Research on Persons With Impaired Decision Making and the Public Trust

Biomedical research on human subjects involves risks, intrusions, and burdens. It is also of immense social value; advances in health care would be virtually impossible without it. Most important for the ensurance of the rights of potential subjects, along with the benefits of potential knowledge, is the ethics of medical scientists. These are reinforced by the notion of informed consent, a concept introduced into clinical medicine by New York State Justice Benjamin Cardozo in 1914, who said, "Every human being of adult years and sound mind has a right to determine what shall be done with his own body" (1). But what of children or those who are not of sound mind, that is, those who do not have the legal capacity to consent? At times, studies of alternative subjects can provide similar information, but this is often impossible, as in studies of disorders that themselves impair decision-making capacity.

The choice is either depriving these populations and, inevitably, all of us of the potential benefits of such research (including even denying individuals the right to make decisions about their future before the loss of capacity) or developing acceptable alternatives to informed consent.

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What is to be done?

The last half century has been marked by a recurrent cycle of

1. Egregious abuse of vulnerable subjects, including those with impaired decision-making capacity, followed by
2. A review of the problem and subsequent policy suggestions with the primary concern of protecting potential subjects, leading to
3. A critical response and rejection of these suggestions by the professional and research community, protesting that they would obstruct the research enterprise, resulting in
4. Some change but failure to develop a general solution, with the most difficult problems being delegated, without clear guidelines, to individual investigators, institutional review boards, or research institutions.

We have been left with a hodgepodge of practices, with decisions often made by those with little authority or expertise and implemented with little consistency or reliability.

Perhaps the first round of this cycle started with the disclosure of the experiments of the Nazi physicians, followed by the formulation in 1947 of the Nuremberg Code, which extended the concept of informed consent from clinical care to research, stating that "The voluntary consent of the human subject is absolutely essential" (2). Henry Beecher, a prominent clinical researcher and bioethicist, responded that this principle would "effectively cripple if not eliminate most research in the field of mental disease" (3). One major cycle was triggered by the Willowbrook experiments, which injected hepatitis virus into retarded children, and the Tuskegee research that observed the course of untreated syphilis in poor rural blacks. A National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was appointed to conduct an investigation and make suggestions, many of which were accepted (4). Guidelines for children were implemented; however, in spite of the commission's urging, the federal government responded to the concerns of the scientific community by failing to issue any guidelines for adults with diminished capacity.

Most recently, in the late 1990s, after publicity regarding human radiation experiments with individuals at risk for impaired decision making and the suicide of a former research subject, a new National Bioethics Advisory Commission conducted a comprehensive study and issued a report: "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity" (5), which included 21 recommendations. Once again, the field responded strongly and negatively. New York (6) and Maryland (7) both appointed state commissions with greater psychiatric representation, whose recommendations differed significantly from those in the national report. There were a number of critical articles and editorials, the flavor of which is conveyed by the title of my piece in the *New England Journal of Medicine*: "Are Research Ethics Bad for Our Mental Health?" (8). The National Bioethics Advisory Commission recommendations were first modified by the National Human Research Protections Advisory Committee (9), the official advisor to the secretary of health and human services, and even then were not adopted (10). The basic situation remains unchanged: a regulatory vacuum with decisions delegated to individual investigators, institutions, and institutional review boards; bioethicists and patients' and subjects' rights groups wanting tighter controls; scientists and disease-oriented support groups fearing them; and politicians and policy makers ducking for cover.

In this issue of the *Journal,* Kim and colleagues discuss the issue from the perspective of a July 2002 workshop convened by the National Institute of Mental Health's Aging Research Consortium. Although their interest is proxy consent in geriatric neuropsychiatric research, the fundamental issues relate to all research on subjects with impaired decisional capacity.

They make clear that while the dilemmas are long-standing, and the solutions continue to be unclear, there is a new context. The science is more promising, while an energetic patients' and subjects' rights community is more suspicious of researchers. As increased public attention has focused on the problem, institutional review boards and their institutions have shifted from permissive to risk-reduction management approaches. In the past, while formal policy was inadequate and actual practice haphazard, there were few real barriers to the conduct of uncontroversial research. However, we are now entering an era in which the absence of clear guidelines not only fails to safeguard subjects but also threatens the research enterprise.

The workshop's recommendations focus on two issues: 1) clarification of the selection and role of surrogates (e.g., legally authorized representatives), traditionally a matter for individual state legislation but one that most states have failed to address, and 2) research oversight, traditionally a matter for federal regulation but when it comes to the decisionally impaired is currently without clear guidelines. It argues that the current ambiguities are interfering with both goals—protection of subjects and facilitation of valuable research—and that the time has come for change.

There is another issue that the workshop recommendations do not discuss: the underlying reason for public mistrust. Why are medical scientists increasingly viewed with misinformed mistrust (rather than, as in earlier years, with uninformed trust)? One reason is the common perception that some clinical research is pursued for the commercial gain of the sponsor or the personal gain of the investigator as much as for public benefit and that subjects must be protected from the sponsor's and the scientist's conflicts of interest as much as from the inherent risks of research. The profession should respond to this perception, and research with decisionally incapacitated subjects is a good place to start. Institutional review boards should ensure that any research involving human subjects has been designed with the primary goal of social value. This would exclude studies in which investigators were not free to publish results or pharmacological protocols designed to obtain regulatory approval that could be but are not modified so that they would be more useful in enlightening clinical practice. This principle should apply to all research, but we know that in practice it has often been ignored. The

institutional review board's assurance to any prospective surrogate that research involving the decisionally incapacitated will be held to this standard would be a good place to start. This could be a first step toward extending it to all human subjects research, thereby helping to regain the public's lost trust of medical scientists.

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