A Draft Report of the National Bioethics Advisory Commission:

Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity

November 12, 1998

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Chapter One: AN OVERSIGHT OF ISSUES ARISING IN THIS REPORT

The Purpose of This Report

A wide variety of important research studies using human subjects[1] have long played an essential and irreplaceable role in advancing biomedical and behavioral science, thus enhancing our ability to treat illness and better understand human behavior. In recent decades, however, researchers and commentators alike have become increasingly sensitive to the ethical issues associated with such research studies, especially as they concern the welfare of the subjects. As a result, government regulations[2], enhanced professional guidelines, and various institution-based mechanisms have been established in countries around the world to help ensure that such studies meet appropriate ethical standards for the protection of human subjects. The two most fundamental measures developed to meet this goal are an independent review of protocols by an institutional review board (IRB) to ensure their scientific validity and importance as well as their ethical acceptability, and the informed consent of human subjects.

[1]In this report, the National Bioethics Advisory Commission (NBAC) refers to persons on whom research interventions are performed (including participants who serve as members of a "control group" in clinical studies) as "human subjects," consistent with the language in current federal regulations. *See* 45 C.F.R. 46.102(f) (1998) (defining human subject as "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"). Since the report also concerns itself with individuals who might be or may become *prospective* research subjects, we will generally refer to "persons" when discussing these individuals.

[2] In the United States, federal regulations protecting human subjects first became effective on May 30, 1974. Promulgated by the Department of Health, Education and Welfare (DHEW), those regulations raised to regulatory status the National Institutes of Health (NIH) Policies for the Protection of Human Subjects, which were first issued in 1966. The regulations established the Institutional Review Board (IRB) as one mechanism through which human subjects would be protected. The federal regulatory protections only apply to: 1) research supported by funding from one of the federal agencies subscribing to the Common Rule; 2) research on an investigational new drug, device or biologic subject to FDA rules; or 3) research conducted at an institution or by an individual investigator at that institution that has executed an assurance with the Federal Government stating that even research not otherwise covered by the regulations will nonetheless be governed by them.

Although existing federal regulations have provided special protections for certain populations that are regarded as particularly vulnerable,[3] persons with mental disorders who may have impaired capacity[4] to make decisions, and therefore to give voluntary informed consent, have not received any such special protections.[5] Mental disorders—which can be heartbreakingly burdensome for victims and their families and frustrating for the professionals who try to treat them—have in recent years been the focus of research studies that have produced not only important and clinically relevant scientific findings but also a certain amount of public controversy, governmental sanctions, and even lawsuits (see the further discussion in Appendix I). One commentator has noted that, while existing human subjects regulations broadly address the need to protect individuals with diminished autonomy, specifically "where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons,"[6] little additional *practical* guidance is provided regarding vulnerable subjects who are not already covered by a set of specific regulations. Although current U.S. regulations note the need to ensure the ethical treatment of human research subjects with mental disorders, they provide no specific guidance for IRBs and investigators. The National Bioethics Advisory Commission (NBAC) believes this is not adequate.

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[3]Department of Health and Human Services, Services (HHS) regulations govern research involving fetuses, pregnant women, human *in vitro* fertilization (45 C.F.R. 46, Subpt. B (1998)) and prisoners (45 C.F.R. 46, Subpt. C (1998)); both HHS and the Department of Education (ED) have regulations governing research involving children (45 C.F.R. 46, Subpt. D.; 34 C.F.R. 97, Subpt. D (1998)). Other potentially vulnerable subjects whose decisionmaking capacity may be compromised by such factors as trauma (e.g., head injury) or physical illness (e.g., cancer or sepsis) will not be considered in this report.

[4] Throughout this report the term "capacity" is used rather than the term "competence" (although the two are often used interchangeably by others), because the latter often refers to a legal determination made by a court, and the former refers to a clinical judgment.

[5]Alison Wichman, "Protecting Vulnerable Subjects: Practical Realities of Institutional Review Board Review and Approval," *Journal of Health Care Law and Policy* 1, no. 1 (1998): 92–3 (hereinafter cited as *Protecting Vulnerable Subjects*) (emphasis added).

[6]45 CFR 46.111(b) (1998).

Clarification should be made at the outset regarding the system of federal protections that apply to human subjects research. Two main categories of protections are discussed in this report.[7] The first set of protections are provided in the Federal Policy for the Protection of Human Subjects; Notices and Rules, also known as the "Common Rule". The Common Rule is a set of regulations adopted independently by 17 federal agencies that support or conduct research with human subjects.[8] The 17 agencies adopted regulations based on the language set forth in Subpart A, Part 46, Title 45 of the Code of Federal Regulations (C.F.R.). Title 45 of the C.F.R. is devoted to regulations promulgated by the Department of Health and Human Services (HHS). Thus, the Common Rule is, for most intents and purposes, Subpart A of HHS's regulations. For simplicity's sake, throughout this report wherever reference is made to a particular section of the Common Rule, e.g., the "General requirements for informed consent," the appropriate title, part, and section of HHS's regulations is cited (in this example, 45 C.F.R. 46.116). The reader should know, then, that wherever HHS's Subpart A (45 C.F.R. 46.101 through 45 C.F.R. 46.124) is cited, those same regulations will in most, if not all, cases apply across the 17 signatory agencies.

The second category of federal protections that relates to human research subjects is the set of rules governing drug, device, and biologics research. These rules are administered by the U.S. Food and Drug Administration (FDA). Research that comes under FDA jurisdiction constitutes an important and growing portion of human subjects research. To the extent that FDA's rules are different from the Common Rule and are relevant to the discussion, reference will be made to them.

[7] NBAC notes the existence of other federal laws that might bear on issues discussed in this report, but due to their apparent limited scope (e.g., 10 U.S.C § 980 (1997), restricting the circumstances in which the Department of Defense may use subjects in research), and because we believe the recommendations stated herein should apply generally, we do not discuss all relevant rules that exist.

[8] Or, in some cases, an agency has been ordered to adopt these regulations.

Despite the existence of a federal policy for the protection of human subjects in research, some concerns have emerged about the adequacy of these protections. In 1995, for example, the Advisory Committee on Human Radiation Experiments (ACHRE), based on its own empirical studies, noted its concern about "serious deficiencies in some parts of the current system for the protection of the rights and interests of human subjects."[9] As part of its work, ACHRE reviewed 125 research proposals involving human subjects in ionizing radiation studies that were approved and funded in fiscal years 1990 through 1993, and found that almost half of these studies involving greater than minimal risk raised "serious or moderate concerns" about risks to human subjects. [10] Among the research protocols that concerned ACHRE were some involving persons at risk for impaired decisionmaking capacity. In particular, ACHRE expressed concern about studies on adults with questionable decisionmaking capacity, specifically research with no prospect of individual benefit to the subject that involves unpleasant procedures and exposes them to greater than minimal risk.[11] ACHRE also surveyed hundreds of people who were ill but who retained decisionmaking capacity and were currently participating in clinical trials, concluding that many of them were not aware of important and relevant elements of the research.[12] Considering the special complexities of research involving persons whose decisional capacity may be affected by mental disorders, ACHRE's concerns must not be overlooked. Indeed, ACHRE provided a basis for further consideration of suitable conditions for involving in research such individuals.

The deliberations that produced NBAC's report, however, were not stimulated by a perceived crisis in the participation of persons from this population in clinical

[9]Advisory Committee on Human Radiation Experiments, (ACHRE) *Final Report* (New York: Oxford University Press, 1995), 510.
[10]Ibid., 456. These concerns related principally to the quality and content of consent forms, but also included other issues such as the level of risk, scientific merit, and recruitment strategies.
[11]Ibid.
[12]Ibid., 459–81.

studies, but by the recognition of considerable confusion about the principles and procedures that should govern such research. Although NBAC heard powerful testimony from members of the public and the professions about the conduct of such research, and received information describing the strengths and weaknesses of the system of human subjects protection, it did not rely on these as sufficient evidence of the need to "fix a broken system." NBAC was informed by this input, and grateful for it, but its approach was a prospective and constructive one to close one of the gaps perceived to exist in human subjects research protection.[13]

The confusion noted above has been evident in several legal cases and in widespread public discussion of the appropriate role of this population in research. One well-publicized and often misunderstood incident which was brought to the public's attention was the suicide, well after the completion of a research protocol, of a former subject in a "washout" study at the University of California at Los Angeles.[14] This particular case led to an investigation by the Office for Protection from Research Risks (OPRR).[15] In addition, a number of organizations and government agencies, both in the United States[16,17,18] and abroad,[19,20,21,22] have recently offered recommendations

[13]James F. Childress, "The National Bioethics Advisory Commission: Bridging the Gaps in Human Subjects Research Protection," *Journal of Health Care Law and Policy* 1, no. 1 (1998): 105–22.

[14] "Washout" studies are protocols that seek to return the individual to a medication-free "baseline" state so that behavior can be assessed or new drugs introduced without the confounding factor of other substances already in the person's system.

[15] OPRR, *Evaluation of Human Subject Protections in Schizophrenia Research Conducted by the University of California, Los Angeles* (1994).

[16]National Institutes of Health Panel Report, *Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards* (February 27, 1998) (short cite needed).

[17]Office of the Maryland Attorney General. Final Report of the Attorney General's Research Working Group, 1998.

[18]The New York Department of Health Working Group.

[19]Council of Europe. Convention on Human Rights and Medicine, November 1996.

[20]United Kingdom. The Law Commission. Mental Incapacity: Item 9 of the Fourth Programme of Law Reform: Mentally Incapacitated Adults, London, England, House of Commons, 1995.

[21]Council for International Organizations of Medical Sciences (hereinafter cited as CIOMS), *Guidelines on Research Involving Human Subjects* (city of pub.: publisher, 1993), pg. no.

[22]Canada. Tri-Council Working Group. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Ottawa, Ontario. August 1998.

regarding research on this population. Numerous scholarly papers have also appeared in the last several years addressing various aspects of the topic.[23,24,25,26,27,28,29,30,31,32] In sum, a critical mass of concern has developed, affording NBAC the opportunity to review and consider these issues in the context of its responsibility to advise the President through the National Science and Technology Council.

Further, many new, potentially useful therapies for treating mental disorders will be developed over the next few years. The prospect of increasing numbers of research protocols, with the attendant potential increase in the number of persons with possibly impaired decisionmaking capacity recruited into in these studies, makes it all the more important to clarify the ethical framework required for such research.

It is generally agreed that those who lack the ability to decide in an informed manner about participating in a research protocol may only be included under certain conditions. For example, the research cannot be conducted with subjects whose capacity to make decisions is not impaired, and the study entails a reasonable level of risk in light of potential benefits and protections involved. NBAC, however, felt that additional guidance is required. In addition, it was mindful of concerns about the

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[23] D.C. Marson et al., "Assessing the Competency of Patients with Alzheimer's Disease under Different Legal Standards," *Archives of Neurology* 52 (1995): 949–54.

[24] B. Stanley et al, "The Elderly Patient and Informed Consent," *Journal of the American Medical Association* 252 (1984): 1302–6.

[25] E. DeRenzo, : The Ethics of Involving Psychiatrically Impaired Persons in Research, *IRB*, (November-December 1994): page numbers

[26] John C. Fletcher and Alison Whitman, "A New Consent Policy for Research with Impaired Human Subjects," 23 *Psychopharmacology Bulletin* (1987): 382.

[27] Author(s)?, *Alzheimer's Disease Research: Ethical and Legal Issues*, eds. J. Berg, H. Karlinsky and F. Lowy (Toronto: Carswell, 1991), page no.

[28] First name Keyserlingk et al., "Proposed Guidelines for the Participation of Persons with Dementia as Research Subjects," *Perspectives in Biological Medicine* 38 (1995): 319.

[29] A. Shamoo and T.J. Keay, "Ethical Concerns About Relapse Studies," *Cambridge Quarterly of Healthcare Ethics* 5 (1996): 373–86.

[30] P.S. Appelbaum and T. Grisso, "Capacities of Hospitalized, Medically Ill Patients to Consent to Treatment," *Psychosomatics* 38 (1997): 119–25.

[31] R. Bonnie , "Research with Cognitively Impaired Subjects," *Archives of Genetic Psychology* 54 (1997): 105, 107.

[32] Moreno, JD. "Regulation of Research on the Decisionally Impaired: History and Gaps in the Current Regulatory System," *Journal of Health Care Law & Policy* 1998, Vol. 1, No. 1, pp. 1-21.

ability of IRBs at some large research centers to actually monitor, as necessary, approved research proposals.

The justification for this report, therefore, is the confluence of several developments, including perceived gaps in the federal system for the protection of human subjects; historical and contemporary cases in which the protection of human subjects appears to have been inadequate; and the need to ensure that research designed to develop better treatments for mental disorders can proceed with full public confidence in its ethical framework. The continuing vitality of the research enterprise ultimately depends on the public's trust that ethical constraints are in place and will be followed.

In this report, NBAC considers how ethically acceptable research can be conducted using human subjects who suffer from mental disorders that may affect their decisionmaking capacity; whether, in fact, additional protections are needed and, if so, what they should be and how they should be implemented. In addition, this report provides an opportunity for investigators, IRB members, persons with mental disorders and their families, and the general public to become better informed about the goals of research and appropriate protections of the human subjects involved.

The Promise of Research on Mental Disorders

Of the 10 leading causes of disability in the world, according to a recent World Health Organization report, 5 are psychiatric conditions: unipolar depression, alcohol use, bipolar affective disorder, schizophrenia, and obsessive-compulsive disorder.[33] It has been estimated that direct and indirect costs of mental illness and substance abuse in the United States totaled more than $313 billion dollars in 1990. [34] Alzheimer's

[33]World Health Organization, *The Global Burden of Disease* (Cambridge, MA: Harvard University Press, 1997) pg. no.

[34]National Institutes of Health, *Disease-specific Estimates of Direct and Indirect Costs of Illness and NIH Support* (1997 update report to Congress, April 1997).

disease now afflicts approximately 4 million people in this country and, with the number of persons over 65 years of age expected to double by the year 2030, the resulting morbidity can be expected to grow proportionately.

The scope of these disorders is so large that when treatments can be identified that can mitigate their impact, the human, social, and economic benefits are enormous. For example, since 1970, the cumulative savings to the U.S. economy from the introduction of lithium as a treatment for bipolar disorder are estimated at $145 billion. Furthermore, no dollar figure can be put on the benefits to patients and families spared the anguish of manic and depressive episodes, which often tear apart the fabric of family life and social relationships. Similarly, the introduction of clozapine for treatment of schizophrenia has been estimated to yield savings of $1.4 billion per year since 1990.[35] Thus, beyond compassion, there are economic incentives as well to improve our understanding of disorders affecting brain function and to develop more effective treatments

Most research on these conditions falls into two broad categories: studies aimed at elucidating the underlying pathophysiologic bases of the disorders, and studies intended to develop or test new treatments for them. Among the most powerful approaches to examining basic aspects of brain function and dysfunction are new techniques that allow imaging of the working brain. Positron emission tomography (PET), functional magnetic resonance imaging (MRI), single photon emission computer tomography (SPECT), and related procedures help identify the anatomic location of brain areas involved in cognitive and affective functions.[36] Comparisons of normal and afflicted populations permit localization of regions affected by the disease

[35]Steven Hyman, Director, National Institute of Mental Health, in testimony to the U.S. Senate Appropriations Subcommittee Hearings, 1997; H.Y. Meltzer et al., "Cost Effectiveness of Clozapine in Neuroleptic-resistant Schizophrenia," *American Journal of Psychiatry* 150 (1993): 1630–8.

[36]N.C. Andreasen, D.S. O'Leary, and S. Arndt, "Neuroimaging and Clinical Neuroscience: Basic Issues and Principles," *American Psychiatric Press Review of Psychiatry* 12, eds. J.M. Oldham, M.B. Riba, and A. Tasman (Washington, DC: American Psychiatric Press, 1993).

process. These techniques also allow monitoring of the effects of treatment regimens at the level of the brain.[37]

Currently, pharmaceuticals are the primary focus of treatment-oriented research, and the development of new medications is being facilitated, for example, by studies of brain neurotransmitter receptors, which allow new molecules to be created that have the desired therapeutic effects with minimal side effects. More innovative approaches that are still in early and speculative development include insertion of new genes to correct identified defects underlying brain disorders (gene therapy), and the use of immunologic therapies, like the recent successful inoculation of rats against the psychostimulant effects of cocaine.[38]

Some basic research (e.g., on brain receptor mechanisms) can be conducted with animals rather than with humans. But when disease processes themselves are under study, the absence of animal models for most psychiatric and many neurologic syndromes means that research on both the underlying dynamics of disease and on promising treatments must involve human subjects. Moreover, unless research is to be limited to the mildest forms of the disorders, some persons whose decisionmaking capacity may be impaired are likely to be required in important protocols. From this reality flows the central dilemma of designing appropriate protections for persons with mental disorders who participate in such research protocols: the protection of subjects from harm must be balanced against the potential for benefit that may arise from their participation and, to some more limited extent, the potential benefit for other persons with the same disorder.

[37] L.R. Baxter et al., "Caudate Glucose Metabolic Rate Changes with Both Drug and Behavior Therapy for Obsessive-compulsive Disorder," *Archives of General Psychiatry* 49 (1992): 681–9.
[38] M.R. Carrera et al., "Suppression of Psychoactive Effects of Cocaine by Active Immunization," *Nature* 378 (1995): 727–30.

Scope of This Report

Persons with mental disorders are not, of course, unique in being at risk for loss of decisionmaking capacity. Accident and trauma victims, highly medicated patients, and many people who are severely ill may be significantly less capable of making autonomous and self-protective decisions than might be the case in other circumstances. Indeed, a comprehensive list of individuals whose decision making might be compromised or placed in question includes, in addition to persons with certain mental disorders, children, comatose patients, critically ill patients, institutionalized individuals, prisoners, people lacking certain language skills, persons with brain disorders (e.g., stroke), and others.[39] NBAC recognizes that many of the issues and concerns raised in this report (and, indeed, many of the ensuing recommended protections) *could* be applied to *all* persons with questionable or diminished capacity. However, NBAC principally focused its attention on those who may be primarily considered for research protocols because it is their particular mental disorder that is being studied.

NBAC recognizes that it is difficult to consistently fit diseases or conditions within particular linguistic categories, particularly in areas such as psychiatry and neurology in which the boundaries of investigation are moving faster than the development of new labels. This difficulty has been noted by the American Psychiatric Association in its *Diagnostic and Statistical Manual of Mental Disorders:*

> Although this volume is titled the *Diagnostic and Statistical Manual of Mental Disorders*, the term *mental disorder* unfortunately implies a distinction between "mental" disorders and "physical" disorders that is a reductionistic anachronism of mind/body dualism. A compelling literature documents that there is much "physical" in "mental" disorders and much "mental" in "physical" disorders. The problem raised by the

[39] Alison Wichman, "Protecting Vulnerable Subjects," 104.

> term "mental" disorders has been much clearer than its solution, and, unfortunately, the term persists in the title of DSM-IV because we have not found an appropriate substitute.
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> Moreover, although this manual provides a classification of mental disorders, it must be admitted that no definition adequately specifies precise boundaries for the concept of "mental disorder." The concept of mental disorder, like many other concepts in medicine and science, lacks a consistent operational definition that covers all situations.[40]

Although this report focuses principally on research involving persons with mental disorders, NBAC recognizes and encourages its use by others seeking guidance for conducting research on other persons whose decisionmaking capacity may be impaired. Many of the recommendations in this report might be generalizable to other populations.

NBAC was mindful of the concerns that could arise from a focus on individuals who are members of a group (i.e., persons with certain mental disorders) rather than on persons who share a common functional characteristic (i.e., questionable decision making). This focus could raise the specter of equating mental disorder with incapacity and thus potentially stigmatize these individuals. NBAC shares this concern and recognizes that not all persons with mental disorders have impaired decisionmaking capacities. Among those who do these impairments do not necessarily compromise the individuals' decisionmaking abilities about research participation. The intent is not to label persons but rather to describe and explain a set of appropriate concerns regarding research involving certain persons and to propose ways to ensure that both appropriate protection and important science proceeds. The recommended measures to protect these individuals are designed for those who are vulnerable *when they are vulnerable* to intended or unintended coercion and exploitation. These measures can only be successful when they do not, as a consequence, discriminate

[40] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders,* xxi, hereinafter DSM-IV.

against those persons who may have a mental disorder, but who do not now, or who may never have decisional impairment of the kind that would limit their ability to decide whether or not to participate in research.

To assume that a diagnosis of a mental disorder implies that a person is incapable of informed consent in deciding whether to participate in a research protocol is prejudicial and incorrect. Such a diagnosis is simply one among many factors that may trigger an assessment of decisionmaking capacity, an assessment that may in turn conclude that a particular person with such a disorder either lacks or fully retains the capacity to make an informed decision about participating in research. Although persons with mental disorders are not necessarily decisionally impaired, much less decisionally incapable, any evidence that places a person's decisionmaking ability into question should trigger a clinical assessment. Although any disorder that alters mentation may adversely affect decisionmaking ability, when such a disorder is present in an early or mild phase the resulting impairment may not affect a research subject's consent to participate, although extra care in the informed consent process may be required. More advanced or severe forms of a disorder, however, may render the subject incapable of a thoughtful (protective of one's interests) and independent choice.

Clearly, special difficulties arise in designing ethically acceptable research protocols that involve human subjects with mental disorders whose decisionmaking capacity, and therefore their ability to give informed consent, may be impaired. Such medical conditions can complicate efforts to respect the rights of human subjects involved in a research project, especially when the research design is such that the subjects themselves will receive no direct benefits.[41] Problems in determining the presence or absence of appropriate decisionmaking capacity, however, represent only

[41]For example, some drug research is intended only to determine at what dosage the medication under study will cause a person to become ill or how rapidly the drug is excreted from the body.

one difficulty in conducting ethically acceptable research involving persons with mental disorders. There are other confounding aspects of conducting research in this population.

Many of the conditions underlying impaired decision making manifest themselves in behaviors that make prospective subjects difficult to understand and may cause discomfort in others. As a result, persons with these diseases have often been stigmatized, and efforts to improve their medical treatment frequently have been marginalized. Moreover, those who are hospitalized in psychiatric units are especially vulnerable by virtue of the special dynamics of that environment. As is the case for other potential research participants, confusion about the goals of a study can easily occur when the physician caring for the patient is also a researcher who may wish to enlist the patient in a research protocol. Finally, because mechanisms for funding appropriate treatment of these diseases are often seriously wanting, this population may be especially vulnerable as its members often do not have adequate access, for financial and other reasons, to health care outside the research context.[42] Despite all this, the etiology and treatment of these diseases need much further study; currently there are too few satisfactory treatments.

Medical science has recently made great strides in understanding the underlying biological and chemical processes that are associated with the mental disorders that affect millions of Americans. Moreover, the future research agenda in this area looks very promising. As a result, issues regarding the appropriate design of research protocols involving persons with disorders that may affect decisionmaking capacity are likely to become more prominent in the near future. The great needs of this population represent a significant opportunity for the pharmaceutical industry to develop effective

[42]The barriers to appropriate care can be due to financial or other factors (e.g., lack of knowledge or of qualified providers, denial, etc.). These barriers may be particularly acute if the initial onset of the disorder occurs before an individual is attached to some social support mechanism.

new medications and for medical research centers and all those dedicated to helping those with these disorders to expand both their understanding of the origins of these disorders and their capacity to develop better treatments. In the United States the increasingly important interactions among private industry, government, academia and other research institutions present a favorable atmosphere for scientific development, but they also present a challenge to create a regulatory framework that can protect individuals while allowing appropriate research and product development to flourish. [43]

In addition, because access to health care for patients with mental disorders is so limited, the "benefits" of being a research subject may easily be exaggerated when in fact clinical studies often are not only uncertain in their potential benefits, but may actually be designed to investigate issues that do not relate to the subject's current therapeutic needs. Further, the patient's understandable interest in access to promising experimental drugs or devices should not distract from the need to ensure that physicians are aware of therapies that have already been recognized as safe and effective that should be incorporated into the treatment of their patients.

The combination of these and other factors again calls attention to the need to consider more specific guidance regarding the appropriate ethical constraints in research protocols involving persons with mental disorders who may have decisionmaking impairments. For a variety of reasons, previous efforts to establish specific protections for adults with mental disorders that may affect decisionmaking capacity have largely failed, although some researchers and institutions have taken

[43] Another complicating factor in efforts to protect human research subjects is the unclear boundary between research and what is often called "innovative treatment." The latter category is intended to suggest that medical intervention is not undertaken as part of a scientific study but is rather an attempt to treat an individual patient who has not responded to standard therapy. For example, a patient whose physician recommends an "off-label" trial of a medication approved for a different use is not, with respect to federal regulation, a research subject unless the physician is engaged in the systematic collection of data about a specific use of the drug. In this kind of clinical situation, certain existing regulatory requirements for ethically sound research, such as prior review of the procedure by an Institutional Review Board, do not apply. Nevertheless, the usual requirement that the treating physician obtain informed consent for any intended treatment does apply, and the patient, or the patient's legally authorized representative, should be informed about, and consent to, the innovative procedure.

important and responsible initiatives in this area. Recently the Department of Health and Human Services (DHHS) Office of the Inspector General issued a report describing such innovative practices,[44] but these addressed IRB review generally, not the review of protocols involving vulnerable populations in particular. It seems that efforts to establish appropriate regulations have been hampered either by longstanding inimical social attitudes toward persons with mental disorders that may affect their decision making capacity or by lack of consensus regarding how the appropriate protections should be structured. Nevertheless, we have an important and continuing obligation to address these issues more effectively for the sake of those who are directly affected by them.

Several tensions are inherent in the current discourse on these issues. On the one hand, those who suffer from these disorders, and those who care about them, desperately want medical science to find ways to improve their conditions. On the other hand, there is disagreement about how this can be done without exploiting those with mental disorders who participate in research protocols, thus causing them still greater suffering.[45] Despite these tensions , much can be done to ameliorate the apparent conflict between the need to continue promising lines of research and the ethical imperative to protect the dignity and well-being of research subjects.

The Nature of Some Mental Disorders That May Affect Decisionmaking Capacity

A relatively small body of research has documented the effects of various disorders on decisionmaking capacity per se, supplemented by data on cognitive functioning in general and by clinical observation of these populations. The following

[44]Department of Health and Human Services, Office of the Inspector General, *Institutional Review Boards: Promising Approaches* (Washington, DC: DHHS, 1998).
[45]*Ethics in Neurobiological Research with Human Subjects,* ed. A.E. Shamoo (Amsterdam: Gordon and Breach Publishers, 1997), page no.

are some of the disorders in which decisionmaking capacity may be affected, although this list is by no means exhaustive.

Dementias

Dementias are characterized by multiple cognitive deficits, most prominently impairment of memory. The best known of these conditions is dementia of the Alzheimer's type, a progressive disorder whose cause is presently unknown. The incidence of Alzheimer's disease increases with age—from 2 to 4 percent in the population over 65 years old and to more than 20 percent in those over 85 years old.[46] Dementias may also be caused by vascular infarcts of the brain, head trauma, HIV infection, and neurological conditions, such as Parkinson's disease and Huntington's disease.

The study of decisionmaking impairment in persons with dementia has focused primarily on Alzheimer's disease. Even patients with mild forms of the disease may exhibit enough deficits in understanding relevant information and reasoning to call their capacities into question. The choices they make about treatment and research, however, may not differ from those of non-impaired populations. As dementia progresses from the mild to the moderate stage, however, the range and magnitude of deficits expand, and individuals may fail even the simplest tests of decisionmaking capacity.[47] The co-occurrence of other disorders such as delirium or depression may exacerbate the impact of dementia on the ability to make decisions.

Delirium

Like dementia, delirium involves alterations in cognition, but usually evolves over hours or days. Disturbances of consciousness and attention are prominent.

[46]APA, DSM-IV, page no.
[47]Marson et al., "Assessing the Competency," 949–54; B. Stanley et al., "The Elderly Patient," 1302–6).

Delirium is often caused by systemic medical conditions, side effects of medications, or intoxication with or withdrawal from psychoactive agents or toxins.[48] Studies demonstrating high rates of decisional impairment in severely ill hospitalized patients are probably detecting the effects of delirium secondary to the underlying conditions and, in some cases, to the treatments being administered.[49] Other work suggests that serious medical illness does not directly impair brain function, even when it results in hospitalization, and is not likely, by itself, to result in limitations on decisionmaking abilities.[50]

Schizophrenia

Schizophrenia is a severe psychiatric disorder marked by delusions, hallucinations, disorganized speech or behavior, and diminished affect and initiative. A variety of cognitive dysfunctions, including several related to processing information, has been associated with the disorder. Its onset typically occurs in early adulthood and, although its course is variable, symptoms often wax and wane, with the result that functional impairment fluctuates over time.[51] Many of its manifestations can be reduced with antipsychotic medication, but residual symptoms are frequent and relapse is not uncommon.

As many as one-half of acutely hospitalized patients with schizophrenia may have substantially impaired decisionmaking abilities, including difficulties in understanding, appreciation, and reasoning.[52] Since many of these impairments appear to be related to active symptoms, the prevalence of reduced capacity is likely to be

[48]APA, *DSM-IV,* pg. no.
[49]L.M. Cohen, J.D. McCue, and G.M. Green, "Do Clinical and Formal Assessment of the Capacity of Patients in the Intensive Care Unit to Make Decisions Agree?" *Archives of Internal Medicine* 153 (1993): 2481–5.
[50]Appelbaum and Grisso, "Capacities," 119–25.
[51]APA, *DSM-IV*, pg. no.
[52]T. Grisso and P.S. Appelbaum, "The MacArthur Treatment Competence Study, III: Abilities of Patients to Consent to Psychiatric and Medical Treatments." *Law and Human Behavior* 19 (1995): 149–74.

lower among outpatient groups.[53] Lack of insight into the presence of illness and need for treatment is common among persons with schizophrenia.[54] This may make it especially difficult for them to anticipate the consequences of their decisions on participation in research as they relate to the risk of future relapse.

Depression

Symptoms of major depression include: depressed mood; feelings of worthlessness; diminished interest and pleasure in most activities; changes in appetite, sleep patterns, and energy levels; and difficulties in concentration.[55] Cognitive impairments may exist in information processing[56] and reasoning,[57] among other functions. Less clear is the extent to which these consequences of depression impede decision making. It has been suggested that decreased motivation to protect their interests may reduce depressed patients' abilities to make decisions[58] or to alter the nature of those decisions.[59] One study suggested that hospitalized depressed patients may manifest decisionmaking problems roughly half as often as patients with schizophrenia may—that is, in about one-quarter of cases.[60] But it is likely that the degree of impairment relates to the intensity of depressive symptoms, and thus will vary across populations.

[53]B. Rosenfeld, E. Turkheimer, and W. Gardner W. "Decision Making in a Schizophrenic Population." *Law and Human Behavior* 16 (1992): 651–62.
[54]X.F. Amador et al., "Awareness of Illness in Schizophrenia ." *Schizophrenia Bulletin* 17 (1991): 113–32.
[55]APA, *DSM-IV*, pg. no.
[56]S. Hartlarge et al., "Automatic and Effortful Processing in Depression," *Psychological Bulletin* 113 (1993): 247–78.
[57]J.E. Baker and S. Channon, "Reasoning in Depression: Impairment on a Concept Discrimination Learning Task," *Cognition and Emotion* 9 (1995): 579–97.
[58]C. Elliott , "Caring About Risks: Are Severely Depressed Patients Competent to Consent to Research?" *Archives of General Psychiatry* 54 (1997): 113–6,
[59]M.A. Lee and L. Ganzini, "Depression in the Elderly: Effect on Patient Attitudes toward Life-sustaining Therapy," *Journal of the American Geriatric Society* 40 (1992): 983–8.
[60]Grisso and Appelbaum," The MacArthur Treatment," pg. no.

Some Other Disorders

Although less subject to formal study in the context of consent to treatment or research, there is good reason to believe that the capacity of persons with other mental disorders to participate in research may, at some time, be impaired. *Mental retardation*, affecting as it does a range of cognitive abilities, is more likely to impair capacities as severity increases. *Bipolar disorder* results in alternating states of depression and mania, the latter comprising elevated mood, increased impulsivity, and reduced attention, among other features; manic patients are known to make poor decisions about money and personal affairs, and it is probable that this deficit extends into research decision making for some subset of this group. *Other psychotic disorders* involve some of the symptoms seen in schizophrenia, including delusions and hallucinations, and may have some of the same consequences for decision making. *Substance abuse disorders*, for example, including use of alcohol and illegal drugs, result in states of intoxication and withdrawal that resemble delirium in their effects on attention, cognition, other mental functions, and, consequently, decision making. There also can be some decisional impairments associated with drug abuse and addiction outside the circumstances of intoxication and certain forms of withdrawal. However, it is important to emphasize that the diagnosis of substance abuse disorders does not imply that decisionmaking capacity is impaired.

<u>Values That Should Guide Research in These Populations</u>

Protecting human subjects from harm in research is perfectly compatible with pursuing important research goals; one does not have to be compromised to accommodate the other. More than three decades of continual improvement in the design of research protocols have evolved from the underlying philosophy that regulatory frameworks are established to ensure that human subjects in biomedical and behavioral research protocols are treated with respect. Over time, researchers have

both refined their understanding of what it means to respect human subjects involved in research protocols and improved their research designs to minimize risks. This report is partly an effort to share that knowledge with the public.

The purpose of medical research is to understand, prevent, and treat disease, and our society is deeply committed to continuing these efforts. We acknowledge that in the pursuit of clinically relevant knowledge, there is often no substitute for a human subject, and this is certainly true of the study of illnesses like depression or delusional states that manifest themselves partly by altering human subjectivity or by impairing cognitive functioning.

If human beings must become research subjects in order for important questions to be answered, their respectful treatment begins with soundness in research design, the sine qua non for ethical research involving human subjects. It has long been recognized, for example, that unless the researcher is a competent investigator and the research design is sound, it is inappropriate to attempt to engage persons as research subjects, regardless of the level of risk.

Even with the best research designs, however, research protocols can rarely eliminate all risks. As long as research is conducted involving human beings, there is a possibility that subjects will be harmed. Anyone who serves as a subject in a research protocol therefore is engaged in a form of public service that may involve risk and for which there may be no direct or tangible personal reward. The unavoidable element of risk has warranted protections for all research subjects, and clearly such protections must never be less stringent for research subjects whose ability to be fully informed and to freely consent is lacking or in doubt than it is for others. This proposition is already well recognized in research with children.

Finally, because freedom from all risk cannot be guaranteed, and because those who have specific impairments in their decisionmaking ability do not have the same opportunity to determine the extent of their research involvement as do others, care

must be taken not to succumb to any temptations to target members of this population for research when their participation is unnecessary. In particular, this population should not be exploited, that is, it should never shoulder all the risks and burdens of a scientific project when the benefits are expected to flow primarily to other segments of the population. NBAC continues to take seriously the relevance of the principle of distributive justice described by the National Commission in the *Belmont Report*:

> Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear the burdens and on the appropriateness of placing further burdens on already burdened persons."[61]

NBAC's views about respect for persons, beneficence, and justice are squarely in the tradition established by the National Commission, and are no less valid today than they were nearly 20 years ago. Yet research has changed, including the way in which it is conducted, its funding sources, and, in many instances, its complexity.

Informed Consent and Decisional Impairments

To say that a person consents to participate in research presupposes that he or she has the capacity to consent. An analysis of informed consent by Faden and Beauchamp, holds that judgments about competence to consent is said to perform a

[61]National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research*, U.S. Government Printing Office, April 18, 1979, page 7 (hereinafter cited as *Belmont Report*).

gatekeeping function: "competence judgments function to distinguish persons from whom consent *should* be solicited from those from whom consent need not or should not be solicited."[62] Every effort must be made, therefore, to engage the prospective subject in the informed consent process as much as his or her ability to participate in that process permits. Thus, an individual who is able to understand the purpose, risks, and possible benefits of a study must be given all the information relevant to make an informed decision about research participation. There is also an obligation to help those with cognitive impairments understand as much as possible the relevant information. The National Commission described this obligation as part of the principle of respect for persons: "Respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection." [63]

An ethically justifiable system of clinical research should take into account the wide variations in the conditions that may affect the decisionmaking capacity of potential human subjects. It is important to recognize that decisionmaking ability may be limited for some people in diverse ways. Appreciating and recognizing this diversity will help in the design of ethically sensitive recruitment and consent procedures and research protocols. As is so often the case, "voluntariness" is easy to require in regulations and guidelines, but much harder to guarantee in real life situations.

At least four types of limitations in decisionmaking ability should be considered when planning and conducting research with this population. First, some individuals might have fluctuating capacity, what is often called waxing and waning ability to make decisions, as in schizophrenia, manic-depressive disorders, and some dementias.

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[62] R.R. Faden and T.L. Beauchamp, *A History and Theory of Informed Consent* (New York: Oxford University Press, 1986), 288.
[63] National Commission, *Belmont Report*, 4.

Second, decisionmaking deficits can be predicted in some individuals due to the course of their disease or the nature of a treatment. Although these individuals are decisionally capable in the early stages of the disease progression, such as in Alzheimer's disease, they have prospective incapacity. Third, most persons with limited capacity are in some way still able to object or assent to research, as in the case of more advanced Alzheimer's. Fourth, persons who have permanently lost the ability to make nearly any decision that involves any significant degree of reflection are decisionally incapable, as in the later stages of Alzheimer's and profound dementia.

These four sorts of decisional limitations— fluctuating, prospective, limited, and complete—provide an initial framework both for the different ways the problem of decisionmaking capacity can manifest itself and for the design of appropriate protections.[64] Some disorders entail limitations on decisionmaking ability that are subtle and hard to identify, and even individuals who fit within a particular diagnostic category may exhibit decisionmaking limitations in different ways.

The situation is further complicated by the fact that two or more of these four categories often apply to the same individual over the course of a disease. Thus someone in the early stages of Alzheimer's disease may have prospective incapacity, then experience very subtle decisionmaking limitations or have fluctuating capacity, and, finally, progress to incapacity. It is therefore critical that researchers who work with this population be familiar with the ways that decisionmaking impairments manifest themselves, and that they design appropriate mechanisms to maximize the subject's ability to decide whether to enter or continue in a study..

In addition, circumstantial factors often affect decisionmaking capacity. All of us feel more empowered and in control in some social situations than we do in others. Similarly, some persons with mental disorders may be more or less capable of making

[64]These categories do not apply to children, whose decisional limitations are developmentally appropriate and are not a result or symptom of an illness.

their own decisions depending on circumstances. For example, some individuals may feel more empowered in dealing with certain health care professionals or family members, and less so in dealing with others; or they may be more effective in expressing their wishes at home than in an institution, or the reverse. Such insights can be critical in helping the individual achieve as high a degree of self-determination as possible.

Finally, a basic difficulty is central to deliberations on research involving those who may be decisionally impaired: our society has not decided what degree of impairment counts as a lack of decisionmaking capacity. Although there are certain clear cases of those who are fully capable and those who are wholly incapable, persons with fluctuating or limited capacity present serious challenges to assessment. When can those whose capacity is uncertain over periods of time be deemed capable to decide about participating in research? In a society that treasures personal freedom and centers its political system on the integrity and value of each individual, this question goes to the very heart of our culture and must therefore be treated with utmost caution.

Additional Issues in Research with Persons with Mental Disorders

Research involving persons with mental disorders must take into account issues beyond those having to do with informed consent, for there are other issues of special relevance to this population. Some of these are briefly described below.

Limitations on Drug Development

Currently, illnesses associated with decisional impairments often involve testing at an earlier stage of drug development than is usually the case in pharmaceutical research, because animal models may not yield data that can be extrapolated to human diseases that cause psychological or cognitive symptoms.

Subjective Experience of Disorders

While all individuals experience their illnesses subjectively, the experiences of those with mental disorders pose additional challenges to research. In some instances, they may perceive that they are at greater risk of harm than is actually the case, because of confusion or other manifestations of their disorder. Their subjective perception is no less real, and therefore no less important, than the subjective perception of pain from physical injury, but it may require researchers to factor more individualized judgments into their projections of risk and benefit than may be the case for researchers in other fields.

Problems in Mental Health Care

Mental health care has a checkered history characterized by periods of patient neglect, abuse, superstition, and stigmatization. Sadly, some of these historical trends can be found even in our own time and among relatively prosperous societies. The outward symptoms of some mental disorders and the fact that many stricken individuals are difficult to treat still make some people uncomfortable. In addition, some primary health care professionals are relatively unfamiliar with the symptoms of these illnesses or the best treatment for them. Some individuals in these groups are difficult to work with in the research setting. For these reasons and others, both clinical care and research in these diseases often have received lower priority than illnesses considered more "medical" in nature.

Another factor that affects research and therapy on illnesses associated with decisional impairments is that financial resources for treating many of these conditions continue to suffer compared to other diseases. Both public and private insurance policies often fail to provide adequate support for the kinds of intervention that may be required. This problem is further aggravated by the disadvantaged economic situation of many persons with mental disorders, since many may have trouble in completing

education and training programs or in securing or retaining employment. As a result, they are often not well connected to social support networks, especially if the onset of the disorder occurs early in life. For all these reasons, there is a significant association between mental illness and poverty. According to a study published in 1992, 21 percent of adults with serious mental illness fall below the poverty threshold, compared with 9 percent of the general adult population.[65] As many as half of homeless Americans are said to suffer from schizophrenia.[66] Moreover, the widespread lack of understanding of the nature and implications of these disorders itself serves, independently of financial issues, as a barrier to appropriate care. In any case, without adequate access to mental health services and other social supports, and without adequate financial resources, these individuals and their families may feel that their participation in a research protocol presents a rare opportunity for treatment. Their hope can thus easily overwhelm their understanding of the various risks and the sometimes remote likelihood of direct benefit, even when they are not decisionally impaired.

Informal Caregiving

Although those who struggle with mental disorders that impair their decisionmaking abilities are much like the rest of us when we are ill and vulnerable, in other respects they may be more vulnerable. For example, having enrolled in a study that holds out the prospect of direct medical benefit those struggling with psychiatric illness might feel dependent on the research institution and study personnel, and fear being released from the study and losing their professional support.

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[65] P.R. Barker et al., "Serious Mental Illness and Disability in the Adult Household Population: United States, 1989," eds. Ronald W. Manderscheid and Mary Anne Sonnenschein Mental Health, United States, 1992 (Washington, DC: Department of Health and Human Services, U.S. Government Printing Office, 1992).
[66] P. Wyden, *Conquering Schizophrenia* (New York: Alfred A. Knopf, 1998), pg. no.

In the blizzard of legal considerations and moral subtleties that swirl around the involvement of decisionally impaired persons in research, it is easy to lose sight of the critical role of informal caregivers, such as family and friends, in an individual's decision to undergo treatment or participate in a research protocol. NBAC was moved by the testimony of those who, though often bearing witness to other matters, conveyed powerful stories of long-term commitment to loved ones struggling with the consequences of debilitating diseases. Their testimony raised two issues of particular relevance to NBAC's deliberations: 1) the persistent problem of providing ongoing care, given limited resources, to persons with mental disorders; and 2) the more implicit problem of insufficient sharing of information about patients-subjects between physicians-researchers and caregivers.

As noted above, our health care system has familiar inadequacies in access to health care, especially in continuity of care, appropriate treatment of those with chronic disease, long-term care, and rehabilitation. One particular example of this problem is the way in which information is shared with family members. Families frequently complain that some mental health professionals fail to include them as members of the team caring for the patient. In the words of NBAC Commissioner Patricia Backlar, "currently mental health providers rarely share relevant information with the informal caregiver, nor do they ask families for information germane to treatment or legal decisions."[67] It is important to note, however, that the complex relationships that exist within families in which one member is identified as a having a mental disorder are not always harmonious. As one public comment observed: "The innately complex nature of this field is illustrated by the fact that there may be varying alliances depending upon the individual situation of either patient with family, patient

[67] P. Backlar, "Ethics in Community Mental Health Care: Confidentiality and Common Sense," *Community Mental Health Journal* 32, no. 6 (1996): 517.

with professional, patient with scientist, or any other configuration of these groups." [68] Families of patients may function as allies or adversaries.

To be sure, communication with informal caregivers raises important issues of individual autonomy and patient confidentiality. In fact, bioethical theory has rarely been sensitive to the underlying interpersonal support mechanisms of family and close friends that are often so important to those with long-term illness. Much theorizing has worked against recognizing and involving others in the process of conducting ethical research. Within the autonomy-based framework of our society's regulatory philosophy, there should also be a place for considering the important roles played by those who care for the potential subject.[69] This can be done without undermining or minimizing the critical role of self-determination in human subjects research. In this report, NBAC notes the important role of families and others in decision making about research participation, and makes recommendations on ways to recognize these roles.

The Possibility of Direct Medical Benefit

Many research studies do not hold out the prospect of direct medical benefit to the human subjects involved. Such studies may be necessary, for example, to understand how a particular drug will function in human beings, or to study the subjects' reactions to particular stimuli (e.g., modeling the dynamics of the disease). In these cases the hope is that the knowledge gained will eventually lead to better treatments. While the individual subject may garner certain indirect benefits—such as closer professional attention—such benefits are not produced by the medication, device, or mechanism being studied.

[68]Herbert Pardes, public comments in a letter to NBAC. Columbia University, July 31, 1998 .

[69]Author(s), *Life Choices: A Hastings Center Introduction to Bioethics*, eds. J.H. Howell and W.F. Sale (Washington, DC: Georgetown University Press, 1995), pg. no.

Other studies include drugs or procedures that have the potential of providing direct medical benefit to subjects. Even in these cases, however, it is not possible for researchers to know for certain whether an intervention would be better for the subject than doing nothing (which often occurs in a placebo control study), or whether the subject would benefit more from the currently available standard treatment. The nature of clinical research is that investigators cannot predict with absolute certainty that a particular study will benefit a particular person, or even predict that it will benefit any subject. Indeed, if researchers were certain of the outcome, there would be no justification for doing the research in the first place. Indeed, what is called "clinical equipoise" is commonly considered to be a prerequisite for ethically justified research, that is, the relevant medical and scientific community must be divided, on the basis of available evidence, about which medication or procedure is more effective or safe.[70] Interest in disease for which there is no adequate recognized treatment may wish to participate in a clinical trial. There is always the danger, therefore, that the desire for a treatment may overwhelm the ability to assess the likelihood of benefit or to balance the risks and potential benefits from the drug or device being studied. The situation is further complicated when the primary caregiver is also the researcher. This "therapeutic misconception"[71] may be especially intense for those whose decision making is impaired. And patient-subjects who do not fully understand the differences between research and therapy may feel betrayed or abandoned when their study participation comes to an end.

The Ethics of Study Design

[70] B. Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 141 (1987): 317.

[71] P. Appelbaum et al., "False Hopes and Best Data: Consent to Research and the Therapeutic Misconception," *Hastings Center Report* 17, no. 2 (April 1987): 20–4.

There is considerable commentary on the ethical prerequisites for research involving human subjects, and much of it is represented in the Nuremberg Code and subsequent professional, national, and international codes and guidelines for research. These considerations include whether the importance of the study is great enough to justify the potential harms to which human subjects are exposed, and whether there is any other reasonably effective way to obtain information that would reduce the level of risk to which the subjects are exposed. As well, there is a widely accepted view in the ethics of human subjects research, particularly since World War II, that some knowledge or potential benefit to others may have to be sacrificed if the costs to individual subjects are too great.

Clearly, those who conduct research with human beings have a responsibility to design studies that are both scientifically and ethically sound. Nonetheless, in some contexts, scientific and ethical considerations are not always seen as *jointly* necessary features of high-quality research design. For example, textbooks on research methods and clinical trials rarely integrate ethical guidance with scientific guidance. [72] At the same time, many granting and regulatory groups recognize that ethical research must meet the requirements of scientific validity and importance, and that scientific investigations using human subjects must be conducted according to ethical principles. The shorthand expression, "good science is a prerequisite for good ethics," is a helpful reminder,[73] but may not capture all of the nuances of what is morally required for designing of high-quality research involving human subjects. Freedman helpfully captured the essence of this problem when he argued that scientific validity and

[72] H.J. Sutherland, Eric M. Meslin, and J.E. Till, "What's Missing from Current Clinical Trials Guidelines? A Framework for Integrating Ethics, Science and Community Context," *Journal of Clinical Ethics* 5, no. 4 (winter 1994): 297–303.

[73] D. Rutstein, *Human Experimentation: A Guided Step into the Unknown,* ed. W.A. Silverman (Oxford: Oxford University Press, 1986), pg. no.

scientific value are among the important requirements for ethical research. [74] While all research should be expected to meet these requirements, studies that involve vulnerable persons would seem to warrant particular attention to these requirements. Deciding which design will best answer the research question, which design minimizes risks to the human subjects involved, what procedures will be used, and which subjects will be studied, are all questions that require both scientific and ethical justifications. Philosophers of science have long pointed out that even the selection of one hypothesis over another has moral implications, insofar as there are opportunity costs associated with this choice. Further, the decision to pursue some hypotheses, and the experimental design that accompanies that decision, can have direct moral consequences. As part of its commitment to familiarize itself with research that has been conducted in this area, the Commission requested from investigators a number of relevant protocols and applicable consent forms. This analysis, the details of which are described in Appendix II, identified several issues relating to study design, including recruitment and selection of subjects, and informed consent, that require further attention.

As has been the case for research with other populations, one of the controversial aspects of research involving persons with mental disorders concerns the ethical acceptability of the basic designs of some studies. There are, for example, significant concerns in some quarters regarding study designs that use drugs to stimulate behavioral or physiological manifestations of the disease under study. The term "challenge study" refers to a general category of psychological and pharmacological provocations.[75] Miller and Rosenstein list among these provocations injection of intravenous amphetamine, inhalation of carbon dioxide, and presentation

[74] B. Freedman, "Scientific Value and Validity as Ethical Requirements for Research: A Proposed Explication." *IRB: A Review of Human Subjects Research* 9 (1987): 7-10.

[75] Miller and Rosenstein, "Psychiatric Symptom-Provoking Studies: An Ethical Appraisal." *Biol. Psychiatry* 1997;42 p. 403.

of a phobic stimulus. The principal scientific rationale for conducting psychiatric symptom-provoking studies is "to learn more about the underlying pathophysiological mechanisms responsible for the symptomatic expression of psychiatric illnesses."[76] In these challenge or "symptom-provocation" studies, the goal is to generate disease manifestations in a controlled setting so that they can be more fully understood and so that appropriate interventions can be designed, attempted, and evaluated.

Challenge studies raise several ethical issues, and NBAC heard testimony on this subject by members of the public, scientists, and others on several occasions. Two concerns emerged from the public testimony and the literature. The first concern is whether it is possible to obtain informed consent to participate in a study designed to provoke symptoms. The second concern is whether the relationship between risks and potential benefits can ever justify enrolling individuals in such studies when the protocols include intentionally inducing what would otherwise be considered harmful.

Another study design that has generated a good deal of concern and debate is a so-called "drug holiday," which deprives the patient of medication prescribed for therapeutic purposes. Sometimes also called a "washout" study, this protocol often seeks to return the individual to a medication-free "baseline" state so that behavior can be assessed or new drugs introduced without the confounding factor of other substances already in the person's system. In other protocols of this type a beneficial drug may be withdrawn for purposes of determining, for example, the appropriate length of the drug therapy. Of particular concern are washout studies in which medication is suddenly or very rapidly withdrawn. Given that existing regulations require that subjects be informed of the consequences of their decision to withdraw from a study, and the procedures for the orderly termination of a study,[77] it is

[76]Ibid., 404
[77]45 CFR 46.116(b)(4) (1998).

appropriate to draw attention to this issue. Often the washout and challenge approaches are combined in a single study.

Finally, the use of placebo controls also raises ethical concerns.[78] Usually conducted in a "blinded" fashion so that neither the subject nor the investigator knows which agent is active and which is placebo, ethical placebo studies require that subjects understand that they will not necessarily receive the experimental intervention. As in the other study designs mentioned, there will be special ethical concerns for persons whose decisionmaking capacity is fluctuating or absent at the time of study enrollment since the idea of a nontreatment arm of a study may not be a familiar one. Moreover, as noted above, the tendency to construe all "medical" interventions as having the potential to provide direct medical benefits may especially affect persons whose cognitive processes are impaired and who are particularly dependent upon physicians and medical institutions.

Given that ethical guidelines and regulations are designed for use by IRBs, it is not surprising that, when reviewed in detail, their focus tends to be on the requirement that there be scientific merit in the proposals.[79] As noted previously, however, both scientific and ethical merit is jointly necessary for conducting human subject research. Washout studies, challenge studies, and placebo-controlled studies with subjects who are the focus of this report require special attention to appropriate ethical constraints, both from IRB members and from researchers who work with persons with mental disorders.

The Responsibilities of Researchers and Institutions

[78] D. Addington, "The Use of Placebos in Clinical Trials for Acute Schizophrenia," *Canadian Journal of Psychiatry* 40 (1995): 171–6; K.J. Rothman and K.B. Michels, "The Continued Unethical Use of Placebo Controls." *New England Journal of Medicine* 331 (1994): 394–398.
[79] H.J. Sutherland et al., 297.

The investigator is the key player in our research system with respect to the protection of human subjects. Indeed, unless individual clinical investigators understand their ethical responsibilities, no regulatory system will function properly. Many of the central issues addressed in this report—standards for decisionmaking capacity, assessment of risk of harms and potential benefits, techniques for improving informed consent, recognition of the involvement of family members and friends—turn on the integrity, compassion, and professionalism of the research physician as well as on his or her ability to conduct high-quality science. No matter how many regulations are put in place or guidelines are written, and no matter how intense the scrutiny by IRBs or other authorities, there can be no substitute for the ongoing commitment by researchers and the institutions in which they work to ethically appropriate behavior throughout the research process. This is true not only during protocol planning and development, but throughout the trials themselves.

There is no "right" to conduct research with human subjects. It is a privilege conferred by society on researchers who are prepared to undergo rigorous scrutiny of their proposed studies. Nevertheless, researchers are under enormous pressure to find treatments for diseases that cause much suffering; thus, there can be a tendency for besieged researchers to view human participation in research as an obligation to society. This thinking is not simply misguided, but morally untenable and dangerous.

Researchers should be in the habit of asking the following questions: Does the scientific importance of my work justify asking people to participate as subjects in my research protocol? Should this patient be recruited into my study? Are the risks and potential benefits of study participation acceptable for this patient? Does this patient have the capacity to decide about participation in this study? Does this patient understand the nature of the research? Is his or her agreement to participate wholly informed and voluntary? Is he or she unusually vulnerable to the therapeutic misconception? The ethically responsible scientist is expected to carry the dual burden

to advance knowledge that can improve the human condition and, at the same time, to recognize the absolute imperative to treat human research subjects with the utmost care and respect.

Many of those who oppose additional special protections note that the research environment is in fact often more beneficial than the usual clinical setting for persons who are ill. As research subjects, they might not only be receiving "cutting edge" treatment as well as standard therapy, but their conditions are probably going to be monitored more carefully than is usually the case. Furthermore, many research participants could not otherwise afford the highly specialized attention available in many protocols.

While there is some truth to these claims, prospective involvement in a study should not be presented or perceived simply as a substitute for health care or as a source of better health care. Further, using the research system as a supplement to a health care system that may not be accessible to many cannot be the principal justification for enrolling human subjects in research protocols. The context of research and health care must not be confused, if for no other reason than that the primary goal of the former is to expand medical knowledge and improve future treatment for particular disorders, and the primary goal of the latter is to provide immediate medical assistance.

Although many have accepted the wisdom of Henry Beecher's observation more than three decades ago that the most important protection for human research subjects is the personal moral character of the researcher,[80] it would be unfair and unrealistic to expect individual clinicians, who often face multiple conflicts of interest, to both recognize and resolve by themselves the complex moral problems arising from the use of human subjects in research trials. It is not adequate to focus these ethical

[80] H.K. Beecher, "Ethics and Clinical Research," *New England Journal of Medicine* 274 (1966): 1354–60.

responsibilities only on the individual investigator who in fact functions within a much broader research environment.

The responsibility for ensuring that the rights and welfare of huma n subjects are protected, therefore, also falls on the investigator's research community, department, or institution. Specific responsibilities include, but are not limited to, educating investigators about the ethics of research and the protection of human subjects, and monitoring, as appropriate, investigators' behavior in relation to the human subjects in their ongoing research. IRBs, for example, as they are presently constituted, do not discharge all of their responsibilities simply by approving an investigator's research protocol. As we will discuss more fully below, IRBs also have considerable authority to review and monitor the research itself.

The Structure of This Report

Three analytical chapters follow this introductory chapter. Chapter 2 focuses on informed consent and decisionmaking capacity. Chapter 3 addresses the issues of advance planning and surrogate decision making, and Chapter 4 presents an analysis of assessment of risks and potential benefits. The final chapter presents NBAC's recommendations for research involving persons with mental disorders that may affect their decisionmaking capacity.

In making these recommendations, NBAC is acutely aware of the already considerable burdens placed upon dedicated clinical scientists and research centers. Some of the recommendations will undoubtedly require a greater investment of resources to enhance the protection of human research subjects. These new investments will be required to strengthen IRBs at the local level, federal offices charged with ensuring compliance with federal regulations regarding human subjects protections, and the National Institutes of Health (NIH) and other relevant federal research agencies. If important research that will benefit society is to flourish, it can

only do so in an environment that adheres in the strictest possible manner to the values and rights that are so central to our society. NBAC believes that, in the long term, such investments will result in increased public support for biomedical research and improved therapies for individuals with mental disorders.

Chapter Two: INFORMED CONSENT AND LIMITATIONS ON DECISIONMAKING CAPACITY

The Centrality of Voluntary and Informed Consent

The principal topic addressed by this report—what are the ethical requisites for research involving persons with mental disorders that may affect their decisionmaking capacity?—raises fundamental questions about governmental and professional regulation of all research with human subjects. Although public attention in the United States to the ethics of research involving human subjects traces its history to the revelations in the trial of the Nazi doctors five decades ago at Nuremberg, the widespread acceptance of the necessity of public oversight of research was not evident for another two decades—arising from the disclosure of ethical lapses in the United States[81] and elsewhere.[82] The regulatory structure (as embodied in 45 CFR 46) and professional norms that have evolved over the past 30 years in the United States have been built on a central premise of the need to ensure adequate respect for research subjects and to protect them from unwarranted harm and exploitation. The result has been a system of prior review of research protocols by Institutional Review Boards, or IRBS, to ensure their scientific and ethical quality and thus to weed out protocols that would expose subjects to inappropriate risks, exploit them, or lack adequate consent.

In recent years, some have argued that ensuring access of all groups to experimental treatments should also become a goal of research regulation.[83] In their view, insistence on obtaining the maximum benefit from research while minimizing the risk of harm to subjects unduly restricts some patients from obtaining new although experimental medical interventions for their conditions. Thus they argue that

[81] H.K. Beecher, "Ethics and Clinical Research," 1354–60.

[82] M.K. Pappworth, *Human Guinea Pigs: Experimentation on Man*,(Boston: Beacon Press, 1968).

[83] See the discussion in Carol Levine, Vanderpool volume, need to complete per J.Childress.

regulatory requirements should be adjusted to allow patient-subjects, especially those for whom existing therapies are inadequate, greater access to participation in research protocols.

While obvious differences exist between these two perspectives—protection versus access—there is nevertheless widespread agreement by both sides on the need for voluntary informed consent of research subjects. The landmark Nuremberg Code, for example, makes such consent the first and essential requisite of ethical research. Similarly, the current demand for greater access to participation in research protocols rests on a model of respect for persons and patient self-determination. In either view, the basic presumption is that research protocols are not acceptable if subjects have not had the opportunity to be informed about the methods, objectives, potential benefits, and risks of research, and to decide whether or not to participate in a voluntary and informed fashion.[84]

Plainly, then, the capacity of the human subject to participate in this process of informed decision making is a critical component , but not the total corpus, of the present system of public oversight of biomedical and behavioral research. Under a strict "protection model" those who lack the capacity to give informed consent, or whose capacity to do so is uncertain, may be excluded from participation as research subjects. In this model there would correspondingly be fewer opportunities to assess promising new clinical approaches to the diseases from which they suffer. Such exclusion under the strict protection model may seem appropriate since the underlying principle is that it is better to protect subjects (who may be unwilling participants) from risks of harm, even at the cost of slowing the progress of scientific investigation and medical advances. The additional cost and the obvious dilemma presented by the strict protection standard is that research leading to therapies for those disorders would

[84]Of course, in some circumstances a surrogate may appropriately authorize a person's participation in research when that person lacks the capacity to decide for himself or herself.

be slowed as a consequence of the limited capacity of those who suffer from such disorders to consent to participate in such research.

Conversely, under the "access model" a total barrier to research for persons with mental disorders is suspect precisely because it would prevent some people from obtaining the potential benefits that such research might offer them, either directly as a result of participating in the research or indirectly as a result of the improved understanding of their illness and of methods for treating it that may result from the research in question. From either perspective, however, informed consent is essential and therefore decisionmaking capacity is a pivotal issue that must be addressed.

Persistent Decisional Impairments

Voluntary, informed consent is normally an essential feature of ethically and legally acceptable research. It embodies the respect for persons that is one of the most fundamental principles on which all physician-patient interactions are based, and it is also seen as one of the critical means of protecting people from unwarranted research risks. As a general rule, therefore, the basic threshold that qualifies an individual for participation in the informed consent process is an adequate level of decisionmaking capacity. Throughout this report the term "capacity" is used rather than the term "competence" (although the two are often used interchangeably by others), because the latter often refers to a legal determination made by a court, and the former refers to a clinical judgment.

Individuals whose capacity to make decisions is uncertain must be evaluated by a qualified professional to assess, as well as possible, that capacity. Following a proper assessment, a person lacking the capacity to make informed decisions may be said to be "decisionally impaired," a condition that can result from a variety of causes including medical illnesses, cognitive difficulties, or constraints on personal freedom due to institutionalization or dependency upon those who provide one's treatment. The

specific concern of this report, however, is with persons whose decisional impairments may be related to the presence of what we currently understand to be a mental disorder.

In a certain sense, all of us are decisionally impaired at various times in our lives. When we have been exposed to anesthetic agents, when we have had too little sleep, when a life event disrupts our equilibrium, or when we have over-indulged in alcoholic beverages, our ability to process information and weigh alternatives in light of our values is likely to be reduced. These acute but temporary forms of decisional impairment are not usually matters of concern, because decisions about participation in a research project can normally wait until the impairment has passed. [85] Rather, the impairments that raise the greatest concern are those that persist or can be expected to recur. Reference to a decisional impairment in this report relates principally, but not exclusively, to a relatively persistent condition, that is, a condition that is ongoing or that may periodically recur. There are other sources of decisional impairment that are normally more temporary, such as the transitory side effects of medical treatment, but that might also call for special planning if participation in a research protocol is being considered. Some of the discussion and recommendations in this report may be relevant to these other factors that may affect decisionmaking capacity but, again, the primary concern of this report is with the potential effect of neurologic or psychiatric conditions on the decisional capacity of potential research subjects.

It is neither ethically acceptable nor empirically accurate to presume that individuals with ongoing mental problems are decisionally impaired. Less obviously, it

[85]The ethical problems of conducting research in emergency settings, in the face of the acute loss of decisionmaking capacity that often accompanies admission to a hospital emergency room, has recently been the subject of new federal regulation. The regulations promulgated by the Food and Drug Administration (FDA) permit a narrow exception to the informed consent requirement for emergency research involving serious conditions for which "current treatment is unproven or unsatisfactory." Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research, Final Rules, 61 Fed. Reg. 51497, 51499 (1996) (codified at 21 C.F.R. 50.24).

is also inappropriate to suppose that those who exhibit some decisionmaking deficit cannot be helped to attain a level of functioning that would enable them to be part of a valid consent process. Once these facts are recognized, the special ethical obligations of scientific investigators and institutions sponsoring or carrying out research with persons who may be decisionally impaired become apparent.

Not only must psychological and medical factors affecting these potential research subjects be taken into account, but a full understanding of the nature of their impaired decision making is required. As previously noted, even those who would not normally be considered to be suffering from a decisional impairment may become disoriented if suddenly thrust into the role of a patient, with all of the attendant social inequities and feelings of vulnerability. Persons with a tendency toward impaired decision making due to a mental disorder may experience the consequences of institutionalization in an even more pronounced manner. Therefore, the conditions under which a consent process takes place, including how information is presented and who is responsible for obtaining consent, can be critical in influencing the quality and therefore the ethical validity of the consent obtained. Appreciating these different perspectives may also provide practical insights that can improve the process, such as the use of peers (other persons with similar mental disorders who have already participated in the research) and/or their advocates in the consent encounter, or the use of written forms to clarify the research details. It is imperative that all those who are engaged in the approval and conduct of research with persons with mental disorders enrich their appreciation of the importance of context in the consent process and thus set an appropriate foundation for ethically acceptable research in this population.

Decisional Impairment and Incapacity

The use of the term “impaired decisionmaking capacity” implies a condition that varies from statistical or species-typical normalcy, especially in the context of

discussions about the ethics of human subjects research. In this sense, for example, normal immaturity should not be regarded as a decisional "impairment" since the very young cannot be expected to have achieved the normative level of decisionmaking capacity. Conversely, normal aging need not involve impaired decision making, and assuming such an impairment is pejorative.

Therefore, "decisional impairments" refers to a limitation or an incapacity that is not part of normal growth and development. For example, senile dementia and schizophrenia are conditions that deviate from regular developmental patterns (e.g., dementia is not part of the normal aging process) and are not captured under regulatory categories intended to address periods in the life cycle (e.g., fetuses and children) or certain defined groups (e.g., pregnant women or prisoners).

In practice, it is not usually difficult to determine whether a person lacks all ability to make decisions, so findings of incapacity in this global sense are not often subject to much disagreement. Much more challenging (and the subject of numerous "hard cases" in the law) is determining whether someone with limited decisional capacity has sufficient capacity to make a particular choice, thereby demonstrating a level of capacity that one, on moral principle, could honor.

Individuals who have some cognitive deficit that renders them incapable of making some treatment decisions may nevertheless be quite functional and independent in activities of daily living. Having a decisional impairment need not imply a particular social or legal status. As a functional term, decisional impairment is neutral with respect to other particular characteristics an individual may possess. As Grisso and Appelbaum have noted, what counts as impaired decision making is partly determined by the standard of competence that is chosen.[86] Persons who are

[86] T. Grisso and P.S. Appelbaum, "Comparison of Standards for Assessing Patients' Capacities to Make Treatment Decisions," *American Journal of Psychiatry* 152 no. 7 (1995): 1033–7.

institutionalized may not be decisionally impaired, just as those who are not institutionalized may be.

Capacity refers to an ability, or set of abilities, which may be situation- or context-specific. There is a growing consensus that the standards for assessing capacity include the ability to evidence a choice, the ability to understand relevant information, the ability to appreciate the situation and its consequences, and the ability to manipulate information rationally.[87] These standards were developed with a focus on the capacity to consent to treatment, not research. Recently, however, the American Psychiatric Association approved guidelines for assessing decisionmaking capacity in potential research subjects, which substantially rely on these same standards.[88] Whether the context is treatment or research the particular standard or combination of standards selected for assessing capacity will determine what counts as impaired decisionmaking. For instance, when more stringent standards are used, the result could be over inclusive and thereby deprive a large number of people of their rights to make treatment decisions. Thus what counts as decisional capacity is dependent on a subtle set of assumptions and evaluations.

When a standard of capacity has been chosen, one must set the threshold that distinguishes those who meet the standard from those who do not. Of course, different mental disorders may have an effect on decisionmaking capacity in different ways—some, not at all; some, intermittently; some, more persistently. The decision regarding where the threshold of capacity is set is influenced in part by a society's values system. In a liberal democratic society such as ours, in which the scope of state authority over individual lives is strictly limited and subject to careful scrutiny, this threshold tends to

[87] P.S. Appelbaum and T. Grisso, "Assessing Patients' Capacities to Consent to Treatment," *New England Journal of Medicine* 319 (1988): 1625–38.
[88] APA, *Guidelines for Assessing the Decisionmaking Capacities of Potential Research Subjects with Cognitive Impairments* (approved by the APA Board of Trustees, Washington, DC July 1998).

be low. But the selection of a threshold of decisional ability is not wholly a political one, as it must be justified by the individual's ability to satisfy certain benchmarks.[89]

Another facet of decisional impairment that is often encountered in the clinical setting is the variable manifestation of such impairments. The gradual loss of capacity rarely follows a straight line, and in psychiatric illnesses such as bipolar disease, cycles of mania and depression sometimes follow substantial periods of lucidity.

For all of these reasons, determining the proper standards and procedures to measure capacity poses a major challenge in formulating policy on research involving subjects with mental disorders affecting decisionmaking capacity. Persons with such disorders vary widely in their ability to engage in independent decision making. They may retain such capacity, or possess it intermittently, or be permanently unable to make decisions for themselves. Individuals with dementia, for example, frequently retain decisionmaking capacity early in the course of the illness, but with time they may become intermittently and then permanently unable to make their own decisions. Some individuals with cognitive disabilities are capable of making many choices for themselves; others completely lack such capacity.[90]

Because of their moral consequences, incorrect capacity determinations can be inadvertently damaging—an assessment that a capable person is incapable of exercising autonomy is disrespectful, demeaning, and stigmatizing, and it may result in the unwarranted deprivation of an individual's civil liberties. [91] Conversely, a judgment that an incapable person is capable leaves that individual unprotected and vulnerable

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[89]For a fuller discussion of certain strengths and weaknesses of capacity assessment instruments, see E.R. Saks, *Competency to Decide on Treatment and Research: The MacArthur Capacity Instruments* (a paper commissioned for the National Bioethics Advisory Commission, 1998).

[90]See generally David A. Thomasma, "A Communal Model for Presumed Consent for Research on the Neurologically Vulnerable," *Accountability in Research* 4 (1996); 227; ____ Sachs (complete reference here?), et al., "Ethical Aspects of Dementia Research: Informed Consent and Proxy Consent," *Clinical Research* 42 (1994): 403.

[91]Sacks, ibid.

to exploitation by others.[92] In addition, the presence of many marginal cases among members of the relevant populations triggers concern about the ability to make those capacity assessments for many individuals.

It is also important to recognize that investigators seeking to enroll subjects face conflicting interests, and some may become too willing, perhaps unconsciously, to label prospective subjects capable when this will advance their research objectives.[93] Investigators must be alert to the possibility—and to its subsequent ramifications—that a research subject's decisionmaking status may change during the protocol.

NBAC's view is that existing federal policy fails to provide adequate guidance to investigators and IRBs on the many complexities related to capacity determinations in research involving persons who are the subject of this report. Currently, individual IRBs determine (or at least approve) how investigators are to address these matters. Without adequate education and guidance, however, IRB members are likely to, albeit inadvertently, vary criteria too much and fail to institute adequate safeguards for such research.[94] NBAC's review of protocols and consent documents failed to find evidence that researchers provide to IRBs a description of how prospective subjects will be evaluated for their ability to consent (see Appendix II). NBAC, along with some other commentators, supports more systematic and specific federal direction on capacity assessment,[95] not only for defining decisional capacity in the research context but also for developing better procedures for assessing such capacity.

Procedures for Capacity Assessment and Information Disclosure

A capacity assessment process must adequately protect the interests of individuals with conditions that increase the risk of decisional impairment. To address

[92]National Commission, *Belmont Report*, pg. no.
[93]See, e.g., Marsonet al., 45 J. Am. Geriatrics Soc'y 453, 455 (1997). See also Shamoo & Keay, supra, at 373 (1996).
[94]Bonnie, supra, at 109.
[95]E.g., id.

this need a variety of approaches to capacity assessment is endorsed in the literature on research involving adults with cognitive impairment. Many commentators believe that IRBs should, at a minimum, require investigators to specify the method by which prospective subjects' decisional capacity will be evaluated and the criteria for identifying incapable subjects.[96] Evaluating decisional capacity is an even more complex task than the above discussion and most philosophical discussions of capacity suggest. Any assessment tool measures capacity indirectly through manifest performance, and a person's performance does not always adequately reflect his or her capacity or potential. Many factors can inhibit performance, including anxiety or environmental conditions, the quality of the assessment instrument itself, and other characteristics of the assessment process.[97] All of us can attest to the variation on one occasion or another between our actual performance—as on an examination or in a job interview—and our actual capacity. The problem is aggravated in populations whose conditions are partly characterized by fluctuating capacity. The capacity-performance distinction suggests why the context in which the capacity assessment is made (under what conditions or by whom, for example) is so important.

There is divergence of opinion on whether capacity assessment and information disclosure should be conducted by an individual not otherwise connected with the research project. The National Commission recommended that, "where appropriate," IRBs should appoint a "consent auditor" for research involving those persons institutionalized as mentally infirm.[98] IRBs would be authorized to determine whether a consent auditor is indicated and how much authority the consent auditor would have. For example, in research involving greater than minimal risk without the prospect of

[96]E.g., Bonnie, supra; Melnick et al., supra.
[97]See, for example, Grisso T, Appelbaum PS. *Assessing Competence to Consent to Treatment: A Guide for Physicians and Health Care Professionals*, New York: Oxford University Press, 1998.
[98]National Commission. Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm, pp. 8-20

direct benefit to the subjects, the National Commission recommended that the auditor observe and verify the adequacy of the consent and assent process, and in appropriate cases observe the conduct of the study to ensure the subjects' continued willingness to participate.[99] The Department of Health, Education and Welfare (DHEW) regulations proposed in 1978 contemplated mandating auditors for all projects involving this subject population, but opposition to this proposal reportedly was one reason the regulations never became final.[100]

More recent commentary includes a spectrum of views on the need for an independent consent auditor. Some echo the National Commission's view that a requirement for an independent evaluator becomes increasingly justified as net research risks to subjects increase. A team of Canadian scholars took this position in its recent recommendations on dementia research,[101] noting that the role of a consent assessor/monitor ordinarily can be filled by a researcher or consultant "familiar with dementias and qualified to assess and monitor competence and consent in such subjects on an ongoing basis." The individual should be knowledgeable about the project and its risks and potential benefits. If, however, the research team lacks a person with these qualifications, if there is "a real danger of conflict of interest" for team members who might evaluate and monitor capacity, or if the project involves greater than minimal risk and no prospect of direct benefit to subjects, an independent assessor/monitor should be appointed.[102]

Others also appear open to the general use of outside observers and examiners. Recent guidelines adopted by the Loma Linda University IRB state, "[c]onsent observers who are independent of the investigator and of the institution will be

[99]Ibid. p. 15.
[100]This source does not support the proposition, but rather asks for public comments on the use of consent auditors—another source should be identified.
[101]Keyserlingk, et al., supra.
[102]Id. at 343-44. See also Melnick, et al., supra.

required by the IRB in those conditions where the potential subject's decisionmaking capacity is suspect."[103] In testimony before NBAC, representatives of Citizens for Responsible Care in Psychiatry and Research recommended that "[a]n independent psychiatrist . . . determine the capacity of [the] potential participant to comprehend the risks and benefits of enrolling in the proposed research study."[104] Recent articles also endorse the participation of a "special research educator" in the disclosure and decision process, particularly to ensure that prospective subjects understand when advancement of general knowledge is the primary goal of the project at hand.[105]

A strong case has also been made for an independent patient-advocate's involvement in making capacity determinations, as well as in assisting and monitoring decision making by family surrogates who are acting for incapable persons. Legal analyst Philip Bein notes that courts have demanded relatively strict procedural safeguards in the context of imposed psychiatric treatment and sterilization for persons with mental disabilities. He makes the following argument for a similar approach in the research context:

> As with psychotropic medication and sterilization, several distinct features of experimentation suggest the need for special protections. First, the history of medical experimentation has been characterized by significant incidents of abuse, particularly where members of vulnerable populations have been enlisted as subjects. Second, the interest of medical researchers in securing participation in the experiment often conflicts with their duties as treating

[103]Orr, Guidelines for the Use of Placebo Controls in Clinical Trials of Psychopharmacologic Agents, 47 Psych. Services 1262 (1996).
[104]Shamoo & Sharev, Unethical Use of Persons With Mental Illness in High Risk Research Experiments, 2 BioLaw S:23 (1997).
[105]DeRenzo, The Ethics of Involving Psychiatrically Impaired Persons in Research, IRB, Nov.-Dec. 1994. In a study of this approach, researchers found that the participation of a trained educator increased the comprehension of psychiatric patients asked to enroll in research. Appelbaum, et al., False Hopes and Best Data: Consent to Research and the Therapeutic Misconception, Hastings Center Rep., April 1987, at 20.

> physicians to inform, advise, and act in the best interests of their patients. Third, experimentation is inherently highly intrusive and dangerous, as the nature and magnitude of risks involved are largely unknown and unknowable.[106]

Bein further suggests that courts have not demanded such safeguards for decisions on life-sustaining treatment, based on the comparative rarity of the potential abuses just described. He also argues that an IRB-administered system of patient-advocates would provide inadequate oversight because such a system would be too responsive to institutional interests.[107]

Other recent commentary proposes more diverse methods for avoiding inappropriate capacity determinations. Legal scholar Richard Bonnie opposes a federal requirement for any specific procedure, contending instead that "the regulations should provide a menu of safeguards" from which IRBs could choose, including "specially tailored follow-up questions to assess subject understanding, videotaping or audiotaping of consent interviews, second opinions, use of consent specialists, or concurrent consent by a family member."[108]

The American Geriatric Society (AGS), in its position statement, “Informed Consent for Research on Human Subjects with Dementia,” suggests that capacity to give informed consent “should be assessed in each individual for each research protocol being considered.” The AGS suggests that the ability to give informed consent to a research protocol is task-specific, and not automatically conferred on individuals affected by dementia.[109]

Many groups advise the involvement of a trusted family member or friend in the disclosure and decisionmaking process. For example, AGS states that investigators

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[106]Bein, supra, at 747-48.
[107]Id. at 762.
[108]Bonnie, supra, at 110.
[109] The American Geriatrics Society, “Informed Consent for Research on Human Subjects with Dementia.” J Am Geriatr Soc Oct. 1998; 46: 1308-1310

should rely on traditional surrogates to assist in research participation decisions because the surrogate has “loving and intimate knowledge of the subject’s wishes or value system.”[110] Capable subjects reportedly are often willing to permit such involvement. Dementia researchers frequently adopt a mechanism called "double" or "dual" informed consent when the capacities of prospective subjects are uncertain or fluctuating.[111] This approach has the virtue of providing a concerned back-up listener and questioner who "may help the cognitively impaired individual understand the research and exercise a meaningful informed consent."[112] However, others have suggested that the presence of a caregiving relative could in some cases put pressure on subjects to enter a research study.[113]

Another suggestion is to require a two-part consent. In this process, information about a study is presented to a prospective subject and a questionnaire administered to determine the individual's comprehension. The subject is then provided with a copy of the questionnaire to refer to as needed. If the individual initially fails to demonstrate an adequate understanding of the material, written or oral information is presented again, and the subject is re-tested. This process is likely to yield more accurate judgments of subject capacity than a less systematic and rigorous inquiry.[114]

Finally, numerous ideas have been offered to make information more accessible to subjects capable of exercising independent choice. Simple perceptual aids, such as increasing the type size of printed material, may enhance the ability of elderly subjects to comprehend the necessary information. Information can also be delivered through

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[110] The American Geriatrics Society, “Making Treatment Decisions for Incapacitated Older Adults Without Advanced Directives.” J Am Geriatr Soc 1996; 44: 986-987

[111] High, et al., supra. See also Bonnie, supra, at 110.

[112] Karlawish & Sachs, Research on the Cognitively Impaired: Lessons and Warnings from the Emergency Research Debate, 45 J. Am. Geriatrics Soc'y 474, 477 (1997).

[113] Id.

[114] Ratzan, Technical Aspects of Obtaining Informed Consent from Persons with Senile Dementia of the Alzheimer's Type, in Alzheimer's Dementia: Dilemmas in Clinical Research 123 (Melnick & Dubler eds., 1985) (citing Miller & Willner, The Two-Part Consent Form, 290 New Eng. J. Med. 964 (1974)).

videotape, slides, or pictorial presentations. Another promising suggestion is for investigators to ask representatives of the affected population to critique drafts of information materials prior to their actual research use. [115]

The literature offers fewer suggestions for ensuring genuine voluntariness. The current Declaration of Helsinki includes a provision advising "the physician obtaining informed consent for the research project [to] be particularly cautious if the subject is in a dependent relationship on him or her or may consent under duress." In these circumstances, "informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship."[116] NBAC holds the view that, to guard against pressure from family or other caregivers, someone should discuss separately with consenting subjects their reasons for participating. Again, the issue is whether a research team member, independent evaluator, or IRB representative should be given this responsibility.

Substantive Requirements for Research Decision Making

An autonomous choice to enter a research study is both informed and voluntary. To be capable of informed choice it is generally agreed that a prospective subject should demonstrate the ability "to understand the nature of the research participation; appreciate the consequences of such participation; exhibit ability to deliberate on alternatives, including the alternative not to participate in the research; and evidence ability to make a reasoned choice."[117] Subjects also should "comprehend the fact that

[115] Melnick, et al., supra.

[116] World Medical Association, supra.

[117] High, et al., Guidelines for Addressing Ethical and Legal Issues in Alzheimer Disease Research: A Position Paper, 8 Alzheimer Dis. Assoc. Disord. 66, 69 (Supp. 4, 1994). In discussing decisional capacity in the research context, many writers also cite the President's Commission's requirements for treatment decisionmaking capacity: (1) possession of a set of values and goals; (2) ability to communicate and comprehend information; and (3) ability to reason and deliberate about the choice at hand. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Making Health Care Decisions: A Report on the Ethical and Legal Implications of Informed Consent in the Patient-Practitioner Relationship 60 Washington , DC: US Government printing Office (1982).

the suggested intervention is in fact research (and is not intended to provide therapeutic benefit when that is the case)," and that they may decide against participation "without jeopardizing the care and concern of health care providers." [118]

There is consensus that decisional capacity requires a certain level of cognitive ability. Less agreement exists on whether subjects should be judged incapable if they lack affective appreciation of the choice before them. In a recent article, Carl Elliott argues that some depressed persons "might realize that a protocol involves risks, but simply not *care* about the risks," or "as a result of their depression, may even *want* to take risks" (italics in original). [119] Elliott believes that judgments about a person's capacity to consent to research should take into account emotional attitudes like these. He also proposes that subjects failing to exhibit a "minimal degree of concern for [their] welfare" should be deemed incapable of independent decision making. Others oppose this position, contending that such an approach could represent excessive paternalism toward persons diagnosed with mental disorders, that insufficient data exist on the extent of incapacitating emotional impairment among depressed persons, that affective impairment is difficult to assess, and that normative consensus is lacking on "how much impairment we as a society are willing to accept before we consider someone incompetent."[120]

It is generally agreed that a prospective subject's capacity to decide whether to participate in a particular research project cannot be determined through a general mental status assessment.[121] Instead, investigators must develop and present the specific material relevant to that project and evaluate the prospective subject's

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[118]Melnick, et al., Clinical Research in Senile Dementia of the Alzheimer Type, 32 J. Am. Geriatrics Soc'y 531, 533 (1984).
[119]Elliot, Caring About Risks, 54 Arch. Gen. Psych. 113 (1997).
[120]Appelbaum, Rethinking the Conduct of Psychiatric Research, 54 Arch. Gen. Psych. 117, 119 (1997). See also Hirschfeld, et al., Protecting Subjects and Fostering Research, 54 Arch. Gen. Psych. 121 (1997).
[121]High, et al., supra; Marson, Determining the Competency of Alzheimer Patients to Consent to Treatment and Research, 8 Alzheimer Disease and Assoc. Disord. 5 (Supp. 4, 1994).

understanding and appreciation of that information. [122] In its 1998 report on "Research Involving Individuals with Questionable Capacity to Consent," a National Institutes of Health panel also concluded that "a key factor in potential participants' decision-making is their appreciation of how the study applies to them (in the context of their lives)."[123] Like other commentators, the NIH panel endorsed a "sliding-scale" approach to decisional capacity in the research setting. [124] This approach demands an increasing level of understanding and appreciation as study risks increase and potential benefits to subjects decrease.[125] Similarly, some suggest that many prospective subjects incapable of independent research decision making remain capable of selecting a research proxy, since "the decision-making capacity that is required to designate a proxy is far less than the capacity required to understand a detailed protocol."[126] The level of capacity required to appoint a proxy need not be as great as that which would be required to consent to participate in research.

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[122] The Common Rule provides that the information given to a subject "shall be in a language understandable to the subject or representative." A subject may not be involved in research without first providing legally effective informed consent, which requires that consent is sought in circumstances that allow the prospective subject or representative "sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." Moreover, to meet the general requirements of informed consent the Common Rule requires that the following information regarding the research to be provided to the prospective subject: (1) that the study involves research; (2) the purposes of the research; (3) the expected length of time of research participation; (4) the procedures to be performed and which, if any, are experimental; (5) reasonably foreseeable risks and discomforts; (6) reasonably expected benefits to subjects or others; (7) alternatives, including treatment, that could benefit the individual more than research participation; (8) the level of confidentiality protecting any identifiable information recorded on the subject; (9) whether compensation and medical treatment will be available for injuries resulting from research; (10) the identity of the person(s) to notify if the subject has questions or suspects research-related injury; and (11) that participation is voluntary, refusal will not be penalized, and participation may cease at any time without penalty. *See* 45 C.F.R. 46.116 (1998). See 45 C.F.R. 46.116(b) (1998) for additional information that must be provided to a prospective subject, when appropriate, such as information about additional costs that a subject may incur as a result of participation in research.

[123]National Institutes of Health Panel Report, "Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs)," February 27, 1998, p. 4.

[124]Ibid.

[125]Elliott, Mentally Disabled and Mentally Ill Persons: Research Issues, in Encyclopedia of Bioethics 1760 (W. Reich ed., rev. ed. 1995); Appelbaum, Drug-Free Research in Schizophrenia: An Overview of the Controversy, IRB, Jan.-Feb. 1996, at 1; Annas & Glantz, Rules for Research in Nursing Homes, 315 New Eng. J. Med. 1157 (1986). See also Schafer. A., "The ethics of the randomized clinical trial." New England Journal of Medicine 307;(12):719-24, (1982).

[126]Sachs, et al., supra at 410.

Besides being an informed one, a decision to enter research should be voluntary. The Nuremberg Code provides descriptive characteristics of a voluntary decision,[127] and the National Commission's *Belmont Report* characterizes a voluntary decision as "free of coercion and undue influence." According to the *Belmont Report*, "[c]oercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence . . . occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance." In addition, the *Belmont Report* notes, an inducement that is not overly persuasive to most adults could unduly influence the judgment of vulnerable subjects. The National Commission acknowledged that terms such as “unjustifiable external influence” or “excessive reward” cannot always be precisely defined, but that "undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would be otherwise entitled."[128]

Due to its limited congressional mandate, the National Commission considered potential pressures to enroll in research on institutionalized persons only. Recent commentary favors expanding this concern to all persons with mental disorders, regardless of where they live, because they are especially vulnerable to similar pressures.[129] Prospective subjects with mental disorders living in the community frequently rely heavily on the assistance of professionals and family members and may perceive research participation as essential to maintaining the approval of their caregivers.[130] Nevertheless, there remains considerable support for retaining special

[127]See p. 5, above.
[128]National Commission, *Belmont Report*, 6.
[129]Bonnie, supra; Levine, Proposed Regulations, supra.
[130]Relatives may view research participation as improving their own chances for avoiding conditions that appear genetically linked or as a means to reduce their caregiving burdens. Keyserlingk, et al., Proposed Guidelines for the Participation of Persons With Dementia as Research Subjects, 38 Perspect. Biol. Med. 319 (1995).

protections to persons in residential facilities due to their near-complete dependence on the good will of the staff.[131]

A final element of decisional capacity, implicit in the above discussion, is the subject's continuing ability—during the research protocol—to make a voluntary and informed choice to continue to participate. Some persons with certain psychiatric disorders can issue an adequately informed and voluntary consent to participate in a study, but subsequently lose their capacity for independent choice. As a result, they become unable to exercise their right to withdraw from a study. Study designs must, therefore, provide for this contingency.

There is some indication from the Commission's review of protocols that practices in the field may not adequately reflect these concerns. Several protocols and corresponding consent forms gave the impression that investigators capitalized on their positions in order to obtain willing subjects. One such protocol reported that "As the PI is the Director of the Department's Out-Patient Psychiatric Division, he is in a good position to ensure a steady flow of patients into the study." Though the consent forms contained language intended to inform subjects that their right to treatment would be unaffected by a refusal to participate in research, persons with mental disorders that may affect decisionmaking capacity who are seeking treatment may nevertheless feel indebted to the provider, or suspect that they are confronted with a quid pro quo--research participation for treatment. For example, one of the protocols reviewed by NBAC offered free health care to persons who would enroll themselves in the research. Neither of the protocols discussed here described methods for ensuring voluntary, uncoerced participation.

[131]Elliott, supra; High & Doole, Ethical and Legal Issues in Conducting Research Involving Elderly Subjects, 13 Beh. Sci. & L. 319 (1995). See also American College of Physicians, Cognitively Impaired Subjects, 111 Ann. Intern. Med. 843 (1989).

The particular instrument and methods used to assess capacity have an important role in determining the outcome of such an assessment. IRBs should be aware of the special characteristics and implications of particular instruments and methods. Studies involving subjects with fluctuating or declining decisional capacity must include mechanisms to ascertain and address this possibility, including provision for appointment of a representative for subjects who become incapable.[132] The next chapter discusses the issue of appointing representatives to assist in the consent process and considers other factors that must be taken into account when informed consent from the potential subject cannot be obtained.

[132] Appelbaum, Drug-Free Research, supra.

Chapter Three: ASSENT/DISSENT, ADVANCE PLANNING AND SURROGATE DECISION MAKING

For those whose decisionmaking capacity is impaired, truly informed consent may not be achievable but it remains the standard against which all efforts to obtain the ethical participation of individuals in research must be judged. While persons with mental disorders at times are incapable of giving valid informed consent to participate in a research protocol, ethically acceptable research involving such persons is quite possible under appropriate circumstances and with special protections. In considering the special conditions that surround study design and consent processes in such cases, it is important never to lose sight of the need to involve human subjects in the consent process as fully as possible given their individual circumstances. NBAC agrees with the National Commission's conclusion in the *Belmont Report* that respect for persons unable to make a fully autonomous choice "requires giving them the opportunity to choose, to the extent they are able, whether or not to participate in research."[133] In this vein, NBAC recognizes that certain opportunities already exist for maximizing subject choice in research, including the designation of appropriate substitute decision makers. It also recognizes that sensitivity and care must be exercised in establishing policy, lest blanket authority be given to enroll subjects in research without due consideration of the consequences to those subjects.

This chapter discusses three mechanisms through which individuals may be enrolled as human subjects in research protocols, even if they are presently unable to decide for themselves. These mechanisms are: 1) the use of assent and dissent; 2) the use of advance planning and surrogate decision making; and 3) the permission of legally authorized representatives.

[133] *Belmont Report*, supra, at 6.

The Role of Assent and Dissent

The National Commission held that, under specified conditions, researchers could obtain *assent* to research participation from subjects incapable of independent decision making and, on the basis of this assent, enroll them in certain minimal risk studies. In its view, persons are capable of assent if they "know what procedures will be performed in the research, choose freely to undergo these procedures, communicate this choice unambiguously, and [know] that they may withdraw from participation." [134] It defined "assent" as an authorization given by a person "whose capacity to understand and judge is somewhat impaired by illness or institutionalization, but who remains functional."[135] In defining assent in this way, the National Commission explicitly acknowledged that full knowledge of all the risks involved in a particular protocol is not absolutely necessary to enroll subjects in certain minimal risk protocols if they choose freely to participate. "Dissent" was not formally defined by the National Commission, which referred instead to a subject's "objection" to participation.[136]

Not all individuals who lack full decisional capacity can provide assent as defined by the National Commission, though some may satisfy certain elements of the standard.[137] One question is whether the physical or verbal indications of persons deemed incapable of assent should be considered in research decision making A related question is "whether the failure to actively object to participation in a protocol is enough to be interpreted as a tacit or implied form of assent or whether some more affirmative agreement is necessary."[138] According to the National Commission, "mere

[134]National Commission, *Report on Institutionalized Persons*, 9.
[135]National Commission, *Report on Institutionalized as Mentally Infirm*, 9.
[136]National Commission, *Report on Institutionalized as Mentally Infirm*, pp. 8-15).
[137]An empirical study found that many dementia patients incapable of independent decisionmaking were nevertheless "able to provide useful information on their values and preferences that was pertinent to making research enrollment decisions." Sachs, et al., supra, at 410.
[138]Kapp, supra, at 34.

absence of objection"ought not be interpreted as assent,[139] and it recommended requiring the consent of a subject's legal guardian to authorize greater than minimal risk research involving non-objecting subjects incapable of assent. Whether this situation could be adequately addressed through less formal procedural safeguards or by imposing special limits on research risks remains unresolved in the existing literature.

Dissent is also an important concept surrounding a person's involvement in research, regardless of their decisionmaking capacity. The National Commission recommended that an incapable subject's overt objection to initial or ongoing participation precludes research involvement unless: (1) the study offers the subject a prospect of direct benefit *and* a court specifically authorizes the subject's participation, *and* (2) the prospective benefit is available solely in the research context.[140]

In addition, the National Commission recommended procedural mechanisms to apply these substantive provisions. In particular, its report recommended the following: (1) IRBs should have discretion to appoint an independent auditor to verify the subject's assent or lack of objection; (2) independent auditors should be required to monitor the incapable subject's initial and ongoing assent in research presenting greater than minimal risk and no prospect of direct benefit to subjects; and (3) subjects should be removed from the study if they subjects object at any time to this category of research.

Recent commentary generally supports a requirement for subject assent or, at a minimum, lack of objection, except in the unusual case when research participation offers the subject the possibility of direct medical benefits not otherwise obtainable in the clinical setting.[141] Yet not all commentators agree that potential direct medical

[139]National Commission, *Report on Institutionalized Persons*, 14.
[140]National Commission, *Report on Institutionalized Persons*, 7-10.
[141]E.g., Berg, supra; High & Doole, supra; High, et al., supra; Melnick, et al., supra.

benefit should be sufficient to override the resistance (whether verbal or behavioral) of persons lacking decisional capacity regarding research participation.

A Canadian group considering research involving persons with dementia recently noted:

> Faced with an objection by a patient of impaired capacity, the justification advanced for nevertheless imposing the investigational intervention is that it holds out the prospect of direct (therapeutic) benefit. However, it is normally not legitimate to impose even established therapy on a patient refusing it. The case for proceeding may be stronger regarding the incompetent . . . patient who objects, but it is difficult to equate an intervention which is investigational in nature—whatever its potential for direct (therapeutic) benefit—with an intervention "which would be ordered in a purely therapeutic context."[142]

This group therefore was "not fully persuaded" that potential direct benefit provides an ethical justification for compelling an objecting subject's research participation. In this group's view, this "is at best a position in need of further debate."[143] The intermediate Appellate Court in the *T.D.* case (discussed in Appendix I) labeled as constitutionally deficient New York's provision allowing the involvement of an objecting incapable subject in research that offers the potential of direct medical benefit because the state regulations failed to provide patients or their representatives notice and an opportunity to challenge this involvement. [144] Although the constitutional portion of the judgment was eventually set aside by the Court of Appeals, these same provisions would not only be ethically objectionable according to the strict Nuremberg principle, among others, but would also continue to be legally suspect. The legislative

[142] Keyserlingk, et al., supra, at 341, quoting Melnick, et al., supra.
[143] Id. at 342.
[144] *T.D., et al. v. New York State Office of Mental Health, et al.*, 650 N.Y.S.2d 173, 192 (N.Y. App. Div. 1996).

proposal currently being developed in Maryland would bar investigators from conducting research involving a decisionally incapable individual who expresses disagreement with or who refuses to perform an action related to the research.[145]

NBAC believes that once subjects become part of a research study, they must always have the freedom to withdraw at any time without prejudice and without regard to their capacity. It is persuaded, however, that even in this case it is not necessary to always interpret such dissent as permanent. To do so might unnecessarily limit research and fail to accomplish the goal of protection. The following example illustrates this view: consider a study involving certain patients with dementia, in which the only invasive intervention in an otherwise noninvasive long-term study is a single blood draw. Recognizing that some subjects may become irritable and dissent from this procedure—perhaps even actively object, by recoiling from the needle—this dissent, which must be honored, should not necessarily be interpreted as an objection to continued participation in the entire study. Certainly the subject has objected to this portion of the study, at this time. And, as previously noted, this dissent must be respected. Moreover, the researcher who would persist and attempt to take the blood would be acting illegally (by possibly committing battery) and unethically by appearing to cross the boundary from voluntary choice to coercion. However, after a reasonable amount of time, the researcher in this study should not be absolutely prohibited from returning to the patient and ascertaining, with appropriate sensitivity, his or her willingness to now give blood. It is important to recognize and emphasize that the line between ascertaining willingness and badgering a person is a delicate one to walk.

<u>The Role of Advance Planning and Surrogate Decision Making</u>

[145] Office of Maryland Attorney General. Supra, at A-23.

Our society has long accepted the idea that people who have the capacity to decide their affairs should also be able to direct at least some aspects of their future as well. So, for example, the law of trusts and wills allows a person to control the disposition of property even after death. In addition, individuals may anticipate the consequences of a possible period of disability by designating someone, by means of a durable power of attorney, to handle their business and financial affairs during the period of disability. Over the past two decades, these advance planning concepts have been widely accepted in clinical medicine.

One can identify three types of anticipatory decision making in the clinical setting. The first might be called a *projection of informed consent*: a competent patient's decision whether to accept or decline a specific future treatment, made now because the person will be decisionally incapacitated when the treatment decision is to be implemented. A commonplace example is a patient's decision whether to have immediate surgery should a biopsy reveal a malignancy. As a result of anesthesia, the patient would be incapable of informed consent when the decision actually presents itself. Yet the patient's anticipatory decision, made prior to the biopsy, is no less an exercise of informed consent. This type of decision making about discrete, future clinical contingencies likewise occurs when a person fills out a “living will,” the original advance directive document. The typical “living will” is an instruction that describes the specific end-of-life interventions a patient would want to have used (or not) in the event of a terminal prognosis. Despite the difficulty in meshing this kind of instruction with what is often a more complex clinical situation, a “living will” nevertheless can serve as a self-executing embodiment of the person's right to decide about these interventions.

The second type of anticipatory decision might be called a *projection of personal values*, rather than a projection of informed consent. Instead of making a treatment-specific decision meant to bind clinicians in the future, a person provides

guidance for decision makers by emphasizing the comparative importance of different aspects of that person's life. For example, a person might state in an advance directive his or her own view of what constitutes a life of sufficient quality to warrant the most aggressive treatment. This guidance would inform whoever was later deciding on a course of treatment after the person had lost the capacity for informed consent.

The third type of anticipatory decision might be called a *projection of personal relationships*. Just as someone may entrust another with responsibility for financial matters during a potential period of future disability, a person may designate a decision maker for health care matters. The legal instrument by which this designation is accomplished, the durable power of attorney for health care (DPA), has become a familiar feature of the clinical landscape. A recent study found about a nine percent usage rate among residents of nursing homes in several states. [146] This designation reflects trust in the integrity, judgment, and decisiveness of the chosen proxy. Of course, the designation can also be coupled with instructions or guidance about the choices that the proxy might face. Because giving effect to all three types of anticipatory decision making embodies respect for personal autonomy, NBAC believes that all three have a place in research involving persons with mental disorders.

First, a person who has given a valid informed consent to enroll in a particular research protocol should be allowed to continue to participate in that protocol, even after a loss of capacity, or in a future iteration of that or a substantially similar protocol (i.e., including similar procedures and minimal risk) provided that suitable measures are in place to protect the person's welfare during that research study.

Second, a person who embodies in an advance directive his or her wishes about participation in research of certain kinds is entitled to have those wishes respectfully considered. However, this kind of advance directive, which does not reflect

[146]Teno JM. "Changes in advance care planning in nursing homes before and after the Patient Self-Determination Act: report of a 10-state survey." *Journal of the American Geriatrics Society* 45:939-944 (1997).

consideration of specific research risks, cannot itself serve as a self-executing instrument of informed consent or trump limitations on research participation that sound public policy requires. It also does not absolve the investigator and surrogate decision maker of responsibility for assessing the effect on the person's welfare of participation in a particular research protocol.

Third, a person may embody in an advance directive his or her choice of a decision maker concerning research participation. NBAC recognizes that people use advance directives to identify others with whom they have a relationship of trust. NBAC concludes that this relationship in and of itself is sufficient to authorize participation in research studies only under certain conditions.

This summary account of the role of advance decision making in research is not intended to gloss over several important issues, such as whether advance directives can be adequately informed, how to safeguard the subject's right to withdraw from research, and whether anticipatory decision making is a morally defensible basis for permitting otherwise prohibited levels of risk and burden in research involving incapable subjects.

The concept of advance research decision making was initially considered in the 1980s. In his volume on clinical research, Robert Levine discussed the "research living will" as an avenue for competent persons to authorize their future research involvement while they are incompetent.[147] In 1987, the NIH Clinical Center adopted a policy, which is currently under review, in which persons "who are or will become cognitively impaired" are asked to complete a durable power of attorney (DPA) document appointing a surrogate research decision maker.[148] Such decision makers

[147]Levine, R., Ethics and Regulation of Clinical Research (Baltimore: Urban and Schwarzenberg, 2nd ed., 1986) 270-74.

[148]Subjects "not seriously impaired" are viewed as capable of completing a research DPA. If a prospective subject is "so seriously impaired as to be incapable of understanding the intent or meaning of the DPA process, a next of kin surrogate may be chosen by the physician." In addition, if a prospective subject has a previously completed health care DPA or a court-appointed guardian, no research DPA is sought. NIH Clinical Center, supra.

may authorize an incapable subject's participation in research presenting greater than minimal risk that offers the prospect of direct benefit to subjects. In such cases, an ethics consultation is conducted to verify the decision maker's capacity to understand information relevant to the research decision. If no DPA exists, the consent of a court-appointed family guardian is required. Research presenting greater than minimal risk is not permitted for subjects lacking a DPA or court-appointed guardian, except in a medical emergency when a physician may give therapy, including experimental therapy, if in his or her judgment it is necessary to protect the life or health of the patient.

In 1989, the American College of Physicians (ACP) gave qualified endorsement to instruction and proxy mechanisms permitting competent persons to register advance consent to research. According to the ACP, investigators seeking advance consent would be required to disclose to the competent person the usual information on a study's purpose, methods, risks, and potential benefits. Moreover, the ACP recognized a need for greater caution regarding advance research decisions than advance treatment decisions:

> In nonexperimental care, advance directives are generally used by patients to indicate their intent to refuse procedures . . . which they believe will be contrary to their interests. Respect for autonomy creates a strong presumption for adherence to instructions for nonintervention. In contrast, advance directives for research purposes would authorize interventions that do not benefit the subject in the case of nontherapeutic research, or that may not benefit the subject in the case of therapeutic research.[149]

[149] American College of Physicians, supra, at 844.

Accordingly, the ACP took the position that research advance directives "may be abrogated if it is later determined that the proposed research would unduly threaten the subject's welfare."[150]

Despite these cautions and restrictions, the ACP deemed an incapable subject's prior consent an acceptable basis for allowing that subject's involvement in higher risk research than is permitted for other incapable subjects. Its position paper states that incapable subjects who have given only informal instructions to a surrogate decision maker about their research preferences should not be involved in research of greater than minimal risk that offers no prospect of direct medical benefit. In contrast, subjects with formal advance directives may be involved in such studies, as long as the above limitations are observed. NBAC is sympathetic to this general approach; but as we discuss below and in our recommendations, we support the idea of advance planning and the appointment of substitute decision makers for research on mental disorders- not the use of advance directives directly.

Other groups and commentators have expressed general support for advance research decision making without addressing the concept in detail. [151] In reviewing the advance directive's potential application to dementia research, Greg Sachs speculates that it is unlikely that many individuals will prepare research directives. He notes that relatively few people make treatment directives, even though many fear excessive treatment at the end of life. Even fewer will make research directives, he predicts, because "the fear of missing out on being a subject in a promising dementia study, or

[150]For example, the proxy decision maker should withdraw an incapable subject from a study if risks or burdens increase due to changes in research methods, changes in the subject's physical condition, or the incapable subject's lack of cooperation with study procedures. Id. at 844.

[151]E.g., Melnick, et al., supra (endorsing research directives and implying that such documents could authorize otherwise questionable research presenting greater than minimal risk and no prospect of direct therapeutic benefit to subjects); Annas & Glantz (competent person diagnosed with disorder expected to produce incapacity could designate proxy decision maker; such document could authorize participation in otherwise prohibited nontherapeutic studies posing "any risk of harm," but should be used only if instructions are specific and address "reasonably well defined" research and subject retains right to withdraw even after becomes incapable).

of being inappropriately volunteered by one's relatives, is simply not a prevalent or powerful concern."[152]

In light of these various possibilities, many commentators agree that a third-party decision maker should be appointed to withdraw the subject from a study if previously unrecognized risks and burdens become apparent.[153] They differ, however, on the standard that third parties should apply when exercising the subject's right to withdraw from the research that the subject previously authorized.

Some favor withdrawal only when the factual circumstances become materially different from those to which the individuals agreed in directives.[154] Others contend that withdrawal should also occur if it becomes apparent to others that research participation threatens the incapable subject's welfare. According to this position, a research proxy's or surrogate's

> obligation to respect the person's prior wishes is limited by the obligation to protect the person. The function of the [third party decision maker] is to promote what subjects think are their best interests, which necessarily excludes consenting to being intentionally harmed or to being unreasonably exposed to the risk of harm.[155]

An intermediate position argues that an advance directive should be overridden if "no direct benefit is anticipated for the subject and it becomes apparent that enrollment or

[152]Sachs, Advance Consent, supra. Sachs refers to unpublished survey data finding that while 16 of 21 ethicists expressed enthusiasm for advance research directives, only 8 out of 74 investigators agreed that directives would be a workable approach. In a different survey of healthy elderly persons, many respondents indicated they would be unwilling to complete "blank checks" authorizing participation in a wide range of future studies. Respondents were more positive about advance directives authorizing research offering a reasonable prospect of direct benefit, but only if interventions were restricted to the specific procedures, pain, and discomfort set forth in the document. Keyserlingk, et al., supra, at 347.

[153]See, e.g., Moorhouse & Weisstub, Advance Directives for Research: Ethical Problems and Responses, 19 Int'l. J. L. & Psychiat. 107, at 135 ("in the event of the development of unforeseen risks, a change in the subject's condition, or an objection expressed by the incapable subject or a concerned third party," subject's surrogate decision maker must have power to remove subject from study).

[154]Berg, supra, at 22 (surrogate has responsibility to withdraw subject only if research or risk-benefit ratio changes substantially from what subject consented to).

[155]Moorhouse & Weisstub, at 135. See also Shamoo & Sharev, supra, at S:29 (advance directives should not bind a subject to research participation).

continued participation would seriously endanger that subject's welfare to an extent not foreseen by the subject, or even if foreseen, to an extent judged by the substitute [decision maker] to be socially or morally unacceptable."[156] This dispute is related to disagreement on the appropriate scope of a competent person's advance consent to research. Commentators are divided on whether policy should permit an incapable subject to be exposed to otherwise impermissible levels of research risks and burdens based on the subject's prior instructions. Moorhouse and Weisstub contend that directives should be restricted to authorizing research "with a negligible or less than substantial risk."[157] Their position is based on the belief that capable individuals cannot predict with complete accuracy how they will experience research as incapable subjects. These authors also argue that the competent individual's freedom to volunteer for research to advance the interests of others is qualified by society's responsibility to protect vulnerable individuals from material harm.

Addressing dementia research, the Canadian group proposed that research directives should apply to studies offering no direct benefit to subjects only if the risk is minimal or a minor increase over minimal.[158] They suggest one exception to this limit, however: "[i]f a subject who provides a directive specifying a willingness to undergo a higher-risk level also provides evidence of having already experienced a similar level of physical or psychological pain or discomfort in another research setting, then the cap of allowable risk for that subject could be raised accordingly."[159]

Berg, by contrast, supports full implementation of advance research directives without regard to the risk level. She argues, "[b]ecause competent subjects do not have limits placed on the types of research in which they can participate while they remain competent (as long as the protocol is approved by an appropriate review board), they

[156]Keyserlingk, supra, p. 352.
[157]Moorhouse & Weisstub, supra, at 134.
[158]Keyserlingk, et al., supra, at 351.
[159]Id.

should not have limits placed on the types of research in which they can consent, in advance, to participate should they become incompetent."[160] Conversely, when an advance directive refuses research participation, Berg suggests that the subject's refusal could be overridden if a study offers possible direct benefit unavailable in the clinical setting. She fails to explain why concern for incapable subjects' best interests justifies disregarding their directive in one situation and not the other.

A few public policy developments are also relevant. Congress has limited the circumstances in which the Department of Defense (DoD) may accept the "consent" of a legal representative for the research participation of another.[161] Currently, DoD is not permitted to fund research without the informed consent of the subject, or, in the case of "beneficial" research, without first obtaining the informed consent of either "the subject or a legal representative." Thus, Congress has prohibited DoD from conducting research that has no potential direct benefit for the human subjects, unless the subjects themselves provide informed consent—regardless of whether the research risk is minimal. A provision similar to this has governed DoD since 1972.

In 1996, the U.S. Food and Drug Administration adopted new regulations governing research involving incapable subjects in the emergency setting.[162] These regulations allow research to proceed in the absence of consent by a subject or a legally authorized representative, under certain conditions. An IRB may approve such research if it finds and documents that there is no reasonable way to identify prospectively the individuals likely to become eligible for participation; the subjects are in a life-threatening situation and, because of their medical condition, cannot give

[160]Berg, supra, at 22.

[161] 10 U.S.C. § 980 (1997).

[162]Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research; Final Rules, 61 Fed. Reg. 51,498 (1996) (codified at 21 C.F.R. 50.23 and 50.24 (1998)). The DHHS Secretary, at the same time, waived the general requirements for informed consent under conditions that are almost identical to FDA regulations. *See* Waiver of Informed Consent Requirements in Certain Emergency Research 61 Fed. Reg. 51,531 (1996).

their informed consent; the intervention must be administered before consent from a legally authorized representative is feasible; available treatments are unproven or unsatisfactory; the research is necessary to determine the safety and effectiveness of some new therapies; and various other conditions are met.[163] According to agency officials, when IRBs determine that investigators can reasonably identify and seek prospective consent from persons likely to become eligible for a study, "[t]hose individuals who either did not make a decision or who refused would be excluded from participation in the investigation."[164] In response to a public comment describing "the difficult task for potential subjects to imagine the kind of research they would want should they suffer a catastrophic illness," officials acknowledged possible difficulties in implementing the prospective decisionmaking process, but suggested that IRBs could adequately address these matters.[165] As has been noted, this is a problem that applies to all advance directives for research participation.

The State of Maryland has initiated a policy effort relevant to advance research decision making. The draft legislation includes a framework for third-party decisions on research for decisionally incapacitated persons—i.e., research is permitted with consent of an incapable subject's "legally authorized representative." Unlike current federal policy, this proposal specifies who may fill this role. Subject representatives may be, in the following priority order: (1) a research agent designated in an advance directive for research; (2) a health care agent designated in an advance directive for treatment; (3) a surrogate—that is, a family member or close friend—authorized by statute to make health care decisions for an incapable person; or (4) a proxy decision maker designated by the IRB to act as a research decision maker for an incapable person.[166]

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[163] *See* 21 C.F.R. 50.24 (1998).
[164] 61 Fed. Reg. 51498, 51510 (1996).
[165] 61 Fed. Reg., 51498, 51510-11 (1996).
[166] Office of the Maryland Attorney General, supra, Parts VI, VII, VIII, & IX.

Thus, the Maryland draft gives substantial decisionmaking authority to third parties expressly chosen by an individual. In the absence of an instruction directive, only research agents and health care agents are authorized to consent to an incapable subject's involvement in research presenting a minor increase over minimal risk and no expected direct benefit. Only a research agent may authorize an individual's involvement in research presenting more than a minor increase over minimal risk and no direct benefit.

The Maryland draft legislation also recognizes a limited role for instruction directives. A monitor may consent to an incapable individual's participation in research presenting minimal risk and no direct benefit if the individual's advance directive explicitly authorizes such participation. A research agent may permit an incapable subject to be involved in research presenting more than a minor increase over minimal risk only if "the research is unambiguously included in the individual's advance directive authorizing research participation." [167] Thus, otherwise prohibited research risk is permitted based on the prior competent choice of a now incapable subject.

The Maryland draft legislation does not discuss the information that must be disclosed to a capable person making an advance research directive; it does address withdrawal from research, however. Any third party consenting to an incapable subject's participation must

> (1) take reasonable steps to learn whether the experience of the individual in the research is consistent with the expectations of the legally authorized representative at the time that consent was granted, including expectations about potential benefits, if any, and risks presented by the research; and
> (2) withdraw consent if:
> (i) the research was initially determined to present a reasonable prospect of direct medical

[167] Id. at A-32.

> benefit to the research subjects but no longer does so for the individual;
> (ii) the research presents a higher level of risk to the individual than initially expected; or
> (iii) considering all relevant circumstances, continued participation would be detrimental to the individual's well-being.[168]

Although advance research decision making has been widely discussed in the literature and included in some recent state-based policy initiatives, numerous conceptual and practical questions remain. The matter could be made moot if very few persons prepare research directives and if rigorous standards for information disclosure are observed. Further, even in the best circumstances, investigators and IRBs face challenges in providing competent individuals with all the necessary information about a future study. Finally, the literature reveals disagreement on the significance that should be assigned to the competent individual's preferences about future research participation posing greater than minimal risk.

In sum, advance research decision making, although recognized as a potentially useful device, poses difficult issues concerning its scope and effect. In NBAC's view, an advance directive can *never* serve as a "blank check" for future research participation. Indeed, an advance directive may itself serve as a sufficient basis for research participation only in very limited circumstances. That is, those in which the most important information relevant to informed consent about future research participation is already known and is presented to a competent person, who then gives consent, and there is no material change in the research protocol or the person's clinical situation (apart from loss of decisionmaking capacity) by the time that research participation is actually to begin. If the person's willingness to participate in research is stated more broadly—for example, in terms of a desire to participate in

[168] Id. at A-26.

research about a disease—that statement should be given considerable weight by whoever has authority to authorize research participation, but it cannot by itself be considered sufficient for enrollment in a particular study. This type of prospective authorization can provide the basis for enrolling subjects in certain kinds of research involving minimal risk. And, as we will discuss below, prospective authorization provides a necessary ground for enrolling a subject in greater than minimal risk research- so long as a designated third party can be identified. We now turn to this issue.

Legally-Authorized Representatives and Research Decision Making

Surrogate decision makers are frequently mentioned as one solution to ethical problems of enrolling persons from certain vulnerable groups in research. In its recent report on "Research Involving Individuals with Questionable Capacity to Consent," the 1998 NIH panel concluded that, "Individuals with questionable capacity (or clear incapacity) to consent may have a family member and/or legally authorized representative serve as a surrogate, with this role documented during the consent process." The panel further recommended that the surrogate's research decisions reflect, to the greatest extent possible, the individual's views prior to the period of incapacity.[169]

Although the term "surrogate" is frequently used in ethical discussions such as that in the NIH Panel Report, the Common Rule uses the phrase "legally authorized representative" (LAR). The concept of a LAR leaves many unanswered questions. Surrogates may be regarded as individuals who have had prior experience with the individual being represented, but legally authorized representatives (for example, legal

[169]National Institutes of Health Panel Report, "Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs)" February 27, 1998, p. 3.

guardians) often do not have such experience. State laws in a broader arena contain general provisions on the standards and procedures governing appointment of guardians for persons declared legally incompetent. Guardianship, for example, requires a judicial proceeding and ordinarily authorizes someone to make financial , personal, or both types of decisions for the incompetent person. Limited guardianships covering a narrower area of decisionmaking responsibility are also possible.

However, as mentioned previously, relatively few states have laws specifically addressing research decision making by legal guardians or other allowable surrogates. Moreover, existing state legislation limits the involvement of incapable subjects in research in various ways. A number of laws require guardians to obtain specific court authorization to make decisions on a ward's participation in a research protocol. Several states currently prohibit certain types of research on persons with mental disorders, particularly research which presents greater than minimal risk and from which subjects are not intended to benefit. Wichman notes that if an IRB were to approve a study in a state that did not have such a statute, the IRB might choose to invoke certain protections, including additional monitoring of the study, requiring a consent auditor, or requiring educational activities for authorized representatives. [170]

Federal research policy is not intended to preempt or otherwise affect state or local laws applying to research, including those conferring additional protection on subjects participating in research protocols.[171] Thus, investigators and IRBs in jurisdictions with specific laws governing the identity and authority of research decision makers for persons lacking decisional capacity must comply with those laws. Yet in the many states without clear law, it will be left to federal policy, investigators, and IRBs to determine who, if anyone, may act as a surrogate decision maker for a person who lacks decisional capacity. At present, legal guardianship is rarely, if ever,

[170] Ibid. pp. 94-95.
[171] 45 C.F.R. 46.101(f) (1998).

sought in the research setting. Instead, close family members, who may or may not have formal guardianship status, are the customary decision makers when the research participation of incapable adults is sought.

Should federal policy require formal legal guardianship for someone to be considered a suitable surrogate for decision making about research? The underlying question is whether such a requirement is necessary or sufficient to provide adequate protection against inappropriate use of a vulnerable population in research to advance the interests of others. The National Commission recommended that the permission of either a legal guardian or a judge be required to authorize the research participation of subjects institutionalized as mentally infirm in the following situations: the incapable subject objects to participation, or the subject is incapable of assent and the research presents greater than minimal risk to subjects. [172]

Subsequent commentary by others questions whether formal legal proceedings are necessary to provide adequate protection for subjects who lack capacity, particularly those not residing in an institutional setting. As one writer notes, IRBs requiring legal guardianship, "to be on the safe side," could end up contributing to a deprivation of general decisionmaking rights of subjects.[173] Moreover, the guardian appointment process ordinarily will not address research participation issues in any explicit way. In most cases, a judicial decision to confer guardianship status on a particular person is made without consideration of that person's suitability to make decisions regarding his or her ward's participation in research protocols.

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[172]National Commission, Research Involving those Institutionalized as Mentally Infirm, supra, at 11-20. At least one commentator supports a requirement for explicit judicial authorization prior to an incapable subject's enrollment in research if relatives are unwilling to act as subject representatives or if a subject-advocate questions a family surrogate's good faith or decisionmaking capacity. Bein, supra. Others have criticized this view as intrusive, unnecessarily adversarial, and too great an impediment to research. Berg, Legal and Ethical Complexities of Consent with Cognitively Impaired Research Subjects: Proposed Guidelines, 24 J. L. Med. & Ethics 18 (1996); Kapp, Proxy Decision Making in Alzheimer Disease Research: Durable Powers of Attorney, Guardianship, and Other Alternatives, 8 Alzheimer Disease & Related Disorders. 28 (Supp. 4, 1994).

[173]Office for Protection from Research Risks, Protecting Human Research Subjects: Institutional Review Board Guidebook 6-30 (1993). See also High & Doole, supra, at 328.

Dissatisfaction with a requirement for legal guardianship has led to alternative proposals for granting authority to act as an incapable person's representative in research decision making. One option is to allow decisionally capable persons to authorize in advance a specific individual to make decisions regarding their research participation during a future period of incapacity. This device, which is modeled on the durable power of attorney for health care, has the virtue of promoting the capable individual's autonomous views on who is best suited to act on his or her behalf in the research context. Its primary advantage, though, is the explicit authority granted by subjects, who presumably will choose someone likely to express their values and protect their welfare. NBAC appreciates the role of personal values and wishes in making advance decisions about research participation. Designating a surrogate decision maker with whom the subject has a close, trusted relationship is one way to express how those values and wishes should be applied to future decisions regarding research participation. As a practical matter, however, it is unclear whether many individuals will be interested in or willing to complete such a DPA. Moreover, the device cannot be applied to the population of persons with mental disorders who are currently incapable and not expected to recover capacity. Still NBAC accepts that such a practive could, if accepted, result in some individuals appointing LARs explicitly for research purposes.

A second potential source of authority is an existing health care power of attorney. It is doubtful that an individual's choice of a proxy to make treatment decisions in the event of incapacity can fairly be taken as an authorization for research decision making as well. Nevertheless, the choice does manifest a high degree of trust in the proxy, and that evidence of trust may entitle the health

care proxy to a decisionmaking role in research. The NIH Clinical Center policy does allow previously chosen health care proxies to make some research decisions for subjects.[174]

A third alternative is to regard state legislation authorizing family members (and, in a few states, friends) to make certain treatment decisions on behalf of relatives as conferring authority for research decisions as well. It might be argued that such legislation recognizes that important health-related decisions for persons lacking decisional capacity are properly assigned to appropriate relatives. Perhaps it would be reasonable to extend the law's application to a statutory proxy's decision regarding research offering potential health benefit to an incapable subject.[175] Others believe that these laws should not be interpreted so expansively and that amendments or new legislation would be required to provide explicit statutory authority for delegating to relatives decisions about the subject's participation.[176]

A final possible option is to assign such decisionmaking authority based on the simple status of being a close relative or a trusted individual. Support for this alternative especially as regards relatives comes from the long-held tradition in health care of relying on families to make decisions for incapable persons, as well as from the belief that relatives are most likely to make decisions in accord with the incapable person's values, preferences, and interests.[177] This approach is easy to administer; moreover, it apparently has been and continues to be a common practice in many research settings.[178]

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[174]NIH Clinical Center, supra.

[175]Bonnie, supra, at 110. The Maryland Attorney General's Office has so construed the authority of surrogates under that state's Health Care Decisions Act. See letter from Assistant Attorney General Jack Schwartz (July 26, 1995).

[176]Kapp, supra.

[177]This position is endorsed in policy guidelines adopted by Alzheimer Disease Centers in the U.S. See High, et al., ("[u]nless there is statutory or case law to the contrary, family members should be recognized as having surrogate authority without prerequisite appointment as guardians or proxies through the use of instruments such as durable powers of attorney").

[178]Kapp, supra; High & Doole, supra.

Each of these options presents advantages and drawbacks. Requiring judicial involvement may cause unproductive delays and raise the costs of research, and may not always advance respect for and protection of incapable persons. Requiring explicit durable powers of attorney for research poses some practical difficulties, since relatively few persons have or can be expected to complete these documents, and it may not be possible to describe the future research protocol completely. Another question is whether the power of DPAs to consent to research risks for an incapable individual should be equal to the power of competent adult subjects to consent to such risks for themselves. New legislation authorizing relatives or a trusted individual to make research decisions for incapable persons would require action by the states; such legislation would emerge slowly or, in some states, not at all.

All of these alternatives also raise questions about the accuracy with which incapable subjects' values and preferences as competent persons will be expressed by formal or informal representatives.[179] The problem of potential conflicts between subjects' interests and those of their representatives exists as well. Those most likely to act as representatives are family members, who may see the subject's research participation as an avenue "that may lighten the burden of caregiving or lead to treatment from which the family member may benefit."[180] Two empirical studies found some family members willing to allow an incapable relative to be entered in a research study even though they thought the relative would refuse if competent. Some family members also stated they would allow an incapable relative to become a subject even though they would refuse to enroll in such a study themselves.[181] At the same time,

[179]See Sachs, Advance Consent for Dementia Research, 8 Alzheimer Disease & Related Disord. 19 (Supp. 4 1994) ("I think it is fair to assume that most proxies [in the current consent process] know very little about their demented relative's preferences regarding research participation").

[180]Keyserlingk, et al., supra, at 346.

[181]Sachs, et al., supra; Warren, et al., Informed Consent By Proxy, 315 New Eng. J. Med. 1124 (1986). There were also cases in which family members would not allow an incapable subject's participation even though they thought the subject would consent if competent or the family members would enter such a study themselves.

NBAC recognizes that such mechanisms might permit some important research to go forward. Moreover, NBAC is satisfied that the argument for encouraging the involvement of LARs is sound so long as the following components are in place: (1) a clear description of the role and authority of the LAR; (2) a description of certain protections that must be in place in order for an IRB to assure itself that the LAR is appropriately acting on behalf of the incapable persons; and (3) a commitment to the ongoing evaluation of LARs within limits.

The Authority of the LAR

There are two mechanisms by which a LAR can be involved in research decision making. One option might be to allow individuals, while competent, to designate their legally authorized representative to give permission to enroll them in research. This scenario requires the designation of an individual whose authority is limited to research involvement. Given the paucity of experience with research-specific LARs in this country, NBAC recognizes the burden that might be created by recommending that only this method be used. Another option would be to permit existing DPAs (the many thousands of individuals who have already been appointed in this country to be health care decision makers for clinical decisions) to make certain research decisions. In both cases, the authority of the LAR requires careful description and limitation.

Three forms of substantive limits on this authority are commonly endorsed. One is to allow guardians, proxies, and informal surrogates to give valid permission for an incapable person's participation only if the incapable person assents or fails to object to initial or ongoing research participation. The second is to require that third parties make research decisions consistent with the incapable subject's prior instructions issued while competent. The third is to permit LARs to authorize the involvement of incapable subjects only in studies that meet certain risk-potential benefit standards.

Many of the recommendations on research involving persons with mental disorders apply each of these limits, but combine them in a variety of ways.

Protections to Ensure that the LAR Is an Ethically Valid Surrogate for Research Decision Making

Given the limited experience in this country with research-specific LARs (or for extending existing health care DPAs to research), NBAC is unwilling to recommend their adoption without also recommending certain protections and methods for their evaluation. In general, NBAC regards the IRB as the proper locus for determining whether these (or any other) protections are adequate. For an IRB to be assured that an LAR's enrollment of a now incapable person with a mental disorder into a research study is acceptable, the IRB might consider requiring certain procedures.

(1) Documentation that the subjects were competent to designate an LAR. This would involve the independent assessment of the capacity of the subjects, perhaps on more than one occasion, including just prior to completing the documentation assigning an LAR.

(2) Documentation that the subject and LAR understood the scope of the authority being granted to the LAR. Because of its concern that LARs could at times have some significant self interest in enrolling a now incapable person into a study, NBAC recommends a documentation that would enable IRBs to satisfy the designation of an LAR. The documentation referred to here would enable IRBs to satisfy themselves that the now incapable subject and his LAR had reasonably understood the scope of the type of study being proposed.This places considerable emphasis on the degree to which the IRB is assured that the prospective subject (when competent) and his designated LAR understood the difference between research and treatment and, in research that imposes greater than minimal risk, between that which offers the prospect of direct benefit to the subject and that which does not. As noted

below for each of the two other protections listed, the value of this particular protection is in need of ongoing empirical testing and validation.

With regard to the standard by which substitute decisions are made, NBAC suggests the following prioritization scheme. Any wishes previously expressed by the subject authorizing participation in a future study should be honored by the LAR. The more specific the authorization is, the more likely it can be applied to a particular study. In the absence of a prior specific authorization by the subject, NBAC favors, in general, giving priority to those decisions by LARs that approximate most closely the now incapable subject's previously expressed preferences. For example, statements about research "of this kind" or "involving these types of risks" should influence the LAR's decision about enrollment. In the absence of this kind of information, LARs would then be expected to make judgments that are consistent with the subject's best interests. NBAC is acutely aware of the difficulties this approach presents and explains the rationale in somewhat more detail in Chapter 5. Here it only indicates the Commission's general view since it relates directly to the assignment of LARs and the protections associated with this assignment.

Ongoing Evaluation of LARs

The protections listed above could provide the IRB some assurance that the LAR has been assigned in a legally and ethically valid way. However, ongoing assessment of the LAR process would be of considerable value. IRBs intending to permit enrollment of a now incompetent subject on the basis of LAR decisions (regardless of how well documented this process might be) would be strongly encouraged to evaluate the effectiveness of LARs. Such evaluation may be considered part of the procedural requirement that institutions utilize under the mechanisms of audit and disclosure, discussed in more detail below. There would be considerable value in having IRBs report on those studies involving greater than minimal risk

research in which enrollment of decisionally incapable subjects with mental disorders was authorized by an LAR. In the absence of good empirical data about the effectiveness of the LAR mechanism in both permitting scientifically valuable research to go forward and, at the same time, ensuring appropriate protections from research harm, NBAC cannot fully endorse it without some reservation. Therefore, while it supports the use of LARs in research, it strongly encourages the research community, led by NIH (in view of its experience in this area), to support studies on the appropriate use of research DPAs. NBAC also encourages studies that assess the extent to which clinical DPAs can be extended to include research decision making.

Independent Professional Support for Subjects and Surrogates

Although consent forms and research protocols normally provide thorough information about the study, they do not provide the individualized information and specific judgment that many people need to make a decision about their own situation. Also, some potential research participants, or their representatives, may be intimidated by the medical research environment, or feel unable to make an independent judgment due to the technical nature of medical research.

One way to provide intellectual and emotional support to these individuals is to ensure that an independent and properly skilled health care professional is available as an advisor for each research participant or their surrogate. This independent advisor should not be involved with the study and preferably should have had a previous relationship with the potential subject. Subjects, or their representatives if subjects lack capacity, should be able to choose their responsible health care professionals**.** The advisor's role would be to help a potential subject and representative decide whether participation in a particular research protocol is a good choice for that subject. For persons who are incapacitated and whose research participation is contemplated, the health care professional could be an invaluable consultant to the LAR. Often this

professional will be a physician; however, other professional caregivers may serve the same role—a nurse-clinician or a social worker, for example. The basic requirement is that such caregivers be familiar with the patient, understand the nature of the research protocol, not be part of the research team, and, if practical, not be part of the organization conducting the research. One could not expect, of course, that health care professionals be required for all research involving persons with mental disorders, but they should be available where the patient lacks capacity to decide or is expected to lose capacity during the course of a study involving greater than minimal risk. For any research, subjects or their LAR should be informed that they may request the opinion of an independent health care professional about participation in research. Investigators must make available any information the independent health care professional requests (including to the subject or research site) in relationship to the investigation.

The British Law Commission recommended a similar system to the House of Commons in 1995, though its proposal applied only to individuals who lack capacity **.** It wrote: "In most cases the appropriate person to carry out an independent check [on research participation] will be a registered medical practitioner who is not involved in the research project. . . . The doctor who knows the person best, by virtue of having responsibility for his or her general medical care, will often be the best candidate." [182] The Maryland proposal assigns this responsibility to a "medically responsible clinician" if research involves withdrawing a group of decisionally incapacitated subjects from a standard treatment or otherwise presents more than minimal risk. [183] At the very least, it seems sensible for a legally authorized representative to have access

[182]The Law Commission, "Mental Incapacity: Item 9 of the Fourth Programme of Law Reform: Mentally Incapacitated Adults" (London, England: House of Commons, 1995), p.101.
[183]Office of the Maryland Attorney General, supra, p. A-19.

to an independent health care professional advisor before entering an individual into a research protocol.

For greater than minimal risk research, whether or not direct medical benefit is anticipated, an independent health care professional must be identified in advance of the start of the research. The subjects or their LARs may or may not utilize the independent health care professional as they wish. When, as is usually desirable, the researcher is not the health care professional responsible for the care of the patient, the treating professional would thus be available to serve as the independent advisor to the patient once enrolled in the research.

This chapter has discussed some of the conceptual and practical problems that arise when informed consent cannot be obtained from potential research subjects, the place of assent/dissent, the use of advance planning, and the role of LARs in permitting some research to go forward. The next chapter describes some of the difficulties that arise in assessing risk and potential benefit and offers some perspectives on their resolution.

Chapter Four: THE ASSESSMENT OF RISK AND POTENTIAL BENEFIT

The Common Rule directs IRBs to ensure that research risks are minimized through careful study design and that risks are "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[184] Many commentators favor placing additional constraints on acceptable risks in research involving persons who, as a result of having certain mental disorders, may sometimes lack decisionmaking capacity.

This chapter discusses some of the conceptual and practical problems that arise not only for IRBs, but for investigators and potential subjects who also must make judgments about the acceptability of risk in relation to the prospect of benefit. First discussed are some of the difficulties inherent in defining risk, followed by an explanation of NBAC's rationale for urging IRBs to evaluate research involving this population under two categories: minimal risk, and greater than minimal risk. Also presented is a discussion of some of the difficulties in defining benefits. Finally, the Chapter comments on the difficulties of assessing research risks in relation to potential benefits to subjects. In particular, this discussion focuses on the protections that should be required for research involving greater than minimal risk that *does* hold out the possibility of direct medical benefit to subjects, and for research involving greater than minimal risk that *does not* hold out the possibility of direct medical benefit to subjects. The final section of this chapteralso proposes procedures to minimize risks to subjects.

[184] 45 C.F.R. 46.111(a)(1) & (2) (1998).

Defining and Assessing Risk

The *concept of risk* is generally understood to refer to the combination of the probability and magnitude of some future harm. According to this understanding, risks are considered "high" or "low" depending on whether they are more (or less) likely to occur, and whether the harm is more (or less) serious. In research involving human subjects, risk is a central organizing principle, a filter through which protocols must pass; research evaluated by IRBs that presents greater risks to potential research subjects will be expected to include greater (or more comprehensive) protections designed to limit the possibility of harm occurring. The ethical basis for this position was usefully summarized in the National Commission's *Belmont Report:* "The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect of persons."[185] In contrast, relatively little progress has been made in describing the *criteria for assessing risk* by IRBs.[186,187] In large part, this is due to the multiple concerns and difficulties inherent in classifying risk judgments. Specifically, the difficulty lies in accurately quantifying risks by reducing a set of complex questions regarding one's perception of various risks by, for example, assigning a particular protocol to a single risk category.[188] [189]

The purpose of having multiple categories of risk is to trigger different requirements from IRBs, just as the "minimal" and "greater than minimal" risk categories trigger different types of minimal protections in the Common Rule. It is not

[185]National Commission, *Belmont Report*, 6.
[186]Shannon TA, Ockene IS, and Levine RJ. Approving high risk, rejecting low risk: the case of two cases. IRB 7 (January-February 1985): 7-8.
[187]Meslin, EM. Risk judgments by IRBs: IRB.
[188]Slovic, P. Perception of risk. Science 236 April 1987: 149-170.
[189]Schrader-Frechette K. Values, scientific objectivity and risk analysis: five dilemmas. In James M. Humber and Robert F. Almeder (eds.) Clifton NH: Humana Press, 1986: 149-170.

necessary, however, to recommend that the Common Rule be amended to provide IRBs with three (or more) levels of risk to consider when assessing risk in relation to potential benefit. NBAC recommends that IRBs use their existing authority to determine whether to add protections above the minimal regulatory requirements for all research involving greater than minimal risk.

Minimal Risk and Greater than Minimal Risk

According to the Common Rule, a study presents minimal risk if "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."[190] Although the concept of minimal risk remains a controversial one in academic and scholarly discussion, it is widely used to determine which set of protections are to be required for particular research protocols. Still, the application of these terms in practice can be difficult. For example, a "typical" minimal risk encountered in everyday life or in clinical care may be perceived differently by some individuals with certain disorders. It is important, therefore, to establish a practical level of minimal risk against which IRBs can measure proposed research in order to decide which protocols require additional protections. The level of minimal risk will change (in one direction or another) over time, as experience and additional knowledge will change the way the research community, IRBs, and research subjects perceive the acceptability of various research risks. Under the current system, IRBs have complete discretion to apply none or only some of the added protections to protocols that they believe to be of greater than minimal risk. For this reason, IRBs should be able to approve protocols involving minimal risk when the prospective subject gives an

[190] 45 C.F.R. 46.102(i) (1998).

informed consent, or the potential subject's LAR authorizes the subject's enrollment. Where the LAR does provide this permission one should also expect that the subject's assent would be sought. As in all research, any subject dissent would be respected.

The Department of Health and Human Services (DHHS) addressed the issue of IRB latitude in its regulations on research involving children by permitting IRBs to approve research presenting no greater than minimal risk as long as requirements for parental permission and child assent are satisfied. However, the regulations stipulate that studies presenting greater than minimal risk must meet additional requirements.

Like these DHHS regulations for children, many proposals on research involving impaired or incapable adults employ the concepts of minimal risk and minor increase over minimal risk. Indeed, many public comments suggested that NBAC group research involving persons with mental disorders into three categories of risk: 1) minimal risk; 2) minor increase over minimal risk; and 3) greater than minimal risk (which encompasses risks greater than a minor increase over minimal risk). The ostensible purpose of this tripartite division is to allow protocols involving only a minor increase over minimal risks to proceed with only minimal additional protections. Otherwise, the claim is that too few protocols will be approvable. As evidence of this difficulty, NBAC received correspondence from the National Institutes of Health[191] describing examples of research that might be limited by retaining the Common Rule's two-level categorization of risk. In several examples, research could be considered as minimal or a slight increment above minimal risk. The Common Rule does not specify that IRBs should (or be expected to) use three categories of risk in making judgments about the acceptability of risks in relation to potential benefits, nor do the regulations

[191] Panel Report to NIH, February 1998; Correspondence from Lana Skirboll, Associate Director of Science Policy, NIH, October 19, 1998; "NIMH Critique of July 1, 1998, Draft Report of the National Bioethics Advisory Commission: Research Involving Subjects with Disorders that May Affect Decisionmaking Capacity ," August 6, 1998

specific to pregnant women or prisoners.[192] Only the regulations pertaining specifically to children describe three categories of risk.[193]

IRBs should consider a range of protections that are related to the perceived level of risk, and whether there are two or more levels should make no difference. Providing clear meaning to these concepts, as noted above, poses serious practical difficulties. The Common Rule's minimal risk definition, which refers to the risks of everyday life and medical care encountered by the population as a whole, often is praised for its flexibility: "It is inescapable and even desirable that determinations of risk level (and its acceptability when balanced with benefit consideration) are matters of judgment rather than detailed definition, judgments which are patient-specific, context-specific, and confirmed after consideration and debate from many points of view."[194] The concept's reference to "risks of everyday life" also conveys a defensible normative judgment that the sorts of risks society deems acceptable in other contexts may be acceptable in research as well.[195]

In contrast to the minimal risk concept's reference to the life and medical experiences of the overall population, the concept of minor increase over minimal risk is, in the case of children, tied to the prospective subject's individual situation. Because persons with mental disorders undergo treatment and tests involving some discomfort and risk, a study presenting similar procedures and potential for harm may qualify as presenting a minor increase over minimal risk to them. [196] For subjects not accustomed

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[192]HHS is the only federal agency that has adopted regulations governing research involving pregnant women and prisoners. See 45 C.F.R. 46 Subpt. B and C (1998).

[193]HHS and ED have adopted regulations governing research with children. *See* 45 C.F.R. 46, Subpt. D; 34 C.F.R. 97, Subpt. D (1998).

[194]Keyserlingk, et al., supra, at 329.

[195]Freedman, Fuks & Weijer, In Loco Parentis: Minimal Risk as an Ethical Threshold for Research Upon Children, Hastings Center Rep., Mar.-Apr. 1993, at 13, 17-18. According to the National Commission, "where no risk at all or no risk that departs from the risk normal to childhood (which NBAC calls `minimal risk,') is evidenced, the research can ethically be offered and can ethically be accepted by parents and, at the appropriate age, by the children themselves" Report on Children, supra, at 137.

[196]The DHHS regulations governing research involving children provide that studies may be approved as presenting a minor increase over minimal risk as long as the risks and experiences "are reasonably commensurate

to or in need of such medical interventions, however, the same study could present a higher level of risk.

In its *Report on Research Involving Children*, the National Commission defended this approach to greater than minimal risk research on grounds that it permitted no child to be exposed to a significant threat of harm. Further, the National Commission noted that the approach simply permits children with health conditions to be exposed in research to experiences that for them are normal due to the medical and other procedures necessary to address their health problems. An example is venipuncture, which may be more stressful for healthy children than for children being treated for a medical condition who are more accustomed to the procedure.

Commentators have criticized both the Common Rule's "minimal risk" definition and the category "minor increase over minimal risk" in the children's regulations. Loretta Kopelman provides perhaps the most detailed critique. First, she finds the notion of "risks of everyday life" too vague to provide a meaningful comparison point for research risks. Ordinary life is filled with a variety of dangers, she notes, but "[d]o we know the nature, probability, and magnitude of these 'everyday' hazards well enough to serve as a baseline to estimate research risk?" Second, though the comparison to routine medical care furnishes helpful guidance regarding minimal risk, it fails to clarify whether procedures such as "X rays, bronchoscopy, spinal taps, or cardiac puncture," which clearly are not part of routine medical care, could qualify as presenting a minor increase over minimal risk for children whose health problems dictate they must undergo these risky and burdensome procedures in the clinical setting. Kopelman argues that the phrase "minor increase

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with those inherent" in the child subjects' actual or anticipated medical or other situations. 45 C.F.R. 46.406(b) (1998).

over minimal risk" should be replaced or supplemented by a clearly defined upper limit on the risk IRBs may approve for any child subject.[197]

Difficulties with the minimal risk standard may be due in part to a historical confusion. Some contend that the drafters of the definition of minimal risk deliberately dropped the National Commission's reference to normal individuals, intending to make the relevant comparison to risks ordinarily encountered by the prospective research subject. This approach would allow classifying research risks as minimal if they were reasonably equivalent to those the subject encountered in his or her ordinary life or routine medical care. Using this approach with persons with mental disorders who face higher-than-average risks in everyday life and clinical care, a research intervention could be classified as minimal risk for them, but classified as greater than minimal risk for healthy persons. If this was the intention of the drafters of the regulations, it is not at all clear in the current Common Rule.

In August 1998, the Canadian Tri-Council Working Group developed a policy statement on "Ethical Conduct for Research Involving Humans" that explicitly adopts the standard of relativizing risk to the potential subject in question. It defines "normally acceptable risk" as "when the possible harms (e.g., physical, psychological, social, and economic) implied by participation in the research are no greater than those encountered by the subject in those aspects of his or her everydaylife. . . ."[198] The

[197]Kopelman, Research Policy: Risk and Vulnerable Groups, in Encyclopedia of Bioethics 2291, 2294-95 (W. Reich ed., rev. ed. 1995); Kopelman, When Is the Risk Minimal Enough for Children to Be Research Subjects? in Children and Health Care: Moral and Social Issues 89-99 (Kopelman & Moskop eds., 1989). See also Berg, supra, at 24 (noting possible interpretations of minimal risk and concluding that "[i]t clearly does not mean only insignificant risk, but its exact scope is unclear"). The Maryland draft legislation adopts a definition of minimal risk similar to that in the Common Rule. It also refers to minor increase over minimal risk, which is defined as "the probability and magnitude of harm or discomfort anticipated in the research, including psychological harm and loss of privacy or other aspects of personal dignity, are only slightly greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." Office of the Maryland Attorney General, supra at A-5.

[198]The Medical Research Council of Canada, The Natural Sciences and Engineering Research Council of Canada, and The Social Sciences and Humanities Research Council of Canada, Code of Ethical Conduct for Research Involving Humans (The Tri-Council Working Group, August 1998) p. 1.5

Canadian code goes on to state that therapeutic risks should be treated differently from nontherapeutic risks. Therapeutic risks can be considered as minimal for patient-subjects, since they are inherent in therapy and thus the everyday life of the subject.

In NBAC's view, a policy on research involving persons with mental disorders that incorporates the concepts of minimal risk and minor increase over minimal risk without providing further guidance to investigators and IRBs would not be helpful, because the concepts can be interpreted in materially different ways. In some cases, procedures presenting greater than minimal risks to people with mental disorders might be treated as such, while in other cases—e.g., in persons with special vulnerability to those procedures—they might not be. A procedure classified as minimal risk at one institution could be classified as higher risk at another, or even from one study to another in the same institution. Magnetic Resonance Imaging (MRI) is such an example since it falls within the category of procedures which qualify for expedited review according to current federal regulations (45 CFR 46), and yet its placement in that list does not directly imply that it should be considered minimal risk. Also needed is further clarification of acceptable risk in research involving incapable adults whose ongoing health problems expose them to risks in their everyday clinical setting. Because some persons with mental disorders who are accustomed to certain procedures may experience fewer burdens when undergoing them for research purposes, some would argue that it may be defensible to classify the risks to them as lower than would be the case for someone unfamiliar with the procedures.

We must guard against assumptions like these. The psychological context of illness may well make some research procedures, however familiar, more burdensome than they would be to someone who enjoys good health. These procedures must not be classified as lower risk for subjects who have had the misfortune of enduring them

in the treatment setting.[199] Like the level of minimal risk, the boundaries that separate particular risk categories can be expected to shift over time in response to many complex and interrelated factors. What is required is a focus on the "package" of reasonably interpreted risks on the one hand and a correspondingly appropriate set of protections on the other.

In short, NBAC is not persuaded that three categories of risk are necessary for accomplishing the twin goals of providing protection for persons with mental disorders while allowing important research to go forward.

One way to reduce variance in risk classification would be to provide examples of studies that ordinarily would be expected to present a certain level of risk to members of a certain research population. For example, the Maryland draft legislation includes in its definition of "minimal risk" research those "types of research that are . . . identified by the United States Department of Health and Human Services as suitable for expedited IRB review."[200] Thus the Maryland proposal effectively incorporates examples like venipuncture, MRI, electroencephalography, and the study of existing biological specimens. Perhaps over a period of time, if there is adequate communication and disclosure, it will become evident to the IRB community that protocols tend to cluster in certain ways. For example, one author proposes that lumbar punctures and positron emission tomography "can be reasonably viewed as having greater than minimal risk for persons with dementia because (1) both procedures are invasive, (2) both carry the risk of pain and discomfort during and after, and (3) complications from either procedure can require surgery to correct."[201] The draft Maryland legislation designates research as presenting more than a minor

[199]Prior exposure to procedures could actually increase the fear and anxiety for some incapable subjects. Incapable adults with memory impairment may not recall undergoing procedures; for them, each procedure will be experienced as a new one.
[200]Office of the Maryland Attorney General, p. A-5.
[201]DeRenzo, supra, at 540.

increase over minimal risk if, as a result of research participation, the subjects would be exposed to more than a remote possibility of “substantial or prolonged pain, discomfort, or distress" or "clinically significant deterioration of a medical condition."[202]

A list of minimal risk procedures for dementia patients includes "routine observation, data collection, answering a questionnaire, epidemiological surveys, venipuncture, and blood sampling," as well as neuropsychological testing.[203] Though some reportedly classify lumbar punctures and bone marrow biopsies as presenting a minor increase over minimal risk, Keyserlingk and colleagues suggest that such procedures may present "greater risks for some patients with dementia who are unable to understand or tolerate the pain or discomfort" accompanying the interventions. [204]

In NBAC’s review of representative research protocols, it witnessed an admirable example of an IRB that turned to experts for assistance in assessing risks. The protocol involved a challenge study which entailed a higher than standard dosage of the challenge agent, although the investigator described the study as minimal risk in the consent form. The expert evidently advised the IRB that the risks were in fact greater than minimal due to the increased dosage and that the dosage should be reduced and properly identified in the consent form. An IRB that seeks expert opinion can dramatically improve both research design and the bases for subjects to provide informed consent.

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[202]Ibid at A-17.

[203]Keyserlingk, et al., supra, at 330.

[204]Id. at 330. In 1980, the President’s Commission issued a paper on the Swedish system for compensation of subjects injured in research. That paper listed procedures by risk groups; those in the first and lowest risk group included sampling of venous blood, administration of approved drugs in recommended doses, intravenous and intramuscular injections, and skin biopsies. The higher risk group list included sternal and spinal punctures, intravenous and intra-arterial infusions, muscle biopsies, and endoscopy and biopsies of the gastrointestinal tract.[204] Thus, a spinal tap might present greater than minimal risk to a patient-subject who is decisionally impaired, but not to a normal, healthy subject, while drawing venous blood might present minimal risk to all subjects.

The philosophical debate about the meaning of minimal risk will surely persist because of the practical difficulties of defining it precisely. But this does not mean that research involving persons with mental disorders cannot be conducted. Rather, it means that research procedures that would entail minimal risk for a general population must be assessed in light of the specific research population. In no case, however, should procedures classified as greater than minimal risk for the overall population be classified as minimal risk for this population. Therefore, research proposals should be more highly scrutinized if they involve persons with mental disorders, and special care may be required to understand particular risk levels for this population. The Commission believes that these special considerations are important and should not prevent the most valuable research from continuing within such constraints.

Assessing Risk

Strictly speaking, risk assessment is a technique used to determine the nature, likelihood, and acceptability of the risks of harm.[205] In actual practice there is always a great deal of controversy about how such assessments should occur. Moreover, few IRBs conduct formal risk assessments, and there may be good reason for this: First, reliable information about risks or potential benefits associated with the relevant alternative interventions is often lacking. As a result, highly accurate risk assessment is a difficult and in many cases impossible task. Second, each component of risk assessment—identification, estimation, and evaluation—involves time and requires particular kinds of expertise.[206] Even at the conceptual level, it is a matter of both scientific and philosophic debate as to whether risk assessment should involve purely objective or purely subjective factors (or both). The "objectivist" school argues that quantitative risk assessment should be a value-free determination limited only by the

[205]Wilson R, and Crouch EAC. Risk assessment and comparisons. Science 1987; 236:267-70.
[206]Meslin EM. Protecting human subjects from harm through improved risk judgments. IRB. Jan/Feb 1990: 7-10.

technical ability to derive probability estimates.[207] In contrast, the "subjectivist" school argues that the values of those who conduct the assessment, those who interpret the results, and those who bear the risks should play a role in the overall assessment of risks.[208] It is reasonable to hold that both schools of thought ought to influence IRB decision making, the former because risk judgments should be empirically based insofar as possible, and the latter because many who have an interest in research can contribute to these assessments despite the lack of formal quantitative data.

The National Commission's *Report on Research Involving Children* advised IRBs to assess risks from the following points of view: "a common-sense estimation of the risk; an estimation based upon investigators' experience with similar interventions or procedures; any statistical information that is available regarding such interventions or procedures; and the situation of the proposed subjects."[209] Evaluating risks to subjects with mental disorders requires familiarity with how such subjects may respond, both generally and individually, to proposed research interventions and procedures. What may be a small inconvenience to ordinary persons may be highly disturbing to those with decisional impairments. Thus, for example, a diversion in routine can, for some dementia patients," constitute real threats to needed order and stability, contribute to already high levels of frustration and confusion, or result in a variety of health complications."[210] Similarly, as the National Commission observed, some subjects institutionalized as mentally infirm may "react more severely than normal persons" to routine medical or psychological examinations.[211] Because of the special vulnerability to harm and discomfort that particular subjects may have, risk

[207]Haefle W. Benefit-risk tradeoffs in nuclear power generation. In Ashely H., Rudman R, Starr C. Eds. Energy and the Environment. New York: Pergammon Press, 1981.
[208]Schrader-Frechette, K. Values, scientific objectivity and risk analysis: five dilemmas, In Humber JM, and Almeder RF, eds. Quantitative Risk Assessment: Humana Press: Clifton, NJ, 1986: 149-70.
[209]National Commission, *Report on Children*, 8-9.
[210]Keyserlingk, et al., supra, at 324.
[211]National Commission, *Report on Institutionalized Persons*, 8-9.

assessment should anticipate the range of reactions subjects may experience to certain proposed study procedures. Difficult as it may be, risk assessment is the key to deciding on the appropriate level of protections.

Defining Benefits

Research involving adult subjects can yield three types of potential benefit: 1) direct medical benefit to subjects; 2) indirect benefit to subjects; and 3) benefit to others.

Direct Medical Benefit

Particular research protocols may hold out the prospect of direct medical benefit to the subjects themselves, even though such benefit can never be absolutely assured. The potential direct medical benefits to the subjects include health improvements which may or may not be related to the disorder responsible for the subject's incapacity.[212] For example, the National Commission stated that research offering potential direct benefits to persons institutionalized as mentally infirm could include:

> studies to improve existing methods of biomedical or behavioral therapy, or to develop new educational or training methods. The studies may evaluate somatic or behavioral therapies, such as research designed to determine differential responsiveness to a particular drug therapy, or to match particular clients with the most effective treatment. Studies may also assess the efficacy of techniques for remedial education, job training, elimination of self-destructive and endangering behaviors, and teaching of personal hygiene and social skills.[213]

[212]Keyserlingk, et al., supra, at 327.
[213]National Commission, *Report on Institutionalized Persons*, 31.

According to the National Commission, "[t]o be considered 'direct,' the possibility of benefit to the subject must be fairly immediate [and t]he expectation of success should be well-founded scientifically."[214] A more recent statement on dementia research limits direct medical benefit to

> a short- or long-range improvement, or a slowing of a degenerative process, in the specific medical condition of the relevant subject, whether in the patient's condition of dementia, a medical symptom associated with dementia, or another physical or mental condition unrelated to dementia. Such direct benefits include those resulting from diagnostic and preventative measures.[215]

Investigators' assertions that research offers the prospect of direct medical benefit to subjects should be carefully scrutinized by IRBs and other reviewers. In practice, incentives such as monetary rewards, free health care and free psychiatric evaluation, in addition to the exaggeration of indirect benefits in consent forms, results in something that resembles coercion. In the protocols reviewed by NBAC, there seemed to be confusion about the definition of direct medical benefit. One protocol referred to the challenge procedure as the "treatment phase." The consent form that accompanied the above protocol described the benefits of the assessment phase as including "a thorough psychological evaluation at no cost, the results of which will be the basis for a treatment recommendation either within or outside of the treatment phase of the study. Benefits of the treatment phase may include decreases in the . . . severity of . . .symptoms." Unless the distinctions between direct medical and indirect

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[214]Id. at 13.

Berg also emphasizes the need to weigh the likelihood of direct benefit to subjects. In clinical trials, for example, "the benefit calculation must take into account how probable it is that a particular subject will get the experimental medium as well as the probability that, once received, the intervention will help." Berg, supra, at 25.

[215]Keyserlingk, et al., supra, at 327. This group notes that currently direct benefits to subjects in dementia research are limited to symptom control. There may be disagreement on whether research with the potential to extend life for someone in the later stages of a progressive dementia ought to be seen as offering the prospect of direct benefit to subjects.

benefits are identified, and their relative significance explored carefully, there is a danger that investigators may construe the concept of direct medical benefit too broadly.[216]

Further, potential direct medical benefits to the subjects participating in the research protocol not only must be carefully evaluated but may not, by themselves, justify experimental interventions that present too great a risk to a subject population. Instead, these possible benefits must be considered in relation to the risks involved. Even though a research protocol may offer potential direct medical benefits to individual participants, it cannot be justified by the possibility of that benefit alone.

Indirect Benefit

Subjects may obtain other forms of benefit from research participation. As the National Commission noted, "[e]ven in research not involving procedures designed to provide direct benefit to the health or well-being of the research subjects, . . . there may be incidental or indirect benefits."[217] Examples of indirect benefits are "diversion from routine, the opportunity to meet with other people and to feel useful and helpful, or . . . greater access provided to professional care and support."[218] NBAC agrees with the view expressed by one group—namely, that an indirect benefit may be acknowledged, but should not be assigned as heavy weight as direct medical benefit in the IRB review and discussions with prospective subjects and their representatives.[219] Thus, it is necessary to examine carefully how risks and potential benefits, especially to others, can be balanced and what protections should be in place to minimize risks for subjects with mental disorders that may affect their decision making capacity.

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[216] This problem was of concern to the intermediate appellate court in the *T.D.* litigation.
[217] National Commission, *Report on Institutionalized Persons*, 31.
[218] Keyserlingk, et al., supra, at 327.
[219] Thus, indirect benefit ought not be deemed sufficient to enter an incapable subject in studies presenting more than a "minor increment over minimal risk." Id. at 333-34. Keyserlingk, et al. characterized indirect benefits as "by nature difficult to predict with any accuracy and . . . often very person-specific." Id. at 327.

There is a continuing debate about whether the reimbursement subjects receive for their time and inconvenience constitutes a direct or indirect benefit of research participation. The benefits of financial incentives for the subject are indirect in the strict sense that they do not stem from the research interventions themselves, but the subject may view them as very important. A secondary concern here, as with research on other potentially vulnerable populations, is who actually receives and controls the funds: the subject or a third party who authorizes research participation?

The principle that financial incentives should not exceed “reimbursement” for the subject’s time and expenses, so as not to establish undue motivation to participate, is well established but not always easy to apply. The problem is complex because healthy volunteers, as well as some who are ill, may agree, for example, to pharmaceutical testing as an important supplement to their income, if not their sole income source, and their main reason for participating. Remuneration must be appropriate to justify their commitment of time and their submission to discomfort, but not be so great as to lead them to take unreasonable risks. Similarly, some who are suffering from an illness, especially those who are uninsured, may be tempted to join a study if it appears that the ancillary medical care will be superior to what they can otherwise obtain.

Research Benefit to Others

This category encompasses benefit to subjects’ families or other caregivers, to persons with the same disorder as subjects, and to persons who will suffer from the same disorder in the future. When such research is invasive and presents no realistic possibility of direct health benefit to the subject, it "poses in the most dramatic form

the conflict between the societal interest in the conduct of important and promising research and our respect for the persons serving as subjects and their interests."[220]

Balancing Risks and Potential Benefits

The National Commission was fully aware of the problems inherent in making risk-benefit assessments when it wrote that:

> It is commonly said that the benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty in making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible.[221]

This report has described some of the difficulties with defining risks and benefits in research; the following describes the difficulties with evaluating their relationship to each other in order for IRBs, as required by current regulations, to assess the ratio of risks to benefits involved in individual research protocols. Most researchers and IRBs take the position that adults who lack decisionmaking capacity may be involved in studies presenting little or no risk, as long as requirements for third party consent are met and the research offers a reasonable prospect of advancing knowledge or benefiting the subject, or both.[222] There is substantial support, however, for adopting additional restrictions and review requirements for studies presenting higher risk, particularly for higher-risk studies that fail to offer subjects a reasonable prospect of direct benefit.[223]

[220]Melnick, et al., supra, at 535.
[221]National Commission, *Belmont Report*, 7.
[222] NIH Clinical Center policy, NIH Panel Report, CIOMS, Council of Europe, etc.
[223] New York State Working Group, Citizens for Responsible Care in Psychiatric Research.

Research presenting greater than minimal risk to subjects i s generally classified into one of two categories. The first category is research offering subjects the prospect of direct medical benefit. The second category is research that is not designed to offer the prospect of direct medical benefit to subjects. Although these categories may seem to imply a distinction between "therapeutic" and "nontherapeutic," that is not the case and, in fact, is a serious misconception. Rather, it should be understood that some research may hold out the prospect of direct medical benefit for some individuals while some research may not.

Greater than Minimal Risk Research that Offers the Prospect of Direct Medical Benefit to Subjects

The general view is that it is permissible to include decisionally incapable subjects in a research project that offers the prospect of direct medical benefit to subjects as long as the research presents a balance of risks and expected direct benefits similar to those available in the normal clinical setting. [224] The American College of Physicians guidelines allow surrogates to consent to research involving incapable subjects only "if the net additional risks of participation (including the risk of foregoing standard treatment, if any exists) are not substantially greater than the risks of standard treatment (or of no treatment, if none exists)." In addition, there should be "scientific evidence to indicate that the proposed treatment is reasonably likely to provide substantially greater benefit than standard treatment (or no treatment, if none exists)."[225]

The Maryland draft legislation deems "research involving direct medical benefit" permissible if an agent or family member or friend acting as surrogate, or an

[224]The standard is similar to the general demand for clinical equipoise when human subjects participate in clinical trials. Freedman, Equipoise and the Ethics of Clinical Research, 317 New Eng. J. Med. 141 (1987).

[225]American College of Physicians, supra, at 845. A limited exception is permitted for incapable individuals who consented to higher risk through an advance directive.

IRB-designated proxy, "after taking into account . . . treatment alternatives outside of the research . . . concludes that participation in the research is in the individual's medical best interest."[226] With the consent of a Durable Power of Attorney (DPA) or court-appointed family guardian, the NIH Clinical Center permits greater than minimal risk research offering a prospect of direct subject benefit if there was an ethics consultation to ensure that the third party decision maker understands the relevant information. For subjects without a DPA or court-appointed guardian, this form of research is permitted "if the situation is a medical emergency, when a physician may give therapy, including experimental therapy, if in the physician's judgment it is necessary to protect the life or health of the patient."[227]

Greater than Minimal Risk Research that Does Not Offer the Prospect of Direct Medical Benefit to Subjects

The American College of Physicians and other groups take the position that greater than minimal risk research offering incapable subjects no reasonable prospect of direct medical benefit should be permitted only when authorized by a research advance directive[228] or after review and approval at the national level, through a

[226]Office of Maryland Attorney General, supra, at A-26–A-28. Other commentators take a similar position. See, e.g., Berg, supra, at 25 (approving this category of research if "no alternative treatment is available of at least equal value, and the experimental treatment is not available through any other source").

Much of the recent controversy over trials involving medication withdrawal for persons with serious psychiatric disorders concerns whether sufficient potential direct benefit exists to justify allowing subjects of questionable capacity to enter or remain in such trials. See Appelbaum, supra; Gilbert, et al., Neuroleptic Withdrawal in Schizophrenic Patients, 52 Arch. Gen. Psych. 173 (1995). The Loma Linda IRB Guidelines for use of placebos in studies involving persons with psychiatric illness present specific exclusion and inclusion criteria for such studies. Enrollment is limited to persons whose use of standard treatment has produced responses or side effects deemed unacceptable by the patient or an independent psychiatrist. Orr, supra, at 1263. Similarly, Appelbaum endorses a requirement for an independent clinician to screen prospective subjects with the goal of excluding those facing a high risk of harm from psychotic deterioration. Appelbaum, supra, at 4.

[227]NIH Clinical Center, supra.

[228]However, the ACP would rule out research that "would unduly threaten the subject's welfare." See pp. 41-42, above. The Maryland draft legislation would permit research presenting more than a minor increase over minimal risk and no reasonable prospect of direct benefit only when subjects appointed a research agent and "the research is unambiguously included in the [incapacitated] individual's research advance directive." Office of Maryland Attorney General, supra, at A-32. Berg proposes that high risk research offering little or no prospect of direct

process resembling that set forth in the current regulations governing research involving children.[229] The National Commission also recommended a national review process for studies that could not be approved under its other recommendations on research involving persons institutionalized as mentally infirm.[230] However, others see this position as either too liberal or too restrictive. In our view, these proposals have considerable merit and we offer a recommendation in Chapter 5 which would establish such a mechanism. NBAC realizes however that such a proposal admits to different points of view.

On the one hand, based on the Nuremberg Code's and the Declaration of Helsinki's convictions that vulnerable and unconsenting individuals should not be put at undue risk for the sake of patient groups or society, some favor an absolute prohibition on moderate- or high-risk research offering no benefit to subjects but great promise of benefit to others. Supporters of this position contend that when these documents were created, "it was presumably well understood that a price of that prohibition would be that some important research could not proceed, some research answers would be delayed, and some promising therapies and preventive measures would for the time being remain untested and unavailable."[231] Some explicitly label this stance the most ethically defensible position.[232]

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subject benefit should be prohibited unless there is clear evidence that a subject's competent preferences would support participation. Berg, supra, at 28.

[229]American College of Physicians, supra, at 846. See also Melnick, et al., supra, at 535 (advising national ethics review prior to any decision to permit studies in this category).

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[231]Keyserlingk, et al., supra, at 334.

[232]Id. at 334. The group would accept this form of research for a small group of incapable subjects who previously consented to it in an advance directive, however. See pp. 45-46, above.

Annas and Glantz also contend that without previous competent and specific consent, incapable nursing home residents should not be enrolled in "nontherapeutic experimentation that carries any risk of harm with it." Annas & Glantz, supra, at 1157. See also Shamoo & Sharev, supra (calling for "moratorium on all nontherapeutic, high risk experimentation with mentally disabled persons which is likely to cause a relapse); Thomasma, supra, at 228 (incapable persons should not be involved research failing to offer direct benefit if study presents more than "very mild risk").

On the other hand, a position paper representing federally funded Alzheimer Disease Centers adopts a somewhat different view: “Research that involves potential risks and no direct benefit to subjects may be justified if the anticipated knowledge is vital and the research protocol is likely to generate such knowledge."[233] This group also believes that a national review process is not necessarily the best way to decide whether to permit research presenting no potential direct benefit and greater than minimal risk to incapable subjects. It acknowledges that "there may be some advantages" to national review, but contends that "immediate and direct monitoring of such research and on-site assurance of its humane ethical conduct are at least as important as the process of evaluation and approval of any proposed research."[234]

Special Review Panel

The regulations governing research involving children subjects provide for a special review process to address studies that offer the subjects no prospect of direct benefit and in which the risks are deemed to be over the minor increment over minimal risk line. The process begins by requiring that, first, an IRB must determine that a study in this category “presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.”[235] Upon such a finding, the Secretary may convene a panel of experts in pertinent disciplines to review the study and should provide the public an opportunity

[233]The group representing the Alzheimer’s Disease centers does not explicitly address whether limits on risk should be applied to this form of research. High, et al., supra, at 72-73.

Two other commentators recently argued in favor of permitting incapable persons to be involved in research offering no direct benefit if the risk is no more than a minor increment over minimal risk. Glass & Speyer-Ofenberg, Incompetent Persons as Research Subjects and the Ethics of Minimal Risk, 5 Camb. Q. Healthcare Ethics 362 (1996).

[234]High, et al., supra, at 72. Another statement from the Alzheimer’s centers’ group questions the assumption that a national review body would be particularly qualified to determine "whether the research in question is indeed extremely important to society or to a class of patients--sufficiently so that standard research norms could be put aside." High, et al., p. 335.

[235]45 C.F.R. 46.407(a), 34 C.F.R. 97.407(a) (1998).

to review and comment on the study.[236] After the panel's review and the public comment period the study may be approved if the Secretary has determined: (1) that the study actually falls into a category of research that the IRB could have approved on its own,[237] or (2) that the research does present the "opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, that the research will be conducted in accordance with sound ethical principles, [and] that adequate provisions are made for soliciting the assent of [the] children and the permission of their parents or guardians." [238]

This process, if modified, offers an additional route for assessing some protocols involving persons with mental disorders. In our view, however, a more flexible and accessible panel is required. We believe that it would be appropriate for the Secretary of DHHS to establish a panel which would have the authority to review and approve on a protocol-by-protocol basis studies involving greater than minimal risk which do not hold out the prospect of direct medical benefit to subjects. Such a panel, which we describe more fully in Chapter 5, would also have the authority to establish guidelines for approving categories of research.

Opportunities to Enhance IRB Education and Decision Making

Some have expressed concern that IRBs, if limited to two categories of risk when making judgments about the acceptability of risks in relation to potential benefits, may be inclined to consider all projects involving greater than minimal risk to require the most comprehensive protections.

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[236] 45 C.F.R. 46.407(b), 34 C.F.R. 97.407(b) (1998).

[237] 45 C.F.R. 46.407(b)(1), 34 C.F.R. 97.407(b)(1) (1998).

[238] 45 C.F.R. 46.407(b)(1)(i)-(iii), 34 C.F.R. 97.407(b)(1)(i)-(iii) (1998).

In particular, NBAC recognizes the concern expressed by some that if research involving what are normally relatively benign interventions (such as PET scans or MRIs) were categorized as greater than minimal risk, this could result in restrictions that might substantially delay or otherwise limit research. It believes, however, that the most appropriate way to address this issue is not to focus on an arbitrary line, which cannot be definitively established, but rather to focus attention on improving the quality of IRB judgments generally, and on the unavoidable responsibility of IRBs to not only ensure an appropriate balance between risks and benefits, but also an appropriate balance between risks and protections. This presents a useful opportunity for enhancing IRB decision making. One possible strategy may be for IRBs individually and collectively to develop "research ethics case law," by publicly disseminating the results of their deliberations so that others may benefit.

The purpose of having a set of risk categories is to enable individuals (in this case, IRBs) to discriminate more precisely when making judgments about whether adequate protections are in place, as well as when making judgments about risk in relation to potential benefits. But since risk will vary along a continuum that involves a number of factors, and since IRBs currently have the authority to require a variety of additional protections for persons involved as subjects (even in minimal risk research), NBAC was not persuaded by the argument that an additional category of risk is needed to assist in these decisions. However, by limiting the categories of research to two, NBAC is not intending for IRBs to require all available protections when they determine that a research protocol poses greater than minimal risk.

A few empirical studies indicate that there is substantial variation in how IRBs and investigators classify protocols using the current federal risk categories. For example, a 1981 survey found differences in how pediatric researchers and department chairs applied the federal classifications to a variety of procedures commonly used in

research involving children.[239] Similarly, there was substantial disparity in how the nine members of a special NIH review panel applied the federal classifications to a trial of human growth hormone in which healthy, short children were subjects.[240] A survey asking research review committee members and chairs in Canada to classify four different dementia studies "confirmed that there is considerable disagreement and uncertainty about what risks and benefits mean and about what is to be considered allowable risk."[241]

NBAC recognizes the difficulty that IRBs may face when making precise risk judgments, particularly about nonphysical harms. For this reason, IRBs may find it useful to collect data on the types of protocols they review involving persons with mental disorders, and to assess whether any patterns emerge in which certain types of protocols fall along a spectrum from the most benign to the most dangerous. This could be accomplished within the context of one of NBAC's recommendations regarding audit and disclosure (see Chapter 5).

NBAC urges the Secretary, DHHS, when constituting the panel that will have the authority to approve such research (which involves subjects with mental disorders that may affect their decisional capacity and which present greater than minimal risk with no prospect of direct medical benefit) to be mindful of the reports NBAC has received from the research community indicating that a significant amount of important research falls into this category and that medical progress for many suffering persons may very well depend upon the progress of this research.

In designing the panel, the Secretary should take into account the experience of the panel mechanism identified in 45 C.F.R. 46.407(b). [add a fn describing this] It should be noted, though, that NBAC does not assume that because this mechanism

[239]Janofsky & Starfield, Assessment of Risk in Research on Children, 98 J. Pediatrics 842 (1981).
[240]See Tauer, The NIH Trials of Growth Hormone for Short Stature, IRB, May-June 1994, at 1.
[241]Keyserlingk, et al., supra, at 326.

has been used only twice that it cannot fulfill its intended purpose. The presumed purpose of this panel would be to permit research that presents risks that are greater than a minor increment over minimal risk and that offers no prospect of direct benefit, when "the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children,"[242] and when the research can be "conducted in accordance with sound ethical principles."[243]

Therefore, NBAC strongly encourages the Secretary to employ innovative methods for ensuring sufficient financing of the panel and to adopt procedures for the operation of the panel such that will: (a) develop guidelines for categories of research that can be used by IRBs; and (b) make case-by-case decisions using a process that is easily accessible to all relevant researchers. In addition, the panel process should include public participation and a conclude with a written decision that explains the panel's rationale.

The system of review recommended here will serve several important functions. Most important to NBAC is that it will increase protections for a subject population believed to have been historically under-protected. Second, it will permit research to go forward that has passed uniform expert and public review of risks and benefits. No longer will IRBs lacking local expertise be faced with the burden of identifying an appropriate expert and establishing a mutually acceptable consulting arrangement. Third, by encouraging OPRR/ the Secretary to establish a creative mechanism for financing the panel, NBAC encourages additional innovations in financing of research review, an important response to the exponential growth in the size of the biomedical and behavioral research enterprise. Finally, the OPRR/Secretary review mechanism

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[242] 45 C.F.R. 46.407(b)(1)(i), 34 C.F.R. 97.407(b)(1)(i) (1998).

[243] 45 C.F.R. 46.407(b)(1)(ii) , 34 C.F.R. 97.407(b)(1)(ii) (1998).

will provide the IRB community with a trial run of a "research ethics case precedent" method.

Independent Research Monitors

In the initial review process, IRBs evaluate a research proposal's risks and expected benefits based both on study design and on predictions of subject response, and it is widely acknowledged that part of that overall evaluation will include safety and data monitoring. The Common Rule directs IRBs to ensure that "[w]hen appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects."[244] After evaluating human subject protections in schizophrenia research conducted at the University of California at Los Angeles (UCLA), the Office for Protection from Research Risks (OPRR) required the institution to "establish one or more independent Data and Safety Monitoring Boards . . . to oversee [DHHS]-supported protocols involving subjects with severe psychiatric disorders in which the research investigators or co-investigators are also responsible for the clinical management of subjects."[245] The institution was directed to submit to federal officials a proposal on creating and operating such monitoring boards.

It is necessary to distinguish the process of monitoring data and safety for the study as a whole from monitoring an individual subject's safety. Data and Safety Monitoring Boards (DSMBs) are well established devices, particularly for multi-site studies, and often recommend the early termination of a study because of evidence that one arm of the study is safer or more efficacious than the other.[246] But a major

[244]45 C.F.R. 46.111(a)(6) (1998). d

[245]Office for Protection from Research Risks, supra, at 27.

[246]See, e.g., Appelbaum, supra, at 4 (noting importance of close monitoring to detect early symptoms of relapse so that medication can be resumed to minimize deterioration); Keyserlingk, et al., supra, at 324 (researchers "must have in place at the start the needed mechanism to monitor subjects, not only as regards the research question, but also in order to identify and prevent unanticipated complications and harms, both physical and psychological").

question is how and when to implement individualized subject monitoring , and whether such monitoring should be conducted by someone who is independent of the research team. For example, detailed provisions on monitoring are included in Loma Linda University IRB guidelines on psychopharmacology research in which placebos are administered. Investigators must specify how often subjects will be assessed for deterioration or improvement during studies. The most appropriate quantitative instruments must be used for assessment, and subjects must be withdrawn if their condition deteriorates to a level "greater than that expected for normal clinical fluctuation in a patient with that diagnosis who is on standard therapy"; if they exhibit previously specified behaviors indicating possible danger to self or others; or if no signs of improvement in their condition are evident after a specified time. [247]

Some have suggested that it would be appropriate to assign monitoring responsibility to the incapable subject's representative as well. According to the *Belmont Report*, the representative "should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest."[248] In this spirit, the Maryland draft legislation directs subject representatives to "take reasonable steps to learn whether the experience of the individual in the research is consistent with the expectations of the legally authorized representative at the time that consent was granted." [249]

An important policy question is whether research team members and subject representatives can provide sufficient protection to impaired or incapable subjects. On the one hand, research team members may face a conflict between protecting subjects and maintaining the study population. [250] On the other hand, it is unlikely that subject

[247]Orr, supra, at 1263.
[248]National Commission, *Belmont Report*, 6.
[249]Office of Maryland Attorney General, supra, at A-25.
[250]In the UCLA schizophrenia research, subjects received clinical care from psychiatrists who also were coinvestigators for the study. There was concern that such a conflict of interest could lead psychiatrists to be insufficiently responsive to signs of possible relapse in patient-subjects.

representatives will be present during every part of an incapable subject's research involvement, and lay persons might not recognize every indication of increased risk to subjects. In these circumstances, IRBs would benefit from guidance on potential approaches to monitoring harms and benefits to individual subjects and on criteria for determining when the involvement of an independent health care professional is needed.[251] NBAC believes that, at certain risk levels in research using persons with mental disorders that may affect their decisionmaking capacity, independent monitoring is essential, and that such monitoring should be an ongoing process. In its review of protocols, NBAC noted that some lacked sufficient, ongoing monitoring. Although one study involved assigning both clinical and home monitors to subjects, the protocol included insufficient information for an IRB to evaluate how monitoring was actually to occur. More frequently the protocols failed to mention either monitoring or the risks of certain procedures like drug washouts, during which a subject's condition is likely to deteriorate. IRBs should expect investigators to describe in their research proposals (particularly in proposing research that involves greater than minimal risks) how potential harms to subjects will be monitored.

The first four chapters of this report surveyed certain critical aspects of the state of research and presented expert commentary on the participation in research of subjects with disorders that may affect their decisionmaking capacity. The final chapter presents NBAC's recommendations for appropriate protections for this population and the summary justifications for them.

[251]See Shamoo & Sharev, supra, at S:29 (researchers and IRBs should be held accountable for monitoring to ensure welfare of subjects protected; physician not associated with research or institution where research conducted should help decide whether subjects' interests served by continued participation).

Chapter Five: MOVING AHEAD IN RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS: SUMMARY AND RECOMMENDATIONS

This report stands in a long line of statements, reports, and recommendations by governmental advisory groups and professional organizations focused on the ethical requirements of research involving human subjects. Some of these reports dealt specifically with research protocols involving persons with mental disorders, and each has left an important legacy. For example, in 1947 the Nuremberg Code established the importance of voluntary consent to research participation. The Declaration of Helsinki in 1964 distinguished between research intended partly to benefit the subject and research intended solely for others' benefit. The Guidelines developed by the Council of International Organizations of Medical Sciences (CIOMS) allow legal guardians to consent to low-risk research that is potentially beneficial to the human subject involved. In addition to proposing ethical principles that should govern all human subjects' research and developing guidelines for research with special populations, in 1978 the National Commission proposed additional protections for those institutionalized as "mentally infirm." Even though these protections resembled those proposed by the National Commission for research with children (which were adopted), the proposed protections for those institutionalized as mentally inform were never adopted in federal regulations (See Appendix 1).

Much has changed since the National Commission's work 20 years ago. There is a greater sensitivity on the part of many to the variety of mental disorders and an improved understanding of the ways that these disorders can be recognized and ameliorated. Diagnostic techniques and treatment methodologies have progressed, sometimes in breathtaking ways, with the promise of still greater breakthroughs on the horizon. More research is being conducted than ever before, and the research environment has become far more complex, involving both a larger societal investment

and a greater role for the private sector. While by no means vanquished, the stigmatization of those who suffer from mental illnesses show signs of abating due to greater understanding of these individuals and the underlying biological and genetic [252] etiology of these disorders.

NBAC hopes that the legacy of this report will be to bring persons with mental disorders more fully and specifically under appropriate additional research protections, such as those that have been extended to other potentially vulnerable persons. It recommends these new protections with the deepest respect for those involved in research on these disorders: the person with a disorder that may affect decisionmaking capacity, whose autonomy must be protected and, when possible, enhanced; the clinical investigators who are dedicated to the alleviation of these terrible afflictions; and informal caregivers, whose own lives are often virtually absorbed by the tragedy that has befallen their loved ones. In view of the ethical uncertainties noted by those involved in such research—as investigators, subjects, or family members—we believe that enhanced protections will promote broad-based support for further research by engendering greater public trust and confidence that subjects' rights and interests are fully respected. This concluding chapter presents the Commission's recommendations and identifies where possible those who should be responsible for their implementation.[253]

Concerns have been expressed that requiring new protections on research involving persons with mental disorders might limit such research and therefore impede the development of new methods of diagnosis or treatment.[254] It is difficult to

[252] See, for example, *Journal of the American Medical Association,* August 19, 1998.

[253] The conclusions and recommendations directly address research that involves adult patients or subjects in research. Those charged with reviewing and implementing the recommendations should consider whether they need to be modified when applied to research with children.

[254]National Institutes of Health Panel Report, "Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs)," February 27, 1998, p. 1.

evaluate such claims because there is, to date, insufficient evidence to support or reject them. NBAC does not believe, however, that the additional protections recommended in this report will excessively burden or hamper the development of effective new treatments. Moreover, it is useful to note that many share the responsibility to protect the interests of those without whom this research could not be done—especially those who may be unable to give full informed consent and who may not themselves directly benefit from the research. All research involving human beings must satisfy appropriate ethical standards. That is, both the means and ends of individual studies must be morally acceptable. This moral imperative is especially acute for potentially vulnerable populations such as individuals with mental disorders.

A cogent case can be made for requiring additional special protections in research involving persons with mental disorders. Although many, indeed, most, of these additional protections could also be considered for research involving others who may have impaired decisionmaking capacity, the focus of this report is on persons with mental disorders. NBAC believes that in addition to the regulations that already apply to all research conducted or sponsored by the federal government, or that is otherwise subject to federal regulation, IRB deliberations and decisions about research involving subjects with mental disorders that may affect decisionmaking capacity should be governed by specific additional regulations.

The following 20 recommendations are clustered into six categories. Many are specific to the development of new federal regulations for the protection of human subjects; others are directed to investigators and IRBs, state legislatures, the National Institutes of Health, health professionals, federal agencies subject to the Common Rule, and others responsible for human subjects protection. These recommendations provide both a set of requirements that we believe must be satisfied in all research protocols involving persons with mental disorders, and several additional or optional protections that may be considered as appropriate in particular circumstances. Taken

together, these recommendations would both enhance existing protections and facilitate continued research on mental disorders.

Recommendations for New Regulations

In the United States, regulations have provided perhaps the most important means of protecting the rights and welfare of human subjects. But they have not been the only means. Clearly, for example, widely accepted professional norms have also played a role. The desirability of additional governmental regulation depends not only on the nature and importance of the problems the proposed new rules aim to address, but also on the regulation's ultimate efficacy. Presumably, the least complex measures taken by governmental entities are the preferred ones, as long as those measures can achieve the important societal goals that have been identified. Many who are familiar with the federal regulations currently governing human subjects research complain that they are already too complex and bureaucratic. Some of those engaged in research on conditions related to mental disorders fear that further regulation will unnecessarily slow scientific progress and inappropriately stigmatize individuals who may be suitable and appropriate research subjects.

Whatever one's view of the current regulations, the period since their adoption has been, in the judgment of some, largely free of the sorts of large-scale problems and abuses that led to their initial promulgation. Others, however, stress that the issues discussed in this report illustrate some of the shortcomings of the Common Rule. In this context, NBAC was obliged to determine whether the outstanding issues and problems in research involving persons with mental disorders warrant new regulations and/or whether some or all of the required reforms could be advanced through other mechanisms. These might include statements of principle or the adoption of guidelines by those individuals and/or professional groups involved in reviewing,

regulating, and carrying out these projects, or the development of educational materials for all relevant parties.

Although we propose a number of recommendations that would require changes in the language of the Common Rule, we are mindful that the time frame for such reforms might be long and the process labor intensive. Many of the proposals made by NBAC for regulatory reform, could, however, also be accomplished by the creation of a new subpart in 45 CFR 46. Adoption of a subpart has the advantage of permitting affected federal agencies to act as expeditiously as they choose to change the regulatory requirements for their own intramural and extramural research.

I. Recommendations Regarding Review Bodies

IRB Membership

Recommendation 1. All IRBs that regularly consider proposals involving persons with mental disorders should include at least two members who are familiar with the nature of these disorders and with the concerns of the population being studied. At least one of these IRB members should be a member of the population being studied, a family member [or trusted friend] of such a person, or a representative of an advocacy organization for this population. These IRB members should be present and voting when such protocols are discussed. IRBs that only irregularly consider such protocols should involve in their discussion two *ad hoc* consultants who are familiar with the nature of these disorders and with the concerns of the population being studied; at least one of these two consultants should be a member of the population being studied, or a family member [or trusted friend] of such a person, or a representative of an advocacy organization for this population.

The issues considered in this report are as complex and as multifaceted as the research protocols designed to advance medical knowledge about mental disorders.

Some of these issues are likely to arise routinely in protocols involving research subjects with such disorders. By increasing representation of the subject population on IRBs and in planning clinical research relevant to their disorders, investigators and their research institutions improve the likelihood that protocols will be both better designed and responsive to the interests of the affected groups.[255] It is for these reasons that the Common Rule directs those IRBs that frequently review research involving a vulnerable subject group to consider including as reviewers persons knowledgeable about and experienced with working with the relevant subject group.[256] The current provision, however, is advisory only; moreover, it refers only to the involvement of expert professionals, not to others who might also represent the interests of vulnerable subject groups. Nonetheless, some agencies and research institutions have already required the inclusion of such individuals on IRBs. For example, the Department of Education's National Institute for Disability and Rehabilitative Research (NIDRR) must comply with a regulation that, "If an [IRB] reviews research that purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research subjects, the IRB must have at least one person primarily concerned with the welfare of these research subjects."[257] This regulation was published on the same day in 1991, as was the Common Rule.

After evaluating schizophrenia studies at University of California, Los Angeles (UCLA), the Office for Protection from Research Risks (OPRR) took the stronger measure of directing the UCLA School of Medicine's IRB to "engage one or more subject representatives as IRB members who will assist the IRB in the review of issues

[255]For example, the NIH Expert Panel also recommended that IRBs include "voting members representing patient advocate groups, family members, and others not affiliated with the research institution." Expert Panel Report to the National Institutes of Health, *Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs),* p. 3 (February 1998).
[256]45 CFR 46.107(f).
[257]34 CFR 97.100.

related to the rights and welfare of subjects with severe psychiatric disorders."[258] This requirement was imposed even though the IRB already had a psychiatrist and a psychologist as members.[259]

This recommendation aims to ensure that the special concerns and knowledge of this population are represented in IRB deliberations and conveyed, as appropriate, to investigators. Persons who have suffered from mental disorders, or those who are familiar with the problems caused by these disorders, are often in a unique and valuable position to help evaluate the potential vulnerability entailed by a specific research protocol.

Creation of a Standing Federal Review Panel

Recommendation 2. The Secretary of HHS should convene a standing Federal Panel on Research and Persons with Impaired Decisionmaking ("RAPID"). The Panel's tasks should include:

(A) reviewing individual protocols that have been forwarded by the IRB to the Panel for its consideration. If the Panel finds that a protocol offers the prospect of substantial future benefit to the population under study, that its risks to subjects are reasonable in relation to this importance, and that it could not be conducted without the proposed population, then the Panel may approve the protocol if it is satisfied that all appropriate safeguards are incorporated;

(B) promulgating guidelines on the basis of protocol-by-protocol review that would permit local IRBs to approve protocols that cannot otherwise be

[258]Office for Protection from Research Risks, supra, at 21-22.

approved under the recommendations described in this report. Such guidelines could suggest that a particular class or category of research using specified research interventions with certain identified populations, could be considered by local IRBs without the need to resort to the Panel for further approval. Under no circumstance, however, should the Panel promulgate guidelines permitting IRBs to enroll subjects who lack decisionmaking capacity in protocols that reasonable, competent persons would decline to enter.

(C) developing data to evaluate the risks of various research interventions and to offer guidance to IRBs about which interventions are likely to be of minimal risk in light of the study population; and

(D) developing data on the attitudes of potential subjects and others toward the prospect of participating in research, with particular attention to attitudes toward participating in research of more than minimal risk that offers no prospect of direct medical benefit.

The RAPID Panel should have members who can represent the diverse interests of the research and patient community, characterized by both broad and relevant expertise and independence. That is, there should be substantial representation from the clinical and research communities, from patients and subjects, and other interested persons. The Secretary should ensure that a range of viewpoints about the acceptability of research with this population is represented in its membership. Its studies, protocol approvals, and guidelines

[259]See also Shamoo & Hassner Sharav, supra, at S:29.

should all be published in an appropriate form that ensures reasonable notice to interested members of the public.

Those Federal agencies that are signatories to the Common Rule should agree to use the RAPID Panel, and the RAPID Panel's effectiveness should be reviewed no later than five years after inception.

In the case of research involving greater than minimal risk that does not hold out the prospect of direct medical benefit, there may be protocols that, while not meeting the requirements of Recommendation 11 below, nevertheless may present a compelling balance of risks and benefits, warranting further review. RAPID would review such protocols on a case-by-case basis. Over time, it could also set guidelines for entire categories of research. Once these guidelines were promulgated to IRBs, protocols consistent with these guidelines could be reviewed and approved by the local IRB. In reviewing individual protocols and considering particular categories of research, the panel should determine whether the research is exceptionally important and could not be conducted without involving subjects with mental disorders. In addition, the panel should specify: (1) any special procedures or protections needed to ensure that the risks to subjects are minimized; (2) the means to maximize the informed and voluntary nature of participation, including the permission obtained from subjects' legally authorized representatives; and (3) the IRB's special obligations to monitor the progress of the research and the on-going adequacy of the protection afforded subjects. RAPID should include members from among the following groups: former patients, members of patients' families, advocates for the rights and welfare of patients, experts in the law and ethics of experimentation, researchers, and clinicians with expertise in the area of research.

This recommendation is intended to provide some genuine flexibility for the system to respond to new knowledge and would help to create a greater uniformity of understanding in what is a controversial area. As stressed throughout this report, there remain certain concerns about the adequacy of protections for persons with mental disorders in research. NBAC is mindful however, that with advances being made in research, and the evolving increase in sensitivity of investigators and IRBs to ethical issues arising in research involving persons with mental disorders, there will be more examples of research that promise either significant scientific benefits for persons with mental disorders or significant increases in understanding of their conditions. By assessing these examples on a case-by-case basis through an open consensus process, the Secretary would have access to a gradually evolving list of research examples (including the procedures used and any special protections required). Such a process might eventually result in an informed delegation to IRBs to approve research of this kind.

As already noted the Secretary's authority within the regulations pertaining to research with children includes a provision for a special review process, which has been rarely used. The intent of this recommendation is to provide the Secretary with a more viable and flexible mechanism to address important concerns addressed by researchers and the public: how, if at all, can potentially important research that does not hold out the prospect of direct benefit to subjects be conducted on persons with mental disorders who lack decision making capacity, when the very ability of the individual subjects to assess the risks of such research may be lacking? How can potential subjects and their families be assured that their rights and welfare are protected? This mechanism may provide a way forward.

II. Recommendations Regarding Research Design

Appropriate Subject Population

Recommendation 3. An IRB should not approve research targeting persons with mental disorders as subjects when such research can be done with other subjects.

One important justification for research involving those with mental disorders is the need for progress in the treatment of these very conditions. However, because of this population's special vulnerability, we should prohibit research targeting them if that research can be conducted equally well with other subjects. At least two reasons support this prohibition. First, it is important, on grounds of justice and fairness, to discourage any tendency to engage these persons in research simply because they are in some sense more available and perhaps more vulnerable than others. Second, this prohibition would further reinforce the importance of informed consent in human subjects research. The principles of respect for persons and justice jointly imply that IRBs should not approve research protocols targeting persons with decisional impairments due to mental disorders when the research does not by design require such subjects.

There are circumstances, however, under which the use of subjects without these disorders may not be scientifically valid or appropriate. For example, if the research bears directly on a disorder that underlies the subject's decisional impairment, and the disorder is commonly associated with such an impairment, then it may not be possible to learn how to improve diagnosis and treatment for that disorder without at some stage involving subjects who are so affected. But if the research involves new ways to protect against diseases that are also common among those who do not have mental disorders that affect their decisionmaking capacity, then individuals with impaired decisionmaking capacity should not be targeted for recruitment.

An individual with impaired decisionmaking ability who, for any reason, is not otherwise an appropriate subject for a particular protocol may have a life-threatening condition for which there is no satisfactory treatment. Under these circumstances, when the protocol is designed to ameliorate or potentially cure the life-threatening condition, current regulations permit these individuals, on compassionate grounds, to obtain the investigational treatment.[260] Therefore, as a matter of justice, all persons, regardless of their decisionmaking capacity, whose best therapeutic alternative may be an innovative treatment, should have access to it. NBAC is not suggesting that individuals with mental disorders should be precluded from participating in research unrelated to their mental disorder. These same individuals, were they able to consent, would be permitted, as any person would, to choose to enter a study unrelated to their condition. This recommendation is in line with current regulations, which provide additional protections to certain potentially vulnerable populations to ensure that they are not unfairly burdened with involvement in research simply because, for example, they may be more easily available.

Justifying Research Design and Minimizing Risks

Recommendation 4. Investigators should provide IRBs with a thorough justification of the research design they will use, including a description of ways to minimize the risk to subjects. In studies that are designed to provoke symptoms, to withdraw patients rapidly from therapies, to randomize patients

[260]The specific term used in the regulations is "treatment use." 21 CFR § 312.34; (b) Criteria. (1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if: (i) The drug is intended to treat a serious or immediately life-threatening disease; (ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; (iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and (iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

into placebo controlled trials, or otherwise to expose subjects to similar risks, IRBs should exercise heightened scrutiny.

The protection of human subjects begins with an ethical study design that not only ensures the scientific validity and importance of the proposed protocol but also minimizes risks to subjects while still allowing the study objectives to be met. This process is accomplished by a variety of approaches, including the use of prior scientific review by established peer review groups and review by an IRB. In many institutions, separate scientific review precedes an IRB's assessment of a protocol. In some institutions, IRBs also ensure the scientific merit of a protocol through using their own members or outside consultants. Regardless of which method is used, investigators and IRBs must consider ways to assess how the particular proposed research protocol would affect subjects in order to design a protocol that will incorporate appropriate protections.

Since several specific designs used in research on mental disorders have raised concerns about the relationship between study design and increased risk to subjects, there is a special obligation, whenever an ethically controversial research design is proposed, for the investigators to make every effort to minimize any risks associated with it. In particular, IRBs should be expected to require a clear justification for studies that include symptom provocation, placebo controls, or washout periods (particularly those involving rapid medication withdrawal), and to review carefully the criteria for including or excluding individuals from a study as well as the likely reasons for subject withdrawal, and follow-up care, if any. In such research, the researcher and the IRB have a special obligation to ensure that the subjects or LARs are fully cognizant of the nature of the clinical trial and possible consequences of these designs.

Because many decisional impairments are associated with mental disorders that can be managed symptomatically with anti-psychotic medication, it can be argued that it is unethical to include a placebo arm in the study when a known risk is the return of

symptoms. Thus, some contend that new drug investigations should use standard therapy as a control, in spite of the additional methodological difficulties of such designs.[261] The possible grounds for excluding placebo arms in particular studies include the following: (1) an individualized assessment reveals that certain patients would be at high risk for relapse if a current or prospective therapeutic regimen were discontinued; (2) a washout period would not be contemplated for these patients if they were not enrolling in a study; or (3) standard therapy is previously proven to be effective, if not ideal.

When drug-free research is conducted (whether as part of a blinded placebo-controlled study or otherwise), it is important to follow patient-subjects who are at risk for relapse. IRBs currently have the authority to follow up studies that they approve. In studies in which patients are at risk of relapse, IRBs should give particular attention to exercising this authority.

Evaluating Risks and Benefits

Recommendation 5. Investigators should provide to IRBs a thorough evaluation of the risks and potential benefits to the human subjects involved in the proposed protocol. The evaluation of risks includes the nature, probability and magnitude of any harms or discomforts to the subjects. The evaluation of benefits should distinguish possible direct medical benefits to the subjects from other types of benefits.

This recommendation reaffirms what is already in the federal regulations, with a particular emphasis on tailoring the risk assessment to the population under study. The assessments should include consideration of the particular procedures proposed and their relationship to the specific conditions of the individuals who may be involved as

[261] Addington D. op cit. Rothman K.J. op cit.

study subjects. IRBs should be alert to the possibility that researcher and subjects may not evaluate the risks and benefits of a particular study in the same way.

Since there has been some apparent confusion about what the current federal regulations say about levels of risk, it must be emphasized that only the regulations relating to children, found at Subpart D of the Department of Health and Human Services' regulations (and its comparable set of regulations in the Department of Education), refer to three levels of risk. These regulations are not part of the Common Rule (which is limited only to Subpart A), [262] and hence are not applicable to all agencies that are signatories to the Common Rule. Under current regulations agencies, investigators, and IRBs may choose voluntarily to adopt a three-tiered approach to risk assessment, should they find it to be useful. In NBAC's view, no change is needed in this component of the Common Rule, but greater attention should be given to the assessment of levels of risk by IRBs and investigators so that judgments of risk in relation to potential benefit and the level of protection provided to subjects can be more appropriately related to the protocols themselves. In particular, this will be important for research in which disagreement exists about whether the risk is minimal. Although the regulations contain language that defines minimal risk, care is needed when determining whether (or how) the definitional category applies to research involving persons with mental disorders.

The risk categories in the current regulations do not automatically apply to particular procedures, but must be applied contextually in light of specific study conditions. Recently, the list of the categories of research has been revised which may

[262] 45 CFR 46.100.

be reviewed by IRBs using an expedited review procedure[263] and provides several examples. The need for sensitivity in the application of risk categories is especially great when persons with mental disorders are among the potential subjects of a study. For some persons with mental disorders their limited ability to understand the rationale for a specific intervention could cause them more distress than it would for someone who fully understood the reason for the intervention. For example, repeated venipunctures (blood draws), which might be innocuous to many people, could be quite disturbing to persons with limited understanding. Thus, a procedure that *per se* presents minimal risk could nonetheless be highly threatening to those who are unable to appreciate the procedure's context or the nature of their current situation.

In particular, those who lack the practical ability to function autonomously, as in the case of institutionalized persons, may have distorted perceptions of otherwise minor interventions. Those whose treating doctor is also the researcher may feel unable to withdraw from a study and may feel more threatened by the risks of a procedure than is objectively the case. Assessments of risk levels by investigators and IRBs may thus need to be adjusted according to the circumstances of individual subjects, because *a priori* categorization may not be sufficient.

As a consequence, clinical investigators who propose to involve persons with mental disorders as subjects in research must carefully articulate to IRBs the nature of their risk evaluation procedures for potential subjects. Even within a given protocol, the same intervention may entail different risk levels for different individuals depending on their particular condition. When the level of risk may be perceived to be higher for some subjects than for others, the determination of risk for the entire

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[263] See for example, the recently revised statement "Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an expedited review procedure" November 1998. Federal Register xxxxxxxx.

subject group should be made conservatively. Moreover, the intensity of informed consent processes and other special protections should increase as the level of risk increases. Both investigators and IRBs should be sensitive to these considerations and adjust the required set of protections accordingly.

III. Recommendations Regarding Informed Consent and Capacity

Informed Consent to Research

Recommendation 6. No person who is capable of making informed decisions may be enrolled in a study without his or her informed consent. When potential subjects are capable of making informed decisions about participation, they may accept or decline participation without involvement by any third parties.

Regardless of a diagnosis of a mental disorder, persons capable of making informed decisions cannot be enrolled in a study without their informed consent (unless, of course, consent is waived). This merely reaffirms what is already in the federal regulations. A third party, such as a relative or friend, may not override the informed decisions of capable people. Where decision-making capacity is expected to decline or fluctuate over time, however, IRBs should ensure that the subject is offered the opportunity to appoint a LAR to make decisions if the subject's decision making capacity becomes impaired capacity is lost, consistent with Recommendation 14 below.

Ethically acceptable research involving either persons with fluctuating capacity or persons who face the prospect of permanent loss of capacity presents special challenges. To be part of an informed consent process, a potential research subject must be able to understand that consent to participate in a research study constitutes an agreement to take part in a project that will occur over a specified and perhaps extended period of time. Moreover, potential subjects should be aware that their

decision-making capacity may fluctuate or decline during the study. Potential subjects also need to recognize that being a research subject is different from being a patient, and that a decision to participate in research may involve agreeing to additional medical procedures.

Dissent from Participation in Research

Recommendation 7. A person's choice not to participate in research or not to continue in a study in which he or she is enrolled must be honored in all circumstances. An investigator, acting with a level of care and sensitivity that will avoid the possibility or the appearance of coercion, may approach people who previously chose not to participate in (or chose to withdraw from) a study to ascertain whether they have changed their minds.

Even when decisionmaking capacity appears to be severely impaired, respect for individual self-determination must prevail over any asserted duty to serve the public good as a research subject. Hence, dissent by a potential or actual subject must be honored, regardless of the level of risk or potential benefit, just as it would in the case of an individual who clearly retains decisional capacity. Respect for self-determination requires that we avoid forcing an individual to serve as a research subject, even when the research may be of direct benefit to the individual, when his or her decisional capacity is in doubt, or when the research poses no more than minimal risk. While dissent must always be respected, situations may arise in which the investigator could understandably return to the subject at a later point to ascertain whether the previous dissent still stands. This does not imply that dissent is not a valid expression of choice.

Assessing Potential Subjects' Capacity to Decide about Participating in a Research Protocol

Recommendation 8. For research protocols that present greater than minimal risk, an IRB should presume that the study will need to employ an appropriate method, administered by an independent, qualified professional, to assess the potential subject's capacity to decide whether to participate in the study. An IRB should permit an investigator to forgo this procedure [only] if persuasive grounds exist for using less formal methods of assessing a subject's capacity.

All potential human subjects are deemed to be capable of making decisions for themselves unless there is a particular reason to suspect that a capacity assessment will be necessary. IRBs, however, should be aware that incapacity may be more frequent among some people with certain mental disorders than in the general population. Therefore, IRBs can begin with the presumption that capacity assessments may be needed more often, and invite investigators to explain why this would be unnecessary for the particular group under study.

Capacity assessments are usually undertaken only when there are reasons to believe that potential subjects may be incapable of deciding about their participation in a study. Requiring a capacity assessment for all potential research subjects with mental disorders does not appear to be necessary. It perpetuates an incorrect assumption about persons in general, and about individuals with mental disorders in particular, namely that they are incapable unless assessed as capable. In a practical sense, requiring that IRBs approve all research (irrespective of risk) only when a capacity assessment has been provided would impose unnecessary and additional burdens on researchers and IRBs without providing an assurance of the intended protection. If a potential subject appears to lack capacity, his or her capacity should be assessed. NBAC's presumption is that for studies involving greater than minimal risk, IRBs will always expect that investigators will have subject capacity assessed by a qualified professional. NBAC notes that for studies involving minimal risk, IRBs would, of

course, also have the authority to require that a particular study include a capacity assessment if there are reasons to believe that potential subjects' capacity is impaired. The value of capacity assessment prior to enrollment of a subject in a minimal risk study is clear: by finding a potential subject incapable of deciding about participation in a study involving minimal risk, investigators would then be obligated to ensure that such subjects are enrolled only when permission has been obtained from a third party who is capable of making a decision on behalf of this person.

Notifying Subjects of Incapacity Determinations and Research Enrollments

Recommendation 9. A conscious person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative (LAR) to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject must then be notified. Should the person object to participating, this objection should, as always, be honored.

To be found decisionally incapable and then enrolled as a subject in a research protocol on the basis of alternative decisionmaking arrangements is to have certain rights curtailed, however justifiable the curtailment may be.

Whenever an individual is found to be decisionally incapable, that individual should be so notified, especially when such a finding could have important consequences for his or her medical treatment—such as enrollment in certain research protocols. [264] Such a notification process might seem, at times, to be an empty ritual that could undermine health professionals' respect for the regulatory system. Nevertheless, ethical treatment

of human subjects demands that this process be observed; failure to do so may potentially deprive the subject of the rights to seek review of the decision and pursue possible judicial intervention. People deserve to know that they have been found to lack the capacity to make a decision for themselves. At a minimum, this is a gesture of respect. And furthermore, this will allow them to express their assent or dissent. Thus, only with unconscious persons is this interaction no more than an empty ritual.

IV. Recommendations Regarding Categories of Research

Research Involving Minimal Risk

Recommendation 10. An IRB may approve a protocol that presents [only] minimal risk, if one of the following conditions applies:

(A) the potential subject gives informed consent; or

(B) the potential subject has given prospective authorization consent, consistent with Recommendation 13; or

(C) the potential subject's LAR gives permission, consistent with Recommendation 14.

Persons who are capable of giving informed consent may participate in research that presents minimal risk, regardless of the prospect of benefit. The types of research falling into this category are those defined by federal regulation. We recognize that some procedures, for example the use of magnetic resonance imaging, may fall within the category of minimal risk because federal regulation considers it a type of research that may be reviewed by an IRB through an expedited review procedure. But we also

[264] Another way to express this issue is whether the assent of incapable subjects should be required. Dresser, R., Research Involving Persons With Mental Disabilities: A Review of Policy Issues and Proposals (Contract Paper for

note that the procedures listed in the categories of research that qualify for expedited review are not to be considered minimal risk by virtue of being on this list. [265]

Research Involving Greater than Minimal Risk with the Prospect of Direct Medical Benefit to Subjects.

Recommendation 11. An IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefit to the subject if one of the following conditions applies:

(A) the potential subject gives informed consent; or

(B) the potential subject has given prospective authorization, consistent with Recommendation 13; or

(C) the potential subject's LAR gives permission, consistent with Recommendation 14.

IRBs must also comply with Recommendations 8 and 9.

Some important research cannot be done without the involvement of persons with mental disorders and some of that research may offer the prospect of direct medical benefit to those who participate. An example is the study of dopamine receptor function and schizophrenia, for which there are currently no suitable alternative models, and which could aid the treatment of individuals participating in the study.[266]

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the National Bioethics Advisory Commission, 1997)

[265] 45 CFR 46.110

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No one is obligated to participate in a study, even if it may be of direct medical benefit to him or her. Therefore, in order for research in this category to go forward, either (1) the potential subject's informed consent must be obtained, or (2) the subject's LAR must give permission for research participation *and* the subject must be given the opportunity to refuse participation. Again, regardless of his or her capacity at the time, the subject's dissent must be honored whenever it is expressed even if the individual has previously expressed a willingness to participate. A dissent may be overridden only through a judicial process, with full due process protections.

Research Involving Greater than Minimal Risk Research that does not Offer the Prospect of Direct Medical Benefit to Subjects

Recommendation 12. An IRB may approve a protocol that presents greater than minimal risk and offers no prospect of direct medical benefit to subjects, if one of the following conditions applies:

(A) the potential subject gives informed consent; or

(B) the potential subject has given prospective authorization, consistent with Recommendation 13; or

(C) the protocol falls within the guidelines announced by the RAPID Panel, and the potential subject's LAR gives permission, consistent with Recommendation 14; or

(D) the protocol is approved conditional upon further approval by the RAPID Panel described in Recommendation 2, and the potential subject's LAR gives permission, consistent with Recommendation 13.

IRBs must also comply with Recommendations 8 and 9.

Research involving persons with mental disorders that presents greater than minimal risk, but does not offer the prospect of direct benefit to these individuals, may be conducted only under the circumstances outlined above. For persons with the capacity to decide whether they want to participate in such a study, their informed consent is required. For persons about whom there is some question as to whether their capacity may fluctuate (or be lost entirely) during the study, their participation would be permitted only with evidence of that they had given prior authorization to such involvement; or, as we recommend above in Recommendation 2, the protocol has been approved by RAPID, or the protocol falls within a set of guidelines developed by RAPID and has been reviewed by an IRB.

VI. Recommendations Regarding Surrogate Decision Making

Prospective Authorization

Recommendation 13. A person who has the capacity to make decisions about participation in research may give prospective authorization to a specific type of research if its general risks, direct benefits, indirect benefits, and other pertinent conditions have been explained. Based on the prospective authorization, a LAR may enroll the subject after the subject has lost the capacity to make decisions, provided the LAR is available to monitor the subject's recruitment, participation, and withdrawal. The greater the risks posed by the research protocol under consideration, the more specific the subject's prospective authorization should be to entitle the LAR to permit enrollment.

Individuals should be permitted to express in advance of their potential involvement in a particular research protocol, or a type of research, their preferences in this regard.

Recommendation 14. A legally authorized representative (LAR) may give permission to enroll a person who lacks the capacity to decide whether to participate in a research protocol if:

(A) the LAR bases decisions about participation upon a best estimation of what the subject would have done if capable of making a decision; and

(B) the LAR is available to monitor the subject's recruitment, participation, and withdrawal from the study;

A legally authorized representative is an individual authorized by state statute, or to the extent permitted by law, or under previously published institutional rules, to make medical decisions on behalf of another individual.

Clinical investigators should incorporate into their protocols a plan to identify legally authorized representatives for potential subjects as part of the consent process. In many instances, individuals who do not have the capacity to participate in an informed consent process are still capable of appointing others whom they want to make important decisions on their behalf. These appointments, which may particularly include family members or close friends, should be recognized in state laws that firmly establish the status of legally authorized representative for research purposes. In order to preserve the subject's autonomy to the greatest extent possible, the legally authorized representative's decisions must be based upon the subject's wishes, so far as they are known; if the subject's wishes are unknown, then these decisions should be based upon the subject's best interests.

Involving Subjects' Family and Friends

Recommendation 15. Investigators and others involved in research with patients with mental disorders should find ways to recognize involved family and

friends of incapacitated patients as part of the healthcare team and to share appropriate information with them.

Professional organizations should begin discussions about methods to pursue this goal. Innovations in this area must, of course, be consistent with the ethical obligation of patient confidentiality.

Expansion of the Category of Legally Authorized Representatives

Recommendation 16. States that do not already recognize relatives and trusted friends as legally authorized representatives should expand their definitions accordingly by statute or judicial decision.

Expansion of the Powers Granted under Durable Powers of Attorney for Health Care

Recommendation 17. States should amend current laws governing "Durable Powers of Attorney" (or equivalent legislation) so that persons creating these kinds of documents would be entitled to grant decision making authority for research participation, as well as for clinical care, if the research either presents no more than minimal risk or presents the prospect of direct medical benefit to the subject.

Although their scope varies considerably, statutes in 36 states and the District of Columbia authorize surrogates (without need of judicial appointment) to make health care decisions when a patient lacks decision making capacity. In the other states, custom recognizes family members as surrogates. Most statutes relating to substitute decision making do not explicitly refer to research, although they may be construed as implicitly authorizing surrogate consent for participation in potential direct benefit research. The Commission is not aware of any state statutes that authorize a third party to enroll an incapable person in research that does not offer the prospect of direct medical benefit, even if the risk is minimal.

In addition, every state recognizes the durable power of attorney for health care (DPA) or an equivalent proxy designation mechanism. As is true of laws relating to substitute decision making, no state statutes authorize a proxy designated under a clinical DPA to consent to the patient-subject's participation in research that does not hold out the prospect of direct benefit to the subjects.

Although NBAC does not endorse the idea of authorizing third parties to enroll incapable subjects in research involving greater than minimal risk without the prospect of direct medical benefit, it is undoubtedly true that matters related to proxy decision making are ordinarily the province of state law, and principles of federalism suggest that deference be given to these state policy judgments. Here, however, each state has already decided to give clinical decision making authority to these proxies. It would do no violence to state prerogatives if, for the reasons stated in this report, the federal government were to extend the authority of these proxies so that they could grant permission for participation in certain federally conducted or funded research. This could be accomplished by an amendment to the Common Rule that would define the term "legally authorized representative" to include those who, under the law of the state where the research is conducted, may serve as proxy decision makers for clinical care. The authority of the legally authorized representative to enroll subjects would, however, extend only to minimal risk research or research involving greater than minimal risk where there is a prospect of direct medical benefit. Where greater than minimal risk research does not hold out the prospect of direct medical benefit, the authority of the LAR would extend only to permitting continued enrollment or withdrawal of the subject.

VII. Recommendations Regarding Education, Research, and Support

Reviewing and Developing Educational Materials Regarding Research

Recommendation 18. Professional associations and organizations should develop (or review their existing) educational materials pertaining to research involving persons with mental disorders.

A serious commitment to ethical research must be carried out at all levels of the research endeavor. Educational outreach through public and private organizations can serve as a valuable tool for ensuring the continuation of this commitment in the field. Agencies should develop educational materials addressing issues in research ethics for IRB members and investigators involved in research with persons who have mental disorders. NBAC further supports the development of educational materials to assist the general public (specifically populations of persons—and their families—who may encounter difficulties with decisionmaking capacity) in deciding about research participation. These materials should include information about risks and potential benefits of participation and should offer guidelines for making informed choices about research participation (e.g., how to protect oneself as a research subject, what questions to ask, who to ask). NBAC recommends that all materials be circulated widely in order to encourage a more general public dialogue regarding the social and scientific issues engendered by research in this field.

Expanding Knowledge about Capacity Assessments and Informed Consent

Recommendation 19. The National Institutes of Health should sponsor research that can expand knowledge concerning the most reliable methods for assessing decisionmaking capacity, the most comprehensive means of evaluating cognitive processes among those whose decisionmaking ability is impaired, and the best techniques for enhancing informed consent processes with persons who have decisional impairments.

NIH has recently sponsored a Request for Applications (RFA) on the subject of informed consent,[267] and has supported training opportunities and grants for courses in research ethics and should be commended for taking this initiative. Moreover, it sponsored a helpful meeting on the subject of research involving persons of questionable capacity, which has been extensively referenced in this report, and has drafted its own guidelines on the subject of this report.[268] In our view, NIH is ideally positioned to support further intensive research on many of the issues identified in our report.

Increased Funding to Support Necessary Protections of Human Subjects

Recommendation 20. When compliance with these recommendations requires additional expenditures, research sponsors (whether Federal or otherwise) should make such additional funds available, either as a new category of direct costs or through reimbursement of indirect costs.

Several of our recommendations, for example the requirement for independent capacity assessment and the establishment and use of additional review procedures, may require addition funds over and above that direct and indirect costs usually funded through federal grants. In our view, these additional protections are necessary and investigators should not be prevented from conducting important research because the resources to provide these necessary protections are unavailable.

Additional Guidance for IRBs

It will take time for the regulatory recommendations listed above to be implemented. Meanwhile, we hope that individual IRBs will adopt, on a voluntary basis, the spirit and substance of the additional protections described above. Those

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IRBs that choose not to adopt such policies should consider publicly disclosing these reasons and the resulting differences in their policies.[269]

The Research Context

IRBs should further consider whether the particular context of a proposed research protocol would tend to undermine the ability of persons with mental disorders to provide informed consent due to their psychosocial vulnerability or to their misconception of therapeutic efficacy. IRBs should be alert to potential conflicts arising from the dependence that in-patient or continuing-care subjects may have on their institutions, or from the dual role played by the potential subject's physician as a member of the research team (e.g., as a recruiter or as a source of names of potential subjects).

Considerations in Research Design

Subjects with serious illnesses are often more vulnerable than others to exploitation when they are involved in randomized clinical trials. Although the study itself must satisfy the condition of clinical equipoise, and may be designed to hold out the prospect of benefit, there will be instances in which the experimental arm of a study turns out to be more beneficial to subjects than the placebo arm (or standard care). One way to ameliorate this problem is to incorporate into the study design a non-research or "wraparound phase" following the conclusion of the research period, one that provides the subject with some beneficial intervention independently of the study itself. However, using a wraparound phase can be problematic because it may

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[269] NBAC is currently reviewing the federal system for overseeing human subjects protection, including the IRB system, and will issue a separate report on this subject. For this reason, this report offers only a few additional areas of guidance for IRBs; other, more comprehensive, recommendations for IRBs will appear in a subsequent report

shift the balance of protection in the opposite and equally problematic direction by providing an inappropriate incentive to participate in studies, that is to derive perceived benefits without having to pay for the treatment. Nevertheless, wraparound phases are suitable follow-ups to certain kinds of research, including those that provoke symptoms. In appropriate circumstances IRBs could require a wraparound phase as part of the overall study design.

Subjects who are included in study arms in which they receive an experimental drug are also vulnerable to unfair and exploitative treatment if the research results indicate that the drug is effective, and then those subjects do not receive it after the study concludes. In such circumstances, IRBs could condition study approval on the manufacturer's commitment to continue to supply the medication to research participants (including any subjects, such as placebo or standard therapy controls, who did not receive it during the study), although such a condition would have to be considered carefully in view of its potential for inappropriate inducement.

Possible Additional Protections for the Consent Process

The use of a consent auditor has been suggested as an additional procedural protection in the recruitment of research subjects who may be decisionally impaired. A consent auditor, who cannot be a member of the study team but may be, for example, a member of the IRB or an institutional ethicist, witnesses the consent process and then either certifies it as valid or informs the principal investigator that, due to the inadequacy of the process, an individual is not able to give valid consent. IRBs could require consent auditors for potential subjects who have conditions often associated with a decisional impairment. A system of audited consent would involve a substantial investment by research institutions, but the requirement could be limited to studies that have certain characteristics, such as those that involve greater than minimal risk and/or those that do not offer the prospect of direct medical benefit to the subject.

Studies with subjects who are decisionally impaired may take place over extended periods. One of the essential conditions of ethical research is the subject's continued voluntary participation, but those who are deeply involved with and dependent on the health care system may feel unable to withdraw from a study. A requirement for periodic reconsenting would help ensure that a patient's continued involvement is truly voluntary,[270] would provide the occasion to reassess decisionmaking capacity and, if necessary, would trigger an advance directive or surrogate arrangement. Reconsent arrangements conform with the spirit of informed consent as a process rather than a single event, and with the view that human research participants are partners in the study process rather than passive subjects.

Although re-consenting is another potentially labor-intensive measure that might add to the cost and complexity of the human research system, some long-term studies supported by the National Institute on Aging already include such a procedure.[271] IRBs should consider attaching a reconsent requirement to certain studies based on their length, on their risks and benefits, and on the mental condition

[270]An expert panel convened by NIH also notes that "repeated exposure to information in 'small doses' over time may greatly improve comprehension." Expert Panel Report to the National Institutes of Health, *Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs)* p14 (February 1998).

[271]One such example is the Baltimore Longitudinal Study of Aging (BLSA). The protocol for reconsenting participants was described to NBAC as follows: "At this time, competency evaluations are done by a working group in the Laboratory of Personality and Cognition composed of Susan Resnick (NIA neuropsychologist), Claudia Kawas (a collaborating neurologist from JHMI), Jeff Metter (physician), and if necessary Chester Schmidt (Chief of Psychiatry at JHBMC). Each BLSA participant has a baseline cognitive assessment done upon entry to the study. Cognition is not formally assessed by serial determinations until participants are 55 years of age when most patients undergo the cognitive battery administered by the Cognition Section of LPC. Once patients enter this phase of the study, their test results are reviewed and if substantial loss of cognitive function is suspected the participant and his/her records (medical and psychometric) are reviewed by Drs. Resnick, Kawas, and Metter. At this time, Dr. Kawas performs a formal neurological evaluation to determine a medical cause of the cognition decline. In the case in which affective disorders are suspected, Dr. Schmidt will be consulted. Family members are immediately involved in the status of the evaluation and if competency is judged to be impaired, family members are asked to provide consent for further participation if the patient is agreeable and the family members believe that participation is in the interest of the patient. Since the BLSA is an observational study, not an interventional clinical one, issues of study-related risks (morbidity and mortality) have not been raised in terms of greater than minimal risk. Personal communication, Dr. Terrie Wetle, Deputy Director, National Institute on Aging, July 2, 1998.

of potential subjects, such as those with progressive neurological disorders or fluctuating capacity.

Further Considerations about LARs

In NBAC's view, LARs should be appointed by the potential subject. As the above recommendations reflect, the twin goals of appropriate protection of subjects and the conduct of high-quality research can be accomplished by utilizing a carefully described advance planning process. Anticipatory planning for research participation is not a "research advance directive" but a version of the standard informed consent process. A critical difference is that the planning process should include the prospect of a loss of decisionmaking capacity during the study period, a consideration that is not routinely part of an informed consent process. Research advance planning could involve the following elements: (a) the identification of a LAR, (b) the completion of a durable power of attorney document, which identifies the person designated as a LAR, and any specific and relevant information which would assist the LAR in making research decisions on behalf of the subjects should they later become incapable of deciding about research participation on their own.

For persons with fluctuating capacity and those who are at risk for loss of capacity during a study, NBAC's view is that comprehensive anticipatory planning for research participation should involve identifying a LAR who can function as a surrogate decision maker. There is always the possibility that unanticipated incidents will occur in a research study, incidents that a surrogate may find relevant to the subject's continued welfare and participation. The surrogate could be an informal caregiver—for example, a family member or close friend—but not a member of the study team.

In such anticipatory planning, the potential subject must understand that he or she has appointed a LAR as a surrogate to make decisions concerning continuing

research participation in a general class of research protocols should the subject become unable to make these decisions. The subject must further understand that the surrogate may never overrule the subject's wish not to participate in the research or in any part of it, but may overrule the subject's instructions to continue participation, under certain conditions. Potential subjects must be aware that they have given the researchers permission to provide their surrogate decision maker and their health care provider with information about treatment. The subjects should appreciate that, should their preferences change, they may alter their instructions at any time they have the capacity to do so, and that they may withdraw from the study at any time, whatever their level of decisionmaking capacity.

In turn, the researchers must agree to discuss information about the research site and the subject's treatment in the study (e.g., possibilities of decompensation, description of likely symptoms, data about medications and potential side effects, and possible danger to self or others) with the surrogate decision maker. The research team must also make adequate provision for a thorough diagnostic assessment of the subject's current clinical status and develop an appropriate continuing treatment plan should the subject decompensate, become unable to cooperate, and drop out of the study.[272]

During the course of the study, the surrogate should work closely with the subject's responsible health care professional to ensure the subject's welfare. The responsible health care professional, who can have no relationship with the research and should be concerned only with subject's well-being and interests, must follow the subject's treatment and be in communication with the surrogate.

Independent Health Care Professional Advisors

[272]This language was suggested in the public comment of Dr. Hermann Diesenhaus, July 31, 1998.

For greater than minimal risk research, whether or not direct medical benefit is possible, IRBs should consider whether to require that an independent health care professional be identified prior in advance of the research to serve as a consultant to the subject or their representative. The subjects or their LARs may or may not utilize the independent health care professional as they wish. Investigators should consider making available or accessible (to the subject or research site) any information the independent health care professional requests in relationship to the investigation.

Voluntary Self-evaluation

IRBs may consider, alone, with other IRBs, or in collaboration with professional organizations, voluntarily adopting NBAC's recommendations and then, after a suitable period of time, assessing the effect on the quality of the IRB review process. For example, since there has been considerable discussion in this report about the appropriateness of using two levels of risk in IRB review, it might be worthwhile to review protocols using this strategy, as compared with a strategy in which three (or more) risk levels are explicitly used. Where this evaluation is conducted in a more formal manner, the results could be published and shared with the IRB and research communities.

Guidance for Institutions

While investigators and IRBs bear a considerable responsibility for ensuring the ethical conduct of research involving human subjects, the institutions in which research occurs share some of this responsibility. In particular, since federal grants are awarded to institutions, not individual investigators, and since an Assurance of Compliance is negotiated between an institution and OPRR, the behavior of institutions may be thought of as the foundation upon which ethical practice is built.

Audit and Disclosure

The policies of IRBs and the institutions they serve play a central role in protecting human subjects, particularly vulnerable populations. Thus, IRBs should consider voluntarily undertaking a series of measures to open their activities to greater public view, accountability, and analysis. In this regard, NBAC makes the following general recommendations.

(1) Each IRB should make publicly available brief descriptions of the policies and procedures that characterize the key aspects of its ongoing work.

(2) Each IRB should provide, on an annual basis, appropriate summary statistics regarding the overall nature and scope of the activities it has approved.

(3) Each institution incorporating an IRB should adopt appropriate internal audit procedures to assure itself that its IRBs are following all appropriate rules and regulations.

It is NBAC's view that IRBs can effectively use the mechanisms of audit (both internal and external) and disclosure to improve accountability and inspire public confidence in their oversight activities. Indeed, these oversight tools can be an excellent substitute for a wide variety of excessively detailed rules and regulations. Furthermore, such mechanisms can be used by all institutions, for all research involving human subjects.

Summary of Recommendations

I. Recommendations Regarding Review Bodies

1. IRB Membership. All IRBs that regularly consider proposals involving persons with mental disorders should include at least two members who are familiar with the nature of these disorders and with the concerns of the population being studied.

2. RAPID. The Secretary of HHS should convene a standing Federal Panel on Research and Persons with Impaired Decisionmaking ("RAPID") to review protocols involving greater than minimal risk without the prospect of direct benefit, to develop guidelines for use by IRBs, and to develop data on risks of research interventions, and on attitudes to participation in research.

II. Research Design

3. Appropriate Subject Population. An IRB should not approve research targeting persons with mental disorders as subjects when such research can be done with other subjects.

4 Justifying Research Design and Minimizing Risks. Investigators should provide IRBs with a thorough justification of the research design they will use.

5 Risk and benefit evaluation. Investigators should provide to IRBs a thorough evaluation of the risks and potential benefits to the human subjects involved in the proposed protocol.

III. Capacity and Informed Consent

6. Informed consent to research. No person who is capable of making informed decisions may be enrolled in a study without his or her informed consent.

7. Dissent. A person's choice not to participate in research or not to continue in a study in which he or she is enrolled must be honored in all circumstances.

8. Capacity assessment. For research protocols that present greater than minimal risk, an IRB should presume that the study will need to employ an appropriate method, administered by an independent, qualified professional, to assess the potential subject's capacity to decide whether to participate in the study.

9. Notification. A conscious person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative (LAR) to enroll that person in the study.

III. Categories of Research

10. Research Involving Minimal Risk. An IRB may approve a protocol that presents minimal risk if the subject consents, or if they have authorized someone else to enroll them in a study.

11. Greater than minimal risk with the prospect of direct medical benefit. An IRB may approve a protocol if the subject consents, or if they have authorized someone else to enroll them in a study. IRBs would also be expected to comply with the recommendations regarding capacity assessment and notification.

12. Research Involving Greater than Minimal Risk Research that does not Offer the Prospect of Direct Medical Benefit to Subjects. An IRB may approve a protocol if

the potential subject gives informed consent; or the potential subject has given prospective authorization; or the protocol falls within the guidelines announced by the RAPID Panel, and the potential subject's LAR gives permission, consistent with Recommendation 14; or

V. Surrogate Decision Making

13. Prospective authorization. A person who has the capacity to make decisions about participation in research may give prospective authorization to a specific type of research if its general risks, direct benefits, indirect benefits, and other pertinent conditions have been explained.

14. Legally Authorized Representatives. A legally authorized representative (LAR) may give permission to enroll a person who lacks the capacity to decide whether to participate in a research protocol if the LAR bases decisions about participation upon a best estimation of what the subject would have done if capable of making a decision and the LAR is available to monitor the subject's recruitment, participation, and withdrawal from the study.

15. Involvement of Family and Friends. Investigators and others involved in research with patients with mental disorders should find ways to recognize involved family

and friends of incapacitated patients as part of the healthcare team and to share appropriate information with them.

16 States laws and LARs. States that do not already recognize relatives and trusted friends as legally authorized representatives should expand their definitions accordingly by statute or judicial decision.

17 State laws and Durable Powers of Attorney. States should amend current laws governing "Durable Powers of Attorney" (or equivalent legislation) so that persons creating these kinds of documents would be entitled to grant decision making authority for research participation

V. Education, Research, Support

18. Reviewing and Developing Educational Materials Regarding Research. Professional associations and organizations should develop (or review their existing) educational materials pertaining to research involving persons with mental disorders.

19. Expanding Knowledge about Capacity Assessments and Informed Consent

The National Institutes of Health should sponsor research that can expand knowledge concerning the most reliable methods for assessing decisionmaking capacity, the most comprehensive means of evaluating cognitive processes among those whose decisionmaking ability is impaired, and the best techniques for enhancing informed consent processes with persons who have decisional impairments.

20. Increased Funding to Support Necessary Protections of Human Subjects.

When compliance with these recommendations requires additional expenditures, research sponsors (whether Federal or otherwise) should make such additional funds available, either as a new category of direct costs or through reimbursement of indirect costs.

Appendix I. HISTORY OF REGULATORY EFFORTS IN THE UNITED STATES

When the National Commission was created in 1974, the decisionally impaired were among the special populations that it intended to consider, partly because of the controversy about lobotomy. In its 1978 *Report and Recommendations on Research Involving Those Institutionalized as Mentally Infirm*,[273] which came at the very end of its tenure, the National Commission rejected both the Nuremberg Code's complete ban and the 1964 Declaration of Helsinki's limitation on the involvement of incapable subjects in research. The members of the National Commission believed a less restrictive approach was justified to avoid indirect harm to incapable persons by crippling research efforts designed to yield potential treatment for these persons' conditions. They introduced this idea as follows:

> [S]ince some research involving the mentally infirm cannot be undertaken with any other group, and since this research may yield significant knowledge about the causes and treatment of mental disabilities, it is necessary to consider the consequences of prohibiting such research. Some argue that prohibiting such research might harm the class of mentally infirm persons as a whole by depriving them of benefits they could have received if the research had proceeded.[274]

This concept marked an important turning point in the social philosophy underlying the regulation of human subjects research, in that benefits to others (particularly others who now or may in the future suffer from the same disorder) who were not participating in a particular research protocol could now be given more weight. The

[273]National Commission, *Report and Recommendations, Research Involving Those Institutionalized as Mentally Infirm* (hereinafter *Report on Institutionalized Persons*) (Washington, DC: Department of Health, Education and Welfare [DHEW], 1978), pg. no.
[274]Ibid. , 58.

National Commission concluded that the dual goals of benefiting mentally infirm persons and protecting individual subjects from undue harm could be met by a third approach: incapable subjects could be involved in studies offering them potential direct benefit, as well as studies that did not offer potential direct benefit, as long as the burdens and risks of research participation did not exceed a certain level.

Based on this general approach, the National Commission created a framework for evaluating research involving incapable subjects. Its proposals regarding children and institutionalized persons with mental impairments were similar, though with some variation. Their common elements included a requirement to justify the involvement of these subject groups rather than alternative but less vulnerable subject populations; a hierarchy of research categories establishing more rigorous substantive and procedural standards for proposals presenting more-than-minimal risk to incapable subjects; and a mechanism for incapable subjects to provide input in the form of "assent" or objection to study participation—that is, a simple yes or no when questioned about willingness to be in a study.

Differences in the recommendations on children and institutionalized persons were based on the National Commission's recognition that some adults institutionalized as mentally infirm retain the ability to give an informed and voluntary decision. Because of concerns about the vulnerability of institutionalized persons, however, the National Commission recommended that IRBs be given discretion to appoint "an auditor to observe and assure the adequacy of the consent process for research" that presents greater-than-minimal risk. Moreover, the National Commission believed such auditors should be *required* in projects presenting no prospect of direct benefit and more-than-minimal risk to subjects. Their proposals also gave incapable

adults more authority than children to refuse study participation.[275] Finally, because incapable adults usually lack the legal guardian that most children have, the National Commission noted that in some cases a court-appointed guardian would be required to authorize research participation.

In response to the National Commission's work, the Department of Health, Education and Welfare (DHEW) proposed regulations to govern research on the two populations. Those affecting children were adopted by the Department of Health and Human Services (DHHS) in June 1983,[276] but those affecting persons institutionalized as mentally disabled never were.[277] The Secretary of DHHS attributed the government's failure to do so to "a lack of consensus" on the proposed regulatory provisions and to a judgment that the general regulations governing human subjects' participation sufficiently incorporated the National Commission's recommendations.[278] Robert Levine blames the reported lack of consensus on DHEW's earlier failure to adhere to the National Commission's recommendations.[279] DHEW's proposed regulations indicated that consent auditors might be mandatory for all research involving institutionalized mentally disabled persons, and suggested that the authorization of an additional person assigned the role of independent advocate might be necessary before an incapable person could become a research subject. During the public comment period, many respondents objected to these additional procedural

[275]The National Commission required explicit court authorization to involve an objecting institutionalized person in research. In contrast, the group recommended that parents be permitted to authorize research over a child's objection if the study presented a prospect of direct benefit to subjects not available outside the research context.

[276]"Protection of Human Subjects, Additional DHHS Protections for Children Involved as Subjects in Research" 48 no. 9818 (8 March 1983): pg. no. , microfiche.

[277]"Protection of Human Subjects, Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled," *Federal Register* 43 no. 53950 (17 November 1978): pg. no. , microfiche.

[278]President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Implementing Human Research Regulations* (Washington, DC: Government Printing Office, 1983): 23–9.

[279]R.J. Levine, "Proposed Regulations for Research Involving Those Institutionalized as Mentally Infirm: A Consideration of Their Relevance in 1996," *IRB* (September-October 1996): 1; see also R. Bonnie, "Research with Cognitively Impaired Subjects," 107. Bonnie also refers to opposition to special regulations for persons with mental illness on grounds that such an approach would foster negative stereotypes about such individuals.

requirements, presumably on the belief that they were unnecessary and overly burdensome to research.[280]

The 1981 DHHS rules largely followed from the National Commission's work. In 1991, these rules were codified for 16 federal agencies that conduct or sponsor research with human subjects and are now known as the "Common Rule."[281] The regulations authorize IRBs to institute additional but unspecified safeguards for research involving vulnerable groups, including the mentally disabled.[282] These safeguards could involve consultation with specialists concerning the risks and benefits of a procedure for this population, or special monitoring of consent processes to ensure voluntariness. It is not known how frequently IRBs actually implement such measures.[283]

In the United States today, research involving adults diagnosed with a condition characterized by mental impairment is governed by no special regulations, but falls instead under the Common Rule, in which a few provisions address research involving persons with mental disabilities. First, the Common Rule identifies "mentally disabled persons" as a vulnerable population, and directs IRBs to include "additional [unspecified] safeguards . . . to protect the rights and welfare" of mentally disabled research subjects. It also advises IRBs to ensure that "subject selection is equitable," and that mentally disabled persons are not targeted for involvement in research that could be conducted on a less vulnerable group.[284] Finally, "[i]f an IRB regularly reviews research that involves a vulnerable category of subjects, such as . . . mentally disabled persons, consideration should be given to the inclusion of one or more

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[280]Ibid.
[281]"Federal Policy for the Protection of Human Subjects: Notices and Rules," *Federal Register* 56 nos. 28002–32 (18 June 18, 1991): pg. no., microfiche.
[282]Ibid.
[283]National Institutes of Health Panel Report, *Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs)* (27 February 1998), pg. no. The report indicated that IRBs regularly exercise this authority.
[284]45 CFR 46.111(a)(3), (b).

individuals who are knowledgeable about and experienced in working with these subjects."[285] The Common Rule allows an incapable individual's "legally authorized representative" to give valid consent to the individual's research participation, [286] but provides no definition of incapacity, no guidance on the identity or qualifications of a subject representative beyond “legally authorized,” and no guidance on what ratio of risks to potential benefits is acceptable.

In the 1980s and 1990s, numerous groups and individuals expressed dissatisfaction with gaps in the existing regulations. After the Advisory Committee on Human Radiation Experiments reviewed eight studies conducted in the early 1990s involving adult subjects with uncertain decisionmaking capacity, and found that four of the studies required subjects to undergo diagnostic imaging that offered them no prospect of direct benefit and that two appeared to present greater-than-minimal risk to the subjects, it noted, "there was no discussion in the documents or consent form of the implications for the subjects of these potentially anxiety-provoking conditions. Nor was there discussion of the subjects' capacity to consent or evidence that appropriate surrogate decision makers had given permission for their participation." [287] Inquiries into studies involving rapid medication withdrawal from persons diagnosed with schizophrenia have also raised questions about the adequacy of current federal policy and the ethical acceptability of certain existing research protocols.[288]

NBAC is not aware of strong evidence that IRBs are actively using, or not using, their existing discretionary authority when reviewing protocols involving individuals with mental or brain disorders. In addition, although IRBs currently have authority to monitor research in progress, including research involving persons with mental disorders, it does not appear that such monitoring routinely occurs, possibly

[285]Ibid., 107(a).
[286]Ibid., 116.
[287]ACHRE, *Final Report*, 706–7.
[288]A. Shamoo, “Ethical Concerns.”

because institutional and other resources have not been devoted to this critical activity. Observers of the review process agree that although the workload of many IRBs at some of the largest research centers has greatly increased in recent years, the institutional support for IRB activities has often not kept pace.[289] While some institutions have responded to this increase by establishing more than one board, the practice may not be widespread enough. According to the report of the DHHS Office of the Inspector General, monitoring of a protocol's progress after its initial approval is practically nonexistent apart from investigators' routine filing of annual progress reports. After the initial stages, local review has only minimal impact on actual research practices.[290]

The lack of more specific federal guidance on research involving persons with mental disorders has also meant that research not under federal jurisdiction has gone its own way, or rather at least 50 different ways, because state laws and regulations vary widely; most states have no rules that specifically apply to research involving this population while some states have quite restrictive regulations. Several states currently prohibit certain types of research on persons with mental disorders, research which presents greater than minimal risk and from which subjects are not likely to benefit. [291]

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[289]Department of Health and Human Services, Office of the Inspector General, *Institutional Review Boards: Their Role in Reviewing Approved Research* (Washington, DC: DHHS, 1998).

[290]U.S. General Accounting Office, *Continued Vigilance Critical to Protecting Human Subjects,* report to the Ranking Minority Member, Committee on Governmental Affairs, U.S. Senate, Scientific Research (Washington, DC: Government Accounting Office, 1996).

[291]Those states are Alaska. See, e.g., Alaska Stat. §47.30.830 (Michie 1996) prohibiting experimental research on state mental health patients that involve "any significant risk of physical or psychological harm"; Delaware Code Ann. tit. 16, §51.75(f) (1995) prohibiting any resident of a state mental hospital from being approached "to participate in pharmaceutical research if [the] patient is incapable of understanding the nature and consequences of [the] patient's consent"); Delaware Code Ann. tit. 16, §51.74 (1995) prohibiting certain classes of mental hospital residents, regardless of competency, from participating in pharmaceutical research; 405 Illinois, Comp. Stat. Ann. 5/2-110 (West 1993) providing that parent or guardian cannot consent to ward's participation in any "unusual, hazardous, or experimental services" without approval by court and determination that such services are in the "best interests" of the ward); Massachusetts Regs. Code tit. 104, §13.01–.05 (1995) prohibiting research on patients in mental facilities that will not provide direct, therapeutic benefit and prohibiting research on patients with mental disabilities where the risk is more than minimal and exceeds the benefit to the subject; Missouri Ann. Stat. §6.30.115 (8) (West Sup. 1997) preventing state mental health patients from being "the subject of experimental research," with exceptions, and prohibiting biomedical or pharmacological research from being

This suggests that both IRBs and researchers may have trouble identifying (and thus following) the procedures and standards that are requisite to ethical and legal investigations involving persons with mental disorders, even in states that have attempted to provide the badly needed guidance.

Uncertainty about legal and ethical norms can contribute to an adversarial tone in public discourse about this kind of research. Indeed, as events in New York State illustrate, advocacy of sharply differing ethical perspectives can result in litigation. In a case called *T.D. v. New York State Office of Mental Health*, several individuals and organizations challenged regulations of the New York State Office of Mental Health with respect to participation in greater than minimal risk research by minors and persons who lacked the capacity to give informed consent. In 1995, the trial court invalidated the regulations on the grounds that the Office of Mental Health lacked statutory authority to adopt them.[292] The next year, the intermediate appellate court in New York agreed with the trial court's conclusion but added a far more wide-ranging critique of the regulations, opining that they violated both constitutional due process rights and substantive protections granted these research subjects under New York's

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performed on any individual with mental disabilities if that research will have no direct therapeutic benefit on the individual research subject; Diane E. Hoffman amd Jack Schwartz, *Proxy Consent to Participation of the Decisionally Impaired in Medical Research,* Maryland's Policy Initiative, I J. Health Care Law and Policy 136, nos. 9 and 12 (1997) citing state statutes which provide restrictions for research on the decisionally impaired; John C. Fletcher and Alison Whitman , *A New Consent Policy for Research with Impaired Human Subjects, Psychopharmacology Bulletin* 23 (1987): 382. Virginia's state statute also [to be completed]. Washington State's statute (RCA 7.70.065) permits consent on behalf of an incompetent subject by (1) the appointed guardian, (2) the person to whom the subject has given a durable power of attorney including the authority to make health care decisions, (3) the subject's spouse, (4) the adult children of the subject, (5) the parents of the subject, and (6) the adult siblings of the subject, in that order of priority. According to this statute, a legally incompetent subject for research purposes is one who is incapable of providing informed consent by reason of unconsciousness, mental illness, developmental disability, senility, excessive use of drugs, or other mental incapacity (RCA 11,88.010).

[292] *Case name?*, 626 N.Y.S. 2d 1015, N.Y. Sup. Ct. 1995.

statutory and common law.[293] Finally, however, New York's highest court narrowed the judicial holding to the original decision of the trial court. [294]

Cognizant of New York's imbroglio, officials in Maryland have undertaken a less adversarial process of policy formulation. A working group under the auspices of the Maryland Attorney General has, over more than two years, produced a series of reports culminating in a proposed state statute that would govern the substantive and procedural aspects of research involving "decisionally incapacitated individuals." [295]

[293] *Case name?*, 650 N.Y.S. 2d 173, N.Y. App. Div. 1996.
[294] *Case name?*, 690 N.E. 2d 1259, N.Y. 1977. According to the New York Court of Appeals, the intermediate appellate court's discussion of constitutional, common law, and other statutory issues was "an inappropriate advisory opinion."
[295] Office of the Maryland Attorney General. *Final Report.*

Appendix 2: Review of Selected Research Protocols and Consent Forms

During the course of writing this report, NBAC became informed in various ways of field practices in research involving subjects with mental disorders that may affect their decisionmaking capacity. NBAC heard oral testimony from researchers, IRB members, persons who had previously been research subjects, and subjects' family members. It received written testimony from numerous interested parties throughout the period. NBAC also solicited widely others' views on a late draft of the report, posting the report on the World Wide Web, and receiving comments via email and by traditional mail. Moreover, NBAC referred to the scientific literature and looked at protocols and consent forms from which research articles evolved. This last category of inquiry was, in shorthand, referred to as the Protocol Project, a description of which follows.

In the Protocol Project NBAC focused on research that met five criteria- the research was recently conducted in United States, appeared to present greater than minimal risk, and offered no direct therapeutic benefit; the subjects were persons with mental disorders that may affect decisionmaking capacity, and the research design included at least one of the following: washout, placebo, or symptom provocation. A Medline search was conducted to identify scientific articles published in the U.S. after 1995, which met these criteria. The Medline

search retrieved a list of articles and summaries which were vetted first by reviewing the article summaries, then, those remaining were further scrutinized by a thorough reading. Any of the articles that did not meet all the criteria were ignored. Having identified articles that fell within the established parameters, NBAC requested from the authors a copy of the underlying protocols and consent forms, with private information redacted. Of the nearly 60 requests for protocols, only 13 sets of materials were provided to NBAC. Given the small numbers, no generalized findings were made. These materials did, however, provide information about capacity some insight into research that has been conducted in this country.

The protocols and consent forms received by NBAC were analyzed. A review sheet was utilized to allow side-by-side comparison of elements expected to be present in the protocol and consent forms. Finally, by comparing the review sheets NBAC identified innovative practices that should be employed more broadly by those practicing in the field, as well as practices that should be avoided.

Several themes emerged from NBAC's protocol review. They included subject recruitment practices that appeared potentially coercive, failure to provide capacity assessment, partial disclosure of risks and research design in the consent form, inappropriate characterization of risks as minimal, overemphasis on benefits, failure to discuss or include monitoring procedures, and the use of psychiatric patients as controls in studies not related to their mental disorder. In this report, NBAC assumes that research is conducted in compliance with requirements of the Federal Policy for the Protection of Human Subjects. However, the disclosure of pertinent information in the consent form,

such as subject inclusion/exclusion criteria and expected risks and benefits, is one requirement that, according to NBAC's brief review, may not receive adequately attention in the field.

1

Protocol Title:

Reviewers Name:

	Protocol			Disclosed to Subject in Consent Form ?
	Approp. Discussed	Mentioned	Not Mentioned	
Subject Selection				
Inclusion/Exclusion				
Capacity Assessment				
Subjects Lack Capacity? Yes No Unclear				
3rd Party Consent Option *(if subject lacks capacity*)				
Methods Placebo Washout Symptom-Provoking				
Risks *(including non-physical)*				
Benefits *(including inducements)* Direct Benefit Indirect Benefit No Benefit				

2 Notes ***(see reverse or attached)***

Appendix 3: Flow Chart for IRBs Reviewing Research Protocols Involving Subjects with Mental Disorders that May Affect Decision Making

Appendix 4: Title 45 CFR Part 46—Federal Policy for the Protection of Human Subjects (enclosed)