Ethical Issues Surrounding the Conduct of Pediatric Clinical Studies

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Introduction

The ethical issues surrounding the conduct and enrollment of children in pediatric clinical drug trials are very important ones for society as a whole because the use of children in research and in clinical trials raises unique ethical concerns. These ethical concerns arise from the interrelated issues of their competence, autonomy and vulnerability ("Ethics in Research," n.d.). Children are among the most vulnerable members of our society. In the context of clinical drug studies, they are vulnerable because they are not considered capable or competent of making an "informed consent", one of the required components of today's clinical trial process, in order to participate in the clinical trial. They are not considered sufficiently competent to fully understand the complex issues involved, such as the risks they "voluntarily" have to accept in order to gain any benefit of participating in clinical studies. The giving of "informed consent" is a requirement of adults before acceptance in a typical clinical trial. In the case of children, the "informed consent" component is obtained from the parents, and the children provide an "assent" to participate in the clinical study. In this situation, parents serve as the guardians of their children's safety and interests. In this process, society has to evaluate the importance it places on these vulnerable members of our society, the potential benefits to be gained by having children participate in a clinical study and the risks it asks of them (and their parents) in return for a potential benefit of a new therapeutic that may be found to be useful for that child to treat their illness or even critically needed for the survival of that child, and that could possibly help other children with the same disease and also of importance, the successful treatment of future children with the same illness for which there is no current treatment.

Historical Background

Children have been participants in medical research for some time. The early vaccine experiments of Jenner in 1776 involved an 8-year old boy. In 1855, a 12-year old boy was given an experimental rabies vaccine in order to save his life. Since then, and as medical science has evolved, children have been excluded from drug experimentation and clinical trials because of their vulnerability and lack of autonomy. In Germany in 1949, the Nuremburg Code was established which held: "The voluntary consent of the human subject is absolutely essential." Additionally, children were excluded from all research (Diekema, 2005). However this practice was not always adhered to. In the 1960s, numerous research studies were conducted on children in the absence of voluntary or informed consent. One such study at Harvard University in 1961 was "Human Radiation Experiments at the Fernald School in Waltham, MA. There, seventy-four "mentally retarded" children were fed radioactive calcium and iron in oatmeal to determine the absorption of those nutrients (Diekema, 2005)." Therefore, there was a lack of governmental regulations formally restricting the use of children and providing guidelines for their appropriate involvement. In 1974 this situation changed with the establishment of the National Commission for the Protection of Human Subjects of Biomedical Research (Diekema, 2005). They established the twin pillars of protection in research defined as:

- An Institutional Review Board (IRB) review of benefits and burdens,
- Informed consent/parental permission/child assent.

These two practices were codified in US regulations in 1981 when written into the FDA regulations regarding informed consent (21 CFR Part 50) and the IRB review of research (21

CFR Part 56) (Roth-Cline, Gerson, Bright, Lee, Nelson, n. d). Additionally, in 1983 and following the recommendations of the National Commission, regulations were written that specifically governed research on children conducted or funded by the Department of Health and Human Services (the Department of Health, Education and Welfare in 1983). In 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA) which broadened the FDA's authority and reformed several areas of regulation. One key provision was an incentive to pharmaceutical manufactures to study their drug candidates in pediatric populations. This provision granted pharmaceutical manufacturers "of a pending or approved NDA for a drug with current exclusivity under the Waxman-Hatch Act or the Orphan Drug Amendments an extra six months of market exclusivity for performing certain studies in pediatric populations." Although this authorization was subject to a sunset provision on January 1, 2002, Congress has reauthorized the provision in 2002, 2007 and its current sunset date is October 1, 2012 (Hyman, 2012)." Pediatric drug study incentives and conditions were reauthorized in July of 2012 ("Pediatric Drug and Device," 2012). Further regulations incentivizing drug manufacturers and drug sponsors were the "Best Pharmaceuticals For Children Act" (BPCA) passed on January 4, 2002 and the "Pediatric Research Equity Act" (PREA) passed on December 3 of 2003 (Hyman, 2012). These two regulations were further approved, without further sunset provisions, and thus made a permanent part of the FDA regulations in July of 2012 ("Pediatric Drug and Device," 2012).

Prior to formal legislation, the use of children as subjects in medical research or drug clinical trials was rare or nonexistent and unregulated until after the 1980s. Generally, up until that time, therapy in children with a disease that fairly equally affected both adults and children, was fundamentally the use of a dose lower than adults because children were assumed to be

simply "small adults." But there are some diseases, such as genetic diseases, metabolic disorders, unique to children or that are fatal in childhood so that these kids never live long enough to see adulthood. Also, in diseases that affected both adults and children, simply lowering the dose based on body weight or surface area differences was not always equally effective and sometimes toxic as some aspects of children's adsorption, elimination and metabolic systems are unique and they do not always process a drug in the same way as an adult system. So evaluation of potentially more effective treatment regimens in children is important and in some cases critical to a child's survival.

In summary, I will evaluate the ethics surrounding the use of the statute for "informed consent" in pediatric studies comparing the Utilitarian and Rights Theories. The stakeholders are: Children, Parents, the Provider (physician), The IRB, the FDA, the Payer (insurance companies), the drug company (Drug Sponsor), and finally, the society in which these pediatric studies take place is a stakeholder as society wants to see benefits and betterment come to its citizens and they are responsible to the extent they allowed these studies to take place via the elected government representatives and various agencies they allow to exist that are involved in pediatric studies. The primary stakeholder is the child as they are the treated subject in the study and bear all the risks from this treatment. The parent is a critical stakeholder as they are confronted with being the guardian of their child and having to weigh the potential benefits and risks as presented by the provider. The provider is a key stakeholder as he (or she) is one of the most medically knowledgeable participants in this situation and has to balance the information provided by the drug maker with the medical risks and benefits involving use of an ill child or use of a healthy child and exposing them to the risks of the drug candidate as well as explaining the case to the parents. The IRB approves the protocol and patient population criteria and

evaluates the informed consent and child assent forms and process to make sure the enrollment criteria and child enrollment regulations are adhered to. The FDA is a key stakeholder as they are tasked with enforcing the regulations that cover the conditions when children can be appropriately used in a clinical study, the enrollment guidelines and ultimately review the clinical data resulting from the study. The Payer is a stakeholder because they provide funding for a subject to participate and will ultimately pay or subsidize the drug costs if the drug is approved for pediatric use. The drug company is an obvious stakeholder because they are the maker of the drug candidate under study, the holder of the drug patent that could have its exclusivity extended if the pediatric study is filled.

Evaluation By Utilitarian Theory

The Utilitarian Theory views for each stakeholder are outlined in table below.

Utilitarian Theory		
Stakeholders	**Perceived Benefit**	**Perceived Cost**
Children	Benefits from treatment	At risk of harm from treatment or no effect at all
Parents	Child benefits from treatment	There is risk of harm from treatment or no effect at all. Parent may assume guilt for any harm done.
Providers (physicians)	Facilitate finding new therapy	If not rigorous in analysis may miss an avoidable harmful outcome
IRB	Facilitate finding new therapy	If not rigorous in analysis may miss an avoidable harmful outcome
FDA	Benefits when regulations are followed and pediatric trials result in new approvals	If tested drugs produce harm to children frequently for a particular therapy or worse, fatalities are observed, then FDA comes under scrutiny

		and regulations may need revision requiring lengthy review and debate
Payers (insurance companies)	Facilitate finding new therapy	Provide support for ineffective or harmful therapy.
Drug Company (Drug Sponsors)	Provide an effective therapy where there was none before.	If tested drugs produce harm to child or worse, fatalities are observed, then the company comes under scrutiny and loss of revenue and reputation result.
Society	The leaders of a society; governmental, regulatory, medical and the general citizenry can feel optimistic that there is a new, more beneficial therapy for the pediatric population where there was none before.	If in numerous cases therapy trials were ineffective or harmful, there will be push for review of situation and call for new regulations to improve the outcome. Possibly use improved technology or science not available at the time of prior regulations.

The Utilitarian theory, in its most common formulation, "Do what is for the greatest good of the greatest number (McCall, 2010)" would support running drug testing studies in pediatric populations. However, in an environment following this moral theory, regulations and protections for the child may not be highly restrictive. This would be because the greatest good would be what would benefit society and future children and the individual child considered for a study would be viewed as an agent for that betterment, an agent to help support the development of improved therapeutics.

Evaluation By Rights Theory

The views of Rights Theory for each stakeholder are outlined in the table below. From a Rights Theory perspective, the basic result will be the same, the advocacy of pediatric studies for the benefit of children. This theory will provide rights to each stakeholder but will provide

stronger rights to children than the Utilitarian Theory because children will be considered, similarly to adult humans, as autonomous beings with inherent value deserving of respect and dignity and possessing free will. However, because of their minor status (the legal interpretation of the term "minor") they are considered vulnerable and lack the competence and autonomy that adults are considered to possess.

Rights Theory		
Stakeholders	**Rights Exercised:** (Allowed entrance into pediatric trial)	**Rights Compromised** (Denied entrance into pediatric trial)
Children	Healthy Children: Right to be free from exposure to more than minimal risk Ill Children: Right to treatment deemed to be of favorable benefit Right to not be coerced into study.	Healthy Children: no immediate denial of rights. But, if they become ill, they may not have a proper treatment available.
Parents	Right to have child eligible for possibly beneficial treatment.	Denial of possible effective therapy for child or participating in a trial that could lead to effective therapy.
Providers (physicians)	Providers have right to effective therapy for child patients or moral obligation to provide best possible treatment option.	Without pediatric tested medications then providers may not decide to give a possibly beneficial drug as it is given in a form where the dose or route causes toxicity in children. Therefore, may prescribe less or be restricted to consider less effective and less risky treatment options.
IRB	IRB has right and obligation to run scientifically justified and properly designed unbiased trials such that the	IRB denied a clinical trial option that can fully evaluate if children need different form of treatment than that

	subject drug can be properly evaluated to be effective or ineffective therapy and identify the drug parameters that are effective	extrapolated from adult form of treatment. Therefore, there may be delay to improved treatment for the pediatric population at present and in the future.
FDA	Right and obligation to provide stakeholders conducting clinical trials (providers, IRB, payers, drug companies, society) with guidelines to scientifically justified design and GCP rules to run effective and sound trial programs	Right has been inhibited
Payers (insurance companies)	Right to treatment options that have been properly tested so they can decide which are appropriate to cover by insurance	Right has been inhibited
Drug Company (Drug Sponsors)	Right to an environment to develop safe and effective drug therapies for all patient types they choose to target for their drug candidates.	Right has been inhibited
Society	There is the desire by society to provide best therapy options to all citizens but not at the detriment of its most vulnerable citizens. Society depends on the agents and agencies that are stakeholders to establish safeguards and guidelines to protect the children from unnecessary risks while moving to develop optimal benefits for all.	Right has been inhibited

Summary

Both Utilitarian and Rights Theories allow for pediatric studies but by conducting an analysis following the Rights Moral Theory a more rigorous protection of children is developed.

The use of a more rigorous "informed consent" process in the conduct of pediatric studies is a step that protects the rights of this vulnerable population at a high level. The process that engages and encourages parents to become fully informed before providing consent protects children from a decision they are not ready or capable to properly make. The other stakeholders, the providers, the IRB and the drug companies, in conjunction with the FDA, work in concert to create a process that is scientifically justified and where risks and benefits are fully evaluated and defined before approval is given to set up a pediatric trial. This helps to ensure the protection of the rights of the pediatric population from inappropriate studies and risks. The other stakeholders are in a highly important and ethically demanding situation to provide the most safeguards and develop rigorous standards so that parents can make a sound and informed decision for their children and children can feel safe and comfortable that the adults in this process are acting in a way that creates and fosters continued trust as they participate in the drug trial.

Update

The Affordable Care Act (ACA) is having a greater influence on the U.S. healthcare system and its policies will affect healthcare provided to children and enrollment in clinical trials, therefore, it is worthwhile exploring whether ACA policies will have any effect on pediatric clinical trials in the U.S. and their ethical conduct.

After a review of the ACA policies, I believe the ACA is likely to increase the level of pediatric care in the U.S. and increase the interest in conducting pediatric clinical trials as well. This is because the number of insured children in the U.S. will increase due to the policy that

they can be carried on their parent's policy up to age 26 and they cannot be denied coverage due to pre-existing conditions ("Key Features," 2010). This number of children gaining insurance coverage could be up to about 8 million ("Children's Defense Fund," 2011). Additionally, a second policy states that insurance companies cannot deny an individual from participating in an approved clinical trial for treatment of cancer or another life-threatening disease or condition nor deny or limit coverage of routine patient costs for items or services in connection with trial participation ("Coverage for Individuals, 2010). These ACA policies should increase the quality of pediatric care these children receive and will have a potential to increase the number and size of pediatric clinical trials.

With a possible 8 million more U.S. children moving from uninsured to insured and some of these having or developing cancer or some other life-threatening disease, there will likely be an increased interest to conduct more and possibly larger pediatric clinical trials to test new potential medicines to address the medical needs of a larger population of ill children. Therefore, there must continue to be a high level of engagement and oversight by all adults and agencies involved in these trials to protect children's rights from both a Utilitarian and Rights Theory perspective. And as above, the greater scrutiny and greater degree of protection of a child's rights again originates from the Rights Theory given its evaluation of "Rights Exercised" versus "Rights compromised (or lost)" perspective.

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