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Can Children Participate in Research?

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The focus on pediatric research in this edition of *The Ochsner Journal* emphasizes the importance of research studies for the health of children. This focus also provides an opportunity to reflect on the ethical concerns raised when the subjects in this very vulnerable population are not able to provide consent for their own participation.

Most philosophers would argue that informed consent provides the foundation for ethical research. Reconciling the primacy of informed consent in the ethical conduct of research with the special circumstances imposed by the maturation of intellectual function as children grow and develop presents a significant challenge. Consent as generally conceptualized is not possible in children. As early as 1931, the Reich Circular[1]—which documented the rules for research in pre–World War II Germany—emphasized the primacy of consent for research and incorporated rules that recognized the difficulty imposed by the inability to obtain consent from children. The document included the following caveat: "The question of whether to use innovative therapy must be examined with particular care where the subject is a child or a person under 18 years of age."[1]

The response to the atrocities committed in the face of the extensive directives formulated in the Reich Circular produced the Nuremburg Code that many believe explicitly prohibits the participation of children in research. The code states, "the voluntary consent of the human subject is absolutely essential"[2] and makes no provision for exceptions to this rule. The conflict of this prohibition with the importance of research in special populations unable to provide consent was recognized and addressed in the first rules for research by the World Medical Association, the Declaration of Helsinki in 1964.[3] The declaration stated, "clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured."[3] Because this statement was ambiguous with respect to children, the statement was revised in 1975 with the addition of following provision: "where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation."[4]

In the United States, research was transformed by the deliberations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, appointed in 1974 in response to concerns that unethical research practices might be endemic in research involving human subjects. These debates culminated in the publication of *The Belmont Report* in 1979.[5] *The Belmont Report* proposed that adherence to 3 basic principles—respect for persons, beneficence, and justice—would provide the foundation for ethical research.

Leading up to the landmark *Belmont Report*, the commission's deliberations produced *Research Involving Children* in 1977.[6] This report outlined the unique nature of scientific questions in children and the importance of addressing these questions as matters of justice and beneficence. The commission contrasted questions of potential benefit to the general welfare of children by including them in research studies against questions of respect for persons raised by the participation of minor subjects in research without specific consent.

The commissioners also carefully considered the evidence for evolution of the ability to participate in a meaningful consent process as children mature against seemingly arbitrary definitions of a means to evaluate the ability of an individual to participate. The commissioners' considerations clearly favored the arguments that an ethical imperative exists to allow children to participate in research and that consent by parents or guardians alone does not balance the equation without some provision for developmentally

appropriate agreement by the child to participate. This latter concept does not meet the requirements of consent, but rather is embodied in the concept of assent: a developmentally appropriate understanding of the reasons that participation in the research proposal is needed, reasonable understanding of the procedures that may be involved, and agreement by the child that he or she will voluntarily participate. Furthermore, respect for persons requires that the child may withdraw assent for participation in the research at any time, just as competent subjects may withdraw from a research protocol at any time after providing consent. The commission voiced support for this process of assent that is similar to the process adopted in 1975 for all intramural research at the National Institutes of Health Clinical Center.

The seminal concepts introduced in *The Belmont Report* led to a complete reformulation of the rules for conducting research involving human subjects supported by funds from Health and Human Services. These rules were codified at 45 Code of Federal Regulations (CFR) Part 46—Protection of Human Subjects in 1983. The detailed recommendations in the 1977 *Research Involving Children* report served as the basis of the regulations guiding participation of pediatric subjects that were enacted as Subpart D of this reformulation of the federal rules. This original formulation has weathered the test of time, with only minor revisions of Subpart D since the initial publication.

Although the regulations in 45 CFR Part 46, Subpart D,[7] serve as a landmark in pediatric research, the provisions for assent in the federal regulations were promulgated with little specific guidance and did not incorporate all of the commission's recommendations. The rules indicate that most decisions regarding assent should be made by the local institutional review board (IRB) with many possible exemptions. The conflict between the ideal of participation in research by only those capable of consent and the importance of research to advance the care of children unable to provide consent has led to sometimes contentious debate regarding the requirements for obtaining meaningful assent. Such debate frequently occurs in IRBs empowered to enforce the rules for research participation, as well as among investigators required to follow the practice of obtaining assent as defined by their local IRB. The problem is further fueled by the ethical debate of philosophers questioning the very participation of children in research and whether assent can play a role in mitigating their ethical concerns. The inability of developmental experts to provide the tools to ascertain meaningful participation in assent for any proposed research does little to modulate these conflicts.

Also, the limited guidance from Subpart D does little to inspire confidence in this process, particularly with the exemption noting that in circumstances where "the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research."[7] This paradigm of research-driven treatment, exempt from the absolute requirement for assent, has produced remarkable advances in survival in childhood cancer. Success in treating formerly lethal diseases clearly justifies research in children as supported by the principles of justice and beneficence. Unfortunately, to some it may appear that respect for persons has taken a back seat in this circumstance where assent is not required because there is significant potential benefit to the subject (the patient) in these studies, blurring the distinction between research and treatment.

How then to reconcile the seemingly irreconcilable imperatives for advancing the health of children as supported by the principles of beneficence and justice with the inability to obtain consent that is necessary to fulfill the respect for persons requirement? Assent appears to mitigate these concerns if the process is meaningful. In the absence of clearly defined protocols for defining the ability of a child to provide assent and with no clear consensus on the definition of meaningful assent, the burden falls on the investigator to go beyond the regulatory requirement of obtaining assent that, according to the rules of the IRB of record, may be met by perfunctory documentation that assent has been obtained. The ethical requirement for assent extends beyond this regulatory burden. The diligent investigator, mindful of the principle of respect for persons, will seek meaningful assent even in those cases where the IRB and federal regulations may not require assent. If assent is not given and the research is pursued under the umbrella of providing treatment, satisfying the respect for persons obligation requires careful explanation in a developmentally appropriate manner of the reason for continuing the study.

As with all matters of ethics in research, the commitment of the investigator to ethical conduct in research will determine the quality of the assent process and whether it fulfills the requirement of respect for persons as intended by the commissioners in *The Belmont Report*, regardless of the regulations. The individual investigator is responsible for ensuring that the child subject has a developmentally appropriate understanding of his or her role in any

proposed research in exchange for the privilege of conducting research in this very vulnerable population.

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