Author's Commentary on "Complex Concerns"

Commentary On
Complex Concerns

This case is meant to bring to the forefront some issues related to the testing of pharmacologic agents in children. As is stated in the case, children physiologically are not always just smaller versions of adults. Disease states may present and progress differently in children than in adult counterparts. For these reasons, not all therapeutic drugs can be given to children in smaller dosage with the assumption that the pharmacological effects will be the same as in adults. A drug may be more or less efficacious in children than in adults, and the side effect profile may be different or less tolerable to a younger person. These issues can be resolved only by controlled clinical trials in the target population.

Part 1 of this case focuses on the problems associated with inadequate studies in children and concerns with designing trials involving the pediatric population. The first ethical concern is raised by pediatricians using Eradovir in children although the drug has Food and Drug Administration approval only for adult use. This kind of prescribing practice is known as "off-label usage." A pediatrician may be faced with this prescribing situation if the drug of choice has not been studied in children for a specific disease state. Prescribing drugs in children without adequate clinical studies could be detrimental to the patient; however, it also may be extremely beneficial, especially in life-threatening diseases such as AIDS. The agents used to treat AIDS can be very toxic but, given in proper dosages, they can prolong life. Without adequate study, pediatricians may not have information regarding appropriate dosages and therefore can over- or under-medicate the child, increasing risk. On the other hand, patients may be denied potentially life-saving drugs because rigorous tests have not been performed on their specific age group.

Part 1 also deals with protocol design. Cureall scientists are debating the justification of a placebo arm to the trial. For a clinical study to determine whether a therapeutic agent has activity against a specific disease, a control group is needed for

comparison of the positive and negative effects of the drug. The control group subjects may be given an inert pill known as a placebo, or, if other drugs are available for use in that disease, the test drug may be compared against the currently used agent, called "standard of care." The problem in this case is that there have been no previous clinical trials with antivirals for AIDS in children, and thus no appropriate therapeutic standard of care has been established. Therefore, Eradovir will need to be tested against a placebo to determine whether it is efficacious. A placebo group in the clinical trial will require that some infected children be given an inactive pill. If Eradovir proves to be effective against AIDS, then the children who received placebo will lose essential treatment time; however, if Eradovir is shown to have untoward effects or to be of little benefit, children in the placebo group will have been spared the risk. American Academy of Pediatrics (AAP) guidelines state that a placebo is ethical to use "when there is no commonly accepted therapy for the condition and the agent under study is the first one that may modify the course of the disease process." (American Academy of Pediatrics, 1995a). In the situation described in this case, a placebo group may be ethically and scientifically justified.

The second question Cureall scientists are discussing is whether compensation of study subjects is appropriate. Subjects in many clinical studies receive a small amount of money or gift certificate as compensation for participating. Ethical issues can arise if the amount paid is so high that it may entice people to take risks they would not normally take for the sake of the financial reward. In the Eradovir study, $100 will be given for every month of study completed in addition to free medical checkups. Since the clinical centers that will be conducting the study are urban hospitals, there is a great chance of having a large percentage of subjects from low-income backgrounds. The study design must guard against parents deciding to enroll their child, regardless of the potential risks associated with Eradovir, for the $100 per month and free medical care. An extra $100 per month may not appear to be a large sum of money, but it may be significant for disadvantaged families. Compensation for any study must be carefully evaluated to minimize the risk of subjects enrolling for financial gain regardless of the risks associated with the study.

In addition to determining participants' compensation, the investigators must decide whether the money will go directly to the child or to the parent/guardian. Is it the child's money or the adult's? The parent or guardian is the one providing the overall care for the child and is responsible for getting the child to the physician's office for

study participation. They are taking time out of their schedule and could be taking time from work. However, the child's body is the one being used to conduct the experiment. It seems more ethically appropriate for payment to go directly to the child than to the parent/guardian. Of course, writing a check in the child's name will not guarantee that the child will receive the money. Also, to most children mature enough to understand the value of money, $100 is not a trivial amount. Such issues need to be carefully evaluated while developing the protocol.

The case continues with Part 2, describing a scene in a physician's office with a foster mother (Mary), the foster child who has AIDS (Liz) and the physician (Dr. Kid). Dr. Kid, an investigator involved with Cureall's Eradovir protocol, is trying to recruit Liz as a study subject. The first ethical issue is addressed by Question 1: Dr. Kid reassures Mary about Eradovir's potentially serious, even fatal, side effects. Could Dr. Kid's comments be considered coercion? Dr. Kid's responsibilities are to answer accurately all of Mary's questions and concerns regarding the protocol. Although Dr. Kid is correct in telling Mary that the fatal side effects are rare and that none of his patients has ever suffered from them, it is inappropriate to tell her that he is unlikely ever to witness such adverse events in his patients. Dr. Kid has no way to determine if one of his patients will suffer such problems from Eradovir therapy in the future. After downplaying the negative effects, Dr. Kid highlights all the potential benefits of therapy. His behavior would be considered coercive. Dr. Kid should be honest in telling Mary that Liz could develop a serious and potentially fatal complication, no matter how rare. Further, quickly refocusing Mary on the potential benefits of being a patient in the study is a way of enticing her.

This case is made more complex by Mary being Liz's foster mother rather than her biological parent. Whether or not a foster parent can enroll a foster child in a trial depends on the laws of that particular state (Levine, 1991). Unfortunately, children may be orphaned by AIDS. We will assume that this case is taking place in a state that allows foster children to be enrolled in clinical studies.

Question 2 focuses on Mary's decision to allow Liz's participation and whether the decision is easier to make since she is not a biological parent. That is a very difficult issue to address. Mary, like most foster parents, may be as loving to Liz as she is or would be with her biological children. Just because a child is not a biological offspring does not mean that a foster parent cannot provide as good or possibly better care than the biological parent. Both biological and foster parents are capable of providing loving and nurturing environments; however, both groups can provide

unhealthy environments as well. It is unfair to assume that Mary is not giving Liz a wonderful home.

Dr. Kid's role here is to evaluate the relationship between Liz and Mary and to try and determine if it is adequate. He definitely needs to take the foster relationship into consideration. How long has Mary been Liz's foster mother? Does Liz appear happy with Mary? Does Mary have a history of providing foster care and, if so, is it a good record? Does Mary have biological children, and, if so, were/are they well cared for? As with all families he encounters, Dr. Kid needs to evaluate how the parent views the child. The child needs to be protected against enrollment in the study for inappropriate reasons (i.e., financial/medical incentives).

Question 3 raises the issue of assent. In the case, Liz is a 3-year-old child and thus too young to intellectually assess the situation and the associated risks and benefits. Typically, assent is sought from children who have an intellectual age of at least 7 years, in addition to parental permission (American Academy of Pediatrics, 1995b). If Liz were a 10-year-old of normal mental capacity, assent should be required for her participation in the study. If she were to decline enrollment it would be unethical to use coercive measures, financial or otherwise, to induce her to participate.

In Question 4, readers are asked to reflect on whether they would allow their own children to enroll in the Eradovir study. Most people would probably agree that there is good medical and scientific reason to study pharmacologic agents in children. However, whose children should be study subjects? If Liz were your offspring, would you allow her to participate in this clinical study knowing she will exposed to the risk of developing severe and possibly fatal side effects? On the other hand, the therapy may extend her life and improve her quality of life. This question really is posed to get the reader to think more personally about research in children. It may seem necessary, as long as the studies do not involve their children.

This case touches on only a few of the ethical issues related to children's participation in research. As difficult as the concerns may be, the knowledge gained from such studies is worth the effort. Carefully devised research protocols aimed at answering questions regarding children's health will allow for better treatment of pediatric populations, but they must guard against unnecessary risk.

References

- American Academy of Pediatrics Committee on Drugs. "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations." *Pediatrics* 95 (1995a): 286-294.
- American Academy of Pediatrics Committee on Bioethics. "Informed Consent, Parental Permission, and Assent in Pediatric Practice." *Pediatrics* 95 (1995b): 314-317.
- Levine, C. "Children in HIV/AIDS Clinical Trials: Still Vulnerable after All These Years." *Law, Medicine and Health Care*. 19 (1991): 231-237.