A Draft Report of the National Bioethics Advisory Commission:

Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity

October 20, 1998

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Chapter One: RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY

The Purpose of This Report

A wide variety of important research studies using human subjects[1] has long played an essential and irreplaceable role in advancing biomedical and behavioral science, thus enhancing our ability to treat illness and understand human behavior more successfully. 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, 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 to protect human subjects. The two most fundamental measures developed to meet these dual goals are an independent review of protocols by an institutional review board to ensure their scientific validity and importance as well as their ethical acceptability, and the informed consent of human subjects.

Although existing regulations have provided special protections for certain populations that are regarded as particularly vulnerable,[2] persons with mental disorders who may have impaired capacity to make decisions have not received any such special

[1]In this report, NBAC refers to persons on whom research interventions are performed (including participants who serve as members of a "control group" in clinical studies) as "subjects," consistent with the language in current federal regulations. Since the report also concerns itself with individuals who are not now (but might beresearch subjects, we will generally refer to "persons" when discussing these individuals.

[2]Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks (hereinafter cited as OPRR), *Title 45: Public Welfare: Code of Federal Regulations, Part 46—Protection of Human Subjects, Subparts B, C, and D* (June 18,1991 revised) provides special protections pertaining to research involving the following vulnerable populations: fetuses, pregnant women, prisoners, and children. 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. As a general rule, consent for research into their disease (e.g., cancer or sepsis) cannot be obtained from persons who lack the capacity for such autonomous consent (hereinafter cited as 45 CFR 46).

protections. 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,"[3] little additional *practical* guidance is provided regarding vulnerable subjects who are not already covered by a set of specific regulations.[4] 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). Ironically, however, although current U.S. regulations highlight the need to ensure the ethical treatment of those human research subjects with mental disorders, they provide no specific guidance for IRBs and investigators. NBAC believes this is not adequate.

In its final report, 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."[5] 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."[6]

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[3]45 CFR 46.111(b).

[4]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 (italics added).

[5]Advisory Committee on Human Radiation Experiments, *Final Report* (New York: Oxford University Press, 1995), 510 (hereinafter cited as ACHRE).

[6]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.

Among the recent research protocols that concerned ACHRE were some involving persons at risk for impaired decisionmaking capacity. Indeed, one of the three examples of controversial and unresolved issues in the ethics of research was research on adults with questionable decisionmaking capacity that offers them no prospect of benefit but involves unpleasant procedures and exposes them to greater than minimal risk of harm.[7] 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.[8] Considering the special complexities of research involving those 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 those persons whose decisional capacity might be impaired.

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 studies, but by the recognition of some considerable confusion about the principles and procedures that should govern such research. While we heard powerful testimony from members of the public and the professions at NBAC meetings, and received materials and information describing the strengths and weaknesses of the system of human subjects protection, NBAC did not rely on these as evidence of the need to "fix a broken system." We were informed by this input, and grateful for it, but our approach was a prospective and constructive one to close one of the gaps perceived to exist in human subjects research protection.[9]

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[7]Ibid.
[8]Ibid., 459–81.
[9]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.

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. This particular case led to an investigation by the Office for Protection from Research Risks (OPRR).[10] In addition, a number of organizations and government agencies, both in the United States[11,12,13] and abroad,[14,15,16,17] have recently considered the matter and offered recommendations. Numerous scholarly papers have also appeared in the last several years addressing various aspects of the topic.[18,19,20,21,22,23,24,25,26,27,28] In sum, a

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[10] OPRR, *Evaluation of Human Subject Protections in Schizophrenia Research Conducted by the University of California, Los Angeles* (1994).
[11]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).
[12]Office of the Maryland Attorney General. Final Report of the Attorney General's Research Working Group, 1998.
[13]The New York Department of Health Working Group.
[14]Council of Europe. Convention on Human Rights and Medicine, November 1996.
[15]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.
[16]Council for International Organizations of Medical Sciences (hereinafter cited as CIOMS), *Guidelines on Research Involving Human Subjects* (city of pub.: publisher, 1993), pg. no.
[17]Canada. Tri-Council Working Group. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Ottawa, Ontario. August 1998.
[18]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.
[19]B. Stanley et al, "The Elderly Patient and Informed Consent," *Journal of the American Medical Association* 252 (1984): 1302–6.
[20]E. DeRenzo, : The Ethics of Involving Psychiatrically Impaired Persons in Research, *IRB*, (November-December 1994): page numbers
[21]John C. Fletcher and Alison Whitman, "A New Consent Policy for Research with Impaired Human Subjects," 23 *Psychopharmacology Bulletin* (1987): 382.
[22]Author(s)?, *Alzheimer's Disease Research: Ethical and Legal Issues*, eds. J. Berg, H. Karlinsky and F. Lowy (Toronto: Carswell, 1991), page no.
[23]First name Keyserlingk et al., "Proposed Guidelines for the Participation of Persons with Dementia as Research Subjects," *Perspectives in Biological Medicine* 38 (1995): 319.
[24]A. Shamoo and T.J. Keay, "Ethical Concerns About Relapse Studies," *Cambridge Quarterly of Healthcare Ethics* 5 (1996): 373–86.
[25]P.S. Appelbaum and T. Grisso, "Capacities of Hospitalized, Medically Ill Patients to Consent to Treatment," *Psychosomatics* 38 (1997): 119–25.
[26]R. Bonnie , "Research with Cognitively Impaired Subjects," *Archives of Genetic Psychology* 54 (1997): 105, 107.

critical mass of concern was developing, and it afforded 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, we anticipate that many new, potentially useful therapies for treating the relevant 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 impaired decisionmaking capacity in these kinds of 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. Among these conditions are an inability to conduct the research with subjects whose capacity to make decisions is not impaired, and a reasonable level of risk in light of potential benefits and protections involved. NBAC felt that additional guidance was required. We were also mindful of worries that have been expressed about the ability of IRBs at some large research centers to actually monitor, as necessary, approved research proposals.

The justification for this report is the confluence of several developments, including the perceived gap that exists in the federal regulatory system established for the protection of human subjects; some historical and contemporary cases in which the protection of human subjects appears not to have been adequate; and the need to ensure that important research designed to develop better treatments for mental disorders can proceed with full public confidence in its ethical framework. The vitality of the research enterprise ultimately depends on the public's trust that ethical constraints are in place and will be followed.

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[27] 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.
[28] J. Berg et al., *Alzheimer's.*

In this report, NBAC will consider 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.

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 thoughtful (i.e., self-protective) decisions than would be the case in other circumstances. Indeed, a comprehensive list of individuals whose decision making may 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.[29] We recognize that many of the issues and concerns that we will raise in this report (and, indeed, many of the recommended protections we are advocating) *could* be applied to *all* persons with questionable or diminished capacity. However, we are principally focusing our attention on those who may be primarily considered for research protocols because it is their particular mental disorder that is being studied.

We recognize that it will be difficult to consistently fit diseases or conditions within particular linguistic categories, particularly in areas such as psychiatry and

[29]A. Wichman, "Protecting Vulnerable Subjects," 104.

neurology in which the boundaries of investigation are moving faster than the development of new labels, a difficulty that 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 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.[30]

Although we intend this report to focus principally on research involving persons with mental disorders, we recognize and encourage its use by others seeking guidance for conducting research on other persons whose decisionmaking capacity may be impaired. Indeed, many of our recommendations might be generalizable to other populations.

We are mindful of the concern that could arise from our focus on individuals who are members of a group (persons with certain mental disorders) rather than on persons who share a common functional characteristic (questionable decision

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

making)—this focus could raise the specter of equating mental disorder with incapacity and thus potentially stigmatize these individuals. We share this concern. We recognize that not all persons with mental disorders have impaired decisionmaking capacities or, among those who do have them, that these impairments necessarily compromise the individuals' decisionmaking abilities about research participation. Our intention is not to label persons—our intention is 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 measures to protect these individuals are designed for those who are vulnerable *when they are vulnerable* to intended or unintended coercion and exploitation; but we fully appreciate that these measures can only be successful when they do not, as a consequence, discriminate 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. The persons about whom this report is especially concerned are those who may be considered for research protocols because it is their particular mental disorder that is being studied.

To assume that a diagnosis of a mental disorder implies that its victim 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.

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.[31] Problems in determining the presence or absence of appropriate decisionmaking capacity, however, represent only one difficulty in conducting ethically acceptable research involving persons with mental disorders.

Many of the conditions underlying impaired decision making manifest themselves in behaviors that make prospective subjects hard to understand and often 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 an intervention can easily be created when the physician caring for the patient is also a researcher who may wish to enlist him or her into 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.[32] Despite all this, many of the diseases from which this population suffers badly require further study, since 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

[31]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.

[32]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.

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 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.

The combination of these and other factors creates a new imperative that calls for special attention from the professions and those institutions that engage in research involving persons who may have decisionmaking impairments. For a variety of reasons, previous efforts to establish specific protections for persons with uncertain decisionmaking capacity have largely failed, although some researchers and institutions have taken important and responsible initiatives in this area. Recently the Department of Health and Human Services (DHHS) Office of Inspector General issued a report describing such innovative practices,[33] but these addressed IRB review generally, not the review of protocols involving vulnerable populations in particular. Overall, however, efforts to establish regulations have been hampered either by longstanding inimical social attitudes toward persons with uncertain decisionmaking 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, so that we can ensure that important research can be encouraged under appropriate conditions and that eventually treatment of these important disorders can be improved.

[33]Department of Health and Human Services, Office of the Inspector General, *Institutional Review Boards: Promising Approaches* (Washington, DC: DHHS, 1998).

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.[34] As we elaborate in this chapter, several factors combine to make some persons with mental disorders especially vulnerable: they may have impaired capacity to consent due to the condition being studied; they are often dependent for care upon researchers who may also be their physicians; many mental disorders remain resistant to available therapies; and persons with mental disorders tend, principally as a result of the disorder itself, to be more economically disadvantaged than other adults. We believe, however, that despite these tensions and special factors, 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.

One way of expressing this dilemma, familiar in academic writings on the ethics of research with human subjects, is as a conflict between the ethical requirement for adequate protection against research risks and the understandable desire to develop additional methods for treating a particular disorder. At the same time, calls either for greater protection of human subjects from research risks or for more research about particular disorders are often generated by an underlying concern unrelated to the particulars of any research protocols—a problem, for example, arising from the perception that insufficient attention is being paid to the emotional needs of persons within the clinical setting.

[34] *Ethics in Neurobiological Research with Human Subjects,* ed. A.E. Shamoo (Amsterdam: Gordon and Breach Publishers, 1997), page no.

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"[35] trial of a medication approved for other use is not, with respect to federal regulation, a research subject unless the physician is engaged in the systematic collection of data about this 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.

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 new therapies that have already been recognized as safe and effective that should be incorporated into the treatment of their patients.

<u>The Nature of Mental Disorders That May Affect Decisionmaking Capacity</u>

[35]Physicians who are licensed to practice medicine are permitted to prescribe medications for therapeutic purposes other than those for which the medication has been tested and approved for manufacture and sale.

As we have said, persons with mental disorders are not necessarily decisionally impaired, much less decisionally incapable. Rather, any evidence that places a person's decisionmaking ability into question should trigger a clinical assessment to determine whether or not his or her decisionmaking capacity from one perspective or another is impaired. 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. Thus, identifying a potential subject's disorder that may impair mentation does not obviate the need for an individualized assessment of that person's actual decisionmaking ability.

A relatively small body of research has documented the effects of various disorders on decisionmaking capacity per se, but this is supplemented in many cases by data on cognitive functioning in general and by a good deal of clinical experience with these populations. The following are just 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 which increases with age—from 2 to 4% in the population over 65 years old to 20% or more in persons over 85 years old.[36] Dementias may also be caused by

[36]APA, DSM-IV, page no.

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 on Alzheimer's disease. Even patients with mild Alzheimer's disease may evidence enough deficits in understanding relevant information and reasoning to call their capacities into question, although the choices they make about treatment and research may not differ at this point from those of nonimpaired populations. As dementia progresses from the mild to the moderate stage, however, the range and magnitude of deficits expand, and persons may fail even the simplest tests of decisionmaking capacity.[37] 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. Delirium is often caused by systemic medical conditions, side effects of medications, or intoxication with or withdrawal from psychoactive agents or toxins.[38] 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.[39] 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.[40]

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[37]Marson et al., "Assessing the Competency," 949–54; B. Stanley et al., "The Elderly Patient," 1302–6).
[38]APA, *DSM-IV,* pg. no.
[39]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.
[40]Appelbaum and Grisso, "Capacities," 119–25.

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, have 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.[41] 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.[42] Since many of these impairments appear to be related to active symptoms, the prevalence of reduced capacity is likely to be lower among outpatient groups.[43] Lack of insight into the presence of illness and need for treatment is common among persons with schizophrenia.[44] 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

[41]APA, *DSM-IV*, pg. no.
[42]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.
[43]B. Rosenfeld, E. Turkheimer, and W. Gardner W. "Decision Making in a Schizophrenic Population." *Law and Human Behavior* 16 (1992): 651–62.
[44]X.F. Amador et al., "Awareness of Illness in Schizophrenia." *Schizophrenia Bulletin* 17 (1991): 113–32.

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.[45] Cognitive impairments may exist in information processing[46] and reasoning,[47] 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[48] or to alter the nature of those decisions.[49] One study suggested that hospitalized depressed patients may manifest decisionmaking problems roughly half as often as patients with schizophrenia—that is, in about one-quarter of cases.[50] But it is likely that the degree of impairment relates to the intensity of depressive symptoms, and thus will vary across populations.

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

[45] APA, *DSM-IV*, pg. no.
[46] S. Hartlarge et al., "Automatic and Effortful Processing in Depression," *Psychological Bulletin* 113 (1993): 247–78.
[47] J.E. Baker and S. Channon, "Reasoning in Depression: Impairment on a Concept Discrimination Learning Task," *Cognition and Emotion* 9 (1995): 579–97.
[48] C. Elliott , "Caring About Risks: Are Severely Depressed Patients Vompetent to Vonsent to Research?" *Archives of General Psychiatry* 54 (1997): 113–6,
[49] 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.
[50] Grisso and Appelbaum,"The MacArthur Treatment," pg. no.

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.

Values that Should Guide Research

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 refined their understanding of what it means to respect human subjects involved in research protocols, and 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 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. The American people need to understand that 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 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 mandated 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 the case of pediatric research.[51]

Of course, all persons suffering from an illness are at risk for impaired decision making due to physiologic and psychologic stress. But some patients have diseases or undergo treatments that often have a direct, primary, and negative effect on abilities that are critical for making decisions, such as memory, analytical capacities, and emotional equilibrium.

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

[51] 45 CFR 46, Subpart D.

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 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. We continue 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."[52]

Some of our recommendations, therefore, are specifically designed to ensure that persons with mental disorders that may affect decisionmaking capacity are not exploited.

In this report, our 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.

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[52]National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (hereinafter cited as the National Commission), *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research* (city of pub.: publisher, date of pub.) page no.

And despite the National Commission's important work, those with mental disorders are not yet specifically recognized by any set of guidelines in current federal regulations. It is therefore time to elaborate on the foundation laid by the National Commission and other thoughtful observers, and the current regulations addressing research involving human subjects.

Informed Consent and Decisional Impairments

The ability or capacity to consent in a fully informed manner to being a research subject is critical to an individual's participation as a human subject in an ethical research protocol. In one well-respected analysis of informed consent by Faden and Beauchamp, competence to consent performs a gatekeeping function in which "competence judgments function to distinguish persons from whom consent *should* be solicited from those from whom consent need not or should not be solicited."[53] 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 the individual who is able to understand the purpose, risks, and possible benefits of the study must have all the relevant information one would need to make an informed decision about being a subject. There is also an affirmative obligation to help those with less ability to be fully informed about the research to understand the relevant information before they may be enrolled. 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.[54]

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

An ethically justifiable system of clinical research will need to take into account the wide variations in the conditions that may affect the decisionmaking capacity of potential human subjects. It is important not to confuse the fact that decisionmaking ability is limited for many people in diverse ways. Appreciating and recognizing this diversity will help in the design of ethically sensitive recruitment and consent procedures and research protocols.

There are at least four types of limitations in decisionmaking ability that need to be taken into account in planning and conducting research with this population. First, persons with fluctuating capacity have what is often called waxing and waning ability to make decisions, as in schizophrenia, manic-depressive disorders, and some dementias. Second, persons whose decisionmaking deficits can be predicted due to the course of their disease or the nature of a treatment, but who are still capable, have prospective incapacity; those who suffer from early stages of Alzheimer's disease fall into this category. Third, most persons with limited capacity are in some way able to object or assent, as in the case of more advanced Alzheimer's. Fourth, persons who have 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.[55] Among those whose capacity fluctuates or is limited, one cannot easily pinpoint the precise nature of a decisional disability from these groupings. Some disorders entail limitations on decisionmaking ability that are subtle and hard to

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

identify, and even individuals who fit within a particular diagnostic category may exhibit their 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 in 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 progress to incapacity. It is therefore critical that researchers who work with persons in this population be familiar with the ways that decisionmaking impairments manifest themselves, and that appropriate mechanisms be designed to maximize the subject's ability to participate in the decision to enter or continue a study, or to choose not to enroll. In Chapter Five of this report, our recommendations suggest certain mechanisms.

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 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 the 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 problems of assessment. When can those whose capacity is uncertain in these senses be said to be able 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 Ethical Issues in Research with Persons with Mental Disorders

Research involving persons with mental disorders must take into account ethical 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 a more primitive stage of drug development than is usually the case in pharmaceutical research, because animal models often cannot yield appropriate data for diseases that cause psychological or cognitive symptoms as these models can for other diseases.

Subjective Experience of Disorders

While all individuals experience their illnesses subjectively, the experiences of those with mental disorders will pose additional challenges. In some instances, their perception that they are at greater risk of harm than is actually present may be a result of confusion or other manifestations of their disorder. This subjective perception is no less real, and therefore no less important, to take account of 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 hard to work with in the research setting. For these reasons and others, both clinical care and research in these diseases often have taken a back seat to disorders perceived as more "medical" in nature.

Access to Care

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 due to their symptoms. 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, as compared with 9 percent of the general adult population.[56] As

[56] 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).

many as half of homeless Americans are said to be suffering from schizophrenia.[57] Moreover, the widespread lack of understanding regarding 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 lacking in financial resources, these people 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 among those who are not decisionally impaired. Researchers and investigators must scrupulously avoid taking advantage of people who might expect therapeutic effects from their research participation.

Formal and Informal Caregiving

We have already observed that while those who struggle with diseases 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 with a reasonable understanding of the possibility of benefit, those struggling with psychiatric disease can more easily feel dependent on the research institution and study personnel, thus developing a fear of being released from the study and losing all of their professional support. As is so often the case, "voluntariness" is easier to require in regulations and guidelines, but much harder to guarantee in real life situations.

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 role of informal caregivers like family and friends. NBAC was moved by the testimony of those who, though often bearing witness to other matters, also sent a powerful

[57] P. Wyden, *Conquering Schizophrenia* (New York: Alfred A. Knopf, 1998), pg. no.

message of commitment over many years to loved ones struggling with the consequences of debilitating diseases. Two issues are of particular relevance: the problem of providing care, given other limited resources; and the more implicit problem of the sharing of information about patients-subjects.

As we noted above, our health care system has familiar inadequacies regarding 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 commonly complain that certain 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."[58] We must also note, of course, 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 with professional, patient with scientist, or any other configuration of these groups."[59] Even 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, but 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. On the contrary, much theorizing has worked against recognizing and involving others in the process of

[58]P. Backlar, "Ethics in Community Mental Health Care: Confidentiality and Common Sense," *Community Mental Health Journal* 32, no. 6 (1996): 517.
[59]Herbert Pardes, public comments in a letter to NBAC. Columbia University, July 31, 1998 .

establishing an ethical research process. The critical role of self-determination in human subjects research should by no means be undermined or minimized. But within the autonomy-based framework of our society's regulatory philosophy, there should also be a place for the actual roles of those with important ongoing caregiving responsibilities to the potential subject.[60] When such roles exist, these important social support networks must be integrated in a more satisfactory fashion into the regulatory framework of research with those who are decisionally impaired far more actively and sensitively than has been done before. NBAC appreciates this issue, and discusses more fully in Chapter Three its recommendations for recognizing the important role of families and others in decision making about research participation.

The Possibility of Direct Medical Benefit

Many research studies do not offer any reasonably expected and/or direct prospect of direct benefit to the human subjects involved. Such studies may be necessary because not enough is known about the way a drug or device will function in human beings, or because the research is not designed to offer subjects the prospect of direct benefit but rather to study the subjects' reactions (e.g., modeling the dynamics of the disease) to particular stimuli or how the drug or device will affect a human host. In these cases, the hope is that the knowledge gained will eventually lead to better treatments. While an individual may benefit from being closely assessed or monitored by the study team, that benefit is not produced by the medication or mechanism being studied.

Many studies do include drugs or procedures that promise potential benefit to subjects. However, it is not possible for researchers to know whether an intervention would be better for the subject than doing nothing (which often occurs in a placebo

[60] 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.

control study), or whether the subject would benefit most from the currently available standard treatment. Indeed, if researchers were certain of the outcome, there would be no justification for doing the research in the first place. Nevertheless, even when there is justifiable uncertainty about which treatment produces better results (when the relevant medical and scientific community is said to be in clinical "equipoise"[61]), the investigator should have some reason to believe that the study might benefit some subjects, as indicated by animal experiments or developing scientific knowledge or both, if it is to be presented as having potential therapeutic benefit. The nature of clinical research, however, 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.

Interest in access to potentially beneficial experimental treatment is not, of course, limited to persons with conditions that may be directly related to decisionmaking impairments. Anyone who suffers from a 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"[62] may be especially intense for those whose decision making is impaired. Because many clinical trials are not primarily therapeutic opportunities, patient-subjects who are not fully informed about the differences between research and therapy may feel betrayed or abandoned when their study participation comes to an end.

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

[62] 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.

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 were psychiatric conditions: unipolar depression, alcohol use, bipolar affective disorder, schizophrenia, and obsessive-compulsive disorder.[63] 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.[64] Alzheimer's 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 is 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 have yielded savings of $1.4 billion per year since 1990.[65] Thus, every incentive exists to improve our understanding of disorders affecting brain function and to develop more effective treatments for them.

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

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

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

[65]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.

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.[66] Comparisons of normal and afflicted populations permit localization of regions affected by the disease process. These techniques also allow monitoring of the effects of treatment regimens at the level of the brain.[67]

Currently, medications are the primary focus of treatment-oriented research. 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 very early and speculative development include insertion of new genes to correct identified defects underlying brain disorders (gene therapy), and use of immunologic therapies, like the recent successful inoculation of rats against the psychostimulant effects of cocaine.[68]

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 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

[66]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).
[67]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.
[68]M.R. Carrera et al., "Suppression of Psychoactive Effects of Cocaine by Active Immunization," *Nature* 378 (1995): 727–30.

capacities 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: respect for persons is always paramount, but in this context 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.

The Ethics of Study Design

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 which 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.[69] At the

[69]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 (winder 1994): 297–303.

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,[70] 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 scientific value are among the important requirements for ethical research.[71] While all research should be expected to meet these requirements, studies that involve vulnerable persons would seem to require particular attention to these requirements. Deciding which design will best answer the research question, what procedures will be used, 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 our commitment to familiarize ourselves with research that has been conducted in this area, a number of protocols and consent forms were requested from investigators. This project, the details of which are described in Appendix II, identified several issues relating to study design, including recruitment, informed consent, and selection of subjects.

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,

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

[71] 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.

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 psychologic and pharmacologic provocations.[72] Miller and Rosenstein list among these provocations injection of intravenous amphetamine, inhalation of carbon dioxide, and presentation 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."[73] 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 has heard testimony on this subject by members of the public, scientists, and others on several occasions. Two concerns have emerged, both from the literature and from public testimony. 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," depriving 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

[72]Miller and Rosenstein, 1997, p. 403. FULL DATA NEEDED HERE.
[73]Ibid., 404

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 the study, and what the procedures are for the orderly termination of a study,[74] it is 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.[75] 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 therapeutic 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.[76] As noted previously, however, both scientific and ethical merit are jointly necessary for conducting human subject research. Washout studies, challenge studies, and placebo-controlled studies done with

[74]45 CFR 46.116(b)(4).
[75]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.
[76]H.J. Sutherland et al., 297.

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 Clinical Investigators

The clinical 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 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 institutions 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 on those individuals who are prepared to undergo rigorous scrutiny of their proposed studies and ongoing research trials. Nevertheless, medical scientists 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 liable to a 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.

While 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 medical scientist,[77] it would be unfair and unrealistic to expect individual clinicians to resolve the complex moral problems arising from human research by requiring them to measure up to standards we have not adequately articulated, then blaming their lack of integrity if they are perceived to have failed. It is not adequate to focus these ethical 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 human subjects are protected, therefore, should also be borne by the investigator's research community, department, or institution. These responsibilities include, but are not limited to, educating investigators about both the ethics of research and protection of human subjects, and the appropriate monitoring of 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 have considerable authority to review and monitor the research itself.

The Structure of This Report

Three analytical chapters follow this chapter. The next chapter focuses on informed consent and decisionmaking capacity. It is followed by chapters on advance planning and surrogate decision making, and the assessment of risks and potential benefits. The final chapter summarizes our recommendations for research involving persons with mental disorders that may affect decisionmaking capacity.

In making these recommendations, we are acutely aware of the already considerable burdens placed upon dedicated clinical scientists and research centers. Some of our recommendations will undoubtedly require a greater investment of

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

resources to enhance the protection of human research subjects. These new investments will be required to support better IRBs at the local level, those federal offices charged with ensuring compliance with federal regulations regarding human subjects protections, and NIH and other research agencies. But if important research that will benefit our society is to flourish as we hope it will, it may 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. It is our view that in the long term such investments will increase support for updated biomedical research.

Chapter Two: INFORMED CONSENT AND LIMITATIONS ON DECISIONMAKING CAPACITY

The Centrality of Voluntary and Informed Consent

The 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[78]and elsewhere.[79] The regulatory structure 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 unjustified and unwarranted harm and exploitation. The result has been a system of prior review of research protocols to ensure their scientific and ethical quality and thus to weed out protocols that would expose subjects to inappropriate risks, would exploit them, or would 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. 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 and still experimental medical interventions for their conditions. Thus they argue that regulatory requirements should be adjusted to allow patient-subjects, especially those

[78]H.K. Beecher, "Ethics and Clinical Research," 1354–60.
[79]M.K. Pappworth, *Human Guinea Pigs: Experimentation on Man*,(Boston: Beacon Press, 1968).

whose existing therapies are inadequate, less restrictive access to participation in research protocols.

While obvious differences exist between these two perspectives, 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 demands for greater access to participation in research protocols rest 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.[80]

Plainly, then, the capacity to participate in this process of informed decision making is a requirement of, 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 such capacity, or whose capacity is uncertain, may be excluded from participation as subjects in research, and there would be fewer avenues to assess the promising new clinical approaches to the diseases from which they suffer. Such exclusion may, under the strict protection model, seem appropriate; according to this view, 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, as a consequence of those disorders, be slowed, perhaps dramatically so.

[80]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.

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, impaired decisionmaking capacity is a pivotal issue that must be addressed.

Persistent Decisional Impairments

Voluntary, informed consent is thus 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. 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), 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, 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.[81] Rather, the impairments that raise the greatest concern are those that persist. When we speak of a decisional impairment in this report we refer principally, but not exclusively, to a relatively persistent condition, 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, our primary concern is with the 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 medical problems are decisionally impaired. Less obviously, it 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 we recognize these facts, we become more aware of the special ethical obligations that are imposed on scientific investigators and institutions

[81]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 in 1996 permit a narrow exception of the informed consent requirement for emergency research involving serious conditions for which there is no proven satisfactory standard treatment: "Protection of Human Subjects, Informed Consent," *Federal Register* 61 no. 51498 (2 October 1996), pg. no., microfiche.

sponsoring or carrying out research and society in general when research with persons who may be decisionally impaired is contemplated.

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 we have said, 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 us with 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, including clinical investigators and IRB members, who are engaged in 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.

Decisional Incapacity and Impairment[82]

Especially in the context of discussions about the ethics of human subjects research, impaired decisionmaking capacity implies a condition that varies from

[82]Although older children and adolescents are not specifically included in the recommendations in this report, current federal regulations require their assent for greater than minimal risk research that does not hold out the prospect of direct benefit. To the extent that an older child or adolescent is unable to provide a meaningful assent to research participation, that constitutes a morally relevant obstacle to enrollment in a study of this kind.

statistical or species-typical normalcy. In this sense, 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, when we speak of decisional impairments in the context of research involving human subjects who suffer from mental disorders, we mean 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).[83]

In practice, it is not usually hard to determine whether a person lacks all ability to make a decision, so findings of incapacity in this global sense are not often subject to much disagreement. Much more challenging for us (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 we, on moral principles, can 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

[83]45 CFR 46, "Protection of Human Subjects," Subparts B, C and D.

determined by the standard of competence that is chosen.[84] Persons who are 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.[85] These standards were developed with a focus on the capacity to consent to treatment, not research. Recently, however, the American Psychiatric Association approved a set of guidelines for assessing decisionmaking capacity in potential research subjects which substantially relies on these same standards.[86] Whether the context is treatment or research, selecting one, more, or all of these standards for assessing capacity will determine what counts as impaired decisionmaking. For instance, when more stringent standards are used, the result could be overinclusive 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.

Even once the 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 political or value system. In a liberal democratic society such as ours, wherein the scope of state authority over individual lives is strictly limited and subject to careful

[84]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.
[85]P.S. Appelbaum and T. Grisso, "Assessing Patients' Capacities to Consent to Treatment," *New England Journal of Medicine* 319 (1988): 1625–38.
[86]APA, *Guidelines for Assessing the Decisionmaking Capacities of Potential Research Subjects with Cognitive Impairments* (approved by the APA Board of Trustees, city, July 1998).

scrutiny, this threshold tends to 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.[87]

Another facet of decisional impairment that is often encountered in the clinical setting is the variable fashion in which such impairments manifest themselves. The gradual loss of capacity rarely follows a straight line, and psychiatric illnesses like bipolar disease are known for their sometimes very substantial periods of lucidity along with cycles of mania and depression.

For all 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. As we said, 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.[88]

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, stigmatizing, and may result in the unwarranted deprivation of an individual's civil liberties.[89] This is a serious matter.

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

[88]See generally 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.

[89]Sacks, ibid.

Conversely, a judgment that an incapable person is capable leaves that individual unprotected and vulnerable to exploitation by others.[90] In addition, the presence of many marginal cases among members of the relevant populations triggers concern about our ability to make those capacity assessments for many individuals. Although it is important to accord due respect to persons with mental disorders capable of autonomous choice, 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.[91] As we have cautioned, investigators must also 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, albeit inadvertently, to vary criteria too much and to fail to institute adequate safeguards for such research.[92] This conclusion finds support in our Protocol Project, in which none of the protocols we reviewed did a researcher provide to the IRB a description of how prospective subjects would be evaluated for their ability to consent. In fact, in one protocol that relied upon subjects with psychiatric disorders to provide informed consent and did not utilize legally authorized representatives, the following exclusionary criteria was applied: "[O]nly seriously ill patients who are judged by established clinical guidelines to require hospitalization will participate. No

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

outpatients will participate." The protocol did not discuss how informed consent was to be obtained under those conditions. We therefore, along with some other commentators, support more systematic and specific federal direction on capacity assessment,[93] 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 this need, a variety of approaches to capacity assessment are 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.[94] Evaluating decisional capacity is an even more complex task than might be deduced either from the above discussion or from most philosophical discussions of capacity. 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 task of assessment in general.[95] 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

[93]E.g., id.

[94]E.g., Bonnie, supra; Melnick et al., supra.

[95]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.

why the context in which the capacity assessment is made (under what conditions or by whom, for example) is so important.

Unlike the discrepancy between capacity and performance, whose differences, though very real, can be subtle, the divergence of opinion on whether capacity assessment and information disclosure should be conducted by an individual not otherwise connected with the research project is very wide. The National Commission recommended that, "where appropriate," IRBs should appoint a "consent auditor" for research involving those persons institutionalized as mentally infirm.[96] 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 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.[97] The proposed Department of Health, Education and Welfare (DHEW) regulations contemplated mandating auditors for all projects involving this subject population, but opposition to this proposal reportedly was one reason the regulations never became final.[98]

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 distinguished team of Canadian scholars took this position in its recent recommendations on dementia research,[99] noting that the role of a consent assessor/monitor ordinarily can be filled by a researcher or consultant

[96]National Commission. Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm, pp. 8-20.
[97]Ibid. p. 15.
[98]DHHS. "Protection of Human Subjects: Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled," *Federal Register* 43, no. 223 (November 17, 1978), 53950–6.
[99]Keyserlingk, et al., supra.

"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.[100]

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 required by the IRB in those conditions where the potential subject's decisionmaking capacity is suspect."[101] 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."[102] 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.[103]

A strong case has been made for an independent, federally employed 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.

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[100]Id. at 343-44. See also Melnick, et al., supra.

[101]Orr, Guidelines for the Use of Placebo Controls in Clinical Trials of Psychopharmacologic Agents, 47 Psych. Services 1262 (1996).

[102]Shamoo & Sharev, Unethical Use of Persons With Mental Illness in High Risk Research Experiments, 2 BioLaw S:23 (1997).

[103]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.

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 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.[104]

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.[105]

[104]Bein, supra, at 747-48.
[105]Id. at 762.

Other recent commentary proposes more diverse methods for avoiding inappropriate capacity determinations. 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."[106]

Many groups advise the involvement of a trusted family member or friend in the disclosure and decisionmaking process. 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.[107] 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."[108] Alternatively, others have suggested that the presence of a caregiving relative could in some cases put pressure on subjects to enter a research study.[109]

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

[106]Bonnie, supra, at 110.
[107]High, et al., supra. See also Bonnie, supra, at 110.
[108]Karlawish & Sachs, Research on the Cognitively Impaired: Lessons and Warnings from the Emergency Research Debate, 45 J. Am. Geriatrics Soc'y 474, 477 (1997).
[109]Id.

again, and the subject is retested. This process is likely to yield more accurate judgments of subject capacity than a less systematic and rigorous inquiry.[110]

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 be delivered through 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.[111]

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."[112] We hold 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

Once again, 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

[110]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)).
[111]Melnick, et al., supra.
[112] World Medical Association, supra.

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."[113] Subjects also should "comprehend the fact that 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."[114]

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).[115] 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

[113] 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 (1982).
[114] Melnick, et al., Clinical Research in Senile Dementia of the Alzheimer Type, 32 J. Am. Geriatrics Soc'y 531, 533 (1984).
[115] Elliot, Caring About Risks, 54 Arch. Gen. Psych. 113 (1997).

on "how much impairment we as a society are willing to accept before we consider someone incompetent."[116]

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.[117] Instead, investigators must develop and present the specific material relevant to that project and evaluate the prospective subject's understanding and appreciation of that information.[118] 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)."[119]

Like other commentators, the 1998 NIH panel endorsed a "sliding-scale" approach to decisional capacity in the research setting.[120] This approach demands an increasing level of understanding and appreciation as study risks increase and potential benefits to subjects decrease.[121] Similarly, some suggest that many prospective

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[116]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).

[117]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).

[118]According to the Common Rule, prospective subjects should understand: (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. 56 Fed. Reg. sec. ___.116(a). Additional information must be disclosed and understood when relevant to a particular study, such as any additional costs subjects may incur as a result of study participation. Id. at sec. ___.116(b).

[119]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.

[120]Ibid.

[121]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

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."[122] In our view, 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; we discuss this matter further in Chapter Three.

Besides being an informed one, a decision to enter research should be voluntary. The Nuremberg Code provides descriptive characteristics of a voluntary decision,[123] 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 r elative and threatening to withdraw health services to which an individual would be otherwise entitled."[124]

Due to its limited congressional mandate, the National Commission considered potential pressures to enroll in research on institutionalized persons only. Recent

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(1986). See also Schafer. A., “The ethics of the randomized clinical trial.” New England Journal of Medicine 307;(12):719-24, (1982).

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

[123]See p. 5, above.

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

commentary favors expanding this concern to all persons with mental disorders, regardless of where they live, because they are especially vulnerable to similar pressures.[125] 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.[126] Nevertheless, there remains considerable support for retaining special protections to persons in residential facilities due to their near-complete dependence on the good will of the staff.[127]

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 psychiatric disorders and dementia 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.

We have some indication from our Protocol Project that practices in the field may not reflect these concerns adequately. We saw several protocols and corresponding consent forms that gave the impression that the 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 that was intended to inform subjects that their rights

[125]Bonnie, supra; Levine, Proposed Regulations, supra.

[126]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).

[127]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) (recommending that IRB "consider asking a committee composed mostly of representative residents of, for example, a nursing home, to review proposed research projects to be conducted at the facility).

to treatment would not be affected by a decision to not participate in the research, we note that persons with mental disorders that may affect decisionmaking capacity who are presenting themselves for help may nevertheless feel either indebted to the provider or that they really are confronted with a quid pro quo--research participation for treatment. Another of the protocols seen by NBAC offered free health care to persons that would enroll themselves in the research. Neither of the protocols discussed here described methods for ensuring voluntary, uncoerced participation. A further troubling aspect of subject recruitment practices that surfaced is the way in which research is described to potential subjects. Some consent forms received by NBAC employed language similar to, "Invitation to Participate in Research." NBAC observes that such language implies both that benefits will accrue from participation, and that participation is a privilege bestowed upon subjects by the investigator.

Since 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.[128] In the next chapter, we discuss the issue of appointing representatives and consider other factors that must be taken into account when informed consent from the potential subject cannot be obtained.

[128]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 is the standard against which all efforts to obtain the ethical participation of individuals in research must be judged. While, at times, persons with mental disorders are incapable of giving valid informed consent for their participation 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. We agree with the National Commission when it noted 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."[129] In this vein, we recognize that certain opportunities already exist for maximizing subject choice in research, including the designation of appropriate substitute decision makers. We also recognize 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. In this chapter we discuss three ways in which individuals may be involved in research, even if they are presently unable to decide for themselves: through the mechanism of assent and dissent; through the use of advance planning and surrogate decision making; and through the authority resting with their legally authorized representatives.

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

The Role of Assent and Dissent

The National Commission recommended that, under specified conditions, researchers obtain *assent* to research participation from subjects incapable of independent decision making: 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."[130] 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."[131] In defining assent in this way, the National Commission explicitly acknowledged that assent "is not intended to serve as a substitute for informed consent." "Dissent" was not formally defined by the National Commission, which referred instead to a subject's "objection" to participation;[132] in so doing, it recognized yet another way in which potential (or active) research subjects with somewhat impaired decisionmaking capacity could exercise choice.

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.[133] Should the physical or verbal indications of persons deemed incapable of assent 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."[134] According to the National Commission, "mere absence of objection" ought not be interpreted as assent,[135] and the members recommended requiring the

[130]Report on Institutionalized Persons, supra, at 9.
[131]National Commission, Report on Institutionalized as Mentally Infirm, p. 9.
[132]National Commission, IMI, pp. 8-15).
[133]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.
[134]Kapp, supra, at 34.
[135]Report on Institutionalized Persons, supra, at 14.

consent of a subject's legal guardian to authorize greater than minimal-risk research involving nonobjecting 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 should preclude 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.[136]

In addition, the National Commission recommended procedural mechanisms to apply these substantive provisions. In particular, its report recommended the following: (1) that IRBs should have discretion to appoint an independent auditor to verify the subject's assent or lack of objection; (2) that independent auditors 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) that they should be removed from the study if 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.[137] Yet not all commentators agree that potential direct medical benefit should be sufficient to override the resistance (whether verbal or behavioral) of persons lacking decisional capacity regarding research participation.

[136]Report on Institutionalized Persons, supra at 7-10.
[137]E.g., Berg, supra; High & Doole, supra; High, et al., supra; Melnick, et al., supra.

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."[138]

This group therefore was "not fully persuaded" that potential therapeutic 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."[139] 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 potentially therapeutic research because the state regulations failed to provide patients or their representatives notice and an opportunity to challenge this involvement.[140] Although the constitutional portion of the judgment was eventually set aside by the Court of Appeals, these same provisions would not

[138] Keyserlingk, et al., supra, at 342, quoting Melnick, et al., supra.
[139] Id. at 342.
[140] T.D. v. New York State Office of Mental Health et al, 650 N.Y.S. 2d at 193.

only be ethically objectionable according to the strict Nuremberg principle, among others, but would also continue to be legally suspect. A legislative 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.[141]

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. We are persuaded, however, that even in this case it is not necessary to always interpret such dissent as being permanent. To do this 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 the procedure—perhaps even actively object, by recoiling from the needle—we are not convinced that this dissent, which must be honored, should be interpreted as an objection to continued participation in the entire study. Certainly the subject has dissented to this portion of the study, at this time. And, as we have 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. However, after a reasonable amount of time, the researcher in this study should not be prohibited from returning to the patient and ascertaining his or her willingness to now give blood. We recognize and wish to emphasize that the line between ascertaining willingness and badgering a person is a delicate one to walk.

Others have come to a similar conclusion. The Canadian group observed that one should not assume that a "transient lack of cooperation always signifies objection;

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

instead, '[d]ecisions as to whether a patient is clearly or probably objecting will obviously be a matter of judgment.' "[142]

The Role of Advance Planning and Surrogate Decision Making

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 his death. In addition, a person 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 specific end-of-life interventions are not to be used in the event of a terminal prognosis. Despite the difficulty in meshing this kind of instruction with what is often

[142] Keyserlingk, supra, p. 341.

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, 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.[143] This designation reflects trust in the integrity, judgment, and decisiveness of the chosen proxy. Of course, the designation can 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.

Informed Consent. 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

[143]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).

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.

Personal Values. 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. This kind of advance directive, however, which does not reflect 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.

Personal Relationships. A person may embody in an advance directive his or her choice of a decision maker concerning research participation. The Commission recognizes that people use advance directives to identify others with whom they have a relationship of trust. We have concluded that this relationship in and of itself is not sufficient to authorize participation in all types of research studies.

This summary account of the role of advance decision making in research is not intended to gloss over several important issues: 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 discussed 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.[144] 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.[145] Such decision makers 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

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

[145]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.

> 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.[146]

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."[147]

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. The ACP 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 greater than minimal risk research offering 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. We are sympathetic to this general approach.

Other groups and commentators have expressed general support for advance research decision making without addressing the concept in detail.[148] In reviewing the

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

[147]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.

[148]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).

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 of being inappropriately volunteered by one's relatives, is simply not a prevalent or powerful concern."[149]

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.[150] 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.[151] 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

[149]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.

[150]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).

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

> 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.[152]

An intermediate position is presented by the Canadian group which argues that an advance directive should be overridden if “no direct benefit” is anticipated for the subject and it becomes apparent that enrollment or 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."[153] 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."[154] 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 proposes that research directives should apply to studies offering no direct benefit to subjects only if the risk

[152]Moorhouse & Weisstub, at 135. See also Shamoo & Sharev, supra, at S:29 (advance directives should not bind a subject to research participation).
[153]Keyserlingk, supra, p. 352.
[154]Moorhouse & Weisstub, supra, at 134.

is minimal or a minor increase over minimal.[155] 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."[156]

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 should not have limits placed on the types of research in which they can consent, in advance, to participate should they become incompetent."[157] 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 the incapable subject's 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 DoD may accept the “consent” of a legal representative for the research participation of another. 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 denied DoD from conducting nonbeneficial research involving human subjects, unless the subjects themselves provide informed consent—regardless of whether the research is minimal risk. A provision similar to this has governed DoD since 1972. In 1996, the Food and Drug Administration

[155]Keyserlingk, et al., supra, at 351.
[156]Id.
[157]Berg, supra, at 22.

adopted new regulations governing research involving incapable subjects in the emergency setting.[158] The 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 due to their medical condition cannot give 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. 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."[159] 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.[160] 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

[158]21 CFR.50.24(a)(2)(iii). The DHHS Secretary, at the same time, waived the general requirements for informed consent under conditions that are almost identical to FDA regulations. See 61. Fed. Reg. 51531 (1996).
[159]Id.
[160]Id.

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.[161]

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."[162] 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

[161]Office of the Maryland Attorney General, supra, Parts VI, VII, VIII, & IX.
[162]Id. at A-32.

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 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.[163]

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 unresolved. 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

[163]Id. at A-26.

on the significance policy should assign to the competent individual's preferences about future research participation posing greater than minimal risk to incapable subjects.

In sum, advance research decision making, although recognized as a potentially useful device, poses difficult issues concerning its scope and effect. In our 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: those in which the most important information relevant to informed consent—e.g., the nature of the procedures and risk—about future research participation is already known and presented to a competent person, the person 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 research about a disease—that statement should be honored by whoever has authority to consent to research participation, but it cannot by itself be considered sufficient warrant for enrollment in a particular study.

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

should reflect, to the greatest extent possible, the individual's views prior to the period of incapacity.[164]

Although the term "surrogate" is frequently used in ethical discussions such as that in the NIH 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 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 decisions, personal decisions, or both types of decisions for the incompetent person. Limited guardianships covering a narrower area of decisionmaking responsibility are also possible.

However, as we have mentioned earlier, 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, 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

[164]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.

protections, including additional monitoring of the study, requiring a consent auditor, or requiring educational activities for authorized representatives.[165]

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.[166] 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, 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 one 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 research use of a vulnerable population 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.[167]

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[165] Ibid. pp. 94-95.

[166]Common Rule, Sec. ___.101(f).

[167]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);

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.[168] 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 their ward's participation in research protocols.

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, discussed previously, 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 the subject, who presumably will choose someone likely to express their values and protect their welfare. 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.

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).

[168]Office for Protection from Research Risks, Protecting Human Research Subjects: Institutional Review Board Guidebook 6-30 (1993). See also High & Doole, supra, at 328 (guardianship process may produce rights deprivation and "is often intrusive, humiliating, expensive, and time-consuming").

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.[169]

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 embodies a recognition 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.[170] 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.[171]

A final possible option is to assign such decisionmaking authority based on the simple status of being a close relative. Support for this alternative 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

[169]NIH Clinical Center, supra.
[170]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).
[171]Kapp, supra.

accord with the incapable person's values, preferences, and interests.[172] This approach is easy to administer; moreover, it apparently has been and continues to be a common practice in many actual research settings.[173]

Each of these options presents advantages and drawbacks, and we have considered them carefully. Requiring judicial involvement may cause unproductive delays and raise the costs of research, and may not necessarily 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 to make research decisions for incapable persons would require action by the states; such legislation would emerge slowly and, 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.[174] 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

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[172]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").

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

[174]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").

treatment from which the family member may benefit."[175] 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.[176] At the same time, we recognize many of the potential advantages that such mechanisms might offer to permit important research to go forward. Moreover, we are satisfied that the argument for expanding the authority of the LAR is sound so long as the following components are in place, which we describe in more detail below: (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 on behalf of both the public and research communities to carefully study and report on the experience of using LARs in this way.

The Authority of the LAR

We recognize that there are two mechanisms by which a LAR can be involved. 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, we recognize 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

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

[176]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.

care decision makers for clinical decisions) to make certain research decisions. In both cases, the authority of the LAR would need careful description.

Three forms of substantive limitations 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 subject representatives 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.

NBAC's view about the authority of the LAR is the following: For research involving a person with a mental disorder, a LAR may authorize research participation in greater than minimal risk research, even if that research does not hold out the prospect of direct benefit to the subject, provided that the potential subject has given consent in advance of the study. When greater than minimal risk research holds out the prospect of direct medical benefit to the subject, the LAR may authorize enrollment of the subject.

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), we are somewhat reluctant to recommend their adoption without also recommending certain protections and methods for their evaluation. In general, we regard the IRB as the proper locus for determining whether these (or any other) protections are adequate. For an IRB to be

assured that the enrollment by an LAR of a now incapable person with a mental disorder into a research study is acceptable, the IRB might consider requiring certain procedures to have taken place in the process of documenting that the LAR is engaged in an ethically valid decision.

(1) Requiring 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) Requiring documentation that the subject and LAR understood the scope of the authority being granted to the LAR. Because of our concern that LARs could have some significant self interest in enrolling a now incapable person into a study, we would favor a process in which the designation of an LAR was documented. The documentation we refer 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 a greater than minimal risk, between that which offered the prospect of direct benefit to the subject and that which did not. As we note 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 favors, in general, giving first priority to those decisions by LARs that approximate most closely the now incapable subject’s previously expressed preferences. In the absence of this information, LARs would be expected to make judgments which are consistent with the subject's best interests. We are acutely aware of the difficulties this approach presents and explain our rationale in somewhat more detail in Chapter 5

below. Here we are only indicating our general view since it relates directly to the assignment of LARs and the protections associated with this. We would expect IRBs to carefully scrutinize LAR decisions on behalf of now incapable subjects.

Ongoing Evaluation of LARs

We wish to emphasize that the protections listed above could provide the IRB some assurance that the LAR has been assigned in a legally and ethically valid way. However, we also believe that 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, which we discuss in more detail below. We believe 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. We also wish to stress that 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, we cannot fully endorse it without reservation. Therefore, we would strongly encourage the research community, led by NIH (in view of its experience in this area), to support studies on the appropriate use of research DPAs. We would also encourage studies which assesses the extent to which clinical DPAs can be extended to include research decision making.

<u>Independent Professional Support for Subjects and Surrogates</u>

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 by ensuring 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 legally authorized representative. 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. We would not expect, of course, that the health care professional be required for all research involving persons with mental disorders, but would be required where the patient lacks capacity to decide or is expected to lose capacity during the course of the study involving greater than minimal risk.

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."[177] 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.[178] At the very least, it seems sensible for a legally authorized representative to have access to an independent health care professional advisor before entering an individual into a research protocol.

A comprehensive system involving an independent health care professional advisor for persons with mental disorders who are potential research participants, or their legally authorized representatives, would involve two elements: For those individuals who have decisionmaking capacity at the time of enrollment in a study, a responsible health care professional would be available to consult with each subject and his or her legally authorized representative as part of the consent planning process. For those individuals who lack decisionmaking capacity at the time of enrollment in a study, a responsible health care professional would be available to advise a legally authorized representative regarding enrollment and whether or not to halt the subject's participation. In each instance, the responsible health care advisor should, whenever possible, have been previously acquainted with the potential subject.

In this chapter we have discussed some of the conceptual and practical problems which arise when informed consent cannot be obtained from potential research subjects, and how legally authorized representatives can play a role in permitting research to go forward. In the next chapter we discuss some of the

[177]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.
[178]Office of the Maryland Attorney General, supora, p. A-19.

difficulties which arise in assessing risk and potential benefit and offer our perspective 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 they are "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[179] These are among the provisions that govern research involving all human subjects. Many commentators and organizations, as well as those who reached the conclusions presented in various international documents, 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.

In this chapter, we discuss 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 we discuss some of the difficulties inherent in defining risk and then explain our rationale for urging IRBs to consider evaluating research involving this population under two categories: minimal risk, and greater than minimal risk. Then we discuss some of difficulties in defining benefits. Finally, we comment on the problem of assessing research risks in relation to potential benefits to subjects and, in particular, on distinguishing between research involving greater than minimal risk that does hold out the possibility of direct medical benefit to the subject, and research involving greater than minimal risk that does not hold out the possibility of direct medical benefit to the subject. In the final section of this chapter, we also propose procedures to minimize risks to subjects.

[179]Sec. ___.111(a).

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 occurring. 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 unanticipated 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."[180] In contrast, relatively little progress has been made to describe the *criteria for assessing risk* by IRBs.[181,182] In large part, this is due to the difficulties inherent in rigidly classifying risk judgments: specifically, accurately quantifying risks and reducing complex judgments that attempt to accommodate one's perception of risk to a single category,[183] incorporating the subjective values of those who make these judgments,[184] and other concerns.

[180]*Belmont Report*, p. 6.
[181]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.
[182]Meslin, EM. Risk judgments by IRBs: IRB.
[183]Slovic, P. Perception of risk. Science 236 April 1987: 149-170.
[184]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.

The purpose of having multiple categories of risk is to trigger different requirements from IRBs, just as "minimal" and "greater than minimal" risks trigger different protections in the Common Rule. We do not think it is necessary, however, to recommend that the Common Rule be amended to provide IRBs with three levels of risk to use when assessing risk in relation to potential benefit. As we will state in Chapter Five, we recommend only that IRBs *consider* adding protections above the minimal regulatory requirements for research involving greater than minimal risk. Our reasons are based both on our belief that IRBs already have considerable discretion to assess the acceptability of risk and, therefore, to require the appropriate protections, and on our understanding of some of the inherent difficulties in clearly defining and consistently applying particular risk categories.

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."[185] Although the concept of minimal risk remains a controversial one in academic and scholarly discussion, it is in widespread use in order to determine which set of protections are to be required for particular research protocols. Still, we understand that 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 mental disorders. We therefore want to emphasize the need to establish a practical level of minimal risk against which IRBs can measure proposed research in order to evaluate those protocols requiring further

[185]Sec_.102(i).

protections. The level of minimal risk will change in 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.

The DHHS addressed this issue 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, many proposals on research involving impaired or incapable adults employ the concepts of minimal risk and minor increase over minimal risk. Indeed, we have received a number of comments from the public suggesting that NBAC recommend grouping research involving persons with mental disorders into three categories of risk: minimal risk, minor increase over minimal risk, and greater than minimal risk (which we understand encompasses risks greater than a minor increase over 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 a set of risks in relation to certain potential benefits, nor do the specific additional regulations relating to pregnant women[186] or to prisoners.[187] Only the regulations pertaining specifically to children describe three categories of risk.[188] Giving real substance to these concepts, as noted above, poses serious practical difficulties. The Common Rule's minimal risk definition is tied to the risks of ordinary life and medical care encountered by the population as a whole, and is often is praised

[186]45 CFR 46.201.
[187]45 CFR 46.301.
[188]45 CFR 46.401. In addition, the Department of Education independently adopted DHHS regulations pertaining to children as of December 26, 1997. See 34 CFR 97.401.

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."[189] The concept's reference to "risks of everyday life" is also supported as conveying a defensible normative judgment that the sorts of risks society deems acceptable in other contexts may be acceptable in research as well.[190]

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 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.[191] For subjects not accustomed 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

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

[190]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.

[191]The DHHS regulations on children in research provide that studies may be approved as presenting a minor increase over minimal risk as long as the risks and experiences "are reasonably commensurate with those inherent" in the child subjects' actual or anticipated medical or other situations.

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 ordinary 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 over minimal risk" should be replaced or supplemented by a clearly defined upper limit on the risk IRBs may approve for any child subject.[192]

Difficulties with the minimal risk standard may partly have to do with a historical confusion. Some contend that the drafters of the definition of minimal risk deliberately dropped the National Commission's reference to normal individuals,

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[192]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.

intending to make the relevant comparison point out the 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 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, but with a caveat. 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 everyday life. . . ."[193] The 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. Adherence to the principle of clinical equipoise will ensure that the balance of risks and benefits is no different between therapeutic interventions[194] The text does not elaborate on the procedures that should accompany the cautious approach it counsels.

In our 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 may be interpreted in materially different ways. In some cases,

[193]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

[194]Id. at 14.

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. 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. 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 and must not be classified as lower risk for subjects who have had the misfortune of enduring them in the treatment setting.[195] 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 risk on the one hand and a correspondingly appropriate set of protections on the other.

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

[195]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.

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."[196] Thus the Maryland proposal effectively incorporates examples like venipuncture, electroencephalography, and the study of existing biological specimens.[197] Perhaps over a period of time, it will become evident to the IRB community that protocols tend to cluster in certain ways, for which a certain consensus is thought to emerge. The discussion could also include general considerations relevant to risk classification. 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."[198] The draft Maryland legislation designates research as presenting more than a minor 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."[199]

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.[200] Though

[196]Office of the Maryland Attorney General, p. A-5.
[197]46 Fed. Reg. 8392 (January 26, 1981). NBAC is addressing the issue of research uses of human biological materials in a separate report.
[198]DeRenzo, supra, at 540.
[199]Ibid at A-17.
[200]Keyserlingk, et al., supra, at 330.

some reportedly classify lumbar punctures and bone marrow biopsies as presenting a minor increase over minimal risk, Keyserlingk suggests 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.[201]

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.[202] 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.

In our Protocol Project we saw an example of an IRB that turned to experts for assistance in assessing risks. The protocol they were reviewing contemplated a challenge study which entailed a higher than standard dosage of the challenge agent, while the PI defined 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.

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

[201]Id. at 330.

[202]Harry Bostrom, "On the Compensation for Injured Research Subjects in Sweden," in Compensation for Research Injuries: Appendix, President's Commission for the Study of Ethical Problem in Medicine and Biomedical and Behavioral Research (Washington, DC: U.S. Government Printing Office, 1980), p. 315.

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. We believe 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.[203] In actual practice, however, there is always a great deal of controversy about how such assessments may 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 quite impossible task. Second, each component of risk assessment—identification, estimation, and evaluation—involves time and particular kinds of expertise.[204] 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 technical ability to derive probability estimates.[205] In contrast, the "subjectivist"

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

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.[206] It would seem to us 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 there are contributions that many who have an interest in research can make 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."[207] Evaluating risks to subjects with mental disorders requires familiarity with how subjects in the relevant population 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."[208] 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.[209] Because of the special vulnerability to harm and discomfort that particular subjects may have, risk

[206]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.
[207]Report on Children, supra, at 8-9.
[208]Keyserlingk, et al., supra, at 324.
[209]Report on Institutionalized Persons, supra, at 8-9.

assessment should anticipate the range of reactions subjects may experience to certain proposed study procedures.

Defining Benefits

Research involving adults who have mental disorders that may cause them to have decisionmaking impairments can yield three types of potential benefit: direct medical benefit to subjects, indirect benefit to subjects, and benefit to others.

In the protocols reviewed by NBAC, there seemed to be confusion about the definition of direct benefit. One protocol referred to the research arm of the study as the "treatment phase." In practice, incentives such as monetary rewards, free health care and free psychiatric evaluation, in addition to overstated benefits, may result in coercion. 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."

Direct Medical Benefit

Particular research protocols may hold out the prospect of direct medical benefit to the subjects themselves, but such benefit can never be absolutely assured. The potential direct benefits to the subjects include health improvements which may or may not be related to the disorder responsible for the subject's incapacity.[210] For example, the National Commission stated that research offering potential direct benefits to persons institutionalized as mentally infirm

> includes studies to improve existing methods of

[210]Keyserlingk, et al., supra, at 327.

> 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.[211]

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."[212] A more recent statement on dementia research limits direct 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

[211]Report on Institutionalized Persons, supra, at 31.

[212]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.

diagnostic and preventative measures.[213]

Investigators' assertions that research offers the prospect of direct medical benefit to subjects should be carefully scrutinized by IRBs and other reviewers. Unless the distinctions between direct and indirect benefits are identified, and their relative significance explored carefully, there is a danger that investigators may construe the concept of direct benefit too broadly.[214]

Further, potential direct benefits to the subjects participating in the research protocol must be carefully evaluated and 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."[215] 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."[216] We agree with the view expressed by one group—namely, that an indirect benefit may be acknowledged,

[213]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.

[214] This problem was of concern to the intermediate appellate court in the *T.D.* litigation.

[215]Report on Institutionalized Persons, supra, at 31.

[216]Keyserlingk, et al., supra, at 327.

but should not be assigned the same weight as direct benefit in research review and discussions with prospective subjects and their representatives.[217]

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 benefit category encompasses benefit to subjects' families or other caregivers, to persons with the same disorder as subjects, and to persons who will

[217]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.

suffer from the same disorder in the future. However, this category of research presents the greatest challenge to those seeking the appropriate balance between subject protection and the welfare of others. As one group noted, 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."[218]

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.[219]

We have described some of the difficulties with defining risks and benefits in research; now we turn to 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.[220] There is substantial support, however, for adopting additional

[218]Melnick, et al., supra, at 535.
[219]Belmont, pg. 7.
[220] Clinical Center of NIH policy, NIMH Panel Report, CIOMS, Council of Europe, etc.

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.[221]

Research presenting greater than minimal risk to subjects is 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 with any expectation that it might offer some prospect of direct medical benefit to subjects. We would emphasize that 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, we are acknowledging that some research may hold out the prospect of direct medical benefit for some individuals while some research may not; this is very different from research that might be described as "therapeutic" or "nontherapeutic."

Greater than Minimal Risk Research that Offers the Prospect of Direct Subject Benefit

The general view is that it is permissible to include impaired or incapable subjects in potentially beneficial research projects as long as the research presents a balance of risks and expected direct benefits similar to those available in the normal clinical setting.[222] 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

[221] New York State Working Group, Citizens for Responsible Care in Psychiatric Research.

[222]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).

treatment is reasonably likely to provide substantially greater benefit than standard treatment (or no treatment, if none exists)."[223]

The Maryland draft legislation deems "research involving direct medical benefit" permissible if an agent or family member or friend acting as surrogate, or an 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."[224] 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."[225]

Greater than Minimal Risk Research that Does Not Offer a Reasonable Prospect of Direct Subject Benefit

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

[224]Office of Maryland Attorney General, supra, at A-26–A-28.

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.

[225]NIH Clinical Center, supra.

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 benefit should be permitted only when authorized by a research advance directive[226] or after review and approval at the national level, through a process resembling that set forth in the current regulations governing research involving children.[227] 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. However, others see this position as either too liberal or too restrictive. 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."[228] Some explicitly label this stance the most ethically defensible position.[229]

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

[227]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).

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

[229]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.

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."[230] 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."[231]

Special Review Panel

The children's regulations provide for a special review process to address an otherwise unapprovable study determined by an IRB to offer "a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children."[232] The Secretary of DHHS may approve such a study if, after consultation with experts in relevant fields and the

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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").

[230]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).

[231]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.

[232] 45 CFR 46.401.

opportunity for public review and comment, he or she concurs with the IRB's finding on research significance and determines that "the research will be conducted in accordance with sound ethical principles" or that the study does in fact fall into an IRB-approvable category. In our view, this process, while rarely used,[233] if modified in certain ways offers an additional route for assessing some protocols involving persons with mental disorders. These modifications, which we discuss in Chapter Five, include greater access to and explicit use of this mechanism by IRBs.

Opportunities to Enhance IRB Education and Decision Making

We have been mindful of the concern expressed by some that IRBs, 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. In particular, we recognize 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 burdensome restrictions that would substantially delay or otherwise limit research. We believe, however, that the most appropriate way of addressing 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 an appropriate balance between risks and protections. We believe that 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."

[233]To date one study has received approval under the provisions of the special review process (D. Becker, "Cognitive Function and Hypoglycemia in Children with IDDM," September 20, 1993), and at least one other was referred back to the applicant institution for possible revision and resubmission (T. Munsat and R. Brown, "Mytoblast Transfer in Duchenne Muscular Dystrophy," August 13, 1991). The latter proposal has never been re-submitted. (Personal communication, Michael Carome, Office for Protection from Research Risks, November 3, 1997.)

The purpose of having a set of 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 whether their judgment about risk in relation to the potential benefits is appropriate. 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), we are not persuaded by the argument that an additional category of risk is needed to assist in these decisions. We would hasten to add, however, that by limiting the categories of research to two, we are not intending for IRBs to require all available protections when they determine that a research protocol poses greater than minimal risk. Stratification of several categories of risk might be a useful educational method for training new IRB members, or could be used to help determine how individual IRB members perceive 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.[234] 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.[235] 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."[236]

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

We recognize 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 our recommendations regarding audit and disclosure.

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."[237] 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 coinvestigators are also responsible for the clinical management of subjects."[238] The institution was directed to submit to federal officials a proposal on creating and operating such monitoring boards.

NBAC believes it desirable to distinguish the process of monitoring a subject's safety from the process of monitoring the data generated by the study. Commentators

[237]Sec. ___.111(a)(6).
[238]Office for Protection from Research Risks, supra, at 27.

also refer to the importance of individual subject monitoring, as distinct from keeping track of data, which may suggest that a study or an individual's participation should be stopped because it seems to pose undue risk to a group of subjects or an individual.[239] Although Data and Safety Monitoring Boards (DSMBs) are well-established devices for multisite studies, a major 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.[240]

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."[241] In this spirit, the Maryland draft legislation directs subject representatives to "take reasonable steps to learn whether the

[239]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").
[240]Orr, supra, at 1263.
[241]*Belmont Report*, supra, at 6.

experience of the individual in the research is consistent with the expectations of the legally authorized representative at the time that consent was granted."[242]

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.[243] On the other hand, it is unlikely that subject 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.[244] NBAC believes that, at certain risk levels in research using persons with mental disorders which may affect their decisionmaking capacity, independent monitoring is essential, and that such monitoring should be an ongoing process. We noted in some of the protocols we reviewed ad apparent lack of sufficient or 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. Indeed, in our view, IRBs should expect investigators to describe in their research proposals how potential harms to subjects will be monitored.

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[242]Office of Maryland Attorney General, supra, at A-25.

[243]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.

[244]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).

These first four chapters have 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 fifth chapter presents NBAC's recommendations for appropriate protections for this population and the summary justifications for them.

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 that 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 been an important legacy for this report. For example, the Nuremberg Code (1947) established the importance of voluntary consent to research participation. The Declaration of Helsinki distinguished between research intended partly to benefit the subject and research intended solely for others' benefit. The Guidelines developed by 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 guidelines for research with special populations, the National Commission also proposed additional protections for those institutionalized as mentally infirm. Even though these protections resembled the ones it successfully proposed for children, they were never adopted in federal regulations.

Much has changed since the National Commission's work 20 years ago. There is a much greater sensitivity to the variety of mental disorders and an improved understanding of the ways that these disorders can be recognized and ameliorated.

Both 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 than ever and a larger role for the private sector. While by no means vanquished, the stigmatization of those who suffer from mental disorders show signs of abating due to greater understanding of these individuals and to the underlying biological and genetic[245] influences on some of their conditions among professionals and the public. 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. We propose these new protections with the deepest respect for all those engaged in research on these disorders: the person with a disorder that affects decisionmaking capacity, whose autonomy must be protected and, when possible, enhanced; the clinical investigators who are dedicated to the alleviation of some of humanity's most 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 many researchers have noted, and the ethical problems some thoughtful observers, subjects, and their families have identified, we believe that the enhanced protections we propose below

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

will promote broad-based support for further research by engendering greater public trust and confidence that subjects' rights and interests are fully respected.

In this concluding chapter, we summarize our recommendations and identify the individuals or groups to implement the recommendations.

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 treatments.[246] It is difficult to validate 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 should excessively burden or hamper the development of effective new treatments. Moreover, it is useful to be reminded that many share in 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. In our view, all research involving human beings must satisfy appropriate ethical standards; otherwise, we should not conduct research with these human subjects at all. This imperative is especially acute for potentially vulnerable populations such as individuals with mental disorders.

[246]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.

We believe a cogent case can be made for requiring additional special protections in research involving persons with mental disorders. We also recognize and acknowledge that many, indeed, most, of these recommendations can be applied to research involving other persons who may have impaired decisionmaking capacity. In this way our recommendations broaden the scope of the report to other potential research subjects while retaining our particular focus on persons with mental disorders.

We direct our recommendations to several different groups. Therefore, although our initial recommendations are geared towards the development of new federal regulations, not all of our recommendations are of this kind. We also make recommendations directed to investigators and IRBs, to state legislatures, to the National Institutes of Health, to health professionals, to agencies subject to the Common Rule, and to others responsible for human subjects protection. The structure of our recommendations provide both a set of requirements that we believe must be satisfied by all research protocols involving human subjects and several possible additional or optional protections that may be used in these cases. Taken together, these recommendations could enhance existing protections and facilitate continued research on these disorders.

<u>Recommendations for New Regulations</u>

The desirability of governmental regulation depends not only on the nature of the problems addressed and the importance of the policy enunciated, but also on the rules' ultimate efficacy. Presumably, the least complex measures taken by governmental entities are the preferred ones, so 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 unjustifiably complex and bureaucratic. Some of those engaged in research on conditions related to mental disorders fear that further regulation will unnecessarily retard scientific progress and inappropriately stigmatize individuals who may be suitable 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 that may affect their decisionmaking capacity warrant new regulations and/or whether some or all of the reforms it believes are required could be advanced through other mechanisms, such as statements of principle or the adoption of professional guidelines by those individuals and/or professional groups involved in reviewing, regulating, and carrying out these

projects; suggested changes in professional guidance; or other educational materials for all relevant parties.

NBAC believes that, in addition to the general 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. We come to this conclusion because regulations provide one of the most important methods used in the United States to uniformly assure the protection of the rights and welfare of human subjects. Below we propose 20 recommendations. We recognize, of course, that regulation is not the only method for achieving the type of reform we believe is necessary. For this reason, we make a number of other recommendations apart from those directly affecting regulation.

<u>Recommendations Directed at the Regulation of IRBs</u>

Several of our recommendations are directed at IRBs. We distinguish here between recommendations for regulatory reform, and those which offer guidance to IRBs.

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 this population. At least one of these IRB members shall belong to the relevant subject's population, or a family member 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 concerns of this population and the nature of the mental disorders that may affect decision making capacity; at least one of these two consultants shall be a member of this population, or a family member 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 various research protocols designed to advance medical knowledge about mental disorders that may affect decisionmaking capacity. At least some of these issues are likely to arise in most protocols involving research subjects with such disorders. In general, representation of the subject population on IRBs and the increased involvement of affected persons in planning clinical research on their disorders are increasingly viewed as good ways to increase the likelihood that the IRBs' decisions will be responsive in appropriate ways to the interests of affected groups. More

specifically, increased subject representation on IRBs and, therefore, in the review and conduct of research, is now a more common strategy for improving the design of research protocols that involve persons with mental disabilities.[247] 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.[248] The current provision, however, is advisory only; moreover, it refers only to the involvement of expert professionals, not to other persons also representing the interests of vulnerable subject groups. On the other hand, 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."[249] This regulation was published on the same day in 1991 as the Common Rule.

After evaluating schizophrenia studies at UCLA, OPRR took the stronger measure of directing the School of Medicine's IRB to "engage one or more subject

[247]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).
[248]45 CFR 46.107(f).
[249]34 CFR 97.100.

representatives as IRB members who will assist the IRB in the review of issues related to the rights and welfare of subjects with severe psychiatric disorders."[250] This requirement was imposed even though the IRB already had a psychiatrist and a psychologist as members.[251]

This recommendation helps ensure that the special concerns and knowledge of this population are more likely to be 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 in a good position to help evaluate the potential vulnerability entailed by a specific research protocol. Especially in a system based on local review, there can be no substitute for this kind of representation. Moreover, with this type of recommendation, research sponsors are also likely to be more aware of the importance of taking these issues into account when working with clinicians to design studies.

Appropriate Subject Recruitment

Recommendation 2. An IRB should not approve research targeting persons with mental disorders as subjects when such research can be done with other subjects.

[250]Office for Protection from Research Risks, supra, at 21-22.
[251]See also Shamoo & Hassner Sharav, supra, at S:29.

NBAC is not suggesting that this recommendation is intended to limit or preclude individuals with mental disorders from participating in research unrelated to their mental disorder. The principle we are invoking is one of fairness in the selection of subjects—persons should not be targeted to participate in research because they are administratively convenient or unusually accessible. 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 some 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.

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 perfectly well with other potential subjects. At least two reasons support this prohibition. First, it is important 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 involving persons with decisional impairments due to mental disorders when the research does not require such subjects.

There are circumstances, however, under which other subjects without these disorders may not be 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 from this population. 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 recruited.

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.[252] Therefore, as a matter of justice, people

[252]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

whose best therapeutic alternative may be an innovative treatment can still have access to it.

Dissent from Participation in Research

Recommendation 3. A subject's refusal to participate in research must be honored (at the point of notification or by halting any research intervention with the subject at that time), whether the subject is currently considerd decisionally incable or not, and whether the subject previously agreed to participate in research when competent to do so or was enrolled by a legally authorized representative following a determination of a lack of decision making capacity. Investigators may, with appropriate care and sensitivity, re-approach the previously dissenting person and ascertain whether the dissent still applies, or whether the person now agrees to participate.

Earlier in this report, we discussed the difficulty in imposing too strict a standard of dissent, and explained that 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.

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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.

Most importantly, notifying a person that they are going to be part of a study also gives them an opportunity to refuse to participate. Even when decisionmaking capacity appears to be severely impaired, 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, his or her decisional capacity is in doubt, or the research poses no more than minimal risk. It should be emphasized that the right to refuse to participate in research is not dependent on establishing a right to choose to participate.

Protections in Research Design

Recommendation 4. Investigators should be required to provide to IRBs a thorough justification of the research design they will use, including any efforts they will utilize to reduce the risk in studies which are designed to provoke symptoms, and/or to withdraw patients rapidly from therapies, and/or to randomize patients into placebo controls.

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 using a variety of approaches, including the use of prior scientific review by established peer review groups and review by the IRB. In many institutions, separate scientific review precedes the IRB's assessment of a protocol. In some instances, IRBs also ensure the scientific merit of a protocol using their own members or outside consultants. Regardless of which method is used, investigators and IRBs must consider ways to measure how the particular proposed research protocol will affect subjects in order to design a protocol that will incorporate appropriate protections. Since several specific designs utilized 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 special risks associated with it. In particular, investigators should expect IRBs 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 prospective reasons for subject withdrawal, and follow-up care, if any.

Subjects with serious illnesses are often more vulnerable than others to exploitation when they are involved in randomized clinical trials. While the study itself may be designed so as to hold out the prospect of benefit, and satisfies the condition of

clinical equipoise described above, there will be instances in which the “drug arm” of a study turns out to be more beneficial to subjects than the placebo arm. One way to ameliorate this problem is to incorporate into the study design a nonresearch 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 may be problematic because it may shift the balance of protection in the opposite and equally problematic direction by providing an inappropriate incentive to participate in studies in order to derive the perceived benefits without having to pay for the drugs. However, wraparounds 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 experimental arms in which they receive a study drug are also vulnerable to unfair and exploitive treatment if study results indicate that the drug is effective but 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 the potential for inducement which it raises.

Many decisional impairments are associated with psychiatric disorders that can be managed symptomatically with neuroleptic medication, so 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.[253] Among the possible grounds for excluding placebo arms in particular studies could be that: (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 generally considered 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.

Investigator Justification for Assessment of Risk

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

Recommendation 5. Investigators should be required to provide to the IRB a detailed explanation of their assessment of risks and potential benefits, including the identification, estimation, and acceptability of the risks to the subjects. This assessment should include consideration of the particular procedures proposed and their relationship to the specific conditions of the individuals who may be involved as study subjects.

Since there has been some apparent confusion about what the current federal regulations say about levels of risk, we want to emphasize an important point: 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),[254] and hence are not applicable to those agencies that are signatories to the Common Rule. Agencies and, indeed, investigators and IRBs may choose voluntarily to adopt the three-tiered approach to risk, should they find it to be useful. In our 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 both IRBs and investigators so that the 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 of

[254] 45 CFR 46.100.

importance for research in which disagreement exists about whether the risk is "minimal." The regulations define minimal risk, but 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 quite appropriately must be applied contextually in light of specific study conditions. 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 may cause them more distress than it would for someone who fully understood the reason for the intervention. For example, repeated venipunctures (blood draws) that 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 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 in research as subjects must carefully articulate to IRBs the nature of their risk evaluation procedures for potential subjects. Even within a 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 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.

Assessing Potential Subjects' Capacity to Decide About Participating in Research

Recommendation 6. For research protocols that present greater than minimal risk, an IRB should presume that an investigator will need to employ an appropriate method, administered by a qualified professional who is independent of the research team, to assess the potential subject's capacity to decide whether to participate in research. An IRB should permit an investigator to forego this

procedure only if persuasive grounds exist for using less formal methods of assessing a subject's capacity.

Notification of Determination of Incapacity and Enrollment in Research

Recommendation 7. A conscious person who has been determined to lack capacity to consent to participate in a research protocol must be notified of that determination before permission can be sought from his or her legally authorized representative to enroll that person in the research; if permission is given to enroll him or her in the research, the potential subject must then be notified. Should they dissent or otherwise object, this should 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. Capacity assessment should only be required when potential subjects are believed to 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 us to be necessary. It perpetuates an incorrect assumption about persons in general, and 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 kind of protection that we intend. If a potential subject appears to lack capacity, their capacity should be assessed. Our 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. Studies involving non-invasive interventions which satisfy the conditions of minimal risk defined in the Common Rule, (e.g., surveys or questionnaires), would probably not result in IRBs expecting such an assessment to occur. IRBs would, of course, have the authority to require that a particular study (involving minimal risk) include a capacity assessment if they reason to believe that the potential subject's capacity is impaired. The value of capacity assessment prior to enrollment of a potential 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 approach a third party to make a decision on behalf of this person.

Some argue that 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 a research protocol.[255] Such a notification process might seem, at times, to be an empty

[255]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 the National Bioethics Advisory Commission, 1997)

ritual and, worse, to be a requirement that could well contribute to undermining health professionals' respect for the regulatory system. Nevertheless, ethical treatment of human subjects demands this process be observed, for to fail to do so is to deprive the subject both of the right to seek review of the decision and of the right to possible judicial intervention. Abrogating the subject's autonomy in such a way is indefensible in a democratic society.[256]

Research that Presents Greater than Minimal Risk and Offers the Prospect of Direct Medical Benefit to the Subject

Recommendation 8. An IRB may approve protocols in this category of research if the potential subjects are capable of making a decision about participation when the potential subjects have provided an informed consent to participate.

Recommendation 9. An IRB may approve protocols in this category of research if the potential subjects are currently incapable of making a decision about participation, when conditions (a) and (b) below are satisfied, or, in the alternative, (c) is satisfied:

[256]Although this report addresses the involvement in research of persons with mental disorders who may lose their decisionmaking capacity, arguably the same notification standard should apply to all decisionally impaired persons who may be entered into a research protocol.

(a) the potential subjects, when previously capable of making a decision about participation in research, expressed their willingness to participate;

(b) the subjects have been notified of the assessment of their capacity, and have not objected to or otherwise dissented from participation;

OR

(c) the subject's legally authorized representative has given permission for the subject to be enrolled in the study. Where the subject has expressed a previous wish not to participate in research, that request must always be honored.

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. The potential subject also needs 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 and/or treatment.

Some important research may not be done without the involvement of persons with mental disorders, and some of that research may possibly offer a direct therapeutic 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.[257]

In addition, some individuals with disorders that affect decisionmaking capacity may be able to give informed consent at certain times during their illness. The presence of a psychiatric disorder should not automatically disqualify an individual from being permitted to volunteer if he or she has sufficient capacity to consent and/or other protections are in place. Moreover, an individual may be able to give consent to participate in a specific study in advance of an anticipated period of incapacity, which may be especially important for research that examines a physiologic state during such a period.

Yet no one is obligated to participate in a study, even if it may be of direct medical benefit to them. 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 legally authorized representative must have given permission for research participation *and* the subject must have been given the opportunity to refuse

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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 wish to participate. A dissent may potentially be overridden only through a judicial process, with full due process protections.

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

Recommendation 10. An IRB may approve protocols in this category of research if a person with the capacity to give informed consent for participation in the research has done so.

Recommendation 11. An IRB may approve protocols in this category of research involving persons who currently lack the capacity to give informed consent for participation in the research if the following conditions apply:

(a) the person has, while capable of informed consent, agreed to participate in this type of study in the future; and

(b) there has been no material change in the nature of the research protocol or the person's situation (apart from the loss of decision making capacity) between the time that the advance planning process took place and the time that the research participation is actually to begin; and

(c) consistent with applicable state law, a legally authorized representative is available to make decisions about continuing or stopping the person's participation in the research.

Research proposals involving persons with mental disorders, but which is not of potential benefit to these individuals, may be conducted only under certain circumstances outlined above. For persons assessed to have 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 consented in advance to such involvement, or, as we recommend below, were a waiver granted by the Secretary of Health and Human Services.

Special Panel to Assess Waiver Requests

Recommendation 12. The Common Rule should be amended to permit the Secretary of Health and Human Services to direct OPRR to establish and convene a standing panel to assess requests for a waiver of regulatory prohibitions when research involving greater than minimal risk that does not offer the prospect of direct benefit to subjects is of exceptional importance but cannot be approved by an IRB because the requirements in Recommendation 11 are not able to be met.

Recommendation 13. Those agencies of the federal government who are signators to the Common Rule should voluntarily agree to utilize the panel established by the HHS Secretary under Recommendation 12 above, mechanism and that after an appropriate period of time, not to exceed five years, an authoritative body review and evaluate the effectiveness of this mechanism and make recommendations regarding its continuation.

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 above, nevertheless are of exceptional importance and have a favorable balance of benefit and risk, hat an opportunity for further review should be provided. This panel would examine waiver requests on a case-by-case basis. It would also be permitted to set guidelines for entire classes of research; protocols consistent with these guidelines would then be presumptively eligible for the case-by-case waiver. In both individual and categorical review, the panel should determine whether the research is exceptionally important and could not be conducted without using mentally incapacitated subjects, and should specify (1) any special procedures or protections needed to ensure that the risks to subjects are minimized, (2) 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

adequacy of the protection afforded subjects. Such a panel should include 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 provides some genuine flexibility for the system to respond to new findings and new understandings of research. The Commission is aware that one of the implications of our recommendation that limits research involving greater than minimal risk without the prospect of direct medical benefit to conditions of prior consent or a waiver by the Secretary of DHHS is the possibility that certain types of research "at the margin" between minimal risk and greater than minimal risk may be more difficult to conduct. We have already explained above why the answer to this difficulty is not to create a new category of risk--"minor increment over minimal risk"-- analogous to that found in the regulations pertaining to children. Rather, we recognize that with advances being made in research, and the evolving increase in sensitivity of investigators and IRBs to ethical issues arising in research on 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 a delegation to IRBs to approve research of this kind.

We noted earlier in this report that the Secretary's authority within the children's regulations to provide for a special review process has been rarely used. The intent of this recommendation is to provide the Secretary with a mechanism (through OPRR) to address an issue which both the research community and the public have expressed to the commission in sometimes opposing ways: how 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 to accept the risks of such research is lacking? How can potential subjects and their families be assured that their rights and welfare are protected? We believe that this mechanism may provide a way forward. The model we are proposing here is based, in part, on the waiver currently available to researchers in studies involving children.

We believe that the twin goals of appropriate protection of subjects and of the conduct of high-quality research can be accomplished by utilizing an advance planning process which is carefully described. In our view, 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 an LAR, (b) the completion of a durable power of attorney document, which identifies the person designated as an 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 legally authorized representative 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 legally authorized representative as a surrogate to make decisions concerning continuing research participation in a general class of research protocols should the subject become unable (while in the study) 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 subject's treatment (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 and responsible health care professional. 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.[258]

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

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

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.

We have reviewed various proposals for extending the decisionmaking authority of individuals in anticipation of a period of incapacity during their participation in research. For studies involving greater than minimal risk, the identification of a legally authorized representative (often informally called a surrogate) should be part of a thorough informed consent process, so that important decisions can be made while the subject is incapacitated. 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.

Additional Guidance for IRBs

It will take time for the recommended amendments to the Common Rule described above to become regulation. Meanwhile, the IRB system should adopt, on a voluntary basis, the spirit and substance of the additional protections described above. Those IRBs that choose not to adopt such policies should publicly disclose these reasons and the resulting differences in their policies. NBAC itself is currently studying the federal system for overseeing human subjects protection, including the IRB system, and intends to issue a separate report on this subject. For this reason, we offer only some additional areas of guidance for IRBs; other, more comprehensive, recommendations for IRBs will appear in that report.

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 inpatient or continuing-care subjects may have on

their institutions, or those arising 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).

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 the consent process 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 require 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 direct benefit to the subject.

Studies with those who are decisionally impaired may take place over extended periods. One of the essential conditions of ethical research is continued voluntary participation, but those who are deeply involved with and dependent upon the health care system may not feel able to withdraw from a study. A requirement for periodic

reconsenting would help ensure that a patient's continued involvement is truly voluntary,[259] and would provide the occasion to reassess decisionmaking capacity and, if necessary, 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 reconsenting 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.[260] IRBs should consider attaching a reconsent requirement to certain studies based on their length, on their risks and benefits, and on the mental condition of potential subjects, such as those with progressive neurological disorders or fluctuating capacity.

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[259]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).

[260]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

Independent Health Care Professional Advisors

IRBs may wish to consider recommending that an independent clinician be available to counsel the subject's responsible health care professional and legally authorized representative, even for research that offers the prospect of direct benefit to subjects.

Voluntary Self-evaluation

IRBs may consider, alone, with other IRBs, or in collaboration with professional organizations (see below), 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 our 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 risk levels are explicitly used. Were this evaluation conducted in a more formal manner, the results could be published and shared with the IRB and research community.

<u>Guidance for Institutions</u>

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minimal risk. Personal communication, Dr. Terrie Wetle, Deputy Director, National Institute on Aging, July 2,

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, institutions may be thought of as the foundation upon which ethical practice is built. During the course of its deliberations, NBAC heard testimony from patients, subjects, institutional administrators, and others. On one occasion, testimony before NBAC led, in part, to an investigation of an institution by the Office for Protection from Research Risks.[261]

Audit and Disclosure

We have noted above the importance of institutional policy regarding research on vulnerable persons. IRBs should voluntarily undertake a series of measures that would open their activities to greater public view, accountability, and analysis. In this regard, NBAC has the following three 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.

1998.

[261]Letter from Susan L. Crandall, MD, Acting Chief, Compliance Oversight Branch, Office for Protection from Research Risks, to Donald E. Wilson, MD, Dean of the Medical School, University of Maryland/Baltimore, April 16, 1998. Letter on file at NBAC.

(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 the IRBs can very effectively use the instrument of audit (both internal and external) and disclosure to provide increased accountability and understanding and to inspire public confidence in their oversight activities. Indeed, these tools can be an excellent substitute for a wide variety of excessively detailed rules and regulations. We recognize that such mechanisms can be used by all institutions, for all research involving human subjects. In an upcoming NBAC report, we will address this issue in more detail.

<u>Recommendations Relating to the States</u>

We are aware that there is interest in the states about many of the issues in this report. Two recommendations are proposed.

Recommendation 14. The Common Rule should be amended to define the term "legally authorized representative" to include those persons who, under the law of the state where research is conducted, may serve as proxy decision makers for clinical care.

Recommendation 15: States should amend current laws governing "Durable Powers of Attorney" (or equivalent legislation) so that persons creating these kinds of documents would be authorized to grant decision making authority for research participation, as well as for clinical care, if the research 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 direct-benefit research. We are 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 no-direct-benefit research.

Although the Commission 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 the Commission's 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.

<u>Recommendation to Professionals and Organizations of Health Care Professionals</u>

Recommendation 16. All professionals whose expertise embraces research involving those with disorders that may affect decisionmaking capacity should find ways to recognize family members, close friends, and other important caregivers as part of the health care team and to share appropriate information with them. Professional organizations should open discussions about methods to pursue this goal. Innovations in this area must, of course, be consistent with the ethical obligation of patient confidentiality.

Recommendation 17. Professional associations and organizations should develop (or review their existing) educational materials pertaining to research involving persons with mental disorders. A growing literature in research ethics exists on this subject, only a small portion of which is referenced in this report. More is emerging on a regular basis. As more is learned about ethical, legal, medical, and social issues in research involving this diverse population, the more important it will be for guidelines and policies to be current.

Recommendations to the National Institutes of Health

Further Research on Informed Consent

Recommendation 18. The National Institutes of Health should sponsor research that can expand knowledge concerning the most reliable methodologies 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 on the subject of informed consent,[262] 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 we have referred to extensively in this report.

Further Research on Advance Planning

Recommendation 19. The National Institutes of Health should support research on the appropriate use of research durable powers of attorney and other advance planning documents for use by persons with mental disorders.

Further Recommendations

Mandatory Registry

Recommendation 20. The appropriate federal agency should establish a mandatory IRB registry. This registry would require that all institutions receiving federal funds for protocols involving human subjects to register annually. The agency housing the registry should have the authority to conduct audits of IRB records and

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procedures without cause. The auditing agency should have the authority to review and publicly annually disclose its findings.

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 that had previously been research subjects, and subjects' family members. NBAC received written testimony from 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 benefit; the subjects were persons with mental disorders which may have affected their 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 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, inappropriately defining risks as minimal, overemphasizing 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.

Protocol Title:

Reviewer=s 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				

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

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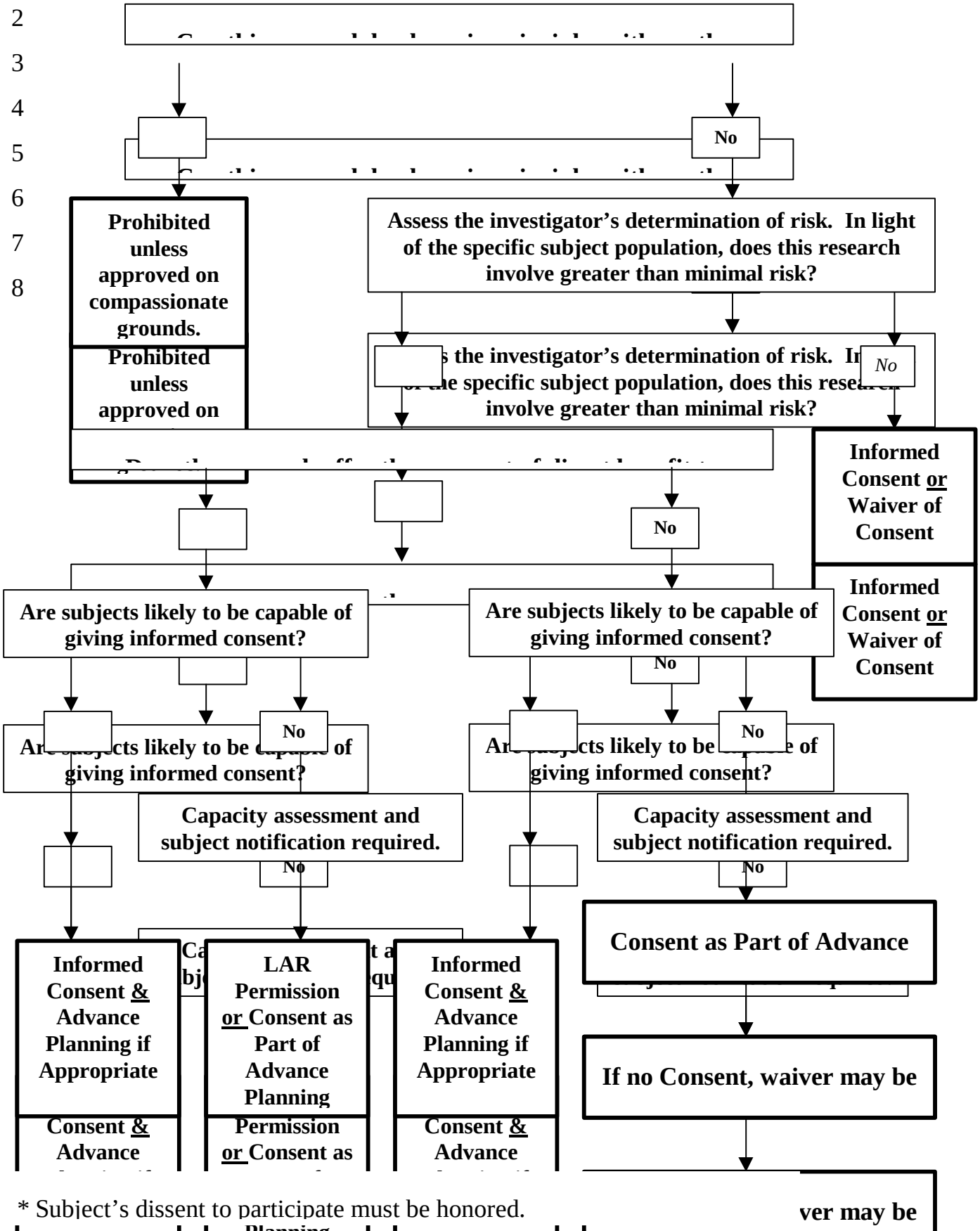
Appendix 3: Flow Chart Summary of Recommended Review Procedures for IRBs



* Subject's dissent to participate must be honored.

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