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Protecting Vulnerable Research Subjects: Practical Realities of Institutional Review Board Review and Approval

Alison Wichman

PROTECTING VULNERABLE RESEARCH SUBJECTS: PRACTICAL REALITIES OF INSTITUTIONAL REVIEW BOARD REVIEW AND APPROVAL

ALISON WICHMAN, M.D.*

I. INTRODUCTION

Illnesses involving some degree of cognitive impairment, such as stroke, some psychiatric illnesses, mental retardation, AIDS dementia complex and many neurological diseases, are serious health problems. For example, currently there are about four million Americans suffering from Alzheimer's disease, and the number is growing along with the increasing age of our population. Research on these and some other disorders presents ethical challenges because dementing and some psychiatric illnesses compromise, or eliminate, a research subject's ability to provide valid informed consent. However, ethical considerations are not limited to informed consent but include serious concerns about our moral obligation to protect from harm some of our society's most vulnerable individuals.

A challenge to institutions and researchers conducting research involving cognitively impaired people is balancing the scientific mission to advance knowledge with society's mandate to protect the rights and welfare of human subjects. Ethical guidelines, federal regulations, institutional review boards (IRBs), and local institutional policies and procedures all contribute to maintaining this balance. Prospective review and approval of research by IRBs — whose mandate is to protect the rights and safeguard the welfare of the subjects — is an important component of the current U.S. system of research review and oversight. This paper will discuss IRBs' roles and responsibilities, provide an overview of a policy used by IRBs at the National Institutes of Health (NIH) when reviewing research involving cognitively impaired subjects, and suggest some ways to improve IRBs' effectiveness in protecting research participants.

* Deputy Director of the Office of Human Subjects Research at the National Institute of Health; Past Member of Ethics Subcommittee of the American Academy of Neurology.

II. CURRENT ETHICAL GUIDELINES AND REGULATORY REQUIREMENTS FOR RESEARCH INVOLVING HUMAN SUBJECTS

Biomedical and behavioral research funded or supported by the Department of Health and Human Services (HHS), including the National Institutes of Health (NIH), is under the purview of Title 45 section 46 of the Code of Federal Regulations (C.F.R.) governing the protection of human subjects.[1] These regulations embody the principles of *The Belmont Report - Ethical Principles and Guidelines for the Protection of Human Subjects.*[2] Taken together, *The Belmont Report* and 45 C.F.R. section 46 articulate the *minimal* ethical and legal obligations of those who conduct, review and oversee research.

Forty-five C.F.R. section 46 was initially issued in 1981, however, the core of the regulations (Subpart A), referred to as the "Common Rule," was adopted by 15 other federal departments and agencies in 1991.[3] All clinical trials in the United States involving investigational drugs are under the regulatory purview of the Food and Drug Administration (FDA) regardless of the funding source.[4]

A. Ethical Foundation

The ethical foundation for the current laws governing human subject research protections is enunciated in the *Belmont Report* which was issued in 1979.[5] It establishes three fundamental ethical principles that are relevant to all research involving human subjects — respect for persons, beneficence, and justice — and demonstrates how they are applied to the conduct of research involving human subjects.[6]

Respect for persons acknowledges the dignity and autonomy of individuals and requires that subjects give informed consent to participation in research. However, not all individuals are capable of self-

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

2. NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH. GPO PUB. NO. 887-809 (1979) [Hereinafter *Belmont Report*].

3. In addition to HHS and the Food and Drug Administration (FDA), the following federal departments and agencies adopted the Common Rule: the Departments of Agriculture, Energy, Commerce, Housing and Urban Development, Justice, Defense, Education, Veterans Affairs, and Transportation; the National Aeronautics and Space Administration; the Consumer Product Safety Commission; the Agency for International Development; the Environmental Protection Agency; the National Science Foundation and the Central Intelligence Agency. The Social Security Administration is required to follow HHS regulations.

4. FDA Regulations for the Protection of Human Subjects, 21 C.F.R. §§ 50, 56 (1996).

5. *Belmont Report*, *supra* note 2, at 5-8.

6. *Id.*

determination and the *Belmont Report* acknowledges that people with diminished autonomy are entitled to additional protection. For example, some individuals may need extensive protection, even to the point of excluding them from activities which may harm them; while others require little protection beyond making sure they undertake research freely, with awareness of the possible adverse consequences.[7]

Beneficence requires that the benefits of research be maximized and possible harms be minimized. This principle finds expression in a careful analysis, by researchers and institutional review boards (IRBs), of the risks and benefits of particular research protocols.

Justice requires fair selection and treatment of research subjects. For example, subjects should be equitably chosen to insure that certain individuals or classes of individuals are not systematically selected for or excluded from research, unless there are scientifically or ethically valid reasons for doing so. Also, unless there is careful justification for an exception, research should not involve persons from groups that are unlikely to benefit directly or from subsequent applications of the research. These three principles are not mutually exclusive. Each principle carries strong moral force, and difficult ethical questions arise when they conflict. However, understanding and applying the principles of the *Belmont Report* helps assure that research subjects will be treated in a respectful and ethical manner.[8]

B. Regulatory Requirements

HHS is the primary federal agency sponsoring biomedical and behavioral research and includes the NIH, the FDA, the Indian Health Service (IHS) and the Centers for Disease Control and Prevention (CDC). Annually, HHS provides $5 billion for research activities involving human subjects.[9] Research must be conducted in accordance with the requirements of 45 C.F.R. section 46. HHS's regulatory apparatus for overseeing the protection of human research subjects consists of two major tiers of review; one at the federal level and the other at the institutional level. For example, as a condition for receipt of HHS research funds, institutions must assure in writing that personnel will abide by ethical principles of the *Belmont Report* and the re-

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7. *See id.* at 4.

8. *See* U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, GUIDELINES FOR THE CONDUCT OF RESEARCH INVOLVING HUMAN SUBJECTS AT THE NATIONAL INSTITUTES OF HEALTH at 19 (1995).

9. *See* U.S. GEN. ACCT'G OFFICE, REPORT TO THE RANKING MINORITY MEMBER, SENATE COMM'N ON GOVERNMENTAL AFFAIRS, CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS, GAO/HEHS Pub. No. 96-72 at 2 (1996) [hereinafter *GAO Report*].

quirements of 45 C.F.R. section 46; these written documents are referred to as Assurances of Compliance.[10] There are several different types of Assurances of Compliance, but all are contract-like agreements which are negotiated and approved by the Office for Protection from Research Risks (OPRR) on behalf of the Secretary of HHS. As of November 1995, OPRR estimated that it held 4,847 assurances.[11] All assurances set forth institutional policies and procedures for the review and monitoring of human subject research activities, including IRB membership requirements and review and record-keeping procedures.[12] A variety of administrative actions can be taken by OPRR for violation of the requirements of 45 C.F.R. section 46, or the terms and conditions of an institution's Assurance of Compliance.[13] For example, OPRR may require that some or all investigators conducting research under an assurance receive appropriate education concerning the protection of human subjects, or for more serious violations, it may recommend to HHS officials that institutions or investigators be declared ineligible to participate in HHS-supported research (i.e., debarment or suspension).[14]

HHS regulations require that proposed clinical research undergo review by an IRB, whose primary mandate is to protect the rights and safeguard the welfare of the subjects.[15] Procedures and minimal requirements for IRB review and approval are provided in 45 C.F.R. section 46 and, in institutions with OPRR-approved assurances, are also supplied in their written assurance documents. For example, IRBs must have at least five members who have expertise in scientific and nonscientific areas.[16] Their membership is expected to be diverse in order to foster a comprehensive approach to safeguarding the rights and welfare of subjects (i.e., lawyers, lay members, bioethicists, nurses, social workers, members of the clergy). Because normally IRBs are situated at the site of the research, members are expected to be familiar with specific conditions affecting the conduct of the research and the protection of the participants. For example,

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10. Assurances of Compliance include Multiple Project Assurances (MPAs), Single Project Assurances (SPAs), and Cooperative Project Assurances (CPAs). Most major United States research hospitals, university medical schools, and other research organizations have MPAs which cover all human subjects research activities carried out in those organizations.

11. This includes 451 MPAs, 3,063 SPAs, and 1333 CPAs. *See GAO Report*, *supra* note 9, at 8.

12. *See* 45 C.F.R. § 46.103 (1996).

13. *See id.*

14. 45 C.F.R. § 46.113.

15. *See id.* §§ 46.108, 46.109.

16. *See id.* § 46.107.

research institutions vary in geographical location and often draw from culturally dissimilar groups. In their deliberations, IRBs are expected to take into account the nature, content and design of the research, ethical principles of the *Belmont Report*, and, when appropriate, the regulatory requirements of HHS and the FDA.[17] The criteria for IRB review and approval are provided in Table 1.[18] Also, IRBs are required to conduct continuing review of each approved research protocol at least yearly, although an IRB may request earlier evaluation if it determines that the research presents significant physical, social, or psychological risks to subjects.[19] An IRB may suspend, modify, or terminate approval of research that has been associated with serious harm to subjects or is not being conducted in accord with federal regulatory requirements, ethical guidelines or institutional policies.[20]

IRBs are important because research investigators have an inherent conflict of interest. As health care professionals, they are dedicated to promoting the welfare of individual patients; as researchers, they seek generalizable knowledge applicable to persons other than their individual patients. Because the second goal may come in conflict with the first, our society has decided that an objective review of human subjects research by a group of diverse individuals is most likely to protect human subjects and promote ethically sound research. Although the IRB system is not perfect, conscientious IRBs reassure the American public that the rights and welfare of human subjects are seriously considered by people who are not directly involved in the research. It is through this process of research review and approval that investigators, research institutions, IRB members and others are held publicly accountable for their decisions and actions.

C. Research Involving Vulnerable Subjects

The principle of respect for persons incorporates two ethical convictions: (1) that individuals should be treated as autonomous agents, and (2) that persons with diminished autonomy are entitled to protection.[21] Also, protecting human subjects with diminished autonomy is addressed broadly in HHS regulations; "where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or

17. *See id.* § 46.103.
18. *See* Appendix to this paper; *see also* 45 C.F.R. § 46.
19. *See id.* § 46.103 (b)(4).
20. *See id.* § 46.113.
21. *See Belmont Report, supra* note 2, at 4.

economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects."[22] However, little additional, practical guidance is provided except when pregnant women,[23] prisoners,[24] or children[25] are the subjects of research.

Vulnerable research subjects are people who are relatively or absolutely incapable of protecting their interests. In other words, "they have insufficient power, prowess, intelligence, resources, strength or other needed attributes to protect their own interests through negotiations for informed consent."[26] Table 2[27] is a non-inclusive list of vulnerable, or potentially vulnerable, research subjects. It lists individuals who have no, or limited, ability to provide informed consent, as well as persons who may be particularly susceptible to undue influence or coercion. For example, because of prisoners' restricted liberty, serious attention must be given to the voluntariness of their informed consent to research participation. Also, people suffering from prolonged or serious illnesses that are refractory to standard therapies, or for which there are no standard therapies, should be considered vulnerable particularly when they are willing to take any risk for even a remote possibility of relief.[28] In the United States, considerable controversy has surrounded research involving comatose and critically ill people, including acute head injury and cardiopulmonary resuscitation research.[29] Not only do these individuals lack the ability to provide informed consent, but in emergency circumstances, there may not be time to seek consent from their representatives. The FDA issued,[30] and HHS agreed to accept,[31] a new regulation allowing for waiver of informed consent by subjects or their representatives to participation in certain emergency research studies.[32]

When reviewing research involving vulnerable or potentially vulnerable subjects, IRBs in consultation with investigators are expected

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22. 45 C.F.R. § 46.111(b).

23. *Id.*

24. *Id.*

25. *Id.*

26. ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 72 (Yale University Press 1988).

27. *See* Appendix to this paper.

28. *See id.*

29. *See, e.g.*, Alison Wichman & Alan L. Sanders, *Research Involving Critically Ill Subjects in Emergency Circumstances; New Regulations, New Challenges*, 48 NEUROL. 1151 (1997).

30. *See* Protection of Human Subjects; Informed Consent: Final rule, 61 Fed. Reg. 51,498- 51,531 (1996) (to be codified at 21 C.F.R. pts. 50, 56, 312, 314, 601, 812, 814).

31. *See id.* at 51,531-51,533.

32. *See* Wichman & Sanders, *supra* note 29, at 1152.

to provide additional safeguards appropriate to the particular research study under consideration.[33] While this approach allows for flexibility, it also means there may be significant variability, between (and perhaps within) institutions, in identifying and implementing practical safeguards.

Currently, there is no national consensus on what constitutes appropriate safeguards for people with progressive dementias such as Alzheimer's and Huntington's disease, although over the last few years, there have been some efforts to establish consistent guidelines.[34] However, most researchers, IRBs and research regulators acknowledge that the extent of the protection afforded to research subjects should depend on the risk of harms and the likelihood of direct benefits to them.[35] Therefore, when reviewing research involving cognitively impaired subjects, IRBs should take into account the nature, degree and clinical course of the intellectual impairment; the risks, harms and discomforts of research participation, and whether there is prospect of direct benefit to the individual subjects. For example, in research which exposes subjects to low risk or little discomfort, an IRB might decide that no additional safeguards are warranted beyond consent by subjects' authorized representatives. However, more stringent safeguards may be necessary for research exposing subjects to more than minimal risk, particularly if they do not stand to benefit directly from research participation. In fact some state statutes prohibit such research.[36] Where such a state statute does not ex-

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33. *See id; see also* Protection of Human Subjects, 45 C.F.R.§§ 46.201-.211 (concerning fetuses, pregnant women and human in vitro fertilization); §§ 46.301-.306 (concerning prisoners); §§ 46.401-.409 (concerning children) (1996).

34. *See* Jessica Wilen Berg, *Legal and Ethical Complexities of Consent with Cognitively Impaired Research Subjects: Proposed Guidelines*, 24 J. L. MED. & ETHICS 18 (1996); Edward W. Keyserlingk, *Proposed Guidelines for the Participants of Persons with Dementia as Research Subjects*, 38 PERSP. BIO. MED. 319 (1995). *See also*, American College of Physicians, *Cognitively Impaired Subjects*, 111 ANNALS OF INT. MED. 843 (1989).

35. *See* Keyserlink, *supra* note 34, at 319.

36. *See, e.g*, ALASKA STAT. § 47.30.830 (Michie 1996) (prohibiting experimental research on state mental health patients that involve "any significant risk of physical or psychological harm"); DEL. CODE ANN. tit. 16, § 51.75(f) (1995) (prohibiting any resident of a state mental hospital from being approached "to participate in pharmaceutical research if [the] patient is incapable of understanding the nature and consequences of [the] patient's consent"); DEL. CODE ANN. tit. 16, § 51.74 (1995) (prohibiting certain classes of mental hospital residents, regardless of competency, from participating in pharmaceutical research); 405 ILL. COMP. STAT. ANN. 5/2-110 (West 1993) (providing that parent or guardian cannot consent to ward's participation in any "unusual, hazardous, or experimental services" without approval by court and determination that such services are in the "best interests" of the ward); MASS. REGS. CODE tit. 104, §§ 13.01-.05 (1995) (prohibiting research on patients in mental facilities that will not provide direct, therapeutic benefit and prohibiting research on patients with mental disabilities where the risk is more than mini-

ist, if an IRB were to approve such research, it might choose to monitor the study closely, require a consent monitor, or ask the researcher to implement educational activities for authorized representatives about their roles and responsibilities when making research-related decisions.

When conducting research involving vulnerable research subjects, researchers and research institutions must be held to a high standard; for example, the scientific and ethical justifications must be particularly strong. Therefore, researchers studying vulnerable subjects should be expected to provide in the protocol justifications for the research, reasons why other (less vulnerable) subjects cannot be studied, and identify what additional safeguards will be implemented to protect subjects' rights and safeguard their welfare. Also, all institutions or research units which conduct research involving cognitively impaired people should have policies or written guidelines concerning appropriate protections. Although the institution's IRB(s) and investigators must take into account the particular circumstances of each individual protocol, the existence of written policies or guidelines demonstrates appropriate extra vigilance to the rights and welfare of these vulnerable research subjects.

III. CLINICAL CENTER POLICY ON THE CONSENT PROCESS IN RESEARCH INVOLVING COGNITIVELY IMPAIRED HUMAN SUBJECTS

NIH's Warren G. Magnuson Clinical Center (CC) is a large clinical research hospital with 350 beds and 13 out-patient units in which the 900 to 1,100 research physicians change frequently. For many years CC researchers have conducted research involving people with cognitive impairments in order to investigate the etiology and develop treatments of these disorders. In 1987, the CC adopted an informed consent policy which provides additional safeguards for research subjects who are, or are likely to become, cognitively impaired during their participation in clinical research.[37] The development

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mal and exceeds the benefit to the subject); MO. ANN. STAT. § 6.30.115 (8) (West Supp. 1997) (preventing state mental health patients from being "the subject of experimental research," with exceptions, and prohibiting biomedical or pharmacological research from being performed on any individual with mental disabilities if that research will have no direct therapeutic benefit on the individual research subject); Diane E. Hoffman & Jack Schwartz, *Proxy Consent to Participation of the Decisionally Impaired in Medical Research - Maryland's Policy Initiative*, 1 J. HEALTH CARE L. & POL'Y 136, nn. 9 & 12 (1997) (citing state statutes which provide restrictions for research on the decisionally impaired).

37. *See* John C. Fletcher & Alison Wichman, *A New Consent Policy for Research with Impaired Human Subjects*, 23 PSYCHOPHARMACOLOGY BULL. 382 (1987).

and description of the CC policy is described in detail elsewhere[38] and only a brief description is given here. The policy was designed to strengthen the role of NIH's fourteen IRBs in providing additional safeguards for:

> [C]ognitively impaired human research subjects and to promote ethically appropriate research in disorders involving cognitive impairment. The policy contains two main features: (1) prior evaluation of proposed research studies by an IRB to allow the appointment of surrogate decision-makers for subjects who are or may become cognitively impaired; and (2) an internal system of oversight and consultation once the appointment of surrogate decision-makers is authorized by the IRB. The policy recognizes eight distinct . . . [research-related] cases that require additional safeguards to the informed consent process.[39] The cases incorporate several considerations: (1) that assent[40] of cognitively impaired subjects is necessary, but not sufficient for participation in research, (2) that the protection should be proportionate to the risk involved, with the least protection required when research involves no more than minimal risk, (3) that the Durable Power of Attorney (DPA) model for the appointment of a surrogate decision-maker is the most ethically and legally supportable practice when future intellectual impairment of research subjects can be predicted on the basis of diagnosis or when existing cognitive impairment is still mild, and (4) that degree of cognitive impairment, level of research risk, and prospect of benefit to individual subjects determine whether DPA or other approaches, including court appointed guardianship, are used in selecting a surrogate decision-maker.[41]

In some cases, consultation with a member of the CC Department of Clinical Bioethics is required before research participation in order to assure that the surrogate decision-maker understands his/her role, and is willing and able to fulfill the responsibilities. For example, in the CC, surrogate decisions are based on the standard of substituted judgment which requires that the surrogate decision-maker "stand in

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38. *See id.*

39. Among research related cases that require consideration of additional protections are: Alzheimer's disease, schizophrenia, manias with suicidal behavior, types of aphasia, and states of partial or total coma. *See id.* at 382.

40. "Assent" means an affirmative agreement to participate in research. *See* Regulations for Protection of Human Subjects, 45 C.F.R. § 46.402(b).

41. *See* Philip J. Candilis et. al., *A Survey of Researchers Using a Consent Policy for Cognitively Impaired Human Research Subjects,* 15 (6) IRB 1, 2 (1993).

the shoes" of the incapacitated individual (and make decisions he/she would make if able to do so). Investigators are encouraged to recruit subjects who are not too impaired to appoint a surrogate; in that case, prospective research subjects and surrogates can be educated about the criteria for choosing a surrogate, that is, the need to be available for consultation with the research team, willingness to serve.

In 1990, after the CC Policy had been in existence for three years,[42] a survey was conducted to learn more about knowledge of and attitudes toward the policy and to evaluate whether hospital educational efforts could be designed more effectively to improve its application.[43] Also, the policy is currently undergoing review in keeping with CC procedures to evaluate and update its research and patient care policies on a regular basis.

IV. IMPROVING THE CURRENT IRB SYSTEM

There is no doubt that in the last 20 years significant advances have been made in implementing protections for research subjects in the United States. Review activities of the estimated 3,000 to 5,000 IRBs in United States universities, hospitals, private and public research facilities have played an important role in educating researchers about, and overseeing compliance with, regulatory requirements.[44] Despite its successes, the IRB system currently is under considerable criticism.[45] Some of the criticism is deserved, and some is not. In some instances, IRBs have become a convenient lightning rod for identifying what is wrong with a complex, and increasingly regulated, system of clinical research. However, since the current IRB system was put into place, the research enterprise has changed considerably.[46] IRBs have been given more responsibilities,[47] and they have been faced with complex new issues such as genetic research which have broad societal impact.

The current IRB system deserves serious reevaluation; its strengths should be acknowledged and supported, and its weaknesses should be addressed. However, some of the strengths of the IRB system also contribute to its potential weaknesses. For example, hav-

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42. *See id.*

43. *See id.* at 1, 3.

44. *See GAO Report, supra* note 9, at 6.

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

46. *See* Harold Edgar & David J. Rothman, *The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation*, 73 MILBANK Q. 489, 498-501 (1995).

47. *See generally* Phillips, *supra* note 46.

ing IRBs situated at the site of the research promotes more timely review and has the advantage of ensuring that research is reviewed by people most likely to be familiar with the researchers and with institutional and other local factors relevant to the protection of research participants. It also provides an important on-site educational resource. For example, NIH has 14 IRBs consisting of about 200 members who provide a significant educational resource to the NIH research community. However, on-site IRB review also introduces some potential problems. For example, a busy IRB may not engage in ongoing educational efforts to assure that members are kept abreast of complex ethical and regulatory issues concerning protocols it reviews; or it may be weighted down with regulatory and paperwork requirements which divert its attention away from human subject protections; or its members may be predominately researchers, thus depriving the IRB committee of important contributions by nonscientists. An IRB's ability to fulfill its mandate is influenced by a number of factors including the knowledge and experience of the members, and institutional resources and commitment. IRB decisions are matters of judgment, and therefore, they depend on an understanding and wise application of ethical guidelines and regulatory requirements, as well as an appreciation of local influences, such as cultural considerations. A research study that is determined to be ethically permissible by one IRB may not be approved by another IRB. Therefore, efforts to improve IRBs' abilities and procedures should be aimed at promoting consistency and thoroughness of the review process within, and between, IRBs.

The current federal regulatory directive concerning "additional safeguards" for vulnerable research subjects is broad and most IRBs would benefit from additional guidance. However, it is not clear that additional federal regulatory or state statutory requirements, such as those currently being proposed in Maryland,[48] are necessary. There are some educational and regulatory steps that can be taken more quickly, and perhaps to better advantage, than legal remedies.

More practical guidance to IRBs is warranted. The current OPRR *Institutional Review Board Guidebook*[49] contains a chapter on research involving cognitively impaired subjects.[50] This chapter should be up-

48. Jack Schwartz, Office of the MD Att'y Gen., Second Report of the Attorney General's Research Working Group (May 1997) (the Second Report is reprinted in the appendix to this issue of the *Journal of Health Care Law & Policy*).

49. OFFICE FOR PROTECTION FROM RESEARCH RISKS, U.S. DEP'T. OF HEALTH & HUMAN SERVICES, PROTECTING HUMAN SUBJECTS, INSTITUTIONAL REVIEW BOARD GUIDEBOOK (1993).

50. *Id.* at 6-33.

dated, expanded, and re-issued either as OPRR "Points to Consider" for IRBs or as an "OPRR Report" which is disseminated to all institutions holding OPRR-approved MPAs. Also, the NIH Institutes which fund research involving cognitively impaired subjects may choose to issue guidelines for researchers conducting and IRBs reviewing such research. This approach has been taken by some NIH Institutes concerning the research administration of alcohol[51] and drugs of abuse[52] to human subjects. If more direct action is warranted, OPRR may choose to require MPAs to include institutional policies concerning research involving cognitively impaired subjects. Institutions re-negotiate the terms and conditions of their MPAs with OPRR every five years. Therefore, within several years all major United States research institutions would be required to have written policies.

Another approach to promote consistency of IRB review and to assure serious attention to the ethical, regulatory and scientific aspects of research involving cognitively impaired subjects is to have fewer researchers conducting such research. For example, funding could be provided only to researchers and research institutions which have demonstrated the knowledge, resources, and ability to conduct the research. The National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Child Health and Human Development (NICHD) have taken this approach successfully in funding research on AIDS in both adults and children. Currently, there are about 50 centers designated by the two institutes as pediatric AIDS research centers. This approach has several strengths. One is that participating centers have demonstrated the ability and necessary resources, including an established IRB, to conduct clinical trials involving ill children. Also, the fact that the centers draw from diverse ethnic groups improves the quality of the knowledge gained. Finally, it is easier to oversee clinical trials and communicate with researchers, IRBs and others, in a few designated research centers.

Improving the effectiveness of IRBs includes not only disseminating relevant information, but also discovering new and innovative ways to educate IRBs dispersed throughout the United States. New educational technologies now allow for centralized, innovative ways to educate IRBs which are located throughout the United States. For

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51. *See* NATIONAL ADVISORY COUNCIL, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM, DEP'T OF HEALTH & HUMAN SERVICES, RECOMMENDED COUNCIL GUIDELINES ON ETHYL ALCOHOL ADMINISTRATION IN HUMAN EXPERIMENTATION (1989).

52. *See* NATIONAL ADVISORY COUNCIL, NATIONAL INSTITUTE ON DRUG ABUSE, DEP'T OF HEALTH & HUMAN SERVICES, RECOMMENDED GUIDELINES FOR THE ADMINISTRATION OF DRUGS TO HUMAN SUBJECTS (1997).

example, computer-based training (CBT) offers new and powerful ways to inform and educate IRB members. NIH has some experience with CBT. NIH's Office of Human Subjects Research (OHSR) has designed and implemented a one hour CBT on the protection of human subjects.[53] In a pilot phase, the CBT was completed and evaluated by over 2000 NIH researchers. Based on the positive results of the pilot phase, completion of the CBT is required of all new NIH employees who conduct research. Researchers can access the program through the internet and also certify their completion of the CBT electronically. NIH's experience educating researchers suggests that CBT may be a valuable, but underutilized tool, to help inform and educate IRBs.

An important part of OPRR's mission is to educate about and provide clarification and guidance concerning ethical issues raised in connection with biomedical and behavioral research involving human subjects. OPRR's educational activities consist of disseminating information to thousands of IRBs, researchers, and members of the public; consultation with researchers, IRBs and IRB regulators; sponsorship of up to six annual workshops throughout the country; and a limited number of institutional site visits for education and technical assistance. However, given the increase in the number of IRBs and the complexity of issues facing them, new and innovative approaches to education are warranted. This can be facilitated by NIH in two ways: by increasing OPRR's educational staff and budget and by offering competitive grants to fund research on innovative educational strategies directed towards IRBs and researchers.

A. Improving the System Based on Knowledge: The Need for More Research on IRBs

There is relatively little published research on IRBs when compared, for example, to published literature on the educational, oversight and self-evaluation procedures of hospital-based clinical ethics committees, or ethical issues in clinical medicine. In particular, published literature or research on the effectiveness of the OPRR assurance mechanism is lacking. For example, OHSR, NIH's primary resource in its Intramural Research Program for information and education concerning regulation and guidelines covering clinical research, recently reported the results of a survey of NIH researchers using OPRR-approved assurances in international collaborative re-

53. Available through the Office of Human Subjects Research's internet home page at <http://helix.nih.gov:8001/ohsr>.

search.[54] Despite the fact that OPRR has been negotiating international assurances for over 15 years, we found no other published information on them.

This lack of empirical information about, and research on, IRBs can be placed in large part squarely at the feet of the federal government, particularly HHS and the NIH. The United States system for protecting human subjects was reviewed in 1975 by the congressionally mandated National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Based upon recommendations of the Commission, the system was substantially revised in the late 1970s and early 1980s. It was only in 1994 that HHS began another systematic evaluation to examine the extent to which the current system provides adequate protection for the rights and welfare of human subjects. Some recommendations on how to improve the system have been provided by other groups, including the President's Advisory Committee on Human Radiation Experiments[55] and the United States General Accounting Office.[56] Also, the Human Subject Protections Subcommittee of the President's National Bioethics Advisory Commission (NBAC) is evaluating federal departments' implementation of the Common Rule. It is expected to provide some recommendations on steps that can be taken to improve the current system of IRB review.

These federal efforts are laudable. However, NIH has a long history as the leader in the federal government's efforts to promulgate human subject protections. Therefore, it has a particular responsibility to support research efforts to gain knowledge about and help implement meaningful changes. Currently there are two competitive NIH research grants to study the informed consent process in research involving individuals with mental disorders[57] and to identify and validate methods for improving the informed consent process in research.[58] However, funding opportunities need to be broadened to include research on IRBs, including research which enhances the work currently being conducted by NBAC and others, and research in areas, which although important, have received little systematic study

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54. Alison Wichman et al., *Collaborative Research Involving Human Subjects: A Survey of Researchers Using International Single Project Assurances*, 19 IRB 1, at 1.

55. ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS: FINAL REPORT (GPO PUB. No. 061-000-00-848-9) (1995).

56. *See GAO Report*, *supra* note 9.

57. NATIONAL INSTITUTES OF HEALTH, *Informed Consent in Clinical Mental Health Research*, Public Announcement 95-080 (1995).

58. NATIONAL INSTITUTES OF HEALTH, *Informed Consent in Research Involving Human Participants*, RFA No. OD-97-001 (1996).

(*e.g.*, the relationship of IRBs to other review groups such as Data Safety Monitoring Boards (DSMBs), and the role of IRBs in federally funded research conducted in foreign countries).

V. CONCLUSION

The current debate about what constitutes ethically permissible research involving cognitively impaired subjects is appropriate. Research involving human subjects, even if they may benefit directly from participation, is a different kind of enterprise from the routine practice of medicine. In research, physician/researchers' goals include not only the welfare of individual research subjects, but also the gathering of scientific data. Therefore, our society has granted a conditional privilege to perform research with human subjects; the condition is that the research must be scientifically sound and conducted in a manner that protects the rights and safeguards the welfare of the participants.

The current United States system of protecting human research subjects, including the role of IRBs, deserves serious and ongoing evaluation. The IRB system is well-developed but ever evolving. Successful evolution depends on learning from the past, understanding more about current and future needs, and applying the knowledge to implement meaningful changes. Researchers, research participants and institutions, and others, particularly the American people who bear the burdens of research and to whom the benefits accrue, all have an important stake in the process.

APPENDIX

TABLE 1

CRITERIA FOR IRB APPROVAL OF RESEARCH
(adapted from 45 CFR 46.111)

(a) In order to approve research the IRB shall determine that all of the following requirements are satisfied:

1. Risks to subjects are minimized;

2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of knowledge that can reasonably be expected to result;

3. Selection of subjects is equitable taking into account the purposes of the research and the setting in which the research will be conducted. The IRB should be cognizant of the special problems of research involving vulnerable populations;

4. Informed consent will be sought from each prospective subject or his/her legally authorized representative; and

5. When appropriate, adequate provisions are provided to monitor data collection to assure safety of subjects and to protect the privacy of subjects.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence; . . . . additional safeguards have been included in the study to protect the rights and welfare of these subjects

TABLE 2
VULNERABLE RESEARCH SUBJECTS

LIMITATIONS TO INFORMED	SUSCEPTIBLE TO COERCION CONSENT OR UNDUE INFLUENCE
comatose people	
critically ill people	
mentally retarded people	
people with dementias/some psychiatric diseases	
children	
institutionalized individuals	
non-English speaking people	
	the educationally/economically deprived
	prisoners
	seriously/terminally ill people
	paid research volunteers