Publication of Unethical Research Studies: The Importance of Informed Consent

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Scientific research on human beings has been reported since the 18th century, when prisoners at Newgate were pardoned if they agreed to undergo variola vaccination (1721), and Edward Jenner began a series of cowpox vaccinations in children (1776) [1]. No ethical guidelines existed, however, until Thomas Percival wrote, in 1803: “...It is for the public good...that new remedies and new methods of chirurgical treatment should be devised [emphasis Percival’s]... And no such trials should be instituted without a previous consultation of the physicians or surgeons according to the nature of the case” [2]. Percival did not mention protecting the interests of human subjects. It was not until the 19th century that William Beaumont, writing about his classic experiments on Alexis St. Martin, expressed the view that research should be carried out only on subjects who voluntarily consented [3].

One of the earliest official guidelines for human research that required informed consent was promulgated in 1931: “Innovative therapy should be carried out only after the subject has unambiguously consented to the procedure in the light of relevant information provided in advance” [4]. It is an irony of the history of medical research that this statement was part of a broad, forward-looking research policy—the Reichsgesundheitsrat Circular—developed in Germany. For it was the atrocious German human experimentation of the Nazi era that led to the Nuremberg Doctors’ Trial of 1946 and the resulting Nuremberg Code, the first international research guidelines. The Code consisted of 10 succinct principles. To emphasize the importance—indeed, the primacy—of consent, the very first line of the Code states, “The voluntary consent of the human subject is absolutely essential.”

Recognizing the need for more detailed guidelines for medical research, the World Medical Association developed and approved such a document at its General Assembly in Helsinki in 1964. The Declaration of Helsinki has been revised five times, most recently in October 2000. The central purpose of this document is to protect human research subjects, including the requirement of voluntary consent of all human subjects of medical research [5]:

20. The subjects must be volunteers and informed participants in the research project.
22. ...The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject’s freely given informed consent.

After notorious research abuses in the United States, exemplified by the Tuskegee syphilis experiments (1932 to 1972) [6] and the Willowbrook hepatitis study (1956 to 1972) [7], the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974. The Commission met at the Belmont Conference Center of the Smithsonian Institution from 1974 to 1978, producing a set of national guidelines for clinical investigations, called the Belmont Report [8]. Later, this document formed the basis for the promulgation of federal regulations in 1981 that were later revised (in 1983 and 1991) and adopted by 16 federal agencies (and is therefore referred to as the “Common Rule”) [9]. The Common Rule spelled out in great detail how federally funded human research studies should be carried out. Most Western countries have similar guidelines for human research. Whether or not particular nations have their own guidelines, researchers in every country are expected, at a minimum, to adhere to the ethical practices described in the Nuremberg Code and the Declaration of Helsinki.

These guidelines are not laws to be enforced by law enforcement agencies. Several mechanisms are available for assuring compliance with them, including oversight by sponsors, institutions, and review boards, and policies of the journals to which manuscripts are submitted for publication. I will focus on journal policies.

A Case of Unethical Research

A prospectively randomized investigation of the role of postoperative radiotherapy in the treatment of squamous cell esophageal cancer is reported in this issue of The Annals of Thoracic Surgery [10]. The study was carried out by Dr Xia and her coworkers during a 12-year period, from 1986 through 1997, and is the largest such study to date. The conclusion of The Annals peer review process was that the study, which showed a clear benefit of...
postoperative radiation, makes an important contribution to knowledge about the treatment of esophageal cancer.

Yet, serious ethical concerns can be raised by this study: the subjects of this clinical investigation were not informed that they were part of an investigation and did not consent to being a subject. Does this study constitute "research," and do the guidelines of the Declaration of Helsinki therefore apply? What is the nature of the ethical violation? Is the label " unethical" appropriate? Is the ethical transgression serious enough to warrant exclusion of this study from publication in a scientific journal?

The context of the investigation was clinical care of patients. Clinically, no indication of a serious ethical breach is evident. The patients had the right of refusal: if they did not agree to surgery or did not agree to radiation therapy after surgery, these procedures were not forced on them. Treatment was apparently voluntary and carried out according to accepted standards of clinical practice. This study was not egregiously unethical, on the order of the Nazi experiments or Tuskegee. The cancer treatments used in both arms of the study were standard procedures, used by many surgeons throughout the world. The Peking Union Medical College, where the study took place, is generally considered to be the most prestigious medical school in China, and there is no apparent reason to question the scientific integrity or benevolent intent of the treating surgeons.

Was this study " research"? A widely accepted definition of research is this: "Research means a systematic investigation...designed to develop or contribute to generalized knowledge" [11]. The study in question was designed meticulously in advance, and was carried out systematically with the intent to publish the results; therefore, it clearly was research.

In considering the ethics of the study, societal factors may be relevant. The social setting in which these surgical scientists work is not conducive to the kind of ethical concerns for patients that predominate in the West. The People's Republic of China is an authoritarian state that practices political repression, social control, and has been accused of many human rights abuses, well documented by international human rights agencies and by the State Department of the United States [12]. Among them are such medical abuses as forced abortions and sterilizations. Although the People's Republic of China has signed the Declaration of Helsinki, informed consent has not been a tradition in that country. Patients are informed of their diagnoses and told what treatment is needed. Quiet acquiescence is the rule, not informed consent. A clinical trial, complete with all the requirements of an institutional review board, would be difficult to carry out in such a sociopolitical environment.

In view of these factors—that this study was a research investigation; that the absence of informed consent violated the Declaration of Helsinki's ethical guidelines for research, yet the social context is not conducive to informed consent; and that the subjects were clinically well treated—should the study be labeled unethical? Again, the answer clearly is yes. Medical abuse or absence of abuse of research subjects is not the issue here. The ethical transgression was that patients were not informed that they were participating in research and were not asked for their consent to be part of a research project. This offense is not a trivial ethical violation, but breaches an internationally accepted fundamental tenet of ethics: individuals have a right not to be used merely as a means to the ends of others. The universality of this basic right is set forth in the Declaration of Helsinki's Principle 9: "...no national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration" [5]. Any nation may develop policies or permit practices that contravene international guidelines, but actions of this kind place them outside the boundaries of acceptable behavior and engender the possibility of sanctions in response. One such potential sanction is refusal of publication by medical journals.

Ethics of Publication

Given that the Xiao study is scientifically valid and contains valuable information, but nevertheless violates internationally accepted ethical principles of research, how should editors approach the question of publishing such research? The Declaration of Helsinki provides an unambiguous answer to this question in Principle 27: "Both authors and publishers have ethical obligations... Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication" [5]. The suggested prohibition of publication is not universally accepted as absolute, however.

Medical journal editors have debated this issue for many years. Many editors may not pay attention to the Declaration of Helsinki's Principle 27 because they are unaware of its existence. Some have been reluctant to make decisions regarding what constitutes an unethical study, preferring to leave such judgments to investigators, research sponsors, and institutional review boards. In the case of clinical studies carried out in areas of the world that have social structures radically different from those in the United States, editors may tend to accept differences in political and social environments, consciously avoiding imposition of Western values on other cultures [13]. Yet, the underlying rationale of the Nuremberg Code and the Declaration of Helsinki in its several iterations is the universal nature of certain rights, in particular, the right to control one's own destiny (including the right not to participate in research as a research subject). The Nuremberg Code was formulated specifically to denounce as morally culpable and unacceptable all violations of the rights of research subjects by authoritarian and politically repressive governments. With this view, cultural differences cannot justify ignoring fundamental individual rights.

Two groups of editors have commented on publication of unethical studies. Guidelines published by the International Committee of Medical Journal Editors have
suggested only that a statement accompanying human research reports should indicate "whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration" [14]. The Council of Science Editors, on the other hand, has been more explicit and exacting: "Editors can and should play their part in upholding ethical standards by refusing to publish reports of work that violates human rights even if the work seems scientifically valid and important" [15]. They reasoned that systematic refusal by editors to publish unethical research would provide a powerful incentive to scientists to avoid ethical transgressions, because publication has been the main route to legitimizing the work of investigators and remains one of the central factors leading to academic advancement.

It seems reasonable, therefore, to expect that a clear policy not to publish unethical studies would be an adequate deterrent to future ethical breaches. Refusal to publish unethical studies also reinforces the primary importance of protecting the interests of research subjects above all other considerations in research. For physicians as scientists, dissemination of scientific knowledge is not and should not be the ultimate value; sharing information should not be allowed to trump such preeminent values as respect for individual rights.

Recognizing the importance of respect for individual rights, we can ask whether competing values exist that may favor publishing a narrowly defined group of unethical research studies. In a closely reasoned analysis of the uses of information derived from unethical experiments, the Council on Ethical and Judicial Affairs of the American Medical Association has argued that besides respecting individual rights, preservation of human life is also a primary tenet for physicians [16]. The Council's report concluded: "If ethically tainted data that have been validated by rigorous scientific analysis are the only data of that nature available, and such data are necessary in order to save lives, then the utilization of such data by physicians and editors may be appropriate" [16]. They also suggested that if such a study is published, it should be accompanied by an editorial disclaimer describing what the ethical violation was and why publication is nevertheless justified.

Along similar lines, Levine [17] has suggested that unethically conducted valuable research should be published, as long as it is accompanied by both an editorial describing the transgression and an invited response from the investigators. He cited several harmful effects of withholding publication. The scientific community would be deprived of useful information, and repeating the study with a new set of subjects would expose those individuals to the risks of the study in order to obtain information that was already available; that in itself could be considered an ethical violation. Withholding publication would hide from view the fact that unethical research is being done, whereas publication would expose such studies to public discussion and would reinforce the importance of ethics in research. The usefulness of public discussions of controversial ethical issues has been demonstrated in a collection of such exchanges [7].

The responsibility for deciding to publish an ethically flawed investigation belongs to a journal's editor. To justify publishing such a study, editors should weigh the preeminent ethical requirement to respect individual rights against the value of the information in the study and other mitigating factors. The Annals' editors and peer reviewers have judged the research of Dr Xiao and her colleagues to contain valuable information, and have elected to publish the study. An editorial note describing the ethical lapse and the mitigating factors that justify publication, and emphasizing the importance of ethics in human research accompanies the article.

The steadily growing rate of submission and publication in The Annals of human research studies from other nations, including those with clouded human rights records, suggests the need for continual vigilance for ethical transgressions and insistence on high ethical standards for research studies. Publication of this ethically flawed study carries with it the hope that the information derived from the results will be of great value in the care of our patients, but also that identification and discussion of its flaws may elevate the level of ethical practices in human research conducted by surgical scientists.

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References