Protecting human participants in long-term care research : the role of state law and policy

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ABBREVIATIONS USED IN THIS REPORT

AAHRPP	Association for the Accreditation of Human Research Protection Programs
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DPOA	Durable power of attorney
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
LTC	Long-term care
NAMI	National Alliance for the Mentally Ill
NBAC	National Bioethics Advisory Commission
NIA	National Institute on Aging
NIMH	National Institute of Mental Health
OHRP	Office of Human Research Protections
OIG	Office of Inspector General
OPRR	Office of Protection from Research Risks
PHS	Public Health Service
QI	Quality improvement
RCT	Randomized clinical trial

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Introduction

Each of us, in some way or another, is a beneficiary of research. We all benefit because advances in knowledge allow health care professionals to better prevent, manage, and/or cure various causes of sickness and disability and to help maintain or improve quality of life. Health care and human service professionals benefit in that biomedical and behavioral research findings add to their available arsenal of weapons in the fight against sickness and disability. Planners, administrators, and consumers of health care financing and delivery systems benefit from the lessons, both positive and negative, taught by health services research. Researchers themselves, as well as their sponsors, have important career and pecuniary interests--in addition to altruistic motivations--in the conduct and outcomes of research.

Older persons and their families and formal caregivers, especially those who require various forms of long-term care (LTC), have a particularly vital stake in the research enterprise, because (among other things) many forms of sickness and disability are age-related. More effective and affordable diagnostic and therapeutic interventions for the horrors of Alzheimer's disease, Parkinson's, heart disease, cancer, and other illnesses that today disproportionately ravage the elderly can only be developed and disseminated if vigorous research efforts about the medical problems themselves, and organizational approaches to dealing with them, are encouraged and facilitated.

Not only do research projects aimed at the problems of old age usually need the participation of older human subjects, but–depending on the research question being studied--many of those older subjects may be receiving care in LTC settings and are especially vulnerable due to significant mental and/or physical impairments such as dementia, depression, or psychosis *(Dunn, Lindamer, Palmer, Schneiderman, & Jeste, 2001)* ***that severely limit or negate their capacity to make voluntary and informed decisions about participation in research.***

Unfortunately, however, the conduct of research is almost never an unalloyed good for older persons or others. Most of the research projects likely to benefit older persons and those who care for, and about, them necessarily involve the use of older persons as subjects or participants whose primary role it is to produce the data from which the researcher may draw generalizable conclusions that may benefit others in the future. However, producing such data entails risks for the research participant. Not only do research projects aimed at the problems of old age usually need the participation of older human subjects, but–depending on the research question being studied–many of those older subjects may be receiving care in LTC settings and are especially vulnerable due to significant mental and/or physical impairments such as dementia, depression, or psychosis (Dunn, Lindamer, Palmer,

Schneiderman, & Jeste, 2001) that severely limit or negate their capacity to make voluntary and informed decisions about participation in research. An example would be research attempting to measure the perceptions that cognitively impaired nursing home residents have about their quality of life (Uman, Hocevar, Urman, Young, Hirsch, & Kohler, 2000).

We have, thus, a Catch-22 situation. On one hand, there is a scientific and ethical imperative to conduct biomedical, behavioral, and health services research on problems pertaining to older persons in order to eventually enhance the length and quality of older persons' lives. At the same time, however, we are unable to conduct such research without the participation of large numbers of older, frequently extremely disadvantaged and dependent human participants both inside (Franzi & Weiler, 1992) and outside of institutional settings. From this caldron emerge a number of perplexing legal and ethical questions about such fundamental matters as the ability to obtain truly voluntary and competent informed consent, the proper role of surrogate decision making in the research context, equitable selection of research subjects, a fair balancing of risks and benefits, confidentiality protections, and payment responsibility for participation and injury within a protocol (Karlawish & Casarett, 2001).

There has been a substantial amount of activity over the past several years, and continues to be substantial activity, addressed at the challenge of (a) protecting the rights and well-being of vulnerable human participants in various kinds of biomedical, behavioral, and health services research protocols, on one hand, without (b) unduly impeding the conduct of research that promises findings that may substantially improve health and the quality of life for many beneficiaries of research, on the other. Many of the emerging recommendations for improved participant protection are relevant to, and in many cases specifically targeted at, vulnerable older persons, including long term, chronically dependent residents of nursing homes or assisted living facilities, as well as recipients of home care. This population of older adults with functional disabilities who may be approached by investigators to participate in research protocols is growing.

Yet, both current federal law and emerging policy recommendations defer–usually without any meaningful elucidation or elaboration–some very important matters about research participation, especially regarding informed consent, determinations of decisional capacity, and surrogate decision making authority, to the law of individual states and the discretion of individual Institutional Review Boards (IRBs).

Thus far, the largest share of the discussion and recommendations regarding human research participant protection pertain to possible legal and policy changes at the federal level. Yet, both current federal law and emerging policy recommendations defer–usually without any meaningful elucidation or elaboration–some very important matters about research participation, especially regarding informed consent,

determinations of decisional capacity, and surrogate decision making authority, to the law of individual states and the discretion of individual Institutional Review Boards (IRBs). Applicable law regarding these particular issues is, and traditionally has been, determined by the separate states as a matter of statute, regulation, or judicial precedent.

The role of specific state legislative, administrative (i.e., regulatory), and common (i.e., judge-made precedent) law and public policy in protecting older LTC consumers who are or may become participants in research studies thus is a vital topic, but one which has received a surprisingly small amount of analysis to date. This report focuses on the state role, concentrating on Ohio, but concerning issues of importance nationally. Ideally, the public policy recommendations contained herein will serve Ohio's LTC research agenda by contributing to the qualitative improvement of LTC research conducted in Ohio (including long-term care research conducted by the State itself), enhancement of the public's confidence in the research process, and protection of the rights and well-being of Ohio citizens who are recipients of or candidates for LTC services and who may be solicited to enroll in research studies.

The author relied on a variety of informational sources in formulating the analysis and recommendations contained in this report. Research included: a comprehensive review of the pertinent health care, legal, and bioethical literature; analysis of reports by public and private agencies that recommend legal and policy changes at the national level; a thorough identification and examination of relevant state statutes, regulations, and case law in Ohio and elsewhere using the Westlaw and Lexis/Nexis databases; a mail survey of IRBs in Ohio asking qualitative questions regarding present protections (and their perceived effectiveness) for older research participants, especially those who are recipients of or candidates for long-term care services; telephone interviews with a convenience sample of ten professionals drawn from academia and private firms who conduct LTC research (mainly health services research) activities in Ohio that enroll older participants; and telephone interviews with a convenience sample of twenty national experts about the state role pertaining to legal and ethical aspects of research participant protection.

The next part of this report sets out background information on the history and content of current federal regulations governing the conduct of research involving human participants, as well as a summary of pertinent criticisms of these regulations. The following section is a general discussion of the state role in this sphere, addressing the justifications for state regulation of research, providing an overview of current state law, and reviewing key principles that ought to guide state policy makers. This discussion is followed by an exploration of specific issues and policy options arising in the context of the state's role in overseeing the ethical propriety of biomedical, behavioral, and health services research generally, and especially the conduct of research involving older and disabled persons who are recipients of LTC. Finally, the author outlines potential non-governmental strategies for achieving desired objectives in this realm.

Federal Regulation of Human Subjects Research

History and General Provisions

The historical developments leading up to the current state of federal command and control regulation of biomedical, behavioral, and health services research involving human subjects in the United States have been amply chronicled (Jonsen, 1998; Rothman, 1991; Wolpe, Moreno, & Caplan, 1999). Beginning with the Nuremberg Code, adopted in 1947 for use in Nazi war crimes trials in which defendant physicians tried to justify their inhumane treatment of human beings under the guise of scientific experimentation (Annas & Grodin, 1992), principles determining the proper conduct of human experimentation have been formalized into more than thirty different international guidelines and ethical codes (Brody, 1998).

In the U.S., federal government involvement in the regulation of research began in earnest in 1966. Officials at the U.S. Public Health Service (PHS) became concerned about the increasing frequency with which human subjects were being used in research. Formulation of a formal PHS policy was initiated, and the resulting guidelines were released in May of 1969. These guidelines served as a model for the development of a Department of Health, Education, and Welfare (DHEW) (now Department of Health and Human Services (DHHS))-wide policy announced in April of 1971. This policy retained the institutional review process initiated by PHS; that is, the administrative review machinery was adjusted to cope with the rising tide of research being conducted with human subjects by switching from the prior centrally conducted, grant-by-grant review procedure to a model of individual institutional responsibility for compliance with ethical standards. The DHEW policy also included more specific requirements for obtaining informed consent than did the earlier PHS guidelines.

In 1974, the DHEW policy was translated into enforceable regulations. These regulations formalized IRBs by withholding DHEW financial research support from those institutions that had not established an organizational review committee that was scrutinized and approved by DHEW. It became incumbent on these internal review committees to provide both general and special assurances of subject protection, as well as documentation of informed consent.

The next significant step was Congressional enactment of Public Law No. 93-348 on July 12, 1974. This statute, commonly known as the National Research Act, established the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (the Belmont Commission). This body was charged to (1) conduct a comprehensive study to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and (2) recommend research guidelines and administrative actions for the implementation of those guidelines. The accelerating public concern with the protection of subjects thought to be at special risk can be seen in Congress' specific directive to the Commission to investigate the ethics of research on, among other enumerated groups, the institutionalized mentally infirm (delineated as those "mentally retarded, emotionally disturbed, psychotic, or senile" persons who reside as patients in health care

institutions). After an extensive series of hearings, meetings, and deliberations, the Commission issued a series of reports and recommendations between 1975 and 1977.

The Belmont Commission followed the thrust of earlier federal pronouncements by recommending: (1) that all research involving human subjects conducted at an institution that receives federal funding be reviewed by an IRB before the research is begun, and (2) that there be prior informed consent by the subjects involved. Final regulations resulting from these recommendations were issued on January 26, 1981, became effective on July 27 of that year, and are codified at 45 Code of Federal Regulations, Part 46.

These regulations originally applied on their face only to research involving human participants that was conducted by the DHHS itself or that was funded in whole or part by DHHS. However, most institutions engaged in human participants research agree to comply with the regulatory requirements for all of their research protocols, regardless of the funding source for any particular study. Additionally, other federal agencies have adopted a Common Rule for human subjects protection in any research study that they sponsor.[1] Research involving the testing of investigational drugs or medical devices is concurrently regulated by the federal Food and Drug Administration (FDA)[2] (Merrill, 1997). The Common Rule and FDA requirements overlap considerably with each other, but are not identical.

As defined in federal regulations, "research means a systematic investigation designed to develop or contribute to generalizable knowledge."[3] Thus, research is different from usual diagnostic and therapeutic health care or human services delivery, the latter consisting of interventions that are designed and expected solely to enhance the well-being of an individual patient/client and that have a reasonable expectation of success.

The Institutional Review Board (IRB) Role

Research to which the federal Common Rule applies must be reviewed and approved by an IRB and is thereafter subject to continuing IRB review (Putney & Gruskin, 2002). IRB approval is necessary initially and at least annually afterwards (Wichman, 1998). In order to approve a protocol, the IRB must determine that each of the following requirements is satisfied:

- Physical and psychological risks to participants will be minimized
- Physical and psychological risks to participants are reasonable in relation to anticipated benefits to those participants and to the importance of the general knowledge that may reasonably be expected to result. This is arguably, and intentionally, an exercise in paternalism, the IRB deciding *for* individuals what is in their best interests.
- Selection of participants is equitable
- Informed consent will be obtained

[1] 45 Code of Federal Regulations Part 46, subpart A. Pertinent portions of the Common Rule are reprinted in Appendix 2.

[2] 21 Code of Federal Regulations §§50.10-40 & 56.101-121.

[3] 45 Code of Federal Regulations §46.102(e).

- Informed consent will be appropriately documented

- The research plan makes adequate provisions for monitoring the data collected to ensure the safety of participants

- There are adequate provisions to protect the privacy of participants and maintain the confidentiality of data

The IRB must police the requirement that no human participant is involved in research unless legally effective informed consent has been obtained and "only under circumstances that provide the prospective subject...sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." The regulatory provisions for informed consent in research are basically a codification and extension of the common law that was developed in the therapeutic setting (Faden & Beauchamp, 1986).

Local IRBs themselves are monitored by the former Office of Protection from Research Risks (OPRR) (McCarthy, 1995), which was moved a few years ago from the National Institutes of Health to the Office of the Secretary, DHHS (Marwick, 1999) and renamed the Office for Human Research Protections (OHRP). OHRP awards the IRB a Federal-Wide Assurance (FWA) that allows each IRB to review studies involving human participants.[4]

Protecting Decisionally Impaired Persons

The Belmont Commission recommended in 1978 that, at least for individuals institutionalized as mentally infirm, the federal government should promulgate distinct regulations controlling research with human participants. Although proposed regulations were published, these were never made final (i.e., legally binding). Among the explanations for this purposeful inaction, beyond a vague admonition in the Common Rule that IRBs should be "particularly cognizant" of the needs of all vulnerable subjects and should require "additional safeguards" when such populations are included in a study,[5] are (1) the objections of the mental health research community that specially targeted requirements would be cumbersome and stifle scientific progress and (2) acceleration of the trend toward deinstitutionalization of the mentally ill and developmentally disabled in the late 1970s and into the 1980s (Childress, 1998).

Neither has action been taken in response to subsequent calls for specific research regulations targeting the decisionally impaired. Recommendations in this vein have emanated from, among other sources, a National Institute on Aging (NIA)-sponsored study group that convened in the early 1980s to discuss the use of demented persons in research (Melnick & Dubler, 1985; Melnick, Dubler, Weisbard, & Butler, 1984) and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1983).

[4]Information on FWAs is available at <http:// osophs. dhhs. gov/ humansubjects/ assurance/fwas.

[5]45 Code of Federal Regulations §46.111(b).

More recently, however, special protections for the decisionally impaired, within both institutional and community settings, have become a renewed item of interest (Dresser, 2001a; Fleischman, 2001; Moreno, 1998; Levine, 1996). The national Alzheimer's Association (1997) has called "upon state and federal authorities to clarify existing laws and regulations as they relate to people with cognitive impairments." The American Geriatrics Society Ethics Committee (1998, p. 1309) has enunciated the position:

> Federal and state authorities should clarify existing laws and regulations as they relate to research on dementia, especially regarding the use of advance directives for research and the status of proxy consent for research in the absence of advance directives. If necessary, pertinent laws and regulations should be amended to facilitate important research on dementia...

Among the various organizations that have developed and adopted relevant research guidelines in this sphere are the American College of Physicians (1989), the Council for International Organizations of Medical Sciences (in collaboration with the World Health Organization) (1993), Council of Europe (de Wachter, 1997), and the British Medical Research Council (1991). The American Psychiatric Association organized a work group for the purpose of formulating ethical guidelines for psychiatric researchers dealing with the decisionally impaired. Several scholars, laboring individually and within groups, also have weighed in with comprehensive policy proposals in the area (Dresser, 1996; High, Whitehouse, Post, & Berg, 1994; Keyserlingk, Glass, Kogan, & Gauthier, 1995).

On December 2-3, 1997, the National Institutes of Health sponsored an Inter-Institute Conference on Research Involving Individuals With Questionable Capacity to Consent: Ethical Issues and Practical Considerations for IRBs, and subsequently published a document from that Conference (National Institutes of Health, 2001). The latest significant foray into this arena was launched with the release of the National Bioethics Advisory Commission (NBAC) (1998) report entitled "Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity."

General Criticisms of the Current Regulatory Structure

In addition to the critiques and activities described above directed specifically at the present vulnerability of research participants with impaired decisional capacity, over the last several years there have been a number of broader criticisms leveled at the current regulatory system. On June 11, 1998, the DHHS's Office of Inspector General (OIG) issued four reports on human subjects research and IRBs (U.S. Department of Health and Human Services, 1998a; 1998b; 1998c; 1998d). Among the concerns noted in these reports were: overburdened IRBs with insufficient time and resources to properly conduct initial and (especially) continuing reviews; ineffective monitoring of and response to adverse events happening to participants; insufficient ethics training for researchers and IRB members; inadequate attention to evaluation of IRB effectiveness; and conflicts of interest involving IRBs and the institutions of which they are a part, especially as research funds become more

scarce. Also in June of 1998, the National Institutes of Health Office of Extramural Research released a contractor's report (James Bell Associates, 1998) that, although considerably less critical than the OIG reports, concluded that protection of human participants could be improved by fine-tuning IRB procedures and providing increased education and training to researchers as well as to IRB members and staff. The OIG and NIH reports were accompanied by well-publicized Congressional hearings before the Subcommittee on Human Resources of the House Committee on Government Reform and Oversight. In April of 2000, the OIG issued a report (U.S. Department of Health and Human Services, 2000) finding that, although the topic of protecting human research participants continues to receive substantial public attention, few of the OIG's specific 1998 recommendations had been implemented.

In 1999, the National Institute of Mental Health (NIMH) announced creation of a new review panel to screen high risk intramural and extramural studies funded by the Institute. That review panel and other NIMH initiatives were driven "by a desire to make sure that the science in NIMH studies is good enough to justify the use of human subjects" (Marshall, 1999). Typically, IRBs have essentially taken a hands-off approach to review of the scientific merits of research protocols, ignoring the logical link between the quality of the science and the justification for allowing any risk to volunteers.

In 2001, the Institute of Medicine of the National Academy of Sciences issued a report (Institute of Medicine, 2001) recommending the establishment of a formal system for accrediting human research participant protection programs. The Association for the Accreditation of Human Research Protection Programs (AAHRPP) recently released Final Accreditation Standards and Procedures (2002) to provide direction to institutional human research protection programs that seek AAHRPP accreditation.

Most significantly, in 2001 the NBAC issued a report (National Bioethics Advisory Commission, 2001) that recommended a variety of substantial changes in the way that legal and ethical oversight of all research involving human participants is now carried out. Among the areas in which consideration of possible federal policy modifications, or at least further study, were suggested were those pertaining to: scope and structure of the oversight system; level of review; education, certification, and accreditation in research ethics; assessing and monitoring compliance; managing conflicts of interest; IRB membership; guidance for assessing risks and potential benefits; the handling of minimal risk protocols; evaluating potential participants' vulnerability; the informed consent process, including waiver and documentation; protecting privacy and confidentiality; monitoring of ongoing research; adverse event reporting; review of cooperative or multi-site research studies; and compensation for research-related injuries.

Current Federal Activities

At present, many of the recommendations of NBAC and other groups are under active consideration by Congressional committees (for potential statutory changes). For example, a hearing was held by the Senate Committee on Health, Education, Labor, and Pensions on April 23, 2002 on "Protecting Human Subjects in Research: Are Current Safeguards Adequate?"

The federal agencies that sponsor, conduct, or otherwise regulate research are actively studying recommended changes in regulations, policies, or practices. OHRP launched in early 2002 a voluntary Quality Improvement (QI) Program intended to help institutions evaluate and improve the quality of their human research protection programs.

One area of substantial controversy (Annas, 2002; Kulynych & Korn, 2002) and uncertainty that has emerged lately in this context revolves around regulatory implementation of the medical privacy requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.[6] HIPAA covers all patient-identifiable health care information in any form–oral, written, or electronic–maintained or transmitted by a wide array of covered entities, including health care providers, clearinghouses, contractors, subcontractors, and health coverage plans. Under the HIPAA statute, patients have the right to inspect, copy, and amend their health care information, authorize or refuse to authorize its use, and receive a formal accounting of how their information is used. Substantial civil and criminal penalties may be imposed on covered entities for permitting unauthorized access to protected information.

Final Rules implementing the HIPAA legislation were published by DHHS on August 14, 2002.[7] Among the most important provisions of those Rules pertaining specifically to the conduct of research involving human participants are:

–An individual's written "[a]uthorization for the use or disclosure of protected health information for a research study may be combined with any other type of written permission for the same research study, including another authorization for the use or disclosure of protected health information for such research or a consent to participate in such research."[8] Because this regulation permits but does not require the combining of forms, it remains within the discretion of researchers or IRBs to determine whether the combining of information authorization and consent forms for research would be appropriate for any particular study.

–A covered entity (such as a nursing home or home care agency) may disclose to researchers protected health information without the written authorization of the individual, or the opportunity for the individual to agree or object to the use or disclosure, when the covered entity has been presented with a written statement that the IRB reviewing a proposal "has determined that the alteration or waiver, in whole or in part, of authorization satisfies the following criteria:

(A) The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

(1) An adequate plan to protect the identifiers from improper use and disclosure;

(2) An adequate plan to destroy the identifiers at the earliest opportunity

[6]Public Law No. 104-191, §262.

[7]67 Federal Register 53181-53273 (August 14, 2002).

[8]45 Code of Federal Regulations § 164.508(b)(3)(i).

consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and

(3) Adequate written assurances [by the researchers] that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted [by these regulations];

(B) The research could not practicably be conducted without the waiver or alteration; and

(C) The research could not practicably be conducted without access to and use of the protected health information."[9]

–An individual may revoke, in writing, an authorization for the disclosure of protected health information at any time, "except to the extent that the covered entity has taken action in reliance thereon."[10] In the Preamble to the HIPAA regulations, DHHS

> [c]larifies that this provision permits covered entities to continue using and disclosing protected health information that was obtained prior to the time the individual revoked his or her authorization, as necessary to maintain the integrity of the research study. An individual may not revoke an authorization to the extent that the covered entity has acted in reliance on the authorization. For research uses and disclosures, this reliance exception at § 164.508(b)(5)(i) permits the continued use and disclosure of protected health information already obtained pursuant to a valid authorization to the extent necessary to preserve the integrity of the research study. For example, the reliance exception would permit the continued use and disclosure of protected health information to account for a subject's withdrawal from the research study, as necessary to incorporate the information as part of a marketing application submitted to the FDA, to conduct investigations of scientific misconduct, or to report adverse events. However, the reliance exception would not permit a covered entity to continue disclosing additional protected health information to a researcher or to use for its own research purposes information not already gathered at the time an individual withdraws his or her authorization. [DHHS] believes that this clarification of the Rule will minimize the negative effects on research caused by participant withdrawal and will allow for important continued uses and disclosures to occur, while

[9] 45 Code of Federal Regulations § 164.512(i).

[10] 45 Code of Federal Regulations § 164.508(b)(5)(i).

> maintaining privacy protections for research subjects.[11]

–A valid authorization for an individual's permission to use or disclose protected health information must include "[a]n expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure. The statement 'end of the research study,' 'none,' or similar language is sufficient if the authorization is for a use or disclosure of protected health information for research, including for the creation and maintenance of a research database or research repository."[12]

State Regulation of Human Subjects Research–General

Despite the extensive federal presence in regulating research involving the enrollment of human participants, there also exists an important role for the individual states to play in this arena.

Despite the extensive federal presence in regulating research involving the enrollment of human participants, there also exists an important role for the individual states to play in this arena. As stated in a background paper prepared for NBAC:

> [S]tate law is hardly irrelevant to the research enterprise. First, to the extent that research is not subject to federal law, pertinent state law (if any) becomes the only legally applicable regulatory regime. Second, federal law, when it does apply to research, expressly preserves any additional state protections. The Common Rule contains the following non-preemption language: "This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects."[13] In addition to this general provision, the Common Rule more specifically recognizes additional state requirements for informed consent: "The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective."[14] Identical language appears in the regulations of the Food and Drug Administration.[15]

This policy decision, to preserve a role for states in the regulation of the research enterprise, is unsurprising, for the protection of human subjects may be seen as an application of the state's core function, protecting its citizens against harm. As the

[11] 67 Federal Register 53225 (August 14, 2002).

[12] 45 Code of Federal Regulations § 164.508(c)(1)(v).

[13] 45 Code of Federal Regulations § 46.101(f).

[14] 45 Code of Federal Regulations § 46.116(e).

[15] 21 Code of Federal Regulations § 50.26(c).

Supreme Court observed many years ago, "The police power of a state...springs from the obligation of the state to protect its citizens and provide for the safety and good order of society...It is the governmental power of self-protection and permits reasonable regulation of rights and property in particulars essential to the preservation of the community from injury."[16] (Schwartz, 2001, p. M3) (citations omitted)

States also have a regulatory interest in the health research enterprise because they provide tangible economic support to this activity in a variety of direct and indirect ways (Schwartz, 2001, p. M9). This includes, for example, grant programs to encourage private research on particular biomedical[17] or health policy (e.g., the Ohio Long-Term Care Research Project, MEDTAPP program of the Ohio Department of Jobs and Family Services) topics of concern, tax abatements and other economic development incentives for research enterprises or facilities, and mandated insurance benefit laws that encompass clinical trials or other research interventions.[18] States also facilitate research by allowing cadaver or organ donation for research purposes.[19] State laws regarding the privacy of personal health records[20] also may influence the conduct of research. Finally, state agencies themselves routinely conduct epidemiologic or other public health research.

At present, only a few states comprehensively regulate research involving human participants. California,[21] Virginia,[22] New York,[23] and Maryland[24] have omnibus medical research statutes; the New York and Maryland statutes were enacted following extensive state task force consideration of the topic (Hoffmann & Schwartz, 1998; Dresser, 2001a). In general, these state statutes reinforce the informed consent, institutional review board, and confidentiality provisions contained in applicable federal law and extend those provisions to all research involving human participants, regardless of sponsor.

Many states restrict the conduct of research involving particular categories of potential participants. For example, many states (including Ohio) have codified a nursing home residents' Bill of Rights which, among other things, specifies "the [resident's] right to refuse, without jeopardizing access to appropriate medical care, to serve as a medical research subject."[25] Some states expressly provide similar protections to home health and hospice patients.

It is against this backdrop that Ohio and other states must review their proper role regarding the regulation of LTC research projects involving the participation of vulnerable care recipients. States must

[16] *Panhandle Eastern Pipe Line Co.* v. *State Highway Commission*, 294 U.S. 613 (1935).

[17] Ohio Revised Code § 183.24.

[18] Ohio Revised Code §§ 1751.85, 3923.68.

[19] Ohio Revised Code § 2108.10.

[20] Ohio Revised Code § 3721.13(A)(10).

[21] Cal. Health & Safety Code §§ 24173-24176.

[22] Va. Code §§ 32.1-162.16, 32.1-162.18, and 32.1-162.19.

[23] N.Y. Public Health Law §§ 2441-2445.

[24] Md. Code–Health §§ 13-1601 through 1606.

[25] Ohio Rev. Code § 3721.13(A)(12).

consider what additional requirements, if any, ought to be imposed on LTC researchers in order to protect the rights and well-being of potential research participants, while at the same time not causing more harm than good by creating or exacerbating unnecessary barriers that discourage the conduct of valuable research, especially involving multi-site, multi-state collaborative protocols. Individuals who were interviewed for this project repeatedly expressed reluctance to advocate for new state regulation regarding the conduct of LTC research involving human subjects, stressing that any state activity in this arena should be carefully thought out to assure that any incremental benefits, in terms of protecting participant rights and well-being, were clearly likely to exceed the financial and non-financial costs imposed. At the same time, certain legal and ethical ambiguities in the current LTC research regulation environment were consistently identified, and interviewees indicated that states might improve the research climate, and hence facilitate the conduct of more ethically appropriate LTC research, by clarifying those ambiguities. A useful review of any expanded role for state law and policy in this area entails several specific inquiries, which are addressed in the next section.

State Regulation of Human Subjects Research–Specific LTC Issues

Should Research Involving Participants Who Lack Decisional Capacity Be Permitted?

Under its inherent *parens patriae* power to protect persons who are unable to protect themselves against possible harm (Kapp, 1995, pp. 51-52), the state has the legal authority to ban outright the conduct of LTC research activities involving human participants who lack the capacity to consent to their own participation. Thus, the threshold public policy question is whether the state ought to exercise that authority. By permitting research to take place enrolling individuals without decisional capacity, the state is making the value judgment that, in particular research projects, the potential long range benefits to society may outweigh the immediate risks to individual study participants. It is once that judgment has been made, explicitly or implicitly, that policy makers must move to a consideration of what requirements should be imposed on LTC researchers to protect the interests of potential and actual human participants while permitting legitimate research to proceed.

Is There a Need for Comprehensive Regulatory Coverage of All Protocols?

As noted earlier, current federal regulations governing the conduct of biomedical, behavioral, and health services research do not apply to all research studies. Certain privately financed studies conducted outside of academic institutions and medical centers may completely elude the oversight imposed by federal law, even if the protocols involve the participation of human subjects, although it would be very difficult to accurately quantify this shortcoming in the current regulatory system. In states that have enacted comprehensive human participants research legislation, the investigators in all research studies seeking to enroll human volunteers are explicitly mandated to comply with the requirements of state law pertaining to consent, confidentiality, and IRB review, regardless of the researcher's professional affiliation (or lack of affiliation) and funding source.

The Ohio legislature could consider enacting legislation that expressly imposes

consent, confidentiality, and IRB oversight requirements on all research studies involving the potential enrollment of human participants. Such legislation could follow the model adopted by the Maryland legislature in 2002 when it enacted House Bill 917, which requires anyone conducting research with human participants to comply with pertinent federal regulations on participant protection.

As noted earlier, a number of national research ethics experts and Ohio long-term care researchers were interviewed for this project. Among these individuals, there was support for legislation like Maryland House Bill 917 as a worthwhile form of protection for some vulnerable individuals who may presently be at risk of exploitation in the research context.

Need for Special Protections for LTC Recipients?

As indicated above, there are no current federal regulations that provide specific, additional protections for potential research participants who are institutionalized and/or mentally disabled. Arguably, such individuals are especially vulnerable and deserve special protections beyond those afforded by generic federal regulations to all research participants. By contrast, the federal regulatory scheme does provide special protections to children whose enrollment in research projects is sought, by requiring that IRBs considering such protocols affirmatively answer the following questions (among others) about each protocol before approving it:[26]

> For research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects–
> (1) Is the risk justified by the anticipated benefit to the participants?
> (2) Is the relationship of the anticipated benefit to the risk at least as favorable to the participants as that presented by available alternative approaches?
> For research involving greater than minimal risk and no prospect of direct benefit to individual participants–
> (1) Does the risk represent only a minor increase over minimal risk?
> (2) Does the intervention or procedure present experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations?
> (3) Is the intervention or procedure likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition?

State legislatures in Ohio and elsewhere could consider enacting legislation that would require IRBs to consider some version of the same inquiries as a prerequisite to approval of research studies entailing the enrollment of members of any vulnerable population, regardless of age (Fleischman, 2001, p. 16). Such legislation would need to include a workable definition of "vulnerability." The definition could be broad,

[26] 45 Code of Federal Regulations Part 483, Subpart D, § 46.606.

such as "having some limitation on autonomy," with application left to each IRB on a case-by-case basis, or categorical, such as (among others) "all institutionalized persons." Such legislation also would need to define clearly what constitutes "minimal risk" and "a minor increase over minimal risk." These definitions would need to be sensitive to the specific characteristics of LTC settings and the persons served in them.

Is There a Need for Clarification of the Regulatory Requirements for Assessing Potential Participants' Decisional Capacity?

Given the centrality of the informed consent doctrine, a legally and ethically challenging set of issues regarding the assessment of potential human participants' decisional capacity frequently arises in the context of research conducted in the LTC arena.

Given the centrality of the informed consent doctrine, a legally and ethically challenging set of issues regarding the assessment of potential human participants' decisional capacity frequently arises in the context of research conducted in the LTC arena. A prospective human research participant must have the mental capacity–both cognitive and emotional–to engage in the rational decision making process necessary for there to be consent to research participation (Karlawish & Casarett, 2001). Individuals cannot autonomously, authentically volunteer to take part in research if they are not currently able to comprehend material information about respective risks and benefits posed by their participation.

Some mentally compromised individuals lack sufficient decisional capacity to validly volunteer for research participation at the time that initial enrollment is requested, while some who are capable of giving autonomous consent to participate at the inception of the protocol may subsequently become unable to give valid consent to continue that participation. Importantly, though, neither old age nor physical or mental disability *per se* necessarily equals decisional incapacity (Kim, Karlawish, & Caine, 2002). Decisional capacity must be assessed on a decision-specific rather than a global basis (American Geriatrics Society, 1998), with a focus on function rather than clinical diagnosis. Many persons with diagnoses of dementia (Rabins, 1998) and other mental illnesses are nonetheless sufficiently able to consent for themselves to research participation if their disability is not too severe at the time, especially if participation would involve only a low degree of risk to the participant. According to the American Psychiatric Association (1998, p. 1650):

> The identification of some degree of decision-making impairment in potential subjects need not result in their automatic exclusion from research participation. Many cognitively impaired subjects can give adequate consents when additional efforts are made to educate them about the nature and consequences of study participation.

NBAC (1998) recommended, consistent with prevailing law, that capable individuals' own consent be accepted as sufficient for enrollment even in studies entailing greater than minimal risk with no prospect of direct benefit to the participant.

We, therefore, must be able to ascertain with some precision whether an individual ought to have his or her own autonomous choice about participation in research honored or, conversely, whether the researchers, LTC providers, and IRB should rely on a surrogate decision maker or an advance directive for research participation (both discussed below) for the particular potential participant.

Explicit substantive standards and procedural requirements concerning the assessment of an individual's capacity to volunteer to participate in a research project, in Ohio and most other states, are not specified in statute or regulation. The resulting legal uncertainty can inhibit and complicate the conduct of valuable LTC research involving participants with questionable decisional capacity; this can have the positive effect of making the researchers and collaborating service settings more (appropriately) cautious about protecting potential participants' rights and well-being (Karlawish & Sachs, 1997, p. 477), but it also can delay or preclude the production of valuable research findings. At the same time, ambiguity about the regulation of capacity assessment standards and procedures might embolden some researchers and collaborators to expose vulnerable LTC clients to inappropriate risks and affronts to dignity.

The American Psychiatric Association (1998) has issued guidelines regarding both standards and procedures for assessing decisional capacity, and numerous commentators (Grisso & Appelbaum, 1998; DeRenzo, Conley, & Love, 1998) have endorsed development of standardized written instruments for assessing capacity to decide about research participation. NBAC did not advocate regulatory imposition of any particular substantive standards or procedural requirements for the assessment of decisional capacity, but it did recommend (NBAC, 1998) that IRBs require that, at least for protocols involving greater than minimal risk, the investigator explicitly describe to the IRB the process the investigator intends to use to assess the decisional capacity of potential human participants. This recommendation that IRBs command researchers to explain how capacity will be evaluated, both at the start of a protocol and continuously throughout the duration of the protocol, is echoed by leading bioethics and legal commentators (Moreno, Caplan, Wolpe, & the Members of the Project on Informed Consent, 1998; Bonnie, 1997).

Many of the LTC researchers interviewed for this project indicated that they already supply details regarding the assessment of potential participants with questionable decisional capacity in the protocols they submit to IRBs. Some researchers indicated that they provide this information on their own initiative, while others reported that they are required to do so by funding sources or internal scientific review committees. Some commentators have noted their concern about an absence of IRB oversight regarding identification of who should be assessing the present (let alone future) decisional capacity of prospective subjects and the standards and methods used to carry out the capacity assessment (Derrickson, 1997). Nonetheless, some interviewees indicated that their respective IRBs require investigators to provide at least proposed methods of capacity assessment in their protocols when there is a possibility that human participants may be compromised in the ability to consent to enrollment on their own. When IRBs impose such a requirement, it generally is limited to protocols entailing greater than minimal risk (what several interviewees described operationally as

protocols entailing an intervention more intrusive than a finger prick). One survey (Leblang & Kirchner, 1996) documented that a number (although a minority) of IRBs already routinely impose that sort of requirement on investigators.

The majority of LTC researchers interviewed for this project stated that, even when IRBs require information in the research protocol about capacity assessment, ordinarily a very subjective, non-structured, virtually "seat-of-the-pants" process conducted by the investigator is what occurs. As one researcher in the field of informal caregiving explained, "[When it comes to assessing the decisional capacity of potential participants,] You don't really know until you get there." In one study of nursing home residents' perceptions of their quality of life, "[t]he major criterion for inclusion is the ability of residents to communicate that they know their name." (Uman et al., 2000).

Many researchers indicated that, all or much of the time, they defer to families or the formal LTC providers to make an initial determination regarding which potential participants are capable of making their own decisions about research participation. Interviewees indicated that families and providers generally are willing to perform that function, since they know the individual best; on some occasions, though, researchers indicate being told, "Don't ask me, ask the patient."

Interviewees indicated that some research sites, especially some nursing homes, require investigators to always approach the family first before even conducting an assessment of the potential research participant's capacity to consent personally; this provider policy was described pejoratively as "infantilizing" to the older person. The LTC provider's role in screening potential research participants for decisional capacity sometimes is specified in the research protocol, while in other situations occurs on a less formal, *ad hoc* basis. At least one major academic medical center IRB presently requires proxy consent, as well as the participant's assent, for every research study in which nursing home residents will be involved, on the overbroad, paternalistic equation of nursing home residence and decisional incapacity. Besides the negative implications for older persons' rights to make personal decisions, allowing LTC providers a too expansive role in screening out potential participants creates the danger of introducing biased sample selection into studies.

One sub-issue addressed by NBAC (1998; Capron, 1999) was whether investigators with research protocols involving the enrollment of persons with questionable decisional capacity should be required to arrange for assessments of potential participants by evaluators who are not professionally or financially interested in the conduct or outcomes of the study. NBAC advocated the promulgation of a regulation mandating that, for any human participants research study involving greater than minimal risk, there be an independent assessment of each potential participant's decisional capacity. This is consistent with the position of the National Alliance for the Mentally Ill (NAMI) (Flynn & Honberg, 1998, p. 185-186):

> In view of potential conflicts of interest, it is not advisable for those directly involved in research to assume the responsibility of making capacity determinations. Rather, we believe that someone

> not directly involved in the research should make capacity determinations. This, we believe, will better ensure that such determinations are made objectively by outside experts who do not have direct interests in the course or outcomes of the research protocols.

The British Medical Research Council Working Party on Research on the Mentally Incapacitated (1991) recommended that the determination of decisional capacity be made by the potential participant's physician if the physician is not involved in the research protocol; otherwise, it should be made by an independent party acceptable to the IRB or its equivalent. Neither NBAC, NAMI, nor the British Medical Research Council Working Party have gone so far as one New York Court of Appeals decision[27] that compelled a formal judicial assessment of incompetence for every potential research participant receiving services in a facility operated or licensed by the state Office of Mental Health. Under that ruling, persons adjudicated incompetent were banned from volunteering, personally or through any proxy, to participate in any research project. The negative reaction to the inhibitory effect of that decision was so severe that it led the New York State Department of Health to establish an Advisory Work Group on Human Subject Research Involving the Protected Classes, and to accept that body's proposal that, with adequate safeguards, research be allowed involving more than minimal risk on decisionally incapacitated participants even in the absence of likely benefit to the participants themselves.

A few researchers interviewed for this project who work at major academic medical centers indicated that, at least for any randomized clinical trial (RCT) (which virtually always would involve a greater than minimal risk of harm to participants), their institutions require independent assessment of potential participants' decisional capacity. In some institutions, this is done by investigators at the institution who are not personally involved or interested in the particular protocol, i.e., different investigators trade off this responsibility with each other. In defense of the feasibility of conducting independent capacity assessments, some interviewees asserted that non-physicians could be trained to administer and interpret assessment instruments containing standardized questions aimed at the individual's understanding, appreciation, and reasoning abilities.

By contrast, most interviewees for this project expressed serious reservations about mandating that independent capacity evaluations be conducted for potential research subjects on a routine basis (as opposed to the IRB having this requirement in its arsenal to be imposed very selectively in particular situations involving particularly vulnerable subjects and significant risks as compared with likely benefits). Three types of problems with a routine requirement of independent capacity assessment for all potential research participants were noted: the practical impossibility of eliminating conflicts of interest on the part of assessors, the amount of resources that an independent evaluation requirement would require for implementation, and the questionable validity and reliability of capacity assessments conducted by independent, isolated strangers.

First, no assessor of potential research participants' decisional capacity can truly be

[27] *T.D.* v. *New York State Office of Mental Health*, 650 N.Y.S.2d 173 (N.Y. App. Div. 1996).

"independent." It was observed that the presence of conflict of interest can never really be eliminated, since the purportedly independent evaluator would be paid directly by the sponsor of the research or the institution conducting the research, either of whom has an interest in the conduct and outcomes of the study. The only solution would be a totally volunteer system, and it is highly unlikely that enough qualified professionals would be willing to conduct capacity evaluations of this type on a continuing *pro bono* basis.

Second, there is a consensus that requiring independent capacity assessment on a routine basis would impose unreasonable costs on the conduct of research. Those intolerable costs would place an unnecessary and unjustified barrier on the research enterprise that is dedicated to producing results that, ultimately, are expected to benefit future persons who suffer or are at risk of suffering from the same ailments as the research participants. Further, there is doubt that an adequate cadre of professionals with the requisite expertise to routinely conduct credible independent capacity assessments in the research context would be available to be hired at any price, especially outside of the largest academic medical centers.

Third, interviewees noted that the better an assessor knows the individual whose capacity needs to be evaluated, the more accurate the evaluation is likely to be. Hence, there is a danger that strangers with no prior connection to the individual, brought in only for the purpose of conducting "snapshot" independent evaluations at one point in time, may be less accurate and reliable assessors than investigators or clinicians who have had a chance to get to know the individual whose capacity is being evaluated. Independent evaluators, interviewees also argued, might be more prone than investigators to conduct global rather than decision-specific capacity assessments, and therefore might be too ready to disqualify some persons who actually possess the capacity to enroll in certain low risk protocols. These dangers are especially worrisome in situations of longitudinal (as opposed to cross-sectional) projects, during which a participant's decision-specific capacity may change. Investigators arguably would be best situated to continuously reevaluate a participant's decisional capacity over time.

A legislative option that could be considered in Ohio and other states is the enactment of a statutory mandate that IRBs in the state require investigators to specify in the template of their research protocols, at least for protocols potentially exposing questionably capable participants to greater than minimal risk: (1) that a structured capacity assessment of each potential participant will be performed and (2) in detail, the standards and procedures the investigator proposes to utilize in assessing the initial and ongoing decisional capacity of potential participants. This part of the protocol template could be structured either by statutorily requiring IRBs to ask investigators certain specified questions about capacity assessment in their application forms, or by requiring IRBs to develop their own list of questions to include on their application forms. Either of those approaches would more likely instill some uniformity in IRB and investigator practice than would asking in an open ended fashion for the investigator's description of the proposed capacity assessment process.

Undergoing a formal capacity assessment may be perceived as burdensome (indeed, sometimes more burdensome than the

research study itself) by the potential participant, especially a person with dementia. Therefore, regulatory intervention must seek to minimize the degree of potential burden imposed in the course of trying to promote the individual's interest in autonomy.

Furthermore, a related legislative option could be a requirement that capacity assessments for research participation purposes be conducted, at least for protocols exposing participants to greater than minimal risk of harm, by independent evaluators. Any such requirement should include provisions minimizing as much as feasible the financial or academic interest of the independent evaluator in the outcome of an evaluation. Such provisions could include, for instance, prohibiting the amount of the evaluator's compensation from being tied to the number of participants enrolled in the study or even to whether or not the study was eventually carried out.

Clarification of Proxy Decision Making for Research Purposes?

As stated by one leading legal commentator:

> Once subjects with possible impairments have been identified, the IRB should take special precautions to ensure that valid consent (or assent) is obtained (and that it remains valid during the course of the study). The IRBs should not be required to use any single procedure. Instead, the regulations should provide a menu of safeguards, and the IRB should be directed to select the procedures that provide the best fit for the particular study, taking into account the nature and prevalence of anticipated decision-making impairments and the degree of risk presented by the study (Bonnie, 1997, p. 110).

There is a need for clarification of state law regarding the issues of: (1) who may act as a decision making proxy for purposes of enrolling a person in a research study; (2) the extent and limits of a proxy decision maker's authority in the research context; (3) the standards that a proxy must use in making decisions about research participation on behalf of a decisionally incapacitated person *(Alzheimer's Association, 1997)****; and (4) the liability implications when a decisionally incapacitated person who has been enrolled in a research project by a proxy is injured as a result of participation in that study.***

Part of the menu of protections that should be enforced by IRBs for research involving participants with significant cognitive and/or emotional impairment must involve reliance on proxies. Proxies may make decisions about participation either for the decisionally incapacitated individual or with the assent of the impaired, but arguably still minimally capable, individual. However, in particular research situations the status and role of the purported proxy may be quite unclear (American Academy of Neurology Ethics and Humanities Subcommittee, 1998, p. 594). There is a need for clarification of state law regarding the issues of: (1) who may act as a decision making proxy for purposes of enrolling a person in a research study; (2) the extent and limits of a proxy decision maker's

authority in the research context; (3) the standards that a proxy must use in making decisions about research participation on behalf of a decisionally incapacitated person (Alzheimer's Association, 1997); and (4) the liability implications when a decisionally incapacitated person who has been enrolled in a research project by a proxy is injured as a result of participation in that study.

Who May Be a Proxy for Research Purposes*?*

Many of the LTC researchers interviewed for this project reported that they often ask a potential research participant's formal or informal LTC provider whether non-research related (e.g., general health care, financial) decisions for that particular individual usually are made by that individual personally or by a proxy acting on the individual's behalf. When the provider's reply is that non-research related decisions are made by a specific proxy, the researchers indicated that they tend to turn to that same proxy for decisions about the individual's participation in research studies, and that this way of proceeding ordinarily has been satisfactory to IRBs that inquire about the role of proxies in a research project. In some situations, investigators review the chart maintained by the LTC provider of a decisionally questionable potential research participant, and then turn for consent to the one indicated in the chart as the "contact person" (Baskin, Morris, Ahronheim, Meier, & Morrison, 1998). (This practice raises confidentiality concerns, especially in light of HIPAA, discussed earlier.) Interviewees reported that, in practice, they generally paid little attention to questions about a proxy's legal authority, if any, to make research enrollment decisions on behalf of the incapacitated person. With a few exceptions, it appears that researchers and IRBs (LeBlang & Kirchner, 1996) do not usually restrict their reliance on proxy decision makers to those who have been appointed to the proxy role through a durable power of attorney document or a guardianship order. This widespread lack of concern about explicit legal authority in this context appears to rest, in large part, on a supposition that most families and LTC providers (especially mission-driven organizations in the not-for-profit sector) can be trusted to be acting in the best interests of incapacitated LTC recipients.

Extent and Limits of Proxy's Authority?

The common practice regarding researchers' reliance on proxy decision makers for decisionally incapacitated research participants often may be inconsistent with the demands of legal theory. According to the strict letter of the law, a proxy would have authority to enroll a decisionally incapacitated individual in a research project only if the proxy had been given such authority explicitly in: (a) a durable power of attorney (DPOA) document executed by the decisionally incapacitated person earlier while still retaining decisional capacity; (b) a guardianship order issued by a court; or (c) a state statute specifically conferring this authority. Since Ohio does not have a state statute specifically conferring such authority on a proxy, in this state a proxy would have official legal authority to act in the research context only through a DPOA or a guardianship order.

In practice, though, few older LTC service recipients who currently lack sufficient decisional capacity to enroll themselves in a research project have a proxy who possesses explicit legal authority to consent to participation on their behalf. DPOAs and judicially created guardianships are rare. Even when an individual, while still decisionally

capable, has executed a DPOA authorizing a named agent to make health care decisions, the DPOA statute in most states (including Ohio)[28] is silent on the specific question of the agent's authority to make decisions about participation in research. The Ohio guardianship statute, like its counterpart in the majority of other states, is silent on the power of a guardian to enroll an incompetent adult ward in research.[29]

Some interviewees advocated a requirement that proxies have formal legal authorization to enroll another person in a research project, at least when the participant would be exposed to an unfavorable risk/direct benefit ratio. Under this approach, decisionally incapacitated persons who had not previously executed a DPOA explicitly giving their agent permission to enroll them in certain research studies and who had not been adjudicated incompetent by a court that expressly authorized a guardian to enroll the ward in research protocols would effectively be disenfranchised from participating in research. A small number of LTC research sites insist on this "no designated agent or guardian, no enrollment" approach as a condition of participating with the investigator. Such insistence, resulting in the exclusion of such residents from research participation, ordinarily is based on perceived risk management considerations affecting the LTC providers.

By contrast, the vast majority of LTC researchers and research ethics experts interviewed for this project objected strenuously to any wholesale exclusion of otherwise eligible participants on the grounds that they fail to have a DPOA or guardianship order that speaks explicitly to the proxy's power to make decisions in the research context. Few individuals would satisfy that qualification. Realistically, this situation is not going to change, since a huge upsurge in the execution of timely, formal advance directives for research participation is unlikely despite the expressed willingness of many individuals to participate in future research if they lose the ability to consent (Wendler, Martinez, Fairclough, Sunderland, & Emanuel, 2002). It was contended by interviewees that such insistence on legal formalism would both deny many LTC service users the opportunity to derive the benefits that might be available to participants in particular research projects and that it would badly skew or bias the representativeness of study sample populations and therefore the validity of study results. Instead of insistence on legal formalism, the weight of informed opinion urges, unless another family member or friend expresses dissent, continued reliance on study enrollment through proxies who lack explicit legal authority but who do not appear to have their judgment clouded by any serious conflicts of interest pertaining to the enrollment decision (American College of Physicians, 1989; American Geriatrics Society Ethics Committee, 1998; Flynn & Honberg, 1998; Rabins, 1998). Researchers and ethics experts afford the greatest presumption of moral authority to informal proxies who have a history of making decisions for the decisionally incapacitated person, who appear to really know the incapacitated individual, and who are likely to be good reporters to the investigator about any adverse reactions of the participant to the research interventions. Family members or others acting as caregivers for decisionally incapacitated persons are

[28]Ohio Rev. Code § 1337.13.

[29]Ohio Rev. Code chap. 2111.

afforded particular deference (Karlawish & Casarett, 2001).

Moreover, most researchers –voluntarily or under individual IRB mandate –place a practical limitation on proxies' authority to enroll decisionally incapacitated persons in studies by requiring participants' assent (affirmative or at least signified by not objecting) to participation, in addition to the proxy's consent. This practice of giving even decisionally incapacitated persons the equivalent of a veto power is consistent with the prevailing ethical consensus. Recommendation 7 in the NBAC report (National Bioethics Advisory Commission, 1998) states, "Any potential or actual subject's objection to enrollment or to continued participation in a research protocol must be heeded in all circumstances." According to the American Geriatrics Society Ethics Committee (1998, p. 1309), "In general, the refusal of a (potential) subject, even if that subject has lost decision-making capacity, should be followed." The state legislature could consider making a potential participant's active or passive assent a requirement for the initial and continuous involvement of that person in a LTC research project.

If we are going to continue to rely on proxies, either *de jure* (i.e., with formal legal authority) or *de facto*, to make decisions about research study participation generally on behalf of decisionally incapacitated persons, are there any explicit legal limits that ought to be set on the proxy's *de jure* or *de facto* authority? For example, both the NBAC report (National Bioethics Advisory Commission, 1998) and the latest version of the Declaration of Helsinki (World Medical Association, 2000) suggest that proxies be permitted to enroll decisionally incapacitated persons only in studies that focus on a condition from which the enrollee suffers, thus discouraging the enrollment of incapacitated participants mainly as a matter of convenience to the investigator. Neither of these documents, however, advocate for restricting enrollment solely to studies involving the possibility of direct benefit to the decisionally incapacitated person. A restriction of that sort could impose major impediments to the conduct of case/control studies, in which the control (non-intervention) participants exist solely as a comparison group, and hence by definition and design are not going to directly benefit from their participation in that particular study (except perhaps through a placebo effect).

Standards for Proxy Decision Making About Research?

A person who, with or without the formal legal authority to do so, is asked for permission to enroll a decisionally incapacitated person in a research study should be given guidance about the standard to be used in carrying out the proxy decision making function. The competing standards available are substituted judgment and best interests (Dresser, 2001a, p. 677, 687-688). The substituted judgment standard emphasizes individual autonomy, by expecting the proxy to try to stand in the shoes ("don the mental mantle") of the decisionally incapacitated person and make decisions consistent with that person's previously expressed or implied values and preferences–to ask, in essence, If the person were currently able to decide, would that person choose to participate in this research study? Under this approach, the proxy really speaks, rather than decides, for the incapacitated person. By contrast, the best interests standard is predicated on the ethical principle of beneficence, or doing good for

others. Under this test, the proxy gets to decide what he or she thinks is the best choice for the incapacitated person, based on the proxy's own weighing of probable benefits and burdens to the incapacitated person.

In Ohio, as generally elsewhere, the statutory, regulatory, and common law are silent on the question of the standard to be applied to proxy decision making in the research context. While Ohio's DPOA for health care statute[30] requires appointed agents to act consistent with the substituted judgment standard when possible and Ohio's guardianship statute embodies the traditional best interests standard, neither of these statutes speak specifically to proxy decisions about entering or continuing a decisionally incapacitated person in a research study.

In practice, proxies often rely on a combination of the substituted judgment and best interests standards when making decisions in the research context, depending mainly on the extent to which credible information is available concerning the pertinent values and wishes of the decisionally incapacitated person (LeBlang & Kirchner, 1996, p. 533). Nevertheless, state law could usefully clarify the order of preference among these two approaches that proxy decision makers are expected to follow in the research context.

Liability Implications of Proxy Decision Making About Research?

If an incapacitated individual is injured in the course of participating in a LTC research protocol and the injury resulted from negligent acts or omissions on the part of the investigator or study site, the ordinary rules of tort and/or contract law would apply to resolve a civil claim for monetary damages brought on behalf of the injured research participant. However, the legal status of a civil action brought on behalf of an injured, decisionally incapacitated research participant based on the claim that the proxy lacked valid authority to consent to participation for the incapacitated person is unclear. Any state legislation or regulation dealing with the other aspects of proxy decision making in the LTC research context discussed above also should clarify the liability implications of proxy consent. Specifically, policy makers need to grapple with such questions as:

- May a civil action in tort and/or contract be brought on a decisionally incapacitated person's behalf, following a research participation related injury, alleging lack of valid consent to research participation even though a proxy gave voluntary and informed permission to enroll the incapacitated person?

- If so, against which party(ies) may such a lawsuit be brought?

- What defenses, if any, could a defendant assert against such a lawsuit?

If LTC investigators and study sites do not feel confident in the legal validity of proxy consent to research participation (i.e., they fear being held liable for violating participants' informed consent rights despite the permission of proxies to enroll the decisionally incapacitated persons, such as

[30]Ohio Rev. Code § 1337.13.

recently happened in Maryland),[31] they will not conduct research involving incapacitated participants. The negative consequences of categorically excluding incapacitated persons from participating in LTC research have been discussed above.

Summary of Policy Issues Regarding Proxy Decision Making

The NBAC report (1998) admonished the states to clarify their laws on proxy decision making for research purposes. The Ohio legislature should consider legislatively clarifying who is legally authorized to act as a proxy for a decisionally incapacitated person in the research context, and under what conditions. More specifically, the legislature should consider enacting or amending statutes that explicitly clarify the following issues:

- whether DPOAs or other forms of advance directives may be used to delegate power to an agent to make decisions about a decisionally incapacitated person's research participation (Dresser, 2001a, pp. 673-674; Dresser, 2001b);

- whether a generic DPOA for health care would suffice for that purpose or a separate and more specific advance directive would be necessary (Dresser, 2000; Moreno, Caplan, Wolpe & the Members of the Project on Informed Consent, 1998);

- whether a general guardianship of the person order encompasses the guardian's authority to enroll the ward in research studies or a separate and more specific judicial order is necessary;

- who (if anyone), in hierarchical order, has authority to enroll a decisionally incapacitated individual in a research study in the absence of a relevant advance directive or guardianship order (considering the enactment of a law analogous to Ohio's default proxy decision maker statute applicable to the sphere of decisions about life-sustaining medical treatments for critically ill persons);[32]

- any limits on the authority of a DPOA agent, guardian, or default proxy regarding the type of research study in which the decisionally incapacitated person may be enrolled through proxy consent; and the standard(s) that a proxy must use for the decision making process in the research context.

- Whether a civil lawsuit for monetary damages may be brought on behalf of a decisionally incapacitated research participant who was injured as a result of research participation, on the grounds that proxy consent to research participation was invalid.

Additionally or alternatively, state law could compel IRBs to require investigators to specify in their protocols how they intend to handle the details of proxy decision making, without imposing on the investigator any particular process and criteria for selecting the proxy and recognizing or limiting the proxy's decision making authority. Such a requirement would allow investigators and IRBs a

[31] Grimes v. Kennedy Krieger Institute, 366 Md. 29, 782 A.2d 807 (2001), reconsideration denied (October 11, 2002).

[32] Ohio Rev. Code § 2133.08.

substantial degree of flexibility, while forcing them to devote considerable *a priori* thought to the pertinent issues.

Non-Governmental Strategies

The focus of this report has been on the current and potential role of governmental action, primarily at the state level, regarding oversight of the conduct of biomedical, behavioral, and health services research in LTC settings. As has been explained, the state has a legitimate interest in protecting the autonomy, dignity, and well-being of vulnerable individuals who may be asked to serve as participants in LTC research; various possible state initiatives for pursuing this interest have been outlined.

However, the long-term care researchers and legal and ethical experts interviewed for this project generally strongly urged caution and restraint in implementing new state laws and policies that might prove to be unnecessary, unhelpful, and so burdensome on honest, competent researchers that they have the effect of counterproductively deterring the conduct of potentially valuable LTC research. The interviewees are correct in their assertion that credible evidence of serious abuses in the LTC research arena has not yet surfaced. Recent well-publicized research ethics problems at major academic medical centers around the country have involved the alleged mistreatment of young, relatively healthy participants in acute care or ambulatory settings, rather than older, decisionally incapacitated persons in LTC settings. The interviewees also consistently and persuasively argued that any research regulations, and the IRBs, research sites, and administrative agencies who are responsible for applying those regulations in practice, need to distinguish among protocols based on risk/benefit ratio considerations. Most of the interviewees making this point come from the world of behavioral and social science research (e.g., chart reviews, observational studies), where the risks to study participants are likely to be much less substantial than those commonly encountered with biomedical research interventions (Glass & Speyer-Ofenberg, 1996).

Instead of, or as a supplement to, aggressive state regulatory actions, a variety of non-governmental initiatives might be supported to further society's responsibility to protect vulnerable persons without creating the risk of depriving those same vulnerable persons of the possible benefits of knowledge derived through research efforts. Such non-governmental initiatives might include:

1. The development and dissemination of consensus guidelines on the ethical conduct of LTC research using human participants by panels convened by private organizations, similar to the way in which private groups convene consensus development panels to establish standards or guidelines for the diagnosis and treatment of various medical problems.

2. The adoption and enforcement of privately established ethical research practice guidelines by foundations and private industry representatives that fund LTC research, with expectations and understandings spelled out clearly in funding applications agreements and financial support withheld or withdrawn from investigators when unacceptable deviations from established private guidelines occur.

3. Professional journals requiring that important issues pertaining to the ethical conduct of the research reported be discussed

either directly in the methodology section of the submitted article or in a separate form that is submitted along with the article, akin to forms currently widely employed for copyright transfer and declaration of conflicts of interest (Yank & Rennie, 2002).

4. Better education of investigators, IRB members, and LTC providers (including governance, administration, and direct care staff of institutions and agencies) about both research ethics and the special characteristics and needs of the various populations receiving LTC services. As part of satisfying federally mandated human subjects protection training, researchers can learn about the issues of decisional capacity and proxy decision making. Special attention should be paid to developing guidance for LTC providers regarding a fair process of reviewing investigators' requests to allow them to conduct research enrolling a provider's patients/clients, to encourage provider responses somewhat more thoughtful than either an automatic "go away" or an automatic "do anything you want." Pertinent information also should be made available to interested family members of LTC clients, to empower families to participate and advocate more effectively regarding decisions about enrollment of their loved ones in research projects and in the ongoing monitoring of those projects. Although primary responsibility for planning and conducting educational activities would best be left to academic institutions and professional organizations and agencies, the state could make a valuable contribution by financially supporting these educational activities.

5. Training of investigators regarding the proper conduct of assessments of decisional capacity of LTC service recipients for research participation purposes.

Conclusion

In the final analysis, both the considerable power and the definite limits of state law and policy in this arena must be acknowledged.

In the final analysis, both the considerable power and the definite limits of state law and policy in this arena must be acknowledged. The law at any level can only guide, facilitate, and reinforce–but never totally substitute for–the ethical sensitivity and integrity of research investigators (Yarborough & Sharp, 2002) and LTC service providers. A malevolent researcher can always find a way to evade regulatory mandates. "One danger of excessive regulations is that they can actually undermine researchers' sense of moral responsibility as their attention shifts from their obligation to research subjects to their compliance with the regulations" (Michels, 1999, p. 1429). In this area as in many others, the state may serve the public best if it skillfully combines its traditional roles of regulator and enforcer with those of moral educator and partner.

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Appendix 1

Questions for State Policy Makers

1. Should the state permit the conduct of LTC research involving participants who lack decisional capacity?

2. Should the state impose regulatory requirements on all LTC research involving human participants, regardless of funding source or investigators' affiliations?

3. Should the state impose requirements to protect participants in LTC research projects that exceed the protections required in other research contexts?

4. What requirements, if any, should the state impose on investigators regarding the assessment of decisional capacity for potential participants in LTC research projects?

5. When investigators seek to enroll decisionally incapacitated persons as participants in LTC research projects, what requirements should the state impose regarding who may act as a proxy decision maker for research purposes, the permissible extent and limits of the proxy's authority in this context, and standards for proxy decision making about a decisionally incapacitated LTC recipient's research participation?

Appendix 2

Common Rule

CODE OF FEDERAL REGULATIONS
TITLE 45
PUBLIC WELFARE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
OFFICE FOR PROTECTION FROM RESEARCH RISKS
PART 46
PROTECTION OF HUMAN SUBJECTS

* * *

Revised November 13, 2001
Effective December 13, 2001

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Subpart A --Federal Policy for the Protection of Human Subjects (Basic DHHS Policy for Protection of Human Research Subjects)Sec.

46.101 To what does this policy apply?
46.102 Definitions.
46.103 Assuring compliance with this policy--research conducted or supported by any Federal Department or Agency.
46.104-
46.106 [Reserved]
46.107 IRB membership.
46.108 IRB functions and operations.
46.109 IRB review of research.
46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
46.111 Criteria for IRB approval of research.
46.112 Review by institution.

46.113 Suspension or termination of IRB approval of research.
46.114 Cooperative research.
46.115 IRB records.
46.116 General requirements for informed consent.
46.117 Documentation of informed consent.
46.118 Applications and proposals lacking definite plans for involvement of human subjects.
46.119 Research undertaken without the intention of involving human subjects.
46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
46.121 [Reserved]
46.122 Use of Federal funds.
46.123 Early termination of research support: Evaluation of applications and proposals.
46.124 Conditions

Authority: 5 U.S.C. 301; Sec. 474(a), 88 Stat. 352 (42 U.S.C. 2891-3(a)).

Note: As revised, Subpart A of the DHHS regulations incorporates the Common Rule (Federal Policy) for the Protection of Human Subjects (56 FR 28003).

The Common Rule (Federal Policy) is also codified at

7 CFR Part 1c Department of Agriculture
10 CFR Part 745 Department of Energy
14 CFR Part 1230 National Aeronautics and Space Administration
15 CFR Part 27 Department of Commerce
16 CFR Part 1028 Consumer Product Safety Commission
22 CFR Part 225 International Development Cooperation Agency, Agency for International Development
24 CFR Part 60 Department of Housing and Urban Development
28 CFR Part 46 Department of Justice
32 CFR Part 219 Department of Defense
34 CFR Part 97 Department of Education
38 CFR Part 16 Department of Veterans Affairs
40 CFR Part 26 Environmental Protection Agency
45 CFR Part 690 National Science Foundation
49 CFR Part 11 Department of Transportation

TITLE 45
CODE OF FEDERAL REGULATIONS
PART 46
PROTECTION OF HUMAN SUBJECTS

* * *

Revised June 18, 1991
Effective August 19, 1991

* * *

Subpart A Federal Policy for the Protection of Human Subjects (Basic DHHS Policy for Protection of Human Research Subjects)

Source: 56 FR 28003, June 18, 1991.

§46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal Department or Agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by Federal civilian employees or military personnel, except that each Department or Agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States.

(1) Research that is conducted or supported by a Federal Department or Agency, whether or not it is regulated as defined in §46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a Federal Department or Agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an Institutional Review Board (IRB) thatoperates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by Department or Agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:1

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

(ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) the human subjects are elected or appointed public officials or candidates for public office; or

(ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs;

(ii) procedures for obtaining benefits or services under those programs;

(iii) possible changes in or alternatives to those programs or procedures; or

(iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food isconsumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or Agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or Agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the Department or Agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent Federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any State or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a Department or Agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the Department or Agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in Department or Agency procedures.

(i) Unless otherwise required by law, Department or Agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes or research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the Department or Agencyhead shall forward advance notices of these actions to the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services (DHHS), and shall also publish them in the Federal Register or in such other manner as provided in Department or Agency procedures.1

1 Institutions with DHHS-approved assurances on file will abide by provisions of Title 45 CFR Part 46 Subparts A-D. Some of the other departments and agencies have incorporated all provisions of Title 45 CFR Part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, Subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, Subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

§46.102 Definitions.

(a) Department or Agency head means the head of any Federal Department or Agency and any other officer or employee of any Department or Agency to whom authority has been delegated.

(b) Institution means any public or private entity or Agency (including Federal, State, and other agencies).

(c) Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) Research subject to regulation, and similar terms are intended to encompass those research activities for which a Federal Department or Agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a Federal Department or Agency solely as part of the Department's or Agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) data through intervention or interaction with the individual, or

(2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) IRB means an Institutional Review Board established in accord with and for the purposes expressed in this policy.

(h) IRB approval means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

(i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) Certification means the official notification by the institution to the supporting Department or Agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

§46.103 Assuring compliance with this policy -- research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a Federal Department or Agency shall providewritten assurance satisfactory to the Department or Agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual Department or Agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, National Institutes Health, DHHS, and approved for Federalwide use by that office. When the existence of an DHHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to Department and Agency heads shall also be made to the Office for Protection from Research Risks, National Institutes of Health, DHHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the Department or Agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. 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 for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to Department- or Agency-supported or regulated research and need not be applicable to any research exempted or waived under §46.101 (b) or (I).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the Department or Agency head, unless in accord with §46.103(a) of this policy, the existence of a DHHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, National Institutes of Health, DHHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the Department or Agency head prescribes.

(d) The Department or Agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the Department or Agency and such experts or consultants engaged for this purpose as the Department or Agency head determines to be appropriate. The Department or Agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the Department or Agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The Department or Agency

head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a Federal Department or Agency and not otherwise exempted or waived under §46.101 (b) or

(i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 of this policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the Department or Agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the Department or Agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

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§§46.104--46.106 [Reserved]
§46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB

§46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in §46.103(b)(4) and to the extent required by §46.103(b)(5).

(b) Except when an expedited review procedure is used (see §46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting §46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

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§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the Federal Register. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, DHHS, Bethesda, Maryland 20892.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Department or Agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§46.111 Criteria for IRB approval of research.

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

(1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disable persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When 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 economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination or approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Department or Agency head.

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§46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the Department or Agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in §46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in §46.103(b)(4) and §46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by §46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research.

All records shall be accessible for inspection and copying by authorized representatives of the Department or Agency at reasonable times and in a reasonable manner.

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§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any
of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or

(d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) a description of any reasonably foreseeable risks or discomforts to the subject;

(3) a description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) any additional costs to the subject that may result from participation in the research;

(4) the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) the approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) the research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) the research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) the research involves no more than minimal risk to the subjects;

(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) the research could not practicably be carried out without the waiver or alteration; and

(4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law.

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§46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

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§46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under §46.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the Department or Agency.

§46.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the Department or Agency, and final approval given to the proposed change by the Department or Agency.

§46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The Department or Agency head will evaluate all applications and proposals involving human subjects submitted to the Department or Agency through such officers and employees of the Department or Agency and such experts and consultants as the Department or Agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the Department or Agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 [Reserved]

§46.122 Use of Federal funds.

Federal funds administered by a Department or Agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The Department or Agency head may require that Department or Agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the Department or Agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the Department or Agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the Department or Agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to Federal regulation).

§46.124 Conditions.

With respect to any research project or any class of research projects the Department or Agency head may impose additional conditions prior to or at the time of approval when in the judgment of the Department or Agency head additional conditions are necessary for the protection of human subjects.