

1 *A Draft Report of the National Bioethics Advisory*
2 *Commission:*

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17 **Research Involving Persons**
18 **with Mental Disorders That May Affect**
19 **Decisionmaking Capacity**

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1 EXECUTIVE SUMMARY

2

3 Mental Disorders and Research Participation

4 Mental disorders cause great suffering and often stigmatize those stricken with
5 them. In the past, little could be done to ameliorate the symptoms of such disorders,
6 but in recent years there have been some striking successes, and there is now renewed
7 optimism within the medical community about promising new approaches to treating
8 many of them. As a result, biomedical and behavioral research involving persons with
9 mental disorders is an increasingly important field of scientific investigation.

10 Because of this renewed hope, the National Bioethics Advisory Commission
11 (NBAC) anticipates that increasing numbers of persons with mental disorders will be
12 recruited as subjects in important research protocols that, by their very nature, present
13 some potential for both benefit and harm to the human participants. Disclosing these
14 benefits and potential harms through an informed consent process, and reviewing the
15 scientific validity and importance of the proposed research protocols by Institutional
16 Review Boards (IRBs), have been the principal methods of protecting human subjects
17 from unwarranted and unnecessary harm.

18 NBAC does not presume that it is merely the presence of mental disorders that
19 renders persons incapable of making informed decisions to participate in research
20 protocols. Indeed, it would be wrong to refer to all persons with mental disorders as if
21 they belonged to a singular group collectively incapable of deciding about participation
22 in research or to imply that only individuals with mental disorders lack decisionmaking
23 capacity to participate in research. Different mental disorders affect decision making
24 in different ways, at different times. It is the effect such conditions can have on their
25 capacity to give valid informed consent that makes their participation in research such
26 a delicate issue. Examples might be the subject's feeling of dependence on caregivers
27 and institutions, or his limited financial resources and social support. Such variables

1 raise important and complex ethical concerns about the special vulnerability of
2 persons with mental disorders and, therefore, the quality of their consent to participate
3 in research protocols. We recognizes the need to address these concerns fully in order
4 to ensure both the appropriate protection of this population and the continued viability
5 of the kind of research that of necessity requires the participation of these individuals.

6

7 The Role of the National Bioethics Advisory Commission (NBAC)

8 There have been previous efforts to extend special additional regulatory
9 protections to persons with mental disorders, but they have not been fully successful.
10 The National Commission for the Protection of Human Subjects of Biomedical and
11 Behavioral Research (hereinafter referred to as the National Commission), which
12 studied the issue from 1974 to 1978, proposed regulations for persons
13 "institutionalized as mentally infirm." Although these proposals were never adopted,
14 scholars and others concerned with the welfare of this population continue to examine
15 their applicability. The National Bioethics Advisory Commission (NBAC) is studying
16 those issues as part of its overall mission to advise both the National Science and
17 Technology Council, chaired by the President, and other government entities on
18 appropriate policies, guidelines, and other instruments addressing the bioethical issues
19 arising from research on human biology and behavior.¹

20 NBAC is examining these concerns not only because of the special needs of
21 these human subjects—including the need for more research—but also because of
22 several highly publicized incidents of research involving this population that brought
23 the issues sharply into focus. In an effort to broaden and deepen its understanding,
24 NBAC commissioned several papers and heard testimony from individuals who

¹Executive Order 12975, Sec 4(a)(1).

1 represent various perspectives: patients, family members, members of advocacy
2 organizations, scientific investigators, and federal officials.

3 During the nearly two decades in which current federal regulations regarding
4 the protection of human subjects have been in place, important scientific research
5 concerning disorders that affect this population has continued and expanded. NBAC
6 acknowledges that important opportunities to develop new therapies from biomedical
7 and behavioral science research will continue to emerge. Its challenge, then, is both to
8 sustain the acquisition of new knowledge and the development of new therapies arising
9 from continued research, and to ensure absolutely the protection of those who
10 participate in such research from unwarranted harm. NBAC is not an investigatory
11 body and therefore did not try to reach an independent conclusion about the extent to
12 which persons with mental disorders may currently undergo risk in particular research
13 protocols. Nevertheless, it has concluded that the absence of specific, additional
14 protections in the federal regulations for persons with mental disorders in research is
15 significant, especially in light of the requirements that have long applied to persons
16 from other potentially vulnerable groups.

17

18 Assessing Risks

19 Informed consent is a critical, necessary prerequisite to ethical research with
20 human subjects, but it is not the only one. Since no one should be exposed to risk or
21 even inconvenience if a scientific project is poorly designed, a second crucial element
22 of ethical research with human subjects is prior review and approval of each protocol
23 by the multidisciplinary group of scientists, clinicians, and lay persons known as an
24 Institutional Review Board (IRB). Each board's primary purpose is to assess the
25 quality of the protocol design, the validity of the informed consent process, and the
26 ability of the investigators to carry out the study.

1 Under current regulations, IRBs already have considerable discretionary
2 authority to impose various requirements on research projects (including protections
3 beyond those required by existing federal regulations). It is not known how often IRBs
4 exercise this authority. Since there is a lack of specific guidance in the current
5 regulations, the extent to which the special needs of persons with mental disorders are
6 independently assessed as the processes of mobilizing and conducting a research
7 protocol are carried out is limited.

8 Another factor in evaluating research risks with this population is the extent to
9 which a subject's particular mental disorder may make him more vulnerable to harm
10 than that which other subjects in the same study might sustain. An example might be
11 his waxing and waning ability to comprehend the need to be subjected to certain
12 procedures, or his capacity for understanding that specific aspects of the protocol may
13 actually provoke the symptoms of his disorder, however briefly. Given that different
14 mental disorders can manifest unique symptoms, all investigators must ensure that the
15 subject's participation remains voluntary throughout the research process and that the
16 risks continue to be reasonable in light of the potential direct benefits to the subject.

17

18 The Recommendations

19 To ensure that the rights and welfare of persons with mental disorders who
20 participate in research are fully protected, and that research involving such persons
21 meets the ethical standards that the American people should expect of scientific
22 investigations, NBAC recommends several measures: new federal regulations,
23 guidance for Institutional Review Boards and the organizations that support them;
24 suggestions for state legislation; proposals for educating health care professionals;
25 projected research to expand our capacity to assess the decisionmaking ability of
26 potential human subjects; and new measures designed to enhance Common Rule
27 protections while allowing important research to continue.

1 NBAC also recommends that IRB memberships be composed of persons who
2 (1) are familiar with the issues that may arise in research involving this population, and
3 (2) are particularly knowledgeable about the population in question. In addition, it is
4 critical for investigators to explain more fully in their proposed protocols why they
5 have chosen their particular study design, why involving persons with mental disorders
6 is necessary, how each subject's capacity to consent to research will be assessed, and
7 how the investigators have evaluated the risks to subjects in the study. We recommend
8 that any dissent prospective subjects may express be respected, no matter what their
9 decisionmaking capacities. If a subject is deemed incapable of deciding whether to
10 participate at all, he should be so informed.

11 In research that offers potential direct benefit but may also present greater-than-
12 minimal risk, persons with mental disorders capable of giving informed consent may
13 participate. In such cases, however, contingency plans should exist if subjects lose
14 their capacity during the study. If they are not capable of giving informed consent at
15 all, a legally authorized representative may give permission, provided the subject does
16 not appear to dissent when informed.

17 In research that is not potentially beneficial to the subject and that presents
18 greater-than-minimal risk to the subject, persons with mental disorders may participate
19 only if they have given informed consent, including consent given as part of an
20 advance planning process. In addition, we recommend the research be permissible
21 only when a legally authorized representative is identified who, with the help of an
22 independent health care advisor, can make decisions about continuing or stopping a
23 subject's participation in research. The role of the independent health care advisor, in
24 turn, is to counsel the potential subject and/or the legally authorized representative
25 about whether the subject's entrance into or continuation within a study is appropriate.

26 We recommend that family members be eligible to serve as legally authorized
27 representatives and urge the states to consider legislation to this effect. We also

1 suggest that research institutions introduce internal audit and disclosure mechanisms
2 for their IRBs in order to open the IRB deliberations process to public scrutiny, and to
3 provide the institutions with the information that will allow them to modify their
4 policies and procedures to be in compliance with federal regulations and to meet their
5 own objectives. We further recommend that the Federal Government use external
6 audit and disclosure procedures. Finally, we urge the National Institutes of Health
7 (NIH) to support studies to find the best ways to assess the capacity of persons with
8 mental disorders to make thoughtful decisions about participating in research, and to
9 ensure that participation by such subjects continues to be informed and voluntary.

10

11

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

3

4 Overview: The Purpose of This Report

5 A wide variety of important research studies using human subjects² has long
6 played an essential and irreplaceable role in advancing biomedical and behavioral
7 science, thus enhancing our ability to treat illness and understand human behavior
8 more successfully. In recent decades, however, researchers and commentators alike
9 have been increasingly sensitive to the ethical issues associated with such research
10 studies, especially as they concern the welfare of the subjects. As a result,
11 governmental regulations, enhanced professional guidelines, and various institutional-
12 based mechanisms have been established in countries around the world to help ensure
13 that such studies meet appropriate ethical standards to protect human subjects (who
14 may include the clinical investigator’s patients) and clarify under what circumstances
15 they may be placed at risk in any research aimed at understanding and alleviating
16 disease. The two most fundamental measures are expert review of protocols to ensure
17 their scientific validity and importance as well as their ethical acceptability, and the
18 informed consent of human subjects.

19 Although special protections have been provided for certain populations that are
20 regarded as particularly vulnerable and unable to give meaningful informed consent to
21 their participation in research protocols,³ persons with mental disorders who may, as a

²In 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 be) research subjects, it will generally refer to “persons” when discussing these individuals.

³45 C.F.R. 46, Subparts B, C, and D (June 18, 1991) 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

1 consequence of their disease, have impaired capacity to make decisions have not
2 received any additional special protections in regulations. Alison Wichman has noted
3 that, while existing human subjects regulations broadly address the need to protect
4 individuals with diminished autonomy, specifically “where some or all of the subjects
5 are likely to be vulnerable to coercion or undue influence, such as children, prisoners,
6 pregnant women, mentally disabled persons, or economically or educationally
7 disadvantaged persons,”⁴ little additional *practical* guidance is provided regarding
8 vulnerable subjects who are not already covered by existing regulation.⁵ Mental
9 disorders—which can be heartbreakingly burdensome for victims and their families
10 and frustrating for the professionals who try to treat them—have in recent years been
11 the object of research studies that have produced not only important and clinically
12 relevant scientific findings but also a certain amount of public controversy,
13 governmental sanctions, and even lawsuits (see the further discussion in Chapter
14 Two). Ironically, however, current U.S. regulations designed to ensure the ethical
15 treatment of these human research subjects with mental disorders provide no special
16 guidance for IRBs and investigators.

17 In its final report, the Advisory Committee on Human Radiation Experiments
18 (ACHRE), based on its own empirical studies, noted its concern about "serious
19 deficiencies in some parts of the current system for the protection of the rights and
20 interests of human subjects."⁶ As part of its work, ACHRE reviewed 125 research
21 proposals involving human subjects and ionizing radiation approved and funded in
22 fiscal years 1990 through 1993, and found that almost half of these studies involving

for research into their disease (e.g., cancer or sepsis) cannot be obtained from persons who lack the capacity for such autonomous consent.

⁴45 CFR 46.111(b).

⁵Alison Wichman, “Protecting Vulnerable Subjects: Practical Realities of Institutional Review Board Review and Approval,” *Journal of Health Care Law and Policy*, Vol. 1, No. 1, 1998, pp. 92-93, *emphasis added*.

⁶Advisory Committee on Human Radiation Experiments, New York: Oxford University Press, 1995, p. 510, hereinafter ACHRE.

1 greater-than-minimal risk raised “serious or moderate concerns.”⁷ Among the recent
2 research protocols reviewed by the Advisory Committee that led to this expression of
3 concern were some involving persons at risk for impaired decisionmaking capacity.
4 Indeed, one of the three examples of controversial unresolved issues in the ethics of
5 research was research on adults with questionable decisionmaking capacity that offers
6 them no prospect of benefit but involves unpleasant procedures and exposes them to
7 greater than minimal risk of harm.⁸ ACHRE also surveyed hundreds of people who
8 were ill but who retained decisionmaking capacity and were currently participating in
9 clinical trials, concluding that many of them were not aware of important and relevant
10 elements of the research.⁹ Considering the special complexities of research involving
11 those whose decisional capacity may be affected by mental disorders, ACHRE’s
12 concerns must be at least as strongly applied.

13 As NBAC's predecessor, ACHRE provided a basis for further consideration of
14 suitable conditions for involving in research those persons whose decisional capacity
15 might be impaired. However, the deliberations that produced NBAC’s report were not
16 stimulated by a perceived crisis in the participation of persons from this population in
17 clinical studies, but by the recognition of substantial confusion about the principles
18 and procedures that should govern such research. While we heard powerful testimony
19 from members of the public and the professions at NBAC meetings, and received
20 materials and information describing the strengths and weaknesses of the system of
21 human subjects protection, NBAC did not rely on these as evidence of the need to “fix
22 a broken system.” We were informed by this input, and grateful for it, but our rationale
23 was not “crisis management”; rather, it was a prospective and constructive approach to

⁷ACHRE, p. 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.

⁸ACHRE, p. 456.

⁹Id., pp. 459-481.

1 closing one of the possible gaps perceived to exist in human subjects research
2 protection.¹⁰

3 Confusion has been evident in several legal cases and in widespread public
4 discussion of the appropriate role of this population in research. One well-publicized
5 and often misunderstood incident which was brought to the public's attention was the
6 suicide, well after the completion of a research protocol, of a former subject in a
7 "washout" study at the University of California at Los Angeles. This particular case
8 led to an investigation by the Office for Protection from Research Risks (OPRR).¹¹ In
9 addition, a number of organizations and government agencies, both in the United
10 States^{12,13,14} and abroad,^{15,16,17,18} have recently considered the matter and offered
11 recommendations. In addition, numerous scholarly papers have also appeared in the
12 last several years addressing various aspects of the topic.^{19,20,21,22,23,24,25,26,27,28,29} In sum,

¹⁰Childress, JF. The National Bioethics Advisory Commission: Bridging the Gaps in Human Subjects Research Protection. *Journal of Health Care Law and Policy*, Vol. 1, No. 1, 1998, pp: 105-122.

¹¹Office for Protection from Research Risks, "Evaluation of Human Subject Protections in Schizophrenia Research Conducted by the University of California, Los Angeles" (1994).

¹²National 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

¹³Office of the Maryland Attorney General. Final Report of the Attorney General's Research Working Group, 1998.

¹⁴The New York Department of Health Working Group.

¹⁵Council of Europe. Convention on Human Rights and Medicine, November 1996.

¹⁶United Kingdom. The Law Commission. Mental Incapacity: Item 9 of the Fourth Programme of Law Reform: Mentally Incapacitated Adults, London, England, House of Commons, 1995.

¹⁷CIOMS, Guidelines on Research Involving Human Subject, 1993.

¹⁸Canada. Tri-Council Working Group. Code of Ethical Conduct for Research Involving Humans, Ottawa, Ontario. June 1998.

¹⁹Marson D.C., Ingram K.K., Cody H.A., Harrell L.E., "Assessing the competency of patients with Alzheimer's disease under different legal standards." *Archives of Neurology* 52:949-954 (1995).

²⁰Stanley B., Guido J., Stanley M., Shortell D., "The elderly patient and informed consent." *Journal of the American Medical Association* 252:1302-1306 (1984).

²¹DeRenzo, E. The Ethics of Involving Psychiatrically Impaired Persons in Research, IRB, Nov.-Dec. 1994.

²²John C. Fletcher & Alison Whitman, A New Consent Policy for Research with Impaired Human Subjects, 23 *Psychopharmacology BULL.* 382 (1987).

²³Berg J, Karlinsky H, and Lowy F (eds.) *Alzheimer's Disease Research: Ethical and Legal Issues* (Toronto: Carswell, 1991).

²⁴Keyserlingk, et al., Proposed Guidelines for the Participation of Persons With Dementia as Research Subjects, 38 *Perspect. Biol. Med.* 319 (1995).

²⁵Shamoo, A. and Keay, T.J. "Ethical Concerns About Relapse Studies," *Cambridge Quarterly of Healthcare Ethics* 5:373-386 (1996).

1 a critical mass was developing, and it afforded NBAC the opportunity to review and
2 consider these issues in the context of its responsibility to advise the President through
3 the National Science and Technology Council.

4 Further, we anticipate that many new, potentially useful therapies for treating
5 the relevant disorders will be developed over the next few years. The prospect of
6 increasing numbers of research protocols, with the attendant potential increase in the
7 number of persons with impaired decisionmaking capacity in these kinds of studies,
8 makes it all the more important to clarify the ethical framework for such research.
9 NBAC was also mindful of worries that have been expressed about the ability of IRBs
10 at some large research centers to actually monitor, as necessary, approved research
11 proposals.

12 Therefore, NBAC's recommendations concerning research involving persons
13 with mental disorders that may have impaired decisionmaking capacity are not in
14 response to a "crisis," but are an effort to articulate appropriate conditions under
15 which these studies should take place.

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

²⁶Appelbaum P.S., Grisso T., "Capacities of hospitalized, medically ill patients to consent to treatment." *Psychosomatics* 38:119-125, (1997).

²⁷Bonnie R., "Research With Cognitively Impaired Subjects," *Arch. Gen. Psych.* 54:105, 107 (1997)

²⁸Jonathan D. Moreno, "Regulation of Research on the Decisionally Impaired: History and Gaps in the Current Regulatory System," which was presented at the conference "Conducting Research on the Decisionally Impaired," University of Maryland School of Law, May 28, 1997.

²⁹Berg.

1 Research Involving Persons with Mental Disorders that May Affect Decisionmaking
2 Capacity

3 Persons with mental disorders are not, of course, unique in being at risk for loss
4 of decisionmaking capacity. Accident and trauma victims, highly medicated patients,
5 and many people who are severely ill may be significantly less capable of making
6 decisions than would be the case in other circumstances. Indeed, a comprehensive list
7 of individuals whose decision making may be compromised or placed in question
8 includes children, comatose patients, critically ill patients, institutionalized individuals,
9 prisoners, people lacking certain language skills, persons with certain mental disorders,
10 persons with brain disorders (e.g., stroke), and others.³⁰ While we recognize that many
11 of the issues and concerns that we will raise in this report (and indeed many of the
12 recommended protections we are advocating) *could* be applied to *all* persons with
13 questionable or diminished capacity, we are not yet confident that this analysis would
14 hold up. Given the limited knowledge which exists about the ability to assess capacity
15 to *participate in research* (as opposed to the ability to assess capacity to designate a
16 financial power of attorney, to designate durable power of attorney for clinical
17 decisions, or to write a will), we are principally focusing our attention on those who
18 may be primarily considered for research protocols because it is their particular mental
19 disorder that is being studied. We recognize, however, that it will be difficult to
20 consistently fit diseases or conditions within particular linguistic categories,
21 particularly in areas such as psychiatry and neurology in which the boundaries of
22 investigation are moving faster than the development of new labels, a difficulty that
23 has been noted by the American Psychiatric Association in its *Diagnostic and*
24 *Statistical Manual of Mental Disorders*:

25 Although this volume is titled the *Diagnostic and Statistical Manual of*

³⁰Wichman, op. cit. p. 104.

1 *Mental Disorders*, the term *mental disorder* unfortunately implies a
2 distinction between “mental” disorders and “physical” disorders that is a
3 reductionistic anachronism of mind/body dualism. A compelling
4 literature documents that there is much “physical” in “mental” disorders
5 and much “mental” in “physical” disorders. The problem raised by the
6 term “mental” disorders has been much clearer than its solution, and,
7 unfortunately, the term persists in the title of DSM-IV because we have
8 not found an appropriate substitute.³¹

9 Moreover, although this manual provides a classification of mental
10 disorders, it must be admitted that no definition adequately specifies
11 precise boundaries for the concept of “mental disorder.” The concept of
12 mental disorder, like many other concepts in medicine and science, lacks
13 a consistent operational definition that covers all situations.

14 For this reason, we intend this report to focus principally on research involving
15 persons with mental disorders, but recognize and encourage its use by others seeking
16 guidance for conducting research on other persons whose decisionmaking capacity
17 may be impaired by their condition.

18 We are mindful of the concern that could arise from our focus on individuals
19 who are members of a group (persons with certain disorders) rather than on persons
20 who share a common functional characteristic (questionable decision making)—this
21 focus could raise the specter of equating mental disorder with incapacity and thus
22 potentially stigmatize these individuals. We share this concern. We recognize that not
23 all persons with mental disorders have impaired decisionmaking capacities or, among
24 those who do have them, that these impairments necessarily compromise the
25 individuals’ decisionmaking abilities about research participation. Our intention is not

³¹American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, p. xxi, hereinafter DSM-IV.

1 to label persons—our intention is to describe and explain a set of appropriate concerns
2 regarding research involving certain persons and to propose ways to ensure that both
3 appropriate protection and important science proceeds. Indeed, this is the basis for the
4 DSM-IV. The measures to protect these individuals are designed for those who are
5 vulnerable *when they are vulnerable* to intended or unintended coercion and
6 exploitation; but we fully appreciate that these measures can only be successful when
7 they do not, as a consequence, discriminate against those persons who may have a
8 mental disorder, but who do not now, or who may never have decisional impairment of
9 the kind that would limit their ability to decide whether or not to participate in
10 research. The persons about whom this report is especially concerned are those who
11 may be considered for research protocols because it is their particular mental disorder
12 that is being studied.

13 To assume that a diagnosis of a mental disorder implies that its victim is
14 incapable of informed consent in deciding whether to participate in a research protocol
15 is prejudicial and incorrect. Such a diagnosis is simply one among many factors that
16 may trigger an assessment of decisionmaking capacity, an assessment that may in turn
17 conclude that a particular person with such a disorder either lacks or fully retains the
18 capacity to make an informed decision about participating in research.

19 Clearly, special difficulties arise in designing ethically acceptable research
20 protocols that involve human subjects with mental disorders whose decisionmaking
21 capacity and, therefore, their ability to give informed consent may be impaired. Such
22 medical conditions can complicate efforts to respect the rights of human subjects
23 involved in a research project, especially when the research design is such that the
24 subjects themselves will receive no direct benefits.³² Problems in determining the
25 presence or absence of appropriate decisionmaking capacity, however, are only one

³²For 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.

1 sort of difficulty in conducting ethically acceptable research involving persons with
2 mental disorders.

3 Many of the conditions underlying impaired decision making are the sort of
4 conditions that manifest themselves in behaviors that make prospective subjects hard
5 to understand and often cause discomfort in others. As a result, persons with these
6 diseases have often been stigmatized, and efforts to improve their medical treatment
7 frequently have been marginalized. Moreover, those who are hospitalized in
8 psychiatric units are especially vulnerable by virtue of the special dynamics of that
9 environment. As is the case for other potential research participants, confusion about
10 the goals of an intervention can easily be created when the physician caring for the
11 patient is also a researcher who may wish to enlist him or her into a research protocol.
12 Finally, because mechanisms for funding appropriate treatment of these diseases are
13 often seriously wanting, this population also may be especially vulnerable as its
14 members often do not have adequate access, for financial and other reasons, to health
15 care outside the research context.³³ Despite all this, many of the diseases from which
16 this population suffers badly require further study, since currently there are too few
17 satisfactory treatments.

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

³³The barriers to access to appropriate care can be financial or a variety of other factors (e.g. lack of knowledge, denial, lack of qualified providers, 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.

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

8 The combination of these and other factors creates a new imperative that calls
9 for special attention from the professions and those institutions that engage in research
10 involving persons who may have decisionmaking impairments. For a variety of reasons
11 that will be described in this report, previous efforts to establish specific protections
12 for persons with uncertain decisionmaking capacity have largely failed, although some
13 researchers and institutions have taken important and responsible initiatives in this
14 area. Recently the DHHS Office of Inspector General issued a report describing such
15 innovative practices,³⁴ but these addressed IRB review generally, not the review of
16 protocols involving vulnerable populations in particular. Overall, however, efforts
17 have been hampered either by longstanding inimical social attitudes toward persons
18 with uncertain decisionmaking capacity and a lack of consensus regarding how the
19 appropriate protections should be structured. Nevertheless, we have an important and
20 continuing obligation to address these issues more effectively for the sake of those
21 who are directly affected by them, so that we can ensure that important research can
22 be encouraged under appropriate conditions and that eventually treatment of these
23 important disorders can be improved.

24 Several tensions are inherent in the current discourse on these issues. On the
25 one hand, those who suffer from these disorders, and those who care about them,

³⁴Department of Health and Human Services, Office of the Inspector General, “Institutional Review Boards: Promising Approaches” (Washington, DC: DHHS, 1998).

1 desperately want medical science to find ways to improve their conditions. On the
2 other hand, there is disagreement about how this can be done without exploiting those
3 with mental disorders who participate in research protocols, thus causing them still
4 greater suffering.³⁵ As we elaborate in this chapter, several factors combine to make
5 some persons with mental disorders especially vulnerable: they may have impaired
6 capacity to consent due to the condition being studied; they are often dependent for
7 care upon researchers who may also be their physicians; many mental disorders
8 remain resistant to available therapies; and persons with mental disorders tend,
9 principally as a result of the disorder itself, to be more economically disadvantaged
10 than other adults. We believe, however, that despite these tensions and special factors,
11 much can be done to ameliorate the apparent conflict between the impetus to continue
12 promising lines of research and the ethical imperative to support the dignity and well-
13 being of research subjects.

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

23 Another complicating factor in efforts to protect human research subjects is the
24 unclear boundary between research and what is often called “innovative treatment.”
25 The latter category is intended to suggest that medical intervention is not undertaken

³⁵Shamoo, A.E. (ed.), *Ethics in Neurobiological Research with Human Subjects* (Amsterdam: Gordon and Breach Publishers, 1997).

1 as part of a scientific study but is rather an attempt to treat an individual patient who
2 has not responded to standard therapy. For example, a patient whose physician
3 recommends an “off-label”³⁶ trial of a medication approved for other use is not, with
4 respect to federal regulation, a research subject unless the physician is engaged in the
5 systematic collection of data about this use of the drug. In this kind of clinical
6 situation, certain existing regulatory requirements for ethically sound research, such as
7 prior review of the procedure by an Institutional Review Board, do not apply.
8 Nevertheless, the usual requirement that the treating physician obtain informed
9 consent for any intended treatment does apply, and the patient, or the patient’s legally
10 authorized representative, should be informed about, and consent to, the innovative
11 nature of the procedure that is to be attempted.

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

21

22 Values that Should Guide Research

23 Protecting human subjects from harm in research is not incompatible with
24 pursuing important research goals; one does not have to be compromised to
25 accommodate the other. More than three decades of continual improvement in the

³⁶Physicians 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.

1 design of research protocols have evolved from the underlying philosophy that
2 regulatory frameworks are established to ensure that human subjects in biomedical and
3 behavioral research protocols are treated with respect. Over time, researchers have
4 refined their understanding of what it means to respect human subjects involved in
5 research protocols, and this report is partly an effort to share that knowledge with the
6 public.

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

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

19 Even with the best research designs, however, research protocols can rarely
20 eliminate all risks. The American people need to understand that despite these
21 measures, as long as research is conducted involving human beings, there is a
22 possibility that subjects will be harmed or wronged despite best efforts to protect
23 them. Thus, in addition to any individual motivations, anyone who serves as a subject
24 in a research protocol is engaged in a form of public service that may involve risk and
25 for which there may be no direct or tangible personal reward. The unavoidable element
26 of risk has mandated protections for all research subjects, and clearly such protections
27 must never be less stringent for research subjects whose ability to be fully informed

1 and to freely consent is lacking or in doubt than it is for others. This proposition is
2 already well recognized in the case of pediatric research.³⁷

3 Of course, all persons suffering from an illness are at risk for impaired decision
4 making due to physiologic and psychologic stress. Health care professionals (including
5 researchers) must improve their understanding of these factors in illness, and health
6 care institutions must improve their methods of dealing with them so that all patients'
7 decisionmaking abilities can be respected and promoted. Indeed, simply having an
8 illness can impair one's decision making. Studies indicate, for example, that those who
9 are ill are generally less able to view their situation and alternatives as objectively as
10 those who are well.³⁸ But this is a different issue from that presented by those whose
11 diseases or treatments have a direct and primary effect on the impairment of abilities
12 which are critical for making decisions, such as memory, analytical capacities, and
13 emotional equilibrium.

14 Finally, because freedom from all risk cannot be guaranteed, and because those
15 who have specific impairments in their decisionmaking ability do not have the same
16 opportunity to determine the extent of their research involvement as do others, care
17 must be taken not to succumb to any temptations to target members of this population
18 for research when their participation is unnecessary. In particular, this population
19 should never shoulder all the risks and burdens of a scientific project when the
20 benefits are expected to flow to other segments of the population overwhelmingly. We
21 continue to take seriously the relevance of the principle of distributive justice
22 described by the National Commission for the Protection of Human Subjects of
23 Biomedical and Behavioral Research in the *Belmont Report*:

24 Justice is relevant to the selection of subjects of research at two levels:
25 the social and the individual. Individual justice in the selection of

³⁷45 C.F.R. 46, Subpart D, 1991.

³⁸Eric Cassell, unpublished data, May 1998.

1 subjects would require that researchers exhibit fairness: thus they should
2 not offer potentially beneficial research only to some patients who are in
3 their favor or select only “undesirable” persons for risky research. Social
4 justice requires that distinction be drawn between classes of subjects that
5 ought, and ought not, to participate in any particular kind of research,
6 based on the ability of members of that class to bear the burdens and on
7 the appropriateness of placing further burdens on already burdened
8 persons.”³⁹

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

12 In this report, our views about respect for persons, beneficence, and justice are
13 squarely in the tradition established by the National Commission, and are no less valid
14 today than they were nearly 20 years ago. Yet research has changed, including the way
15 in which it is conducted, its funding sources, and, in many instances, its complexity.
16 And despite the National Commission’s important work, those with mental disorders
17 are not yet specifically recognized by any set of guidelines in current federal
18 regulations. It is, therefore, time to elaborate on the foundation laid by the National
19 Commission, other thoughtful observers, and the current regulations treating research
20 involving persons with mental disorders.

21 22 The Nature of Mental Disorders That May Affect Decisionmaking Capacity

23 While there are a variety of mental disorders that can affect decisionmaking
24 capacity, persons with mental disorders are not necessarily decisionally impaired,
25 much less decisionally incapable. Rather, any evidence that places a person’s

³⁹National Commission, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research*. p, 7

1 decisionmaking ability into question should trigger a clinical assessment to determine
2 whether or not his or her decisionmaking capacity from one perspective or another is
3 impaired. Any disorder that alters mentation may adversely affect decisionmaking
4 ability. When such a disorder is present in an early or mild phase, the resulting
5 impairment may not affect a research subject's consent to participate, although extra
6 care in the informed consent process may be required. More advanced or severe forms
7 of a disorder, however, may render the subject incapable of a thoughtful (protective of
8 one's interests) and independent choice. Thus, identifying of a potential subject's
9 disorder that may impair mentation does not obviate the need for an individualized
10 assessment of that person's actual decisionmaking ability.

11 A relatively small body of research has documented the effects of various
12 disorders on decisionmaking capacity per se, but this is supplemented in many cases
13 by data on cognitive functioning in general and by a good deal of clinical experience
14 with these populations. The following are just some of the disorders in which
15 decisionmaking capacity may be affected, although this list is by no means exhaustive.

16

17 *Dementia*

18 Dementias are characterized by multiple cognitive deficits, most prominently
19 impairment of memory. The best known of these conditions is dementia of the
20 Alzheimer's type, a progressive disorder whose cause is presently unknown, the
21 incidence of which increases with age—from 2 to 4% in the population over 65 years
22 old to 20% or more in persons over 85 years old.⁴⁰ Dementias may also be caused by
23 vascular infarcts of the brain, head trauma, HIV infection, and neurological
24 conditions—such as Parkinson's disease and Huntington's disease.

⁴⁰American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorder (4th ed.) [DSM-IV] (Washington DC: APA, 1994).

1 The study of decisionmaking impairment in persons with dementia has focused
2 on Alzheimer’s disease. Even patients with mild Alzheimer’s disease may evidence
3 enough deficits in understanding relevant information and reasoning to call their
4 capacities into question, although the choices they make about treatment and research
5 may not differ at this point from those of nonimpaired populations. As dementia
6 progresses from the mild to the moderate stage, however, the range and magnitude of
7 deficits expand, and persons may fail even the simplest tests of decisionmaking
8 capacity.⁴¹ The co-occurrence of other disorders, such as delirium or depression, may
9 exacerbate the impact of dementia on the ability to make decisions.

10

11 *Delirium*

12 Like dementia, delirium involves alterations in cognition, but usually evolves
13 over hours or days. Disturbances of consciousness and attention are prominent.
14 Delirium is often caused by systemic medical conditions, side effects of medications,
15 intoxication with or withdrawal from psychoactive agents or toxins.⁴² Studies
16 demonstrating high rates of decisional impairment in severely ill, hospitalized patients
17 are probably detecting the effects of delirium secondary to the underlying conditions
18 and, in some cases, to the treatments being administered.⁴³ In contrast, other work
19 suggests that serious medical illness does not directly impair brain function, even when
20 it results in hospitalization, and is not likely, by itself, to result in limitations on
21 decisionmaking abilities.⁴⁴

⁴¹Marson D.C., Ingram K.K., Cody H.A., Harrell L.E., “Assessing the competency of patients with Alzheimer’s disease under different legal standards.” *Archives of Neurology* 52:949-954 (1995). Stanley B., Guido J., Stanley M., Shortell D., “The elderly patient and informed consent.” *Journal of the American Medical Association* 252:1302-1306 (1984).

⁴²American Psychiatric Association, DSM-IV, *op. cit.*

⁴³Cohen L.M., McCue J.D., Green G.M., “Do clinical and formal assessment of the capacity of patients in the intensive care unit to make decisions agree?” *Archives of Internal Medicine* 153:2481-2485 (1993).

⁴⁴Appelbaum P.S., Grisso T., “Capacities of hospitalized, medically ill patients to consent to treatment.” *Psychosomatics* 38:119-125, (1997).

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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.⁴⁵ 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.⁴⁶ 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.⁴⁷ Lack of insight into the presence of illness and need for treatment is common among persons with schizophrenia.⁴⁸ This may make it especially difficult for them to anticipate the consequences of their decisions on participation in research as they relate to the risk of future relapse.

Depression

Symptoms of major depression include depressed mood; feelings of worthlessness; diminished interest and pleasure in most activities; changes in appetite,

⁴⁵American Psychiatric Association, DSM-IV, *op. cit.*
⁴⁶Grisso T., Appelbaum P.S. “The MacArthur Treatment Competence Study, III: Abilities of patients to consent to psychiatric and medical treatments.” *Law and Human Behavior* 19:149-174 (1995).
⁴⁷Rosenfeld B., Turkheimer E., Gardner W. “Decision making in a schizophrenic population.” *Law and Human Behavior* 16:651-662 (1992).
⁴⁸Amador X.F., Strauss D.H., Yale S.A., Gorman J.M. “Awareness of illness in schizophrenia.” *Schizophrenia Bulletin* 17:113-132 (1991).

1 sleep patterns, and energy levels; and difficulties in concentration.⁴⁹ Cognitive
2 impairments may exist in information processing⁵⁰ and reasoning,⁵¹ among other
3 functions. Less clear is the extent to which these consequences of depression impede
4 decision making. It has been suggested that decreased motivation to protect their
5 interests may reduce depressed patients' abilities to make decisions⁵² or to alter the
6 nature of those decisions.⁵³ One study suggested that hospitalized depressed patients
7 may manifest decisionmaking problems roughly half as often as patients with
8 schizophrenia—that is, in about one-quarter of cases.⁵⁴ But it is likely that the degree
9 of impairment relates to the intensity of depressive symptoms, and thus will vary
10 across populations.

11

12 *Some Other Disorders*

13 Although less subject to formal study in the context of consent to treatment or
14 research, there is good reason to believe that the capacity of persons with mental
15 disorders to participate in research may, at some time, be impaired. *Mental*
16 *retardation*, affecting as it does a range of cognitive abilities, is more likely to impair
17 capacities as severity increases. *Bipolar disorder* results in alternating states of
18 depression and mania, the latter comprising elevated mood, increased impulsivity, and
19 reduced attention, among other features; manic patients are known to make poor
20 decisions about money and personal affairs, and it is probable that this deficit extends
21 into research decision making for some subset of this group. *Other psychotic disorders*

⁴⁹American Psychiatric Association, DSM-IV, op. cit.

⁵⁰Hartlarge S., Alloy L.B., Vazquez C., Dykman B. "Automatic and effortful processing in depression." *Psychological Bulletin* 113:247-278 (1993).

⁵¹Baker J.E., Channon S. "Reasoning in depression: impairment on a concept discrimination learning task." *Cognition and Emotion* 9:579-597 (1995).

⁵²Elliott C. "Caring about risks: are severely depressed patients competent to consent to research?" *Archives of General Psychiatry* 54:113-116, (1997).

⁵³Lee M.A., Ganzini L. "Depression in the elderly: effect on patient attitudes toward life-sustaining therapy." *Journal of the American Geriatric Society* 40:983-988, (1992).

⁵⁴Grisso and Appelbaum, op. cit.

1 involve some of the symptoms seen in schizophrenia, including delusions and
2 hallucinations, and may have some of the same consequences for decision making.
3 *Substance abuse disorders*, for example, including use of alcohol and illegal drugs,
4 result in states of intoxication and withdrawal that resemble delirium in their effects on
5 attention, cognition, other mental functions, and, consequently, decision making.
6 There also can be some decisional impairments associated with drug abuse and
7 addiction outside the circumstances of intoxication and certain forms of withdrawal.
8 However, it is important to emphasize that the diagnosis of substance abuse disorders
9 does not imply that decisionmaking capacity is impaired.

10

11 Informed Consent and Decisional Impairments

12 The ability or capacity to consent in a fully informed manner to being a research
13 subject is critical to an individual’s participation as a human subject in an ethical
14 research protocol. In one well-respected analysis of informed consent by Faden and
15 Beauchamp, competence to consent performs a gatekeeping function in which
16 “competence judgments function to distinguish persons from whom consent *should* be
17 solicited from those from whom consent need not or should not be solicited.”⁵⁵ Every
18 effort must be made, therefore, to engage the prospective subject in the informed
19 consent process as much as his or her ability to participate in that process permits.
20 Thus the individual who is able to understand the purpose, risks, and possible benefits
21 of the study must have all the relevant information one would need to make an
22 informed decision about being a subject. There is also an affirmative obligation to help
23 those with less ability to be fully informed about the research to understand the
24 relevant information before they may be enrolled. The National Commission described
25 this obligation as part of the principle of respect for persons. “Respect for persons

⁵⁵Faden RR and Beauchamp TL. *A History and Theory of Informed Consent*. New York: Oxford, 1986, p. 288.

1 incorporates at least two ethical convictions; first, that individuals should be treated as
2 autonomous agents, and second, that persons with diminished autonomy are entitled to
3 protection.⁵⁶ It is generally agreed, however, that those who lack the ability to decide
4 in an informed manner about participating in a research protocol may only be included
5 under certain conditions. Among these conditions are an inability to conduct the
6 research with subjects whose capacity to make decisions is not impaired, and a
7 reasonable level of risk in light of potential benefits and protections involved.

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

14 There are at least four types of limitations in decisionmaking ability that need to
15 be taken into account in planning and conducting research with this population. First,
16 persons with fluctuating capacity have what is often called waxing and waning ability
17 to make decisions, as in schizophrenia, manic-depressive disorders, and some
18 dementias. Second, persons whose decisionmaking deficits can be predicted due to the
19 course of their disease or the nature of a treatment, but who are still capable, have
20 prospective incapacity; those who suffer from early stages of Alzheimer's disease fall
21 into this category. Third, most persons with limited capacity are in some way able to
22 object or assent, as in the case of more advanced Alzheimer's. Fourth, persons who
23 have lost the ability to make nearly any decision that involves any significant degree of
24 reflection are decisionally incapable, as in the later stages of Alzheimer's and
25 profound dementia.

⁵⁶National Commission, *The Belmont Report*, p. 4.

1 These four sorts of decisional limitations— fluctuating, prospective, limited,
2 and complete—provide an initial framework both for the different ways the problem of
3 decisionmaking capacity can manifest itself and for the design of appropriate
4 protections.⁵⁷ Among those whose capacity fluctuates or is limited, one cannot easily
5 pinpoint the precise nature of a decisional disability from these groupings. Some
6 disorders entail limitations on decisionmaking ability that are subtle and hard to
7 identify, and even individuals who fit within a particular diagnostic category may
8 exhibit their decisionmaking limitations in different ways.

9 The situation is further complicated by the fact that two or more of these four
10 categories often apply to the same individual in the course of a disease. Thus someone
11 in the early stages of Alzheimer’s disease may have prospective incapacity, then
12 experience very subtle decisionmaking limitations or have fluctuating capacity, and
13 progress to incapacity. It is therefore critical that researchers who work with persons in
14 this population be familiar with the ways that decisionmaking impairments manifest
15 themselves, and that appropriate mechanisms be designed to maximize the subject’s
16 ability either to participate in the decision to enter or continue a study, or to choose not
17 to enroll. In Chapter Six of this report, our recommendations suggest certain
18 mechanisms.

19 In addition, there are circumstantial factors that affect decisionmaking capacity.
20 All of us feel more empowered and in control in some social situations than we do in
21 others. Similarly, some persons with mental disorders may be more or less capable of
22 making their own decisions depending on circumstances. For example, some
23 individuals may feel more empowered in dealing with certain health care professionals
24 or family members, and less so in dealing with others; or they may be more effective
25 in expressing their wishes at home than in an institution, or the reverse. Such insights

⁵⁷These categories do not apply to children, whose decisional limitations are developmentally appropriate and which are not a result or symptom of an illness.

1 can be critical in helping the individual achieve as high a degree of self-determination
2 as possible.

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

12

13 Other Additional Ethical Issues in Research with Persons with Mental Disorders

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

17

18 *Limitations on Drug Development*

19 Currently, illnesses associated with decisional impairments often involve testing
20 at a more primitive stage of drug development than is usually the case in
21 pharmaceutical research, because animal models often cannot yield appropriate data
22 for diseases with psychological or cognitive symptoms as for other diseases.

23

24 *Subjective Experience of Disorders*

25 While all individuals experience their illnesses personally and subjectively, the
26 subjective experience of some persons with mental disorders will pose additional
27 challenges. In some instances, the perception that they are at greater risk of harm than

1 is actually present may be a result of confusion or other manifestations of their
2 disorder. This subjective perception is no less real, and therefore no less important to
3 take account of, than the subjective perception of pain from a physical injury, but it
4 may require researchers to factor more individualized judgments into their projections
5 of risk and benefit than may be the case for researchers in other fields.

6

7 *Problems in Mental Health Care*

8 Mental health care has a checkered history characterized by periods of patient
9 neglect, abuse, superstition, and stigmatization. Sadly, some of these historic trends
10 can be found even in our own time and among relatively prosperous societies. The
11 outward symptoms of some mental disorders, and the fact that many stricken
12 individuals are difficult to treat, still make people uncomfortable. In addition, some
13 primary health care professionals are relatively unfamiliar with the signs of these
14 illnesses or the best treatment that is available for them. Some individuals in these
15 groups are hard to work with in the research setting. For these reasons and others, both
16 clinical care and research in these diseases often have taken a back seat to disorders
17 perceived as more “medical” in nature.

18

19 *Access to Care*

20 Another factor that affects research and therapy on illnesses associated with
21 decisional impairments is that financial resources for treating many of these conditions
22 continue to suffer compared to other diseases. Both public and private insurance
23 policies often fail to provide adequate support for the kinds of intervention that may be
24 required. This problem is further aggravated by the disadvantaged economic situation
25 of many persons with mental disorders, since many may have trouble completing
26 education and training programs or in securing or retaining employment due to their
27 symptoms. As a result, they are often not well connected to social support networks,

1 especially if the onset of the disorder occurs early in life. For all these reasons, there is
2 a significant association between mental illness and poverty. According to a study
3 published in 1992, 21 percent of adults with serious mental illness fall below the
4 poverty threshold, as compared with 9 percent of the general adult population.⁵⁸ As
5 many as half of homeless Americans are said to be suffering from schizophrenia.⁵⁹
6 Moreover, the widespread lack of understanding regarding the nature and implications
7 of these disorders itself serves independently of financial issues as a barrier to
8 appropriate care. In any case, without adequate access to mental health services and
9 other social supports and lacking in financial resources, these people and their families
10 may feel that their participation in a research protocol presents a rare opportunity for
11 treatment. Their hope can thus easily overwhelm their understanding of the various
12 risks and the sometimes remote likelihood of direct benefit, even among those who are
13 not decisionally impaired. Researchers and investigators must scrupulously avoid
14 taking advantage of people who might expect therapeutic effects from their research
15 participation.

16

17 *Formal and Informal Caregiving*

18 We have already observed that while those who struggle with diseases that
19 impair their decisionmaking abilities are much like the rest of us when we are ill and
20 vulnerable, in other respects they may be more vulnerable. For example, having
21 enrolled in a study with a reasonable understanding of the possibility of benefit, those
22 struggling with psychiatric disease can more easily feel dependent on the research
23 institution and study personnel, thus developing a fear of being released from the study
24 and losing all of their professional support. As is so often the case, “voluntariness” is

⁵⁸Barker, P.R., et al., “Serious Mental Illness and Disability in the Adult Household Population: United States, 1989,” U.S. Department of Health and Human Services (Ronald W. Manderscheid and Mary Anne Sonnenschein, eds.), *Mental Health, United States, 1992* (Washington, D.C.: U.S. Government Printing Office, 1992).

⁵⁹Wyden, P., *Conquering Schizophrenia* (New York: Alfred A. Knopf, 1998).

1 easier to require in regulations and guidelines, but much harder to guarantee in real life
2 situations.

3 In the blizzard of legal considerations and moral subtleties that swirl around the
4 involvement of decisionally impaired persons in research, it is easy to lose sight of the
5 role of informal caregivers like family and friends. NBAC was moved by the testimony
6 of those who, though often bearing witness to other matters, also sent a powerful
7 message of commitment over many years to loved ones struggling with the
8 consequences of debilitating diseases. Two issues are of particular relevance: the
9 problem of providing care, given other limited resources; and the more implicit
10 problem of the sharing of information about patients-subjects.

11 As we noted above, our health care system has familiar inadequacies regarding
12 access to health care, especially in continuity of care, the appropriate treatment of
13 those with chronic disease, long-term care, and rehabilitation. It must also be noted, of
14 course, that the complex relationships that exist within families in which one member
15 is identified as having a mental disorder are not always harmonious. As one public
16 comment noted: “The innately complex nature of this field is illustrated by the fact
17 that there may be varying alliances depending upon the individual situation of either
18 patient with family, patient with professional, patient with scientist, or any other
19 configuration of these groups.”⁶⁰ Even families of patients may function as allies or
20 adversaries. One particular example of this problem is the way in which information is
21 shared with family members. Families commonly complain that certain mental health
22 professionals fail to include them as members of the team caring for the patient. In the
23 words of Commissioner Patricia Backlar, “currently mental health providers rarely

⁶⁰Herbert Pardes, Columbia University, July 31, 1998

1 share relevant information with the informal caregiver, nor do they ask families for
2 information germane to treatment or legal decisions.”⁶¹

3 To be sure, communication with informal caregivers raises important issues of
4 individual autonomy and patient confidentiality, but bioethical theory has rarely been
5 sensitive to the underlying interpersonal support mechanisms of family and close
6 friends that are often so important to those with long-term illness. On the contrary,
7 much theorizing has worked against recognizing and involving others in the process of
8 establishing an ethical research process. The critical role of self-determination in
9 human subjects research should by no means be undermined or minimized. But within
10 the autonomy-based framework of our society’s regulatory philosophy, there should
11 also be a place for the actual roles of those with important ongoing caregiving
12 responsibilities to the potential subject.⁶² Where they exist, these important social
13 support networks must be integrated in a more satisfactory fashion into the regulatory
14 framework of research with those who are decisionally impaired far more actively and
15 sensitively than has been done before. NBAC appreciates this issue, and discusses
16 more fully in Chapter Four its recommendations for recognizing the important role of
17 families and others in decision making about research participation.

18

19 *The Possibility of Direct Benefit*

20 Many research studies do not offer any reasonably expected and/or direct
21 prospect of direct benefit to the human subjects involved. Such studies may be
22 necessary because not enough is known about the way a drug or device will function in
23 human beings, or because the research is not designed to study direct therapeutic
24 benefit to the subjects but rather to study the subjects’ reactions (e.g., modeling the

⁶¹Backlar, P., “Ethics in Community Mental Health Care: Confidentiality and Common Sense,” *Community Mental Health Journal* 32(6):517 (1996).

⁶²Howell J.H. and Sale W.F. (eds.), *Life Choices: A Hastings Center Introduction to Bioethics* (Washington DC: Georgetown University Press, 1995).

1 dynamics of the disease) to particular stimuli or how the drug or device will affect a
2 human host. In these cases, the hope is that the knowledge gained will eventually lead
3 to better treatments. While an individual may benefit from being closely assessed or
4 monitored by the study team, that benefit is not produced by the medication or
5 mechanism being studied.

6 Many studies do include drugs or procedures that have the prospect of potential
7 benefit to subjects. However, it is not possible for researchers to know whether an
8 intervention would be better for the subject than doing nothing (which often occurs in
9 a placebo control study), or whether the subject would benefit most from the currently
10 available standard treatment. Indeed, if researchers were certain of the outcome, there
11 would be no justification for doing the research in the first place. Nevertheless, even
12 when there is justifiable uncertainty about which treatment produces better results
13 (when the relevant medical and scientific community is said to be in clinical
14 “ equipoise ”⁶³), the investigator should have some reason to believe that the study
15 might benefit some subjects, as indicated by animal experiments or developing
16 scientific knowledge or both, if it is to be presented as having potential therapeutic
17 benefit. The nature of clinical research, however, is that investigators cannot predict
18 with absolute certainty that a particular study will benefit a particular person, or even
19 predict that it will benefit any subject.

20 Interest in access to potentially beneficial experimental treatment is not, of
21 course, limited to persons with conditions that may be directly related to
22 decisionmaking impairments. Anyone who suffers from a disease for which there is no
23 adequate recognized treatment may wish to participate in a clinical trial. There is
24 always the danger, therefore, that the desire for a treatment may overwhelm the ability
25 to assess the likelihood of benefit or to balance the risks and potential benefits from

⁶³Freedman, B. “Equipoise and the Ethics of Clinical Research.” *New England Journal of Medicine* 141:317 (1987).

1 the drug or device being studied. The situation is further complicated when the
2 primary caregiver is also the researcher. This “therapeutic misconception”⁶⁴ may be
3 especially intense for those whose decision making is impaired. Because many clinical
4 trials are not primarily therapeutic opportunities, patient-subjects who are not fully
5 informed about the differences between research and therapy may feel betrayed or
6 abandoned when their study participation comes to an end.

7

8 The Promise of Research on Mental Disorders

9 Mental disorders that may render persons decisionally impaired account for an
10 enormous amount of illness and human and economic costs. Of the 10 leading causes
11 of disability in the world, according to a recent World Health Organization report, 5
12 were psychiatric conditions: unipolar depression, alcohol use, bipolar affective
13 disorder, schizophrenia, and obsessive-compulsive disorder.⁶⁵ It has been estimated
14 that direct and indirect costs of mental illness and substance abuse in the United States
15 totaled more than \$313 billion dollars in 1990.⁶⁶ Alzheimer’s disease now afflicts
16 approximately 4 million people in this country and, with the number of persons over
17 65 years of age expected to double by the year 2030, the resulting morbidity can be
18 expected to grow proportionately.

19 Given the scope of these disorders, when treatments can be identified that could
20 mitigate their impact the human, social, and economic benefits are enormous. For
21 example, since 1970, the cumulative savings to the U.S. economy from the
22 introduction of lithium as a treatment for bipolar disorder is estimated at \$145 billion.
23 Furthermore, no dollar figure can be put on the benefits to patients and families spared

⁶⁴Appelbaum, P., et al., “False hopes and best data: consent to research and the therapeutic misconception.”
Hastings Center Report 17(2):20-4 (April 1987).

⁶⁵World Health Organization, The Global Burden of Disease (Cambridge, MA: Harvard University Press, 1997).

⁶⁶National Institutes of Health. Disease-specific estimates of direct and indirect costs of illness and NIH support.
Report to Congress, 1997 Update. April 1997.

1 the anguish of manic and depressive episodes, which often tear apart the fabric of
2 family life and social relationships. Similarly, the introduction of clozapine for
3 treatment of schizophrenia has been estimated to have yielded savings of \$1.4 billion
4 per year since 1990.⁶⁷ Thus, every incentive exists to improve our understanding of
5 disorders affecting brain function and to develop more effective treatments for them.

6 Most research on these conditions falls into two broad categories: studies aimed
7 at elucidating the underlying pathophysiologic bases of the disorders, and studies
8 intended to develop or test new treatments for them. Among the most powerful
9 approaches to examining basic aspects of brain function and dysfunction are new
10 techniques that allow imaging of the working brain. Positron emission tomography
11 (PET), functional magnetic resonance imaging (MRI), single photon emission
12 computer tomography (SPECT), and related devices facilitate identification of the
13 anatomic location of brain areas involved in cognitive and affective functions.⁶⁸
14 Comparisons of normal and afflicted populations permit localization of regions
15 affected by the disease process. These techniques also allow monitoring of the effects
16 of treatment regimens at the level of the brain.⁶⁹

17 Currently, medications are the primary focus of treatment-oriented research.
18 Development of new medications is being facilitated, for example, by studies of brain
19 neurotransmitter receptors, which allow new molecules to be created that have the
20 desired therapeutic effects with minimal side effects. More innovative approaches that
21 are still in very early and speculative development include insertion of new genes to
22 correct identified defects underlying brain disorders (gene therapy), and use of

⁶⁷Testimony of Steven Hyman, Director, National Institute of Mental Health, U.S. Senate Appropriations Subcommittee Hearings, 1997. Meltzer H.Y., Cola P., Way L., Thompson P.A., et al, "Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia." *American Journal of Psychiatry* 150:1630-1638 (1993).

⁶⁸Andreasen N.C., O'Leary D.S., Arndt S. "Neuroimaging and clinical neuroscience: basic issues and principles." Oldham J.M., Riba M.B., Tasman A. (eds.), *American Psychiatric Press Review of Psychiatry*, Vol. 12 (Washington, DC: American Psychiatric Press, 1993).

⁶⁹Baxter L.R., Schwartz J.M., Bergman K.S., et al., "Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder." *Archives of General Psychiatry* 49:681-689 (1992).

1 immunologic therapies, like the recent successful inoculation of rats against the
2 psychostimulant effects of cocaine.⁷⁰

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

15

16 The Ethics of Study Design

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

⁷⁰Carrera MR, Ashley J, Parsons LH, Wirshing P, Koob GR, Janda KD. Suppression of psychoactive effects of cocaine by active immunization. *Nature* 378:727-730, 1995.

1 Clearly, those who conduct research with human beings have a responsibility to
2 design studies which are both scientifically and ethically sound. Nonetheless, in some
3 contexts, scientific and ethical considerations are not always seen as *jointly* necessary
4 features of high-quality research design. For example, textbooks on research methods
5 and clinical trials rarely integrate ethical guidance with scientific guidance.⁷¹ At the
6 same time, many granting and regulatory groups recognize that ethical research must
7 meet the requirements of scientific validity and importance and that scientific
8 investigations using human subjects must be conducted according to ethical principles.
9 The shorthand expression “good science is a prerequisite for good ethics” is a helpful
10 reminder,⁷² but may not capture all of the nuances of what is morally required for
11 designing of high-quality research involving human subjects. Freedman helpfully
12 captured the essence of this problem when he argued that scientific validity and
13 scientific value are among the important requirements for ethical research.⁷³ While all
14 research should be expected to meet these requirements, studies that involve
15 vulnerable persons would seem to require particular attention to these requirements.
16 Deciding which design will best answer the research question, what procedures will be
17 used, which subjects will be studied, are all questions that require both scientific and
18 ethical justifications. Philosophers of science have long pointed out that even the
19 selection of one hypothesis over another has moral implications, insofar as there are
20 opportunity costs associated with this choice. Further, the decision to pursue some
21 hypotheses, and the experimental design that accompanies that decision, can have
22 direct moral consequences.

⁷¹Sutherland H.J., Meslin E.M., Till J.E., “What's missing from current clinical trials guidelines? A framework for integrating ethics, science and community context.” *Journal of Clinical Ethics* 5(4): 297-303 (Winter 1994).

⁷²Rutstein, D., *Human experimentation, A Guided Step into the Unknown*, W.A. Silverman (ed.) (Oxford: Oxford University Press, 1986).

⁷³Freedman B., “Scientific value and validity as ethical requirements for research: a proposed explication.” *IRB: A Review of Human Subjects Research* 9:7-10 (1987).

1 As has been the case for research with other populations, one of the
2 controversial aspects of research involving persons with mental disorders concerns the
3 ethical acceptability of the basic designs of some studies. There are, for example,
4 significant concerns in some quarters regarding study designs that use drugs to
5 stimulate behavioral or physiological manifestations of the disease under study. The
6 term “challenge study” refers to a general category of psychologic and pharmacologic
7 provocations.⁷⁴ Miller and Rosenstein list among these provocations injection of
8 intravenous amphetamine, inhalation of carbon dioxide, and presentation of a phobic
9 stimulus. The principal scientific rationale for conducting psychiatric symptom-
10 provoking studies is “to learn more about the underlying pathophysiological
11 mechanisms responsible for the symptomatic expression of psychiatric illnesses.”⁷⁵ In
12 these “challenge” or “symptom-provocation” studies, the goal is to generate these
13 disease manifestations in a controlled setting so that they can be more fully understood
14 and so that future appropriate interventions can be designed, attempted, and evaluated.

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

23 Another study design that has generated a good deal of concern and debate
24 entails a period without the medication that a patient has been prescribed for
25 therapeutic purposes, a so-called “drug holiday.” Sometimes also called “washout”

⁷⁴Miller and Rosenstein, 1997, p. 403

⁷⁵Miller and Rosenstein, 1997, p. 404

1 studies, this design often seeks to return the individual to a medication-free “baseline”
2 state so that behavior can be assessed or new drugs introduced without the
3 confounding factor of other substances already in the person’s system. In other
4 protocols of this type a beneficial drug may be withdrawn for purposes of determining,
5 for example, the appropriate length of the drug therapy. Of particular concern are
6 washout studies in which treatment is suddenly or very rapidly withdrawn. Given that
7 existing regulations require that subjects be informed of the consequences of their
8 decision to withdraw from the study, and what the procedures are for the orderly
9 termination of a study,⁷⁶ it is appropriate to draw attention to this issue. Often the
10 washout and challenge approaches are combined in a single study.

11 Finally, no study design has led to more discussion than the use of placebo
12 controls.⁷⁷ Usually conducted in a “blinded” fashion so that neither the subject nor the
13 investigator knows which agent is active and which is placebo, ethical placebo studies
14 require that subjects understand that they will not necessarily receive the experimental
15 intervention. As in the other study designs mentioned, there will be special ethical
16 concerns for persons whose decisionmaking capacity is fluctuating or absent at the
17 time of study enrollment since the idea of a nontreatment arm of a study may not be a
18 familiar one. Moreover, as noted above, the tendency to construe all “medical”
19 interventions as therapeutic may especially affect persons whose cognitive processes
20 are impaired and who are particularly dependent upon physicians and medical
21 institutions.

22 Given that ethical guidelines and regulations are designed for use by IRBs, it is
23 not surprising that, when reviewed in detail, their focus tends to be on the requirement

⁷⁶45 CFR 46.116(b)(4).

⁷⁷Addington D. “The use of placebos in clinical trials for acute schizophrenia.” *Canadian Journal of Psychiatry* 40:171-176 (1995). Rothman, K.J., Michels K.B. “The continued unethical use of placebo controls.” *New England Journal of Medicine* 331:394-398 (1994).

1 that there be scientific merit in the proposals.⁷⁸ As noted previously, however, both
2 scientific and ethical merit are jointly necessary for conducting human subject
3 research. “Washout” studies, “challenge” studies, and placebo-controlled studies done
4 with subjects who are the focus of this report require special attention to appropriate
5 ethical constraints, both from IRB members and from researchers who work with
6 persons with mental disorders.

7 The Responsibilities of Clinical Investigators

8 The clinical investigator is the key player in our research system with respect to
9 the protection of human subjects. *Indeed, unless the individual clinical investigator*
10 *understands their ethical responsibilities, no regulatory system will function properly.*
11 Many of the central issues in this report—standards for decisionmaking capacity,
12 assessment of risks of harms and potential benefits, techniques for improving informed
13 consent, recognition of the involvement of family members and friends—turn on the
14 integrity, compassion, ability to conduct high-quality science, and professionalism of
15 the research physician. No matter how many regulations are put in place or guidelines
16 written, and regardless of the intensity of scrutiny by IRBs or other authorities, *there*
17 *can be no substitute for the ongoing commitment by researchers and institutions to*
18 *ethically appropriate behavior throughout the research process.* This is true not only
19 as the research project is planned and protocols are developed, but throughout the
20 trials themselves.

21 There is no right to conduct research with human subjects. It is a privilege
22 conferred on those individuals who are prepared to undergo rigorous scrutiny of their
23 proposed studies and ongoing research trials. Nevertheless, it is also commonplace
24 that medical scientists are under enormous pressure to find treatments for diseases that
25 cause much suffering. Under these conditions, the privilege of conducting human

⁷⁸Sutherland H.J., Meslin E.M., Till J.E., p. 297.

1 subjects research can slide too easily into the notion that there is a social obligation for
2 particular individuals to serve as research subjects. This thinking, when it occurs, is
3 not simply wrong and misguided, but inappropriate and dangerous.

4 Researchers should be in the habit of asking the following questions: “Does the
5 scientific importance of my work justify asking people to participate as subjects in my
6 research protocol? Should this patient be recruited into my study? Are the risks and
7 potential benefits of study participation acceptable for this patient? Does this patient
8 have the capacity to decide about participation in this study? Does this patient
9 understand the nature of the research? Is his or her agreement to participate wholly
10 informed and voluntary? Is he or she unusually liable to a therapeutic misconception?”
11 The ethically responsible scientist is expected to carry the dual burden to advance
12 knowledge that can improve the human condition and at the same time to recognize
13 the absolute imperative to treat human research subjects with the utmost care and
14 respect.

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

22 While there is some truth to these claims, prospective involvement in a study
23 should not be presented or perceived simply as a substitute for health care. Further,
24 using the research system as a supplement to a health care system that may not be
25 accessible to many cannot be the principal justification for enrolling human subjects in
26 research protocols. The context of research and health care must not be confused, if
27 for no other reason than that the primary goal of the former is to expand medical

1 knowledge and improve future treatment for particular disorders, and the primary goal
2 of the latter is to provide immediate medical assistance.

3 While many have accepted the wisdom of Henry Beecher's observation more
4 than three decades ago that the most important protection for human research subjects
5 is the personal moral character of the medical scientist,⁷⁹ it would be unfair to expect
6 individual clinicians to resolve the complex moral problems arising from human
7 research by requiring them to measure up to standards we have not adequately
8 articulated and then threatening them with moral blame if they are perceived to have
9 failed. It is not adequate to focus these ethical responsibilities only on the individual
10 investigator who in fact functions within a much broader research environment.

11 The responsibility for ensuring that the rights and welfare of human subjects are
12 protected, therefore, should also be borne by the investigator's research community,
13 department, or institution. These responsibilities include, but are not limited to,
14 educating investigators about the ethics of research and the protection of human
15 subjects, as well as appropriate monitoring of the behavior of investigators in relation
16 to their human subjects in the ongoing conduct of their research. IRBs, as they are
17 presently constituted, do not discharge all of their responsibilities simply by approving
18 an investigator's research protocol. As we will discuss more fully below, IRBs have
19 considerable authority to review and monitor research.

20

21 The Structure of This Report

22 Four analytical chapters follow this chapter. The next chapter offers an account
23 of the history of past efforts to regulate research involving persons with mental
24 disorders. It is followed by chapters on informed consent and decisionmaking
25 capacity; advance planning and surrogate decision making; and the assessment of risks

⁷⁹Beecher, HK. Ethics and clinical research. *New England Journal of Medicine*, 274 1354-60 (1966).

1 and potential benefits. The final chapter summarizes our recommendations for
2 research involving persons with mental disorders that may affect decisionmaking
3 capacity.

4 In making these recommendations, we are acutely aware of the already
5 considerable burdens placed upon dedicated clinical scientists and research centers.
6 Some of our recommendations will undoubtedly require a greater investment of
7 resources to enhance the protection of human research subjects. These new
8 investments will be required to support better IRBs at the local level, those federal
9 offices charged with ensuring compliance with federal regulations regarding human
10 subjects protections, and NIH and other research agencies. But if important research
11 that will benefit our society is to flourish as we hope it will, it may only do so in an
12 environment that adheres in the strictest possible manner to the values and rights that
13 are so central to our society. It is our view that in the long term such investments will
14 increase support for updated biomedical research.

15

1 Chapter Two: HISTORY OF REGULATORY EFFORTS

2 Debate about the propriety and necessity of research involving persons whose
3 decisionmaking capacity may be affected by a mental disorder is not new.^{80,81,82,83,84}
4 Historically, many of these discussions have been couched in the context of particular
5 conditions such as sexually transmitted diseases and schizophrenia. More recently,
6 research with subjects affected by Alzheimer's disease has emerged as a focus of
7 concern.⁸⁵ There is, however, an important history in which significant experiments
8 involving human subjects with mental disorders raised sufficient concern to have an
9 impact on contemporary approaches to the public oversight of research in this area.
10 Like other areas of medicine, psychiatry and neurology were not immune to cases of
11 unethical research, including research conducted by very distinguished scientists.⁸⁶
12 Unfortunately, not all instances of ethically questionable research practices involving
13 those who are decisionally impaired were intended to benefit the subjects, nor even
14 intended to yield knowledge of the sources of the impairment that affected the
15 particular subject population. Rather, they may have an entirely unrelated purpose,
16 such as determining the effects of an agent on the human body, or the body's effect on
17 the agent. In these cases, the decisionally impaired subject was included in research
18 because he or she was readily available, especially if the subject was institutionalized.

⁸⁰Annas G.J. and Grodin M.A. *The Nazi Doctors and the Nuremberg Code* (New York: Oxford University Press, 1992), pp. 127-128, see also Grodin M.A., "Historical Origins of the Nuremberg Code," George J. Annas and Michael A. Grodin, (eds), *The Nazi Doctors and the Nuremberg Code* (New York: Oxford University Press, 1992), pp. 129-31.

⁸¹Grob G., *The Mad Among Us* (Cambridge, MA.: Harvard University Press, 1994).

⁸²Rothman D.H., *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making* (New York: Basic Books, 1991).

⁸³Faden R.R. and Beauchamp T.L., *A History and Theory of Informed Consent* (New York: Oxford University Press, 1986).

⁸⁴Katz J., *Experimentation with Human Beings* (New York: Russell Sage Foundation, 1972).

⁸⁵Berg J, Karlinsky H, and Lowy F. (Eds.) *Alzheimer's Disease Research: Ethical and Legal Issues* (Toronto: Carswell, 1991).

⁸⁶Moreno, 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.

1 One illustration of this scenario⁸⁷ occurred during the 1950s, although it became
2 generally known only much later.

3 In 1952, Harold Blauer was 42 years old and employed as a tennis pro at
4 Manhattan's Hudson River Club. Apparently despondent over a divorce from his wife,
5 with whom he had two young daughters, Blauer checked himself into Bellevue
6 Hospital. He was diagnosed with clinical depression and transferred to the Psychiatric
7 Institute, a New York State facility staffed by Columbia University faculty.
8 Unbeknownst to Blauer, the researcher had a secret contract with the Army Chemical
9 Corps to conduct research on a mescaline derivative, methyl-di-amphetamine (MDA).
10 In mid-January 1953, Blauer was given several injections of various forms of
11 mescaline. Following one of the injections Blauer went into convulsions and died some
12 hours later. The Army and New York State arranged a cover-up of the actual
13 circumstances of Blauer's death and split an \$18,000 payment to his widow and two
14 young children. Over two decades later, after the true story finally came to light, a
15 court awarded Blauer's daughters \$750,000 as compensation from the Federal
16 Government.⁸⁸ This case and others make up part of the history that ultimately led to
17 the development of the federal regulations for the protection of human subjects. In
18 what follows below, we review some of the international and then U.S. efforts to
19 regulate the involvement of vulnerable persons in research.

20

21 History of International Regulatory Efforts

22 Most efforts to regulate the use of vulnerable human subjects have been
23 generated by understandable concerns about the use of children as human subjects in
24 research protocols and, to a lesser extent, about the use of pregnant women, fetuses,
25 and, later, prisoners. Nonetheless, prior to the 1970s there were also some attempts to

⁸⁷ For an extended discussion of this and other historical examples, see Moreno, op. cit.

⁸⁸ *Barrett v. U.S.*, 660 F. Supp. 1291 (S.D.N.Y. 1987).

1 develop guidelines for the involvement of the decisionally impaired in research
2 protocols.

3 *The Nuremberg Code*

4 One of these attempts arose from a 1930 incident in Weimar, Germany, when a
5 doctor named Julius Moses reported that 75 children had died in Lubeck as a result of
6 pediatricians' experimenting with a tuberculosis vaccine. The German press, already
7 highly critical of powerful chemical manufacturers using hospital patients to test their
8 new products, helped fuel the social opprobrium directed at the exploitation of
9 vulnerable persons.

10 It happened that Moses was also a member of the German Parliament from the
11 Social Democratic Party, and in 1931 he played a key role in pressuring the Interior
12 Ministry to respond to the Lubeck scandal. The regulations that ensued were far more
13 comprehensive and sophisticated than anything introduced until then, and still
14 compare quite favorably with modern regulations.⁸⁹ They included a requirement for
15 consent from informed human subjects, with special protections for the mentally ill.

16 Hitler's regime, however, which used tens of thousands of concentration camp
17 inmates in inhumane experiments, trampled on these regulations. After the war, at the
18 Nuremberg trial of the Nazi doctors in 1947, the prosecution team tried to use the
19 Interior Ministry guidelines as evidence of prior standards that should have governed
20 the Nazis' actions, but defense lawyers were able to call the guidelines' legal status
21 into question because they were not cited by international organizations monitoring
22 health law in the 1930s and 1940s.⁹⁰

23 However, the team that investigated Nazi crimes did note Germany's abuse of
24 the mentally ill in the context of the T-4, or euthanasia, program that led to the

⁸⁹Sass, H.M., "Reichsrundschreiben 1931: Pre-Nuremberg German Regulations Concerning New Therapy and Human Experimentation" *Journal of Medicine and Philosophy* 8:99-111(1983).

⁹⁰Grodin M.A., *op cite*.

1 extermination of many psychiatric patients and was, in effect, a rehearsal for the mass
2 murders in the concentration camps. The chief medical advisor to the Nuremberg
3 judges, Leo Alexander, unraveled the horrific story of the camp experiments from the
4 records of SS Chief Heinrich Himmler, records that made the Nuremberg prosecutions
5 possible. Near the end of the trial, Alexander wrote a memorandum to the judges,
6 portions of which were incorporated into their decision. That portion, which posterity
7 knows as the Nuremberg Code, embodies the judges' attempt to set out the rules that
8 should guide research protocols involving human subjects.

9 In that memorandum, Alexander also singled out the mentally ill as those who
10 should be given special protections,⁹¹ but the judges omitted this population in their
11 final draft, perhaps because they did not wish to be perceived as interfering in
12 legitimate medical judgments about innovative treatment and instead wished only to
13 prohibit nonbeneficial and highly risky experiments with easily coerced healthy
14 subjects like prisoners. The Code's celebrated first line, "The voluntary consent of the
15 human subject of research is absolutely essential," based as it is on the ethical
16 requirement to respect persons, has become the most important reference point in all
17 subsequent discussions of research with human beings. But in characterizing voluntary
18 consent as "absolutely essential," the Code seems to rule out research with children,
19 with emergency patients, and with the decisionally impaired.

20

21 *The Declaration of Helsinki*

22 The World Medical Association's Declaration of Helsinki, first issued in 1964
23 (and subsequently revised in 1975, 1983, 1989, and 1996), attempted to clarify this
24 particular situation by providing for limited research involvement by incapable
25 subjects. The most recent (1996) version of the Declaration states, "[i]n the case of

⁹¹Id. at 135.

1 legal incompetence, informed consent should be obtained from the legal guardian in
2 accordance with national legislation."⁹² The Declaration divides research into two
3 categories: "therapeutic" and "nontherapeutic," and appears to rule out the
4 participation of incapable subjects in research that fails to offer them the possibility of
5 direct medical benefit. When research has as its sole objective the advancement of
6 knowledge to benefit others, the Declaration states, "[t]he subjects should be
7 volunteers. . . ." Most codes of research ethics following in the Helsinki tradition
8 tended to adopt the therapeutic/nontherapeutic distinction, one which Levine has
9 appropriately criticized as confusing and illogical.⁹³ In recent years, however, this
10 distinction has slowly been abandoned. NBAC's view, discussed more fully below, is
11 that research involving humans will, in practice, present certain risks of harm to
12 particular individuals but, at the same time, can be considered to fall either in the class
13 of research protocols that hold out the prospect of direct medical benefit to individual
14 subjects, or the alternative class that does not hold out such a prospect of benefit.

15

16 *CIOMS Guidelines*

17 The International Ethical Guidelines for Biomedical Research, issued in 1993
18 by the Council for International Organizations of Medical Sciences (CIOMS) and the
19 World Health Organization (WHO), allow a "legal guardian or other duly authorized
20 person" to permit an incapable individual's research participation but only if "the
21 degree of risk attached to interventions that are not intended to benefit the individual
22 subject is low" and if "interventions . . . intended to provide therapeutic benefit are
23 likely to be at least as advantageous to the individual as any alternative." These
24 guidelines also dictate that incapable subjects' objections to participation must be

⁹²World Medical Association, Declaration of Helsinki, Journal of the American Medical Association 277:927 (1997).

⁹³Levine RJ. Ethics and Regulation of Clinical Research, 1986, p. 8-10.

1 respected; the sole exception would be the rare case in which "an investigational
2 intervention is intended to be of therapeutic benefit to a subject, . . . there is no
3 reasonable medical alternative, and local law permits overriding the objection."⁹⁴
4

5 *The Council of Europe*

6 In November 1996, the Council of Europe's Committee of Ministers adopted
7 the "Convention for the Protection of Human Rights and Dignity of the Human Being
8 with Regard to the Application of Biology and Medicine."⁹⁵ This document allows
9 persons without the capacity to consent to be involved in research if *all* the following
10 conditions are met: (1) "[T]he results of the research have the potential to produce real
11 and direct benefit to his or her health"; (2) "research of comparable effectiveness
12 cannot be carried out on individuals capable of giving consent"; (3) participation is
13 authorized by the incapable person's "representative or an authority or a person or
14 body provided by law"; and (4) the incapable person does not object to participation.
15 The Convention document also contains language that permits research that fails to
16 offer subjects potential direct health benefit if the study meets conditions two through
17 four above, and: (1) is designed to produce knowledge for the benefit of persons with
18 the same condition; and (2) "entails only minimal risk and minimal burden for the
19 individual concerned."⁹⁶

20 Given its proximity to the United States and certain shared values about
21 medicine and research, it is worth also noting the comprehensive guidelines recently
22 produced by the three major funding agencies in Canada. In its *Policy Statement on*
23 *Research Involving Humans*, the Tri-Council Working Group describes permissible

⁹⁴CIOMS/WHO, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS 1993).

⁹⁵Council of Europe, *Convention on Human Rights and Medicine* (Nov. 1996), Articles 6 and 17.

⁹⁶Council of Europe, *Ibid.* No further explanation is given concerning definitions of the terms minimal risk and minimal burden. The convention is open for signature by member States and those with Observer status. The United States falls under the latter category.

1 conditions under which research involving persons who cannot consent for themselves
2 may occur.⁹⁷ This policy statement includes several conditions pertaining to research
3 involving cognitively impaired persons including: a requirement that protocols must
4 include an assessment of competence; a prohibition on involving persons in research
5 who are incompetent, or of doubtful competence in research which poses more than
6 minor harms without substantial benefit for the individual. There are two exceptions to
7 the latter requirements. Research may involve persons with cognitive impairments
8 which pose more than minimal risk if a prior directive has been prepared, and if a third
9 party has been appointed and authorizes subject enrollment.

10

11 Regulatory Efforts in the United States

12 When the National Commission for the Protection of Human Subjects of
13 Biomedical and Behavioral Research was created in 1974, the decisionally impaired
14 were among the special populations that it intended to consider, partly because of the
15 controversy about lobotomy. In its 1978 *Report and Recommendations on Research*
16 *Involving Those Institutionalized as Mentally Infirm*,⁹⁸ which came at the very end of
17 its tenure, the National Commission rejected both the Nuremberg Code's complete ban
18 and the 1964 Declaration of Helsinki's limitation on the involvement of incapable
19 subjects in research. The members of the National Commission believed a less
20 restrictive approach was justified to avoid indirect harm to incapable persons by
21 crippling research efforts designed to yield potential treatment for these persons'
22 conditions. They introduced this idea as follows:

23 [S]ince some research involving the mentally infirm cannot be
24 undertaken with any other group, and since this research may

⁹⁷Canada. Tri-Council Working Group, Code Conduct for Research Involving Humans, Ottawa, June 1998.

⁹⁸National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Report and Recommendations, Research Involving Those Institutionalized as Mentally Infirm (DHEW, 1978) [hereinafter Report on Institutionalized Persons].

1 yield significant knowledge about the causes and treatment of
2 mental disabilities, it is necessary to consider the
3 consequences of prohibiting such research. Some argue that
4 prohibiting such research might harm the class of mentally
5 infirm persons as a whole by depriving them of benefits they
6 could have received if the research had proceeded.⁹⁹

7 This strategy marked an important turning point in the social philosophy underlying
8 the regulation of human subjects research, in that benefits to others (particularly others
9 who now or may in the future suffer from the same disorder) who were not
10 participating in a particular research protocol could now be given more weight. The
11 National Commission concluded that the dual goals of benefiting mentally infirm
12 persons and protecting individual subjects from undue harm could be met by a third
13 approach: incapable subjects could be involved in studies offering them potential
14 direct benefit, as well as studies that did not offer potential direct benefit, as long as
15 the burdens and risks of research participation did not exceed a certain level.

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

⁹⁹Id. at 58.

1 Differences in the recommendations on children and institutionalized persons
2 were based on the National Commission's recognition that some adults
3 institutionalized as mentally infirm retain the ability to give an informed and voluntary
4 decision. Because of concerns about the vulnerability of institutionalized persons,
5 however, the National Commission recommended that IRBs be given discretion to
6 appoint "an auditor to observe and assure the adequacy of the consent process for
7 research" that presents greater-than-minimal risk. Moreover, the National Commission
8 believed such auditors should be *required* in projects presenting no prospect of direct
9 benefit and more-than-minimal risk to subjects. Their proposals also gave incapable
10 adults more authority than children to block study participation.¹⁰⁰ Finally, because
11 incapable adults usually lack the legal guardian that most children have, the National
12 Commission noted that in some cases a court-appointed guardian would be required to
13 authorize research participation.

14 In response to the National Commission's work, the Department of Health,
15 Education and Welfare (DHEW) proposed regulations to govern research on the two
16 populations. Those affecting children were adopted by the Department of Health and
17 Human Services (DHHS) in June 1983,¹⁰¹ but those affecting persons institutionalized
18 as mentally disabled were never adopted.¹⁰² The Secretary of DHHS attributed the
19 government's failure to do so to "a lack of consensus" on the proposed regulatory
20 provisions and to a judgment that the general regulations governing human subjects'
21 participation sufficiently incorporated the National Commission's recommendations.¹⁰³

¹⁰⁰The National Commission required explicit court authorization to involve an objecting institutionalized person in research. In contrast, the group recommended that parents be permitted to authorize research over a child's objection if the study presented a prospect of direct benefit to subjects not available outside the research context.

¹⁰¹"Protection of Human Subjects, Additional DHHS Protections for Children Involved as Subjects in Research" Fed. Reg. 48: 9818 (Mar. 8, 1983).

¹⁰²"Protection of Human Subjects, Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled," Fed. Reg.43:53950 (Nov. 17, 1978).

¹⁰³President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Implementing Human Research Regulations 23-29 (1983).

1 Robert Levine blames the reported lack of consensus on DHEW's earlier failure to
2 adhere to the National Commission's recommendations.¹⁰⁴ DHEW's proposed
3 regulations indicated that consent auditors might be mandatory for all research
4 involving institutionalized mentally disabled persons, and suggested that the
5 authorization of an additional person assigned the role of independent advocate might
6 be necessary before an incapable person could become a research subject. During the
7 public comment period, many respondents objected to these additional procedural
8 requirements, presumably on the belief that they were unnecessary and overly
9 burdensome to research.¹⁰⁵

10 With the exception of the Institutionalized as Mentally Infirm
11 recommendations, the 1981 DHHS rules largely followed from the National
12 Commission's work. In 1991, these rules were codified for 16 federal agencies that
13 conduct or sponsor research with human subjects and are now known as the "Common
14 Rule."¹⁰⁶ The regulations authorize IRBs to institute additional but unspecified
15 safeguards for research involving vulnerable groups, including the mentally
16 disabled.¹⁰⁷ These safeguards could involve consultation with specialists concerning
17 the risks and benefits of a procedure for this population, or special monitoring of
18 consent processes to ensure voluntariness. It is not known how frequently IRBs
19 actually implement such measures.¹⁰⁸

20 In the United States today, research involving adults diagnosed with a condition
21 characterized by mental impairment is governed by no special regulations, but falls

¹⁰⁴Levine R.J., "Proposed Regulations for Research Involving Those Institutionalized as Mentally Infirm: A Consideration of Their Relevance in 1996," *IRB*, (Sept.-Oct. 1996) at 1. See also Bonnie R., "Research With Cognitively Impaired Subjects," *Arch. Gen. Psych.* 54:105, 107 (1997). Bonnie also refers to opposition to special regulations for persons with mental illness on grounds that such an approach would foster negative stereotypes about such individuals.

¹⁰⁵*Ibid.*

¹⁰⁶"Federal Policy for the Protection of Human Subjects; Notices and Rules," *Fed. Reg.* 56:28002-28032 (June 18, 1991).

¹⁰⁷*Ibid.*

¹⁰⁸The recent NIH Panel Report indicated that IRBs regularly exercise this authority, Panel Report, p. XX.

1 instead under the Common Rule, the general federal provisions governing human
2 subjects research. However, a few Common Rule provisions do address research
3 involving persons with mental disabilities. First, the Rule identifies "mentally disabled
4 persons" as a vulnerable population, and directs institutional review boards to include
5 "additional [unspecified] safeguards . . . to protect the rights and welfare" of mentally
6 disabled research subjects. The Common Rule also advises IRBs to ensure that
7 "subject selection is equitable," and that mentally disabled persons are not targeted for
8 involvement in research that could be conducted on a less vulnerable group.¹⁰⁹ Finally,
9 "[i]f an IRB regularly reviews research that involves a vulnerable category of subjects,
10 such as . . . mentally disabled persons, consideration should be given to the inclusion
11 of one or more individuals who are knowledgeable about and experienced in working
12 with these subjects."¹¹⁰ The Common Rule allows an incapable individual's "legally
13 authorized representative" to give valid consent to the individual's research
14 participation,¹¹¹ but provides no definition of incapacity, no guidance on the identity or
15 qualifications of a subject representative beyond "legally authorized," and no guidance
16 on what ratio of risks to potential benefits is acceptable.

17 In the 1980s and 1990s, numerous groups and individuals expressed
18 dissatisfaction with gaps in the existing regulations. After the Advisory Committee on
19 Human Radiation Experiments reviewed eight studies conducted in the early 1990s
20 involving adult subjects with uncertain decisionmaking capacity, and found that four
21 of the studies required subjects to undergo diagnostic imaging that offered them no
22 prospect of direct benefit and that two appeared to present greater-than-minimal risk to
23 the subjects, it noted, "there was no discussion in the documents or consent form of
24 the implications for the subjects of these potentially anxiety-provoking conditions. Nor

¹⁰⁹Sec. ____ .111 (a)(3) & (b).

¹¹⁰Sec. ____ .107(a).

¹¹¹Sec. ____ .116

1 was there discussion of the subjects' capacity to consent or evidence that appropriate
2 surrogate decision makers had given permission for their participation."¹¹² Inquiries
3 into studies involving rapid medication withdrawal from persons diagnosed with
4 schizophrenia have also raised questions about the adequacy of current federal policy
5 and the ethical acceptability of certain existing research protocols.¹¹³

6 We are not aware of strong evidence that IRBs are actively using, or not using,
7 their existing discretionary authority when reviewing protocols involving individuals
8 with mental or brain disorders. Although IRBs currently have authority to monitor
9 research in progress, including research involving persons with mental disorders, it
10 does not appear that such monitoring routinely occurs, possibly because institutional
11 and other resources have not been devoted to this critical activity. Observers of the
12 review process agree that although the workload of many IRBs at some of the largest
13 research centers has greatly increased in recent years, the institutional support for IRB
14 activities has often not kept pace.¹¹⁴ While some institutions have responded to this
15 increase by establishing more than one board, the practice may not be widespread
16 enough. According to the report of the DHHS Office of the Inspector General,
17 monitoring of a protocol's progress after its initial approval is practically nonexistent
18 apart from investigators' routine filing of annual progress reports. After the initial
19 stages, local review has only minimal impact on actual research practices.¹¹⁵

20 The lack of more specific federal guidance on research involving persons with
21 mental disorders has also meant that research not under federal jurisdiction has gone
22 its own way, or rather at least 50 different ways, because laws and regulations vary

¹¹²ACHRE Final Report, *supra*, at 706-07.

¹¹³Shamoo, A. and Keay, T.J. "Ethical Concerns About Relapse Studies," *Cambridge Quarterly of Healthcare Ethics* 5:373-386 (1996).

¹¹⁴Department of Health and Human Services, Office of the Inspector General, "Institutional Review Boards: Their Role in Reviewing Approved Research" (Washington, DC: DHHS, 1998).

¹¹⁵U.S. General Accounting Office, Report to the Ranking Minority Member, Committee on Governmental Affairs, U.S. Senate, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects* (Washington, D.C.: U.S.G.A.O., 1996).

1 widely; most states have no rules that specifically apply to research involving this
2 population while some states have quite restrictive regulations. Several states currently
3 prohibit certain types of research on persons with mental disorders, research which
4 presents greater than minimal risk and subjects are not likely to benefit.¹¹⁶ This
5 suggests that both IRBs and researchers may have trouble identifying (and thus
6 following) the procedures and standards that are requisite to ethical and legal
7 investigations involving persons with mental disorders, even in states that have
8 attempted to provide the badly needed guidance.

9 Uncertainty about legal and ethical norms can contribute to an adversarial tone
10 in public discourse about this kind of research. Indeed, as events in New York State
11 illustrate, advocacy of sharply differing ethical perspectives can result in litigation. In
12 a case called *T.D. v. New York State Office of Mental Health*, several individuals and
13 organizations challenged regulations of the New York State Office of Mental Health

¹¹⁶Those states are Alaska See, e.g. ALASKA STAT. § 47.30.830 (Michie 1996) (prohibiting experimental research on state mental health patients that involve 'any significant risk of physical or psychological harm'); DEL. CODE ANN. tit. 16, § 51.75(f) (1995) (prohibiting any resident of a state mental hospital from being approached "to participate in pharmaceutical research if [the] patient is incapable of understanding the nature and consequences of [the] patient's consent"); DEL. CODE ANN. tit. 16, § 51.74 (1995) (prohibiting certain classes of mental hospital residents, regardless of competency, from participating in pharmaceutical research); 405 ILL. Comp. STAT. ANN. 5/2-110 (West 1993) (providing that parent or guardian cannot consent to ward's participation in any "unusual, hazardous, or experimental services" without approval by court and determination that such services are in the "best interests" of the ward); MASS. REGS. CODE tit. 104, §§ 13.01-.05 (1995) (prohibiting research on patients in mental facilities that will not provide direct, therapeutic benefit and prohibiting research on patients with mental disabilities where the risk is more than minimal and exceeds the benefit to the subject); Mo. ANN. STAT. § 6.30.115 (8) (West Sup. 1997) (preventing state mental health patients from being 'the subject of experimental research,' with exceptions, and prohibiting biomedical or pharmacological research from being performed on any individual with mental disabilities if that research will have no direct therapeutic benefit on the individual research subject); Diane E. Hoffman & Jack Schwartz, Proxy Consent to Participation of the Decisionally Impaired in Medical Research—Maryland's Policy Initiative, *I J. Health Care Law and Policy* 136, no. 9 & 12 (1997) (citing state statutes which provide restrictions for research on the decisionally impaired) See John C. Fletcher & Alison Whitman, A New Consent Policy for Research with Impaired Human Subjects, *23 Psychopharmacology BULL.* 382 (1987). Virginia's state statute also [to be completed]. Washington State's statute (RCA 7.70.065) permits consent on behalf of an incompetent subject by (1) the appointed guardian, (2) the person to whom the subject has given a durable power of attorney including the authority to make health care decisions, (3) the subject's spouse, (4) the adult children of the subject, (5) the parents of the subject, (6) the adult siblings of the subject in that order of priority. A legally incompetent subject for research purposes, according to this statute is one who is incapable of providing informed consent by reason of unconsciousness, mental illness, developmental disability, senility, excessive use of drugs, or other mental incapacity (RCA 11,88.010)

1 with respect to participation in greater than minimal risk research by minors and
2 persons who lacked the capacity to give informed consent. In 1995, the trial court
3 invalidated the regulations on the grounds that the Office of Mental Health lacked
4 statutory authority to adopt them.¹¹⁷ The next year, the intermediate appellate court in
5 New York agreed with the trial court's conclusion but added a far more wide-ranging
6 critique of the regulations, opining that they violated constitutional due process rights
7 and substantive protections granted these research subjects under New York's
8 statutory and common law.¹¹⁸ Finally, however, New York's highest court narrowed
9 the judicial holding to the original decision of the trial court.¹¹⁹

10 Recognizing the problem of uncertainty, officials in Maryland have undertaken
11 a less adversarial process of policy formulation. A working group under the auspices
12 of the Maryland Attorney General has, over more than two years, produced a series of
13 reports culminating in a proposed state statute that would govern the substantive and
14 procedural aspects of research involving "decisionally incapacitated individuals."¹²⁰

15

16 The Role of NBAC

17 In undertaking a review of the ethical, legal, and scientific issues arising from
18 research involving persons with mental disorders, NBAC is carrying out the functions
19 assigned to it by the President in the Executive Order which established NBAC. In that
20 Executive Order, President Clinton directed NBAC, as a first priority, to turn its
21 attention to the consideration of the protection of the rights and welfare of human
22 research subjects.¹²¹ As we noted in Chapter 1, the justification for undertaking this

¹¹⁷626 N.Y.S.2d 1015 (N.Y. Sup. Ct. 1995).

¹¹⁸650 N.Y.S.2d 173 (N.Y. App. Div. 1996).

¹¹⁹690 N.E.2d 1259 (N.Y. 1977). According to the New York Court of Appeals, the intermediate appellate court's discussion of constitutional, common law, and other statutory issues was "an inappropriate advisory opinion."

¹²⁰Office of the Maryland Attorney General. *Final Report of the Attorney General's Research Working Group* (1998).

¹²¹Executive Order 12975. Sec 5(a).

1 review is a result of the confluence of many developments including certain historical
2 and contemporary cases in which protection of subjects appears not to have been
3 adequate; the perceived gap that exists in the federal regulatory system established for
4 the protection of human subjects, and our desire to ensure that important research that
5 maximizes the opportunity to develop treatments for these disorders is able to proceed.
6 We are persuaded that there is substantial public concern about actual or potential
7 failures to protect persons suffering from mental disorders from inappropriate research
8 protocols. We also believe that many clinical investigators may feel unsure about how
9 they should conduct themselves when carrying out research with this population, and
10 that authorities in New York, Maryland, and elsewhere have indicated a sense of
11 unease about the lack of federal guidance. With those considerations in mind, certain
12 elaborations of the present system for the protection of human research subjects now
13 appear to be warranted with regard to those who suffer from mental disorders.
14

1 Chapter Three: INFORMED CONSENT AND LIMITATIONS ON
2 DECISIONMAKING CAPACITY

3

4 The Centrality of Voluntary and Informed Consent

5 The topic addressed by this report—what are the ethical requisites for research
6 involving persons with mental disorders that may affect their decisionmaking
7 capacity?—raises fundamental questions about governmental and professional
8 regulation of all research with human subjects. Although public attention to the ethics
9 of research involving human subjects traces its history to the revelations in the trial of
10 the Nazi doctors five decades ago at Nuremberg, the more widespread acceptance of
11 the necessity of public oversight of research was not evident for another two
12 decades—arising from the disclosure of ethical lapses in the United States¹²²and
13 elsewhere.¹²³ The regulatory structure that has evolved over the past 30 years in the
14 United States has been built on a central premise of the need to regulate human
15 subjects research in order to ensure adequate respect for research subjects. This
16 respect is achieved by protecting subjects from unjustified and unwarranted harm
17 through the establishment of barriers to research that do not meet appropriate ethical
18 and scientific standards. In the United States, the result has been a system of prior
19 review of research protocols to ensure the scientific and ethical quality of the protocol
20 and thus to weed out protocols that would expose subjects to inappropriate risks.

21 In recent years, some have argued that ensuring access of all groups to
22 experimental treatments should also become a goal of research regulation, pointing out
23 that preventing the exploitation of individuals may not be the only legitimate
24 regulatory objective. In their view, insistence on obtaining the maximum benefit from
25 research while minimizing the risk of harm to subjects unduly restricts some patients

¹²²Beecher HK, Ethics and clinical research. *New England Journal of Medicine* 274 (1966): 1354-1360.

¹²³Pappworth, MK. *Human Guinea Pigs: Experimentation on Man*, Boston: Beacon Press, 1968.

1 from obtaining new and still experimental medical interventions for their conditions.
2 Thus they argue that regulatory requirements should be adjusted to allow patient-
3 subjects, especially those whose existing therapies are inadequate, less restrictive
4 access to participation in research protocols.

5 While obvious tensions exist between these two paradigms, there is widespread
6 agreement in North America and many other countries about the centrality of
7 voluntary and informed consent of research subjects. As we have mentioned, the
8 Nuremberg Code makes such consent the first and essential requisite of ethical
9 research. Similarly, the current demands for greater access to participation in research
10 protocols rest on a model of respect for persons, individual autonomy, and patient self-
11 determination. In either view, research protocols are not acceptable if subjects have
12 not had the opportunity to be informed about the methods, objectives, potential
13 benefits, and risks of research and to decide whether or not to participate in a free and
14 informed fashion.

15 Plainly, then, the capacity to participate in this process of informed decision
16 making is a requirement of but not the total corpus of the present system of public
17 oversight of biomedical and behavioral research. Under a strict protection model,
18 those who lack such capacity, or whose capacity is uncertain, may be excluded from
19 participation as subjects in research, and there would be no way to assess the
20 promising new clinical approaches to the diseases from which they suffer. Such
21 exclusion may seem appropriate; according to this view, the underlying principle is
22 that it is better to protect subjects (who may be unwilling participants) from harm,
23 even at the cost of slowing the progress of scientific investigation and medical
24 advances. The additional cost, and the obvious dilemma presented by the strict
25 protection standard, is that research leading to therapies for those disorders that—as a
26 manifestation of those disorders themselves—would be halted in the absence of
27 subject consent.

1 Conversely, under the “access model,” a total barrier to research for persons
2 with mental disorders is suspect precisely because it would prevent some people from
3 obtaining the potential benefits that such research might offer them, either directly as a
4 result of participating in the research or indirectly as a result of the improved
5 understanding of their illness and of methods for treating it that may result from the
6 research in question. From either perspective, impaired decisionmaking capacity is a
7 pivotal issue that must be addressed.

8

9 Persistent Decisional Impairments

10 Voluntary, informed consent is thus an essential feature of ethically and legally
11 acceptable research. It embodies the respect for persons that is one of the most
12 fundamental principles on which all physician-patient interactions are based, and it is
13 also seen as one of the critical means of protecting people from unwarranted research
14 risks. The threshold that qualifies an individual for participation in the informed
15 consent process is an adequate level of decisionmaking capacity. Throughout this
16 report the term capacity is used rather than the term competence, as the latter often
17 refers to a legal determination made by a court, and the former refers to a clinical
18 judgment. Although the terms competence and capacity are sometimes used
19 interchangeably, in this report we will be referring, for the most part, to capacity.

20 Individuals whose capacity to make decisions is uncertain must be evaluated by
21 a qualified professional to assess, as well as possible, that capacity. Following a proper
22 assessment, a person who lacks the capacity may be thought of as “decisionally
23 impaired,” a condition that can result from a variety of causes including medical
24 illnesses, cognitive difficulties, even constraints on personal freedom due to
25 institutionalization or dependency upon those who provide one’s treatment. The
26 specific concern of this report, however, is with persons whose decisional impairments

1 may be related to the presence of what we currently understand to be a mental
2 disorder.

3 In a certain sense, all of us are decisionally impaired at various times in our
4 lives. When we have been exposed to anesthetic agents, when we have had too little
5 sleep, when a life event disrupts our equilibrium, or when we have over-indulged in
6 alcoholic beverages, our ability to process information and weigh alternatives in light
7 of our values is likely to be reduced. These acute but temporary forms of decisional
8 impairment are not usually matters of concern, because decisions about participation
9 in a research project can normally wait until the impairment has passed.¹²⁴ Rather, the
10 impairments that raise the greatest concern are those that persist. When we speak of a
11 decisional impairment in this report we refer principally, but not exclusively, to a
12 relatively persistent condition, a condition that is ongoing or that may periodically
13 recur. There are other sources of decisional impairment that are normally more
14 temporary, such as the transitory side effects of medical treatment, but that might also
15 call for special planning if participation in a research protocol is being considered.
16 Some of the discussion and recommendations in this report may be relevant to these
17 other factors that may affect decisionmaking capacity but, again, our primary concern
18 is with the effect of conditions on the decisional capacity of potential research
19 subjects.

20 It is neither ethically acceptable nor empirically accurate to presume that
21 individuals with ongoing medical problems are decisionally impaired. Less obviously,
22 it is also inappropriate to suppose that those who exhibit some decisionmaking deficit

¹²⁴The 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. Department of Health and Human Services, Food and Drug Administration, Protection of Human Subjects; Informed Consent, 61 Fed. Reg. 51498 (Oct. 2, 1996).

1 cannot be helped to attain a level of functioning that would enable them to be part of a
2 valid consent process. Once we recognize these facts, we become more aware of the
3 special ethical obligations that are imposed on scientific investigators and institutions
4 sponsoring, carrying out research and society in general when research with persons
5 who may be decisionally impaired is contemplated.

6 Not only must psychological and medical factors affecting these potential
7 research subjects be taken into account, but a full understanding of the nature of their
8 impaired decision making is required. As we have said, even those who would not
9 normally be considered to be suffering from a decisional impairment may become
10 disoriented if we are suddenly thrust into the role of a patient, with all of the attendant
11 social inequalities and feelings of vulnerability. Persons with a tendency toward
12 impaired decision making due to a mental disorder may experience the consequences
13 of institutionalization in an even more pronounced manner. Therefore, the conditions
14 under which a consent process takes place, including how information is presented and
15 who is responsible for obtaining consent, can be critical in influencing the quality and
16 therefore the ethical validity of the consent obtained. Appreciating these different
17 perspectives may also provide us with practical insights that can improve the process,
18 such as the use of peers (other persons with similar mental disorders who have already
19 participated in the research and/or their advocates) or advocates in the consent
20 encounter or in drafting forms to clarify them. It is imperative that those who are
21 engaged in research with persons with mental disorders, including clinical
22 investigators and IRBs, enrich their appreciation of the importance of context in the
23 consent process and, therefore, in setting an appropriate foundation for ethically
24 acceptable research.

25

1 Decisional Incapacity and Impairment¹²⁵

2 Especially in the context of discussions about the ethics of human subjects
3 research, impaired decisionmaking capacity implies a condition that varies from
4 statistical or species-typical normalcy. In this sense, normal immaturity should not be
5 regarded as a decisional “impairment,” since the very young cannot be expected to
6 have achieved the normative level of decisionmaking capacity. Conversely, normal
7 aging need not involve impaired decision making, and assuming such an impairment is
8 pejorative.

9 Therefore, when we speak of decisional impairments in the context of research
10 involving human subjects who suffer from mental disorders, we mean an incapacity
11 that is not part of normal growth and development. For example, senile dementia is not
12 part of normal aging, and schizophrenia is a biologically based disease. These are
13 examples of conditions that deviate from regular developmental patterns and are not
14 captured under regulatory categories intended to address periods in the life cycle
15 (fetuses and children) or certain defined groups (e.g., pregnant women or prisoners).¹²⁶
16 If those who are decisionally impaired are to be identified as in need of special
17 treatment under research regulations, they must be carefully distinguished from other
18 special populations.

19 In practice, it is not usually hard to determine whether a person lacks all ability
20 to make a decision, so findings of incapacity in this global sense are not often
21 challenging or subject to much disagreement. Much more challenging for us (and the

¹²⁵Although 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.

¹²⁶Title 45 Code of Federal Regulations Part 46- “Protection of Human Subjects,” Subparts B - Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization, Subpart C- Additional DHHS Protections Pertaining to Biomedical and Behavioral research Involving Prisoners as Subjects and Subpart D- Additional DHHS Protections for Children Involved as Subjects in Research.

1 subject of numerous “hard cases” in the law) is determining whether someone from
2 this population with limited decisional capacity has sufficient capacity to make a
3 particular choice of a certain type, thus allowing us to support and respect that choice.

4 Individuals who have some cognitive deficit that renders them incapable of
5 making some treatment decisions may nevertheless be quite functional and
6 independent in the activities of daily living. Having a decisional impairment need not
7 imply a particular social or legal status. As a functional term, decisional impairment is
8 neutral with respect to other particular characteristics an individual may possess. As
9 Grisso and Appelbaum have noted, what counts as impaired decision making is partly
10 determined by the standard of competence that is chosen.¹²⁷ Persons who are
11 institutionalized may not be decisionally impaired and those who are not
12 institutionalized may have impaired decisionmaking capacity. Capacity refers to an
13 ability, or set of abilities, which may be situation or context specific. There is a
14 growing consensus that the standards for assessing capacity include: the ability to
15 evidence a choice, ability to understand relevant information, the ability to appreciate
16 the situation and its consequences, and the ability to manipulate information
17 rationally.¹²⁸ These standards focus on the capacity to consent to treatment, not
18 research. Recently, however, the American Psychiatric Association approved a set of
19 guidelines for assessing decisionmaking capacity in potential research subjects which
20 substantially relies on these same standards.¹²⁹ Thus what counts as decisional
21 capacity is dependent on a subtle set of assumptions and evaluations.

22 Even once the standard of capacity has been chosen, one must set the threshold
23 that distinguishes those who meet the standard from those who do not. Of course,

¹²⁷Grisso T., and Appelbaum P.S., “Comparison of Standards for Assessing Patients’ Capacities to Make Treatment Decisions,” *American Journal of Psychiatry* 152:7(1995)1033-1037.

¹²⁸Appelbaum PS, Grisso T. Assessing patients’ capacities to consent to treatment. *New England Journal of Medicine* 319 (1988): 1625-1638.

¹²⁹American Psychiatric Association. Guidelines for Assessing the Decisionmaking Capacities of Potential Research Subjects with Cognitive Impairments. (Approved by the APA Board of Trustees, July 1998).

1 different mental disorders may have an effect on decisionmaking capacity in different
2 ways—some, not at all; some, intermittently; some, more persistently. The decision
3 regarding where the threshold of capacity is set is influenced in part by a society’s
4 political or value system. In a liberal democratic society such as ours, wherein the
5 scope of state authority over individual lives is strictly limited and subject to careful
6 scrutiny, this threshold tends to be low. But the selection of a threshold of decisional
7 ability is not wholly a political one, as it must be justified by the individual’s ability to
8 satisfy certain benchmarks.¹³⁰

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

14 For all these reasons, determining the proper standards and procedures to
15 measure capacity poses a major challenge in formulating policy on research involving
16 subjects with mental disorders affecting decisionmaking capacity. As we said, persons
17 with such disorders vary widely in their ability to engage in independent decision
18 making. They may retain such capacity, or possess it intermittently, or be permanently
19 unable to make decisions for themselves. Individuals with dementia, for example,
20 frequently retain decisionmaking capacity early in the course of the illness, but with
21 time they may become intermittently and then permanently unable to make their own
22 decisions. Some individuals with cognitive disabilities are capable of making many
23 choices for themselves; others completely lack such capacity.¹³¹

¹³⁰For a fuller discussion of certain strengths and weaknesses of capacity assessment instruments, see Saks, ER. Competency to decide on treatment and research: The MacArthur Capacity Instruments. A paper commissioned for the National Bioethics Advisory Commission.

¹³¹See generally Thomasma, A Communal Model for Presumed Consent for Research on the Neurologically Vulnerable, 4 Accountability in Research 227 (1996); Sachs, et al., Ethical Aspects of Dementia Research: Informed Consent and Proxy Consent, 42 Clin. Res. 403 (1994).

1 Because of their moral consequences, incorrect capacity determinations can be
2 inadvertently damaging—an assessment that a capable person is incapable of
3 exercising autonomy is disrespectful, demeaning, stigmatizing, and may result in the
4 unwarranted deprivation of an individual’s civil liberties.¹³² This is a serious matter.
5 Conversely, a judgment that an incapable person is capable leaves that individual
6 unprotected and vulnerable to exploitation by others.¹³³ In addition, the presence of
7 many marginal cases among members of the relevant populations triggers concern
8 about our ability to make those types of capacity assessments for many individuals.
9 Although it is important to accord due respect to persons with mental disorders
10 capable of autonomous choice, it is also important to recognize that investigators
11 seeking to enroll subjects face conflicting interests, and some may be too willing,
12 perhaps unconsciously, to label prospective subjects capable when this will advance
13 their research objectives.¹³⁴ As we have cautioned, investigators must also be alert to
14 the possibility—and to its subsequent ramifications—that a research subject’s
15 decisionmaking status may change during the protocol.

16 NBAC’s view is that existing federal policy fails to provide adequate guidance
17 to investigators and IRBs on the many complexities related to capacity determinations
18 in research involving persons who are the subject of this report. Currently, individual
19 IRBs determine (or at least approve) how investigators are to address these matters.
20 Without adequate education and guidance, however, IRB members are likely, albeit
21 inadvertently, to vary criteria too much and to fail to institute adequate safeguards for
22 such research.¹³⁵ Therefore we, along with some other commentators, support more

¹³²Saks, *Ibid.*

¹³³National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (1979) [hereinafter *Belmont Report*].

¹³⁴See, e.g., Marson, et al., 45 *J. Am. Geriatrics Soc'y* 453, 455 (1997). See also Shamoo & Keay, *supra*, at 373 (1996).

¹³⁵Bonnie, *supra*, at 109.

1 systematic and specific federal direction on capacity assessment,¹³⁶ not only for
2 defining decisional capacity in the research context but also for developing better
3 procedures for assessing such capacity.
4

¹³⁶E.g., id.

1 Procedures for Capacity Assessment and Information Disclosure

2 A capacity assessment process must adequately protect the interests of
3 individuals with conditions that increase the risk of decisional impairment; to address
4 this need, a variety of approaches to capacity assessment are endorsed in the literature
5 on research involving adults with cognitive impairment. Many commentators believe
6 that IRBs should at minimum require investigators to specify the method by which
7 prospective subjects' decisional capacity will be evaluated and the criteria for
8 identifying incapable subjects.¹³⁷ Evaluating decisional capacity is an even more
9 complex task than might be inferred either from the above discussion or from most
10 philosophical discussions of capacity. Any assessment tool measures capacity
11 indirectly through manifest performance, and a person's performance does not always
12 adequately reflect his or her capacity or potential. Many factors can inhibit
13 performance, including anxiety or environmental conditions, the quality of the
14 assessment instrument itself, and other characteristics of the task of assessment in
15 general.¹³⁸ All of us can attest to the variation on one occasion or another between our
16 actual performance—as on an examination or in a job interview—and our actual
17 capacity. The problem is aggravated in populations whose conditions are partly
18 characterized by fluctuating capacity. The capacity-performance distinction suggests
19 why the context in which the capacity assessment is made (under what conditions or
20 by whom, for example) is so important.

21 Unlike the discrepancy between capacity and performance, whose differences,
22 though very real, can be subtle, a major point of contention is whether capacity
23 assessment and information disclosure should be conducted by an individual not
24 otherwise connected with the research project. The National Commission

¹³⁷E.g., Bonnie, *supra*; Melnick et al., *supra*.

¹³⁸See, 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.

1 recommended that, “where appropriate,” IRBs should appoint a “consent auditor” for
2 research involving those persons institutionalized as mentally infirm.¹³⁹ IRBs would
3 have this authority to determine whether a consent auditor would be appropriate, and
4 how much authority the consent auditor would have. For example, in research
5 involving greater than minimal risk without the prospect of direct benefit to the
6 subjects, the National Commission recommended that the auditor would observe and
7 verify the adequacy of the consent and assent process, and in appropriate cases
8 observe the conduct of the study to ensure the subjects’ continued willingness to
9 participate.¹⁴⁰ The proposed DHEW regulations contemplated mandating auditors for
10 all projects involving this subject population, but opposition to this proposal reportedly
11 was one reason the regulations never became final.

12 More recent commentary includes a spectrum of views on the need for an
13 independent consent auditor. Some echo the National Commission's view that a
14 requirement for an independent evaluator becomes increasingly justified as net
15 research risks to subjects increase. A distinguished team of Canadian scholars took
16 this position in its recent recommendations on dementia research.¹⁴¹ According to this
17 group, the role of consent assessor/monitor ordinarily can be filled by a researcher or
18 consultant "familiar with dementias and qualified to assess and monitor competence
19 and consent in such subjects on an ongoing basis." The individual should be
20 knowledgeable about the project and its risks and potential benefits. On the other
21 hand, if the research team lacks a person with these qualifications, if there is "a real
22 danger of conflict of interest" for team members who might evaluate and monitor
23 capacity, or if the project involves greater-than-minimal risk and no prospect of direct

¹³⁹National Commission. *Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm*, pp. 8-20.

¹⁴⁰Ibid. p. 15.

¹⁴¹Keyserlingk, et al., *supra*.

1 benefit to subjects, Keyserlingk and his group argued that an independent
2 assessor/monitor should be appointed.¹⁴²

3 Others also appear open to the general use of outside observers and examiners.
4 Recent guidelines adopted by the Loma Linda University IRB state, "[c]onsent
5 observers who are independent of the investigator and of the institution will be
6 required by the IRB in those conditions where the potential subject's decisionmaking
7 capacity is suspect."¹⁴³ In testimony before NBAC, representatives of Citizens for
8 Responsible Care in Psychiatry and Research recommended that "[a]n independent
9 psychiatrist . . . determine the capacity of [the] potential participant to comprehend the
10 risks and benefits of enrolling in the proposed research study."¹⁴⁴ Recent articles also
11 endorse the participation of a "special research educator" in the disclosure and
12 decision process, particularly to ensure that prospective subjects understand when
13 advancement of general knowledge is the primary goal of the project at hand.¹⁴⁵

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

21 As with psychotropic medication and sterilization,

¹⁴²Id. at 343-44. See also Melnick, et al., *supra*.

¹⁴³Orr, Guidelines for the Use of Placebo Controls in Clinical Trials of Psychopharmacologic Agents, 47 *Psych. Services* 1262 (1996).

¹⁴⁴Shamoo & Sharev, Unethical Use of Persons With Mental Illness in High Risk Research Experiments, 2 *BioLaw S*:23 (1997).

¹⁴⁵DeRenzo, 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.

1 several distinct features of experimentation suggest
2 the need for special protections. First, the history
3 of medical experimentation has been characterized by
4 significant incidents of abuse, particularly where
5 members of vulnerable populations have been enlisted
6 as subjects. Second, the interest of medical
7 researchers in securing participation in the experi-
8 ment often conflicts with their duties as treating
9 physicians to inform, advise, and act in the best
10 interests of their patients. Third, experimentation
11 is inherently highly intrusive and dangerous, as the
12 nature and magnitude of risks involved are largely
13 unknown and unknowable.¹⁴⁶

14
15 Bein further suggests that courts have not demanded such safeguards for decisions on
16 life-sustaining treatment, based on the comparative rarity of the potential abuses just
17 described. He also argues that an IRB-administered system of patient-advocates would
18 provide inadequate oversight because such a system would be too responsive to
19 institutional interests.¹⁴⁷

20 Other recent commentary proposes more diverse methods for ensuring against
21 inappropriate capacity determinations. Richard Bonnie opposes a federal requirement
22 for any specific procedure, contending instead that "the regulations should provide a
23 menu of safeguards" from which IRBs could choose, including "specially tailored
24 follow-up questions to assess subject understanding, videotaping or audiotaping of

¹⁴⁶Bein, *supra*, at 747-48.

¹⁴⁷*Id.* at 762.

1 consent interviews, second opinions, use of consent specialists, or concurrent consent
2 by a family member."¹⁴⁸

3 Many groups advise the involvement of a trusted family member or friend in the
4 disclosure and decisionmaking process. Capable subjects reportedly are often willing
5 to permit such involvement. Dementia researchers frequently adopt a mechanism
6 called "double" or "dual" informed consent when the capacities of prospective subjects
7 are uncertain or fluctuating.¹⁴⁹ This approach has the virtue of providing a concerned
8 back-up listener and questioner who "may help the cognitively impaired individual
9 understand the research and exercise a meaningful informed consent."¹⁵⁰ On the other
10 hand, others have suggested that the presence of a caregiving relative could in some
11 cases put pressure on subjects to enter a research study.¹⁵¹

12 Another suggestion is to require a two-part consent. In this process, information
13 about a study is presented to a prospective subject and a questionnaire administered to
14 determine the individual's comprehension. The subject is then provided with a copy of
15 the questionnaire to refer to as needed. If the individual initially fails to demonstrate
16 an adequate understanding of the material, written or oral information is presented
17 again, and the subject is retested. This process is likely to yield more accurate
18 judgments of subject capacity than a less systematic and rigorous inquiry.¹⁵²

19 Finally, numerous ideas have been offered to make information more accessible
20 to subjects capable of exercising independent choice. Simple perceptual aids, such as
21 increasing the type size of printed material, may enhance the ability of elderly subjects

¹⁴⁸Bonnie, *supra*, at 110.

¹⁴⁹High, et al., *supra*. See also Bonnie, *supra*, at 110 ("participation of surrogate decision makers can be a useful safeguard even if the subject has the requisite capacity to provide legally valid consent").

¹⁵⁰Karlawish & Sachs, Research on the Cognitively Impaired: Lessons and Warnings from the Emergency Research Debate, 45 J. Am. Geriatrics Soc'y 474, 477 (1997).

¹⁵¹*Id.*

¹⁵²Ratzan, 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)).

1 to comprehend the necessary information. Information can be delivered through
2 videotape, slides, or pictorial presentations. Another promising suggestion is for
3 investigators to ask representatives of the affected population to critique drafts of
4 information materials prior to their actual research use.¹⁵³

5 The literature offers fewer suggestions for ensuring genuine voluntariness. The
6 current Declaration of Helsinki includes a provision advising "the physician obtaining
7 informed consent for the research project [to] be particularly cautious if the subject is
8 in a dependent relationship on him or her or may consent under duress." In these
9 circumstances, "informed consent should be obtained by a physician who is not
10 engaged in the investigation and who is completely independent of this official
11 relationship."¹⁵⁴ We hold the view that, to guard against pressure from family or other
12 caregivers, someone should discuss separately with consenting subjects their reasons
13 for participating. Again, the issue is whether a research team member, independent
14 evaluator, or IRB representative should be given this responsibility.

15

16 Substantive Requirements for Research Decision Making

17 An autonomous choice to enter a research study is both informed and voluntary.
18 To be capable of informed choice, it is generally agreed that a prospective subject
19 should demonstrate the ability "to understand the nature of the research participation;
20 appreciate the consequences of such participation; exhibit ability to deliberate on
21 alternatives, including the alternative not to participate in the research; and evidence
22 ability to make a reasoned choice."¹⁵⁵ Subjects also should "comprehend the fact that

¹⁵³Melnick, et al., *supra*.

¹⁵⁴World Medical Association, *supra*.

¹⁵⁵High, 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,

1 the suggested intervention is in fact research (and is not intended to provide
2 therapeutic benefit when that is the case)," and that they may decide against
3 participation "without jeopardizing the care and concern of health care providers."¹⁵⁶

4 There is consensus that decisional capacity requires a certain level of cognitive
5 ability. Less agreement exists on whether subjects should be judged incapable if they
6 lack affective appreciation of the choice before them. In a recent article, Carl Elliott
7 argues that some depressed persons "might realize that a protocol involves risks, but
8 simply not *care* about the risks," or "as a result of their depression, may even *want* to
9 take risks" (italics in original).¹⁵⁷ Elliott believes that judgments about a person's
10 capacity to consent to research should take into account emotional attitudes like these.
11 He also proposes that subjects failing to exhibit a "minimal degree of concern for
12 [their] welfare" should be deemed incapable of independent decision making. Others
13 oppose this position, contending that such an approach could represent excessive
14 paternalism toward persons diagnosed with mental disorders, that insufficient data
15 exist on the extent of incapacitating emotional impairment among depressed persons,
16 that affective impairment is difficult to assess, and that normative consensus is lacking
17 on "how much impairment we as a society are willing to accept before we consider
18 someone incompetent."¹⁵⁸

19 It is generally agreed that a prospective subject's capacity to decide whether to
20 participate in a particular research project cannot be determined through a general
21 mental status assessment.¹⁵⁹ Instead, investigators must develop and present the

Making Health Care Decisions: A Report on the Ethical and Legal Implications of Informed Consent in the Patient-Practitioner Relationship 60 (1982).

¹⁵⁶Melnick, et al., Clinical Research in Senile Dementia of the Alzheimer Type, 32 J. Am. Geriatrics Soc'y 531, 533 (1984).

¹⁵⁷Elliott, Caring About Risks, 54 Arch. Gen. Psych. 113 (1997).

¹⁵⁸Appelbaum, 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).

¹⁵⁹High, 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).

1 specific material relevant to that project and evaluate the prospective subject's
2 understanding and appreciation of that information.¹⁶⁰ In its 1998 report on “Research
3 Involving Individuals with Questionable Capacity to Consent,” a National Institutes of
4 Health panel also concluded that “a key factor in potential participants’ decision-
5 making is their appreciation of how the study applies to them (in the context of their
6 lives).”¹⁶¹

7 Like other commentators, the 1998 NIH panel endorsed a "sliding-scale"
8 approach to decisional capacity in the research setting.¹⁶² This approach demands an
9 increasing level of understanding and appreciation as study risks increase and potential
10 benefits to subjects decrease.¹⁶³ Similarly, some suggest that many prospective
11 subjects incapable of independent research decision making remain capable of
12 selecting a research proxy, since "the decision-making capacity that is required to
13 designate a proxy is far less than the capacity required to understand a detailed
14 protocol."¹⁶⁴ In our view, the level of capacity required to appoint a proxy need not be

¹⁶⁰According 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).

¹⁶¹National 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.

¹⁶²Ibid.

¹⁶³Elliott, Mentally Disabled and Mentally Ill Persons: Research Issues, in *Encyclopedia of Bioethics* 1760 (W. Reich ed., rev. ed. 1995); Appelbaum, Drug-Free Research in Schizophrenia: An Overview of the Controversy, *IRB*, Jan.-Feb. 1996, at 1; Annas & Glantz, Rules for Research in Nursing Homes, 315 *New Eng. J. Med.* 1157 (1986). See also Schafer, A., “The ethics of the randomized clinical trial.” *New England Journal of Medicine* 307;(12):719-24, (1982).

¹⁶⁴Sachs, et al., *supra* at 410.

1 as great as that which would be required to consent to participate in research: we
2 discuss this further in Chapter Four.

3 Besides being informed, a decision to enter research should be voluntary. The
4 Nuremberg Code provides descriptive characteristics of a voluntary decision,¹⁶⁵ and
5 the National Commission's *Belmont Report* characterizes a voluntary decision as "free
6 of coercion and undue influence." According to the *Belmont Report*, "[c]oercion
7 occurs when an overt threat of harm is intentionally presented by one person to
8 another in order to obtain compliance. Undue influence . . . occurs through an offer of
9 an excessive, unwarranted, inappropriate or improper reward or other overture in order
10 to obtain compliance." In addition, the *Belmont Report* notes, an inducement that is
11 not overly persuasive to most adults could unduly influence the judgment of
12 vulnerable subjects. The National Commission acknowledged that terms such as
13 "unjustifiable external influence" or "excessive reward" cannot always be precisely
14 defined, but that "undue influence would include actions such as manipulating a
15 person's choice through the controlling influence of a close relative and threatening to
16 withdraw health services to which an individual would be otherwise entitled."¹⁶⁶

17 Due to its limited congressional mandate, the National Commission considered
18 only the potential pressures on institutionalized persons to enroll in research. Recent
19 commentary favors expanding this concern on grounds that persons with mental
20 disabilities are especially vulnerable to similar pressures no matter where they
21 reside.¹⁶⁷ Prospective subjects with mental disorders living in the community
22 frequently rely heavily on the assistance of professionals and family members and may
23 perceive research participation as essential to maintaining the approval of their

¹⁶⁵See p. 5, above.

¹⁶⁶*Belmont Report*, supra, at 6.

¹⁶⁷Bonnie, supra; Levine, Proposed Regulations, supra.

1 caregivers.¹⁶⁸ On the other hand, there remains considerable support for retaining
2 special protections to persons in residential facilities due to their near-complete
3 dependence on the good will of the staff.¹⁶⁹

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

11 Since the particular instrument and methods used to assess capacity have an
12 important role in determining the outcome of such an assessment, IRBs should be
13 aware of the special characteristics and implications of particular instruments and
14 methods. Studies involving subjects with fluctuating or declining decisional capacity
15 must include mechanisms to ascertain and address this possibility, including provision
16 for appointment of a representative for subjects who become incapable.¹⁷⁰ In the next
17 chapter, we discuss the issue of appointing representatives and consider other factors
18 that must be taken into account when informed consent from the potential subject
19 cannot be obtained.

¹⁶⁸Relatives 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).

¹⁶⁹Elliott, *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).

¹⁷⁰Appelbaum, Drug-Free Research, *supra*.

1 Chapter Four: ASSENT/DISSENT, ADVANCE PLANNING, AND SURROGATE
2 DECISION MAKING

3
4 For those whose decisionmaking capacity is impaired, truly informed consent
5 may not be achievable but it is the standard against which all efforts to obtain the
6 ethical participation of individuals in research must be judged. While, at times, persons
7 with mental disorders are incapable of giving valid informed consent for their
8 participation in a research protocol, under appropriate circumstances and with special
9 protections, ethically acceptable research involving such persons is quite possible. In
10 considering the special conditions that surround study design and consent processes in
11 such cases, it is important never to lose sight of the need to allow human subjects to
12 participate in the consent process as fully as possible given their individual
13 circumstances. We agree with the National Commission when it noted in the *Belmont*
14 *Report* that respect for persons unable to make a fully autonomous choice "requires
15 giving them the opportunity to choose, to the extent they are able, whether or not to
16 participate in research."¹⁷¹ In this vein, we recognize that certain opportunities already
17 exist for maximizing subject choice in research, including the designation of
18 appropriate substitute decision makers. We also recognize that sensitivity and care
19 must be exercised in establishing policy, lest blanket authority be given to enroll
20 subjects in research without due consideration of the consequences to those subjects.
21 In this chapter we discuss three ways in which individuals may be involved in
22 research, even though they may be presently unable to decide for themselves: the role
23 of assent and dissent when individuals cannot consent on their own behalf; the use of
24 advance planning and surrogate decision making; and the particular functions and
25 authority of legally authorized representatives.

¹⁷¹*Belmont Report*, supra, at 6.

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The Role of Assent and Dissent

The National Commission recommended that, under specified conditions, researchers should obtain *assent* to research participation from subjects incapable of independent decision making. According to the National Commission, 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."¹⁷² The National Commission 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."¹⁷³ 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;¹⁷⁴ 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.¹⁷⁵ 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

¹⁷²Report on Institutionalized Persons, *supra*, at 9.
¹⁷³National Commission, Report on Institutionalized as Mentally Infirm, p. 9.
¹⁷⁴National Commission, IMI, pp. 8-15).
¹⁷⁵An 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.

1 necessary."¹⁷⁶ According to the National Commission, "mere absence of objection"
2 ought not be interpreted as assent.¹⁷⁷ The National Commission recommended
3 requiring the consent of a subject's legal guardian to authorize greater-than-minimal-
4 risk research involving nonobjecting subjects incapable of assent. Whether this
5 situation might be adequately addressed through less formal procedural safeguards, or
6 by imposing special limits on research risks, remains unsettled in the existing
7 literature.

8 Dissent is also important in involving persons in research, regardless of their
9 decisionmaking capacity. The National Commission recommended that an incapable
10 subject's overt objection to initial or ongoing participation should preclude research
11 involvement unless the study offers the subject a prospect of direct benefit *and* a court
12 specifically authorizes the subject's participation, and when the prospective benefit is
13 available solely in the research context.¹⁷⁸

14 In addition, the National Commission recommended procedural mechanisms to
15 ensure application of these substantive provisions. In particular, the report
16 recommended the following: (a) that IRBs should have discretion to appoint an
17 independent auditor to verify the subject's assent or lack of objection; (b) that
18 independent auditors be required to monitor the incapable subject's initial and ongoing
19 assent in research presenting greater-than-minimal risk and no prospect of direct
20 benefit to subjects; and (c) that if subjects object at any time to this category of
21 research, they should be removed from the study.

22 Recent commentary generally supports a requirement for subject assent or, at
23 minimum, lack of objection, except in the unusual case when research participation
24 offers the subject direct medical benefits not otherwise obtainable in the clinical

¹⁷⁶Kapp, *supra*, at 34.

¹⁷⁷Report on Institutionalized Persons, *supra*, at 14.

¹⁷⁸Report on Institutionalized Persons, *supra* at 7-10.

1 setting.¹⁷⁹ Yet not all commentators agree that potential direct medical benefit should
2 be sufficient to override the resistance (whether verbal or behavioral) of persons
3 lacking decisional capacity with regard to research participation.

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

6 Faced with an objection by a patient of impaired
7 capacity, the justification advanced for neverthe-
8 less imposing the investigational intervention is
9 that it holds out the prospect of direct (therapeutic)
10 benefit. However, it is normally not legitimate to
11 impose even established therapy on a patient refusing
12 it. The case for proceeding may be stronger regarding
13 the incompetent . . . patient who objects, but it is
14 difficult to equate an intervention which is investi-
15 gational in nature—whatever its potential for direct
16 (therapeutic) benefit—with an intervention "which
17 would be ordered in a purely therapeutic context."¹⁸⁰

18
19 This group therefore was "not fully persuaded" that potential therapeutic benefit
20 provides an ethical justification for compelling an objecting subject's research
21 participation. In their view, this "is at best a position in need of further debate."¹⁸¹ The
22 current legislative proposal being developed in Maryland would completely bar
23 investigators from conducting research involving a decisionally incapable individual

¹⁷⁹E.g., Berg, *supra*; High & Doole, *supra*; High, et al., *supra*; Melnick, et al., *supra*.

¹⁸⁰ Keyserlingk, et al., *supra*, at 342, quoting Melnick, et al., *supra*.

¹⁸¹ *Id.* at 342.

1 who expresses disagreement with or who refuses to perform an action related to the
2 research.¹⁸²

3 NBAC believes that once subjects become part of a research study, they must
4 always have the opportunity to withdraw at any time without prejudice and without
5 regard to subject capacity. We are persuaded, however, that by imposing too strict a
6 standard of dissent, we might both unnecessarily limit research and fail to accomplish
7 the goal of protection. The following example illustrates this view: consider a study
8 involving certain patients with dementia, in which the only invasive intervention in an
9 otherwise noninvasive long-term study is a single blood draw. Recognizing that some
10 subjects may become irritable and dissent from the procedure—perhaps even actively
11 object, by recoiling from the needle—we are not convinced that this dissent, which
12 must be honored, should be interpreted as an objection to continued participation in
13 the entire study. Certainly the subject has dissented to this portion of the study, at this
14 time. And, as we have noted, this dissent must be respected. Moreover, the researcher
15 who would persist and attempt to take the blood would be acting illegally (by possibly
16 committing battery) and unethically. However, after a reasonable amount of time, the
17 researcher in this study should not be prohibited from returning to the patient and
18 ascertaining his or her willingness to now give blood. We recognize and wish to
19 emphasize that the line between ascertaining willingness and badgering a person is a
20 delicate one to walk.

21 Others have come to a similar conclusion. Keyserlingk and his colleagues
22 observed that one should not assume that a "transient lack of cooperation always
23 signifies objection; instead, '[d]ecisions as to whether a patient is clearly or probably
24 objecting will obviously be a matter of judgment.' "¹⁸³ The intermediate appellate

¹⁸² Office of Maryland Attorney General. *Supra*, at A-23.

¹⁸³ Keyserlingk, *supra*, p. 341. This is an example of the potential value of involving a health care professional as an advisor for such research, a topic we discuss more fully below.

1 court in the *T.D.* case (discussed above) labeled as constitutionally deficient New
2 York's provision allowing the involvement of an objecting incapable subject in
3 potentially therapeutic research because the state regulations failed to provide patients
4 or their representatives notice and an opportunity to challenge this involvement.¹⁸⁴
5 Although the constitutional portion of the judgment was eventually set aside for quite
6 different reasons by the Court of Appeals, these same provisions would also be both
7 ethically objectionable according to the Nuremberg principle, among others, and
8 continue to be legally suspect.

9

10 The Role of Advance Planning and Surrogate Decision Making

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

19 One can identify three types of anticipatory decision making in the clinical
20 setting. The first might be called a projection of informed consent: a competent
21 patient's decision whether to accept or decline a specific future treatment, made now
22 because the person will be decisionally incapacitated when the treatment decision is to
23 be implemented. A commonplace example is a patient's decision whether to have
24 immediate surgery should a biopsy reveal a malignancy. As a result of anesthesia, the
25 patient would be incapable of informed consent when the decision actually presents

¹⁸⁴*T.D. v. New York State Office of Mental Health et al*, 650 N.Y.S. 2d at 193.

1 itself. Yet the patient's anticipatory decision, made prior to the biopsy, is no less an
2 exercise of informed consent. This type of decision making about discrete, future
3 clinical contingencies likewise occurs when a person fills out a living will, the original
4 advance directive document. The typical living will is an instruction that specifies end-
5 of-life interventions not be used in the event of a terminal prognosis. Despite the
6 difficulty in meshing this kind of instruction with what is often a more complex
7 clinical situation, a living will nevertheless can serve as a self-executing embodiment
8 of the person's right to decide about these interventions.

9 The second type of anticipatory decision might be called a projection of
10 personal values, rather than a projection of informed consent. Instead of making a
11 treatment-specific decision meant to bind clinicians in the future, a person provides
12 guidance for decision makers by emphasizing the comparative importance of different
13 aspects of the person's life. For example, a person might state in an advance directive
14 his or her own view of what constitutes a life of sufficient quality to warrant the most
15 aggressive treatment. This guidance would inform whoever was later deciding on a
16 course of treatment after the person lost the capacity for informed consent.

17 The third type of anticipatory decision might be called a projection of personal
18 relationships. Just as someone may entrust another with responsibility for financial
19 matters during a potential period of future disability, a person may designate a
20 decision maker for health care matters. The legal instrument by which this designation
21 is accomplished, the durable power of attorney for health care, has become a familiar
22 feature of the clinical landscape; a recent study found about a nine percent usage rate
23 among residents of nursing homes in several states.¹⁸⁵ This designation reflects trust in
24 the integrity, judgment, and decisiveness of the chosen proxy. Of course, the

¹⁸⁵Teno 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).

1 designation can be coupled with instructions or guidance about the choices that the
2 proxy might face.

3 Because giving effect to all three types of anticipatory decision making
4 embodies respect for personal autonomy, NBAC believes that all three have a place in
5 research involving persons with mental disorders.

6

7 *Informed Consent*

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

13

14 *Personal Values*

15 A person who embodies in an advance directive his or her wishes about
16 participation in research of certain kinds is generally entitled to have those wishes
17 respected. This kind of advance directive, however, cannot itself serve as a self-
18 executing instrument of informed consent and does not absolve the investigator and
19 surrogate decision maker of responsibility for assessing the effect on the person's
20 welfare or participation in particular research.

21

22 *Personal Relationships*

23 A person may embody in an advance directive his or her choice of a decision
24 maker concerning research participation. Because of the trust reposed in the person, a
25 proxy named in a research advance directive ought to have authority to agree to
26 research participation under circumstances closed to other decision makers.

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

6 The concept of advance research decision making was initially discussed in the
7 1980s. In his volume on clinical research, Robert Levine discussed the "research living
8 will" as an avenue for competent persons to authorize their future research
9 involvement while incompetent.¹⁸⁶ In 1987, the NIH Clinical Center adopted a policy,
10 which is currently under review, in which persons "who are or will become cognitively
11 impaired" are asked to complete a durable power of attorney (DPA) document
12 appointing a surrogate research decision maker.¹⁸⁷ Such decision makers may
13 authorize an incapable subject's participation in research presenting greater-than-
14 minimal risk to subjects. In such cases, an ethics consultation is conducted to verify
15 the decision maker's capacity to understand information relevant to the research
16 decision. If no DPA exists, the consent of a court-appointed family guardian is
17 required. The NIH Clinical Center policy deems a subject's prior exercise of choice an
18 acceptable basis for permitting higher-risk research than is otherwise permitted for
19 decisionally incapable subjects lacking court-appointed family guardians.¹⁸⁸

20 In 1989, the American College of Physicians (ACP) gave qualified endorsement
21 to instruction and proxy mechanisms permitting competent persons to register advance
22 consent to research. According to the ACP, investigators seeking advance consent

¹⁸⁶Levine, R., *Ethics and Regulation of Clinical Research* (Baltimore: Urban and Schwarzenberg, 2nd ed., 1986) 270-74.

¹⁸⁷Subjects "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*.

¹⁸⁸Research presenting greater-than-minimal risk is not permitted for subjects lacking a DPA or court-appointed family guardian.

1 would be required to disclose to the competent person the usual information on a
2 study's purpose, methods, risks, and potential benefits. Moreover, the ACP recognized
3 a need for more caution regarding advance research decisions than advance treatment
4 decisions:

5 In nonexperimental care, advance directives are
6 generally used by patients to indicate their intent
7 to refuse procedures . . . which they believe will be
8 contrary to their interests. Respect for autonomy
9 creates a strong presumption for adherence to
10 instructions for nonintervention. In contrast,
11 advance directives for research purposes would
12 authorize interventions that do not benefit the
13 subject in the case of nontherapeutic research, or
14 that may not benefit the subject in the case of
15 therapeutic research.¹⁸⁹

16 Accordingly, the ACP took the position that research advance directives "may be
17 abrogated if it is later determined that the proposed research would unduly threaten the
18 subject's welfare."¹⁹⁰

19 Despite these cautions and restrictions, the ACP deemed an incapable subject's
20 prior consent an acceptable basis for allowing that subject's involvement in higher-risk
21 research than is permitted for other incapable subjects. The ACP position paper states
22 that incapable subjects who have given only informal instructions to a surrogate
23 decision maker about their research preferences should not be involved in greater-
24 than-minimal risk research offering no prospect of direct benefit. In contrast, subjects

¹⁸⁹ American College of Physicians, *supra*, at 844.

¹⁹⁰ 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.

1 with formal advance directives may be involved in such studies, as long as the above
2 limitations are observed. We are sympathetic to this approach.

3 Other groups and commentators have expressed general support for advance
4 research decision making without addressing the concept in detail.¹⁹¹ In reviewing the
5 advance directive's potential application to dementia research, Greg Sachs speculates
6 that it is unlikely that many individuals will prepare research directives. He notes that
7 relatively few people make treatment directives, even though many fear excessive
8 treatment at the end of life. Even fewer will make research directives, he predicts,
9 because "the fear of missing out on being a subject in a promising dementia study, or
10 of being inappropriately volunteered by one's relatives, is simply not a prevalent or
11 powerful concern."¹⁹²

12 Federal policy establishes stringent disclosure requirements for investigators
13 recruiting competent persons for research. An individual considering whether to
14 authorize future research participation ought also to be informed about any
15 prospective study being contemplated.

16 In light of these possibilities, many commentators agree that a third party
17 decision maker should be appointed to withdraw the subject from a study if previously
18 unrecognized risks and burdens become apparent.¹⁹³ They differ, however, on the

¹⁹¹E.g., Melnick, et al., *supra* (endorsing research directives and implying that such documents could authorize otherwise questionable research presenting more-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).

¹⁹²Sachs, *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.

¹⁹³See, 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).

1 standard that third parties should apply when exercising the subject's right to withdraw
2 from the research that the subject previously authorized.

3 Some favor withdrawal only when the factual circumstances become materially
4 different from those to which the individuals agreed in directives.¹⁹⁴ Others contend
5 that withdrawal should also occur if it becomes apparent to others that research
6 participation threatens the incapable subject's welfare. According to this position, a
7 research proxy's or surrogate's

8 obligation to respect the person's prior wishes is
9 limited by the obligation to protect the person. The
10 function of the [third party decision maker] is to
11 promote what subjects think are their best interests,
12 which necessarily excludes consenting to being
13 intentionally harmed or to being unreasonably exposed
14 to the risk of harm.¹⁹⁵

15
16 An intermediate position is presented by the Canadian group which argues that
17 an advance directive should be overridden if “no direct benefit” is anticipated for the
18 subject and it becomes apparent that enrollment or continued participation would
19 seriously endanger that subject's welfare to an extent not foreseen by the subject, or
20 even if foreseen, to an extent judged by the substitute [decision maker] to be socially
21 or morally unacceptable".¹⁹⁶ This dispute is related to disagreement on the appropriate
22 scope of a competent person's advance consent to research. Commentators are divided
23 on whether policy should permit an incapable subject to be exposed to otherwise

¹⁹⁴Berg, *supra*, at 22 (surrogate has responsibility to withdraw subject only if research or risk-benefit ratio changes substantially from what subject consented to).

¹⁹⁵Moorhouse & Weisstub, at 135. See also Shamoo & Sharev, *supra*, at S:29 (advance directives should not bind a subject to research participation).

¹⁹⁶Keyserlingk, *supra*, p. 352.

1 impermissible levels of research risks and burdens based on the subject's prior
2 instructions. Moorhouse and Weisstub contend that directives should be restricted to
3 authorizing research "with a negligible or less than substantial risk."¹⁹⁷ Their position
4 is based on the belief that capable individuals cannot predict with complete accuracy
5 how they will experience research as incapable subjects. These authors also argue that
6 the competent individual's freedom to volunteer for research to advance the interests
7 of others is qualified by society's responsibility to protect vulnerable individuals from
8 material harm.

9 Addressing dementia research, the Canadian group proposes that research
10 directives should apply to studies offering no direct benefit to subjects only if the risk
11 is minimal or a minor increase over minimal.¹⁹⁸ They suggest one exception to this
12 limit, however: "[i]f a subject who provides a directive specifying a willingness to
13 undergo a higher-risk level also provides evidence of having already experienced a
14 similar level of physical or psychological pain or discomfort in another research
15 setting, then the cap of allowable risk for that subject could be raised accordingly."¹⁹⁹

16 Berg, on the other hand, supports full implementation of advance research
17 directives without regard to the risk level. She argues, "[b]ecause competent subjects
18 do not have limits placed on the types of research in which they can participate while
19 they remain competent (as long as the protocol is approved by an appropriate review
20 board), they should not have limits placed on the types of research in which they can
21 consent, in advance, to participate should they become incompetent."²⁰⁰ Conversely,
22 when an advance directive refuses research participation, Berg suggests that the
23 subject's refusal could be overridden if a study offers possible direct benefit
24 unavailable in the clinical setting. She fails to explain why concern for the incapable

¹⁹⁷Moorhouse & Weisstub, *supra*, at 134.

¹⁹⁸Keyserlingk, et al., *supra*, at 351.

¹⁹⁹*Id.*

²⁰⁰Berg, *supra*, at 22.

1 subject's best interests justifies disregarding his directive in one situation and not the
2 other.

3 A few public policy developments are also relevant. In 1996, the Food and Drug
4 Administration adopted new regulations governing research involving incapable
5 subjects in the emergency setting.²⁰¹ The regulations allow research to proceed in the
6 absence of consent by a subject or a legally authorized representative, under certain
7 conditions. An IRB may approve such research if it finds and documents that there is
8 no reasonable way to identify prospectively the individuals likely to become eligible
9 for participation; the subjects are in a life-threatening situation and due to their
10 medical condition subjects cannot give their informed consent; the intervention must
11 be administered before consent from a legally authorized representative is feasible;
12 available treatments are unproven or unsatisfactory; the research is necessary to
13 determine the safety and effectiveness of some new therapies; and various other
14 conditions are met. According to agency officials, when IRBs determine that
15 investigators can reasonably identify and seek prospective consent from persons likely
16 to become eligible for a study, "[t]hose individuals who either did not make a decision
17 or who refused would be excluded from participation in the investigation."²⁰² In
18 response to a public comment describing "the difficult task for potential subjects to
19 imagine the kind of research they would want should they suffer a catastrophic
20 illness," officials acknowledged possible difficulties in implementing the prospective
21 decisionmaking process, but suggested that IRBs could adequately address these
22 matters.²⁰³ As has been noted, this is a problem that applies to all advance directives
23 for research participation.

²⁰¹21 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).

²⁰²Id.

²⁰³Id.

1 The State of Maryland has initiated a policy effort relevant to advance research
2 decision making. The draft legislation includes a framework for third party decisions
3 on research for decisionally incapacitated persons—i.e., research is permitted with
4 consent of an incapable subject's "legally authorized representative." Unlike current
5 federal policy, this proposal specifies who may fill this role. Subject representatives
6 may be, in the following priority order: (1) a research agent designated in an advance
7 directive for research; (2) a health care agent designated in an advance directive for
8 treatment; (3) a surrogate—that is, a family member or close friend—authorized by
9 statute to make health care decisions for an incapable person; or (4) a proxy decision
10 maker designated by the IRB to act as a research decision maker for an incapable
11 person.²⁰⁴

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

19 The Maryland draft legislation also recognizes a limited role for instruction
20 directives. A monitor may consent to an incapable individual's participation in research
21 presenting minimal risk and no direct benefit if the individual's advance directive
22 explicitly authorizes such participation. A research agent may permit an incapable
23 subject to be involved in research presenting more than a minor increase over minimal
24 risk only if "the research is unambiguously included in the individual's advance

²⁰⁴Office of the Maryland Attorney General, *supra*, Parts VI, VII, VIII, & IX.

1 directive authorizing research participation."²⁰⁵ Thus, otherwise prohibited research
2 risk is permitted based on the prior competent choice of a now incapable subject.

3 The Maryland draft legislation does not discuss the information that must be
4 disclosed to a capable person making an advance research directive. Withdrawal from
5 research is addressed, however. Any third party consenting to an incapable subject's
6 participation must

7 (1) take reasonable steps to learn whether the
8 experience of the individual in the research is
9 consistent with the expectations of the legally
10 authorized representative at the time that consent was
11 granted, including expectations about potential benefits,
12 if any, and risks presented by the research; and

13 (2) withdraw consent if:

14 (i) the research was initially determined to
15 present a reasonable prospect of direct medical
16 benefit to the research subjects but no longer
17 does so for the individual;

18 (ii) the research presents a higher level of risk to
19 the individual than initially expected; or

20 (iii) considering all relevant circumstances,
21 continued participation would be detrimental
22 to the individual's well-being.²⁰⁶

23 Advance research decision making has been widely discussed in the literature
24 and included in some recent state-based policy initiatives. Numerous conceptual and
25 practical questions remain unresolved, however. The matter could be made moot if

²⁰⁵Id. at A-32.

²⁰⁶Id. at A-26.

1 very few persons prepare research directives and if rigorous standards for information
2 disclosure are observed. Further, even in the best circumstances, investigators and
3 IRBs face challenges in providing competent individuals with all the necessary
4 information about a future study. Finally, the literature reveals disagreement on the
5 significance policy should assign to the competent individual's preferences about
6 future research participation posing more-than-minimal risk to incapable subjects.

7 In sum, advance research decision making, although recognized as a potentially
8 useful device, poses difficult issues concerning its scope and effect. In our view, an
9 advance directive can *never* serve as a "blank check" for future research participation.
10 Indeed, an advance directive may itself serve as a sufficient basis for research
11 participation only in very limited circumstances: those in which the most important
12 information relevant to informed consent—e.g., the nature of the procedures and
13 risk—about future research participation is already known and presented to a
14 competent person, the person gives consent, and there is no material change in the
15 research protocol or the person's clinical situation (apart from loss of decisionmaking
16 capacity) by the time that research participation is actually to begin. If the person's
17 willingness to participate in research is stated more broadly—for example, in terms of
18 a desire to participate in research about a disease—that statement should be given
19 respectful attention by whoever has authority to consent to research participation, but
20 it cannot by itself be considered sufficient warrant for enrollment in a particular study.

21

22 Representatives and Research Decision Making

23 Surrogate decision makers are frequently mentioned as one solution to ethical
24 problems of enrolling persons from certain vulnerable groups in research. In its recent
25 report on "Research Involving Individuals with Questionable Capacity to Consent,"
26 the 1998 NIH panel concluded that "Individuals with questionable capacity (or clear
27 incapacity) to consent may have a family member and/or legally authorized

1 representative serve as a surrogate, with this role documented during the consent
2 process.” The panel further recommended that the surrogate’s research decisions
3 should reflect, to the greatest extent possible, the individual’s views prior to the period
4 of incapacity.²⁰⁷

5 Although the term “surrogate” is frequently used in ethical discussions such as
6 that of the NIH report, the Common Rule uses the phrase “legally authorized
7 representative.” This concept (the LAR) leaves many unanswered questions.
8 Surrogates may be regarded as individuals who have had prior experience with the
9 individual being represented, but legally authorized representatives (for example, legal
10 guardians) often do not have such experience. State laws in a broader arena contain
11 general provisions on the standards and procedures governing appointment of
12 guardians for persons declared legally incompetent. Guardianship, for example,
13 requires a judicial proceeding and ordinarily authorizes someone to make financial
14 decisions, personal decisions, or both types of decisions for the incompetent person.
15 Limited guardianships covering a narrower area of decisionmaking responsibility are
16 also possible.

17 As we have mentioned earlier, however, relatively few states have laws
18 specifically addressing the area of research decision making by legal guardians or
19 other allowable surrogates. Moreover, existing state legislation limits the involvement
20 of incapable subjects in research in various ways; a number of laws require guardians
21 to obtain specific court authorization to make decisions on a ward's participation in a
22 research protocol. Several states currently prohibit certain types of research on persons
23 with mental disorders, research which presents greater than minimal risk and from
24 which subjects are not likely to benefit. Wichman notes that if an IRB were to approve

²⁰⁷National 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.

1 a study in a state which did not have such a statute, the IRB might choose to invoke
2 certain protections, including additional monitoring of the study, requiring a consent
3 auditor, or requiring educational activities for authorized representatives.²⁰⁸

4 Federal research policy is not intended to preempt or otherwise affect state or
5 local laws applying to research, including those conferring additional protection on
6 subjects participating in research protocols.²⁰⁹ Thus, investigators and IRBs in
7 jurisdictions with specific laws governing the identity and authority of research
8 decision makers for persons lacking decisional capacity must comply with that law.
9 Yet in the many states without clear law, it will be left to federal policy, investigators,
10 and IRBs to determine who, if anyone, may act as a surrogate decision maker for a
11 person who lacks decisional capacity. At present, legal guardianship is rarely, if ever,
12 sought in the research setting. Instead, close family members, who may or may not
13 have formal guardianship status, are the customary decision makers when the research
14 participation of incapable adults is sought.

15 Should federal policy require formal legal guardianship for one to be considered
16 a suitable surrogate for decision making about research? The underlying question is
17 whether such a requirement is necessary or sufficient to provide adequate protection
18 against inappropriate research use of a vulnerable population to advance the interests
19 of others. The National Commission recommended that the permission of either a
20 legal guardian or a judge be required to authorize the research participation of subjects
21 institutionalized as mentally infirm in the following situations: the incapable subject
22 objects to participation; or the subject is incapable of assent, and the research presents
23 more-than-minimal risk to subjects.²¹⁰

²⁰⁸ Ibid. pp. 94-95.

²⁰⁹ Common Rule, Sec. ____ .101(f).

²¹⁰ National Commission Report, 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,

1 Subsequent commentary by others questions whether formal legal proceedings
2 are necessary to provide adequate protection for subjects who lack capacity,
3 particularly those not residing in an institutional setting. As one writer notes, IRBs
4 requiring legal guardianship "to be on the safe side" could end up contributing to a
5 deprivation of general decisionmaking rights of subjects.²¹¹ Moreover, the guardian
6 appointment process ordinarily will not address research participation issues in any
7 explicit way. In most cases, a judicial decision to confer guardianship status on a
8 particular person is made without consideration of that person's suitability to make
9 decisions regarding their ward's participation in research protocols.

10 Dissatisfaction with a requirement for legal guardianship has led to alternative
11 proposals for granting authority to act as an incapable person's representative in
12 research decision making. One option, referred to previously, is to allow decisionally
13 capable persons to authorize in advance a specific individual to make decisions
14 regarding their research participation during a future period of incapacity. This device,
15 which is modeled on the durable power of attorney for health care, has the virtue of
16 promoting the capable individual's autonomous views on who is best suited to act on
17 his or her behalf in the research context. Its primary advantage, though, is the explicit
18 authority granted by the subject, who presumably will choose someone likely to
19 express their values and protect their welfare. As we have said, intramural research at
20 the National Institutes of Health Clinical Center is governed by a policy that
21 encourages this approach, and the American College of Physicians and numerous

unnecessarily adversarial, and too great an impediment to research. Berg, Legal and Ethical Complexities of Consent with Cognitively Impaired Research Subjects: Proposed Guidelines, 24 J. L. Med. & Ethics 18 (1996); Kapp, Proxy Decision Making in Alzheimer Disease Research: Durable Powers of Attorney, Guardianship, and Other Alternatives, 8 Alzheimer Disease & Related Disorders. 28 (Supp. 4, 1994).

²¹¹Office of 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").

1 others express support for use of these instruments.^{212, 213} As a practical matter,
2 however, it is unclear whether many individuals will be interested in or willing to
3 complete such a DPAs.²¹⁴ Moreover, the device cannot be applied to the population of
4 persons with mental disorders who are currently incapable and not expected to recover
5 capacity.

6 A second potential source of authority is an existing health care power of
7 attorney. It is doubtful that an individual's choice of a proxy to make treatment
8 decisions in the event of incapacity can fairly be taken as an authorization for
9 research decision making as well. Nevertheless, the choice does manifest a high
10 degree of trust in the proxy, and that evidence of trust may entitle the health
11 care proxy to a decisionmaking role in research. The NIH Clinical Center policy does
12 allow previously chosen health care proxies to make research decisions for subjects.²¹⁵

13 A third alternative is to recommend state legislation authorizing family
14 members (and, in a few states, friends) to make certain treatment decisions on behalf
15 of relatives as conferring authority for research decisions as well. It might be argued
16 that such legislation embodies a recognition that important health-related decisions for
17 persons lacking decisional capacity are properly assigned to appropriate relatives.
18 Perhaps it would be reasonable to extend the law's application to a statutory proxy's
19 decision regarding research offering potential health benefit to an incapable subject.²¹⁶
20 Others believe that these laws should not be interpreted so expansively and that

²¹²Fletcher & Wichman, A New Consent Policy for Research With Impaired Human Subjects, 23 *Psychopharm. Bull.* 382 (1987); NIH Clinical Center, Consent Process in Research Involving Impaired Human Subjects (Mar. 30, 1987). If no relative or friend is available, prospective subjects may designate the Center's patient representative or a chaplain, or social worker not assigned to the research unit.

²¹³American College of Physicians, *supra*. See also Kapp, *supra*; Melnick, et al., *supra*.

²¹⁴See High & Doole, *supra*.

²¹⁵NIH Clinical Center, *supra*.

²¹⁶Bonnie, *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).

1 amendments or new legislation would be required to provide explicit statutory
2 authority for delegating to relatives decisions about the subject's participation.²¹⁷

3 A final possible option is to assign such decisionmaking authority based on the
4 simple status of being a close relative. Support for this alternative comes from the
5 long-held tradition in health care of relying on families to make decisions for incapable
6 persons, as well as from the belief that relatives are most likely to make decisions in
7 accord with the incapable person's values, preferences, and interests.²¹⁸ This approach
8 is easy to administer; moreover, it apparently has been and continues to be a common
9 practice in many actual research settings.²¹⁹

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

²¹⁷Kapp, *supra*.

²¹⁸This 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").

²¹⁹Kapp, *supra*; High & Doole, *supra*.

1 All of these alternatives also raise questions about the accuracy with which
2 incapable subjects' values and preferences as competent persons will be expressed by
3 formal or informal representatives.²²⁰ The problem of potential conflicts of interest
4 between subjects' interests and those of their representatives exists as well. Those most
5 likely to act as representatives are family members, who may see the subject's research
6 participation as an avenue "that may lighten the burden of caregiving or lead to
7 treatment from which the family member may benefit."²²¹ Two empirical studies found
8 some family members willing to allow an incapable relative to be entered in a research
9 study even though they thought the relative would refuse if competent. Some family
10 members also stated they would allow an incapable relative to become a subject even
11 though they would refuse to enroll in such a study themselves.²²² At the same time, we
12 recognize many of the potential advantages that such mechanisms might offer to
13 permit important research to go forward. Moreover, we are satisfied that the argument
14 for expanding the authority of the LAR is sound so long as the following components
15 are in place, which we describe in more detail below: (1) a clear description of the role
16 and authority of the LAR, (2) a description of certain protections that must be in place
17 in order for an IRB to assure itself that the LAR is appropriately acting on behalf of
18 the incapable persons, and (3) a commitment on behalf of both the public and research
19 communities to carefully study and report on the experience of using LARs in this
20 way.

21

22 *The Authority of the LAR*

²²⁰See 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").

²²¹Keyserlingk, et al., supra, at 346.

²²²Sachs, 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.

1 We recognize that there are two mechanisms by which a LAR can be involved.
2 One option might be to allow individuals, while competent to designate their legally
3 authorized representative, to give permission to enroll them in research. This scenario
4 requires the designation of an individual whose authority is limited to research
5 involvement. Given the paucity of experience with research-specific LARs in this
6 country, we recognize the burden that might be created by recommending that only
7 this method be used. Another option would be to permit existing DPAs (the many
8 thousands of individuals who have already been appointed in this country to be health
9 care decision makers for clinical decisions) to make certain research decisions. For
10 both mechanisms, the authority of the LAR would need careful description.

11 Three forms of substantive limitations on this authority are commonly
12 endorsed. One is to allow guardians, proxies, and informal surrogates to give valid
13 consent to studies if the incapable subject assents or fails to object to initial or ongoing
14 research participation. The second is to require that third parties make research
15 decisions consistent with the incapable subject's prior instructions issued while
16 competent. The third is to permit subject representatives to authorize the involvement
17 of incapable subjects only in studies that meet certain risk-potential benefit standards.
18 Many of the recommendations on research involving persons with mental disorders
19 apply each of these limits, but combine them in a variety of ways.

20 NBAC's view is the following: for research involving a person with a mental
21 disorder, a LAR may authorize research participation in greater than minimal risk
22 research, even if that research does not hold out the prospect of direct benefit to the
23 subject, provided
24 d that an IRB has assured itself that certain protections are in place and are being
25 monitored for compliance by the IRB and others as described below.

26

1 *Protections to Ensure That The LAR Is An Ethically Valid Surrogate for Research*
2 *Decision Making*

3 Given the limited experience with using research-specific LARs (or for
4 extending existing health care DPAs to research) in this country, we are
5 understandably reluctant to recommend their adoption without also recommending
6 certain protections and methods for their evaluation be put in place. In general, we
7 regard the IRB as the proper locus for determining whether these (or any other)
8 protections are adequate. For IRBs to be assured that the enrollment by an LAR of a
9 now incapable person with a mental disorder into a research study is acceptable, the
10 IRB might consider requiring certain procedures to have taken place in the process of
11 documenting that the LAR is engaged in an ethically valid decision.

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

16 (b) Requiring documentation that the subject and LAR understood the scope of
17 the authority being granted to the LAR. Because of our concern that LARs may have
18 some significant self interest in enrolling a now incapable person into a study, we
19 would favor a process where the designation of an LAR was documented. The
20 documentation we refer to here would enable IRBs to satisfy themselves that the now
21 incapable subject and his LAR had reasonably understood the scope of the type of
22 study being proposed. This places considerable emphasis on the degree to which the
23 IRB is assured that the prospective subject (when competent) and his designated LAR
24 understood the difference between research and therapy, and between research that
25 imposes a greater than minimal risk which is with and without the prospect of direct
26 benefit to the subject. As we note below for each of the two other protections listed,
27 the value of this particular protection is in need of empirical testing and validation.

1 With regard to the standard by which substitute decisions are made, NBAC
2 favors, in general, giving first priority to those decisions by LARs that approximate
3 most closely the now incapable subject's previously expressed preferences. In the
4 absence of this information, LARs would be expected to make judgments which are
5 consistent with the subject's best interests. We are acutely aware of the difficulties this
6 approach presents and explain our rationale in somewhat more detail in Chapter 5
7 below. Here we are only indicating our general view since it relates directly to the
8 assignment of LARs and the protections associated with this. We would expect IRBs
9 to carefully scrutinize LAR decisions on behalf of now incapable subjects: the greater
10 the risk in the study, the more IRBs should require of the LAR that the substitute
11 decision approximates the subject's preferences.

12 c) Monitoring of the process of designating the DPA. It has been suggested that
13 a further protection would involve designating a person to monitor the LAR
14 designation.

15

16 *Ongoing Evaluation of LARs*

17 We wish to emphasize that the protections listed above could provide the IRB
18 some assurance that the LAR has been assigned in a legally and ethically valid way.
19 However, we also believe that ongoing assessment of the LAR process would be of
20 considerable value. IRBs intending to permit enrollment of a now incompetent subject
21 on the basis of LAR decisions (regardless of how well documented this process might
22 be) would be strongly encouraged to evaluate the effectiveness of LARs. Such
23 evaluation may be considered as part of the procedural requirement that institutions
24 utilize under the mechanisms of audit and disclosure, which we discuss in more detail
25 below. We believe there would be considerable value having IRBs report on those
26 studies involving greater than minimal risk research in which enrollment of
27 decisionally incapable subjects with mental or brain disorders was authorized by an

1 LAR. We also wish to stress that in the absence of good empirical data about the
2 effectiveness of the LAR mechanism in both permitting scientifically valuable research
3 to go forward and, at the same time, ensuring appropriate protections from research
4 harm, we cannot fully endorse it without reservation. Therefore, we would strongly
5 encourage the research community, led by NIH (in view of its experience with
6 research DPAs), to support research on the appropriate use of research DPAs. We
7 would also encourage research which assesses the extent to which clinical DPAs can
8 be extended to include research decision making.

9

1 Independent Professional Support for Subjects and Surrogates

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

8 One way to provide intellectual and emotional support to these individuals is by
9 ensuring that an independent and appropriately skilled health care professional (e.g.,
10 physician, nurse, social worker) is available as an advisor for each research participant
11 or their surrogate. This independent advisor should not be involved with the study and
12 preferably should have had a previous relationship with the potential subject. Subjects,
13 or their representatives if subjects lack capacity, should be able to choose their
14 responsible health care professionals. The advisor's role would be to help a potential
15 subject and representative decide whether participation in a particular research
16 protocol is a good choice for that subject. For persons who are incapacitated and
17 whose research participation is contemplated, the health care professional could be an
18 invaluable consultant to the legally authorized representative. Often this professional
19 will be a physician; however, other professional caregivers may serve the same role—a
20 nurse-clinician or a social worker, for example. The basic requirement is that such
21 caregivers be familiar with the patient, understand the nature of the research protocol,
22 not be part of the research team, and, if feasible, not part of the organization
23 conducting the research. We would not expect, of course, that the health care
24 professional be required for all research involving persons with mental disorders, but
25 would be required where the patient lacks capacity to decide or is expected to lose
26 capacity during the course of the study.

1 The British Law Commission recommended a similar system to the House of
2 Commons in 1995, though their proposal applied only to individuals who lack
3 capacity. They wrote: “In most cases the appropriate person to carry out an
4 independent check [on research participation] will be a registered medical practitioner
5 who is not involved in the research project. . . . The doctor who knows the person best,
6 by virtue of having responsibility for his or her general medical care, will often be the
7 best candidate.”²²³ The Maryland proposal assigns this responsibility to a “medically
8 responsible clinician” if research involves withdrawing a group of decisionally
9 incapacitated subjects from a standard treatment or otherwise presents more than
10 minimal risk. ²²⁴ At the very least, it seems sensible for a legally authorized
11 representative to have access to an independent health care professional advisor before
12 entering an individual into a research protocol.

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

²²³The Law Commission, “Mental Incapacity: Item 9 of the Fourth Programme of Law Reform: Mentally Incapacitated Adults” (London, England: House of Commons, 1995), p.101.

²²⁴Office of the Maryland Attorney General, *supra*, p. A-19.

1 Chapter Five: THE ASSESSMENT OF RISK AND POTENTIAL BENEFIT

2

3 The Common Rule directs IRBs to ensure that research risks are minimized
4 through careful study design, and that they are "reasonable in relation to anticipated
5 benefits, if any, to subjects, and the importance of the knowledge that may reasonably
6 be expected to result."²²⁵ These are among the provisions that govern research
7 involving all human subjects. Many commentators and organizations, as well as the
8 conclusions presented in international documents described earlier, favor placing
9 additional constraints on acceptable risks in research involving persons who, as a
10 result of having certain mental disorders, may sometimes lack decisionmaking
11 capacity.

12 In this chapter, we discuss some of the conceptual and practical problems that
13 arise not only for IRBs, but also for investigators and potential subjects who also must
14 make judgments about the acceptability of risk in relation to the prospect of benefit.
15 First we discuss some of the difficulties inherent in defining risk and then explain our
16 rationale for urging IRBs to consider evaluating research involving this population as
17 falling within two categories of risk: minimal risk, and greater than minimal risk. Then
18 we discuss some of difficulties in defining benefit. Finally, we comment on the
19 problem of assessing research risks in relation to potential benefits to subjects and, in
20 particular, on distinguishing between research involving greater than minimal risk that
21 holds out the prospect of potential benefit to the subject, and research involving
22 greater than minimal risk that does not hold out the prospect of potential benefit to the
23 subject. In the final section of this chapter, we also discuss and propose procedures to
24 minimize risks to subjects.

25

²²⁵Sec. ____ .111(a).

1 Defining and Assessing Risk

2 The *concept of risk* is generally understood to refer to the combination of the
3 probability and magnitude of some future harm occurring. According to this
4 understanding, risks are considered "low" or "high" depending on whether they are
5 more (or less) likely to occur, and whether the harm is more (or less) serious. In
6 research involving human subjects, risk is a central organizing principle, a filter
7 through which protocols must pass: research evaluated by IRBs that present greater
8 risks to potential research subjects will be expected to include greater (or more
9 comprehensive) protections designed to limit the possibility of harm occurring. The
10 ethical basis for this position was usefully summarized in the National Commission's
11 *Belmont Report*: "The requirement that research be justified on the basis of a
12 favorable risk/benefit assessment bears a close relation to the principle of beneficence,
13 just as the moral requirement that informed consent be obtained is derived primarily
14 from the principle of respect of persons."²²⁶ In contrast, relatively little progress has
15 been made to describe the *criteria for assessing risk* by IRBs.²²⁷²²⁸ In large part this is
16 due to the difficulties inherent in rigidly classifying risk judgments; specifically, the
17 difficulty in accurately quantifying risks, in reducing complex judgments that attempt
18 to accommodate one's perception of risk to a single category,²²⁹ in incorporating the
19 subjective values of those who make these judgments,²³⁰ and other concerns.

20 The purpose of having multiple categories of risk is to trigger different
21 requirements on the part of IRBs, and we appreciate that there may be some intuitive
22 sense that having several levels of risk may make the task of IRBs somewhat easier.

²²⁶*Belmont Report*, p. 6.

²²⁷Shannon TA, Ockene IS, and Levine RJ. Approving high risk, rejecting low risk: the case of two cases. *IRB* 7 (January-February 1985): 7-8.

²²⁸Meslin, EM. Risk judgments by IRBs: *IRB*.

²²⁹Slovic, P. Perception of risk. *Science* 236 April 1987: 149-170.

²³⁰Schrader-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.

1 “Minimal” and “greater than minimal” risks do trigger different protections in the
2 Common Rule. We do not think it is necessary, however, to recommend that the
3 Common Rule be amended to provide IRBs with three levels of risk to use when
4 assessing risk in relation to potential benefit. As we will state in Chapter 6, we
5 recommend only that IRBs **consider** adding protections above the minimal regulatory
6 requirements for research involving greater than minimal risk. Our reasons are based
7 both on our belief that IRBs already have considerable discretion to assess the
8 acceptability of risk and, therefore, to require the appropriate protections, and on our
9 understanding of some of the inherent difficulties in clearly defining and consistently
10 applying particular risk categories.

11

12 *Minimal Risk and Greater than Minimal Risk*

13 According to the Common Rule, a study presents minimal risk if "the
14 probability and magnitude of harm or discomfort anticipated in the research are not
15 greater in and of themselves than those ordinarily encountered in daily life or during
16 the performance of routine physical or psychological examinations or tests."²³¹
17 Although the concept of minimal risk remains a controversial one in academic and
18 scholarly discussion, it is in widespread use in order to determine which set of
19 protections are to be required for particular research protocols. Still, we understand
20 that the application of these terms in practice can be difficult operational tasks. For
21 example, a "typical" minimal risk encountered in everyday life or in clinical care may
22 be perceived rather differently by some individuals with certain mental disorders). For
23 NBAC, the most salient issue is describing carefully that the level at which the "bar"
24 of minimal risk is set will determine how many projects are seen by IRBs to require
25 additional protections. Currently, IRBs have complete discretion to apply none or only

²³¹Sec. 102(i).

1 some of the added protections to protocols that they believe to be of greater than
2 minimal risk. This bar cannot of course be set for all time, because experience and
3 new knowledge will change how the research community, IRBs, and research subjects
4 perceive the acceptability of various research risks.

5 The DHHS addressed this issue in its regulations on research involving children
6 by permitting IRBs to approve research presenting no more-than-minimal risk as long
7 as requirements for parental permission and child assent are satisfied. The regulations
8 stipulate that studies presenting greater-than-minimal risk, on the other hand, must
9 meet additional requirements.

10 Like the current DHHS regulations on research involving children, many
11 proposals on research involving impaired or incapable adults employ the concepts of
12 minimal risk and minor increase over minimal risk. Indeed, we have received a
13 number of comments from the public suggesting that NBAC recommend grouping
14 research involving persons with mental disorders into three categories of risk: minimal
15 risk, minor increment over minimal risk, and greater than minimal risk (which we
16 understand to mean, risks greater than a minor increment over minimal risk). The
17 Common Rule does not specify that IRBs should (or be expected to) use three
18 categories of risk in making judgments about the acceptability of a set of risks in
19 relation to certain potential benefits, nor do the specific additional regulations relating
20 to pregnant women²³² or to prisoners.²³³ Only the regulations pertaining specifically to
21 children describe three categories of risk.²³⁴ Giving real substance to these concepts, as
22 noted above, poses serious practical difficulties. The Common Rule's minimal risk
23 definition is tied to the risks of ordinary life and medical care encountered by the
24 population as a whole. The minimal risk concept often is praised for its flexibility: "It

²³²45 CFR 46.201.

²³³45 CFR 46.301.

²³⁴45 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.

1 is inescapable and even desirable that determinations of risk level (and its acceptability
2 when balanced with benefit consideration) are matters of judgment rather than detailed
3 definition, judgments which are patient-specific, context-specific, and confirmed after
4 consideration and debate from many points of view."²³⁵ On the other hand, the
5 concept's reference to "risks of everyday life" is supported as conveying a defensible
6 normative judgment that the sorts of risks society deems acceptable in other contexts
7 may be acceptable in research as well.²³⁶

8 In contrast to the minimal risk concept's reference to the life and medical
9 experiences of the overall population, the concept of minor increase over minimal risk
10 is tied to the prospective subject's individual situation. Because persons with mental
11 disorders undergo treatment and tests involving some discomfort and risk, a study
12 presenting similar procedures and potential for harm may qualify as presenting a minor
13 increase over minimal risk to them.²³⁷ For subjects not accustomed to or in need of
14 such medical interventions, however, the same study could present a higher level of
15 risk.

16 In its *Report on Research Involving Children*, the National Commission
17 defended this approach to more-than-minimal risk research on grounds that it
18 permitted no child to be exposed to a significant threat of harm. Further, the National
19 Commission noted that the approach simply permits children with health conditions to
20 be exposed in research to experiences that for them are normal due to the medical and
21 other procedures necessary to address their health problems. An example is

²³⁵Keyserlingk, et al., *supra*, at 329.

²³⁶Freedman, 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.

²³⁷The 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.

1 venipuncture, which may be more stressful for healthy children than for children being
2 treated for a medical condition who are more accustomed to the procedure.

3 Commentators have criticized both the Common Rule's "minimal risk"
4 definition, and the category "minor increase over minimal risk" in the children's
5 regulations. Loretta Kopelman provides perhaps the most detailed critique. First, she
6 finds the notion of "risks of ordinary life" too vague to provide a meaningful
7 comparison point for research risks. Ordinary life is filled with a variety of dangers,
8 she notes, but "[d]o we know the nature, probability, and magnitude of these
9 'everyday' hazards well enough to serve as a baseline to estimate research risk?"
10 Second, though the comparison to routine medical care furnishes helpful guidance
11 regarding minimal risk, it fails to clarify whether procedures such as "X rays,
12 bronchoscopy, spinal taps, or cardiac puncture," which clearly are not part of routine
13 medical care, could qualify as presenting a minor increase over minimal risk for
14 children whose health problems dictate they must undergo these risky and burdensome
15 procedures in the clinical setting. Kopelman argues that the phrase "minor increase
16 over minimal risk" should be replaced or supplemented by a clearly defined upper
17 limit on the risk IRBs may approve for any child subject.²³⁸

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

²³⁸Kopelman, 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.

1 intending to make the relevant comparison point out the risks ordinarily encountered
2 by the prospective research subject. This approach would allow classifying research
3 risks as minimal if they were reasonably equivalent to those the subject encountered in
4 ordinary life or routine medical care. Using this approach with persons with mental
5 disorders who face higher-than-average risks in everyday life and clinical care, a
6 research intervention could be classified as minimal risk for them, but classified as
7 more-than-minimal risk for healthy persons. If this was the intention of the drafters of
8 the regulations, it is not at all clear in the current Common Rule.

9 In July 1997, the Canadian Tri-Council Working Group developed a “Code of
10 Ethical Conduct for Research Involving Humans” that explicitly adopts the standard of
11 relativizing risk to the potential subject in question, but with a caveat. It defines
12 “normally acceptable risk” as “when the possible harms (e.g., physical, psychological,
13 social, and economic) implied by participation in the research are within the range
14 encountered by the participant in everyday life. . . .”²³⁹ The Canadian code goes on to
15 state: “In cases in which the everyday lives of prospective participants are already
16 filled with risk, the test for a threshold for normally acceptable risk must be applied
17 with caution.”²⁴⁰ The text does not elaborate on the procedures that should accompany
18 the cautious approach it counsels.

19 In our view, a policy on research involving persons with mental disorders that
20 incorporates the concepts of minimal risk and minor increase over minimal risk
21 without providing further guidance to investigators and IRBs would not be helpful,
22 because the concepts may be interpreted in materially different ways. In some cases,
23 procedures presenting greater-than-minimal risks to people with mental disorders that
24 may affect decisionmaking capacity might be treated as such, while in other cases the

²³⁹The 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, July 1997) p. 16

²⁴⁰Id. at 14.

1 special vulnerability of those subjects with respect to those procedures might not be
2 taken into account. A procedure classified as minimal risk at one institution could be
3 classified as higher risk at another, or even from one study to another. Also needed is
4 more discussion and clarification of acceptable risk in research involving incapable
5 adults whose ongoing health problems expose them to risks in their everyday clinical
6 setting. Because some persons with mental disorders who are accustomed to certain
7 procedures may experience fewer burdens when undergoing them for research
8 purposes, some would argue that it may be defensible to classify the risks to them as
9 lower than would be the case for someone unfamiliar with the procedures.

10 To be sure, we must guard against using the fact that an individual often
11 undergoes medical procedures due to an illness as an excuse to perform additional
12 procedures of the same sort for someone's else's benefit. The psychological context of
13 illness may well make some research procedures, however familiar, more burdensome
14 than they would be to someone who enjoys good health. Moreover, some procedures
15 entail material burdens each time they are administered. Procedures of this sort should
16 not be classified as lower risk for subjects who have had the misfortune of enduring
17 them in the treatment setting.²⁴¹ In particular, "familiarity" with certain procedures
18 should never be used to expose this population to greater burdens than would be
19 imposed on others. Even the concept of minimal risk admits of no absolute or
20 unchanging definition. Rather, the boundaries that separate particular risk categories
21 can be expected to shift over time in response to many complex and interrelated
22 factors. What is required is a focus on the "package" of reasonably interpreted risk on
23 the one hand and a correspondingly appropriate set of protections on the other. In
24 short, we are not persuaded that three categories of risk are necessary for

²⁴¹Prior 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.

1 accomplishing the twin goals of providing protection for persons with mental disorders
2 while encouraging important research to go forward.

3 One way to reduce variance in risk classification would be to provide examples
4 of studies that ordinarily would be expected to present a certain level of risk to
5 members of a certain research population. For example, the Maryland draft legislation
6 includes in its definition of "minimal risk" research those "types of research that
7 are . . . identified by the United States Department of Health and Human Services as
8 suitable for expedited IRB review."²⁴² Thus the Maryland proposal effectively
9 incorporates examples like venipuncture, electroencephalography, and the study of
10 existing biological specimens.²⁴³ Perhaps over a period of time, it will become evident
11 to the IRB community that protocols tend to cluster in certain ways, for which a
12 certain consensus is thought to emerge. The discussion could also include general
13 considerations relevant to risk classification. For example, one author proposes that
14 lumbar punctures and positron emission tomography "can be reasonably viewed as
15 having greater-than-minimal risk for persons with dementia because (1) both
16 procedures are invasive, (2) both carry the risk of pain and discomfort during and
17 after, and (3) complications from either procedure can require surgery to correct."²⁴⁴
18 The draft Maryland legislation designates research as presenting more than a minor
19 increase over minimal risk if, as a result of research participation, the subjects would
20 be exposed to more than a remote possibility of "substantial or prolonged pain,
21 discomfort, or distress" or "clinically significant deterioration of a medical
22 condition."²⁴⁵

²⁴²Office of the Maryland Attorney General, p. A-5.

²⁴³46 Fed. Reg. 8392 (January 26, 1981). NBAC is addressing the issue of research uses of human biological materials in a separate report.

²⁴⁴DeRenzo, *supra*, at 540.

²⁴⁵*Ibid* at A-17.

1 A list of minimal risk procedures for dementia patients includes "routine
2 observation, data collection, answering a questionnaire, epidemiological surveys,
3 venipuncture, and blood sampling," as well as neuropsychological testing.²⁴⁶ Though
4 some reportedly classify lumbar punctures and bone marrow biopsies as presenting a
5 minor increase over minimal risk, Keyserlingk suggests that such procedures may
6 present "greater risks for some patients with dementia who are unable to understand or
7 tolerate the pain or discomfort" accompanying the interventions.²⁴⁷

8 In 1980, the President's Commission commissioned a paper on the Swedish
9 system for compensation of subjects injured in research. That paper listed procedures
10 by risk groups. The first and lowest risk group included sampling of venous blood,
11 administration of approved drugs in recommended doses, intravenous and
12 intramuscular injections, and skin biopsies. The next risk group included sternal and
13 spinal punctures, intravenous and intra-arterial infusions, muscle biopsies, and
14 endoscopy and biopsies of the gastrointestinal tract.²⁴⁸ Taking these examples, a spinal
15 tap might present more-than-minimal risk to a patient-subject who is decisionally
16 impaired, but not to a normal, healthy subject, while drawing venous blood might
17 present minimal risk to all subjects.

18 Although the philosophical debate about the meaning of minimal risk in
19 research will surely persist, it is clear that practical difficulties remain. For some
20 persons with mental disorders, risks that are minimal for a general population may
21 pose special psychological burdens. Even with regard to interventions that a person
22 may be more familiar with due to his or her disorder, there is no reason to believe that
23 familiarity with an unpleasant experience lessens the unpleasantness of the experience.

²⁴⁶Keyserlingk, et al., *supra*, at 330.

²⁴⁷*Id.* at 330.

²⁴⁸Harry 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.

1 Therefore, the risks associated with specific research procedures should not be
2 underestimated by citing the subjects' other experiences, including those in their
3 everyday lives or those associated with their ongoing health care.

4 This approach does not imply that research involving persons with mental
5 disorders cannot be conducted. Rather, it means that research procedures that would
6 entail minimal risk for a general population must be assessed in light of the specific
7 research population. In no case, however, should procedures classified as minimal risk
8 for this population be classified as greater-than-minimal risk for the overall population.
9 Therefore, research proposals should be more highly scrutinized if they involve
10 persons with mental disorders, and special care may be required to understand
11 particular risk levels. We believe that these special considerations are important and
12 should not prevent the most valuable research from continuing within such constraints.

13

14 *Assessing Risk*

15 Strictly speaking, risk assessment is a technique used to determine the nature,
16 likelihood, and acceptability of the risks of harm.²⁴⁹ In actual practice, however, there
17 is always a great deal of controversy as to how this occurs. Moreover, few IRBs
18 conduct formal risk assessments, and there may be good reason for this: First, because
19 reliable information about risks or potential benefits associated with the relevant
20 alternative interventions is often lacking. As a result, highly accurate risk assessment is
21 a difficult and in many cases quite impossible task. Second, each component of risk
22 assessment—identification, estimation, and evaluation—involves time and particular
23 kinds of expertise.²⁵⁰ Even at the conceptual level, it is a matter of both scientific and
24 philosophic debate as to whether risk assessment should involve purely objective or
25 subjective factors (or both). The "objectivist" school argues that quantitative risk

²⁴⁹Wilson R, and Crouch EAC. Risk assessment and comparisons. *Science* 1987; 236:267-70.

²⁵⁰Meslin EM. Protecting human subjects from harm through improved risk judgments. *IRB*. Jan/Feb 1990: 7-10.

1 assessment should be a value-free determination limited only by the technical ability to
2 derive probability estimates.²⁵¹ In contrast, the "subjectivist" school argues that the
3 values of those who conduct the assessment, those who interpret the results, and those
4 who bear the risks should play a role in the overall assessment of risks.²⁵² It would
5 seem to us that both schools of thought ought to influence IRB decision making, the
6 former because risk judgments should be empirically based insofar as possible, and the
7 latter because there are contributions that many who have an interest in research with
8 persons who have impaired decisionmaking capacity can make to these assessments
9 despite the lack of formal quantitative data.

10 The National Commission's *Report on Research Involving Children* advised
11 IRBs to assess risks from the following points of view: "a common-sense estimation of
12 the risk; an estimation based upon investigators' experience with similar interventions
13 or procedures; any statistical information that is available regarding such interventions
14 or procedures; and the situation of the proposed subjects."²⁵³ Evaluating risks to
15 subjects with mental disorders requires familiarity with how subjects in the relevant
16 population may respond, both generally and as individuals, to proposed research
17 interventions and procedures. What may be a small inconvenience to ordinary persons
18 may be highly disturbing to some persons with decisional impairments. Thus, for
19 example, a diversion in routine can for some dementia patients "constitute real threats
20 to needed order and stability, contribute to already high levels of frustration and
21 confusion, or result in a variety of health complications."²⁵⁴ Similarly, as the National
22 Commission observed, some subjects institutionalized as mentally infirm may "react
23 more severely than normal persons" to routine medical or psychological

²⁵¹Haefle 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.

²⁵²Schrader-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.

²⁵³Report on Children, *supra*, at 8-9.

²⁵⁴Keyserlingk, et al., *supra*, at 324.

- 1 examinations.²⁵⁵ Because of this special vulnerability to harm and discomfort, risk
- 2 assessment should incorporate reliable knowledge on the range of anticipated reactions
- 3 particular subjects may have to particular proposed study procedures.

²⁵⁵Report on Institutionalized Persons, *supra*, at 8-9.

1 Defining Benefits

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

5
6 *Direct Medical Benefit*

7 Particular research protocols may hold out the prospect of direct medical
8 benefit to the subjects themselves, but such benefit can never be absolutely assured.
9 The potential direct benefits to the subjects include health improvements which may or
10 may not be related to the disorder responsible for the subject's incapacity.²⁵⁶ For
11 example, the National Commission stated that research offering potential direct
12 benefits to persons institutionalized as mentally infirm
13 includes studies to improve existing methods of
14 biomedical or behavioral therapy, or to develop
15 new educational or training methods. The studies
16 may evaluate somatic or behavioral therapies, such
17 as research designed to determine differential
18 responsiveness to a particular drug therapy, or to
19 match particular clients with the most effective
20 treatment. Studies may also assess the efficacy
21 of techniques for remedial education, job training,
22 elimination of self-destructive and endangering
23 behaviors, and teaching of personal hygiene and
24 social skills.²⁵⁷

²⁵⁶Keyserlingk, et al., supra, at 327.

²⁵⁷Report on Institutionalized Persons, supra, at 31.

1 According to the National Commission, "[t]o be considered 'direct,' the possibility of
2 benefit to the subject must be fairly immediate [and t]he expectation of success should
3 be well-founded scientifically."²⁵⁸ A more recent statement on dementia research limits
4 direct benefit to

5 a short- or long-range improvement, or a slowing
6 of a degenerative process, in the specific medical
7 condition of the relevant subject, whether in the
8 patient's condition of dementia, a medical symptom
9 associated with dementia, or another physical or
10 mental condition unrelated to dementia. Such
11 direct benefits include those resulting from
12 diagnostic and preventative measures.²⁵⁹

13 Investigators' assertions that research offers the prospect of direct benefit to subjects
14 should be carefully scrutinized by IRBs and other reviewers. Unless the distinctions
15 between direct and indirect benefits are identified, and their relative significance
16 explored carefully, there is a danger that investigators may construe the concept of
17 direct benefit too broadly.²⁶⁰

18 Further, potential direct benefits to the subjects participating in the research
19 protocol must be carefully evaluated and may not, by themselves, justify experimental
20 interventions that present too great a risk to a subject population. Instead, these
21 possible benefits must be considered in relation to the risks involved. Even though a

²⁵⁸Id. 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.
²⁵⁹Keyserlingk, 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.

²⁶⁰This problem was of concern to the intermediate appellate court in the *T.D.* litigation.

1 research protocol may offer potential direct benefits to individual participants, it
2 cannot be justified by the possibility of benefit alone.

3

4 *Indirect Benefit to Subjects*

5 Subjects may obtain other forms of benefit from research participation. As the
6 National Commission noted, "[e]ven in research not involving procedures designed to
7 provide direct benefit to the health or well-being of the research subjects, . . . there
8 may be incidental or indirect benefits."²⁶¹ Examples of indirect benefits are "diversion
9 from routine, the opportunity to meet with other people and to feel useful and helpful,
10 or . . . greater access provided to professional care and support."²⁶² We agree with the
11 view expressed by one group, namely that an indirect benefit may be acknowledged,
12 but should not be assigned the same weight as direct benefit in research review and
13 discussions with prospective subjects and their representatives.²⁶³

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

22 The principle that financial incentives should not exceed "reimbursement" for
23 the subject's time and expenses, so as not to establish undue motivation to participate,

²⁶¹Report on Institutionalized Persons, *supra*, at 31.

²⁶²Keyserlingk, et al., *supra*, at 327.

²⁶³Thus, 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.

1 is well established but not always easy to apply. The problem is a complex one
2 because normal volunteers, as well as some who are ill, may agree, for example, to
3 pharmaceutical testing as an important supplement to their income, if not their sole
4 income source, and their main reason for participating. Remuneration must be
5 appropriate to justify their commitment of time and their submission to discomfort, but
6 presumably not so great as to take unreasonable risks. Similarly, some who are
7 suffering from an illness, especially among those who are uninsured, may be tempted
8 to join a study if it appears that the ancillary medical care will be superior to what he
9 or she can obtain otherwise.

10

11 *Research Benefit to Others*

12 Research benefit to others encompasses benefit to subjects' families or other
13 caregivers, to persons with the same disorder as subjects, and to persons who will
14 suffer from the same disorder in the future. However, this category of research
15 presents the greatest challenge to those seeking the appropriate balance between
16 subject protection and the welfare of others. As one group noted, when such research
17 is invasive and presents no realistic possibility of direct health benefit, it "poses in the
18 most dramatic form the conflict between the societal interest in the conduct of
19 important and promising research and our respect for the persons serving as subjects
20 and their interests."²⁶⁴

21

22 Balancing Risks and Potential Benefits

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

²⁶⁴Melnick, et al., supra, at 535.

1 It is commonly said that the benefits and risks must be “balanced” and shown to
2 be “in a favorable ratio.” The metaphorical character of these terms draws
3 attention to the difficulty in making precise judgments. Only on rare occasions
4 will quantitative techniques be available for the scrutiny of research protocols.
5 However, the idea of systematic, nonarbitrary analysis of risks and benefits
6 should be emulated insofar as possible.²⁶⁵

7 We have described some of the difficulties that attend the definitions of risk and
8 benefit in research; now we turn to the difficulties in combining these two in the
9 judgments that IRBs are required by current regulation to make: an assessment of the
10 risks and potential benefits from individual research protocols. Most researchers and
11 IRBs take the position that adults who lack decisionmaking capacity may be involved
12 in studies presenting little or no risk, as long as requirements for third party consent
13 are met and the research offers a reasonable prospect of advancing knowledge or
14 benefiting the subject, or both. There is substantial support, however, for adopting
15 additional restrictions and review requirements for studies presenting higher risk,
16 particularly for higher-risk studies that fail to offer subjects a reasonable prospect of
17 direct benefit.

18 Research presenting greater-than-minimal risk to subjects is generally classified
19 into one of two categories. The first category is research offering subjects the prospect
20 of direct medical benefit. The second category is research that is not designed with any
21 expectation that it might offer some prospect of direct benefit to subjects. While
22 NBAC recognizes that describing research in this way may be seen as adopting an
23 unhelpful distinction between “therapeutic” and “nontherapeutic” research,²⁶⁶ this is
24 not our intention. Rather, we are acknowledging that research may often intend to

²⁶⁵Belmont, pg. 7.

²⁶⁶Levine, RJ, *Ethics and Regulation of Clinical Research*, 2nd ed. New York: Urban and Schwarzenberg, 1986, pp: 8-9.

1 offer the prospect of benefit for some individuals; this is not identical with describing
2 research as being “therapeutic” or, worse, with describing research that may not offer
3 the prospect of benefit as being “nontherapeutic.”

4

5 *Greater-than-Minimal Risk Research that Offers the Prospect of Direct Subject*
6 *Benefit*

7 The general view is that it is permissible to include impaired or incapable
8 subjects in potentially beneficial research projects as long as the research presents a
9 balance of risks and expected direct benefits similar to those available in the normal
10 clinical setting.²⁶⁷ The American College of Physicians guidelines also allow
11 surrogates to consent to research involving incapable subjects only "if the net
12 additional risks of participation (including the risk of foregoing standard treatment, if
13 any exists) are not substantially greater than the risks of standard treatment (or of no
14 treatment, if none exists)." In addition, there should be "scientific evidence to indicate
15 that the proposed treatment is reasonably likely to provide substantially greater benefit
16 than standard treatment (or no treatment, if none exists)."²⁶⁸

17 The Maryland draft legislation deems "research involving direct medical
18 benefit" permissible if an agent or family member or friend acting as surrogate, or
19 IRB-designated proxy, "after taking into account . . . treatment alternatives outside of
20 the research . . . concludes that participation in the research is in the individual's
21 medical best interest."²⁶⁹ The NIH Clinical Center permits greater-than-minimal risk

²⁶⁷The 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).

²⁶⁸American College of Physicians, *supra*, at 845. A limited exception is permitted for incapable individuals who consented to higher risk through an advance directive.

²⁶⁹Office 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

1 research offering a prospect of direct subject benefit with the consent of a Durable
2 Power of Attorney (DPA) or court-appointed family guardian, following an ethics
3 consultation to ensure that the third party decision maker understands the relevant
4 information. For subjects without a DPA or court-appointed guardian, this form of
5 research is permitted "if the situation is a medical emergency, when a physician may
6 give therapy, including experimental therapy, if in the physician's judgment it is
7 necessary to protect the life or health of the patient."²⁷⁰

8

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

11 The American College of Physicians and other groups take the position that
12 greater-than-minimal risk research offering incapable subjects no reasonable prospect
13 of direct benefit should be permitted only when authorized by a research advance
14 directive²⁷¹ or after review and approval at the national level, through a process
15 resembling that set forth in the current regulations governing research involving
16 children.²⁷² The National Commission also recommended a national review process for
17 studies that could not be approved under its other recommendations on research

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.

²⁷⁰NIH Clinical Center, *supra*.

²⁷¹However, 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.

²⁷²American 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).

1 involving persons institutionalized as mentally infirm. However, others see this
2 position as either too liberal or too restrictive. On the one hand, some favor an
3 absolute prohibition on moderate- or high-risk research offering no benefit to subjects
4 but great promise of benefit to others, based on the Nuremberg Code's and the
5 Declaration of Helsinki's conviction that vulnerable and unconsenting individuals
6 should not be put at undue risk for the sake of patient groups or society. Supporters of
7 this position contend that when these documents were created, "it was presumably well
8 understood that a price of that prohibition would be that some important research
9 could not proceed, some research answers would be delayed, and some promising
10 therapies and preventive measures would for the time being remain untested and
11 unavailable."²⁷³ Some writers explicitly label this stance the most ethically defensible
12 position.²⁷⁴

13 On the other hand, a position paper representing federally funded Alzheimer
14 Disease Centers adopts a somewhat different view: "Research that involves potential
15 risks and no direct benefit to subjects may be justified if the anticipated knowledge is
16 vital and the research protocol is likely to generate such knowledge."²⁷⁵ This group
17 also believes that a national review process is not necessarily the best way to decide
18 whether to permit research presenting no potential direct benefit and more-than-

²⁷³Keyserlingk, et al., *supra*, at 334.

²⁷⁴*Id.* at 334. The group would accept this form of research for a small group of incapable subjects who previously consented to it in an advance directive, however. See pp. 45-46, above.

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

²⁷⁵The 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).

1 minimal risk to incapable subjects. It acknowledges that "there may be some
2 advantages" to national review, but contends that "immediate and direct monitoring of
3 such research and on-site assurance of its humane ethical conduct are at least as
4 important as the process of evaluation and approval of any proposed research."²⁷⁶

5 Procedures for Evaluating and Monitoring Risks

6

7 *Special Review*

8 The children's regulations provide for a special review process to address an
9 otherwise unapprovable study determined by an IRB to offer "a reasonable
10 opportunity to further the understanding, prevention, or alleviation of a serious
11 problem affecting the health or welfare of children."²⁷⁷ The Secretary of DHHS may
12 approve such a study if, after consultation with experts in relevant fields and the
13 opportunity for public review and comment, he or she concurs with the IRB's finding
14 on research significance and determines that "the research will be conducted in
15 accordance with sound ethical principles" or that the study does in fact fall into an
16 IRB-approvable category. In our view, this process, while rarely used,²⁷⁸ offers an
17 additional route for assessing protocols involving persons with mental disorders.

18

19 *Opportunities to Enhance IRB Education and Decision Making*

²⁷⁶High, 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.

²⁷⁷ 45 C.F.R. 46.401.

²⁷⁸To 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, "Myotblast 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.)

1 We have been mindful of the concern expressed by some that IRBs, limited to
2 two categories of risk when making judgments about the acceptability of risks in
3 relation to potential benefits, may be inclined to consider all projects involving greater
4 than minimal risk as requiring the most comprehensive protections. In particular, we
5 recognize the concern expressed by some that if research involving relatively benign
6 interventions (such as PET scans or MRIs) were categorized as greater than minimal
7 risk, this could result in burdensome restrictions that would either substantially delay
8 or otherwise limit research. We believe, however, that the most appropriate way of
9 addressing this issue is not to focus on an arbitrary line, which cannot be definitively
10 established, but rather to focus attention on improving the quality of IRB judgments
11 generally, and on the unavoidable responsibility of IRBs to not only ensure an
12 appropriate balance between risk and benefit, but a balance between risks and
13 protections. We believe that this presents a useful opportunity for enhancing IRB
14 decision making. One possible strategy may be for IRBs individually and collectively
15 to develop "research ethics case law."

16 The purpose of having a set of categories is to enable individuals (in this case,
17 IRBs) to discriminate more precisely when making judgments about whether adequate
18 protections are in place, and whether their judgment about risk in relation to the
19 potential benefits is appropriate. But since risk will vary along a continuum that
20 involves a number of factors, and since IRBs currently have the authority to require a
21 variety of additional protections for persons involved as subjects (even on minimal risk
22 research, should they so choose), we are not persuaded by the argument that an
23 additional category of risk is needed to assist in these decisions. We would hasten to
24 add, however, that by limiting the categories of research to two, we are not intending
25 for IRBs who determine that research which poses greater than minimal risk should
26 require all available protections, nor are we presuming that having several categories
27 of risk might serve an important heuristic purpose for IRBs. Such stratification might

1 be a useful educational method for training new IRB members, or could be used to
2 help determine how individual IRB members perceive risk.

3 A few empirical studies indicate that there is substantial variation in how IRBs
4 and investigators classify protocols using the current federal risk categories. For
5 example, a 1981 survey found differences in how pediatric researchers and department
6 chairs applied the federal classifications to a variety of procedures commonly used in
7 research.²⁷⁹ Similarly, there was substantial disparity in how the nine members of a
8 special NIH review panel applied the federal classifications to a trial of human growth
9 hormone in which healthy, short children were subjects.²⁸⁰ A survey asking research
10 review committee members and chairs in Canada to classify four different dementia
11 studies "confirmed that there is considerable disagreement and uncertainty about what
12 risks and benefits mean and about what is to be considered allowable risk."²⁸¹

13 We recognize the difficulty that IRBs may face when making precise risk
14 judgments, particularly in making judgments about nonphysical harms. For this reason,
15 IRBs may find it useful to collect data on the types of protocols they review
16 involving persons with mental disorders, and to assess whether any patterns
17 emerge in which certain types of protocols fall along a spectrum from the most
18 benign to the most dangerous. This could be accomplished within the context of
19 one of our recommendations regarding audit and disclosure.

20

21 *Independent Research Monitors*

22 In the initial review process, IRBs evaluate a research proposal's risks and
23 expected benefits based both on study design and on predictions of subject response.
24 In many cases, IRBs will predict a range of responses, some of which may prove

²⁷⁹Janofsky & Starfield, Assessment of Risk in Research on Children, 98 J. Pediatrics 842 (1981).

²⁸⁰See Tauer, The NIH Trials of Growth Hormone for Short Stature, IRB, May-June 1994, at 1.

²⁸¹Keyserlingk, et al., supra, at 326.

1 inaccurate as research progresses. As a result, subjects' health status and experiences
2 must be evaluated on an ongoing basis to ensure that subjects can be removed from the
3 protocol if risks become excessive. In particular, the assessment of potential harms
4 and benefits should be individualized for the subject in question, placing the proposed
5 subject's medical, psychosocial, and financial situation in context.

6 For purposes of this report, NBAC believes that the need for subject monitoring
7 is distinct from monitoring the data being generated by the study. The need for safety
8 and data monitoring is widely acknowledged. The Common Rule directs IRBs to
9 ensure that "[w]hen appropriate, the research plan makes adequate provision for
10 monitoring the data collected to ensure the safety of subjects."²⁸² After evaluating
11 human subject protections in schizophrenia research conducted at the University of
12 California at Los Angeles (UCLA), the Office for Protection from Research Risks
13 (OPRR) required the institution to "establish one or more independent Data and Safety
14 Monitoring Boards . . . to oversee [DHHS]-supported protocols involving subjects
15 with severe psychiatric disorders in which the research investigators or coinvestigators
16 are also responsible for the clinical management of subjects."²⁸³ The institution was
17 directed to submit to federal officials a proposal on creating and operating such
18 monitoring boards.

19 Commentators also refer to the importance of individual subject monitoring, as
20 distinct from keeping track of data, which may suggest that a study or an individual's
21 participation should be stopped because it seems to pose undue risk to a group of
22 subjects or an individual.²⁸⁴ Although Data Safety Monitoring Boards (DSMBs) are
23 well-established devices for multisite studies, a major question is how and when to

²⁸²Sec. ____ .111(a)(6).

²⁸³Office for Protection from Research Risks, *supra*, at 27.

²⁸⁴See, 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").

1 implement individualized subject monitoring, and whether such monitoring should be
2 conducted by a person who is independent of the research team. Detailed provisions
3 on monitoring are also included in Loma Linda University IRB guidelines on
4 psychopharmacology research in which placebos are administered. Investigators must
5 specify how often subjects will be assessed for deterioration or improvement during
6 studies. The most appropriate quantitative instruments must be used for assessment,
7 and subjects must be withdrawn if their condition deteriorates to a level "greater than
8 that expected for normal clinical fluctuation in a patient with that diagnosis who is on
9 standard therapy"; if they exhibit previously specified behaviors indicating possible
10 danger to self or others; or if no signs of improvement in their condition are evident
11 after a specified time.²⁸⁵

12 Some have suggested that it would be appropriate to assign monitoring
13 responsibility to the incapable subject's representative as well. According to the
14 *Belmont Report*, the representative "should be given an opportunity to observe the
15 research as it proceeds in order to be able to withdraw the subject from the research, if
16 such action appears in the subject's best interest."²⁸⁶ In this spirit, the Maryland draft
17 legislation directs subject representatives to "take reasonable steps to learn whether the
18 experience of the individual in the research is consistent with the expectations of the
19 legally authorized representative at the time that consent was granted."²⁸⁷

20 An important policy question is whether research team members and subject
21 representatives can provide sufficient protection to impaired or incapable subjects,
22 since research team members may face a conflict between protecting subjects and
23 maintaining the study population.²⁸⁸ Further, it is unlikely that subject representatives

²⁸⁵Orr, *supra*, at 1263.

²⁸⁶*Belmont Report*, *supra*, at 6.

²⁸⁷Office of Maryland Attorney General, *supra*, at A-25.

²⁸⁸In 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.

1 will be present during every part of an incapable subject's research involvement, and
2 lay persons might not recognize every indication of increased risk to subjects. In these
3 circumstances, IRBs would benefit from guidance on potential approaches to
4 monitoring harms and benefits to individual subjects and on criteria for determining
5 when the involvement of an independent health care professional is needed.²⁸⁹ NBAC
6 believes that, at certain risk levels in research using persons with mental disorders
7 which may affect their decisionmaking capacity, independent monitoring is essential,
8 and that such monitoring should be an ongoing process. Indeed, in our view, IRBs
9 should expect investigators to describe in their research proposals how potential harms
10 to subjects will be monitored.

11 These first five chapters have surveyed certain critical aspects of the state of
12 research and expert commentary on the participation in research of subjects with
13 disorders that may affect their decisionmaking capacity. The sixth chapter presents
14 NBAC's reasoned judgment about appropriate protections for this population and the
15 justification for those recommended protections.

²⁸⁹See 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).

1 Chapter Six: MOVING AHEAD IN RESEARCH INVOLVING PERSONS WITH
2 MENTAL DISORDERS: SUMMARY AND RECOMMENDATIONS

3
4 This report stands in a long line of statements, reports, and recommendations by
5 governmental advisory groups and professional organizations that focused on the
6 ethical requirements of all research involving human subjects. Some of these reports
7 dealt specifically with research protocols involving persons with mental disorders, and
8 each has been an important legacy for this report. For example, the Nuremberg Code
9 established the importance of voluntary consent to research participation. The
10 Declaration of Helsinki distinguished between research intended partly to benefit the
11 subject and research intended solely for others' benefit. CIOMS guidelines allow legal
12 guardians to consent to low-risk research that is potentially beneficial to the human
13 subject involved. In addition to proposing ethical principles that should govern all
14 human subjects research, and guidelines for research with special populations, the
15 National Commission also proposed additional protections for those institutionalized
16 as mentally infirm. Even though these protections resembled the ones it successfully
17 proposed for children, they were never adopted in federal regulations. The Common
18 Rule attempted to bring all federal agencies conducting and/or sponsoring human
19 subjects research under a common set of regulations and guidelines whose key
20 elements include informed consent and prior IRB review of research proposals.

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

1 larger role for the private sector. While by no means vanquished, the stigmatization
2 and marginalization of those who suffer from mental disorders that put them at risk for
3 impaired decision making show signs of abating as improved understanding of and
4 empathy for those individuals, as well as a new appreciation of the underlying biology
5 and, increasingly, the genetic bases of some of their conditions,²⁹⁰ gradually increase
6 among the professional and lay communities.

7 NBAC hopes that the legacy of this report, like its predecessors', will be to
8 bring persons with mental disorders more fully and specifically under appropriate
9 additional protections, such as those that have been extended to other vulnerable
10 groups under the Federal Government's Common Rule. We propose these new
11 protections with the deepest respect for all those engaged in research on these
12 disorders: the person with a disorder that affects decisionmaking capacity, whose
13 autonomy must be protected and, when possible, enhanced; the clinical investigators
14 who are dedicated to the alleviation of some of humanity's most terrible afflictions;
15 and informal caregivers, whose own lives are often virtually absorbed by the tragedy
16 that has befallen their loved ones. In view of the ethical uncertainties many researchers
17 have noted, and the ethical problems some thoughtful observers, subjects, and their
18 families have identified, we believe that the protections we propose below will
19 promote broad-based support for further research by engendering greater public trust
20 and confidence that subjects' rights and interests are fully respected.

21 In this concluding chapter, we summarize our recommendations and identify the
22 individual s or groups to implement the recommendations.

23 Concerns have been expressed that requiring new protections on research
24 involving persons with mental disorders might limit such research and therefore

²⁹⁰ See, for example, *Journal of the American Medical Association*, August 19, 1998.

1 impede the development of new treatments.²⁹¹ It is difficult to validate such claims
2 because there is, to date, insufficient evidence to support or reject them. NBAC does
3 not believe, however, that the additional protections recommended in this report
4 should excessively burden or hamper the development of effective new treatments.
5 Moreover, it is useful to be reminded that many share in the responsibility to protect
6 the interests of those without whom this research could not be done—especially those
7 who may be unable to give full informed consent and who may not themselves directly
8 benefit from the research. In our view, all research involving human beings must
9 satisfy appropriate ethical standards; otherwise, we should not conduct research with
10 these human subjects at all. This imperative is especially acute for potentially
11 vulnerable populations such as individuals with mental disorders.

12 We believe a cogent case can be made for requiring additional special
13 protections in research involving persons with mental disorders. We also recognize
14 and acknowledge that many, indeed, most, of these recommendations can be applied to
15 research involving other persons who may have impaired decisionmaking capacity. We
16 direct our recommendations to several different groups. Therefore, although our initial
17 recommendations are geared towards the development of new federal regulations, not
18 all of our recommendations are of this kind. We also make recommendations directed
19 to investigators and IRBs, to state legislatures, to the National Institutes of Health, to
20 health professionals, to agencies subject to the Common Rule, and to others
21 responsible for human subjects protection. In the interim, before new regulations are
22 formally adopted, we encourage all to voluntarily adopt the spirit and substance of our
23 recommendations. The structure of our recommendations provide both a set of
24 requirements that we believe must be satisfied by all research protocols involving

²⁹¹National 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.

1 human subjects and several possible additional or optional protections that may be
2 used in these cases. Taken together, these recommendations could enhance existing
3 protections and facilitate continued research on these disorders.

4

5 Recommendations for New Regulations

6 The desirability of governmental regulation depends not only on the nature of
7 the problems addressed and the importance of the policy enunciated, but also on the
8 rules' ultimate efficacy. Presumably, the least complex measures taken by
9 governmental entities are the preferred ones, so long as those measures can achieve
10 the important societal goals that have been identified. Many who are familiar with the
11 federal regulations currently governing human subjects research complain that they are
12 already unjustifiably complex and bureaucratic. Some of those engaged in research on
13 conditions related to mental disorders fear that further regulation will unnecessarily
14 retard scientific progress and inappropriately stigmatize individuals who may be
15 suitable research subjects.

16 Whatever one's view of the current regulations, the period since their adoption
17 has been, in the judgment of some, largely free of the sorts of large-scale problems and
18 abuses that led to their initial promulgation. Others, however, stress that the issues
19 discussed in this report illustrate some of the shortcomings of the Common Rule. In
20 this context, NBAC was obliged to determine whether the outstanding issues and
21 problems in research involving persons with mental disorders that may affect their
22 decisionmaking capacity warrant new regulations and/or whether some or all of the
23 reforms it believes are required could be advanced through other mechanisms, such as
24 statements of principle by those individuals involved in reviewing, regulating, and
25 carrying out these projects; suggested changes in professional guidance; or other
26 educational materials for all relevant parties.

1 NBAC believes that, in addition to the general regulations that already apply to
2 all research conducted or sponsored by the Federal Government or that is otherwise
3 subject to federal regulation, IRB deliberations and decisions about research involving
4 subjects with mental disorders that may affect decisionmaking capacity should be
5 governed by specific additional regulations. We come to this conclusion because
6 regulations provide one of the most important methods used in the United States to
7 uniformly assure the protection of the rights and welfare of human subjects. Below we
8 propose 14 recommendations directed at the regulation of IRBs. We recognize, of
9 course, that regulation is not the only method. For this reason, we make a number of
10 other recommendations apart from those directly affecting regulation.

11

12 Recommendations Directed at the Regulation of IRBs

13 Fourteen of our 20 recommendations are directed at IRBs. We distinguish here
14 between recommendations for regulatory reform, and those which offer guidance to
15 IRBs.

16

17 *IRB Membership*

18 **Recommendation 1: All IRBs that regularly consider proposals involving**
19 **persons with mental disorders should include at least two members who are**
20 **familiar with the nature of these disorders and with the concerns of this**
21 **population.** At least one of these IRB members shall belong to the relevant subject's
22 population, or a family member of such a person, or a representative of an advocacy
23 organization for this population. These IRB members should be present and voting
24 when such protocols are discussed. IRBs that only irregularly consider such protocols
25 should involve in their discussion two ad hoc consultants who are familiar with the
26 concerns of this population and the nature of the mental disorders that may affect
27 decisionmaking capacity; at least one of these two consultants shall be a member of

1 this population, or a family member of such a person, or a representative of an
2 advocacy organization for this population.

3 The issues considered in this report are as complex and as multifaceted as the
4 various research protocols designed to advance medical knowledge about mental
5 disorders that may affect decisionmaking capacity. At least some of these issues are
6 likely to arise in most protocols involving research subjects with such disorders. In
7 general, representation of the subject population on IRBs and the increased
8 involvement of affected persons in planning clinical research on their disorders are
9 generally viewed as good ways to increase the likelihood that the IRBs' decisions will
10 be responsive in appropriate ways to the interests of affected groups. More
11 specifically, increased subject representation on IRBs and, therefore, in the review and
12 conduct of research, is now an increasingly common strategy for improving the design
13 of research protocols that involve persons with mental disabilities.²⁹² It is for these
14 reasons that the Common Rule directs those IRBs that frequently review research
15 involving a vulnerable subject group to consider including as reviewers persons
16 knowledgeable about and experienced with working with the relevant subject group.²⁹³
17 The current provision, however, is advisory only; moreover, it refers only to the
18 involvement of expert professionals, not to other persons also representing the
19 interests of vulnerable subject groups. On the other hand, the Department of
20 Education's National Institute for Disability and Rehabilitative Research (NIDRR)
21 must comply with a regulation that, "If an [IRB] reviews research that purposefully
22 requires inclusion of children with disabilities or individuals with mental disabilities as
23 research subjects, the IRB must have at least one person primarily concerned with the

²⁹²For 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).

²⁹³45 CFR 46.107(f).

1 welfare of these research subjects.”²⁹⁴ This regulation was published on the same day
2 in 1991 as the Common Rule.

3 After evaluating schizophrenia studies at UCLA, OPRR took the stronger
4 measure of directing the School of Medicine's IRB to "engage one or more subject
5 representatives as IRB members who will assist the IRB in the review of issues related
6 to the rights and welfare of subjects with severe psychiatric disorders."²⁹⁵ This
7 requirement was imposed even though the IRB already had a psychiatrist and a
8 psychologist as members.²⁹⁶

9 This recommendation helps ensure that the special concerns and knowledge of
10 this population are more likely to be represented in IRB deliberations and conveyed, as
11 appropriate, to investigators. Persons who have suffered from mental disorders, or
12 those who are familiar with the problems caused by these disorders, are in a good
13 position to help evaluate the potential vulnerability entailed by a specific research
14 protocol. Especially in a system based on local review, there can be no substitute for
15 this kind of representation. Moreover, with this type of recommendation, research
16 sponsors are also likely to be more aware of the importance of taking these issues into
17 account when working with clinicians to design studies.

18

19 *Appropriate Subject Recruitment*

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

23 NBAC is not suggesting that this recommendation is intended to limit or
24 preclude individuals with mental disorders from participating in research unrelated to

²⁹⁴34 CFR 97.100.

²⁹⁵Office for Protection from Research Risks, *supra*, at 21-22.

²⁹⁶See also Shamoo & Hassner Sharav, *supra*, at S:29 (IRBs reviewing proposals to involve mentally disabled subjects should include at least two patient-representatives).

1 their mental disorder. The principle we are invoking is one of fairness in the selection
2 of subjects—persons should not be targeted to participate in research because they are
3 administratively convenient or unusually accessible. These same individuals, were they
4 able to consent, would be permitted, as any person would, to choose to enter a study
5 unrelated to their condition. This recommendation is in line with current regulations,
6 which provide additional protections to some potentially vulnerable populations to
7 ensure that they are not unfairly burdened with involvement in research simply
8 because, for example, they may be more easily available.

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

20 There are circumstances, however, under which other subjects without these
21 disorders may not be appropriate. For example, if the research bears directly on a
22 disorder that underlies the subject’s decisional impairment, and the disorder is
23 commonly associated with such an impairment, then it may not be possible to learn
24 how to improve diagnosis and treatment for that disorder without at some stage
25 involving subjects from this population. But if the research involves new ways to
26 protect against diseases that are also common among those who do not have mental

1 disorders that affect their decisionmaking capacity, then individuals with impaired
2 decisionmaking capacity should not be recruited.

3 An individual with impaired decisionmaking ability who, for any reason, is not
4 otherwise an appropriate subject for a particular protocol may have a life-threatening
5 condition for which there is no satisfactory treatment. Under these circumstances,
6 when the protocol is designed to ameliorate or potentially cure the life-threatening
7 condition, current regulations permit these individuals, on compassionate grounds, to
8 obtain the investigational treatment.²⁹⁷ Therefore, as a matter of justice, people whose
9 best therapeutic alternative may be an innovative treatment can still have access to it.

10

11 *Assessing Potential Subjects' Capacity to Decide About Participating in Research*

12 **Recommendation 3. An IRB should not approve research protocols**
13 **involving persons with mental disorders unless investigators employ an**
14 **appropriate method, administered by an expert who is independent of the**
15 **research team, to assess the potential subjects' capacity to decide whether to**
16 **participate in the research.**

17

18 *Notification of Determination of Incapacity and Enrollment in Research*

19 **Recommendation 4. A conscious person who has been determined to lack**
20 **capacity to consent to participate in a research protocol must be notified of that**
21 **determination before permission can be sought from his or her legally authorized**

²⁹⁷The specific term used in the regulations is "treatment use." 21 CFR § 312.34; (b) Criteria. (1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:

(i) The drug is intended to treat a serious or immediately life-threatening disease; (ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; (iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and (iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

1 **representative to enroll that person in the research; if permission is given to**
2 **enroll him or her in the research, the potential subject must then be notified.**

3 To be found decisionally incapable and then enrolled as a subject in a research
4 protocol on the basis of alternative decisionmaking arrangements is to have certain
5 rights curtailed, however justifiable the curtailment may be. Some argue that whenever
6 an individual is found to be decisionally incapable, that individual should be so
7 notified, especially when such a finding could have important consequences for his or
8 her medical treatment—such as enrollment in a research protocol.²⁹⁸ Such a
9 notification process might seem, at times, to be an empty ritual and, worse, to be a
10 requirement that could well contribute to undermining health professionals' respect for
11 the regulatory system. Nevertheless, ethical treatment of human subjects demands this
12 process be observed, for to fail to do so is to deprive the subject both of the right to
13 seek review of the decision and of the right to possible judicial intervention.
14 Abrogating the subject's autonomy in such a way is indefensible in a democratic
15 society.²⁹⁹

16

17 *Dissent from Participation in Research*

18 **Recommendation 5. A subject's refusal to participate in research must be**
19 **honored (at the point of notification or by halting any research intervention with**
20 **the subject at that time), whether the subject is currently able or unable to make**
21 **decisions, and whether the subject previously agreed to participate in research**
22 **when competent to do so or was enrolled by a legally authorized representative**
23 **following a determination of a lack of decisionmaking capacity.**

²⁹⁸ 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)

²⁹⁹ 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.

1 **Recommendation 6. Investigators may, with appropriate care and**
2 **sensitivity, reapproach the previously dissenting person and ascertain whether**
3 **the dissent still applies, or whether the person now agrees to participate.**

4 Earlier in this report, we discussed the difficulty in imposing too strict a
5 standard of dissent, and explained that while dissent must always be respected,
6 situations may arise in which the investigator could understandably return to the
7 subject at a later point to ascertain whether the previous dissent still stands. This does
8 not imply that dissent is not a valid expression of choice.

9 Most importantly, notifying a person that they are going to be part of a study
10 also gives them an opportunity to refuse to participate. Even when decisionmaking
11 capacity appears to be severely impaired, individual self-determination must prevail
12 over any asserted duty to serve the public good as a research subject. Hence, dissent
13 by a potential or actual subject must be honored, regardless of the level of risk or
14 potential benefit, just as it would in the case of an individual who clearly retains
15 decisional capacity. Respect for self-determination requires that we avoid forcing an
16 individual to serve as a research subject, even when the research may be of direct
17 benefit to the individual, his or her decisional capacity is in doubt, or the research
18 poses no more than minimal risk. It should be emphasized that the right to refuse to
19 participate in research is not dependent on establishing a right to choose to participate.

20
21 *Investigator Justification of the Determination of a Level of Risk, Informed Consent*
22 *Procedures, Recruitment Strategies, and Other Design Issues*

23 **Recommendation 7. Investigators should be required to provide a detailed**
24 **explanation of their assessment of risks and potential benefits, including the**
25 **identification, estimation, and acceptability of the risks to the subjects.** This
26 assessment should include consideration of the particular procedures proposed and

1 their relationship to the specific conditions of the individuals who may be involved as
2 study subjects.

3 Since there has been some apparent confusion about what the current federal
4 regulations say about levels of risk, we want to emphasize an important point: only the
5 regulations relating to children, found at Subpart D of the Department of Health and
6 Human Services' regulations (and its comparable set of regulations in the Department
7 of Education), refer to three levels of risk. These regulations are not part of the
8 "Common Rule" (which is limited only to Subpart A),³⁰⁰ and hence are not applicable
9 to those agencies that are signatories to the Common Rule. Agencies and, indeed,
10 investigators and IRBs may choose voluntarily to adopt the three-tiered approach to
11 risk, should they find it to be useful. In our view, no change is needed in this
12 component of the Common Rule, but greater attention should be given to the
13 assessment of levels of risk by both IRBs and investigators so that the judgments of
14 risk in relation to potential benefit and the level of protection provided to subjects can
15 be more appropriately related to the protocols themselves. In particular, this will be of
16 importance for research in which disagreement exists about whether the risk is
17 "minimal." The regulations define minimal risk, but care is needed when determining
18 whether (or how) the definitional category applies to research involving persons with
19 mental disorders.

20 The risk categories in the current regulations do not automatically apply to
21 particular procedures, but quite appropriately must be applied contextually in light of
22 specific study conditions. The need for sensitivity in the application of risk categories
23 is especially great when persons with mental disorders are among the potential
24 subjects of a study. For some persons with mental disorders, their limited ability to
25 understand the rationale for a specific intervention may cause them more distress than

³⁰⁰45 CFR 46.100.

1 it would for someone who fully understood the reason for the intervention. For
2 example, repeated venipunctures (blood draws) that might be innocuous to many
3 people could be quite disturbing to persons with limited understanding. Thus, a
4 procedure that per se presents minimal risk could nonetheless be highly threatening to
5 those who are unable to appreciate the procedure's context or the nature of their
6 current situation.

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

14 As a consequence, clinical investigators who propose to involve persons with
15 mental disorders in research as subjects must carefully articulate to IRBs the nature of
16 their risk evaluation procedures for potential subjects. Even within a protocol, the
17 same intervention may entail different risk levels for different individuals depending
18 on their particular condition. When the level of risk may be perceived to be higher for
19 some subjects than for others, the determination of risk for the entire subject group
20 should be made conservatively. Moreover, the intensity of informed consent processes
21 and other special protections should increase as the level of risk increases. Both
22 investigators and IRBs should be sensitive to these considerations and adjust the
23 required set of protections accordingly.

24

25 *Protections in Research Design*

26 **Recommendation 8. Investigators should be required to provide a detailed**
27 **justification of the research design they will use, including any efforts they will**

1 **utilize to reduce the risk in studies which are designed to provoke symptoms, to**
2 **withdraw patients rapidly from therapies, or to randomize patients into placebo**
3 **controls.**

4 The protection of human subjects begins with an ethical study design that not
5 only ensures the scientific validity and importance of the proposed protocol but also
6 minimizes risks to subjects while still allowing the study objectives to be met. This
7 process is accomplished using a variety of approaches, including the use of prior
8 scientific review by established peer review groups and review by the IRB. In many
9 institutions, separate scientific review precedes the IRB's assessment of a protocol. In
10 some instances, IRBs also ensure the scientific merit of a protocol using their own
11 members or outside consultants. Regardless of which method is used, investigators and
12 IRBs must consider ways to measure how the particular proposed research protocol
13 will affect subjects in order to design a protocol that will incorporate appropriate
14 protections. Since several specific designs utilized in research on mental disorders
15 have raised concerns about the relationship between study design and increased risk to
16 subjects, there is a special obligation, whenever an ethically controversial research
17 design is proposed, for the investigators to make every effort to minimize any special
18 risks associated with it. In particular, investigators should expect IRBs to require a
19 clear justification for studies that include symptom provocation, placebo controls, or
20 washout periods (particularly those involving rapid medication withdrawal), and to
21 review carefully the criteria for including or excluding individuals from a study as well
22 as the prospective reasons for subject withdrawal, and follow-up care, if any.

23 Subjects with serious illnesses are often more vulnerable than others to
24 exploitation when they are involved in randomized clinical trials. While the study itself
25 may be designed so as to hold out the prospect of benefit, and satisfies the condition of
26 clinical equipoise described above, there will be instances in which the "drug arm" of a
27 study turns out to be more beneficial to subjects than the placebo arm. One way to

1 ameliorate this problem is to incorporate into the study design a nonresearch or
2 wraparound phase following the conclusion of the research period, one that provides
3 the subject with some beneficial intervention independently of the study itself.
4 However, using a wraparound phase may be problematic because it may shift the
5 balance of protection in the opposite and equally problematic direction by providing an
6 inappropriate incentive to participate in studies in order to derive the perceived
7 benefits without having to pay for the drugs. However, wraparounds are suitable
8 followups to certain kinds of research, including those that provoke symptoms. In
9 appropriate circumstances, IRBs could require a wraparound phase as part of the
10 overall study design.

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

19 Many decisional impairments are associated with psychiatric disorders that can
20 be managed symptomatically with neuroleptic medication, so it can be argued that it is
21 unethical to include a placebo arm in the study when a known risk is the return of
22 symptoms. Thus, some contend that new drug investigations should use standard
23 therapy as a control, in spite of the additional methodological difficulties of such
24 designs.³⁰¹ Among the possible grounds for excluding placebo arms in particular
25 studies could be that: (1) an individualized assessment reveals that certain patients

³⁰¹Addington D. op cit. Rothman K.J. op cit.

1 would be at high risk for relapse if a current or prospective therapeutic regimen were
2 discontinued; (2) a washout period would not be contemplated for these patients if
3 they were not enrolling in a study; or (3) standard therapy is generally considered
4 effective, if not ideal.

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

10

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

13 **Recommendation 9. An IRB may approve protocols in this category of**
14 **research if the potential subjects are capable of making a decision about**
15 **participation when the potential subjects have provided an informed consent to**
16 **participate.**

17 **Recommendation 10. An IRB may approve protocols in this category of**
18 **research if the potential subjects are currently incapable of making a decision**
19 **about participation, are of fluctuating capacity, or are likely to become incapable**
20 **during the course of the study, when the following conditions occur: the potential**
21 **subjects, when previously capable of making a decision about participation in**
22 **research, have previously expressed their agreement to participate in a durable**
23 **power of attorney document; the subjects have been notified of the assessment of**
24 **their capacity, and have not objected to or otherwise dissented from**
25 **participation; and the subject's legally authorized representative has given**
26 **permission for the subject to be enrolled in the study.**

1 **Recommendation 11. An IRB may approve protocols in this category of**
2 **research if the potential subjects have never been capable of making a decision to**
3 **participate, when the following conditions occur: the subjects have been notified**
4 **of the assessment of their capacity, and have not objected to or otherwise**
5 **dissented from participation; and the subject’s legally authorized representative**
6 **has given permission for the subject to be enrolled in the study.**

7 Ethically acceptable research involving either persons with fluctuating capacity
8 or persons who face the prospect of permanent loss of capacity presents special
9 challenges. To be part of an informed consent process, a potential research subject
10 must be able to understand that consent to participate in a research study constitutes
11 an agreement to take part in a project that will occur over a specified and perhaps
12 extended period. The potential subject also needs to recognize that being a research
13 subject is different from being a patient, and that a decision to participate in research
14 may involve agreeing to additional medical procedures and/or treatment.

15 Some important research may not be done without the involvement of persons
16 with mental disorders, and some of that research may possibly offer a direct
17 therapeutic benefit to those who participate. An example is the study of dopamine
18 receptor function and schizophrenia, for which there are currently no suitable
19 alternative models, and which could aid the treatment of individuals participating in
20 the study.³⁰²

21 In addition, some individuals with disorders that affect decisionmaking capacity
22 may be able to give informed consent at certain times during their illness. The
23 presence of a psychiatric disorder should not automatically disqualify an individual
24 from being permitted to volunteer if he or she has sufficient capacity to consent and/or
25 other protections are in place. Moreover, an individual may be able to give consent to

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1 participate in a specific study in advance of an anticipated period of incapacity, which
2 may be especially important for research that examines a physiologic state during such
3 a period.

4 Yet no one is obligated to participate in a study, even if it may be of direct
5 medical benefit to them. Therefore, in order for research in this category to go
6 forward, either (1) the potential subject's informed consent must be obtained, or (2)
7 the subject's legally authorized representative must have given permission for research
8 participation *and* the subject must have been given the opportunity to refuse
9 participation. Again, regardless of his or her capacity at the time, the subject's (taking
10 into account Recommendations 5 and 6 above) dissent must be honored.

11
12 *Research that Presents Greater than Minimal Risk and Does Not Offer the Prospect of*
13 *Direct Benefit to the Subject*

14 **Recommendation 12. An IRB may approve protocols in this category of**
15 **research if one of the following conditions apply:**

16 **(a) a person with the capacity to give informed consent for participation in**
17 **the research has done so;**

18 **(b) a person with the capacity to give informed consent for participation in**
19 **specified future research has given consent to do so in an advance directive; there**
20 **has been no material change in the research protocol or the person's situation**
21 **(apart from loss of decisionmaking capacity) between the time that the advance**
22 **directive was executed and the time that the research participation is actually to**
23 **begin; and, in accordance with a state statute or, to the extent permitted by state**
24 **law, previously approved and published institutional rules, a legally authorized**
25 **representative is available to make decisions about continuing or stopping the**
26 **person's participation in the research;**

1 (c) in accordance with a state statute or, to the extent permitted by state
2 law, previously approved and published institutional rules, a person with the
3 capacity to execute an advance directive has done so, designating a research
4 proxy and describing the research in which the person is willing to participate;
5 the particular research is within the description in the advance directive; the
6 designated research proxy gives informed consent to the person's participation;
7 and the designated research proxy is available to make decisions about
8 continuing or stopping the person's participation in the research; or

9 (d) a person had, while competent, executed a durable power of attorney
10 for health care or comparable type of advance directive authorized by state law;
11 in the judgment of the IRB, the research does not present a substantial risk of
12 harm to the person; the designated health care proxy gives informed consent to
13 the person's participation; and the designated health care proxy is available to
14 make decisions about continuing or stopping the person's participation in the
15 research.

16 In addition, the IRB must ensure that there is a responsible health care
17 professional identified and available to counsel the subject and/or the subject's LAR
18 about enrolling, continuing to participate, or to withdraw from a study.

19 **Recommendation 13. An IRB may approve protocols in the category of**
20 **research if the potential subjects have never been capable of making a decision to**
21 **participate, when the following conditions occur: the subjects have been notified**
22 **of the assessment of their capacity and have not objected to or otherwise**
23 **dissented from participation; and the subject's legally authorized representative**
24 **has given permission for the subject to be enrolled in the study.** In addition, the
25 IRB must ensure that there is a responsible health care professional identified and
26 available to counsel the subject and/or the subject's LAR about enrolling, continuing
27 to participate in, or withdrawing from a study. In these cases, the IRB should be

1 especially vigilant in requiring that the presence of a mental disorder should not
2 automatically disqualify an individual from being permitted to volunteer for a study
3 relevant to his or her disorder, if he has sufficient capacity to consent, that cannot be
4 conducted on others. Research proposals involving persons with mental disorders, but
5 which is not of potential benefit to these individuals, may be conducted only under
6 certain circumstances. For persons assessed to have the capacity to decide whether
7 they want to participate in such a study, their informed consent is required. For
8 persons about whom there is some question as to whether their capacity may fluctuate
9 (or be lost entirely) during the study, their participation would be permitted only with
10 the permission of a legally authorized representative, whose authority we discussed
11 previously but we reiterate below. Because the representative will not ordinarily have
12 the training to make a judgment about the subject's medical well-being, a health
13 professional who is not a part of the study team should also be selected to advise the
14 representative about the subject's continued participation. Depending on the level of
15 risk involved, IRBs should consider whether to introduce other protections as well.

16 **Recommendation 14. IRBs should not approve protocols of the kind**
17 **described in Recommendations 10 through 13 unless they are satisfied that**
18 **investigators have adequately described the mechanisms to be used for advance**
19 **research planning.**

20 We believe that the twin goals of appropriate protection of subjects and of the
21 conduct of high-quality research can be accomplished by utilizing an advance planning
22 process which is carefully described. In our view, anticipatory planning for research
23 participation is not a "research advance directive" but a version of the standard
24 informed consent process. A critical difference is that the planning process should
25 include the prospect of a loss of decisionmaking capacity during the study period, a
26 consideration that is not routinely part of an informed consent process. Research
27 advance planning could involve the following elements: (a) the identification of an

1 LAR, (b) the completion of a durable power of attorney document, which identifies the
2 person designated as an LAR, and any specific and relevant information which would
3 assist the LAR in making research decisions on behalf of the subjects should they later
4 become incapable of deciding about research participation on their own.

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

13 In such anticipatory planning, the potential subject must understand that he or
14 she has appointed a legally authorized representative as a surrogate to make decisions
15 concerning continuing research participation in a general class of research protocols
16 should the subject become unable (while in the study) to make these decisions. The
17 subject must further understand that the surrogate may never overrule the subject's
18 wish not to participate in the research or in any part of it, but may overrule the
19 subject's instructions to continue participation, under certain conditions. Potential
20 subjects must be aware that they have given the researchers permission to provide
21 their surrogate decision maker and their health care provider with information about
22 treatment. The subjects should appreciate that, should their preferences change, they
23 may alter their instructions at any time they have the capacity to do so, and that they
24 may withdraw from the study at any time, whatever their level of decisionmaking
25 capacity.

26 In turn, the researchers must agree to discuss information about the research
27 subject's treatment (e.g., possibilities of decompensation, description of likely

1 symptoms, data about medications and potential side effects, and possible danger to
2 self or others) with the surrogate decision maker and responsible health care
3 professional. The research team must also make adequate provision for a thorough
4 diagnostic assessment of the subject's current clinical status and develop an
5 appropriate continuing treatment plan should the subject decompensate, become
6 unable to cooperate, and drop out of the study.³⁰³

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

12 We have reviewed various proposals for extending the decisionmaking authority
13 of individuals in anticipation of a period of incapacity during their participation in
14 research. For studies involving greater-than-minimal risk, the identification of a legally
15 authorized representative (often informally called a surrogate) should be part of a
16 thorough informed consent process, so that important decisions can be made while the
17 subject is incapacitated. A legally authorized representative is an individual authorized
18 by state statute, or to the extent permitted by law, or under previously published
19 institutional rules, to make medical decisions on behalf of another individual. Clinical
20 investigators should incorporate into their protocols a plan to identify legally
21 authorized representatives for potential subjects as part of the consent process. In
22 many instances, individuals who do not have the capacity to participate in an informed
23 consent process are still capable of appointing others whom they want to make
24 important decisions on their behalf. These appointments, which may particularly
25 include family members or close friends, should be recognized in state laws that firmly

³⁰³This language was suggested in the public comment of Dr. Hermann Diesenhaus, July 31, 1998.

1 establish the status of legally authorized representative for research purposes. In order
2 to preserve the subject's autonomy to the greatest extent possible, the legally
3 authorized representative's decisions must be based upon the subject's wishes, so far
4 as they are known; if the subject's wishes are unknown, then these decisions should be
5 based upon the subject's best interests.

6

7 Additional Guidance for IRBs

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

17

18 *The Research Context*

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

27

1 *Possible Additional Protections for the Consent Process*

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

13 Studies with those who are decisionally impaired may take place over extended
14 periods. One of the essential conditions of ethical research is continued voluntary
15 participation, but those who are deeply involved with and dependent upon the health
16 care system may not feel able to withdraw from a study. A requirement for periodic
17 reconsenting would help ensure that a patient's continued involvement is truly
18 voluntary,³⁰⁴ and would provide the occasion to reassess decisionmaking capacity and,
19 if necessary, trigger an advance directive or surrogate arrangement. Reconsent
20 arrangements conform with the spirit of informed consent as a process rather than a
21 single event, and with the view that human research participants are partners in the
22 study process rather than passive subjects.

23 Although reconsenting is another potentially labor-intensive measure that might
24 add to the cost and complexity of the human research system, some long-term studies

³⁰⁴An 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).

1 supported by the National Institute on Aging already include such a procedure.³⁰⁵ IRBs
2 should consider attaching a reconsent requirement to certain studies based on their
3 length, on their risks and benefits, and on the mental condition of potential subjects,
4 such as those with progressive neurological disorders or fluctuating capacity.

5

6 *Independent Health Care Professional Advisors*

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

11

12 *Voluntary Self-evaluation*

13 IRBs may consider, alone, with other IRBs, or in collaboration with
14 professional organizations (see below), voluntarily adopting NBAC's
15 recommendations and then, after a suitable period of time, assessing the effect on the
16 quality of the IRB review process. For example, since there has been considerable
17 discussion in our report about the appropriateness of using two levels of risk in IRB

³⁰⁵One such example is the Baltimore Longitudinal Study of Aging (BLSA). The protocol for reconsenting participants was described to NBAC as follows: "At this time, competency evaluations are done by a working group in the Laboratory of Personality and Cognition composed of Susan Resnick (NIA neuropsychologist), Claudia Kawas (a collaborating neurologist from JHMI), Jeff Metter (physician), and if necessary Chester Schmidt (Chief of Psychiatry at JHBMC). Each BLSA participant has a baseline cognitive assessment done upon entry to the study. Cognition is not formally assessed by serial determinations until participants are 55 years of age when most patients undergo the cognitive battery administered by the Cognition Section of LPC. Once patients enter this phase of the study, their test results are reviewed and if substantial loss of cognitive function is suspected the participant and his/her records (medical and psychometric) are reviewed by Drs. Resnick, Kawas, and Metter. At this time, Dr. Kawas performs a formal neurological evaluation to determine a medical cause of the cognition decline. In the case in which affective disorders are suspected, Dr. Schmidt will be consulted. Family members are immediately involved in the status of the evaluation and if competency is judged to be impaired, family members are asked to provide consent for further participation if the patient is agreeable and the family members believe that participation is in the interest of the patient. Since the BLSA is an observational study, not an interventional clinical one, issues of study-related risks (morbidity and mortality) have not been raised in terms of greater than minimal risk. Personal communication, Dr. Terrie Wetle, Deputy Director, National Institute on Aging, July 2, 1998.

1 review, it might be worthwhile to review protocols using this strategy, as compared
2 with a strategy in which three risk levels are explicitly used. Were this evaluation
3 conducted in a more formal manner, the results could be published and shared with the
4 IRB and research community.

5

6 Guidance for Institutions

7 While investigators and IRBs bear a considerable responsibility for ensuring the
8 ethical conduct of research involving human subjects, the institutions in which
9 research occurs share some of this responsibility. In particular, since federal grants are
10 awarded to institutions, not individual investigators, and since an Assurance of
11 Compliance is negotiated between an institution and OPRR, institutions may be
12 thought of as the foundation upon which ethical practice is built. During the course of
13 its deliberations, NBAC heard testimony from patients, subjects, institutional
14 administrators, and others. On one occasion, testimony before NBAC led, in part, to an
15 investigation of an institution by the Office for Protection from Research Risks.³⁰⁶

16

17 *Audit and Disclosure*

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

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

³⁰⁶Letter 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.

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

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

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

13

14 Recommendation to State Legislatures

15 We are aware that there is interest in the states about many of the issues in this
16 report, but only one is directly relevant to our discussion.

17 **Recommendation 14: The states should legislate a definition of a legally**
18 **authorized representative for purposes of deciding on a subject's enrollment in a**
19 **research protocol. That legislation should recognize family members and close**
20 **friends as appropriate candidates for this role, as well as individuals specifically**
21 **designated by potential subjects while those subjects are still competent.**

22

23 Recommendation to Professionals and Organizations of Health Care Professionals

24 **Recommendation 15. All professionals whose expertise embraces research**
25 **involving those with disorders that may affect decisionmaking capacity should**
26 **find ways to recognize family members, close friends, and other important**
27 **caregivers as part of the health care team and to share appropriate information**

1 **with them.** Professional organizations should open discussions about methods to
2 pursue this goal. Innovations in this area must, of course, be consistent with the ethical
3 obligation of patient confidentiality.

4 **Recommendation 16. Professional associations and organizations should**
5 **develop (or review their existing) educational materials pertaining to research**
6 **involving persons with mental disorders.** A growing literature in research ethics
7 exists on this subject, only a small portion of which is referenced in this report. More
8 is emerging on a regular basis. As more is learned about ethical, legal, medical, and
9 social issues in research involving this diverse population, the more important it will
10 be for guidelines and policies to be current.

11

12 Recommendations to the National Institutes of Health

13 *Further Research on Informed Consent*

14 **Recommendation 17. The National Institutes of Health should sponsor**
15 **research that can expand knowledge concerning the most reliable methodologies**
16 **for assessing decisionmaking capacity, the most comprehensive means of**
17 **evaluating cognitive processes among those whose decisionmaking ability is**
18 **impaired, and the best techniques for enhancing informed consent processes with**
19 **persons who have decisional impairments.**

20 NIH has recently sponsored a Request for Applications on the subject of
21 informed consent,³⁰⁷ and should be commended for taking this initiative. Moreover, it
22 sponsored a helpful meeting on the subject of research involving persons of
23 questionable capacity, which we have referred to extensively in this report.

24

25 *Further Research on Advance Planning*

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1 **Recommendation 18. The National Institutes of Health should support**
2 **research on the appropriate use of research durable powers of attorney and other**
3 **advance planning documents for use by persons with mental disorders.**
4

1 Further Recommendations

2 *Special Expert Panel*

3 **Recommendation 19. In protocols that promise either significant scientific**
4 **benefits for persons with mental disorders or significant increases in**
5 **understanding their conditions, but that do not observe the rules proposed in this**
6 **report, the Secretary of the Department of Health and Human Services should**
7 **convene an expert panel to determine whether the specific protocol meets all**
8 **appropriate scientific and ethical standards—that it is, in fact, promising enough**
9 **to justify its approval.** Some research involving persons with mental disorders that
10 may affect decisionmaking capacity that is not otherwise approvable under our
11 recommendations may nevertheless have the potential for important scientific benefits
12 for this population or may significantly further the understanding of their condition. In
13 such cases only the Secretary of the Department of Health and Human Services (or his
14 or her specifically designated alternate) should be able to approve such research, but
15 only after consultation with an expert panel to determine whether the research satisfies
16 appropriate scientific and ethical standards.

17

18 *Mandatory Registry*

19 **Recommendation 20. The appropriate federal agency should establish a**
20 **mandatory IRB registry.** This registry would require that all institutions receiving
21 federal funds for protocols involving human subjects to register annually. The agency
22 housing the registry should have the authority to conduct audits of IRB records and
23 procedures without cause. The auditing agency, with full compliance of federal
24 agencies, should have the authority to review and publicly disclose the results of its
25 findings. Information gathered under paragraph 1, above, should be published
26 annually. All federal actions with respect to IRB compliance and conduct should also
27 be published annually.

1 Appendix 2: Flow Chart Summary of Recommended Review Procedures for

2 IRBs

3

- 1 Appendix 3: Title 45 CFR Part 46—Federal Policy for the Protection of Human
- 2 Subjects (enclosed)
- 3
- 4
- 5