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The National Bioethics Advisory Commission: Bridging the Gaps in Human Subjects Research Protection

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THE NATIONAL BIOETHICS ADVISORY COMMISSION: BRIDGING THE GAPS IN HUMAN SUBJECTS RESEARCH PROTECTION

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I. INTRODUCTION: THE FORMATION OF THE NATIONAL BIOETHICS ADVISORY COMMISSION

The National Bioethics Advisory Commission (NBAC) was established by a Presidential Executive Order in late 1995[1] to "provide advice and make recommendations to the National Science and Technology Council (NSTC) [in the White House], other appropriate entities and the public, on bioethical issues arising from research on human biology and behavior, including the clinical applications of that research."[2]

According to NBAC's charter, its eighteen presidentially-appointed members are to be selected from "knowledgeable non-government experts and community representatives with special qualifications and competence to deal effectively with bioethical issues."[3] At least one member should come from each of five categories: (1) philosophy/theology, (2) social/behavioral science, (3) law, (4) medicine/allied health professions, and (5) biological research.[4] NBAC's members were appointed during 1996 and its first meeting was held in October 1996. Why NBAC, why now? In the 1970s, the disclosure of several unethical experiments, including the U.S. Public Health Service's "Tuskegee Study of Syphilis in the Negro Male,"[5] led

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1. Exec. Order No. 12,975, 60 Fed. Reg. 52,063 (1995) [hereinafter Exec. Order No. 12975].

2. National Bioethics Advisory Commission Charter (July 26, 1996) (on file with the *Journal of Health Care Law & Policy*).

3. *Id.*

4. *See id.*

5. The Tuskegee Syphilis Study Legacy Comm., Final Report of the Tuskegee Syphilis Study Legacy Committee (citing Jean Heller, *Syphilis Victims in the U.S. Study Went Untreated for 40 Years*, N.Y. Times, July 26, 1972, at 1, 8) (May 20, 1996) (unpublished report, on file with the *Journal of Health Care Law & Policy*). The Tuskegee Syphilis Study was initiated by the U.S. Public Health Service to investigate the natural history of syphilis in 399 poor

to the formation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("National Commission"), which made several substantive and procedural recommendations for protecting research subjects.[6] Procedurally, the National Commission relied on institutional review boards (IRBs), which had already emerged as important mechanisms to protect human subjects.[7] Substantively, it formulated several principles and guidelines,[8] many of which became formal regulations in the Department of Health, Education and Welfare (later the Department of Health and Human Services)[9] and were later incorporated into what became known as the "Common Rule," which will be discussed below.[10] Everything seemed settled: In the 1980s, discussants of research ethics observed that the main controversies concerned the use of animals rather than the use of humans in research. However, in a prophetic note, Alexander M. Capron observed in 1989 that "today the subject [of research involving human subjects] is often naively viewed as one of settled ethical principles, detailed statutory and regulatory requirements, and multifaceted procedures. History suggests that such claims must be viewed skeptically: the principles may be less conclusive and the guidelines less protective than they appear."[11]

The work of the Advisory Committee on Human Radiation Experiments (ACHRE), chaired by Ruth Faden of the Johns Hopkins University School of Public Health from 1994 to 1995, paved the way for a new commission, with the study of protections in research involving human subjects as one of its two main tasks.[12] ACHRE was established by President Clinton partly in response to stories that put a

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Black sharecroppers from Alabama. *See id.* at 2. Physicians conducting the study deceived the participants by telling them they were being treated for "bad blood." *Id.* The physicians deliberately denied treatment to participants and went to great lengths to ensure that they would not receive therapy from other sources. *See id.* The participants received free meals, free medical exams, and burial insurance in exchange for their participation. *See id.*

6. *See* Belmont Report: Ethical Principles and Guidelines for Research Involving Human Subjects, 79 Fed. Reg. 12,065 (1979) [hereinafter Belmont Report]. The Belmont Report was the product of the National Commission's monthly deliberations over a period of four years. *See* THE 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 2 (GPO Pub. No. 201-778/80319) (1988).

7. *See id.*

8. *See, e.g., id.*

9. *See* Regulations for Protection of Human Subjects, 45 C.F.R. § 46 (1996).

10. *See infra* notes 32-35 and accompanying text.

11. Alexander M. Capron, *Human Experimentation, in* MEDICAL ETHICS 125, 128 (ROBERT M. VEATCH ED., 1989).

12. ADVISORY COMM. ON HUMAN RADIATION EXPERIMENTS, FINAL REPORT (GPO Pub. No. 061-000-00-848-9) (1995).

human face on some information and data that had been around for years. For instance, a series of reports in the *Albuquerque Tribune* disclosed the names of Americans who had been injected with plutonium, the man-made material that was a key ingredient of the atom bomb.[13] ACHRE examined the records of several thousand experiments funded and conducted, mostly in secret, by different branches of the federal government as part of the Cold War.[14] These experiments included feeding cereal with minute amounts of radioactive material to the science club at the Fernald School for the Retarded,[15] total body irradiation of cancer patients,[16] and testicular irradiation of inmates in Oregon and Washington prisons.[17] ACHRE not only made recommendations about how the federal government should now respond to its past actions, but also how it could learn from the legacy of these Cold War experiments.[18] NBAC was one result: it was designed to respond to some specific issues raised by ACHRE, but also, more generally, to provide a national public forum for dialogue on ethical issues in research involving human subjects.[19]

II. NBAC's PRIORITIES

According to its charge, NBAC must give first priority to two main areas: (1) protection of the rights and welfare of human research subjects; and (2) issues in the management and use of genetic information including, but not limited to, human gene patenting.[20] In addition to responding to NSTC's requests for advice and recommendations, NBAC may accept congressional and public suggestions, and identify other bioethical issues that it wants to examine, subject to NSTC's approval.[21]

Beyond the tasks that have first priority, NBAC, according to its charter, shall use four criteria in determining its priorities: (1) the public health or public policy urgency of the bioethical issue; (2) the relation of the bioethical issue to the goals for federal investment in science and technology; (3) the absence of another body able to delib-

13. *See id.* at 2.
14. *See id.*
15. *See id.* at 342.
16. *See id.* at 366.
17. *See id.* at 421.
18. *See id.* at xxiv.
19. *See* U.S. GOV'T HUMAN RADIATION INTERAGENCY WORKING GROUP, BUILDING PUBLIC TRUST: ACTIONS TO RESPOND TO THE REPORT OF THE ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS 11 (GPO PUB. NO. 061-000-00880-2) (1997).
20. *See* National Bioethics Advisory Commission Charter (July 26, 1996).
21. *See id.*

erate fruitfully about the bioethical issue; and (4) the extent of government-wide interest in the issue.[22] The charter further notes that NBAC will usually consider only bioethical issues that are of interest to more than one department.[23]

NBAC was divided into two formal subcommittees in order to address its two tasks with top priority.[24] One is the Human Subjects Subcommittee (HSSC), which I chair. The other is the Genetics Subcommittee, which is chaired by Tom Murray of Case Western Reserve University. Although these subcommittees are responsible for most of the preliminary work in their respective areas, NBAC as a whole is ultimately responsible for producing any reports or making any recommendations.[25]

These two subcommittees' responsibilities differ considerably. The Genetics Subcommittee has to work largely from scratch because of the general absence — or, at most, the patchwork — of laws, regulations, and guidelines. It has decided to concentrate first on stored tissue samples. Although this topic might seem, at first glance, quite narrow, it is, in fact, broadly significant because of the crucial questions it raises about the ownership of such samples; the kind of consent, if any, that must be provided for the use of tissue samples in research; the way DNA research involves parties other than the one from whom the tissue came; concerns about discrimination; and the like. Obviously this topic also connects in important ways with human subjects research, as reflected, for instance, by an interagency conference in late June, 1997, which focused on "Genetics Research and Human Subjects: The Changing Landscape."[26]

By contrast, extensive and substantial governmental regulations and guidelines already exist for research involving human subjects, along with settled professional standards.[27] Hence, the HSSC's task is to examine what appears in law, regulations, guidelines, and practices

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22. *See id.* These criteria also appear, with slightly different wording, in the Executive Order that established the Commission. *See* Exec. Order No. 12975, *supra* note 1.

23. *See* National Bioethics Advisory Commission Charter (July 26, 1996).

24. These two subcommittees were created by NBAC's chair, Princeton's president, Harold Shapiro.

25. *See* National Bioethics Advisory Commission Charter (July 26, 1996).

26. *Dep't of Energy/Protection of Human Subjects Program, Nat'l Inst. of Health (NIH) Human Genome Program, and the Interagency Human Subjects Subcommittee/Office of Protection from Research Risks, Interagency Human Subjects Conference. Genetics Research and Human Subjects: The Changing Landscape* (June 26-27, 1997); *see also* Eric T. Juengst, *Respecting Human Subjects in Genome Research: A Preliminary Policy Agenda, in* THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY, 401-429 (Harold Y. Vanderpool, ed., 1996) (discussing the connections between human subjects research and genetics research).

27. *See* Regulations for Protection of Human Subjects, 45 C.F.R. § 46 (1996).

to determine where there are important "gaps." Whereas the Genetics Subcommittee often has to create anew rather than improve what already exists, the main task for the HSSC is to identify and plug gaps, often by modifying or adding to what already exists. This does not mean, of course, that the HSSC's task is simple, because there will be vigorous debates about perceived gaps and about possible ways to close them while taking into account major moral principles and values. Keeping with the metaphor of gaps, I now want to examine several possible areas of concern.

III. POSSIBLE GAPS IN HUMAN SUBJECTS PROTECTIONS

A. Federal Agency Protection of Human Subjects

NBAC has one mandated task in the area of research involving human subjects. That task, as established by the Presidential Executive Order, required each executive branch department and agency conducting, supporting, or regulating research involving human subjects to review its policies and procedures for protecting those subjects' rights and welfare, in light of the recommendations contained in the ACHRE report.[28] These departments and agencies were also instructed to report the results of their reviews to NBAC within 120 days.[29] These reports were expected to identify "measures that the department or agency plans or proposes to implement to enhance human subject protections."[30]

The departments and agencies submitted their reports, even though NBAC did not exist until several months later. Within its first year, despite the delays created by "Dolly,"[31] NBAC expects to issue a report on federal department and agency protection of human subjects. In preparing this report, NBAC is seeking to determine whether there are gaps in adherence to the Federal Policy for the Protection of Human Subjects (known as the Common Rule).[32]

In 1991, sixteen federal departments or agencies accepted the Common Rule,[33] according to which federally conducted or spon-

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28. *See* Exec. Order No. 12975, *supra* note 1.

29. *See id.*

30. *See id.*

31. Virtually all NBAC's work between late February and early June focused on a report and recommendations on the cloning of humans — a task that President Clinton asked NBAC to complete within 90 days, in the wake of the report of Scottish researchers' success in cloning a sheep. *See infra* note 40.

32. *See* 45 C.F.R. § 46.

33. Federal Policy for the Protection of Human Subjects; Notices and Rules, 56 Fed. Reg. 28,002-32 (1991) (codified at 34 C.F.R. pt. 97). The Food and Drug Administration

sored research cannot proceed without local IRB approval of the research protocol, according to several criteria which include: Risks to subjects must be minimized and must be "reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result;" and selection of subjects must be equitable (fair, just) in light of research purposes and setting and the special problems of vulnerable populations, including children, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons (special guidelines apply to some of these populations). The criteria also require informed consent; monitoring, if appropriate; and privacy and confidentiality.[34]

Although written reports from federal departments and agencies were available by the time NBAC came into existence, NBAC wanted to know more about the structures and processes of protecting human subjects than most written reports provided. Thus, it proceeded to gather additional information through interviews conducted by a team of NBAC staff. The interviews and reports address both *structures*, which have formally been put in place, and *processes of implementation*. Efforts to learn more about the structures in Phase I, conducted by NBAC, involve interviews with the responsible agency personnel. Efforts to learn more about the processes in Phase II concentrate on individuals in each organization who have direct responsibility for, or participate in, its IRBs or review of extramural research in a few agencies.[35]

It is too early to anticipate what recommendations, if any, NBAC may advise to strengthen federal department and agency protection of human research subjects. Although NBAC will pay particular attention to federal adherence to the Common Rule, it is also interested in other measures that some departments and agencies may have already devised and adopted to protect human subjects because such innovations may be instructive to other agencies.

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has also adopted the Common Rule for research involving products it regulates. *See id.* at 28,004.

34. *See id.* at 28,015-16.

35. *See* Human Subjects Subcommittee, National Bioethics Advisory Committee, Survey of Federal Departments and Agencies Concerning Their Implementation of Protection For Human Subjects in Research (unpublished research protocol, on file with author).

B. Extension of the Common Rule to Other Federal Agencies and to Privately-Funded Research

In its consideration of possible gaps in the protection of human research subjects, NBAC will consider whether the Common Rule should be extended to federal agencies that have not already endorsed it. NBAC will also consider whether the Common Rule should be extended to research not currently addressed in some federal agencies, because it is not now viewed as research, that is, as a systematic effort to generate generalizable knowledge.

At NBAC's first meeting, Gary Ellis, Director of the Office of Protection from Research Risks, noted that the most vulnerable research subjects are those not protected by the Common Rule — for example, subjects in privately-funded research in settings without multiple assurances.[36] In addition, Commissioner Alta Charo has argued strongly over several months that NBAC ought to affirm the principle or ideal or universal protection through IRB review and informed consent.[37] NBAC could endorse this principle or ideal without regard to how it might be implemented — for example, without recommending Senate Bill 193, "Human Research Subjects Protections Act of 1997," introduced by Senator John Glenn, or any other specific legislation.[38] As a principle or ideal, it could serve as a standard or point of reference for all our discussions and deliberations. However, some commissioners thought that it would be preferable to consider the need for such protection, how it might be implemented, and how much the implementation might cost before affirming the principle or ideal.[39] Commissioner Charo's proposal was finally adopted in the context of an NBAC recommendation regarding the cloning of humans:

> If a legislative ban is not enacted, or if a legislative ban is ever lifted, clinical use of somatic cell nuclear transfer techniques to create a child should be preceded by research trials that are governed by the twin protections of independent review

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36. *See* Gary B. Ellis, Remarks before the National Bioethics Advisory Commission (October 4, 1996), *in* BIOLAW, December 1996, at S:242-43. *See* also, *infra* note 60 (defining multiple assurances).

37. *See, e.g.*, Comm'r Alta Charo, Proposal at Meeting of the National Bioethics Advisory Commission, 35 (March 13, 1997) (unpublished transcript, on file with author).

38. S. 193, 105th Cong. (1997).

39. *See generally*, Meeting of the National Bioethics Advisory Commission, Human Subjects Sucommittee (March 13, 1997) (unpublished transcript, on file with the author).

and informed consent, consistent with existing norms of human subjects protection.[40]

C. *Gaps and Other Problems in the Common Rule Itself*

Many worry that extending the Common Rule to plug gaps in protection will be inadequate unless some gaps are closed in the Common Rule itself. One area of widespread public interest is the protection of vulnerable or special populations. Guidelines already exist for some vulnerable populations such as prisoners,[41] children,[42] and pregnant women.[43] NBAC tentatively plans, sometime next year, to examine some of these guidelines in more detail by carefully looking at the guidelines for research with children and adolescents, with particular attention to ways of defining and determining such categories as minimal risk, greater than minimal risk, and minor increase over minimal risk.[44] One author has characterized vulnerability in two ways: (1) vulnerability due to coercion and manipulation (e.g., prisoners); and (2) vulnerability because of limited or no capacity to consent (e.g., children).[45] However, the HSSC is interested in conceptualizing "vulnerability" more broadly by exploring ideas such as relational vulnerability, that is, vulnerability in the context of interactions between researcher and subject, rather than simply as a characteristic of the research subject.[46]

At the first HSSC meeting, cognitively impaired or decisionally impaired research subjects (the exact description of this population is not yet settled) emerged as a possibly vulnerable population in need of additional protections.[47] As a result, subsequent HSSC meetings have regularly focused on this population.[48] The National Commission had proposed guidelines for those institutionalized as mentally

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40. REPORT AND RECOMMENDATIONS OF THE NATIONAL BIOETHICS ADVISORY COMMISSION, CLONING HUMAN BEINGS at iv (1997).

41. *See* 45 C.F.R. §§ 46.301-306 (1996).

42. *See id.* §§ 46.401-409.

43. *See id.* §§ 46.201-211.

44. *See* Meeting of the National Bioethics Advisory Commission, Human Subjects Subcommittee (December 16, 1996) (unpublished transcript, on file with the *Journal of Health Care Law & Policy*) [hereinafter Meeting of the NBAC].

45. *See* Loretta M. Kopelman, *Research Policy: Risk and Vulnerable Groups*, 4 ENCYCLOPEDIA OF BIOETHICS 2291-92 (WARREN THOMAS REICH ED., REV. ED. 1995).

46. *See* Meeting of the NBAC, *supra* note 44.

47. *See id.*

48. *See id; see also* Meeting of the National Bioethics Advisory Commission, Human Subjects Subcommittee (July 15, 1997) (unpublished transcript, on file with *Journal of Health Care Law & Policy*) [hereinafter July 15, 1997 Meeting of the NBAC].

infirm.[49] However, these guidelines were never adopted for various reasons, including additional and (too many) burdensome mechanisms such as the use of consent auditors in all cases and possibly a subjects advocate, that the Department of Health, Education, and Welfare (DHEW) had added in proposing regulations.[50] The trend toward de-institutionalization of the mentally ill accelerated, thereby making the proposed guidelines less relevant. According to many, the lack of guidelines protecting human subjects poses a serious problem: some necessary research is not conducted while other research is poorly conducted.[51] The HSSC will probably draft a report and make recommendations on research with decisionally impaired subjects for NBAC's consideration by early 1998. The process will include review of testimony and papers from various researchers and from the National Institute of Mental Health, as well as public testimony, including public hearings conducted in September, 1997.

D. Possible Gaps in Implementation: Questions About IRBs

The Common Rule is currently implemented through local IRBs. IRBs must examine each research protocol (except for those in exempt categories) to determine whether the protocol meets the criteria to justify the use of human subjects.[52] Over the last twenty years, research involving human subjects has greatly expanded, and the number of protocols has increased dramatically.[53] In addition, many protocols are now multi-site protocols involving various teams of investigators and large numbers of research subjects.[54] Although regulations have increased, institutional support given to IRBs is often minimal, and individual members feel overworked and underappreciated.[55] Furthermore, conflicts of interest are not uncommon.[56]

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49. *See* National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, RESEARCH INVOLVING THOSE INSTITUTIONALIZED AS MENTALLY INFIRM, DHEW Publication No. (OS) 78-0006 (February 2, 1978).

50. *See* Proposed Regulation on Research Involving Those Institutionalized as Mentally Disabled, 43 Fed. Reg. 223, 53950-56.

51. *See, e.g.*, Richard J. Bonnie, *Research With Cognitively Impaired Subjects*, 54 ARCHIVES GEN. PSYCHIATRY (1997); Rebecca Dresser, *Mentally Disabled Research Subjects*, 276 JAMA 67 (1996).

52. *See supra* note 35 and accompanying text.

53. Donald F. Phillips, *Institutional Review Boards Under Stress: Will They Explode or Change?*, 276 JAMA 1623 (1996).

54. *See id.* at 1623-24.

55. *See id.* at 1625.

56. *See id.*

As a result, worries abound that IRBs may not be able to adequately protect research subjects.[57]

The truth is that we don't really know how well IRBs are protecting research subjects, and it is difficult, as well as very expensive, to try to find out. Even if there is considerable variability in IRBs' judgments about particular protocols and in what they require, for instance, in the way of disclosure of information for informed consent/refusal, it may still be unclear whether this variability falls within an acceptable or an unacceptable range.

In *Building Public Trust*, the United States Government Human Radiation Interagency Working Group notes that in light of ACHRE's report, which:

> Highlighted the limited state of knowledge regarding some key issues in human subjects research . . . NBAC will be reviewing and evaluating the IRB Process . . . . NBAC has undertaken to review the current IRB system and intends to finish that project within a year. The Administration anticipates specific recommendations from NBAC regarding reform of IRBs, including recommendations that address ACHRE's concerns.[58]

These concerns include mechanisms to ensure a sharper focus on studies that pose more than minimal risk to subjects, better ways to explain the distinction between research and treatment and various benefits and risks, and ways to ensure that potential subjects understand sponsors and purposes of the research.[59]

That is an excessively optimistic view of what NBAC can accomplish in its effort to understand the possibilities and limitations of IRBs given the changes in research, sources of funds, and so forth. Thus, NBAC will probably wait until the results of two other major studies become available, probably, at least in preliminary form, by the end of 1997 or early 1998. One of these studies, in an effort to assess the impact of the reforms carried out in the 1980s and to determine whether further program refinements are needed, focuses on the 445

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57. *See generally*, U.S. GEN. ACCOUNTING OFFICE, SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS, B-259279 (1996); Harold Edgar & David J. Rothman, *The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation*, 73 THE MILBANK Q. 489 (1995); Phillips, *supra* note 53.

58. U.S. GOV'T HUMAN RADIATION INTERAGENCY WORKING GROUP, BUILDING PUBLIC TRUST: ACTIONS TO RESPOND TO THE REPORT OF THE ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS 12-13 (1997).

59. *See id.*

active IRBs functioning under Multiple Project Assurances.[60] The other study, being conducted by the Office of Inspector General of the Department of Health and Human Services, is designed to examine the major challenges that face hospital-based IRBs in a changing healthcare environment, provide promising approaches that these IRBs have developed to address these challenges, and identify the policy implications intended to ensure effective IRB functioning for the Department of Health and Human Services (DHHS)/National Institute of Health (NIH) and Food and Drug Administration (FDA).[61] Once NBAC has the results of these two studies, it can determine whether it has enough information to diagnose problems and make recommendations or whether it first needs to arrange for additional studies.

Proposed alternatives to local IRBs have included regional boards, national boards, and speciality boards. Mechanisms to supplement or supersede IRB review have developed, both on an ad hoc and on an extended basis. On the one hand, special review boards have been used when conflicts have emerged about particular research protocols. For instance, NIH set up a special review board to examine a controversial clean-needle exchange program protocol in Anchorage, Alaska.[62] The study will compare health outcomes between participants who are allowed to exchange dirty syringes for clean syringes and participants who would only be instructed on where to purchase

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60. *See* Evaluation of NIH implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects (Charles MacKay, project officer) (research protocol on file with author). As a condition for receipt of federal research funds, research institutions must assure in writing that personnel will abide by ethical principles specified in the Belmont Report and 45 C.F.R. § 46. *See* Alison Wichman, *Protecting Vulnerable Research Subjects: Practical Realities of Institutional Review Board Review and Approval*, n.10 and accompanying text, 1 J. HEALTH CARE L. & POL'Y 136 (1997). These written assurances are referred to as *Assurances of Compliance. See id.* Assurances of Compliance which cover all human subjects research activities carried out by a particular research institution are referred to as Multiple Project Assurances (MPAs). *See id.*

> Assurances applicable to federally supported or conducted research shall at a minimum include: (1) a statement of principles governing the institution in the discharge of its responsibilities . . . (2) designation of one or more IRBs established in accordance with the requirements of this policy . . . (3) a list of IRB members . . . (4) written procedures which the IRB will follow . . . (5) written procedures for ensuring prompt reporting to the IRB. . . .

45 C.F.R. § 46.103(b)(1)-(5) (1996).

61. Office of Evaluation and Inspections, Office of Inspector General, Department of Health and Human Services, Hospital-Based IRBs in a Changing Healthcare Environment: Challenges to Ensuring Human-Subject Protections (OEI-01-97-00190) (March 18, 1997) (research protocol on file with author).

62. Warren E. Leary, *Questions on Ethics Lead to Review of Needle-Exchange Study*, N.Y. TIMES, Oct. 18, 1996, (National), at A22.

syringes.[63] On the other hand, national review panels have been proposed or used for some types of protocols. For instance, human gene therapy protocols have been reviewed by the Recombinant DNA Advisory Committee, and it might be plausible to argue for national review of certain types of protocols, such as xenograft transplants, that raise public health concerns or that are likely to go beyond the expertise available at a particular institution.[64]

E. Gaps Created by Shifting Paradigms of Research

Another gap has emerged because of a fundamental shift in paradigms of research and, consequently, a shift in the perceptions of ethical issues in research. The earlier paradigm focused on the risks and burdens of research and on the need to protect potential and actual research subjects from harm, abuse, exploitation and the like. The ethical guidelines for this paradigm emphasized voluntary, informed consent — that's where the Nuremberg Code begins.[65] The basic approach to research in the United States "was born in scandal and reared in protectionism."[66] The dominant model for such protectionist policies is non-therapeutic research, that is, research that doesn't promise any therapeutic benefit to the subject.

This paradigm has been shifting from protection to access, from non-therapeutic to therapeutic research (e.g., clinical trials of promising new therapeutic agents), and from risks and burdens to possible benefits of clinical research. This shift has resulted particularly (but not only) because of the epidemic of Human Immunodeficiency Virus (HIV) infection and Acquired Immunodeficiency Syndrome (AIDS). AIDS activists pressured the FDA to expand access to new treatments for those infected with HIV and AIDS.[67] They became well informed about emerging treatments, and they pressured the FDA to expand the options.[68]

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63. *See id.*

64. *See, e.g.*, INSTITUTE OF MEDICINE, XENOTRANSPLANTATION: SCIENCE, ETHICS, AND PUBLIC POLICY 2-4 (1996) (recommending that "a mechanism be established within the Department of Health and Human Services to ensure needed coordination of the federal agencies and other entities involved in development, oversight, and evaluation of established guidelines").

65. The Nuremberg Code (1948) *reprinted in* THE NAZI DOCTORS AND THE NUREMBURG CODE 2 (George J. Annas & Micheal A. Grodin eds., 1992).

66. Carol Levine, *Changing Views of Justice after Belmont: AIDS and the Inclusion of "Vulnerable" Subjects, in* THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY 105-06 (Harold Y. Vanderpool ed., 1996).

67. *See id.* at 107-10.

68. *See id.*

The earlier protectionist paradigm should not be completely abandoned in favor of the newer inclusionist paradigm. We have to be careful to retain what was important — and remains important — in the protectionist paradigm even as we incorporate what is important in the inclusionist paradigm.

F. Gaps in Compensation for Research-Related Injuries

Injuries sometimes occur in research, despite the best possible precautions. Some members of the HSSC have expressed an interest in and support for policies to fill what they perceive to be gaps in compensation for research-related injuries. However, it is not clear that this topic will be on NBAC's agenda, because, as another member put it, "this appears to be a solution in search of a problem, at least without substantial evidence that some research subjects suffer because of the lack of a mechanism for compensation."[69] Nevertheless, in the absence of comprehensive information about the number of research subjects, it is hard to imagine comprehensive data about the extent of research-related injuries.

This topic has been discussed for over twenty years, with various groups recommending compensation for research-related injuries, or at least a trial period for the compensation program.[70] Even though injuries do not appear to be common, they do occur, and sometimes deaths even occur. If those injuries are caused by negligence, subjects have recourse to the tort system. If, however, the injuries are not negligently caused, subjects usually depend on the generosity of institutions and professionals, since many research protocols do not promise compensation.

Years ago I argued that compensatory justice requires that society compensate subjects for their research related injuries because they assume a position of risk on behalf of the society, regardless of their particular motivations for participation in research.[71] Another, more communitarian argument will appear in the next section. Nevertheless, it remains to be seen whether NBAC will actually address compensation for research-related injuries.

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69. July 15, 1997 Meeting of the NBAC, *supra* note 48.

70. *See, e.g.*, U.S. DEP'T OF HEALTH, EDUCATION, AND WELFARE, SECRETARY'S TASK FORCE ON THE COMPENSATION OF INJURED RESEARCH SUBJECTS, DHEW Publication No. OS-77-003 (1977); U.S. PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH, COMPENSATING FOR RESEARCH INJURIES: A REPORT ON THE ETHICAL AND LEGAL IMPLICATIONS OF PROGRAMS TO REDRESS INJURIES CAUSED BY BIOMEDICAL AND BEHAVIORAL RESEARCH II-2 (1982).

71. *See* James F. Childress, *Compensating Research-Related Injuries*, 6 THE HASTINGS CENTER REPORT 21, 22 (Dec. 1976).

G. Gaps in the Belmont Principles and/or in Their Interpretation

Although I have used the metaphor of "gaps," NBAC is not merely filling holes in regulations and guidelines while leaving unchanged what is already in place. Much of what NBAC is doing and will do involves conceptual analysis (e.g., what counts as "research," and which subjects are "vulnerable" and why), and normative deliberation (e.g., which principles and guidelines should govern research and why). NBAC's charter indicates that it will not review and approve or disapprove particular research projects; rather it will examine the "broad, overarching principles to govern the ethical conduct of research."[72] A question has emerged about whether gaps exist in our current principles.

Three broad principles, articulated by the National Commission in the 1970s, still govern research involving human subjects.[73] Various guidelines and regulations specify these principles,[74] and, where guidelines and regulations are incomplete or unclear, IRBs further interpret the principles to determine whether to approve or reject particular research protocols.[75] These three principles are as follows:

(1) Respect for Persons: This principle requires that researchers respect the autonomous choices of those who are autonomous, and protect those with diminished autonomy.[76] Rules of consent/refusal specify this principle, but in practice the emphasis often falls on the signed consent form — that is, what local IRBs examine — when what is critical is the consent process, which is generally not monitored. As a result, IRBs do not really know — and no one else really knows — whether the consent process is adequate.

(2) Beneficence: This principle requires benefitting and not harming. Because both parts often cannot be fully realized simultaneously, it is necessary to balance benefits (to subjects and others) and harms (to subjects only). The rules that specify this principle require not harming, and also maximizing possible benefits and minimizing possible harms.

(3) Justice: This principle entails fairness in distributing burdens and benefits, especially in protecting from exploitation those who might be selected because of "easy availability, . . . compromised posi-

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72. National Bioethics Advisory Commission Charter (July 26, 1996).

73. Belmont Report, *supra* note 6, at 3-5.

74. *See id.* at 3.

75. *See id.*

76. *See id.* at 4.

tion, or . . . manipulability, rather than for reasons directly related to the problem being studied."[77]

At the first NBAC meeting, Commissioner Ezekiel Emanuel contended that these three principles and related guidelines, along with their interpretations, do not adequately address *community*.[78] Attention to community could mean, among other possibilities, that we should add community as a fourth principle or that we should interpret all of these principles in a communitarian rather than a merely individualistic manner. This second approach would involve reexamining the principles and guidelines through the lens of community. At any rate, it is likely that NBAC will reconsider these principles to make certain that community is sufficiently included. Following are a few illustrations of what this might mean.

Reinterpreted through the lens of community, the principle of respect for persons would consider participants not merely as isolated individuals, who consent or refuse to consent to participation in research, but also as members of the community. However, caution is also appropriate because it is not possible or justifiable to determine an individual's wishes and choices by extrapolating them from community traditions, beliefs, and values.

Beneficence already includes attention to society's welfare, which has been part of the benefit to be balanced against the risks to subjects. However, attention to community might also require, as has become more common, attention to the harms to a particular community, such as the Native American community, rather than merely harms to individuals.

Justice, as a final example, concerns more than fairly selecting research subjects and fairly distributing the benefits and burdens of participation in research. It may include the participation of various communities in the design and evaluation of research. Beyond participation, it might include compensation for research-related injuries as an expression of the community's solidarity with research subjects who assume a position of risk on behalf of the community and who are non-negligently injured in the process. From this standpoint, it might not be sufficient to disclose on the consent form whether there will be any compensation for research-related injuries that are non-negligently caused; instead, compensation should be provided.[79]

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77. *Id.* at 5.

78. Meeting of the National Bioethics Advisory Committee (Oct. 4, 1996) (unpublished transcript, on file with *Journal of Health Care Law & Policy*).

79. At its November 1996 meeting with representatives of commissions in other countries, NBAC learned that other countries, with a commitment to universal access to health

As the above examples suggest, it is important to revisit these principles in light of concerns about community, but to do so in a way that does not neglect or distort what is important in earlier, more individualistic interpretations. It is presently unclear what might emerge if NBAC takes this course. At the very least, NBAC expects to contract for a paper that examines the concept of community and its possible uses in research involving human subjects. Another paper, currently under contract, will examine vulnerability from a relational perspective. This latter paper could propose another way to move beyond construing the potential or actual research subject as an isolated individual, and beyond viewing vulnerability mainly as a problem of the potential research subject and his/her institutional setting (e.g., a prison).

H. Gaps in Public Trust

One indication of the lack of community in our society is that some groups lack trust in researchers and research institutions. For example, there is evidence that the story of the federal government's syphilis study in Tuskegee, Alabama, continues to breed distrust among African-Americans. This distrust can thwart participation in research as well as have a negative impact on the donation of organs for transplantation, and even adversely affect willingness to seek medical care.[80]

In part as a way to restore a sense of community, President Clinton, this past spring, publicly apologized to the few survivors and relatives of the 399 African-American subjects of the federal government's syphilis study in Tuskegee.[81] President Clinton stated that the United States Government "did something that was wrong — deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens. . . . We cannot be one America when a whole segment of our nation has no trust in America."[82] NBAC had earlier supported public calls for a presidential apology, and endorsed administration consideration of the recommendations

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care, do not view compensation for research-related injuries as a problem. Meeting of the National Bioethics Advisory Committee (November 21, 1996) (unpublished transcript, on file with *Journal of Health Care Law & Policy*). Such injuries would be routinely covered, at least for medical expenses. *Id.* Of course, there are always questions of the scope of compensation. *Id.*

80. Jeff Stryker, *Tuskegee's Long Arm Still Touches a Nerve*, N.Y. TIMES, April 13, 1997, at Sec. 4, at 4.

81. Alison Mitchell, *Survivors of Tuskegee Study Get Apology From Clinton*, N.Y. TIMES, May 17, 1997, at Sec. 1, at 10.

82. *Id.*

of the Tuskegee Syphilis Study Legacy Committee.[83] As part of his apology, President Clinton announced a $200,000 planning grant to Tuskegee University to help establish and create a Center for Bioethics in Research and Health Care, and fellowships for post-graduate studies in bioethics, with special attention placed on minority student recruitment.[84] Furthermore, President Clinton asked Donna Shalala, the Secretary of the Department of Health and Human Services, to report within six months on how communities, especially minority communities, could be involved in research and assessing health care, particularly in view of widespread attitudes of distrust.[85] As an additional action, President Clinton extended NBAC's life until 1999.[86]

IV. CONCLUSIONS

I have used the metaphor of gaps to suggest some concerns that members of NBAC and others have raised about the protection of human subjects in biomedical and behavioral research.[87] It is not clear how well NBAC, even with an extended life expectancy, a more adequate budget, and valuable testimony and studies provided by others, can close gaps in information that may be important in revising policies to protect human subjects. Important gaps in knowledge include, for example, the way IRBs function. There are also gaps in our knowledge about the process of informed consent, in contrast to our information about consent forms. It is often noted that we have more information about animals in research than about humans in research. A fundamental question facing NBAC is how much information is necessary in order to identify a substantive or procedural gap in need of attention.

Finally, even though the metaphor of gaps is suggestive, it is not fully adequate. Protection of human research subjects may fail because substantive and procedural guidelines are too complex and thus

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83. The Tuskegee Syphilis Study Legacy Comm., Final Report of the Tuskegee Syphilis Study Committee (May 20, 1996) (unpublished report, on file with *Journal of Health Care Law & Policy*); *see generally* Meeting of the National Bioethics Advisory Committee (Mar. 13, 1997) (unpublished transcript, on file with the *Journal of Health Care Law & Policy*).

84. *See* Mitchell, *supra* note 81, at 10.

85. *See id.*

86. *See id.*

87. One major gap I have not discussed in this paper concerns international research, especially research funded by developed countries but conducted in developing countries. It appears that NBAC will take up this topic, at least to some extent. *See* July 15, 1997 Meeting of the NBAC, *supra* note 48 at 123-25). For an excellent set of essays on this topic, see THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY ch. 10-12 (Harold Y. Vanderpool ed., 1996).

too burdensome. As a result, many believe that investigators and IRBs spend too much time, energy, and resources on what is not so important and too little time, energy, and resources on what really is important. Hence, some propose that if NBAC attempts to close some gaps in substantive and procedural guidelines, it should also try to reduce requirements that are less important or suggest that they receive less attention or lower priority.