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ARTICLES

ARE THE RATIONALE AND REGULATORY SYSTEM FOR PROTECTING HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH OBSOLETE AND UNWORKABLE, OR ETHICALLY IMPORTANT BUT INCONVENIENT AND INADEQUATELY ENFORCED?

*Gerald S. Schatz**

ABSTRACT

Many critics of U.S. regulation to protect human subjects of biomedical and behavioral research deem the system inherently unworkable and variously inadequate or unnecessary. Many deem its rationale, the Belmont Report, outdated and philosophically deficient. Some would scrap or revamp the system. These criticisms and prescriptions are challenging factually, legally, and ethically. Similar minimalist, audited self-regulation operates smoothly elsewhere in life science. Events suggest Belmont's continuing validity in its administrative-law role as interpretive touchstone for human subjects protection regulations. U.S. human subjects protection and related regulations are constitutionally grounded and consistent with U.S. obligations under human rights law. Criticisms that the system is inconvenient do not respond to ethical and legal duties—to acknowledge the innate dignity of human subjects of research, to recognize and squarely face ethical issues in human subjects research,

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to heed applicable domestic and international law, to say no to projects when no is warranted, to foster researcher involvement in the system, to focus on substance rather than form, and to resist automaticity. If the system is to function protectively and reasonably efficiently, then the legitimacy of the pertinent law and Belmont's legal role should be recognized as the primary resource for interpreting the human subjects regulations; the system and proposed changes should be viewed critically for efficacy rather than convenience; and policy and practice should emphasize (a) predictability, stability, and clarity of the regulatory system, and (b) resources and will to comply and enforce.

INTRODUCTION

Ethical and regulatory implications in reconsidering protection of human subjects of biomedical and behavioral research

Recent, rapid expansion of the use of human subjects in biomedical and behavioral research has been accompanied, not surprisingly, by criticisms of the U.S. regulatory system and its underlying rationale for protection of these persons. The system has been attacked as insufficiently protective, especially in view of reported abuses, and, conversely, as unnecessarily protective and inefficient as against perceived medical urgency. The regulatory rationale — its factual and ethical basis — has been attacked as largely irrelevant and inadequate.

Is the regulatory arrangement as unworkable as its critics claim? Is its rationale no longer valid and useful? This essay is not an exegesis of either the criticisms or the old rationale. This discussion, rather, is intended to show some of the kinds and sources of pertinent criticisms in the public policy arena and to reflect on some of the broader issues. The regulatory problem may not be in the system itself so much as in how it is allowed to operate. The value controversies may stem from too much or too little concern about the willingness of researchers to take great care as to how they may use other human beings. The issues are both regulatory and normative.

The salient and inescapable characteristic of biomedical and behavioral research on human beings is that it is, for the most part, the use of some human beings for the purposes of other human beings.¹ How to do it ethically and whether it should be done at all is a problem ancient and challenging in theory and in fact — the old questions of

1. Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, 98 *DAEDALUS* 219 (1969).

who can fairly use whom how, when, and for what. Researchers have no special claim on other people; researchers and subjects are persons of equal dignity, on the same moral plane.² This is a discomfiting challenge. It should be kept in mind as research on human beings is contemplated and conducted and as the regulatory system is reviewed and re-reviewed. It is too easy to dismiss or lose sight of these issues in this era of scientific optimism, accomplishment, good intentions, and routinization of procedures for the ostensible protection of the human subjects of research.³

The Belmont Report — *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, the 1979 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research⁴ — and the regulatory system⁵ to

2.

[A]s soon as animate, feeling beings become the subjects of experiment, as they do in the life sciences and especially in medical research, . . . innocence of the search for knowledge is lost and questions of conscience arise. The depth of which moral and religious sensibilities can become aroused over these questions is shown by the vivisection issue. Human experimentation must sharpen the issue as it involves ultimate questions of personal dignity and sacrosanctity.

Id. at 219.

3. For example:

Despite the obvious need for conducting research on children, during the 1970s, extremists voicing ethical concerns came close to prohibiting such activity when they insisted on a very strict interpretation of the need for informed consent, according to Dr. Alexander [Duane Alexander, M.D., director, National Institute of Child Health and Human Development]. See Nat'l Institutes of Health, Director's Council of Public Representatives, Spring 2001 Meeting Minutes (May 1, 2001), available at <http://copr.nih.gov/minutes/spring2001.shtm#children> (last visited Nov. 22, 2003).

4. Ethical Principles and Guidelines for the Protection of Human Subjects of Research [Belmont Report], National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Office of the Secretary, U.S. Department of Health, Education, and Welfare,], 44 Fed. Reg. 23,192 (April 18, 1979) [hereinafter *Belmont Report* or *Belmont.*]. "Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research," the Commission excluded "social experimentation" from its policy recommendations although not from its ethical construct. *Id.* at 23,193 & n. [3] [unnumbered in original]. The Department of Health and Human Services has continued to reissue *Belmont* as guidance; available at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm> (last visited November 22, 2003).

which the Commission gave moral focus have had a hard time recently. Absent caution and reflection, Belmont's moral and practical insights and the consequent awkward but remarkable regulatory arrangement could give way to ignorance, timidity, convenience, and of course supposed reform.

Criticisms of the Belmont Report and regulatory system

Some of the discussion at the nexus of public policy, government, biomedical research administration, and biomedical ethics takes a markedly utilitarian turn in considering what to do about regulation for the protection of human subjects of research. The regulatory system for protecting human subjects in federally funded biomedical and behavioral research and in drug studies is criticized as insufficiently protective and as slow, clumsy, and burdensome.⁶ Some critics would revamp the system dramatically.⁷ Without detailed

5. See, e.g., U.S. Dep't of Health & Human Servs., Protection of Human Subjects, 45 C.F.R. pt. 46 (2002), and related procurement regulations, and similar regulations of other federal agencies.

6. See, e.g., U.S. Dep't of Health & Human Servs., Office of the Inspector Gen., Institutional Review Boards: A Time for Reform (1998); U.S. Dep't of Health & Human Servs., Office of the Inspector Gen., Protecting Human Research Subjects: Status of Recommendations (2000); Nat'l Bioethics Advisory Commission, Ethical and Policy Issues in Research Involving Human Participants, Vol. I, Report and Recommendations (Aug. 2001); Anne Wood, Christine Grady & Ezekiel J. Emanuel, The Crisis in Human Participants Research: Identifying the Problems and Proposing Solutions (presented to President's Bioethics Council, Sept. 2002), available at [http://www.bioethics.gov/background/emanuel paper.html](http://www.bioethics.gov/background/emanuel%20paper.html) (last visited November 22, 2003).

7. The National Bioethics Advisory Commission recommended centralization of authority to regulate human subject protection in federally funded research and at the same time recommended that requirements to Institutional Review Boards (charged with human subject protections) shift "away from procedure," that "the regulatory burden on IRBs, investigators, and institutions" be reduced, and that (presumably) less risky research be subject to less IRB scrutiny. NAT'L BIOETHICS ADVISORY COMMISSION, *supra* note 6, at 136. A committee of the Institute of Medicine of the National Academy of Sciences recommended improving support for, strengthening, and clarifying roles of local IRBs, which the committee would rename. INST. OF MED. OF THE NAT'L ACAD. OF SCI., RESPONSIBLE RESEARCH: A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS (Daniel D. Federman et al. eds., 2002), available at <http://www.nap.edu/books/0309084881/html/> (last visited November 22, 2003). Ezekiel Emanuel, chief of the Department of Clinical Bioethics at the Warren G. Magnuson Clinical Center of the National

examination, some critics would dismiss concern about whole categories of research.⁸ Some critics show open frustration with

Institutes of Health, and colleagues proposed doing away with the system of local IRBs altogether:

The current system of protecting human research participants is firmly rooted in review and oversight at on the local, institutional level. The rationale of reason and convenience that originally led to this structure, however, no longer holds for the modern research endeavor. Not only does the research community and public feel that it has become burdensome and inefficient, but it has contributed to participant harms.

While many groups are attempting to respond to these issues, they do so in a piecemeal fashion that addresses only specific issues. We propose a more comprehensive solution - a system of REBs [Regional Ethics Boards], RRCs [Regional Review Committees], and EPCs [Ethics Policy Committees] - that completely restructures the system of human participants protections. In doing so, this new system promotes protection of human participants in research while alleviating the distress of the research community, honoring both the interests of human participants and the interests of the research community.

WOOD, GRADY & EMANUEL, *supra* note 6. Emanuel testified:

I think it's fair to say that everyone seems dissatisfied with the current system of protecting human research participants. Many of our researchers find the system onerous and more of a hurdle to get over than something that is value-added. . . . The pharmaceutical and biotechnology industry finds the process very time-consuming, very inefficient, and very resistant to innovative and novel approaches in research. . . .

. . . I think, yes, they [regional boards and committees] are going to be distant from you, but, on the other, they are also going to be—they might be more efficient.

Ezekiel J. Emanuel, Testimony at President's Bioethics Council, Sixth Meeting, Session 2: Regulation 6: Institutional Review Boards (IRBs) (Sept. 12, 2002) (transcript available at <http://www.bioethics.gov/transcripts/sep02/session2.html> (last visited November 22, 2003)). See also Jeffrey M. Drazen, *Controlling Research Trials*, 348 NEW ENG. J. MED. 1,377, 1,379 (2003) (contending that the National Institutes of Health, not the Office for Human Research Protections, Department of Health and Human Services, is the proper agency to investigate de novo concerns over whether research design raises issues of research subject safety). Drazen maintains that a clinical trial proposal that survives multiple levels of scrutiny by science review panels before reaching an ethics review board "must have merit." *Id.*

8. For example:

Most social and behavioral research presents no more than minimal risk. The statement . . . "no procedures for which written consent is normally

emphasis on autonomy and informed consent in opposition to notions of group rights.⁹ On an Internet bioethics list-serve, Belmont is trashed as philosophically inadequate and regulatorily insufficient¹⁰ Even some who contributed to Belmont declare that conditions have so changed¹¹ that issues of distributional justice in connection with

required outside of the research context” is stated with reference to medical procedures.

Consent forms are not used to document the patient’s willingness to be interviewed or to complete questionnaires. To cut to the bottom line here, our group would like to present the argument that if we apply the same standards to social research as are applied to biomedical research, that it’s rare that social research gets much more invasive or threatening than what’s asked in a routine family history during a routine medical examination. And this then is one of the criteria for waiving the requirement for documentation of consent.

In the current regulatory climate many IRBs treat social and behavior research as if it were very risky. The focus on very minor or unlikely risks has resulted in lengthy negotiations between IRBs and investigators and overly detailed, insultingly paternalistic, informed consent procedures.

Robert Levine, Remarks at the Meeting of the Nat’l Human Research Protections Advisory Comm. (April 29, 2002)(transcript, vol. I, at 329 ll. 4-25 available at <http://ohrp.osophs.dhhs.gov/nhrpac/mtg04-02/mtg0402.htm> (last visited Nov. 22, 2003).

9. Areas of disagreement in research ethics include human-subjects research “in societies in which individually informed consent would be culturally inappropriate” and whether to “allow for cultural exceptions to the informed consent requirement . . . because the subjects, as members of the cultural community in question, would neither expect nor want, even if they could understand, the insistence upon individual informed consent.” Baruch A. Brody, *Research Ethics: International Perspectives*, 6 CAMBRIDGE Q. HEALTH L. ETHICS 376, 376-384 (1997).

10. See, e.g., IRB Forum (Children’s Hospital of Philadelphia), at <http://www.irbforum.org>, 2002 *passim* (last visited November 22, 2003).

11. Until the 1990s, the paradigm for ethical analysis focused on the *risks and burdens* of research, especially nontherapeutic research, and on the need to protect potential and actual research subjects from harm, abuse, and exploitation. This history in the United States, as Carol Levine notes, “was born in scandal and reared in protectionism.” The regulation of research sought to protect vulnerable persons from exploitation in scientific efforts to benefit others. The dominant model in protectionist policies is *nontherapeutic* research, i.e., research that offers no prospect of direct therapeutic benefit to the subject. The concern is about an unfair distribution of *burdens*. However, a paradigm shift recently occurred, in part because of the interest of patients with AIDS in gaining access to new,

access to health care now dwarf all other justice issues in biomedical ethics.¹² The critics differ in perception of and prescription for the regulatory system but agree at least that it is neither as efficacious nor as practical as it ought to be.

Because Belmont and the system that developed from it are on the chopping block, it is important to look clearly at the moral and practical considerations that Belmont and the consequent regulatory system seem to embody and to ask why Belmont and the regulatory system are under attack. Are Belmont's lessons no longer of interest? Is the regulated community behaving nicely now? Is the regulatory system so clumsy and inconvenient as to defeat its ostensible intent? Is Belmont philosophically adequate? Is Belmont insufficient as a regulatory instrument? Is the emphasis on autonomy outdated? Can we not exclude the possibility that in public biomedical ethics there is either (a) naïveté about fundamental moral questions posed by human subjects research, or (b) distress equally at hearing biomedical ethics doubted and seeing it practiced?

experimental drugs within as well as outside of clinical trials. The focus shifted to *therapeutic* research and to the possible *benefits* of clinical trials (deemphasizing their risks). As a result, justice as *fair access to research* (both participation in research and access to the results of research) became as important as protection from exploitation. Similar observations apply to the participation of women in research.

TOM L. BEAUCHAMP & JAMES F. CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS* 226-227 (5th ed. 2001) (annotations omitted). Beauchamp and Childress depict the protection of human subjects of research as a distributional justice issue rather than one of rights, possible infringement of autonomy, or non-maleficence. The Belmont Report, to which both contributed, mentions benefits and burdens of research (these may be incommensurable) but does not do so within an analysis of theoretical issues of justice—distributional or otherwise. The extensively documented memoir in commission member Albert Jonsen, *THE BIRTH OF BIOETHICS* (1998), does not discuss Belmont's burdens-benefits statement or how commissioners thought the local review system would play out in practice. This should not be surprising. Often in legislative practice, of which the National Commission was a piece, the outcome differs from what the participants had in mind at the time.

12. "Policies of just access to and financing of health care, together with strategies of efficiency in health care institutions, dwarf in social importance every other issue considered in this book." *Id.* at 272.

Distinguishing inherent problems from attitude problems

The complaints frequently heard are numerous and sometimes conflicting. This regulatory system slows things down; it does not slow things down. It works; it does not work. Institutional Review Boards (IRBs), responsible for review of ethical aspects of research covered by this regulatory system, are slow and under-resourced. Interpretations of the rules are inconsistent. Compliance sometimes is desultory. Safety of subjects is not monitored properly. Oversight and enforcement are confusing and episodic. Therefore it is important to distinguish between problems that inhere in the regulatory scheme and the problems that are artifacts of enforcement policy and/or attitudes toward compliance.

Regulatory Structure

In administrative law and regulatory practice, the common sense expectations of a practical and efficacious regulatory regime are that the nature of the arrangement be plain to see, that due process obtains in its administration, that the regulatory structure and its operation are stable and predictable, and that the regulated community be invested in the regime's successful operation.

The regulatory structure here is a form of audited self-regulation,¹³ minimalist regulation appropriate enough where the issues tend to be fact-intensive, judgment and common sense are required, and the regulated community buys into the system.¹⁴ The regime's basic

13. Audited self-regulation "is the exercise of . . . delegated power subject to review by a federal agency." DOUGLAS C. MICHAEL, ADMIN. CONF. U.S., FEDERAL AGENCY USE OF AUDITED SELF-REGULATION AS A REGULATORY TECHNIQUE 6 (1993 & Supp. Rep. 1994). This regulatory technique is advantageous where technical issues are involved and flexibility is required. *Id.* at 12-13. The technique is disadvantageous where agency enforcement is inadequate and/or public interests are not considered. *Id.* at 21-22. See also ADMIN. CONF. U.S., ANN. REP. (1993) at 9 (noting breath of use of this regulatory technique).

14. Researchers in the human-subjects protection system are active in operating the system but because of requirements for outside and non-scientist IRB members and the persuasive power of recorded dissent cannot fully control it.

By endorsing . . . institutional review boards, the Commission created local forums where research was discussed—not in the abstract, but in the concrete particulars of specific protocols. Institutional review boards . . . do not debate protocols without guidance: definitions and rules

outlines are clear, spelled out in 45 C.F.R. part 46 for the Department of Health and Human Services and in almost identical regulations for several other agencies. The U.S. Government cannot fund proposed research or approve drug trial results if that work involves human subjects and is covered by the regulations unless the work is approved by IRBs — local ethics review bodies comprised of insiders, outsiders, scientists, and non-scientists. The arrangement respects scientific expertise while mandating exposure of proposals to evaluation from perspectives and reward structures other than those of the proposer. It is directed toward deliberation (although some institutions try to short-cut or eliminate deliberation). These regulations require similar protections for U.S.-funded transnational research. The system is overseen by the federal agencies that sponsor or evaluate the research.¹⁵

Is such a system inherently unworkable for science where ethical problems must be faced and where there is pressure to do research of seeming promise for human health? In form and function, the U.S. system for regulation of research on animals is almost identical to the IRB system.¹⁶ Anti-vivisection is long established in U.S. politics, and opponents of animal research pay the system close, critical attention. Although many would shut down all animal research, and the

are conveyed to them through federal regulations, supplemented by guidebooks, and enhanced by the . . . experiences of the reviewers. The IRB system, while not perfect in conception or realization, has succeeded in preventing abusive research for over two decades and, more importantly, has introduced the ethical problems into the realm of public discourse. Thousands of persons, from health professionals to hospital chaplains, have served on IRBs and become familiar with the language and the topics of clinical research. . . .

ALBERT JONSEN, *THE BIRTH OF BIOETHICS* 157 (1998) (annotation omitted). Regulatory systems may fail if the regulated community does not perceive itself as benefiting from the regulations. The prevalent defiance of highway speed laws illustrates the failure of a regulatory system without buy-in from the regulated community.

15. See, e.g., 45 C.F.R. pt. 46 (2002).

16. This system differs from the human subjects research regulation primarily in that the U.S. Department of Agriculture regulates the activity rather than federal spending, while the Public Health Service does its own enforcement by restricting spending but defers to Agriculture's standards. Dep't of Agric., Animal Welfare, 9 C.F.R. §§ 2.1- 2.11 (2003); Office of Laboratory Animal Welfare, *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, available at <http://grants.nih.gov/grants/olaw/references/phspol.htm> (last visited November 22, 2003).

regulations and regulatory guidance are tweaked from time to time, the system functions routinely without significant opposition to the regulatory structure itself. So the basic regulatory structure is not necessarily the problem, although, of course, the stakes in and moral responsibility for human subjects research are vastly higher.

Is the human subjects regulatory regime stable and predictable? Because the topic has become so politicized and enforcement has been episodic,¹⁷ it is hard to say. The U.S. Department of Health and Human Services reorganized and ostensibly elevated its human subjects protection enforcement program. But its initial director's time in this regulatory office was marked by mixed signals, beginning with an appearance before the National Bioethics Advisory Commission to eschew a regulatory role.¹⁸ Interest in consistent regulation was not apparent.¹⁹ A committee of the Institute of

17. See, e.g., Drazen, *supra* note 7, at 1380 (arguing against suspension of acute respiratory distress studies by the Government pending resolution of questions of research design safety). "The methods used to resolve the dispute must be well defined, transparent, and time-sensitive." *Id.*

18. Nat'l Bioethics Advisory Comm'n (Sept. 12, 2000) (testimony of Greg Koski incoming director, Office of Health and Human Services), at <http://www.georgetown.edu/research/nrcbl/nbac/transcripts/sept00/9-00day1.pdf> (last visited Nov. 22, 2003). Dr. Koski stated:

I believe that the current model is one that is largely confrontational in its foundation. It is a model that is focused primarily on compliance, and I don't believe that it is well suited to meet the challenges we are going to face in the next two decades of research.

....

... It just seems to me inherent in any process where there are a set of regulations that are going to govern what one group of individuals are going to do, you know, with another that is subject to an oversight process. That oversight process is going to be one that is stuck in the middle and will invariably be seen as an adversarial type process. That, I believe, is destructive to the overall process, and that is why I said that if we can manage to get the IRBs out of the middle and instead incorporate everyone into a collaborative, cooperative process that focuses on protection of human subjects, we will be better off[f].

Id. at 196, 209-210.

19. Rick Weiss, *Research Protection Chief to Leave HHS; 2-Year Tenure Gets Mixed Reviews*, WASH. POST, Oct. 17, 2002, at A19, reporting:

Koski's... tenure had received mixed reviews in recent months, with some saying he had improved protections and others saying his tenure has been long on talk but short on action.

....

Medicine of the National Academy of Sciences concluded, “Eventually, Congress will need to take the necessary steps to broaden and strengthen the federal oversight system”²⁰

Monitoring as needed for safety of subjects is already required. Confusion regarding due process traces back to a departmental tradition of heavy reliance on informal guidance rather than on straightforward notice-and-comment rulemaking and clear enforcement procedures.

Conceptually then, the major open questions seem to be less about the regulatory system than about the quality and extent of regulatory

Koski said the office has created programs to help research institutions “Do it right, together,” the office motto he coined. Also in the works is a voluntary accreditation system for institutions that conduct human research.

....

Koski . . . found himself between two very vocal factions, one calling for new and formalized federal rules governing patient safety and conflicts of interest, and the other favoring voluntary standards that would largely be overseen by research institutions themselves.

On several occasions, sources said, Koski triggered grumbling on Capitol Hill for taking positions without first going through the usual political channels, or for releasing formal documents that had not first been approved by the Office of Management and Budget – moves that one insider attributed to a mix of naiveté and Koski’s growing frustration with the system.

Id. See also Joceylyn Kaiser, *Protecting Human Subjects: Koski Steps Down After Bumpy Ride*, 298 *SCIENCE* 721, 721-22 (2002), reporting:

OHRP has begun developing a system in which institutions—rather than the government—grade themselves on their oversight programs. A report . . . from the Institute of Medicine supports this approach, as well as voluntary accreditation of human-subjects protection programs.

....

Some patient advocates and members of Congress, however, are pushing for mandatory standards. . . .

Id. A few days after leaving office, Dr. Koski disparaged what he termed “hyperprotectionism” and said he would not accord protection as a research subject to a mentally retarded teen-ager whose bone marrow would be taken for transplant to an ailing sibling who was the primary subject on a clinical research project. Greg Koski, “When Is a Child a Research Subject?,” Ethics Grand Rounds, Warren G. Magnuson Clinical Center, National Institutes of Health, December 4, 2002, at <http://videocast.nih.gov/PastEvents.asp?c=22> (last visited November 22, 2003); Rebecca Spieler Trager, *Human research oversight system has let scientists abdicate ethics, Koski asserts*, WASH. FAX, December 12, 2002.

20. Inst. of Med. of the Nati’l Acad. Sci., *supra* note 7, at 18.

oversight, the extent of institutional support for good-faith compliance, and recognition of ethical issues in human subjects research. Here Belmont takes on its special significance, not only because of its content but, more important, because it is the justifying document referenced in the preamble to the initially promulgated modern human subjects protection regulations²¹ and in administrative law is thus to be used in interpreting those regulations.²²

The Belmont Report

Belmont is a regulatory, not a philosophic, document.²³ It calls for unflinching recognition of ethical issues, notwithstanding the nobility of intentions or predispositions as to whether contemplated research would be ethically permissible. It calls for judgment. It calls for squarely recognizing, well before a possible program or project of biomedical or behavioral research on human beings begins, that the researcher and the research subject are of equal moral status, and that fundamental, universal legal and ethical norms proscribe the coerced use of one human being for the purpose of another except in extraordinary circumstances under due process of law.

II. LEGAL AND ETHICAL ISSUES

Fundamental, universal legal and ethical norms proscribe the coerced use of one human being for the purposes of another

Fundamental, universal legal and ethical norms proscribe the coerced use of one human being for the purposes of another absent

21. Office of Science and Technology Policy, Executive Office of the President, Federal Policy for the Protection of Human Subjects Final Rule, 56 Fed. Reg. 28,003 (June 18, 1991) (Common Rule, adopted by 16 agencies, and preamble incorporating Belmont Report by reference directly in some respects, as by reference to burdened populations, and indirectly, by reference to Federal Register notices of reports of the President's Commission, in turn citing the predecessor National Commission).

22. 5 U.S.C. § 552.

23. The legislation creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research required prompt, substantive agency response to the Commission's reports and recommendations, 41 U.S.C. § 300v-1(b), and continues to be cited as regulatory authority by the Department of Health and Human Services, 45 C.F.R. pt. 46.

due process of law. The proposed use of human beings as the subjects of research presents two ethical issues at the outset:

(a) Whether one human being is used merely as a means to attain the purposes of another. This is sometimes ethically permissible, sometimes not, depending on purposes and protections.

(b) Whether the human subject of research is coerced. Coercion of potential and actual research subjects is ethically and legally impermissible, worldwide. "In particular, no one shall be subjected without his free consent to medical or scientific experimentation."²⁴

These norms are expressed in international law, transcending cultures; in domestic law; in international and domestic policy statements; in philosophical and religious writings; in professional codes and statements; and in literature.²⁵

U.S. protection of human subjects of biomedical and behavioral research is constitutionally grounded and reflects U.S. international obligations

The U.S. Government promulgated regulations for the protection of human subjects of research well before ratifying the International Covenant on Civil and Political Rights. The U.S. interpretation, in its initial report of compliance, is that the Covenant's Article 7 proscription against unconsented medical experimentation stands independent of that same article's prohibition of torture; that U.S. regulation to protect human subjects of research is constitutionally grounded; and that U.S. human subjects protection regulations comply with U.S. international obligations.²⁶ The sweep of

24. Int'l Covenant on Civil & Political Rights, Dec. 16, 1966, at http://www.unhchr.ch/html/menu3/b/a/_ccpr.htm (last visited November 22, 2003) (entered into force March 28, 1979, ratified June 8, 1992; 149 ratifications.) Article 7 is non-derogable even in times of emergency pursuant to ¶ 2 art. 4.

25. See, e.g., JOHN LE CARRÉ, *THE CONSTANT GARDENER* (2001) (novel on pharmaceutical industry operations in Africa).

26. See also MANFRED NOWAK, *U.N. COVENANT ON CIVIL & POLITICAL RIGHTS: CCPR COMMENTARY* 137-141 (1993). Nowak says the term "in particular" implies that the prohibition "does not extend to experiments whose interference with personal integrity does not reach the degree of degrading or inhuman treatment," and (in his view) "clinical testing of pharmaceutical products without the knowledge and/or consent of the person concerned falls within the scope of Art. 7 only when the effects . . . constitute degrading or inhuman

the U.S. interpretation on the latter two points is breathtaking and provides *inter alia*.²⁷

178. *Medical or scientific experimentation.* Non-consensual experimentation is illegal in the U.S. Specifically, it would violate the Fourth Amendment's proscription against unreasonable searches and seizures (including seizing a person's body), the Fifth Amendment's proscription against depriving one of life, liberty or property without due process, and the Eighth Amendment's prohibition against the infliction of cruel and unusual punishment.

179. Comprehensive control of unapproved drugs is vested by statute in the federal Food and Drug Administration (FDA). The general use of such drugs is prohibited, *see* 21 U.S.C. section 355(a), but the FDA permits their use in experimental research under certain conditions. 21 U.S.C. sections 355(i), 357(d); 21 C.F.R. section Part 50. The involvement of human beings in such research is prohibited unless the subject or the subject's legally authorized representative has provided informed consent, with the limited exceptions described below. The FDA regulations state in detail the elements of informed consent. 21 C.F.R. sections 50.41-50.48.

180. An exception is made where the human subject is confronted by a life-threatening situation requiring use of the test article, legally effective consent cannot be obtained from the subject, time precludes consent from the subject's legal representative, and there is no comparable alternative therapy available. The Commissioner of the FDA may also determine that obtaining consent is not necessary if the appropriate Department of Defense official certifies that informed consent is not feasible in a specific military operation involving combat or the immediate threat of combat. This regulatory exception has been challenged in litigation and upheld as consistent with the

treatment," but "[r]egard must also be paid to the indications in the travaux préparatoires that the lack of free consent is to be considered a sign of the inhuman character of a medical experiment." *Id.* at 141(emphasis added).

27. U.S., INITIAL REPORTS OF STATES PARTIES DUE IN 1993: UNITED STATES OF AMERICA, art. 7, §178-87 (CCPR Human Rights Comm., State Party Report CCPR/C/81/Add.4, 1994, at [http://www.unhchr.ch/tbs/doc.nsf/\(Symbol\)/da936c49e d8a9a8f8025655c005281cf?Opendocument](http://www.unhchr.ch/tbs/doc.nsf/(Symbol)/da936c49e d8a9a8f8025655c005281cf?Opendocument) (last visited November 22, 2003). *See also* Sell v. United States, 123 S. Ct. 2174 (2003) (reaffirming prisoner's due process liberty interest in freedom from government-imposed, unwanted psychiatric treatment).

governing statutes and the U.S. Constitution. *Doe v. Sullivan*, 938 F.2d 1370 (D.C. Cir. 1991).

181. The United States has also undertaken substantial efforts to diagnose and redress injuries that may have been caused by past exposure to potentially dangerous military agents. Thus, it continues to fund epidemiological studies in an attempt to resolve lingering scientific and medical uncertainty surrounding the long-term health effects of exposure to herbicides containing dioxin and to ionizing radiation. It has also provided military veterans with an expeditious means of obtaining compensation for claims based on exposure to such herbicides during service in the Republic of Viet Nam, or exposure to ionizing radiation during atmospheric nuclear tests or the American occupation of Hiroshima and Nagasaki, and has established guidelines for evaluating and applying the latest scientific evidence. The Veterans Dioxin and Radiation Exposure Compensation Standards Act, Pub. L. No. 98-542, 98 Stat. 2727 (1984). Civilian residents of the relevant areas put at risk by nuclear testing or employed in uranium mining can also recover sizeable compensation if they have developed any of a number of specified diseases. Radiation Exposure Compensation Act, Pub. L. No. 101-426, 104 Stat. 920 (1990).

182. In December 1993, it became widely known that between 1944 and 1974 the United States Government conducted and sponsored a number of experiments involving exposure of humans to radiation. While certain experiments resulted in valuable medical advances including radiation treatment for cancer and the use of isotopes to diagnose illnesses, a number of the experiments may not have been conducted according to modern-day ethical guidelines. Moreover, the majority of the records of the experiments were kept secret for years. The United States Government has taken a number of steps to investigate the propriety of the experiments. For instance, the Department of Energy established a centralized information centre in Washington, D.C., that holds 270,000 records on nuclear testing and 7,000 records on all types of human experiments, and identified approximately 2,500 records of human radiation experiments and placed them in public reading rooms around the country. By executive order in January 1994, the President established the Advisory Committee on Human Radiation Experiments, which is charged with investigating the propriety and ethics of all human radiation experiments conducted by the Government, and determining whether researchers obtained informed consent from their subjects. . . .

183. Experimentation on prisoners is restricted by the Fourth, Fifth, and Eighth Amendments to the United States Constitution, by statutes, and by agency rules and regulations promulgated in response to such provisions. As a general matter, in the United States, “[e]very human being of adult years or sound mind has a right to determine what shall be done with his own body ...”. *Schloendorff v. Society of New York Hospitals*, 211 N.Y. 125, 105 N.E. 92, 93 (1914). Accordingly, prisoners are almost always free to consent to any regular medical or surgical procedure for treatment of their medical conditions. Consent must be “informed”: the inmate must be informed of the risks of the treatment; must be made aware of alternatives to the treatment; and must be mentally competent to make the decision. But due to possible “coercive factors, some blatant and some subtle, in the prison milieu”, (James J. Gobert and Neil P. Cohen, *Rights of Prisoners*, New York: McGraw Hill, Inc., 1981, pp. 350-51) prison regulations generally do not permit inmates to participate in medical and scientific research.

184. The Federal Bureau of Prisons prohibits medical experimentation or pharmaceutical testing of any type on all inmates in the custody of the Attorney General who are assigned to the Bureau of Prisons. 28 C.F.R. section 512.11(c).

185. Moreover, the federal government strictly regulates itself when conducting, funding, or regulating research in prison settings. An Institutional Review Board, which approves and oversees all research done in connection with the federal government must have at least one prisoner or prisoner representative if prisoners are to be used as subjects in the study. Research involving prisoners must present no more than a minimal risk to the subject, and those risks must be similar to risks accepted by non-prisoner volunteers. See 28 C.F.R. Part 46. Furthermore, guidelines established by the Department of Health and Human Services provide that the research proposed must fall into one of four categories:

“(1) Study of the possible causes, effects, and processes of incarceration, and of criminal behaviour, provided that the study presents no more than a minimal risk and no more than inconvenience to the subject;

(2) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subject;

(3) Research on conditions particularly affecting prisoners as a class;

(4) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health and well-being of the subject.”

45 C.F.R. section 46.306(a)(2).

186. Similar standards have been developed within the broader correctional community that strictly limit the types of research conducted in prisons, even with an inmate’s consent. . . .

187. Non-medical, academic research on inmates is normally allowable in federal and state prisons with the inmate’s express consent. This type of research normally consists of inmate interviews and surveys. Inmates are not required to participate in any research activities other than those conducted by correctional officials for purposes of inmate classification, designation, or ascertaining inmate programme needs (e.g., employment preparation, educational development, and substance abuse and family counselling).²⁸

This report of compliance is a commitment by the United States under its multilateral treaty obligations and arguably under customary international human rights law. Softening the overall U.S. commitment under the International Covenant on Civil and Political Rights would likely incur unacceptably heavy political costs at home and abroad. Probably due to agency and academic parochialism, this material does not appear in bioethics literature or in U.S. regulatory guidance. Nevertheless, it is the U.S. Government’s most elaborate, although not necessarily comprehensive, formal position on its own obligations in international law.

Biomedical and behavioral research on human beings raises ethical challenges

Research on human beings involves the use of these persons at least partly for someone else’s purposes. The interests of researcher and research subject may coincide or conflict.²⁹ Power disparities in relationship between researcher and subject are inevitable, stemming especially from a subject’s relative ignorance, limited range of

28. INTIAL REPORTS OF STATE PARTIES, *supra* note 27.

29. ROBERT M. VEATCH, *BASICS OF BIOETHICS* 140-143 (2d ed. 2003) (distinguishing research from therapy and elaborating on ethical concerns in research on human subjects).

alternatives, trust, fear, and the psychological auras of effects of science, government, and medicine. The subject may be particularly vulnerable — as a patient, a child, an incompetent, or one of a class of people whose individuality and rights are not always respected. The roles and obligations of researchers are not necessarily clear to researcher or subject. Researcher, subject, or both may entertain the illusion that the research is necessarily therapeutic, that is, for the subject's benefit. Neither researcher nor subject may adequately understand the research, its purposes, and its possible effects.

Biomedical and behavioral research on human beings may be ethically desirable and may be ethically acceptable or impermissible

Biomedical and behavioral research on human beings may be essential to alleviate human suffering generally.³⁰ Biomedical and behavioral research may help alleviate the condition of an individual patient. Research on human beings may be done in a manner consistent with the rights of subjects and the ethical obligations of health professionals. But some moral questions concerning research may be unavoidable. Conscripting of human research subjects on the grounds of social utility squarely conflicts with human rights.

The starting point for deciding whether to conduct biomedical or behavioral research on human beings should be to consider the possibility that the research as contemplated may not be ethically permissible. Filling out the relevant forms correctly and getting the requisite approvals do not make biomedical and behavioral research on human beings ethically permissible.

III. ETHICALLY CHALLENGING RESEARCH AND RESEARCH PROPOSALS RECUR

Law to restrict federal spending on biomedical research likely to transgress the rights of human subjects is now institutionalized, although it is criticized and not necessarily well enforced. Arguably, the bare bones of the regulatory scheme are well known to the regulated community. At least a minimal acquaintance with the controlling regulatory arrangement is required of that community.

30. Edmund D. Pellegrino, *The Necessity, Promise, and Dangers of Human Experimentation*, in *EXPERIMENTS WITH MAN: REPORT OF AN ECUMENICAL CONSULTATION 31-56* (Hans-Ruedi Weber ed., 1969).

Additionally, there is an apparent self-vs.-community conflict in discussions of who bears burdens and who gets benefits.

Perhaps Belmont is passé, the problem addressed, many of the recommendations followed, and the world now resolved to act rightly. Belmont, from a time long past, is a political document, a response to the offenses then embodied most notably in the Tuskegee and Public Health Service scandal. Surely, no one now would pretend to treat poor, black men for syphilis while studying them as they go untreated. There was the repeated plasmapheresis of prisoners to the point of anemia, but that was still in the 1970s, after the Tuskegee scandal but before Belmont. Maybe taking blood products from prisoners was an oversight. There were the unconsented radiation studies,³¹ some post-Tuskegee but pre-Belmont; they were Cold War artifacts. On the whole, the U.S. biomedical research community changed in response to Belmont. The U.S. system for protection of the human subjects of research became a remarkable model, despite the difficulties that attend any regulatory scheme.

Perhaps there is no more call to forestall or deter bad acts by researchers. Perhaps biomedical ethics no longer has anything to inquire about in this regard. These assumptions, however, do not appear to be the case.³² Individual, responsible judgment is still

31. Advisory Comm. on Human Radiation Experiments, Final Report (1995).

32. See generally Dep't of Human Servs, Office of the Inspector Gen., *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects* (2001), at <http://www.oig.hhs.gov/oei/reports/oei-01-00-00190.pdf> (last visited November 22, 2003); see also Joe Stephens et al., *The Body Hunters*, WASH. POST, Dec. 17-22, 2000 (reporting unethical practices in biomedical research on human subjects in underdeveloped), available at <http://www.washingtonpost.com/wp-dyn/world/issues/bodyhunters/> (last visited November 22, 2003); see also *Abdullahi v. Pfizer, Inc.*, No. 01 Civ. 8118, 2002 U.S. Dist. LEXIS 17436 (S.D.N.Y. Sept. 17, 2002) (rejecting defendant's motion for dismissal for failure to state a claim under Alien Tort Claims Act, (28 U.S.C. § 1350), alleging research abuses against Nigerian children in Nigeria, and provisionally dismissing on grounds of forum non conveniens, provided defendant did not object to trial in Nigeria and that Nigeria would consider the claim), *vacated, remanded*, 2003 U.S. App. LEXIS 20704 (2d Cir. N.Y., Oct. 8, 2003) (absence of alternative forum). See also Memorandum from P. Wray Nelda, Chief Research and Dev. Officer, to ACOS/R (Mar. 6, 2003), at http://www1.va.gov/resdev/fr/stand_down/memo.cfm (last visited November 22, 2003):

1. Background: In the eight short weeks since I assumed responsibility as Chief Research and Development Officer (CRADO), I have had to address a number of incidents concerning the protection of human subjects involved in interventional research studies that have the potential

required as to who may use whom for what, and when, why, and with what protections in place,³³ but the need for such judgment may be buried, finessed, forgotten, or dismissed.

Three current research programs illustrate the challenge to candidly face and address the ethical implications of contemplated research on human beings, well before that contemplated research program or project acquires momentum and well before encountering such regulatory details as how to categorize apparent risk. The following three programs each implicate individual ethical responsibility in a large organizational context. The impetus for each program is political (response to public constituencies), organizational (response to agency imperatives and folkways), individual (responses to career interests and to perceived public needs), and scientific (response to perceived needs for knowledge). Each program involves or is proposed to involve hundreds or thousands of subjects. The subjects in these examples are presumably more vulnerable than ordinary people. Each program is intended for the benefit of a class of persons from which the subject is drawn but is not intended for the identifiable benefit of any particular, identifiable subject.

Vaginal flora research:

The effects and persistence of vaginal flora in a Southern U.S. public clinic population have been under study for several years. This program includes microbial sampling and behavioral research.³⁴

to put research subjects at risk. Those incidents include the falsification of individual patient data that contributed to the death of one or more patients; the inadvertent overdosing with a study medication of a research participant; an experimental procedure that was conducted without the prior approval of either the Institutional Review Board (IRB) or Research and Development (R&D) Committee; and a phase 4 drug study that was conducted without a principal investigator (PI) of record with clinical privileges to prescribe and monitor the study medication and the failure of an IRB to meet even the minimal standards required by the Common Rule.

Id. See also Robert Pear, *Nationwide Inquiry at Veterans' Hospitals*, N.Y. TIMES, April 13, 2003, at A14.

33. For example: "Among people who do work like . . . studies on the very young, the very sick, there is no shortage of cowboys," says Steven Hyman, who was the director of the National Institute of Mental Health . . ." *Sheryl Gay Stolberg, Preschool Meds*, NEW YORK TIMES MAGAZINE, Sept. 17, 2002, at 59, 60.

34. Nat'l Inst. of Child Health & Human Dev., *Current Research: Longitudinal study of vaginal flora* (2003), at <http://www.nichd.nih.gov/despr/epirsh.htm> (last visited November 22, 2003).

Purposes notwithstanding, such research in a clinic population raises questions of (1) whether recruitment is suggested by gatekeepers to these subjects' care; (2) whether subjects would understand fully that the research is not therapeutic; (3) whether subjects might misperceive the study as one in which they would be notified of findings from study of their tissues; and (4) whether there is a non-negligible possibility of violation of privacy.

Children's Health Initiative and the National Children's Study:

A multi-agency federal program will undertake a large set of observational epidemiological and behavioral studies, ultimately involving approximately 100,000 children, with a focus on physical and social environment and with involvement of local public school and social service authorities.³⁵ The studies will involve identified primary subjects and identified third parties and probably will involve the taking of tissues from children deemed autistic. Effective legal mechanisms for safeguarding confidentiality do not exist. Recruitment of subjects will be encouraged by school systems and local booster committees. Numerous National Institutes of Health and interagency committees, including an ethics committee appointed for this purpose, are involved. As the program was getting organized, the ethics committee noted that several ethical issues remained to be addressed, including recruitment questions, informed consent, the right to withdraw from the study, rights concerning tissue samples, and privacy and confidentiality.³⁶ A member of a behavioral sciences subcommittee of the National Human Research Protections Advisory Committee had reported that social research is by definition minimal risk.³⁷

Alzheimer's tissue banking:

A large, federally funded, expanding multi-institution program gathers tissue from Alzheimer's Disease patients and their families

35. Children's Health Act of 2000, Pub. L. No. 106-310, 114 Stat. 1101 (2000); See The Nat'l Children's Study, Organizational Chart, at [http://www.nationalchildrensstudy.gov/committees/\(detailing scope of study\)](http://www.nationalchildrensstudy.gov/committees/(detailing%20scope%20of%20study))(last visited November 22, 2003).

36. Env'tl. Protection Agency & Nat'l Institutes of Health, *National Children's Study: Ethics Working Group Report* (undated), available at <http://nationalchildrensstudy.gov/committees/ethics/report.cfm> (last visited Nov. 22, 2003).

37. Levine, *supra* note 8.

for Alzheimer's-related genetics studies in the unspecified future.³⁸ That the tissues are needed for the study of urgent health issues is not in question. At a public discussion of related ethical concerns,³⁹ this work was described as (1) minimal risk and (2) unjustifiably hindered by state law barring research on individuals who could not themselves legally consent unless the research was for the purpose of benefiting the specific patient. Discussants did not address vulnerability of families to discrimination or the vulnerability of some subjects to coercion. No one present openly characterized the proposal as one for the conscription of some persons, under color of government or law, for the purposes of others. Two persons suggested that autonomy had run its course and that it was time to think of the larger society, and one person maintained that the rights of researchers had to be considered.

These programs seem innocuous, possibly useful, perhaps dearly needed. Each program might be rationalized by a reasonable local Institutional Review Board as ethically acceptable with suitable protections. To some readers, these examples may suggest failures of ethical review or of the system. No such charge is intended here; anyone can disagree with any board's findings. These examples illustrate projects with potential to misuse human subjects in ways that are difficult to pinpoint without reflection on the spirit of the human subjects protection regulations.⁴⁰ In these contexts, compliance with

38. ELISA EISEMAN & SUSANNE B. HAGA, HANDBOOK OF HUMAN TISSUE SOURCES: A NATIONAL RESOURCE OF HUMAN TISSUE SAMPLES 36-40 (1999); Nat'l Inst. on Aging, National Cell Repository: Selected Future Research Directions in Alzheimer's Disease and the Neuroscience of Aging (2002) at http://www.nia.nih.gov/fy2003%5Fcongress/justification.html#future_dir (last visited Nov. 22, 2003).

39. September 9, 2002, at the National Institutes of Health.

40. See EISEMAN & HAGA, *supra* note 37, at 1. Taking of tissues should prompt particularized inquiries "as recent and rapid advances in biological and medical research made it possible to analyze DNA from almost any minuscule sample of human tissue, concerns about privacy and informed consent have been raised. Complicating these issues is the paucity of information addressing tissue acquisition, use, and storage." *Id.* See also N.Y. STATE TASK FORCE ON LIFE AND THE LAW, GENETIC TESTING & SCREENING IN THE AGE OF GENOMIC MEDICINE 68-73, 101-102 (2000). Experimental design, no matter how sophisticated, is by no means free of ethical implications. Thus, an editorial in the *Journal of Clinical Oncology* says of the acceleration of phase I (toxicity) trials of a chemotherapeutic agent:

[T]he study design was not conducive to maximal risk reduction as it potentially exposed more patients than necessary to doses exceeding the maximum tolerated dose. For example, there was an unacceptably high

no more than the letter of the law is insufficient ethically and legally. Administrative lawyers are taught to look to Federal Register preamble statements and references (here Belmont) to interpret regulations, as the Administrative Procedure Act requires.⁴¹ It is not obvious to non-lawyers that the copy of Belmont that accompanies the copy of the regulations provided to scientists and ethics board members is of binding importance, even though the Government's published regulatory guidance should have made that clear.⁴²

No published records are available to show whether or how Belmont was used to interpret the research subject protection regulations as applied to these programs. But these programs obviously prompt questions for which Belmont remains an appropriate interpretive guide — in its totality and implications rather than as a set of discrete rules to be applied specifically as reason for the researcher to proceed or not. Belmont does not say expressly whether the burden of persuasion to proceed with a project should be on the researcher or on the reviewing entity. Belmont does not give a default rule. That is, it does not say expressly to be (a) maximally restrictive, i.e., allowing

incidence of intolerable toxicity by any standards . . . ; six (50%) of 12 patients experienced severe (grade 3) nonhematological dose-limiting toxicity, including five patients in the first course of treatment rather than the maximally accepted norm of two patients. . . . [T]he simultaneous entry of multiple patients provides little opportunity to apply the “brakes” that should be built into the study to prevent or minimize toxicity in other patients once severe toxicity is recognized.

Andrew W. Tolcher, Chris H. Takomoto, & Eric K. Rowinsky, *Editorial: The Multifunctional, Multi-Institutional, and Sometimes Even Global Phase I Study: A Better Life for Phase I Evaluations or Just “Living Large”?* 20 J. CLIN. ONCOL. 4,276, 4,276-4,278 (2002).

41. 5 U.S.C. § 522.

42. See Office for Protection from Research Risks, Institutional Review Board Guidebook: Protecting Human Research Subjects 9 (1993). “[T]he Belmont Report . . . sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence, and justice, are now accepted as the three quintessential requirements for the ethical conduct of research involving human subjects.” *Id.* See also Alison Wichman & Alan L. Sandler, *Institutional Review Boards*, in *Principles and Practices of Clinical Research* 51-62 at 59 (John I. Gallin ed., 2002), (stating “[t]he ethical foundation for the current laws governing human subject research protections is enunciated in the *Belmont Report* . . .”). Wichman and Sandler are from the Office of Human Subjects Research, Intramural Research Program, National Institutes of Health; Gallin is director of the Warren G. Magnuson Clinical Center, National Institutes of Health.

only those projects that clearly could not be expected to violate any violate precept or rule; (b) minimally restrictive, i.e., allowing all projects that present no red flag; or (c) something in between. Instead, Belmont gives researchers and reviewing entities sets of issues to consider in determining whether a research project as proposed or conducted warrants ethical doubt, and, if so, how the regulations should be interpreted and applied in order to achieve an ethically acceptable result.⁴³ Review boards often require stipulated modifications where necessary to alleviate their ethical concerns.

These examples suggest that Belmont would perform this function well. Each of these programs intrudes into the personal lives of vulnerable research populations, lends itself to misunderstanding, and is not for the direct benefit of the prospective subjects. These are matters of justice, as in the rights of persons to be free of unwarranted intrusion into their lives. These are matters of respect for persons, as in full disclosure of risks and benefits and in eliciting of fully voluntary informed consent or refusal. These are matters of beneficence in that

43.

[R]ules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles [respect for persons; beneficence; and justice], or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

Belmont Report, 44 Fed. Reg. 23,192 at 23,196 (April 18,1979). This is quite different from a meet-the-requirements approach. See Ezekiel J. Emanuel, David Wendler, & Christine Grady, *What Makes Clinical Research Ethical?*, 283 J. AM. MED. ASS'N 2,701-2,711 (2000) (which deems their essay's enumerated requirements interpretable but "sufficient" and does not discuss *Belmont*). Emanuel, et al. characterize 45 C.F.R. part 46 and the Council of Europe Convention on Human Rights and Biomedicine, both legal documents, as "guidelines," along with non-government documents such as the Declaration of Helsinki; they do not mention the International Covenant on Civil and Political Rights. *Id.*

the first interest of the biomedical or behavioral researcher working with human subjects should be the best interests of the subject.

The use of Belmont in interpreting whether the intent of the rules had been satisfied would have had the researchers and reviewing entities consider in detail: How does the proposed selection of research subjects and the research itself comport with respect for these particular persons? How might the proposed research put these particular persons at non-negligible risk? Would these uses of these persons be fair?⁴⁴ How might the selection of research subjects or the nature of the research be modified to accord with Belmont's precepts?⁴⁵ These are not hard questions. Who are these people, why and how do we propose to use them? Belmont does not delineate rules; it suggests some, but certainly not all, points that should prompt ethical concerns. Belmont makes plain that ethical concerns about research on human beings should be resolved in favor of the proposed or actual research subjects. This is Belmont's simple message as to

44.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

Belmont Report, 44 Fed. Reg. at 23,196-23,197.

45. "When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits." *Belmont Report*, 44 Fed. Reg. at 23,196.

how regulations for the protection of human subjects of biomedical and behavioral research should be interpreted.

Current events in research suggest strongly that the Belmont Report's central insights and lessons are still in point

Because Belmont was a response directly and cogently to actual, notorious wrongs and the likelihood of their repetition, it has special and credible emotional force. The report stems from reality, not prescriptive assumptions. In contrast, the current critiques stem in large part from concerns regarding inconvenience, delay, and expense.

Belmont is not a philosophical disquisition or ethical formulation. It is unusual as a public policy document in that it is a secular articulation of individual rights and societal values to be protected in the conduct of research on human subjects.

Belmont sets forth not a checklist or fixed way of thinking about proposed research. Rather, it urges that the moral challenges endemic to research on human beings be carefully considered from several standpoints—including respect for persons, beneficence (including non-maleficence), and justice. These values are well served by independent ethical review, informed consent, and special concern for persons who are especially vulnerable. The modern, semi-independent Institutional Review Board structure, to which the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research gave rise, draws its credibility and effectiveness from the reality that gave it birth and from providing for both public participation and researcher participation. In administrative law terms, the regulated community is encouraged to buy into the system, subject to conflict-of-interest restrictions. As the three research program examples above make clear, the need for the Belmont touchstones and the regulatory structure continue.

IV. COUNTER-ARGUMENTS

Generally, the counter-arguments to the foregoing fall into a few categories. Self-pleading complaints about being regulated may be deemed without ethical merit,⁴⁶ although, as will be seen, not without

46. See, e.g., Mary L. Durham, *How Research Will Adapt to HIPAA [Health Insurance Portability and Accountability Act of 1996]: A View from Within the Healthcare Delivery System*, 28 AM. J.L. & MED. 491, 492 (2000) (summarizing dire warnings against initial promulgation of the Common Rule).

implications. Some of the utilitarian criticism of Belmont and its legacy is rooted not in selfishness but in deep, morally based concern about the burden of illness. Criticism that there are no universals, that this system and rationale are inapplicable to international projects where they have no meaning in the local cultural setting, is not to be dismissed. Criticism of how the system may fail or that it is unduly burdensome should not be dismissed but should be considered carefully.

The argument that the current regulatory system and rationale fail for lack of anticipation of such new modes of research as multi-site clinical trials is, on balance an argument not for abolishing the system or rejecting its rationale but rather for heeding the rationale and adapting to new circumstances,⁴⁷ thereby strengthening the regulatory system through appropriate enforcement policy and practice.

The argument that the examples offered above would not have materialized had the regulatory system and its rationale been adequate fails on two counts. First, it assumes that a research proposal that triggers thought about moral consequences is therefore unethical not only originally but also as it might be modified in light of critical questioning. Second, it assumes that unanimity on the moral acceptability of a research proposal as presented or modified is essential.

The argument that Belmont and the current regulations should be scrapped because abuses of human subjects have occurred and the intent of the regulations has been flouted is an argument not for ignoring the rationale and doing away with the current regulatory mechanism but rather for heeding the rationale and enforcing and strengthening regulatory protections. The strongest, most detailed investigation ever undertaken into research abuses in the United States was that by the Advisory Committee on Human Radiation

47. The National Cancer Institute, for example, arranged for a central institutional review board to work in cooperation with local IRBs in a multi-site clinical trial. That would be consistent with the intent behind the regulation. NCI apparently sought and got advance OHRP comment on its proposed central-IRB pilot. According to the Institute, the initiative was "in collaboration with" the departmental Office of Human Research Protections. NATIONAL CANCER INSTITUTE, INTRODUCTION TO MANUAL.DOC (April 16, 2002), *available at* http://www.ncicirb.org/sops/Introduction_to_Manual.PDF (last visited November 22, 2003). But "collaboration," implying that OHRP here was a co-performer or regulatory consultant, which roles would conflict with regulatory neutrality, could have been an overstatement or a genuine failure to understand regulatory posture. *Id.*

Experiments, which found substantial strengthening of human research protections since Belmont and the Common Rule, although with some continuing deficiencies.⁴⁸ The Committee recommended greater emphasis on compliance with the Common Rule and recommended strengthening but not abolishing it.⁴⁹ Belmont and the Common Rule are far from perfect, but an attempt to replace either or both would likely become an exercise in discounting old but still valid important and powerful lessons, and in jockeying for researcher and institutional advantage, with the interests of research subjects unrepresented. As a result, existing protections could well be lost. However, the current human subject protection regulations leave room for forthright enforcement guidance to the effect that good-faith compliance includes clear, unprejudicial procedures for appointing and discharging IRB members; ensuring that IRBs have the resources and true organizational independence they need to do their work; guarding against conflicts of interests; distinguishing between sincere ethical review and paperwork; and transforming of reward structures in order to encourage ethical design, review, and conduct of research. Taking seriously the need to train and encourage students, researchers, and practitioners in ethical discernment is not a regulatory matter, but it is no less a duty of educators, mentors, and other persons who set the examples.

The argument that regulation is unnecessary where people behave properly begs the question of making reasonably clear the kinds of insensitivity and conduct that transgress ethical bounds in the use of human subjects in biomedical and behavioral research. American political history is replete with such arguments. The implications, when these arguments are raised by persons with bioethics in their titles, are that the current system and rationale are somehow defective ethically. Policy-makers and ethicists should beware of crediting that kind of argument without deeper assessment of what the system actually is, how it works or does not work, and what changes might lead to what results.

The argument that more people will suffer, absent regulatory streamlining, is and should be troubling. But while it is easy to demonstrate that a given research subject may be at risk, it is very difficult to prove that a given biomedical or behavioral experiment will benefit that person or any persons (other than the investigators, perhaps). If safety and efficacy were assured, then the intervention

48. ADVISORY COMM.ON HUMAN RADIATION EXPERIMENTS, FINAL REPORT 816-17 (1995).

49. *Id.*

would not be experimental. Moreover, even in utilitarian terms, there is no demonstrated connection between (a) shortcuts in protection of human subjects, and (b) relief of human suffering. Those arguments manifest the therapeutic illusion that biomedical and behavioral experiments, even in hopes of therapeutic benefit, are designed for the specific purpose of providing benefit for the individual subject or patient. Even if some group benefit were to be found in short-cutting protections, the challenge of fairness to individuals would persist. The related argument that “this is for their own good” begs all of these questions.

This regulatory scheme and rationale bar research on persons in cultures that submerge individual rights and identity in group values. That limitation has been criticized as culturally insensitive and as unjustly denying the benefit of participation as experimental subjects to desperately poor persons and societies in the midst of epidemics. This criticism presupposes, worse yet, that the limitation bars possibly useful research in those places where particular diseases or varieties of disease occur uniquely. There are no universals, it has been said. Such arguments⁵⁰ disregard international law on informed consent and conflate the therapeutic illusion with ideals of distributional justice. There is almost no assurance of health benefit. That a disease or condition may be unique to an isolated culture that does not respect individual rights does not necessarily conflict with medical obligations of beneficence. Research short of work on human subjects may proceed, and doctors are not precluded from doing what they can to reduce suffering or from urging appropriate public health measures. Ignorance can be overcome, and lack of regard for human rights need not be accepted as a given. Cultural sensitivity is not necessarily a good excuse.⁵¹ The assertion by some researchers and some ethicists

50. See, e.g., Angeles Tan Alora & Josephine M. Lumitao, *An Introduction to an Authentically Non-Western Bioethics*, in *BEYOND A WESTERN BIOETHICS: VOICES FROM THE DEVELOPING WORLD* 18-19 (Angeles Tan Alora & Josephine M. Lumitao eds., 2001) (stating “research must be placed within the particular cultural, religious, and metaphysical context of particular developing countries” but such concerns “set much of the developing world in direct contrast with the world of Western bioethics”). The authors, dealing with the Philippines, thus ignore the significance of their own reprint of the Philippines’ legal requirements for informed consent in medicine and medical research. *Id.*

51.

A researcher should not pick and choose which elements of a culture he or she accepts based upon the way in which it will help or hinder the research. “Cross-cultural sensitivity” does not give an experimenter license to bend and break norms of professional conduct....

that no universals bar research in those difficult circumstances prompts the question of why those individuals believe themselves uniquely exempt from the non-derogable stricture in the International Covenant on Civil and Political Rights, "... In particular, no one shall be subjected without his free consent to medical or scientific experimentation."

Argument that the system is exhausting and over-protective is not proved and is probably not susceptible to proof or disproof. The argument that it is burdensome financially is not an ethical question and depends on how the institution chooses to allocate its resources. There seems little question that institutional review boards are overburdened and under-resourced; that is an institutional management question. The argument that the system forces researchers and institutional review boards to thread a regulatory needle in order to meet regulatory minima raises the questions of why honest ethical doubt is undesirable and why researchers and boards may feel they must resort to elaborate rationalization in order to go ahead with a project. A related criticism is that informed consent documents may amount to efforts not to completely inform the prospective research subject but to evade liability. That amounts to criticism not of the informed consent requirement but of institutional evasion and of laxity of enforcement. Some critics argue that the system is at fault because review boards are too restrictive. That seems to call for understanding by boards and researchers of their common obligations to research subjects. But it is not a substantive criticism of the system.

Experimental protocols may need to pass two ethical tests, a general ethical test of respect for persons and a more specific test of how true respect may be obtained in a particular culture.

This specific ethical test would not abandon basic values but rather ask how such values are to be enfolded in culturally different contexts. . . . On occasion, . . . a true impasse might arise because of a genuine clash of values themselves. At such times, the experimenter may very well find it ethically necessary to abandon a particular experiment in a particular culture. Such cross-cultural sensitivity may benefit not only the subjects of the experimentation but the ethical person who is the experimenter as well.

Thomas A. Nairn, *The Use of Zairian Children in HIV Vaccine Experimentation: A Cross-Cultural Study in Medical Ethics*, in *ON MORAL MEDICINE* 919, 928-929 (Stephen E. Lammers & Allen Verhey eds., 1998).

CONCLUSIONS

Criticisms that the current regulatory system as applied is clumsy and inconvenient do not respond to the challenge, clear in Belmont as in Hans Jonas, to recognize ethical dilemmas, face them squarely, say no when no is warranted, foster researcher involvement in the regulatory system, focus on substance rather than form, and resist automaticity.

If the regulatory system is to function well—i.e., protectively and reasonably efficiently—then:

- (1). Belmont's proper role should be recognized—not as a relict document handed to review board members by way of background but rather, as the law requires, as the primary legal resource for interpretation in deciding how the human subjects regulations apply.
- (2). The United States' acknowledged, fundamental obligations to protect research subjects under domestic and international law should be recognized in the ethics and research communities.
- (3). Both the system and proposed changes should be viewed critically, in terms of efficacy rather than convenience.
- (4). Attention should focus on ensuring predictability, stability, and clarity of the regulatory system and resources and will to enforce and comply—in letter and in spirit.

These are ethical and legal responsibilities of persons responsible for protection of human subjects of biomedical and behavioral research.

