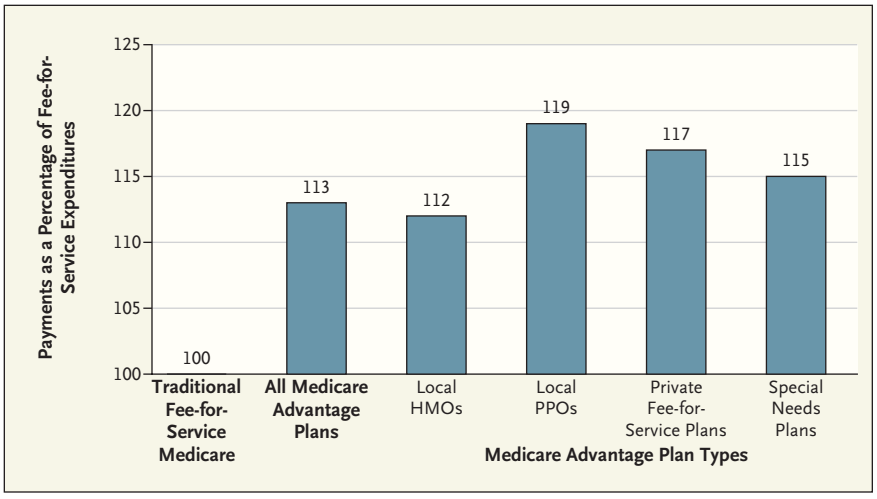


Average Payments to Medicare Advantage Plans Relative to Traditional Fee-for-Service Medicare in 2007.

HMO denotes health maintenance organization, and PPO preferred provider organization. Data are from the Kaiser Family Foundation.

are respected. The CMS must also invest heavily in the development of the technology for measuring and reporting health plan performance, including the development of information on the cost and quality of care provided under fee-for-service Medicare.

Accountability is the holy grail in health care purchasing. It is nearly impossible for the government to hold the nation's hundreds of thousands of physicians and thousands of hospitals individually accountable for health care quality and efficiency. It is certainly very difficult, but perhaps not completely impossible, for some combination of the government (through active management) and beneficiaries (through their choice of coverage) to hold health plans accountable for the care they provide.

To do so, the CMS would need to actively manage competition among plans, armed with a flexible set of rewards and sanctions to encourage plans to perform well. It is not clear whether Congress would be comfortable providing the CMS with the discretion or administrative resources needed to create greater accountability, nor is it clear whether effectively managed competition would produce value for beneficiaries and taxpayers. However, it is clear that as long as the CMS lacks the mandate, resources, and flexibility to hold private health plans accountable, these plans will not add value to the Medicare program. And given the intrinsic difficulties in improving quality and efficiency under fee for service, attempting to nurture the development of accountable health plans is a sensible approach.

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Globalized Clinical Trials and Informed Consent

George J. Annas, J.D., M.P.H.

The increasing globalization of clinical research trials calls for more effective ethical and legal rules to protect both research subjects and scientific integrity.[1] Some observers noted more than a decade ago that research was being conducted in developing countries without concern for adherence to the international ethical principles for human-subjects research contained in the 1947 Nur-

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emberg Code and the 1964 Declaration of Helsinki (see box).[2] The situation has not improved. For example, late last year, the Food and Drug Administration (FDA) decided that research studies submitted to it for review need no longer be bound by the Declaration of Helsinki — they must only follow the industry-sponsored Guidelines for Good Clinical Practice outlined by the International Conference on Harmonisation.[3]

What is the legal status of the Nuremberg Code and the Declaration of Helsinki? Are they outdated ethical rules that researchers can ignore with impunity? Or have they arrived at the status of international human rights law that must be followed? The question remains open, but just as the clinical trials attempting to interrupt the mother-to-child transmission of HIV in the mid-1990s gave rise to a continuing debate about global standards of care and benefit sharing, so another mid-1990s research trial in Africa has brought international research rules back to center stage.[2]

In late 2000, the *Washington Post* broke the story of a 1996 medical experiment conducted by Pfizer researchers in Kano, Nigeria, during a major meningitis epidemic.[4] The story created a sensation, especially with its lead, which described the slow death of a 10-year-old girl known only as Subject 6587-0069. The researchers, who were working for Pfizer, monitored her dying without modifying her treatment, following the protocol designed to test their antibiotic Trovan (trovafloxacin) in children. The *Post* noted that its investigation had uncovered other such corporation-sponsored experiments "in Africa, Asia, Eastern Europe, and Latin America" that were "poorly regulated" and "dominated by private interests" — studies, it remarked, that "far too often betray" their promises to research subjects and consumers.[4]

After the exposé was published, the families of the Kano subjects brought suit against Pfizer in Nigeria and, later, in the United States, charging the company with conducting medical experiments without informed consent. Until recently, Pfizer had successfully argued in court both that there was no international norm requiring its physicians to obtain informed consent for the use of experimental drugs and that any lawsuit against them by subjects and their families should be tried in Nigerian courts, not U.S. courts. Pfizer abandoned this latter claim when, in 2006, an internal report by the Nigerian Ministry of Health was made public. The report concluded that the study violated Nigerian law, the Declaration of Helsinki, and the United Nations' Convention on the Rights of the Child. The Nigerian government then filed both a criminal and a civil suit against Pfizer in Nigeria. A settlement in this case has reportedly been reached, but the details of the agreement have not yet been made public.

More important than the case in Nigeria, however, is the January 2009 opinion of the U.S. Court of Appeals for the Second Circuit, which covers New York, Connecticut, and Vermont. That opinion reversed the trial court's dismissal of the U.S. lawsuit against Pfizer and sent it back for trial.[5] In the area of human rights, the Second Circuit is best known for its 1980 opinion that a physician from Paraguay could sue the inspector general of police of Asunción, Paraguay, in the United States for the murder and torture of his son in Paraguay; the court ruled that he could do so under the Alien Tort Statute because torture is universally condemned as a violation of international human rights law and "the torturer has become — like the pirate and the slave holder before him — *hostis humani generis*, an enemy of all mankind." To oversimplify slightly, the question before the Second Circuit in the Pfizer case was whether researchers who experiment on humans without their informed consent violate a substantially similar international human rights law.

The case has not yet been tried, and the Nigerian families may not be able to prove the facts they have alleged. Nonetheless, for the purposes of deciding whether the families could have their day in a U.S. court, the Second Circuit had to assume that the allegations are true. These allegations are primarily that in the midst of a meningitis epidemic in Nigeria, Pfizer dispatched physicians to the Kano Infectious Diseases Hospital to conduct a study involving 200 sick children, comparing the efficacy of oral Trovan with the FDA-approved antibiotic ceftriaxone (Rocephin). Trovan had never been tested in children in its oral form. The phase 3 trial, in which half the children were given Trovan and the other half received a low dose of Rocephin, was conducted over a 2-week period, and then the Pfizer team abruptly left. According to the families, "the tests caused the deaths of eleven children, five of whom had taken Trovan and six of whom had taken the lowered dose of ceftriaxone, and left many others blind, deaf, paralyzed, or brain-damaged."[5]

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Codes Relied on by the Second Circuit.

Nuremberg Code (articulated in 1947 by U.S. judges): "The voluntary consent of the human subject is absolutely essential . . . [and includes] legal capacity . . . free power of choice . . . sufficient knowledge and comprehension of the [nature, duration, and purpose of the experiment] . . . to make an understanding and enlightened decision."

International Covenant on Civil and Political Rights (international treaty became effective in 1976): "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation."

Declaration of Helsinki of the World Medical Association (promulgated in 1964 and revised eight times since): "The physician should obtain the subject's freely-given informed consent, preferably in writing. . . . [But in clinical research] if the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to [an] independent committee."

International Ethical Guidelines for Biomedical Research Involving Human Subjects (published in 1993, and since revised, by the Council for International Organizations of Medical Science): "The investigator must obtain the voluntary, informed consent of the prospective subject [or legally authorized representative]. . . . Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee."

The central allegation is that "Pfizer, working in partnership with the Nigerian government, failed to secure the informed consent of either the children or their guardians and specifically failed to disclose or explain the experimental nature of the study or the serious risks involved" or to inform them that alternative treatment proven to be effective was immediately available from Médecins sans Frontières at the same facility.[5]

The U.S. Supreme Court has cautioned lower courts to be conservative in determining whether a category of actions contravene "the law of nations" accepted by the "civilized world" as a norm of customary international law. So for the Second Circuit to permit this case to proceed in the United States, it had to conclude that the prohibition of nonconsensual medical experiments on humans has become such a norm. The court reached this conclusion because the informed consent requirement is sufficiently "(i) universal and obligatory, (ii) specific and definable, and (iii) of mutual concern," to be considered a "customary international law norm" that can support a claim under the Alien Tort Statute.

The court found the 1940s war-crimes trials at Nuremberg, especially the Doctors' Trial, to be foundational. Even though the major war-crimes trial, the International Military Tribunal (IMT), was the only multinational trial at Nuremberg, the court found that the subsequent U.S. military trials, including the Doctors' Trial, "effectively operated as extensions of the IMT." The Doctors' Trial produced the 1947 Nuremberg Code, the first precept of which is the requirement for voluntary, competent, informed, and understanding consent of the research subject. In the Second Circuit court's words, "The American tribunal's conclusion that action that contravened the Code's first principle constituted a crime against humanity is a lucid indication of the international legal significance of the prohibition on nonconsensual medical experimentation."[5] Moreover, the requirement of informed consent in research has been widely adopted in international treaties (including the International Covenant on Civil and Political Rights and the Geneva Conventions), domestic law, and nonbinding international codes of ethics such as the Declaration of Helsinki (see box).

The court found that in addition to being universal, the norm is specific in its requirement and is of mutual concern among nations. On this latter point, the court concluded that promoting the global use of essential medicines can help reduce the spread of contagious disease, "which is a significant threat to international peace and stability." Conducting drug trials in other countries without informed consent, however, "fosters distrust and resistance . . . to critical public health initiatives in which pharmaceutical companies play a key role."[5] The example the court cited was local distrust of international pharmaceutical companies that led to a 2004 Kano boycott of polio vaccination efforts — which allowed a polio outbreak to spread across Africa, making global eradication all the more difficult.

Post–World War II ethical standards of clinical research have not effectively protected subjects or ensured scientific integrity. The Second Circuit's persuasive opinion that the doctrine of informed consent has attained the status of

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an international human rights norm that can be enforced in the world's courts should help persuade international corporations and researchers alike to take informed consent — and perhaps the other principles of the Nuremberg Code — much more seriously.

No potential conflict of interest relevant to this article was reported.

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