Editorial

The Challenge of Informed Consent in Neonatal Research

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The modern doctrine of informed consent dates back only about a half century to the Nuremberg Code. Its first premise “The voluntary consent of the subject is absolutely essential” established the bedrock principle of protection of human research subjects. In subsequent decades, some investigators ignored the Code in the belief that it was written for criminals rather than for well-meaning scientists. In 1964, its relevance for physician-investigators was articulated clearly in the World Medical Association’s Declaration of Helsinki. Still, it was not until the US National Research Act of 1974 created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research that things began to change. The Commission’s work led to the Belmont Report and the Code of Federal Regulations. The latter established Institutional Review Boards. Only after these were in place did informed consent become the norm for US investigators whose research involved human subjects.

From that shaky beginning, the understanding and practice of informed consent has matured, slowly but surely. While the letter of the law can be fulfilled by a signature on a piece of paper, the spirit demands more. Informed consent is properly thought of as a process, rather than a document. To be sure, the document is a necessary record, but to be truly informed a prospective subject needs a discussion with the investigator, an opportunity to ask questions and to have them answered. Even given that process, misunderstandings abound in research that involves treatment of ill subjects. In this setting, the physician-investigator has two roles and two sets of obligations. The duties of a physician to a patient are different from the obligations of a researcher to a research subject and to science. At times these differing obligations may be in conflict. The patient-subject must also be seen in two perspectives, as patient and as research subject. If it is difficult for physician-investigators to appreciate these differences, it may be nearly impossible for patients (and parents of patients) to do so.

The term “therapeutic misconception” describes this conflation of treatment and research. It is perhaps most prevalent in Phase I clinical trials of chemotherapeutic agents for treatment of cancer. The stated purpose of Phase I trials is to establish dose-limiting toxicity, not to provide direct benefit to the subjects. Yet, in one study,¹ 85% of cancer patients in a Phase I trial said that they enrolled for reasons of possible therapeutic benefit.

Given the tendency for subjects to misunderstand the purpose, risks and benefits of research that involves treatment of sick individuals, it is appropriate that investigators look critically at their consent process and ask “What did the patient (or parent) understand?” In this issue of the Journal, Ballard, et al.² report on having done just that. Parents whose infants had been subjects in the NEOPAIN study were interviewed later to determine whether the parents had adequate knowledge to provide valid informed consent. Their findings, though disturbing, are similar to those of many other studies evaluating validity of consent for participation in research. Among the 64 parents interviewed, five (7.8%) had no recollection of the study. Of those who did remember the study only 68% could state the purpose. Most disturbing is that only 5% could name even one risk of the study. Using a stringent set of criteria, only 3% of parents were considered to have given valid informed consent.

These are sobering findings for neonatologists who seek to enroll their patients in clinical studies. What could account for this apparent lack of understanding? First, one must ask whether the investigators provided the right information, at the right time, in the right manner, and in the right setting. Although such an assessment could only be made by a third-party observer, the measures taken by the original study team to assure adequate communication seem appropriate and were probably equal or superior to those generally employed. Second, parents’ circumstances, including the stress of having an imperiled infant, the large volume of clinical information and the uncertainty of the outcome may be unavoidable factors that overwhelm parents’ ability to comprehend information. Third, parents’ trust in their infants’ physicians may have replaced their careful attention to what they were being told. Finally, interpretation of the findings would seem to be limited by the long time intervals (3 to 28 months) between the study and the parent interviews. There was

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poor correlation between length of the interval and parents' recollection; nevertheless, even 3 months may erase memory in parents who are coping with the stresses of rearing a premature baby.

The authors conclude that obtaining valid consent in the antenatal/perinatal period is difficult, if not impossible, to obtain. There can be no argument about the difficulty, but we should not consider the task impossible without further efforts to improve the process. Ballard and associates suggest a number of ways in which the process of seeking informed consent may result in better understanding; they believe that an institution-specific analysis to determine areas of deficiency may be needed. Such an analysis might include attention to the timing, the setting, and the manner of presentation, as well as the content of information presented to parents. A "reader-friendly" consent form, void of medical jargon,

is a necessary but not sufficient component of the process. A disinterested third-party observer might point out communication failures that are not apparent to members of the research team. It is clear that a major research task lies ahead, to test ways in which the process of informed consent can become more effective.

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