APPROPRIATE COMPENSATION OF PEDIATRIC RESEARCH PARTICIPANTS: THOUGHTS FROM AN INSTITUTE OF MEDICINE COMMITTEE REPORT

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Over the past century, the health of children in the United States has dramatically benefited from advances in biomedical research, including vaccines that have nearly eradicated polio[1] and chemotherapy to treat pediatric cancer.[2] All of these medical advances resulted from clinical research involving children as participants. The critical role of well-designed research involving children continues today as we translate the scientific knowledge gained from genomics, proteomics, and other frontiers of molecular biology into new life-saving therapies for a variety of pediatric disorders. Yet in recent years, the majority of studies testing safety and efficacy of new medications have included only adults. Even in the past decade, only 20% of new drugs have been approved for pediatric labeling.[3] As a result, clinicians caring for children are frequently forced to empirically treat children with therapies untested in this population. Legislation in the late 1990s, including the US Food and Drug Administration (FDA) Modernization Act of 1997[4] and the subsequent FDA "Pediatric Rule" in 1998,[5] has provided both incentives and requirements to pharmaceutical companies to test the safety and efficacy of drugs in children. Congress subsequently passed the Best Pharmaceuticals for Children Act of 2002,[6] extending the Pediatric Exclusivity Act of 1997 to 2007 and thereby providing 6 months additional market exclusivity to companies that test the safety and efficacy of their drugs in children. In addition, this Act established a federal funding program to study drugs off-patent for pediatric usage. Although it is very encouraging that these measures should provide children more rapid access to new therapies, we, as a society, must always balance this acquisition of new knowledge against the protection of these vulnerable research participants who lack the legal right and, frequently, intellectual capacity to decide whether they wish to accept risk for uncertain benefit. Because of concerns about the adequacy of the system for protecting child participants in research, the Best Pharmaceuticals for Children Act of 2002[6] requested that the Institute of Medicine (IOM) prepare a report reviewing federal regulations and recommending optimal practices for the ethical conduct of research involving children. The IOM established a 14-member committee, chaired by Dr Richard Behrman, in January 2003 to focus on seven charges outlined in the Act, including: (1) the appropriateness of the regulations for children of various ages; (2) the interpretation of regulatory criteria for approaching research; (3) the processes for securing parents' and children's agreement to a child's participation in research; (4) the expectation and comprehension of children and parents about participating in research; (5) the appropriateness of payments related to the child's participation in research; (6) compliance with and enforcement of federal regulations; and (7) the unique roles and responsibilities of Institutional Review Boards (IRBs).[6,7]

The committee reviewed federal regulations, as well as existing data in the literature and federal reports. Public forums were held to receive input from patients, families, advocacy groups, and professional societies. The committee formed a consensus and developed both overarching themes and recommendations that were published in a book entitled, *Ethical Conduct of Clinical Research Involving Children*.[7] I had the opportunity to participate as a member of this committee and to share in the provocative and enlightening discussions as we all weighed the critical balance between furthering knowledge and protection against harm. It is beyond the scope of this article to review all aspects of the IOM report. I will focus on one of the important charges we addressed: whether payment (financial or otherwise) may be made to a child, parent, guardian, or legally authorized representative for participation of the child in research.[6]

PAYMENTS TO CHILDREN FOR RESEARCH PARTICIPATION

As the committee reviewed the limited existing data from the literature regarding payment of pediatric research participants, we weighed the difficult balance between the use of monetary or other forms of compensation to incentivize research participation versus protection of children and families against undue influence of the perceived reward.

To make our recommendations, we carefully reviewed federal regulations and subsequent guidance documents from federal agencies, including the Office of Human

CF	Cystic fibrosis	IOM	Institute of Medicine
CFR	Code of Federal Regulations	IRB	Institutional Review Board
FDA	US Food and Drug Administration		

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Research Protection and the FDA. We also looked to professional societies or international councils that have previously considered the ethics of payment of children for research. We considered the types of payments to children, parents, and guardians that were or were not appropriate, and who should make these decisions, and we discussed the circumstances that bring the child and family to seek medical care and how that may impact compensation. The reader is encouraged to read Chapter 6 of the committee report,[7] which summarizes the committee's recommendations.

The federal regulations provided in 45 Code of Federal Regulations (CFR) 46[8] and 21 CFR 50[9] are not prescriptive with regard to the type or amount of monetary or other compensation to research subjects of any age. Rather, they provide principles upon which institutional boards and investigators should make their judgment. It is stated in 45 CFR 46.116 and 21 CFR 50.20 that informed consent must be sought "under circumstances that minimize the possibility of coercion or undue influence" and that participants must be provided "a statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled" (45 CFR 46.116 (a) and 21 CFR 50.25 (a)). The key ethical concept of these regulations is minimizing undue influence, which is essential to the concept of a voluntary consent process. Undue influence could result from the size of the inducement, the method of payment (eg, requiring subjects to complete a study before payments), or the penalty of withdrawal from research (eg, loss of free medical care). All these ramifications of payment must be considered.

More recently, two guidance documents have more directly addressed payments for patient recruitment, including pediatric research. In 2000, the FDA issued a guidance developed by the International Conference on Harmonisation entitled, Guidance on E11 Clinical Investigation of Medicinal Products in Pediatric Population.[10] Excerpts from this report state that "the pediatric population represents a vulnerable subgroup. Therefore, special measures are needed to protect the rights of pediatric study participants and to shield them from undue risk." The report goes on to state that recruitment (Section 2.6.2) of study participants "should occur in a manner free from inappropriate inducements either to the parent(s) or legal guardian or study participant. Reimbursement and subsistence costs may be covered in the context of a pediatric clinical study. Any compensation should be reviewed by the IRB/IEC." The Council for International Organizations of Medical Sciences was even more detailed and prescriptive in its *Ethical Guidelines for Biomedical Research Involving Human Subjects*, Guideline 7.[11] It states that "subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment (undue inducement). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee." With regard to vulnerable subjects, the guidelines state that "a guardian asked to give permission on behalf of an incompetent person should be offered no recompense other than a refund of travel and related expenses."

Federal regulations and guidance place the review process for patient recruitment, including monetary or other inducements, as a responsibility of IRBs (45 CFR 46.116 and 21 CFR 50.20). FDA guidance recommends that IRBs "review the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence."[12] Based upon limited published data[13] from a survey of IRBs reviewing pediatric protocols, it appears that only a minority of boards have any written policy or formula for determining a monetary value for appropriate payment. Of the 128 institutions responding (36%), 84 (66%) had approved payment to children for participation, of which 42% approved payment to both parent/guardian and child, 31% to parent only, and 19% to child only. A second study surveying nonpediatric IRBs[14] also found that only a minority has written guidelines. Not surprisingly, the IRB policies tend to follow federal guidance and require disclosure of payment to parent/guardian and child during the informed consent process before enrollment. This approach contrasts with the 1995 guidelines published by the American Academy of Pediatrics Committee on Drugs.[15] This guideline accepted the use of payment to children for research participation, but it recommended that "it [remuneration] is not discussed before the study's completion" and should not go beyond a token gesture to minimize undue influence.

The IOM committee also sought data on the frequency and types of payment that are currently being provided to pediatric research participants. There is, unfortunately, very limited data available on payment of pediatric participants. A review of one public listing of clinical trials, Centerwatch,[16] in 2000, suggested that approximately 25% of pediatric trials offered payment.[17] This lack of published data is not surprising because there has been no systemic collection of data on the number and type of clinical trials in the United States or number and demographic information on research participants. Thus, it is impossible to ascertain the true scope of payment practices. Recommendations from two IOM committees, *Responsible Research: A Systems Approach to Protecting Research Participants*[18] and *Ethical Conduct of Clinical Research Involving Children,*[7] stressed the importance of obtaining such data on clinical research. The recent statement by the International Committee of Medical Journal Editors[19] has recommended registration of all clinical trials that may impact clinical practice. Although payment practices are currently not part of the information collected in this registration process, at a minimum these recent changes will allow investigators and consumers to better understand the research process and its ethical conduct.