Swinging on the Pendulum

Shifting Views of Justice in Human Subjects Research

by Anna Mastroianni and Jeffrey Kahn

Federal policies on human subjects research have performed a near-about face. In the 1970s, policies were motivated chiefly by a belief that subjects needed protection from the harms and risks of research. Now the driving concern is that patients, and the populations they represent, need access to the benefits of research.

Justice has long been one of the central principles in the ethical conduct of research on human subjects. But its application, as reflected in federal policies pertaining to human subjects research, has undergone a remarkable shift over a relatively short span of time. Understanding this shift is important not only for interpreting claims about justice in human subjects research, but also for assessing the status and adequacy of policies for protecting subjects.

In the 1970s, these policies emphasized the protection of human subjects from the risks of harm in research, and justice was seen as part of this protection. Since the early 1990s, however, justice as applied in research ethics has empasized the need to ensure access to the potential benefits that research has to offer. That such a dramatic shift could occur so quickly is extraordinary, especially in light of the understanding, coalescing over the same period, that subjects have an inadequate understanding of the research in which they are participating and are inadequately protected by existing practices and policies. The tension between these developments offers an important lesson for research protection as the context of human subject research becomes more complex. Our goal here is to attempt to understand how the pendulum has swung from protection to access, where in its arc we are, and where we should be.

Anna Mastroianni and Jeffrey Kahn, "Swinging on the Pendulum: Shifting Views of Justice in Human Subjects Research," *Hastings Center Report* 31, no. 3 (2001): 21-28.

Justice in the Belmont Era: Protection from Exploitation

The development of human subject protection policy in the United States was driven by a history of exploitation of subjects, most notably by research on

"vulnerable" subject populations that came to light between the mid-1960s and the early 1970s. The landmark examples were the Willowbrook State School hepatitis vaccine research on institutionalized children; the Jewish Chronic Disease Hospital cancer research, involving the injection of cancer cells into elderly nursing home residents; and the so-called Tuskegee Syphilis Study, which had been under way for decades but was exposed to an appalled nation in 1972.[1] Those examples contributed to a sense that human subjects research in the United States permitted scandalous practices—inadequate attempts to inform subjects about research and obtain their consent, exploitive recruitment strategies, the use of vulnerable subject populations, and a willingness to expose subjects to significant risk without any potential for direct medical benefit. Further, there was a sense that the risks and benefits of research were split apart—the risks were borne by subjects, the benefits accrued to others.

Thus the early history of U.S. research ethics policy focused on the risks rather than the benefits of research, and on preventing subjects from being exposed to unacceptable

Arizona's Cancer Clinical Trials Law: *Flawed Process, Flawed Product*

by J. Kristin Olson-Garewal and Kristen Hessler

For many cancer patients, participation in a clinical trial is more attractive than receiving standard therapies, which may be limited in effectiveness. Lately, however, this choice has been complicated by the fact that many insurers explicitly refuse to reimburse for expenses incurred as part of a clinical trial.

In the pre-managed care era, experimental procedures were routinely covered by a combination of sources: the administrative and experimental agent costs of clinical trials were borne by the pharmaceutical industry or the government (through the National Institutes of Health or the Veterans Administration), and other costs were unwittingly absorbed by patients' third-party insurers.[1] As managed care review brought this expenditure to light, insurers began to deny reimbursement for "investigational" or "experimental" regimens, on the grounds that covering unproven services was outside the intended use of the pooled funds for which managed care insurers were responsible. Clinical researchers at first responded to this refusal by persuading insurers to cover investigational treatments on a case-by-case basis, or by camouflaging a patient's research participation so as to slip the claims through the increasingly vigilant payment systems.[2]

In spite of increases in government funding for clinical research, an ongoing conflict evolved among doctors, patients, and insurers over the question of whether insurers should reimburse for investigational procedures. Some patients have gone to court when faced with the prospect of paying for an investigational intervention themselves, or when they were unable to pay for an experimental therapy that they saw as a last chance treatment. But attempts to resolve this controversy in the courts have resulted in such varied and at times illogical outcomes that no consistent legal direction has emerged.[3] In response, researchers and patients have taken the problem to Congress and to state legislatures.

Thus Arizona's Cancer Clinical Trials legislation. In April 2000, the governor of Arizona signed into law a bill requiring insurers to provide coverage for some costs associated with their enrollees' participation in cancer clinical trials. The bill was modeled on legislation already enacted in Georgia, Maryland, and Rhode Island, among other states, and was developed in the same year as similar legislation in Illinois and Louisiana.[4] In Arizona, the legislation had been sharply contested since its inception, and it remained controversial at the time it was signed into law. Predictably, oncologists at academic medical centers, cancer patients, and their advocates were the most vocal supporters of the bill, while third party payers, including Medicaid medical administrators, were opposed to it.

Problems with the Law

The Cancer Clinical Trials bill was supposed to respond to the fact that cancer clinical trials are underenrolled.[5] Most people from both sides of the debate agreed that only 3 percent of cancer patients currently enroll in clinical trials, while up to 20 percent may be eligible. The hypothesis behind the legislation was that patients do not participate in clinical trials because they would have to pay for it themselves, since most managed care insurers explicitly refuse to reimburse their enrollees for any experimental interventions.

The trouble with this hypothesis is that it is flatly contradicted by the best evidence available. According to a study by the United States General Accounting Office, insurers tend to make case-by-case exceptions to their general policy not to cover experimental interventions.[6] The finding was corroborated by lobbyists for managed care organizations during public hearings on the Arizona bill, as well as by research oncologists in a study at the University of Arizona's Medical Center.[7] The GAO study con-

J. Kristin Olson-Garewal and Kristen Hessler "Arizona's Cancer Clinical Trials Law: Flawed Process, Flawed Product," *Hastings Center Report* 31, no. 3 (2001): 22-24.

or exploitive levels of risk, particularly without the prospect of offsetting direct medical benefits. *The Belmont Report*, issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978, identified justice as requiring the fair distribution of the burdens and benefits of research in subject selection and recruitment; in practice, however, justice was interpreted as requiring the prevention of any further exploitation of vulnerable groups.[2] The emphasis was realized through the promulgation of research policies that staked much on protection and that singled out particular groups—namely, prisoners, children, and pregnant women and fetuses—for additional protections.

Prisoners were deemed vulnerable because of the nature of their living environment. Adequate informed consent, it was believed, was not possible when subjects lived in a setting that constrained the autonomy on which the concept of informed consent is based. This view actually ran counter to information collected by the National Commission, which found in interviews with prisoners who participated in research that the prisoners wanted to be enrolled in

cluded that "many factors, in addition to insurance coverage practices, can influence patient participation in clinical trials." These include physicians' ignorance about the existence of relevant trials, physicians' lack of time to enroll patients in the relevant trials, patients' lack of interest in participating in a trial or reluctance to be randomized into a control arm of a clinical study, and eligibility restrictions. Thus it is not at all clear that lack of insurance coverage is a major factor inhibiting enrollment in clinical trials, and a mandate requiring insurance coverage for clinical trials is not likely to increase enrollment in cancer clinical trials to any significant degree.

These claims aside, the bill might have stood little chance of increasing enrollment rates anyway, given that it applies only to a minority of the state's citizens: 24 percent of Arizonans are without insurance at all,[8] and over 60 percent of people with employer-provided insurance in Arizona are not subject to state health insurance mandates because their employers (not insurance companies) are the direct bearers of risk and federal legislation exempts these employers from state insurance laws. Moreover, Arizona's Cancer Clinical Trials law does not apply to those patients covered by government programs such as Medicaid, Medicare, or Veterans' Administration plans.

A further problem with the Cancer Clinical Trials legislation is that it threatens to increase the already unacceptably high number of uninsured people in Arizona. Mandating specific insurance benefits assigns additional costs to insurers without providing additional funds. The predictable result is an increase in premiums for private insurers, and a reduction in either the number of people or the number of services covered by public insurers that cannot increase their rates to cover the additional expense. And when premiums increase, a further predictable result is that fewer people will purchase insurance.[9]

Some supporters of the legislation claimed, in response to this concern, that there is no reason to expect insurers' costs to increase as a consequence of mandating coverage for clinical trials. There are at least two problems with this claim. First, the relevant studies are equivocal on this score, and research on the question is ongoing.[10] Therefore, at the very least, insurers' concerns about cost should be taken seriously in developing policy. Second, some of the reasons insurers worry about costs were not adequately addressed in those studies. For example, it is quite likely that many patients who receive an investigational therapy in a clinical trial will not be cured by that therapy. Such patients will then need either the standard regimen, or hospice care, after the investigational therapy fails. In that case, the investigational regimen augments, rather than replaces, the original treatment. Insurers who cover the investigational regimen in such cases will essentially have to pay twice.

Problems with the Legislative Process

On the whole, Arizona's legislative process essentially ignored insurers' reasons for opposing the Cancer Clinical Trials legislation. During its initial drafting, some attempt was made to get input from insurers, and to this end, the bill was discussed in meetings attended by oncologists, insurers, and representatives of the bill's main sponsors.[11] In the bill eventually introduced to the legislature, however, many of the objections raised by insurers in those meetings were simply disregarded.

For example, the insurers opposed any requirement that they cover their enrollees' participation in Phase I trials, which measure a drug's toxicity by allocating increasing doses to successive cohorts of subjects until a fixed percentage of subjects experience severe (but usually reversible) toxic reactions. Phase I trials are not designed to be therapeutic, even though a few subjects may have a therapeutic response.[12] Thus, the insurers argued, it is inappropriate to ask insurers to fund them. These objections were raised during committee hearings on the bill as well as during the original informal meetings, and as is evident from the minutes of the committee hearings in the legislature, they were never convincingly rebutted. Nonetheless, the version of the bill later introduced in the Arizona legislature—and the version that is now law—mandated coverage for trials in phases I through IV.

Without a consensus behind the mandate, the implementation of the Cancer Clinical Trials legislation is on shaky ground. If insurers feel excluded from the legislative process, or feel they've been given a mandate that conflicts

studies and were highly motivated research subjects, for a variety of reasons—the opportunity to earn a few extra dollars, the perks that might come with research participation, access to more frequent and potentially improved health care, and a belief that participating in research offered a way for them to make a contribution to society. Most interesting was the finding that it was not the least powerful and arguably most vulnerable prisoners who participated in research, but the most powerful.[3] Prisoners often viewed research as an opportunity to be seized rather than a hazard to be avoided; they apparently did not worry that anyone was taking advantage of them. Even so, policies were promulgated, and remain in place today, that made it impossible to perform research on prison populations unless the research either offers a prospect of direct medical benefit to the individual subjects themselves, as in clinical trials for HIV infection, or aims at understanding or improving the prison environment, such that it would potentially benefit prison populations generally.

Children were deemed vulnerable because of similar concerns about informed consent and the potential for

with their mission, they may attempt to "game the system"—to comply with the letter of the law while getting around its intent. For example, under Arizona's Cancer Clinical Trials law, health plans are free to contract with doctors who do not refer patients to clinical studies, effectively short-circuiting the bill's intent.

It is this concern that motivated New Jersey oncologists to develop a voluntary agreement with insurers to cover clinical investigations, instead of resorting to legislation. In December 1999, New Jersey's governor announced that a coalition of health plans, which together cover 98 percent of New Jersey's insured population, had agreed to pay patient care costs for those enrollees who participate in clinical trials.[13] This shows that it is possible to work with insurers, rather than relentlessly against them, on expanding benefits. Unfortunately, although Arizona's Cancer Clinical Trials bill was still under consideration at the time the New Jersey agreement was announced, the New Jersey model was not pursued in Arizona.

There is an element of irony here: in New Jersey, the proponents of an arrangement similar to that required by the Arizona Cancer Clinical Trials law were willing to discuss the issue with insurers, and to work out a voluntary agreement. Although such arrangements smack of compromise, the New Jersey negotiators may have obtained more securely what the Arizona oncologists got, less securely, via a legal mandate.

Acknowledgment and Disclosure

The authors are grateful to the Greenwall Foundation for support of this research. All opinions expressed in this article are the authors'.

J. Kristin-Olson Garewal holds stock in Cigna Corporation. She received the stock as part of a compensation package when employed at Cigna Health Plan.

References

1. Even managed care insurers sometimes are unaware that they are paying for expenses associated with clinical trials. See R. Mechanic and A. Dobson, "The Impact of Managed Care on Clinical Research: A Preliminary Investigation," *Health Affairs* 15, no. 3 (1996): 72-89.

2. E.H. Morreim, "Gaming the System: Dodging the Rules, Ruling the Dodgers," *Archives of Internal Medicine* 151, no. 3 (1991): 443-47.

3. J. Ferguson, M. Dubinsky, and P. Kirsch, "Court-Ordered Reimbursement fot Unproven Medical Technology, *JAMA* 269, no. 16 (1993): 2116-21.

4. See Arizona State Senate's Fact Sheet for S.B. 1213 (Final Revised version), <http://www.azleg.state.az.us/legtext/44leg/2r/summary/s.1213fsfinal.doc.htm>. See also T. Reynolds, "Cost Studies Show Clinical Trials, Standard Therapy May Be Equal," *Journal of the National Cancer Institute* 92, no. 14 (2000): 1116-18.

5. Actually, the publicly stated aim of the legislation was to help individual patients desperate for an experimental, last chance therapy. Since all agreed that insurers generally approved such requests when medical evidence supported them, research oncologists turned to the justification that the Cancer Clinical Trials legislation was necessary to improve the quality of treatments for cancer.

6. United States General Accounting Office, "NIH Clinical Trials: Various Factors Affect Patient Participation," Letter Report, 30 September 1999, GAO/HEHS 99-182.

7. Arizona State Senate, 44th Legislature, Second Regular Session, Minutes of Committee on Financial Institutions and Retirement, 12 January 2000. Also, K. Olson and K. Hessler, "Mandating Insurance Coverage for Clinical Research," unpublished manuscript, available on request.

8. Kaiser Commission on Medicaid and the Uninsured, "Health Insurance Coverage in America, 1999 Data Update," December 2000. Table 12, www.kff.org/content/2001/2222/2222.pdf.

9. G.A. Jensen and M.A. Morrisey, "Employer-Sponsored Health Insurance and Mandated Benefit Laws," *Milbank Quarterly* 77, no. 4 (1999): 425-59.

10. Several studies seem to indicate that costs for patients enrolled in clinical trials may be comparable to costs for patients on standard therapies. Fireman, Fehrenbacher, Gruskin, and Ray, "Cost of Care for Patients in Cancer Clinical Trials," *Journal of the National Cancer Institute*, Vol. 92, no. 2, January 2000: pp. 136-142. However, these studies were generally small and difficult to control, and a major study is now under way. See ref. 3, Reynolds, "Cost Studies."

11. J. Bezozo, Senior Legislative Research Analyst for the Arizona Senate Health Committee, personal communication, 10 October 2000; and D. Hughes, executive director of Arizona Association of HMOs, personal communication, 10 October 2000.

12. M. Miller, "Phase I Cancer Trials: A Collusion of Misunderstanding," *Hastings Center Report* 30, no. 4 (2000): 34-42.

13. "New Jersey Insurers to Cover Cancer Trials," *The San Francisco Chronicle*, 17 December 1999.

taking advantage of their reliance on others. Such concerns were vividly illustrated in the infamous Willowbrook case, where hepatitis vaccine research was performed on institutionalized, mentally retarded children whose parents seemed to have little choice but to agree to their children's participation—thereby picking out the most vulnerable from among the potential pool of children. The rules developed to prevent this sort of exploitation limited research in which children could participate to studies involving either minimal risk or direct medical benefit.

Pregnant women and fetuses were deemed especially vulnerable and deserving of protection. Influenced by the abortion debate and memories of thalidomide, policymakers protected pregnant women from research that carried risk of harm to protect them and their fetus. The implementation of this policy was expanded in practice to include not only pregnant women but also women of childbearing capacity, both to prevent unwitting risk to fetuses and to protect the future health of the women. This practice represented the logical conclusion of a regulatory culture and process that emphasized the protection of subjects from risk as paramount.

From Protection to Access

The research regulatory culture that emphasized protection from risk in the 1970s began to shift during the late 1980s and early 1990s. Due to a growing belief that research increasingly offered real benefits, the application of justice in research began to emphasize the fair distribution of the benefits of research instead of its risks. Advocacy groups, particularly those representing the interests of people with AIDS and women's health groups, argued this view to great effect before Congress and elsewhere. The thrust of their position was that fairness demands not only protection from the risks of research, but increasingly demands the opportunity for inclusion in research. The shift was taking place: from justice as protection to justice as access.

With the waiver of informed consent in research in emergency settings we have backed away from the cornerstone concept of informed consent, dating back to the Nuremberg era, in the protection of research subjects.

The HIV/AIDS advocacy community was at the forefront of making the case for justice as access. As the first clinical trials for AZT were being undertaken, groups like ACT-UP organized rallies protesting the limited enrollments in them. At a time when subjects were sharing their research medication with friends to spread around whatever potential benefit could be had from these drug trials, protestors were marching in large cities across the country carrying placards proclaiming "Clinical trials are health care too!"[4] Such a sentiment, conflating research participation with medical care, represented not just a shift in emphasis but a total reversal of the ethics of research from protection to access.

Through the late 1970s and 1980s, there was a growing sense that cutting edge therapy could be found in research participation, particularly for cancer, where the best therapeutic outcomes were thought to be in research protocols, and where standard treatment modalities were largely viewed as less effective. It was certainly true that the benefits from the major investments in biomedical research were being realized and applied. The problem was that those benefits were limited to the populations represented in the subject populations—largely although not exclusively adult males. Whatever the complex of reasons for excluding women, racial and ethnic minorities, and children from research participation, the policy was largely predicated on protection from harm and exploitation. But as advocates began to point out, such policies had the effect not only of preventing harm and exploitation, but also of preventing benefit—resulting, claimed one commentator, in a climate that protected some groups to death.[5] Exclusion denies access to the benefits of research at two levels—first to the individuals who may themselves receive the direct medical benefit of research participation, and more notably to the groups from which the subjects come.

There are numerous examples of the research system's failure to provide equitable benefits to women. Among the most notable is the United States Physicians Study, a longitudinal study that assessed the effectiveness of low dose aspirin for preventing heart attacks.[6] It yielded strong evidence of success, but it couldn't be applied outside the research population, comprised exclusively of men, because women are not merely smaller versions of men. Similarly, children are not merely smaller versions of adults, and racial and ethnic groups may differ from each other in disease pathology, drug response, and the like.

The realization that policy and practice had emphasized protection and a denial of the real and perceived benefits of research pushed the pendulum of research policy toward recognizing the importance of access to the benefits of biomedical research,

by means of policies requiring inclusion in research set against a background of protection. In 1994, less than twenty years after the first federal policies on research protections were promulgated, the NIH issued the first policy requiring *inclusion* of particular groups in research—the Guideline on Inclusion of Women and Minorities in Research.[7] The guideline represents an unprecedented sea change in thinking about the ethics of research on human subjects.

Implementing Justice in Policy

The implementation of the 1994 NIH guideline flipped the presumption about research participation from exclusion to inclusion. Researchers were and are now required to include representative populations of women and minorities in their protocols unless there are special reasons for excluding them. It would make no sense, for example, to include women in a clinical trial testing a new drug for prostate cancer, nor would it be reasonable to conduct research on conditions in racial or ethnic groups in which those conditions are not found.

Policy on the participation of children in research is following a similar path, driven by similar arguments. In an effort to protect children, children have been excluded from research that carried greater than minimal risk unless the research also had the potential to provide direct medical benefit to the subjects. Thus federal regulations (subpart D of 45 CFR 46) bar the participation of children in phase I drug trials, which are used to assess the safety of new drugs before their approval. But excluding children from such research has meant there is limited information about the safety of drugs in pediatric populations. This information has instead been pieced together after the drugs are approved and marketed for adults: children have received drug doses based only on the most general calculations of their size relative to the adults for whom drugs are approved, and on the clinical experience (read "trial and error") of pediatricians who have begun to try the drugs on children.

Recent directions from both the NIH and the Food and Drug Administration are changing the presumption from exclusion to inclusion, and requiring a special justification to exclude children.[8] The change in approach has not been completely achieved, however. Reversing the presumption about participation has resulted in a policy that reflects the tension between ensuring access to the benefits of research and protecting subjects from research harms. The dictates of subpart D, as currently written, do not easily coexist with a policy of inclusion. It appears that the long-standing commitments to protection will be weakened as part of the trend toward assuring access to the benefits of research.

Changes in the rhetoric of health policy are further evidence of the emphasis on access to the benefits of research, reaching to the highest levels of our government. Richard Klausner, director of the National Cancer Institute, testifying before Congress in 1998 about the need for large increases in the overall NIH budget (which were eventually granted), argued that substantial additional resources were required "to ensure that all people who wish to participate in a clinical trial are able to do so."[9] The comment both presupposes that there is a real benefit to be had by the subjects of clinical research and reflects a remarkable commitment to universal access to research participation, particularly in a country where there is no similar commitment concerning basic health care.

Klausner's commitment has now been realized in policy, at least for those who have health insurance or are eligible for Medicare. In 1999, United Healthcare, one of the largest managed care organizations in the country, became the first third-party payer to agree to pay the costs associated with their subscribers' participation in clinical trials.[10] The decision was hailed as a major step in removing one of the substantial barriers to participation in clinical trials, since the policy of most health insurers has been to deny payment for the costs of clinical trial participation on the grounds that the treatment rendered is experimental. Whether the change in policy is a function of a changed view of the benefits of research participation, a response to the demands of its customers, or a commitment to supporting the research that yields the clinical advances on which health care depends, it certainly delivers a message to patients. If your insurance company thinks research is worth paying for, it must be worth participating in. Not long after the decision was announced, then-President Bill Clinton directed the Health Care Financing Administration to ensure that all Medicare recipients would enjoy similar access to clinical trial participation, leaving it to policymakers to determine the conditions under which patients would be eligible for such a benefit.[11] This theme even became part of the rhetoric of the presidential campaign when Al Gore incorporated a reference to access to research participation in his standard stump speech on health care issues.[12]

The final piece of evidence that the pendulum has swung fully from protection to access is the waiver of informed consent in research in emergency settings, written into federal regulations in 1996.[13] The waiver is the ultimate endorsement of an emphasis on the benefits of research since it suggests that research participation is so beneficial, to individuals and society, that we must guarantee access even for those unable to consent. With this step we have now backed away from the cornerstone concept of informed consent, dating back to the Nuremberg era, in the protection of research subjects.

A New Era in the Protection of Human Subjects?

What are the implications for research oversight of the swing from protection to access? The protection of the rights and interests of research subjects is rightly the preeminent concern in research oversight, but how do we ensure that protection is adequately balanced against access? There is ample evidence that even in an environment stressing protection there are serious shortcomings in the process of informed consent,[14] and subjects are persistently confused about the distinction between research and clinical care[15] and the benefits they stand to realize by participating in research.[16] Thus an overemphasis on the benefits of research participation can undermine the reality that research inherently carries risk and very often holds no benefits to the subject.

It is a confusing time to be a subject—or to be thinking about becoming one. The media presents stories about the need for more research and research funding alongside reports of serious harms to subjects in research trials. The death of Jesse Gelsinger in a gene transfer study at the University of Pennsylvania resulted in a swirl of reportage, congressional hearings, university investigations, and new restrictions and reporting policies for gene transfer research.[17] The *Seattle Times* recently reported on alleged conflicts of interest and failures to obtain informed consent in two clinical trials in which some subjects died unexpectedly, both at Seattle's Fred Hutchinson Cancer Research Center.[18] The *Los Angeles Times* ran a story on "seven deadly drugs" that were fast-tracked to approval by the Food and Drug Administration and were subsequently withdrawn from the market after they were discovered to have serious side effects, sometimes leading to death.[19] And it was recently reported that the FDA has asked for an additional $36 million in the next fiscal year to increase its "emphasis on high-risk trials, such as those enrolling vulnerable populations (mentally impaired and pediatric populations, for example) and sponsor-investigators who have a proprietary interest in the product under study."[20] How do we reconcile these divergent messages to subjects, investigators, IRBs, and institutions, and properly balance the requirements of justice in research? If we fail to answer this question adequately we risk a serious erosion of trust in the research enterprise.

Recent announcements encourage us to overlook the nagging, recurring, and fundamental shortcomings in research protections.

Looking ahead

Accountability for balancing protection and access falls to those at every level in the conduct of research: the physicians who refer their patients to investigators, the investigators themselves, the IRBs that oversee research, and the institutions where research is performed. Policymaking does not occur in a vacuum; regulatory and spending decisions respond to the perceived needs and expressed desires of the public. Without trust from the public, there can be no research, as there will be no research subjects willing to participate and no willingness on the part of the public to support research with tax dollars. Research is a privilege not to be presumed or exploited, but earned through building and maintaining the public trust. This requires a careful balancing of access and protection.

Recent announcements by the Department of Health and Human Service's Office of Human Research Protections focus on conflicts of interest in research—at base an effort to secure public trust by ensuring that investigators are not motivated to overlook subjects' protection.[21] The Institute of Medicine recently completed a study recommending, among other things, the accreditation of IRBs.[22] But both of these steps seem to be aimed at assuring that paperwork requirements are met, which is at best a weak proxy for assuring adequate protection of subjects. Thus both efforts seem to miss the point—certification and oversight provide a way of inspecting the implementation of policies aimed at protection rather than a way of exercising them. And thus these approaches encourage us to overlook the nagging, recurring, and fundamental shortcomings in research protections that continue to undermine the trust central to any effort to protect the rights and interests of research subjects, including ensuring their access to the benefits of research.[23]

In the current research climate, the pendulum may have swung as far as it can toward an emphasis on benefits. When a pendulum has finished swinging in one direction, it inevitably starts back in the other, and it eventually comes to a rest in the middle. But the direction in which research ethics policy is swinging at any given time will be a function of how well we manage the balance between policies and practices at either of its two ends. Increasing policy attention to conflicts of interest, reporting, and regulatory oversight of the research environment seems to imply that the pendulum has begun its swing back toward an emphasis on protection. But paperwork requirements are not enough, and may distract us from efforts that will modulate the swing. What remains to be

seen is how far the pendulum will go, and whether we have the tools to control it.

References

1. J. Jones, *Bad Blood* (New York: Free Press, 1993).

2. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Bethesda, Md.: Department of Health, Education, and Welfare, 1978).

3. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Research Involving Prisoners* (Bethesda, Md.: Department of Health, Education, and Welfare, 1976); V. Cohn, "Prisoner Test Ban Opposed," *Washington Post*, 14 March 1976.

4. R. Shilts, *And the Band Played On: Politics, People, and the AIDS Epidemic* (New York: St. Martin's Press, 1987).

5. R.A. Charo, "Protecting Us to Death: Women, Pregnancy, and Clinical Research Trials," *Saint Louis University Law Journal* 38, no. 1 (1993): 135-87.

6. J.E. Manson et al., "Aspirin in the Primary Prevention of Angina Pectoris in a Randomized Trial of United States Physicians," *American Journal of Medicine* 89 (1990): 772-76.

7. "NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research," *Federal Register* 59 (28 March 1994): 14508.

8. "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects," NIH Guide, 6 March 1998, <www.nih.gov/grants/guide/1998/98.03.06>.

9. R. Pear, "Medical Research to Get More Money from Government," *New York Times*, 3 January 1998.

10. G. Kolata and K. Eichenwald, "Insurers Come In from the Cold on Cancer," *New York Times*, 19 December 1999.

11. R. Pear, "Clinton to Order Medicare to Pay New Costs," *New York Times*, 7 June 2000.

12. J. Dao, "Gore Urges Doubling of Funds in War against Cancer," *New York Times*, 2 June 2000.

13. "Waiver of Informed Consent Requirements in Certain Emergency Research," *Federal Register* 61 (2 October 1996): 51531; "Protection of Human Subjects; Informed Consent," *Federal register* 61 (2 October 1996): 51498.

14. Advisory Committee on Human Radiation Experiments, "Research Proposal Review Project," in *The Human Radiation Experiments* (New York: Oxford University Press, 1996), 439-58; C.H. Braddock, "Advancing the Cause of Informed Consent: Moving from Disclosure to Understanding," *American Journal of Medicine* 105 (1988): 354-55; E.D. Kodish et al., "Informed Consent in the Children's Cancer Group: Results of Preliminary Research," *Cancer* 82 (1988): 2467-81.

15. Advisory Committee on Human Radiation Experiments, "Subject Interview Study," in *The Human Radiation Experiments* (New York: Oxford University Press, 1996): 459-81; N.E. Kass et al., "Trust: The Fragile Foundation of Contemporary Biomedical Research," *Hastings Center Report* 19 (1989): 25-29.

16. P.S. Appelbaum, L.H. Roth, and C.W. Lidz, "The Therapeutic Misconception: Informed Consent in Psychiatric Research," *International Journal of Law and Psychiatry* 5 (1982): 319-29; C. Daugherty et al., "Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials," *Journal of Clinical Oncology* 13 (1995): 1062-72.

17. D.S. Greenberg, "Stricter Regulation Proposed for U.S. Gene Therapy Trials," *Lancet* 355 (1977): 2000.

18. D. Wilson and D. Heath, "Uninformed Consent," *The Seattle Times*, 11-15 March 2001.

19. D. Willman, "How a New Policy Led to Seven Deadly Drugs," *Los Angeles Times*, 20 December 2000.

20. *Health News Daily*, 11 April 2001.

21. J. Brainard, "U.S. Agency Seeks Power to Fine Universities That Violate Rules on Human Research Subjects," *Chronicle of Higher Education*, 24 May 2000.

22. S.G. Stolberg, "Experts Call for New Rules on Research," *New York Times*, 18 April 2001.

23. J.P. Kahn and A.C. Mastroianni, "Moving From Compliance to Conscience: Why We Can and Should Improve on the Ethics of Clinical Research," *Archives of Internal Medicine* 161 (2001): 925-28.