that defining benefits often becomes an issue of pulling out any useful aspect of a protocol that can occur. He described, "I found it rather difficult actually. You can cite intentional benefits and possible benefits but it's really hard to say this is going to be a benefit."

Relying on the theory of measurable benefit causes conceptual problems for some people who review pediatric protocols. IRB 3 said that state child protective agencies insist that protocols display direct benefits before allowing their wards to participate. She was told in one communication, that the agency "feels that they as the guardians of the rights and protectors of these kids cannot agree to studies in which the outcome may only benefit the class of patient rather than the individual."

This quote also shows that while some people consider not only the individual good and harm, others also try to factor into the equation the aggregate good that can be accrued by either society or the general seropositive population when research occurs. It is harder to generalize harm, as risks tend to be individual, particularly for things such as drug side affects and toxicities. IRB 3 believed that "Minimal risks, it's complicated because it has to do with what you would expect given your condition."

IRB 1 continued "Now the argument was in terms of the
magnitude of, and the probability of, the harm that clearly, you knew objectively, that if you loaded up the kids with the AZT that you were gonna (sic) have an issue of toxicity."

The seven physicians tended to emphasize the benefits of trials. However, such benefits tended to be defined broadly. MD 4 described benefits thus: "I think the experimental part of the trials always offers a reasonable explication of it as good benefit [sic] as the so called established treatment since the established treatments are far from perfect."

The physicians tended to make a tautology of research benefits in the context of their belief that the alternative of not taking protocol drugs was a harm, therefore taking the drug must be a benefit. MD 5 stated his belief that "...this disease ...as far as we know, it's 100 percent fatal. We were willing to license the drug for children because we felt that it was as likely to have children face [the same] results [as] in adults." MD 7 echoed this conviction, saying "...whatever the side effects of AZT are, I doubt they're as significant as the side effects of HIV virus..."

**Individualizing risk to benefit assessments** The ten nurses spoke more about specific risks and benefits. Four talked of discrete harm in the research process, but they termed the specific risks as minor, such as changes in daily
life or extra blood drawing sessions. However, they emphasized that these were real problems and that as nurses, they addressed them to help families cope. RN 5 uses counselling to aid the families. As she said "I think that even though often the side effects are not a high risk, there are some effects, some kids are going to get them and they have to realize that." RN 8 recounted how she supports parents with concerns:

I assure them that I have already precalculated the weight of the child and how much blood I'm taking out...And I really have to reinforce it to them that I will not in any way, shape or form harm their child.

Many of the benefits that the nurses mentioned were non-drug-related, such as paying for transportation, being available for extra consultation and care, and the opportunity for the families to be in a special therapeutic relationship.

RNs 3 and 4 both believed that the opportunity for the research subject to help other people was a benefit of the study. RN 5 stated that sometimes the research team sees the benefit as accruing less to the child than to everyone involved in the protocols. She said "...you can bring that back to a family and, very honestly say, 'Look, there are some pieces to this research that are really lousy. But we need it.'"
The seven parents divided their responses into two topics. The first subject was how they decided to enroll their children in protocols. This discussion centered on possible benefits that the parents perceived as available in the trial(s). Definitions of such benefits were couched in vague terms, such as "doing something good," "drugs that can possibly help," and "hopefully boost her counts."

Parent 5 defined her view of benefits by stating "The bottom line is something that can help her, prolong her life with quality. I don't want quantity, I want quality."

The second area which the parents focused on was how they would handle the actual harm that their children experienced. Five of the parents recounted declines in their children's conditions that necessitated protocol modification. Their responses reflected an attitude of resignation. Parent 1 said "You just go ahead and do it and if, one month after your visit and they tell, well, your liver is going or something, you just get off of it"

Parent 7 recounted how she had to decide whether to change to another trial:

Well, there's a couple of things... His heart got weaker and I don't know if that's from the disease or the drug but I know he's taken a lot of drugs that could have adverse reactions in his body, you know, I take it one day at a time and as it comes because I know this is a devastating illness that he has.
In this category, the physician and IRB respondents spoke of generalizable risk to benefit assessments, with the physicians believing that the research itself can provide so much good as opposed to the harm of HIV disease that few protocols should be forbidden. The nurses focused on the individual effects of risks and benefits to the families, while the parents described how risk to benefit appraisals were used by them to plan their child's care.

Standards of Care Two IRB members, six physicians, six nurses and three parents discussed how the experience of entering a child in a research protocol affected the basic standard of care that the child received. The effects of protocol entry on such care was felt to have moral ramifications.

Differences in care available to children because of their enrollment in drug trials Two IRB respondents identified that enrollment in trials has a discernible impact on the standard of care delivered when measured against care given to nonenrolled patients. IRB 3 stated "It was important because there was almost certainly a significant impact just on regular visits and involvement in the medical care system with an intensity that most of these patients haven't had before..." IRB 1 recounted the controversy that arose over a proposed trial that would have changed the basic care for seropositive children with
certain symptoms: "We get this protocol that comes down. The kids go off AZT; do not get Bactrim. Question: that standard of care in this hospital. How come...they'll just have to go without it?"

Parent 1 saw no change in her child's care whether on or off protocol. Parent 7, however, saw her child thrive on one protocol, and then begin a decline in health after the drug trial ended. After a year, she was able to persuade the team to put him back on that drug in a nontrial status. Parent 3 wanted her child to have the best care possible and believed that it was available only through protocols.

**AZT as the accepted standard of care for seropositive children** The six physicians believed that the current standards of pediatric HIV care included AZT as the accepted therapy of choice. This view, which they considered both the lay and professional worlds to have adopted, was seen as both help and hindrance. In a positive vein, because many protocols involve combination therapies with AZT, enrollment in such a trial was not considered "experimentation" by some people outside the research domain. MD 3 believed that "It's not as if putting children in clinical trial puts them...means that they're not getting the best, the accepted therapy... (sic)"
However this belief was seen by the physicians as a double-edged sword. As MD 7 stated, further inquiry is needed into AZT, for "Nobody knows when the best time to start an antiretroviral at this point." Acceptance of the drug as basic care could hinder its development, for as MD 1 noted "...a lot [of people] get AZT by prescription." This bypasses the research process.

The second issue is that if AZT (or any drug) is accepted as a basic standard of care, it limits investigation into other therapies. MD 2 exclaimed:

Their [Social Services] issue with that protocol is that they believe that AZT was the standard of therapy for pediatric HIV infection... I think one of the problems is that...drugs have been licensed with much less information [that] would have been necessary for almost anything else...

Six nurses agreed that there was an acceptance of some standards of care, but these standards were related to the specific institution's definition of the standards. RN 6 claimed that intravenous gammaglobulin, once the focus of a controversial protocol, is now standard therapy for her patients. This was not a standard at the other sites. RN 1 provided a thoughtful discussion about AZT as the basic standard. She noted that even though it is now the conventional therapy, there are no specific recommendations for its use in children. Neither dosages nor degrees of HIV
illness have been established. She is also seeing use of
the drug extended to children with few symptoms; a
population in which AZT was not originally tested. Finally,
she stated: "We find often that when our kids are enrolled
in clinical trials that you have to have their AZT reduced
or stopped when we wouldn't ordinarily do that if they were
not on a clinical trial."

RN 8 teaches parents whose children are entering trials
that their child's standard of care will change, sometimes
for the better and sometimes, for the worse. This is an
example of how a drifting standard of care can affect the
measurement of risks and benefits.

In this category, two of the parents joined the IRB
respondents in identifying a relationship between entrance
into protocols with an increase in their child's standard of
care. The nurses and doctors discussed the reality that the
current standard of care in pediatric HIV care includes AZT
and what this means for patients.

Research as Access to Care Three IRB members, five
physicians, nine nurses, and four parents believed that
there was a direct relationship between participation in
trials and the accession of children into the health care
system.
Research as access to basic care  The three IRB members observed that enrollment in trials was, under certain circumstances such as the introduction of new drugs, the only way to access care. All three also noted that care was presented to parents as a benefit of research. IRB 1 strongly objected to this approach and recalled a scenario in which parents were told "'You'll have another opportunity to be with us and that in itself is a benefit,' and we got very good at [saying], 'No that is not a benefit. That could actually be harm.'"

Research as access to superior care  There were two main topics that the physicians identified when they discussed research as a means of access to care. The first is the reality that without pediatric HIV research, there would be no pediatric HIV care, at least not as a discrete disease grouping. MD 1 explained:

Everything that we do depends on putting children onto protocols...Whether this program goes on, expands, is cut, folds, is directly related to how many kids go on protocols. Directly...the dividing line between research and care is a very fuzzy one in this business...

Secondarily, care that is provided as part of a research protocol carries benefits that ordinary clinical care does not. MD 6 recalled that in early pediatric HIV clinical research "Many of the things that were being
studied in the trials were only available through the trials..." Even today, many believe that combination therapies are the best means of therapy. MD 5 stated that "Well, the only way you can get that combination for your child is to enroll them into a protocol..." The implication is that the most beneficial care is accessible only through protocol.

The nine nurses who brought up participation in a research study as a pathway to care reflected some of the same ideas expressed by the physicians. However, the one differing characteristic of their descriptions was that not only did protocols offer state-of-the-art experimental drugs, they also meant that subjects could be the beneficiaries of above average clinical care.

Nurses saw their roles as intertwined. RN 10 summed it up when he stated "I'll be able to get more data and more accurate data while at the same time providing quality and holistic nursing and patient care." RN 8 was just as forceful, stating "I say if I'm going to give any kind of care it's going to be good care and it's not going to be just as an offshoot from research so we can retain them."

Several of the nurses did acknowledge that their clinical care duties sometimes created a tension with the role of research nurse. But RN 5 said that "After awhile you begin to grow into the whole concept of clinical research and you try to find a nice mix between clinical
care and the data that you really have to get."

Parents 1 and 2 both believed that participating in a study provided no extra benefits other than access to new drugs. Conversely, parents 3 and 4 saw research as access to better care. As one stated: "The quality of care on a protocol is much higher. They get a better examination every month, there's more time spent with them by the doctor and nurses. Mostly the nurses."

IRB members in this category discussed their concerns that access to care was available only through protocols. The other eighteen respondents believed that basic health care was accessible outside protocols but that entering the children in a research study provided superior care.

**Research Methods** Two IRB members, four parents, and all seventeen nurses and physicians believed that how pediatric HIV clinical research is conducted had ethical implications. This specifically included methodologies employed in the trials.

**Concerns over the appropriateness of randomized controlled trials in pediatric patients** The ethics of randomized controlled trials was a concern for IRB 3. She pointed out that one of the main controversies is that in placebo controlled trials, the researchers cannot ethically assure the subjects that they are getting the most beneficial (or sometimes even a therapeutic) substance. She
noted that, ironically, the only time one can recommend entry into a placebo-controlled trial was "...if one does not know whether the tested agent is going to do more good than harm."

The physicians in the study were reticent about changing research methods solely to increase benefits. MD 7 stated the traditional position:

That is the way one proceeds when you have a new disease that is serious, that you don't know whether the way to treat it (sic). We have answers because we have placebo controls. Otherwise, we'd have a bunch of hypotheses thrown out and we'd never learn anything.

MD 3 says that proper methodology means constructing the trial, then recruiting, and not the other way around: "I don't think any of this in terms of children who are symptomatic and who should be on therapy."

The crux of the issue in research methodology and risk/benefit analysis lies in how much benefit one can assume when most of the seminal studies in HIV antiretroviral therapy have been done in adults. When adult studies have shown efficacy in adult HIV, MD 3 says "I don't think placebo control trials in terms of therapy are ... appropriate." This represents the consensus of the physicians on this topic.
However, MD 2 believes "We keep going back and looking at the data that was used to make certain conclusions that were used to justify licensing or whatever. You say, 'You know that was pretty slim.'" Therefore she argues for continued pediatric trials that run concomitantly with adult trials. This portrays a conviction that possible benefits for children in trials cannot be gained without exposing these subjects to some risks.

Randomized controlled trials affecting individual care of subjects The seven nurses who were concerned about blinded trials did not speak about the need to subjugate clinical care to scientific necessity. Rather, they felt that randomized trials truly limited, in some cases, a family's chance to attain any benefit from a study. RN 9 talked about a study that had two arms: AZT and placebo or AZT combined with DDI. She said "We do not know what each child is getting but we do know that each child is getting AZT. We're not sure whether they're getting AZT or ...AZT with DDI." AZT is available off study by prescription. Therefore, a child who might clinically improve by adding another antiretroviral must endure the rigor of the study and even then may not receive the second antiretroviral drug. RN 7 voiced another fear of hers:

I'm worried that if the AZT is a placebo drug and DDI is their good drug and the kids really hate the medicine and the mother might in her mind think, 'Oh,
well, you know, at least they're getting the other medicine,' which technically could be sugar syrup...

Several nurses feel another significant issue is when the desire for methodological rigor sacrifices possible individual and collective benefits. RN 1 spoke about how entry criteria limit the number of subjects: "The study that we're doing that's looking at a high vs low doses of AZT. That could have easily been done in a generic patient population. Without the rigidness of, you know, the inclusion, exclusion criteria of that study." This rigidity is particularly emphasized in mildly ill children, who are not yet eligible for compassionate use research drugs, such as DDI or DDC. Instead they must go on a trial in order to gain access to the drugs. RN 8 related a story of one of her patients who is mildly symptomatic:

He's been on AZT which he failed. He's also on that 138 study... placebo vs actual Med. He might very well be on placebo. I mean our hands are tied. We can't give him DDC without being on the study and the study is placebo v DDC.

Four nurses pointed out that once they enroll a child on trial and the drug appears to be therapeutic, if for some reason their eligibility to continue in the trial is threatened, they work hard to maintain the child's access to the drug. RN 10 spoke of such an incident involving one of his patients: "One of the physicians said 'But if we treat
her with IVIG she'll be thrown off the study' and I said, 'Well, who cares if she's thrown off the study. If she needs IVIG that's what she'll have to get.'"

Four of the parents noted that having their child on a blind study had some effect on the child's care. Parent 6 reported asking for information about what her child was getting, "I had asked them 'What's wrong with his protocol? You know, is he high or low?' They told me they couldn't give me that." Parent 5 said that "...the only thing we didn't know was whether or not she was getting gamma globulin or placebo, which was basically the only kind of trial I didn't like."

Duty to Be a Research Subject
or the Right to Refuse?

Though the essential ethical benchmark of participation in clinical research is voluntariness, familiarity with the biomedical field reveals that there is little pure altruism among subject populations. For relatively healthy volunteers, inducements of many forms are offered for participation. In many clinical trials, subjects are non-afflicted members of an at-risk population that may benefit from the research, therefore participation may be in their best possible interest.

In many instances, subjects who may benefit from their entrance into experiments do not place themselves at
significant risk by not doing so. But what of those individuals who are seriously afflicted by an illness that demands immediate attention, such as HIV disease? Should they be compelled to participate in research or should they be able to access therapies that are not well investigated through other mechanisms?

The following three categories represent the respondents' beliefs about whether children with HIV are considered to be potential subjects or a captive population that requires entrance into experiments. The first theme examines how respondents viewed the choices and alternatives that may exist in pediatric HIV clinical research. The second category scrutinizes how the informed consent process is believed to work. The last category studies the issue of how children are recruited and enrolled into research studies.

**Choices/Alternatives** One IRB member, six physicians, four parents, and all ten nurses spoke about how the existence or lack thereof of the choices available in putting children on trials had possible ethical implications.

**Existence of choices** All 21 respondents testified that parents have choices and alternatives when making treatment decisions. The four parents with views on this subject believed that the research teams were truthful about the options available. Parent 2 articulated a complex decision
she had to make:

They would tell me that the other drug was coming out, DDI, on a study for kids so I could like wait for that to come and still try DDC or go back on the AZT and wait until DDI comes out and I decided to stay on the DDC give it a shot...

The parents stated that no coercive measures, such as a threat of withdrawal of care, had limited their right to consider different alternatives of care.

IRB 3 spoke of allowing parents to choose one protocol over another that "...scientifically [it] is of some concern that you might bias who gets directed to study A and who gets directed to study B if you have a choice." Nonetheless, she said that at her institution, parents are told whether alternative protocols that their child may benefit from are offered at the site.

Nature of available choices The physicians defined the one available choice as the ability of families to make the decision whether to enter a protocol or not. They all denied that refusing to enroll in a protocol would jeopardize a child's care. They agreed with the prior statement of IRB 3 about wanting to avoid pitting one study against another by leaving the choice of entrance up to the families. However, MD 6 did note that if two studies had the same entry criteria, parents would be told of this and given the option to choose which study they wished to enter.
MD 5 believed that the freedom of choice was preserved because ". . . if a child can't comply with the study for some reason, then they can without jeopardy of their care, they can be put on a known dose of AZT."

The nurses discussed two concerns about parents being able to make choices. The first concern was the ability of the families to refuse or withdraw from specific studies. RN 1 emphasized that she discusses options throughout the study: "Periodically, every few months, at least twice a year, we talk to the families about this, the study, and that if they want to stop it, they always have that option."

The other topic focuses on how choices will affect the family and the child. RNs 6 and 9 said that sometimes parents want to stop a protocol and the nurses feel comfortable with the decision only after counselling the parents that stopping the trial frees the child from surveillance but does not address the child's ongoing need for the drug. RN 5 tells parents to consider several factors when considering trials: "You need to sometimes quiet them down and say, 'Look, this isn't the only study that's out there. You need to look at whether your kid will grow up doing this.'"

There seems to be a growing awareness among parents that there are more options available for their children. RN 10 said "...there isn't a strong impetus to get kids into the trials now if they can get the same kind of treatment
outside of the trials..."

According to the respondents, alternatives and choices exist for parents seeking care for their seropositive children. The IRB member and doctors were concerned that increasing choices might be methodologically problematic and nurses believe that some parental wishes to withdraw from trials may reflect a need for more information about the study (see comments of Parents, p. 101-2).

**Informed Consent**  Four IRB members, five physicians, nine nurses, and four parents identified the informed consent process as having ethical ramifications in pediatric HIV clinical research.

The process of informed consent  The four IRB members displayed concerns about the contents of a legal consent process. IRBs 1, 2, and 3 spoke of the technical aspects of consent: obtaining proper signatures, making sure forms were understandable, and what information should be contained in the form.

IRB 2 also was concerned about how the information that was included or deleted from consent forms may affect parents' decisions. He worried that such information might be "biasing people in a way that maybe we don't have the right to bias them." In this instance, he was discussing whether families should have access to the identity of funding sources of trials.
The parents who talked about the consent process were able to describe what they were told. Parent 1 noted "I had to basically do what I did for you. Read over all the material that they gave me and consent to it." None of the parents had any problems verbalizing that the medications they had consented to were considered experimental.

The meaning of informed consent Three of the doctors talked about the actual practices of getting consent and what it means. MDs 1 and 7 specifically believed that consent implies that trust is placed in the research people. MD 7 stated his belief that "Informed consent is I think more a lawyer's concept than a physician's." He went on to state "The ultimate question is [whether] there [is] anything wrong when one asks to trust a physician because the physician understands better having had the education."

Comprehension of informed consent Concerns about parental comprehension dominated the nurses' remarks. However, their considerations were marked by efforts to ensure that informed consent is continually reinforced, that parents have their knowledge base periodically updated during the course of a trial. They start by making the initial permission procedure lengthy and detailed. RN 1 says

I don't think that right away you can give informed consent. I just don't think that your brain can process it right away. I just think that you look at
your options and say, "I have to do that because it's all there is or I can't do that."

RNs 4, 5, 6, and 7 also described encouraging parents to take time to complete the consent process, usually by separating the educational and signing parts of the form into distinct sessions.

The nurses' roles in the consent process was to increase the comprehension of the parents, particularly by making sure the parents had access to needed information, particularly if such material had to be given in the parent's language. They did continual reality checks and clarified misconceptions. RN 10 recalled that in the IVIG versus placebo trial "Parents come in and they say he's here for his IVIG and we say, 'Well, remember it may not be IVIG,' and some things just don't make the impression and we can say it over and over again."

The physicians also challenged whether, under the best conditions, if most parents could truly comprehend the research process. MD 7 was pessimistic on this point, saying "If you take informed consent to its logical conclusion, almost no patient understands it fully."

Informed consent, apparently, represents different concepts for each group of respondent. The IRB members saw it important to make the process significant by including significant information while the nurses saw the pertinent part of the procedure as education. The doctors attached
little meaning to it beyond its legal ramifications while the parents viewed it as a required task.

**Recruitment/Enrollment** Three IRB respondents, four physicians, two parents, and all ten nurses associated the recruitment and enrollment process with one ethical issue.

**Over-recruitment vs limiting access** IRB respondents 1, 2, and 3 brought up the issue of the pediatric HIV population being small at their respective institutions and that many differing research protocols were recruiting the same patients. IRB 1 said "...when we got in and saw how many of those protocols were coming in and how many of those kids were really in [studies], nursing raised a question, 'Aren't these kids being overstudied?'

IRB 3 however said that limiting available protocols in an institution can limit choices. She also stated that the decision to limit competing protocols at her site was not to protect potential subjects, but to safeguard drug company interests. Discussing a protocol that the investigators at her site wanted to do that would have had the same eligibility criteria as an already ongoing study, she said "But we would do that not as an official protocol because the drug companies had refused a head to head comparisor of the two drugs."

The nurses noted that there was a push to at least consider all patients for protocols, but they portrayed this
practice as a result of an efficient system of 
identification and referral of all eligible children at 
their sites. At this point in the history of pediatric HIV 
clinical research, recruitment has become quite formalized 
at the pediatric ACTUs. All of the nurses noted that they 
have set up systems by which the areas that deliver clinical 
care to seropositive patients know to refer the children to 
the researchers, if such care is not given by the 
researchers themselves. RN 5 estimated

I think I will probably reach the point that I won't 
have a child who's virus positive that's not on some 
sort of clinical trial. Right now I would guess about 
50 percent of my virus positive kids are on some sort 
of drug in terms of clinical trial.

RNs 2 and 3 described an efficient system by which mothers 
and unborn children are recruited for surveillance studies 
once the pregnant women are found to be seropositive. Their 
names are forwarded (sometimes without their permission) to 
researchers doing drug trials. RN 2 noted "...my study 
piggybacks with somebody else's study, it piggybacks 
with..., we have some patients who are enrolled in 3 
studies..."

Four of the nurses discussed the mixed reactions of 
parents when recruited. RN 3 described being yelled at when 
she approached one mother to enroll her baby. However, the 
response of most of the patients, even if they do not
enroll, is to listen and investigate their options.

The physicians believed that they had been quite successful in convincing parents to enroll their seropositive children in trials. MD 2 estimated "96 percent" of the families they have approached have given consent. The physicians stated that the process of recruitment has become more formalized than in the early years of pediatric HIV clinical research. Also the authors of national protocols seem to have a better understanding of the physiologic and demographic characteristics of the eligible population, which the physicians see as advantageous to more successful recruitment. MD 6 stated that "The system is learning that the inclusion, exclusion criteria have to be adapted to the population we're trying to study...It's a lot better now than they were a few years ago."

MD 2 believes that the proper use of the increased numbers of protocols is not to try to register every child for each study but instead to offer multiple protocols that meet the varied needs of many children. She said "The issue is what are the appropriate children for the different and various phases of the protocols."

The two parent respondents in this category could not recall the specific reason for which their children were recruited for their particular protocols.
Threats to Parental Authority

The pathway for a parent seeking health care for his or her HIV seropositive child is filled with roadblocks. Practical problems exist for many members of this population, such as a lack of health insurance, language barriers, and the reality that many of the parents themselves are sick. These issues can lead to more abstract challenges for families as they try to deal with their isolation, guilt, and sometimes, fear. Some caretakers of children with HIV assume care voluntarily as foster parents, entering a system where they trade their care and emotions for a role that has limited decision-making authority in relation to the children's health care.

Three categories are presented that describe phenomena that may affect parental decision-making when their child is in a research trial. The first category looks at some general aspects of decisions that are influenced. The second category demonstrates that many people enter the sphere of parental decision-making when children are HIV seropositive. The third category focuses on caretaker decisions which are limited by third parties.

Parents as Decision Makers  One IRB member, three physicians, nine nurses, and five parents viewed the process of parental decision-making about protocols as having ethical implications.
Factors affecting parents' decision-making

Seven of the nine nurses who talked about the parents' role in decision-making emphasized that they expect the caretaking parent(s) to make the final determination that the child should go on a protocol. However, they admit that such decisions may not be truly free ones. RN 6 said "...the ultimate decision is theirs but there's probably more pressure, no matter how subtle, to have them sign."

The factors that the nurses see influencing parents include denial of their own or their child's sickness, misunderstanding of the illness, and confusion over the function of the research process. RN 4 admitted that "Sometimes it's really hard to remind them that it's not a cure." Constant education must be done, for RN 1 believes "...we've had patients now who've been on study for years, 2 or 3 years and I'm not really sure that they all remember what the original study was. We only have to get consent once."

Sometimes nurses limit the parental role in decision-making by assuming the research team can make the determinations for them. RN 1 told about a family she cares for:

I have always wondered ...about Mother's ability to give appropriately informed consent. If we could appropriately inform her. You know, she always said yes...We felt always that we were doing what was best
for this child, that she was really making decisions that were right for this child...

RN 10 stated that if he was unsure of a parent's ability to consent, he would go ahead and enroll the child, as long as the parent would sign the forms. RN 3 portrays such actions by the nurse as being protective:

I think many times it's a hard call to make to even allow access to a child when, you know, even though you know that you've promised that anything that's available to a child in this institution will be known to the parent so that the parent can make the decision, the actual ability to say at this point in time 'Is this good for this parent, is this parent ready to hear this information?'

**Caretakers as decision-makers** IRB 2 noted that when children in foster care are recruited for protocols, there is no mechanism for eliciting input from foster parents nor legal requirement to do so. He suggested that some specific means of involving them should be constructed.

MDs 1 and 2 talked about the complicated family dynamics that affect decision-making regarding children as subjects. Even when the birth parents are alive, there may be other relatives in the household who do much of the child's care and researchers must become familiar with who actually shares in the care. Sometimes a parent's consent is meaningless if the child's significant caretakers are not
involved in the counselling process about the trial.

The six parents who discussed the issue of parental authority were divided equally between birth parents and foster parents. The birth parents believed that their decision-making capacities had been honored by the research team, while the foster parents often felt powerless and needed to fight to keep some semblance of authority. Birth parents 1, 2, and 7 all related anecdotes about how they had made final decisions about the course of their child's participation in trials.

The foster parents, however, all spoke of frustrations and the need to negotiate when they disagreed with a proposal. The biggest disagreements were with the social service agencies that controlled the child's case. All three parents noted that these agencies held veto power over parental negotiations with health care providers. Another point of friction was that sometimes decisions between foster parents and care givers/researchers were delayed while the social service agency looked for absent birth parents to ask for their consent. Foster parents saw this as being unnecessary.

The foster parents generally had positive feelings about the respect paid them by the child's research team. But as Parent 3 said "I think the people that are involved respect our opinions. But I don't know if they have to listen to our opinions." Parent 4 described a confrontation
with the team that was ultimately resolved amicably: "We felt the protocol was better but it was something where even if we had dug our heels in and said no, it still would have made no difference. They still would have gone ahead with it... over our objection."

Despite their efforts to increase parental comprehension about protocols (see p. 136-7), the nurses felt at times differing factors affected decision-making of parents and that the nurse was justified in assuming what was best for the child if the parent did not actively object. The other nine respondents focused on the point that often the direct caretaker of a child in a study is not involved in the judgments about the child's care.

**Community Issues and Attitudes** Three IRB members, three physicians, five nurses, and one parent identified that people in the community, loosely defined as non-participants in pediatric trials, had beliefs and authority that influenced the research process.

**Discrimination against seropositive people** IRB 1 firmly believed that, early in the HIV pandemic, discrimination against seropositive people, including children, was strong. He described the established medical community's attitude as having "no sense of poverty, no sense of social circumstances, no sense of giving... [not] saying 'You don't have to live this way ...there is, you
know, there is hope, we're here to help you'. . ." IRB 3 concurred, describing that a colleague "...in reviewing the application for doing it [research] at his outpatient facility, was quite concerned, as was his staff, about the nature of the families that would be in their waiting room."

The one parent who brought up this topic said that she felt that she needed to hide the fact that she and her child had HIV, even when he was in the hospital, because she felt that discrimination against seropositive people was a reality.

Influence of community activists Pressure has emerged from the community to correct past discrimination. IRB 3 said that "...there was a loud feminist cry especially from women who really had very little to do with either the treating cohort or the treated cohort that women were being used as incubators or thought of as incubators and not as people." The IRB members felt that outspoken local community members often did not understand the issues or the needs of the patients.

The physicians' attitude toward the community was that the people who chose to get involved could either facilitate or hinder research and it was best to tolerate them rather than ignore them. MD 5 described the activity around his site: "But we have a very active community board that meets every other month or so and the parents come to that and then we discuss all of these things in an open public forum.
and I think it's terribly important." Of his community board, MD 1 said "So they tend on the whole to be on the activist end of things although obviously there are people there who are anxious to protect the rights of the minors and babies and fetuses..."

For the most part, the doctors found the community boards useful. MD 1 said "They are anxious to go over our consent forms, they're anxious to know what are we doing, they're anxious to review our protocols and make sure that they think that they're ok, etc." However, MD 7 found the groups obstructive at times: "I found the objections to that study rather contrived..." Taking a different position, MD 2 said "I think there's been a change to a complacency in the community at large because people I think view AZT [as a cure]..."

RN 1 spoke of several issues she had with community advisory boards:

I started to feel like the community advisory board was getting overzealous about enrolling patients...The community advisory board was actually basically telling us that we didn't know what families meant when they said they didn't want to be in an experiment. And it almost sounded to me like they were pushing us to force families who don't want to be in studies to be on them. Activism in pediatric HIV was not described as being as confrontational as in the adult sphere of research. Most
disagreements tended to be about how much protection is appropriate for children in trials and if local policies hindered or helped the access of patients into trials.

Child Protective Agencies and Protocols Two IRB members, six physicians, six, nurses, and three parents had comments about how the involvement of child protective agencies influenced the conduct of trials. In both states where data were collected, children who are removed from parental custody cannot be entered into research protocols that have not been approved by the state child protective agency (CPA) (sometimes referred to as DSS-Department of Social Services).

Effect of foster care on research participation IRB 3 revealed that the IRB has no contact with the CPA. Only the investigators consulted with the CPAs about enrolling children into studies. IRB 2 and 3 both noted that although CPAs only wanted to approve protocols that provided individual benefits to children, some exceptions were made. Regarding surveillance trials, IRB 3 acknowledged that "They've also approved trials that are nontherapeutic trials and initially they had a little bit more trouble with that." She also reported "They have approved some studies that are randomized trials because they are studies that might benefit the very same kid [because] the entry criteria and the goals are such that an outcome could then benefit that
Providing another perspective, IRB 3 noted "I think that it's not unreasonable to say that a parent can accept altruism for this kid and a state guardian should not..."

The six physicians echoed the same comments as the IRB members. Additionally, MD 2 discussed the problem that occurs when children in CPA care are not allowed in trials "[We] may have been able to do it (the protocol) a little more rapidly with the DSS (Department of Social Services) approval."

When the birth parents do not have parental authority, the children's physical care may improve, but their access to research suffers. Six nurses had patients who had lost the opportunity to enter or complete protocols when they were removed from the home of their birth parents. RN 4 related an anecdote about a mother with AIDS who was so sick she could not care for her child:

I had one little baby, a nine month old. That Mom really wanted her to be on protocol but meanwhile Mom was in ______ Hospital with PCP so I was going to go to ________ Hospital to meet with her but it ended up that DSS took child. Understand, Mom really couldn't care for this child anymore so, you know, we kind of lost that child...
RN 10 sees restrictions on entry into research as discriminatory: "We really felt there were two classes of children in the hospital. Those who could get care which were [in] natural care of their parents or kids of foster care who were excluded." RN 1 agrees: "And they (DSS) actually have rejected our AZT-DDI combination study. They don't want any of their children to go on it. We have 4 patients who are in DSS custody who qualified for the study." On the other hand, all potential children subjects, whether or not they are in foster care, can be affected if CPA refuses to approve participation of the seropositive children in its care in protocols. The resultant lack of adequate numbers can alter the pace of a protocol. RN 5 declared "Right now we have 2 protocols that are on hold, trying to figure out whether the DSS will accept them."

RNs 7 and 10 commented on the fact that even while in CPA custody, absent birth parents can veto wishes of the present foster parents. RN 10 explained

If there is a natural [birth] parent and we can get their consent, even if the child is still involved in the foster care agency, even if they have no contact with that child, they can sign consent and the child is allowed into the study. And that's even if the foster care mother disapproves.

Parent Six matter-of-factly noted that she is the last person that the foster care agency speaks to when deciding
if her foster child goes on a protocol after they look for the birth parents.

**Intimidation of foster parents** Parents 2 and 3, speaking from the perspective of foster parents, asserted their belief that if they refused to support the determination to have their foster children participate in research trials, it would have an adverse affect on their custody rights.

When children are diagnosed with the HIV infection, the illness experience involves the entire family. The three categories in this theme displayed that while the caretakers of the child must prepare to care for their child with a chronic illness, they must also ready themselves for the input of many people into the care of their child. While many of these outside people have legitimate authority to provide input, they also can challenge the authority of the caretakers in many ways. At times, multiple caretakers can have deleterious effects on the health of the child.

**Pregnant Women and Their Infants:**

**An Exemplar Case in Research Ethics**

While discussing separate topics on the subject of research ethics and pediatric HIV, four IRB members, five physicians, and seven nurses referred to the subject of how to address the research and care needs of seropositive pregnant women. Each time it was brought up in the
interviews, it was represented as a particularly difficult and controversial area that had persisted from the beginning of the HIV pandemic and still remains contentious in many arenas, such as IRB meetings and community board forums.

Before presenting the data from the interviews, some background information is necessary. In Appendix E is a copy of NIAID protocol 076. Protocol 076 is a treatment trial in which the efficacy of AZT to reduce vertical transmission rates of HIV from seropositive women to their fetuses is being tested. This protocol contains several elements that many people with an interest in pediatric HIV find factious. These elements include

1. The trial is a randomized, placebo-controlled trial. The subject will receive either AZT or an inert substance;

2. The methodology includes giving AZT to women during their pregnancy who may not be symptomatic enough to usually warrant treatment;

3. AZT will be withdrawn from mothers six weeks after they deliver and their opportunity to receive the drug ends unless they develop symptoms;

4. Infants who are seronegative will continue taking the drug until six weeks of age; and

5. The father of the fetus must give informed consent, if he is "available."
Conflict between the interests of the mother and the infant. IRB 3 spoke of her IRB's consideration of HIV drug protocols: "I think the biggest issue we've had was the treatment of women who are HIV positive and pregnant with AZT for indications that did not have to do with their own treatment but with preventive transmission in the baby." She noted that one area of concern focuses on when do the treatment needs of the mother override worries about the effect of the drug on the baby? She said that labelling this a prevention study seemed to surfeit some objections of her IRB.

The rights of the mother to consent not only for her care, but also that of her unborn child was questioned. Before 076, IRB 2 believed "...women are being cut out of a lot of drug trials because they [drug companies] don't want to take the risk of pregnancy during the drug trial" IRB 1 asked "Does she have the right to consent to take all of this stuff in if it's going to affect the child? Is the child "hers?"

Aspects of risk and benefit assessment. IRB 1 emphasized that the discussion of risks and benefits dominated his Board's consideration of study 076, which was originally turned down. He noted they questioned whether "Is it better that 70% of the kids should be loaded up with this for the sake of 30% or is it worse that 70% of the kids have gotten this toxicity (sic) for something that may
benefit the 30%." MD 7 reconciled his agreement with 076, saying

The objections were that most of the babies aren't infected so the babies shouldn't get AZT... Well, that's if we didn't know what the side effects of AZT were and couldn't, and couldn't monitor them. That might be a problem...

MD 2 notes that in balancing risks and benefits that "...it's at least more justifiable to me to put children who are relatively asymptomatic on a drug for whom we had no [prior] information."

Knowledge problems MD 5 clarified the one significant issue of the 076 type studies: "You are still treating for 6 weeks a group of babies that are noninfected and there's no way to know who they are until later on and included in that may be some infants who have infection prevented because they were on the AZT." His point is how can the infants who turn or remain seronegative by eighteen months and received AZT be differentiated into groups of who would and would not have seroconverted naturally?

Subject comprehension RN 7 discussed the issue of how this protocol is a conceptually difficult one for the mothers to understand and that the consent process is crucial:

I heard one of the women telling the others that how she was going to take AZT while she was pregnant
because that would make her baby definitely not get [HIV] and she just didn't understand although... I was there when we went over the consent with her...

**Prevention aspect** MD 1 revealed that one reason that he feels that it is ethically justified to proceed with 076 is because "...the imperative there is even greater because what we're trying to do is prevent the disease rather than treat it and prevention has a higher imperative than treatment."

**Community attitudes** RN 1 talked about how the community responded to the 076 proposal, saying

...at the community advisory board level half of whom thought that not enough women were being enrolled in protocols and half of whom thought that this wasn't the kind of protocol that women should be enrolled in and that it wasn't good for the babies or that it was good for the babies...

RN 3 talked about how dispassionate discourse about the topic of treating pregnant women and their fetuses is almost impossible, for some people have negative attitudes toward the women. She noted that "...half of the Moms knew before they were pregnant that they were HIV infected. And people will say 'Why did they ever get pregnant?' and 'How could they do this to a child?'"
Synopsis  RN 10 gave a detailed description of what it was like to be involved as a researcher in the 076 protocol: We also run protocol 76 which was the first maternal transmission study and of course there was a lot of discussion about that and that took almost 2 years for us to resolve all the issues within our team as well as dealing with the community because what protocol 76 does, it tries to prevent maternal transmission of HIV by giving women during their second and third trimester AZT, giving them AZT during their labor and giving the AZT to the child the first 6 weeks vs the same procedure for giving a placebo. So what do we think about that? Well, we thought that maybe we're giving a placebo to women who could benefit from the AZT and possibly prevent their transmission of HIV. The other part of that is, are we giving AZT to pregnant women that may have an adverse effect on the development of their child and who knows what that's going to mean when the child becomes...if the child does become 10, 11, or 20 years old? The effects, long term are just not known. We believe that it was up to the woman after receiving an informed description of the trial whether they wanted to join and I think we spent more than enough time going over and over with the women exactly what the study involved and what they may or may not be getting. We never meet a woman the
first day, describe the trial, and ask them to sign the
dotted line because we felt some discomfort with this
trial to begin with and received a lot of flack from
AIDS activists pro and con about you shouldn't be doing
this to pregnant women and children and also you should
be doing this to pregnant women and children so we
got it from both ends and we had gotten nasty letters
and were picketed and one of our physicians received
physical threats so we had to weigh all that but it
essentially comes down that it was the only thing
available through the ACTG that even came close to
looking at the issue of maternal transmission and
therefore if we gave the women enough information about
the study, they can make up their own mind and some
women did choose not to participate.

Summary

The data analysis contained five main themes, which
included fourteen categories. Thirty-three subcategories
with significant ethical implications for pediatric HIV
clinical research were studied.

Twenty-eight respondents from four sites provided data
for analysis. The individual respondents were from one of
four groups, IRB members, research physicians, research
nurses, and parents of children in HIV drug trials.
The largest number of respondents contributing data in any given category was 28; the lowest was eleven. IRB 4 provided data in the fewest categories of all of the respondents, four; while RN 1 spoke about 14 categories, the highest of any of the respondents. To further study the quantitative statistics of the study, consult Appendix F.
Chapter VI
Discussion

In this chapter, the two identified predominant ethical issues are presented. These issues are discussed within the context of the ethics of pediatric HIV clinical research. Other special issues are considered. Included is a discussion of the ethical issues from the viewpoints of the two ethical theories in the theoretical framework.

Effects of Research on Delivery of Care

One significant ethical problem identified in the study was that HIV seropositive children's access to care was affected by whether or not they were research subjects. The first issue that reflects this problem is the conflict that occurs because of the differing goals of caring and research. The second issue discussed is how the status of being in foster care can limit a child's access to care.

Conflict between Care and Research—Findings suggest that researchers experience pressure because of the dual responsibility to provide therapy to current patients while simultaneously accumulating knowledge to help future ill children. While several physicians, nurses, IRB members and parents denied that such conflict occurs, all 21 professional respondents who raised this issue described how they reconciled such conflicts. This suggests that conflict does occur in the research process. The question is whether
the tension resulting from the conflicts truly can affect
the care of a research subject.

The reason that this question arises in pediatric HIV
research is because of the researcher-subject relationship.
As described in the data, much of the clinical care
available to the seropositive children was available only
within the context of the research institution and delivered
by the researchers. This is in contravention of the
accepted norm that the two roles should be separate. One
reason for this traditional dichotomy has been because the
clinician has a primary ethical imperative of beneficence
for the patient while the researcher has as a goal the
attainment of knowledge for the whole. Therefore, any
factor that threatens to limit access to research is
necessarily going to have an effect on care when research
and care is intertwined.

The data in the theme of Present vs Future revealed two
major points of ethical concern. The first point suggests
that conflicts exist in the process that influence the
decision-making of both the research cohort and the subject
population's caretakers. The second issue suggests that the
increasing amount of data on the natural history of HIV and
the drug therapies is often confusing and can increase the
conflicts of those relying on such knowledge to provide care
and/or carry out more research.
The respondents believed that the two goals of their research, care and knowledge development, do not conflict. However they describe the pathways to such ends as inevitably causing some friction. Recognize that while RN 1 was torn over the need for tools to treat she also understood the problem of using little-tested drugs in such treatment. Recall that MD 7 commented that his impetus to begin doing research was to deliver care.

This concept of conflict between research and care was repeated by many of the respondents. This stress in the moral beliefs of some researchers was manifested by their equal concerns for immediate outcomes and long term, sound knowledge development. While some commentators argue that such personal moral strife was inflicted on the researchers by outside forces, such as AIDS activists (Campbell, 1991), the study respondents indicated that just as much pressure comes from ostensible supporters, such as funding sources.

No matter what the genesis of such conflict is, the ethicist's role is to appraise the ethics of the empirical actions of the people involved. However, attempting to analyze these actions seems beyond typical principle-based theories. Should the entire change that seems to be occurring in research methods relative to investigating and accessing drugs be attributed to a mass utilitarian movement to optimize the greatest good?. AIDS activists would reject this contention, believing no one has a right to his/her
body but would also reject the deontological view that a patient's personhood is being held paramount (Spiers, 1991).

The point is that principle-based ethical systems falter when the bioethical problem being addressed mandates that personhood be honored but that deontological reasoning cannot be used to defend such a personal concept. Traditional bioethical reasoning about research correctly identifies protection of the subject as a paramount intent. However, the same theory system argues that the overall goal of such research is the good of the whole. This line of reasoning is acceptable if the subject is truly a volunteer and fully comprehends that his or her actions are less an imperative and more a virtue. The system of principle-based ethics fails in the case of pediatric HIV clinical research when, as the data implies, the subject is vulnerable and is almost tangential to the moral decision-making that occurs.

Instead, an ethic of care applies itself well to this context of research conflicts. Rorty (1992) writes that there are several feminist themes that emerge from an ethic of care. Pertinent to conflicts in research ethics is the belief that personhood qua individual is not paramount. Simple existence as a human is not enough to guarantee respect for one's personhood; instead it is the individual's standing in his or her own community and the relationships and communication with others that allows one to claim a moral standing. Furthermore, the anti-individualistic
posture of the ethic of care forces a redirection of reasoning away from rationalizing the utilitarian use of large groups of young subjects for their or other's "greatest good," for some philosophers do not agree that principle-based ethics do an adequate job of protecting the weak (Dewey, 1935).

If the ethic of care forces reconsideration of the traditional bioethical reasoning on this topic, how does it offer its own rationalizations? Two means of reasoning have been offered by feminist authors on the ethic of relationship which allows individuals to enter into therapeutic relationships in which one agent assumes the protective role while the other person receives the proffered care. Each view begins by recognizing that the cardinal values of principle-based ethics, universalism and impartiality, are discarded (Klein, 1990) and the focus is to be placed on the individual relationships that evolve during the therapeutic interaction.

The first view purports that each ethical agent moves away from his/her own personal context and appreciates the frame of reference of the other (Noddings, 1984). The second, similar argument, claims that each person in the interaction is interdependent and connected (Gilligan, 1982). There is an implication of a sharing of interests, for while there is not a universal good that all are working toward, the individual desired ends are equally important to
each party and efforts to attain agreed upon goals can be co-mingled voluntarily.

This ethical line of reasoning can provide illumination for some of the conflicting issues associated with research goals. Recognition of the needs of both, researcher and subject can be individually accomplished. For example, parents can admit confusion about issues such as sharing information with their children while researchers can be forthcoming about the urgent need for both information and adequate numbers of enrollees to make protocols successful and justify the continuing existence of research programs. Also, those caretakers who determine that the child will or will not enter a trial can decide that the individual child's safety will be a paramount concern. Any surveillance and efficacy measurements will be fixed by predetermined guidelines that take into account the knowledge needs of the child's condition as representative of a larger group. Therefore, a child who takes an experimental drug that is known to be hepatotoxic will still periodically have bloodwork done to check for liver problems, while parents, without imperiling their child's participation, can tell researchers who want to do frequent phlebotomies on enrolled children who show no signs of theoretical toxicities that they will not permit the tests. Discussion can then ensue between individual researchers and parents over proper courses of action instead of becoming
mired in detailed ethical analyses of specific issues, such as autonomy, that will have no satisfying end.

It appears that in this study, the nurses employ versions of both ethical frameworks. They seem to be quite frank about discussing things with the parents but also assume some responsibility for the child's care when parents do not seem capable of making such choices. An example is when RN 7 felt a protocol was too complicated for a given parent to participate in and refused to offer it to her. The nurses, doctors, and parents all see some meaning in a system that conducts systematic inquiry while providing care, a viewpoint that supports a caring ethic which meets the needs of all participants.

Because the caring ethic claims that the its basic communal concept is relationship, it must provide ethical guidance about two types of relationships involved in the research domain. The first is the parental-child role and includes whether adequate protection is being provided for subjects, for despite the interdependent relationship of a child and family, this metaphor may not be effective for the child who is not in a secure relationship and does not see his or her surrogate ethical protectors except once monthly for medication. Also, when should the caring ethic help guide the removal of a child from the home? This troubles researchers and further deliberation must occur on this issue.
The second relationship is that of the researcher-subject. Veatch (1987) has suggested that the classic discrepancy that exists between the goals of research and care is no longer considered proper, for this leads to a devaluing of the human relationship between researcher and subject. One reason for this traditional dichotomy has been because the clinician has a primary ethical imperative of beneficence for the patient while the researcher has as a goal the attainment of knowledge for the whole.

To enforce such a separation would be to virtually eliminate care and research for children with HIV. In a recent report on AIDS research ethics, a study group reiterated that "the relationship between patient and physician and between subject and investigator are different and may be ambiguous when a physician acts as both primary care doctor and investigator" (Levine, Dubler, & Levine, 1991, p. 13). The study group declined to offer any moral justification for why this situation may be permissible and did not comment on the state of pediatric HIV research. Instead, perhaps bowing to the reality of the situation, they simply restated the warning that if the subject decides to end participation in a research study, the professional's obligation is to see that the patient's care is not threatened.
From a caring perspective, this dual relationship seems quite rational. Rorty (1992) has noted that "the strong sense in feminist ethics of being responsible for, of being in a special relationship, of the radical particularity of the patient/other, have strong resonances for the front line health professional" (p. 10). Such a special relationship that focuses on the virtue of sharing (of the subject with the professional and vice versa) and also on the context of the health care action can provide for such seemingly dualistic roles as researcher/caregiver being combined in an ethically acceptable manner. Care is mutual and can be best understood within the context of the society where it occurs (Benner & Wrubel, 1989). Therefore, perhaps a relationship in which there is agreement of the subject and the researcher that they will trust each other to work toward the many needs of health, knowledge attainment and knowledge sharing, may be an example of a high form of ethical practice.

The Effects of Foster Care on Research Participation of Seropositive Children  Categorical data that made up this theme reflected two main areas of concern. Does involvement of child protective agencies cause harm to children with HIV by restricting access to research studies? Additionally, how should equal access of children in foster care to clinical trials be assured?
As defined earlier, the meaning of the personhood of a minor has been defined in principle-based ethics as physical protection. What is the effect of this conceptual ontology? For research purposes, one bypasses benefits and looks toward protection from risks. The other outcome is that anyone arguing for a role as a surrogate parent must pass minimal muster that they will not hurt the child. Ackerman (1981) actually has drawn a stricter standard, claiming that respect for a child's personhood requires that those involved in a caring relationship must promote the growth and development of the child by providing education, emotional support, and physical needs.

The prevailing legal and moral thought in this country is that when parents cannot meet the standard of protecting their child(ren) from physical and emotional harm, the state has a legitimate interest that allows the removal of the child(ren) from parental custody (Steinfels, 1982). In the context of pediatric research, does such an interest extend to refusing or mandating participation in clinical trials for a child whose parent is judged to be an inappropriate caretaker?

Can the state argue that restricting some of its seropositive wards from participation in protocols is protecting them from harm? Not if, as all of the respondents seem to think, enrollment in trials actually improves care. In fact, such constraints may actually cause
harm. Should the state insist on the promise of benefit as being a precondition of enrollment? Yes, but only if such benefits are guaranteed to all subjects. No researcher or clinician ever promises in full faith that drug X will do this for patient Y. Therefore, state wards should be eligible for any pediatric trial for which their condition suits them.

Note that this framework is quite individualistic, an irony when one considers that state agencies rarely have the luxury of individualizing care for separate patients. Therefore, it would seem advisable to examine the possibility that as soon as possible after suspending the rights of birth parents, the state CPA or DSS transfer health care decision-making power to a third party.

It has been suggested that an advocate be used to facilitate the entrance of children in foster care into clinical trials (Levine, Dubler, & Levine, 1991). Such an advocate would be a person with health care expertise entrusted with the responsibility to advise consenters about health care choices. For children not in home environments, such as boarder babies living in hospitals, such an arrangement might be appropriate. However, the data from this study indicate that the present system not only is slow and sometimes unyielding, it also ignores the involvement of the people most enmeshed with the seropositive child, the foster parent. It seems incongruous that the same foster
parents who are entrusted with the responsibility for the child's daily health routine, from nutrition to drug administration, are excluded from final decisions about inclusion or exclusion from the drug trials. Soliciting their input and energy while separating them from determinations can only be a factor in alienating these crucial people in a child's life.

While recognizing that granting foster parents the authority of medical decision-making for their wards represents a change in traditional family law policy, it can be argued that the special case of HIV seropositive children warrants a trial of new procedures in child protection. Because any person who assumes the burden of care for a seropositive child must devote so much work to the special health needs of the child, authority for health care decisions would be a useful power to grant them. Because, as this study has showed, care for seropositive children is sometimes inseparable from research, decision-making authority of foster parents should be extended to allow them to consent for the children to enter studies. This change would have the dual effect of making the foster care role more meaningful while also simplifying the entrance of foster children into appropriate trials.

The tortuous exercise described by several respondents in which absent birth parents are located to sign consent forms only serves to make a mockery of the parental bond and
cannot increase the protection of the child. Instead, part of granting foster care rights to altruistic community members should include entrusting them with the power to provide consent for their wards. This would strengthen the interdependent relationship between the foster parent and the health care team members while also reminding the research team of the child's dependence on his/her foster parents. Strong moral arguments can be made for this change, which would force amendments in legal codes affecting foster care. Further studies in the fields of ethics and family systems could provide more substantiation for this recommendation.

Shift in the Research Ethics Paradigm:
From Nonmaleficence to Beneficence

There was one dominant issue in this theme. Perhaps because of the ethical weight attached to risk and benefit in theoretical ethics, all of the respondents provided input on this topic.

Problems with Risk to Benefit Assessments—There are two aspects to this issue. The first is that risk-to-benefit assessments are difficult for professionals to calculate, because benefits are difficult to appraise. Secondly, there are differences in the values that the professionals and the parents in the study attached to various risks and benefits.
The issue of difficulties in risk-to-benefit assessment becomes pertinent because such determinations affect many other ethical issues. Ethical decisions, such as the morality of research methods, often hinge on how much risk and benefit a protocol offers to a child subject.

The data in this theme continually reflected that the accepted ethical norms that the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1977) had enumerated were still not fully coherent to investigators and IRB members when the AIDS pandemic began pressuring the biomedical domain to produce more pharmaceuticals for use in children as well in adults. Following the Commission's principle-based ethical approach, protection of the individual child was emphasized and vulnerable groups were to be safeguarded. Additionally, individual protection was to be constructed on the basis of assessing an acceptable level of risk to children subjects, with minimal risks being the only one acceptable unless certain benefits would occur through participation in a research trial.

That intellectual turmoil has occurred over pediatric HIV clinical research is not surprising. Ackerman (1990) has pointed out that the DHHS workshop on Pediatric HIV Infection (Novella, 1988) called for phase I trials of antiretrovirals (as did MD 2) in children--a position that he describes as incompatible with the current Federal
Regulations. Ackerman's argument is based on the fact that not all phase I trials are compatible with the child's best interest. Benefits of such trials are not guaranteed and assumed risks are therefore not balanced.

The data reflected that two levels of benefits are being offered to potential subjects. The first level is the tangible benefit of access to care. Parents can assess and decide for their children whether to receive clinical care through clinical trials. Many of the respondents acknowledged that clinical care through trials is superior, but there is also an acceptable standard of clinical care and access to some drugs outside of trials. The second level of benefit is the ephemeral and theoretical benefit of receiving experimental drugs.

The current method of risk-to-benefit assessment ignores these two levels of benefits. Instead, benefits and risks are partially revealed in a mixed fashion to parents. Parents are then told to sort out the confusion themselves. How the parents do so is the key to how this process should work. Recall how the six parents decided to enroll their children in trials. They said they knew what the benefits would be, and they thought ahead about how to deal with the possible harms.

Carol Levine (1991a) stated that AIDS has caused a shift in emphasis in research ethics. Promotion of autonomy now should be manifested less by absolute protectionism than
by allowing subjects a greater role in choosing access and participation to experimental drugs. This includes allowing subjects to assume responsibility for risks (that are fully explained) in exchange for access to possible benefits (which also must be explicaded).

Perhaps a new ethic is to allow parents to decide how to maximize benefits. The first step is to explain the tangible and theoretical benefits that trials offer. These benefits will be essentially the same for all eligible entrants. In addition, a cogent description of possible harm must be given to parents. By definition of the discrete individuality of each child, discussions of possible harms must be made specific for that child. This will enable the parent to envision how harm may affect the family. There is already in use a tool for measuring harm that includes estimating the magnitude and probability of harm that may be incurred during a trial (Meslin, 1990). Investigators could individualize this harm assessment by figuring in the child's present condition and estimate the likelihood of possible damage.

Separating risk assessment from harm assessment has several advantages. It allows a joint decision through counselling between the investigators and parents, rather than the take it or leave it approach which is now existent. It meets the need for benefits to be part of trials thus allowing more foster children into trials. Also, because
benefits are assumed, investigators will be able to presume that a protocol meets the Federal Regulations' requirement that more than minimal risks are countered by some benefits to the child.

This path of analysis is offered because it appears from the data that it already is in place, at least in the parents' minds. Whereas IRB members and investigators agonize over definitions of risks and benefits, parents reflected no such anguish nor claimed that they were deceived. In fact, the risks the parents seemed to want more information about were the individual things the nurses passed along, such as how participation in the protocol would affect the child's lifestyle.

Special Issues

Pregnant Women and Their Infants: An Exemplar Case in Research Ethics

Three major issues deserve attention in this theme. The first is whether the status of carrying a possibly infected infant should affect a woman's ability to enter clinical trials for her own HIV disease. Second, should asymptomatic infants under the age of eighteen months be entered into trials (or be treated with) anti-HIV drugs? Third, when are placebo controlled trials inappropriate in HIV clinical research?
Pregnancy and the Status of the Seropositive Woman

In principle-based ethical theory, problems arise when the exercise of the ethical rights of a woman cause conflicts with the rights and/or interests of her child. Moral questions that occur include when maternal rights are paramount over those of the child, if the rights of a fetus are equal to those of a borne child and if it is advisable for medical authorities to interfere with decisions within the maternal-child relationship (Twomey, 1989c).

Several factors enter into determining the care of a pregnant women with HIV, including the decision to enter clinical trials. There is consensus that pregnancy itself is not a potentiatior of HIV (Fox, 1991). Pregnant or not, the usual decision to recommend drugs on or off trial to a seropositive woman depends on considerations for her own condition. The 076 trial does not meet this criterion, for it offers AZT to possibly asymptomatic women. Therefore one condition of the trial must be rigorous counselling of potential participants that this trial theoretically offers them nothing no matter which randomized arm they are assigned. Furthermore, another question is whether future drugs that may have no therapeutic value for seropositive pregnant women should be tested for efficacy in preventing vertical transmission.
Asymptomatic Children Who are Less than Eighteen Months Old and Trials—The administration of experimental therapy to infants in the 076 trial represents a further issue with scientific and bioethical perspectives. How appropriate is it to give a speculative treatment to asymptomatic children when their ultimate seropositive status is unknown? Does the ethical issue change if the drug treatment is labelled as "prevention" rather than "treatment."

Whether a mother is enrolling her unborn or seropositive infant in a trial, the questions remain the same. From a risk-to-benefit assessment framework, it is difficult to advise the expectant woman of either harm or good coming from the trial for the unborn child. This is particularly true because of the unknown nature of the ostensible foci of the study which include when HIV is vertically transmitted to the infant and if antiretrovirals either prevent transmission of the virus or slow progression to AIDS. At this time, seroconversion rates of the cohort of babies born to seropositive women are accurate but prediction of individual cases of seroconversion remains elusive. Therefore, it will be mandatory that requests to clients to enroll be accompanied by detailed emphasis that they are entering a trial with many questions that will not be answered at its conclusion.
Placebo Controlled Trials—This trial provides much ethical haziness because of its methodology. Placebo controlled trials are still believed to be acceptable in HIV disease (Levine, Dubler, & Levine, 1991), however it is questionable why this research design was chosen to study the question of infant transmission. From a statistical standpoint, how will analysis be done on the efficacy of the treatment? Because of the randomized sample, it will be unknown how many of the sample in both the treatment and control groups would have been infected or would have seroconverted to negative. Because of the relatively strong epidemiological data that exist on seroconversion in infants, it would seem prudent to first conduct this trial simply with an antiretroviral and monitor the effect against the recognized normal seroconversion rate to see if there is an experimental effect.

The strongest argument for allowing this trial to go on is to promote the autonomy of the mother. From the viewpoint of the principled framework this makes sense, particularly because the historical exclusion of all women from opportunities to be research subjects has prevented them from reaping the benefits that come from the increase in scientific knowledge about their health (Levine, 1991b). From a care perspective, there is a danger that entering women into trials of dubious value will cause them to lose trust in the community of caretakers who are necessary to
their health.

**Conclusion**

The ethical problems discussed in this chapter represent distinctive issues that have arisen in the pediatric HIV clinical research domain. While none illustrate absolutely original ethical problems, the unique context that this research presents to clinical bioethics does demand discussion of the issues that occur.

Cooper (1991) has demonstrated that at the normative level, clinical nurses use a mixed framework of principle-oriented ethics and the ethic of care in their moral reasoning. The data from this study suggests that some of the respondents in this study likewise used a combination of theories in describing their experiences. Use of multiple frameworks to assess the ethics of pediatric HIV clinical research allows for varying perspectives to judge the moral actions of involved participants in clinical trials. By examining these different perspectives, additional guidance can be provided by ethicists to the involved parents and professionals.
Chapter VII
Summary and Conclusions

This chapter briefly summarizes the study. It describes the research problem, methodology, sample and major findings. Limitations of the study within the qualitative research paradigm are noted. Conclusions from the study are drawn and implications for clinical practice, education, and further research are discussed.

Description of the Study

Research Problem  The emergence of pediatric HIV disease has necessitated enrolling many afflicted children in clinical drug trials to find effective therapies and to enlarge the scant knowledge base about the course of the virus in the younger population, particularly those under the age of three years. While there is a widely accepted theoretical framework of bioethics that is applied to the conduct of research, its applicability to the population of children with HIV has not been tested. Indeed, a major limitation of contemporary theory on the ethics of research is the limited amount of empirical testing that has been done to test its usefulness. Therefore, this study proposed to describe the ethical issues that occur in the conduct of clinical pediatric HIV research from the perspective of several groups of people who would be expected to be typical of those involved in this specific research domain.
Methods This qualitative study used a descriptive design to study the phenomena of the ethics of pediatric HIV drug research. Because little theoretical work on this subject has taken place and a paucity of empirical knowledge exists, this investigation, through the use of audiotaped interviews, collected data from four groups of people postulated to have had significant experience with the identified phenomena. Using constant comparative analysis through the perspective of a conceptual framework that consisted of traditional principle-based bioethical principles and a newer paradigm of an ethic of care, the data were analyzed and pertinent ethical questions were discussed.

Sample This study drew its randomized sample from a sites designated as pediatric AIDS Clinical Trials Units in the Northeast United States. The sample size represented roughly thirteen percent of all such sites. At the sites, purposive samples of people involved with pediatric HIV clinical research were recruited. The four groups interviewed included physicians and nurses who conducted the research, parents of children with HIV enrolled in clinical trials and Institutional Review Board members who had reviewed proposals for pediatric HIV research at their respective institution.
Results and Findings  Twenty-eight interviews were conducted. Data analysis produced five main themes, which contained fourteen categories and 33 subcategories. Ten ethical issues were identified.

Two paramount ethical topics of concern were distinguished within the ten ethical issues. These are the factors that affect access to care and concerns over the amount of risk appropriate for those afflicted children who are research subjects.

Pressures that Affect Access to Care  Seropositive children in this study had access to basic care. Involvement in research studies undoubtedly improved this basic care by increasing the amount of surveillance care available to them and allowing them to attain drug therapy not obtainable outside studies. While parents did not describe overt pressures on them to enter their children in studies, the other three groups of respondents felt that some undue influences on parents to enroll their children in studies existed. This strain happened partly because of the researchers' needs to draw large samples of subjects. Additionally, there was a striving by all participants to develop therapies for pediatric HIV as quickly as possible. However, this urgency influences research and care because poor data may be generated which impacts both present and future care.
There were other factors that also influenced access to care. Participation in research studies was affected by the child's family status. Children in foster care often had limited opportunities to enter trials. Children in the care of their birth families sometimes had restricted access to research trials because of parental inability to comply with the specifications of a complicated protocol, even if a child's condition warranted inclusion in a trial.

**Questions about Appropriate Amounts of Risk to Which Children in HIV Research Trials Should be Subjected**

A constant theme in the data was that accepted means of determining the risk-to-benefit ratios of a protocol neither provided a meaningful amount of protection nor rendered guidance on how to understand the benefits available to research subjects. The data suggested that traditional risk-to-benefit assessments actually hindered participation of some children in research.

Part of the problem resulted from the system of oversight practice that the Federal Government promulgates in its Regulations concerning human subjects research. The Regulations (Department of Health and Human Services, 1983b, March 8) require investigators to display measurable benefits if research risks to minors will be more than minimal. The conceptual discordance such a specification raises is significant, particularly in an illness such as HIV in which both benefit and harm could be extensive.
The study shows that in the populations that are at most risk, those seropositive children with active symptoms, the researchers, IRB members, and responsible caregivers are willing to subject the children to more risks even if the possible benefits are only theoretical and include a reduction of symptoms, but not a cure. This acceptance of a new paradigm of assuming more risk when benefit is not assured is ethically acceptable only when its implications are well understood by all parties. Its moral worth strengthens when the paradigm is put into practice by increasing communication between parents and researchers throughout the process, waiving some traditional research practices such as complete blinding of participants, and easing the most stringent requirements of fastidious science by allowing protocols that value individual health as highly as the attainment of pure data.

**Limitations of the Study**

Critiquing this study necessitates recognition of its qualitative design (Kahn, 1992). Central to such an examination is how well the primary instrument used, the human investigator, was able to study the phenomena of interest (Lincoln & Guba, 1985).

The investigator brought a strong clinical background in general pediatrics and care of children with chronic pediatric diseases to this study. He has conducted several
small studies using interview techniques and qualitative
data analysis, including a prior study on this topic
(Twomey, 1989b). The investigator also has advanced formal
education on the topic of clinical research bioethics. It
has to be assumed then that while his background had
prepared him to study the phenomena, his qualitative
research skills are still developing and future studies
conducted by him on this topic will produce even stronger
data.

Regarding the existence of the phenomena of interest in
the field, several observations must be made. This study
attempted to describe the phenomena at several sites and
appears to confirm that several general ethical themes found
in the literature can be observed in practice at the sites
visited. While the methodology and design of this study
preclude claims of generalizability of the findings to other
similar sites, the usefulness of this study beyond its
boundaries as a field study are twofold: the study produced
verification of some ethical problems surrounding the
phenomena of interest that had been suggested in the
bioethics literature and it suggests further areas of
inquiry at comparable sites in the country where the
phenomena exists. Additionally, individuals practicing at
pediatric HIV clinical research sites can use the
information from this study to compare the data collected to
their own context to judge its applicability.
Because of the consistency of the categories that developed in the analysis, it is obvious that the phenomena could be studied accurately at the chosen field sites. However, it can be argued that an intensive experience at fewer sites, with more time spent in observation of actual practices and more followup conversations with participant respondents may produce data that is more amenable to interpretive analysis and eventually be productive in building a more coherent conceptual framework of research bioethics that would aid in the analysis of the morality of pediatric HIV clinical trials.

The qualitative paradigm accepts its limitations as well as its strengths. The meaningfulness of this study will be extended if its initial findings, interpretations, and succeeding qualitative investigations are augmented by practices such as development of alternative data collection instruments, such as questionnaires. Sharing the data with other members of the scholarly community for input will provide more areas for future investigation.

**Implications for Future Study**

This study represents an initial effort devoted to investigating whether empirical data exists that supports the current bioethical theories on clinical research. Additionally, this is the first study of any kind that explores the bioethical issues in the conduct of pediatric
HIV clinical research. The data clearly reflect that ethical issues not only occur in this area of clinical practice but that such moral problems must be considered by all participants in pediatric HIV clinical research when making judgments about topics such as parental decision-making and professional roles in the research/caring process. Certainly, continued research on this phenomena deserves consideration.

Research Design. The four groups of respondents provided rich data for the study and are an appropriate set of subjects for continued study. Future studies might include sampling separate groups of foster and natural parents of HIV seropositive children, for some of the data reflected a definition of discrete views on issues that was ascribable to the nature of the parenting relationship.

Regarding design, this study visited four sites but for the sake of data analysis grouped all the respondents together and included little institutional context into the analysis. A case study approach to compare and contrast the research practices of two or more institutions is a viable way of looking deeper into how or why institutional practices evolve and differ (Yin, 1989).

Methodologically, two measures should be considered that would increase the ability of researcher-ethicists to investigate the phenomena in this study. A Delphi study methodology could be used to circulate the repeated issues
that emerge from continued investigation in this area and identify phenomena that are truly pertinent in pediatric clinical HIV research ethics. In the same vein, as more interviews on this topic are done and investigators find saturation of categories and themes occurring, a formal, structured interview instrument could be developed and tested for reliability and validity. Ultimately this could lead to a written questionnaire that would reduce the cost of collecting data on the phenomena and make data collection from distant respondents more efficient.

**Research Issues**  The data from the respondents reflected the daily issues they confronted as part of their involvement with pediatric HIV clinical research and how they dealt with them. While several vignettes were presented that reflected classic ethical dilemmas, such as whether to violate a family's confidentiality by reporting child neglect, the majority of the data represented different issues and how these issues were viewed and managed by the respondents. Therefore, much of the analysis and discussion focused on the theoretical reasoning behind the respondents' chosen actions.

It is obvious from the data that true conflicts in pediatric HIV clinical research continue to exist and some new issues could provide equally difficult resolutions. These conflicts include:
Access to Care  The data clearly reflected that in the areas visited, enrollment in research studies meant an increase in the amount of care delivered to seropositive children. This may or may not have affected the level of care the children received. At some sites, children not on study had access to some of the research resources, such as the investigators' expertise. But at Sites 1 and 3, not enrolling a child in a study meant finding care elsewhere. Such care may be accessible only if the family had insurance or was eligible for Medicaid. A policy question to be considered is whether pediatric ACTUs should not be certified by the government unless their parent institution also provides noninvestigational care.

Placebo-controlled trials  At present, the use of randomized trials that result in a symptomatic child receiving a placebo are unacceptable. Two further issues need examination. The first is the methodology of active drug vs active and placebo drugs. The parents of a child randomized to the active and placebo arm may not administer the active drug but only the placebo. Measures for monitoring compliance, such as measuring residuals of remaining drugs during clinic visits may be unreliable. In a trial of an experimental drug on a healthy client, noncompliance only threatens the trial's validity. In a population in which failure to receive the drug may undermine the children's health, noncompliance can be quite
deleterious to health. Restricting multiple-armed trials using placebos to families who totally understand the concept of the trial should be mandatory, even if the inherent bias of this recruitment measure must be controlled for statistically. The second issue is whether nonsymptomatic children should receive a placebo vs active drug when it is unknown how the dependent variable or clinical endpoint, such as effect on seropositive status, will be measured.

**Vaccine studies** Major issues in vaccine studies will include methodology. Placebo-controlled vaccine studies are sure to be suggested by the purely scientific minded researchers. To even consider such a design conjures images of past use of at-risk, disadvantaged populations. Furthermore, the question of equity must be extended to consider what communities will receive promising vaccines when phase I and II trials are done?

**Results of studies** During all drug protocols sponsored by the Federal Government, Data Safety Monitoring Boards examine interim data and make decisions about safety and efficacy and determine if trials can continue. Such information is kept confidential so as to avoid weakening the reliability of the data. If the concept of making research subjects partners in scientific inquiry is to be meaningful, consideration must be given to use the information reviewed periodically by these Boards so that
parents can more fully make decisions whether to continue a protocol. If a child is mildly symptomatic and shows no change in condition after a year on drug A, perhaps parents would appreciate the opportunity, and as importantly, may be willing to participate in further studies if told that the drug seems to be causing little response, either harmful or helpful, in the cohort receiving the drug.

**Implications for Nursing**

**Educational Issues** Clinical bioethical training is only now becoming a mainstream educational offering (Siegler, Pellegrino, & Singer, 1990). It focuses particularly on the relationship between patient and professional care provider. Its usefulness will be accepted when it can be shown that clinical bioethics can bridge the gap between ethical theory and empirical experiences. Part of this educational offering must include empirical information on research bioethics, for many basic ethical concepts about relationships and obligations occur within the investigator-subject relationship.

The group of nurses interviewed proved conversant in the language of principle-based ethics but recounted actions using rationales that were more cogently recognized as coming from a caring background. Nurses in both clinical and research settings should be made aware that the ethical issues involved in relationships with children with HIV are
complex and not easily amenable to analysis using singular theories. Recognition that multiple processes affect decisions that have moral impact will lead nurses to more closely examine their roles in the research/care domains.

How to educate nurses in such complex moral thinking is problematic. The majority of the nurses in this study had basic entry level nursing education, as do most nurses who are involved in care of children with HIV in primary and tertiary care settings. Bioethics education at the basic level of nursing education varies from formal courses to "integration" of ethical material into other courses. The drawback of either type of ethics orientation is that it tends, in the latter case, to be topical and related to specific cases, while in the former situation, courses may be taught by non-nurses, stress principle-based theories, and fail to recognize the unique bioethical perspective that nurses bring to the clinical setting.

Ethical education of nurses should be an ongoing process. Formal bioethics courses should be offered at the basic entry level of preparation and include content that is theory-based and looks at different ethical theories that have clinical implications. Such instruction can be part of value clarification courses that help students recognize the distinctive attitude that the nursing profession possesses about the personhood of patients. Further postgraduate education through the use of continuing education courses
and ethical grand rounds conducted by nurse ethicists can enrich the moral practice of the nursing clinician.

Graduate education in nursing should focus on producing clinical bioethicist-nurses at the masters level who can bring expert consultant skills to the specialty nursing areas and directly aid patients experiencing ethical problems and dilemmas in the health care setting. Nurses with doctoral level preparation in ethics can continue investigating the moral theories that affect nursing practice and explicate the uniqueness of the moral perspective of the nurse.

**Practice Issues** Knowledge gained from this study can be utilized by nurses who work with families with HIV who seek care for their illness or may be candidates for inclusion in clinical trials. Whether the nurse is involved in both care and research or just one of the domains, awareness is needed of some of the issues and problems that are described in this study.

The first practice issue involves the patient-nurse relationship. This relationship encompasses several factors. The first factor is access. How does the patient get into the system and what implications has this for the nurse-patient relationship? The nurse must first acknowledge to her or himself that the typical family with HIV is facing a chronic illness with few resources and may become quite dependent on the professional relationship.
This relationship must then be defined. If the patient will not enter a research trial, will the relationship continue and if not, what are the obligations incurred to maintain the care of the family? If the relationship will see the nurse in both a caregiver and research role, how will those roles be explicated to the family so that neither role will exploit the family? One means of maintaining the moral standing of all parties in this relationship is for the nurse to consider all interactions with the family to be part of the informed consent process by which the family is being educated about the roles, obligations, and rights of all parties. This will include revealing the tenuous nature of research funding and the need to try to include as many children as possible in studies, not just for the sake of knowledge, but because it is considered to be in the best interest of seropositive children who need drug therapy to receive it under the auspices of a research protocol.

A second practice issue develops because of nurses' general unfamiliarity with Federal Regulations about research protocols. One topic that arose in the study frequently was the frustration of nurses because of constraints placed by IRBs on their research practices, such as enrollment in certain protocols. This usually occurred because the Regulations force reviewers to examine risks while clinicians focus on benefit to patients. This issue is discussed in Chapter VI. Involving research nurses in
protocol writing (which only one of the interviewed nurses described as one of her experiences) would allow them to become cognizant of the Regulations and the moral theory supporting them while also contributing their input on how to operationalize the guidelines in a way that provides the best opportunities for families to access promising drugs.

A third issue that mandates more nurse input is advocating for better treatment of children not in the care of their birth parents. Sharing information about the plight of foster parents and their wards with local decision-makers can help increase the rights of foster parents and further protect the ill child. Additional study into the impact of foster parents on the health care of their wards is something that nurses are capable of doing if they systematically observe and record how the health interests of HIV seropositive children are integrated into the general foster family sphere.

Finally, research nurses must contribute more to the dialogue on controversial issues such as use of placebo controls and enrollment of seropositive, nonsymptomatic children in drug trials. The physicians in this study were much more vocal about their opinions on these topics and it became apparent that nursing involvement often was after the fact, when the protocol was approved. The tone of their discussions (except for that of RN 10 at the end of Chapter V) lacked the firmness of the MDs on these issues and
suggests that the nurses need to further examine the topics from a theoretical perspective, not just from the viewpoint of how such decisions affect their individual patients.

**Research Issues** Replication of this study on a larger population certainly is indicated. Continued exploratory, descriptive studies on this topic may reveal further ethical issues. Conceptually, conducting a study on this phenomena using only a sample of research nurses could provide data that could be used for further theory construction on the conceptual framework that this study began to describe. The nurses in this study had consistently more complex rationales and questions about their experiences than the other respondents. One research question could include why research nurses use principled ethics language to explain their actions which actually are more consistent with the tenets of caring ethics. An additional question would include how research nurses reconcile their actions with current theories?

**Conclusion**

The original research bioethics theories based on universal principles provided a foundation to begin constructing a conceptual framework that allowed scientific inquiry to be conducted while protecting the rights of subjects. While some dissenters have questioned its basic premises (Marshall, 1986), most bioethicists believed that
this principled ethical framework answered most moral questions about research.

The HIV pandemic has forced a reexamination of such assumptions. Perhaps because the people who have borne the brunt of the disease, women, children and groups that face discrimination such as homosexuals and drug users, are considered disadvantaged in our society, the traditional research ethic framework has been challenged and even declared irrelevant (Spiers, 1991). The data in this study indicates that while reliance on principle-based ethics has not ceased, this system has proven insufficient for analysis of many ethical issues in pediatric HIV clinical research. Significant people in the venue of research have described the thinking behind their actions using rationalizations that can be described more comprehensively by use of concepts both within and outside the traditional system.

The application of an ethic of care combined with principle-based ethics to clinical research reveals that there is a reconceptualization of the moral behaviors of those involved in scientific inquiry. This study has shown that basic issues such as the primacy of the principle of autonomy, the role of paternalism in pediatric research and how to empower significant people in the lives of ill children must be considered when testing the efficacy of bioethical theories that claim to have applicability to clinical research. Traditional scientific practices such as
randomized controlled protocols must be further examined. Pediatric HIV disease itself has posed strenuous tests to basic ways of thinking and it appears that normative practices to address these issues are pushing theoretical boundaries for more answers.
References


of the polymerase chain reaction for early detection of the proviral sequences of human immunodeficiency virus in infants born to seropositive mothers. New England Journal of Medicine, 320, 1649-54.


Appendix A

Semi-structured Interview Schedule

When open-ended questions were not productive in eliciting responses from the respondents during the interviews, several direct, topical questions would be asked of the respondents. As the number of interviews increased, the accumulated data led to several typical questions being directed toward the respondents. The following interview schedule has been reconstructed from the tape transcripts.

The interviews typically began with open-ended questions, such as asking the professionals "Tell me about some issues that have arisen during your experiences in pediatric HIV research that you felt were ethical in nature." For parents, the question would be phrased "Tell me how it has been to have your child in the drug trials?" If these opening questions elicited responses, follow-up would be along the lines of the topics that the respondent brought up.

Eventually, it was found that several typical topics emerged and directive questions would be asked if the respondent did not bring these topics up. Examples include, for Professionals:
Some people have identified informed consent as having some issues or risk benefit problems. Have you seen any of that come up in the trials you've been involved in?

Now that you do have AZT in open-label status, has that posed any problems with subsequent drugs, are people having any problems identifying what is an experimental drug?

Has this area had any problems with activist groups making demands on you as a researcher or causing you any problems?

Now you do have foster care kids who are involved in your trials. Have there been any issues with involving natural parents in consent?

Tell me your feelings on placebo control trials for kids who have HIV?

Have you ever felt any tension whether it be ethical or otherwise, professional tension with being both a child's provider and a child's researcher?

Some questions have come up in the literature regarding when kids are on randomized trials and if their condition starts deteriorating, whether researchers have access to the codes of the drugs and know exactly what they're getting. Has
that posed any issues for you at all?

One of the questions that comes up at some sites is that there is a limited population of kids. We have so many trials that are becoming more available. Are there concerns about going back to that same population and asking them to be on one trial and then another trial?

Now if a child has to come off of trial at this institution, do you feel as a provider that affects there overall care?

In other interviews I've talked to people about there have been questions about the consent of parents who are infected themselves. Have you seen any problems with consent?

Have you felt that the parents adequately understand the difference between the treatment and the research?

For Parents:

to be on this protocol what did you have to do?

Did they discuss with you the possible benefits of the drug or side effects of the drug? How did you understand that?
Have you ever been approached to put her on more than one trial?

Do you feel that her care has changed at all, either getting better or getting worse because she's been on the trial?

Has being on the trial meant she's had more tests or blood drawn or anything like that?

Has she ever talked to you about how she feels about taking the drugs?

Had you ever felt that your child should have been on AZT, or did they ever ask you if you wanted your child to be on AZT and not be in the trial?

for Foster Parents:
When you had him in his trial, was he already in your care - were you involved in the decision making?

Did you understand when you took him into your care that the drugs here he's getting were experimental or how was that explained to you.

What decision making role do you have regarding his participation in research at this point?
Appendix B

School of Nursing
University of Virginia
Charlottesville, VA 22908

Dear Colleague,

You are invited to participate in a research study that examines the bioethical beliefs of selected individuals who are involved in the conduct of clinical drug research with children who are HIV-seropositive. You were selected to be a participant in this study because you are either a nurse or physician who is involved in such research, or a member of your institution's human investigation committee that reviews research protocols regarding such protocols. This study is a multi-center, qualitative study that is part of the primary researcher's doctoral dissertation work in bioethics at the University of Virginia. It has been approved by the human investigation committee at your institution as well as that at the University of Virginia Health Sciences Center.

If you agree to participate, you will spend approximately one hour with the primary researcher in an open-ended interview that will be directed at your beliefs about the ethics of clinical research that you have developed because of your personal experiences working with pediatric HIV drug protocols. The interview will be tape-recorded. At any time during the interview, you may withdraw from the project and all data collected from your interview will be discarded.

All identifying names will be removed from the tape-recordings and transcripts will have codes on them for identification. Only the primary researcher and several colleagues at the University of Virginia will have access to the raw data which will be stored in locked files in the primary researcher's files.

Data collected in the 28 planned interviews will be analyzed and broken into general ethical themes and categories. Eventually, a national panel of experts in research bioethics will be surveyed on these themes and categories for input on this topic.

Thank you for your considerations about participating. Please direct any questions about this study to the primary researcher at the phone and address below.

John G. Twomey, Jr., MS, RNC

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Appendix C

Informed Consent Form

You are asked to participate in a research study that looks at the moral actions of people who do research with children who have the HIV infection. You have been chosen because you are the parent or guardian of a child who has HIV who has been or is currently in a research trial that tests HIV drugs.

It is not expected that the information gained from this study will be of help to you or your child. Yet, it is hoped that the information may help researchers, nurses, and doctors who work with children with the infection HIV to learn more about how people act when doing HIV research. You will not be paid for helping in this project.

If you agree to participate in this study, you will meet with the person who is doing the research, for about one hour. He will ask you questions about your ideas abut your child being in HIV drug tests. The interview will be tape recorded. No one at the hospital or clinic will listen to your answers. Your answers will be seen only by the person you talk with and several people at the University of Virginia in Charlottesville, Virginia. However, only the researcher will be able to identify you. The information in your answers will be used in the researcher's doctoral dissertation, which is a part of his
at the University of Virginia. The information from your answers may be published in the future but your identity will be kept secret.

It is not believed that meeting with the person you talk with will hurt you. At any time during the conversation, you may stop talking and the meeting will end. If you do this, no records of your talk will be used.

If you have questions about this meeting that is about your child being in HIV drug testing, you may call the person you spoke with at the number below. You also may call at this institution or at the University of Virginia. You will be given a copy of this form for your records.

____________________
Print Name

____________________  ________________
Signature Date

____________________
John G. Twomey, Jr., RN, MS.
Appendix D

**Categories and Sub-categories**

**Issues of Present Care vs Future Knowledge Development**

**Concerns About Pressures on Researchers**
- Pressure to produce results
- Pressure to provide care

**Concerns about Pressures on Parents**
- Concerns about the present
- Future concerns

**Concerns about IRB Process**
- IRB authority
- IRB decisions

**Knowledge Development**
- Current knowledge about pediatric HIV
- Effects of knowledge problems on treatment of children
Shift in the Research Ethic Paradigm
From Nonmaleficence to Beneficence

Risks and Benefits
Making generalizable risk to benefit assessments
Individualizing risk to benefit assessments

Standards of Care
Differences in care available to children because of their enrollment in drug trials
AZT as the accepted standard of care for seropositive children

Research as Access to Care
Research as access to basic care
Research as access to superior care

Research Methods
Concerns over the appropriateness of randomized controlled trials in pediatric patients
Randomized controlled trials affecting individual care of subjects
Duty to Be a Research Subject
or the Right to Refuse?

Choices/Alternatives

Existence of choices
Nature of available choices

Informed Consent

The process of informed consent
The meaning of informed consent
Comprehension of informed consent

Recruitment/Enrollment

Over-recruitment vs limiting access
Threats to Parental Authority

Parents as Decision Makers
Factors affecting parents' decision making
Caretakers as decision makers

Community Issues and Attitudes
Discrimination against seropositive people
Influence of community activists

Child Protective Agencies and Protocols
Effect of foster care on research participation
Intimidation of foster parents
Pregnant Women and Their Infants:
An Exemplar Case in Research Ethics

Conflict between the interests of the mother and the infant
Aspects of risk and benefit assessment
Knowledge problems
Subject comprehension
Community attitudes
What is the purpose of the study?

The purpose of the study is twofold: to attempt to learn how AZT might prevent transmission of HIV from mother to child; and to further study the safety and efficacy of AZT treatment in women during pregnancy and through childbirth, and in infants through their first six weeks of life. Very little is known about the mechanism of perinatal transmission of HIV, but the hypothesis is that AZT could influence transmission by reducing viremia (the amount of virus) in the mother, thereby reducing the fetus’s exposure to the virus, and/or act as a protective agent for the fetus. There is no other way to test this hypothesis in humans than through the conduct of this study in mother/infant pairs. Eventually it is hoped that researchers may be able to stop perinatal transmission, but this will only be possible if they can understand how it occurs.

What animal studies support this hypothesis?

At present, no good animal models exist for in utero retroviral infection of embryos or fetuses, and there are no animal studies that directly address the capability of AZT to prevent infection in utero. Several animal models have been developed however, that simulate in utero infection, including the use of transgenic mice that activate virus during gestation, and the use of direct inoculation of virus into embryos or fetuses. It is known that AZT is transported across the placenta in animal models as well as in humans, and that it reaches levels in the fetus that are similar to those in maternal circulation. In several animal models AZT has been shown to prevent progression of disease in the neonate. These studies have also shown that the sooner the drug is started, the greater its efficacy. In one study, when mouse embryos were directly inoculated with retrovirus, AZT treatment of the mothers during pregnancy and lactation prevented infection of the neonates and onset of the disease.

Have any animal studies of AZT shown carcinogenic effects?

The Public Health Service (PHS) has carefully reviewed results of standard lifetime carcinogenicity studies of AZT in mice and rats. The studies, which were conducted by Burroughs Wellcome Co., showed that AZT, when given at doses higher than those that will be given in ACTG 076, caused vaginal tumors in rats and mice. No tumors occurred at middle or low doses in rats, and only one mouse developed a tumor at middle dose. It is important to note that the test animals received the drug over the majority of their lifespans. The metabolism of AZT by humans and rodents differs greatly. Very high concentrations of
the drug occur in rodent urine. It is also known that the cells in the rodent vagina divide more rapidly than in humans. It is hypothesized that the rodent vaginal tumors may have been induced by chronic local contact of the rapidly dividing vaginal mucosa with high concentrations of AZT in urine. These studies were reviewed by the PHS, which concluded that the studies did not establish that the drug has a carcinogenic effect in humans, and recommended that HIV-infected persons receiving AZT should continue their therapy.

What other studies have evaluated the safety of AZT in pregnant women?

ACTG protocol 082 was initiated in July 1989 as a pilot study for 076 to look at the safety of AZT in the third trimester of pregnancy. To date, no adverse effects have been found in any of the 20 mother/infant pairs enrolled in the study. In fact, safety data from this trial convinced the investigators, NIAID staff, and the FDA and its advisory committee that proceeding with 076 will not subject either the pregnant woman or her infant to unacceptable risks.

Burroughs Wellcome Co. maintains a registry of at least 50 HIV-infected pregnant women who have received AZT at some time during pregnancy. A certain percentage of fetal abnormalities may occur in any population, but there is no evidence in this group of women that AZT contributed to abnormalities in their offspring.

Are there any other data on treatment of women with AZT?

NIAID has analyzed data on women who participated in ACTG Protocol 019, a large study that showed that AZT slows the progression of HIV symptoms in asymptomatic HIV-infected individuals with T4 cell counts below 500. Data could be analyzed on 106 women who participated in the study. This represented only 8% of the total number of participants and was considered too small a group for separate analysis. Differences between the placebo and treatment groups were not obvious. Overall study results and a lack of any data showing different responses to the drug in men and women led researchers to conclude that AZT was likely to be equally efficacious in women. In this study, side effects of both high and low dose AZT were minimal for all participants and there were no gender-specific side effects. These data are unpublished.

What other studies have been conducted using AZT in newborn infants?

A Phase I study has been conducted, evaluating the safety and pharmacokinetics of intravenous and oral doses of AZT in 32 infants from birth up to three months of age who were born to women infected with HIV. The babies were treated for 4 to 6 weeks at progressively increasing doses, commensurate with body weight. Therapy was continued for up to 12 months in the infants proven to be infected with HIV. The drug was well tolerated by all infants in the study, with only 9 developing presumably drug-related anemia. Dosing of infants in ACTG 076 is based on results of this study.
How likely is transmission of HIV from a pregnant woman to her fetus?

Estimates of intrauterine transmission range from 13 to 40 percent. Transmission rates are discussed in the protocol consent form.

Why does the consent form require the father's consent?

The consent of the father is required by the Code of Federal Regulations (CFR) Part 46.207 of the Regulations for the Protection of Human Subjects. This is tempered by the fact that the father's consent need not be secured if any of the following apply: (1) The purpose of the study is to meet the health needs of the mother. (2) His identity or whereabouts cannot be reasonably ascertained. (3) He is not reasonably available. (4) The pregnancy resulted from rape. The Office of Protection from Research Risks (OPRR) has further commented that the local Institutional Review Boards (IRB) have had considerable experience in interpreting the regulation.

Who will pay the medical and hospital costs for the mother and child?

There will be no costs to the participants for medication, clinical visits or laboratory tests associated with the study. In accordance with the usual practice of clinical research, the medical care costs associated with delivery and the newborn nursery care will not be covered by the study. However, each site is committed to helping patients find resources to aid them in meeting the financial obligations related to their health care.

What other studies for women is NIAID supporting currently and planning for the future?

In December 1990, NIAID coordinated the first national conference on women and HIV infection. Some 1700 attendees, including several hundred HIV-infected women convened to provide research recommendations and input to federal government programs.

The most pressing research need identified was a large-scale women's epidemiological cohort study. Such a study is viewed as scientifically vital to assess women's specific issues, such as gynecological manifestations relevant to HIV infection, and to provide cross comparisons with studies of homosexual/bisexual males and intravenous drug users. The Multicenter AIDS Cohort Study (MACS), set up in 9183 to follow homosexual/bisexual men has provided much needed information, and a similar study for women is now in development.

A protocol to test the efficacy of fluconazole in preventing fungal infections in HIV-infected women is being developed by NIAID's Community Programs for Clinical Research on AIDS (CPCRA). In addition, questions regarding the natural history of HIV infection in women are being addressed in the CPCRA Observational Data Base study. Recognizing that historically there have been barriers to the participation of women as well as other populations in clinical trials, the CPCRA has initiated a Women, Children and Minorities Interest Group with a
newly formed Women’s Caucus. The caucus will review protocols to ensure maximal participation of women and identify high priority scientific questions that could be added to the CPCRA scientific agenda.

On Monday, March 11, 1991, the AIDS Clinical Trials Group (ACTG) will hold the first meeting of the newly formed Women’s Health Committee, a full scientific committee of the ACTG. A core committee of experts in front-line treatment, diagnosis and research for women with AIDS will be setting an aggressive course of direction for the NIAID research program. Areas of interest include manifestations of opportunistic infections and malignancies in women, and other gender-specific issues.

What other studies is NIAID planning on perinatal transmission of HIV?

DAIDS has issued two Requests for Application to develop animal and in vitro models to study placental transmission of HIV to the fetus and to assess the metabolism and transport of AIDS therapies in the placenta and in the fetus and neonate. This preclinical information will help in the design of new, safe and effective anti-HIV therapies to prevent or interrupt the transmission of HIV from mother to offspring.

Why are women who are planning to breastfeed excluded from the study?

Some data suggest that the HIV infection can be transmitted through breast milk.

What happens to the infants who are diagnosed with HIV infection while in this study?

Once an infant is diagnosed with HIV infection, he/she is no longer a participant in Protocol 076, because the terms of the study dictate that HIV infection is the study “endpoint.” However, the infant will immediately be eligible for other treatments and protocols now being conducted through the AIDS Pediatric Clinical Trials program and other programs. By virtue of enrollment in an ACTG study, the mother and child will be seen and treated by health care professionals who are the leading experts in the field of pediatric AIDS, and in an equally top-line health care setting. Networks have been developed to ensure continued state-of-the-art treatment for the subjects of every ACTG study.

Are women treated after delivery?

At the time of delivery, if a woman’s T4 count is between 200 and 500, she will receive AZT and be closely followed over the next 6 weeks. At that time she will be referred to an appropriate outpatient facility for continued outpatient management and evaluation.

Prepared by:
Office of Communications
National Institute of Allergy and Infectious Diseases
Bethesda, Maryland  20892
STATEMENT

Study of AZT in HIV-Infected Pregnant Women and Their Offspring to Begin

HIV-infected pregnant women will soon be enrolled at three initial pilot sites within NIAID's AIDS Clinical Trials Group (ACTG) for an unprecedented study on whether AZT can prevent transmission of the AIDS virus from mother to infant, and on the safety and tolerance of AZT in pregnant women and in newborns. The protocol, ACTG 076, has been in development for more than two years to ensure the full consideration of all scientific and ethical concerns for these special patient populations.

The initial pilot sites are the University of Medicine and Dentistry of New Jersey in Newark, New Jersey, the University of Miami School of Medicine, in Miami, Florida, and Baylor College of Medicine in Houston, Texas. Eventually up to 10 sites will participate in this phase of the protocol whose purpose is to fine tune the details and logistics of this extremely complicated study. Once it is completed, the protocol will open nationwide at the NIAID's AIDS Clinical Trials Units (ACTU's) with a target enrollment of 748 women.

"This is a very important study since the number of cases of babies born with HIV is growing at a tragic and alarming rate and since the only route to curbing this growth is by stopping transmission from mother to child. The scientific rationale for the study is based upon information from animal models that suggests that AZT, the best available treatment we have today, might prevent infection of the infant. The study is also designed to provide some much needed additional information about the safety of the drug in pregnant women and their offspring," said Daniel F. Hoth, M.D., Director of NIAID Division of AIDS (DAIDS).

Twenty-eight hundred cases of pediatric AIDS have been reported in the United States since 1982, a figure that is expected to rise to between 6,000 and 20,000 in the next few years. The virus is transmitted from mother to infant in between 13-40 percent of all HIV-infected pregnancies, according to published studies. However, the prognosis for HIV-infected children is grim. The median survival from diagnosis is 38 months, and only 6 months for those diagnosed with AIDS at less than one year old.

"Many HIV-infected women are eager to take part in a study that may prevent transmission of HIV during pregnancy. There is a lot of need for 076, and a lot of interest," said protocol co-author Janet Mitchell, M.D., M.P.H., Chief of Perinatology at Harlem Hospital Center, in New York, New York. She also commented on concerns raised by AIDS
activists about the ethics of conducting a perinatal treatment study in pregnant women. "In
the process of protecting other people's rights, one ought to avoid becoming paternalistic. I
know the women who will enroll in Protocol 076, and I know they are capable of making
decisions in their own right."

Traditionally, pregnant women have been excluded from clinical drug trials because of
the inherent risks to mother and child. "In the case of HIV disease, however, the objective is
to block passage of infection from mother to infant during pregnancy and/or delivery,"
according to Dr. Hoth. NIAID launched a Phase I trial (ACTG 082) in July 1989, to study
the safety of AZT in HIV-infected pregnant women in the third trimester. To date,
researchers have found no significant adverse effects in the 20 mother/infant pairs enrolled.

Protocol 076 is a placebo-controlled, randomized, double-blinded trial, meaning that half
of the women will receive a placebo, and half will receive AZT, with neither doctors nor
patients knowing which treatment the women are receiving.

The study has been extensively reviewed by the Antiviral Advisory Committee of the
Food and Drug Administration. In addition, the local Institutional Review Boards of the
participating institutions, must also approve the protocol before it is initiated at their site. A
comprehensive set of guidelines to protect participants has been developed. These guidelines
include the following requirements:

- Women with an AIDS-defining illness or a T4 cell count below 200 (a sign of a
  severely compromised immune system) will be excluded from the trial. Because
treatment with AZT is recommended for these patients, randomization would be
unethical.

- Women in the placebo group will be switched immediately to the AZT treatment
group if their T cell counts drop below 200. The women will still be followed, and
their infants will remain in the study.

- The study is only open to women in their second and third trimesters (14-36 weeks)
of pregnancy, to decrease the possibility of fetal malformations that could result from
AZT treatment. Birth defects are most likely to occur in the critical first trimester,
when organs are being developed.

- If any fetal abnormalities are detected by sonogram during the course of the protocol,
the study drug will be discontinued. Sonograms will be done at least every four
weeks.

- An eight-page appendix to the protocol outlines the monitoring requirements for the
constellation of symptoms, toxicities and adverse outcomes that mandate
discontinuation of the study drug.

Women randomized to drug treatment will take 100 mg capsules of AZT orally five
times a day until they begin labor, when they will receive the drug intravenously.
Immediately after childbirth, all women will be offered AZT, following standard treatment guidelines for six weeks while follow-up medical care is arranged.

Newborns will receive, for up to six weeks, the same study treatment to which their mothers were assigned at the initiation of the study, taking oral doses of either AZT or placebo, or intravenous doses if they cannot tolerate fluids. The babies will be evaluated for evidence of HIV-infection at weeks 1, 2 or 3, 6, 12, and every 3 months thereafter until week 78, when follow-up will be completed.

All study drugs for this trial will be provided at no cost by Burroughs Wellcome Co.

The study is designed to determine whether AZT delays evidence of HIV infection in the infant during or after the six-week treatment period. Laboratory evidence includes positive viral culture and/or two positive ELISA confirmed by Western Blot (for infants 15 months and older). In addition, the safety and tolerance of AZT in both mother and infant will be evaluated.

Signed informed consent forms will be required from the mother for herself and, to the extent possible and in accordance with Federal law, from both mother and father, for the infant. Patient confidentiality will be ensured by assigning code numbers to each participant and securing the records. Clinical information will not be released without the written permission of the patient.

There will be no costs to the participants for medication, clinical visits or laboratory tests associated with the study. In accordance with the usual practice of clinical research, the medical care costs associated with delivery and the newborn nursery care will not be covered by the study. However, each site is committed to assisting patients with financial problems related to their care.

Prepared by:
Office of Communications
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892
(301) 496-5717
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<th>Present Versus Future</th>
<th>Paradigm Ethics Shift from Nonmaleficence to Beneficence</th>
<th>Duty to Be a Research Subject or the Right to Refuse</th>
<th>Threats to Parental Authority</th>
<th>Parent Goals/Concerns</th>
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<th>Knowledge Development</th>
<th>Researcher Goals/Concerns</th>
<th>Risks and Benefits</th>
<th>Standard of Care</th>
<th>Research as Access to Care</th>
<th>Research Methods</th>
<th>Choices Alternatives</th>
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<th>Recruitment/Enrollment</th>
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