A Draft Report of the National Bioethics Advisory Commission:

Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity
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EXECUTIVE SUMMARY

Mental Disorders and Research Participation

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

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

NBAC does not presume that it is merely the presence of mental disorders that renders persons incapable of making informed decisions to participate in research protocols. Indeed, it would be wrong to refer to all persons with mental disorders as if they belonged to a singular group collectively incapable of deciding about participation in research or to imply that only individuals with mental disorders lack decisionmaking capacity to participate in research. Different mental disorders affect decision making in different ways, at different times. It is the effect such conditions can have on their capacity to give valid informed consent that makes their participation in research such a delicate issue. Examples might be the subject’s feeling of dependence on caregivers and institutions, or his limited financial resources and social support. Such variables
raise important and complex ethical concerns about the special vulnerability of
persons with mental disorders and, therefore, the quality of their consent to participate
in research protocols. We recognizes the need to address these concerns fully in order
to ensure both the appropriate protection of this population and the continued viability
of the kind of research that of necessity requires the participation of these individuals.

The Role of the National Bioethics Advisory Commission (NBAC)

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

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

¹Executive Order 12975, Sec 4(a)(1).
represent various perspectives: patients, family members, members of advocacy organizations, scientific investigators, and federal officials.

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

Assessing Risks

Informed consent is a critical, necessary prerequisite to ethical research with human subjects, but it is not the only one. Since no one should be exposed to risk or even inconvenience if a scientific project is poorly designed, a second crucial element of ethical research with human subjects is prior review and approval of each protocol by the multidisciplinary group of scientists, clinicians, and lay persons known as an Institutional Review Board (IRB). Each board’s primary purpose is to assess the quality of the protocol design, the validity of the informed consent process, and the ability of the investigators to carry out the study.
Under current regulations, IRBs already have considerable discretionary authority to impose various requirements on research projects (including protections beyond those required by existing federal regulations). It is not known how often IRBs exercise this authority. Since there is a lack of specific guidance in the current regulations, the extent to which the special needs of persons with mental disorders are independently assessed as the processes of mobilizing and conducting a research protocol are carried out is limited.

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

The Recommendations

To ensure that the rights and welfare of persons with mental disorders who participate in research are fully protected, and that research involving such persons meets the ethical standards that the American people should expect of scientific investigations, NBAC recommends several measures: new federal regulations, guidance for Institutional Review Boards and the organizations that support them; suggestions for state legislation; proposals for educating health care professionals; projected research to expand our capacity to assess the decisionmaking ability of potential human subjects; and new measures designed to enhance Common Rule protections while allowing important research to continue.
NBAC also recommends that IRB memberships be composed of persons who
(1) are familiar with the issues that may arise in research involving this population, and
(2) are particularly knowledgeable about the population in question. In addition, it is
critical for investigators to explain more fully in their proposed protocols why they
have chosen their particular study design, why involving persons with mental disorders
is necessary, how each subject’s capacity to consent to research will be assessed, and
how the investigators have evaluated the risks to subjects in the study. We recommend
that any dissent prospective subjects may express be respected, no matter what their
decisionmaking capacities. If a subject is deemed incapable of deciding whether to
participate at all, he should be so informed.

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

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

We recommend that family members be eligible to serve as legally authorized
representatives and urge the states to consider legislation to this effect. We also
suggest that research institutions introduce internal audit and disclosure mechanisms for their IRBs in order to open the IRB deliberations process to public scrutiny, and to provide the institutions with the information that will allow them to modify their policies and procedures to be in compliance with federal regulations and to meet their own objectives. We further recommend that the Federal Government use external audit and disclosure procedures. Finally, we urge the National Institutes of Health (NIH) to support studies to find the best ways to assess the capacity of persons with mental disorders to make thoughtful decisions about participating in research, and to ensure that participation by such subjects continues to be informed and voluntary.
Overview: The Purpose of This Report

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

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

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

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4 45 CFR 46.111(b).
greater-than-minimal risk raised “serious or moderate concerns.”⁷ Among the recent research protocols reviewed by the Advisory Committee that led to this expression of concern were some involving persons at risk for impaired decisionmaking capacity. Indeed, one of the three examples of controversial unresolved issues in the ethics of research was research on adults with questionable decisionmaking capacity that offers them no prospect of benefit but involves unpleasant procedures and exposes them to greater than minimal risk of harm.⁸ ACHRE also surveyed hundreds of people who were ill but who retained decisionmaking capacity and were currently participating in clinical trials, concluding that many of them were not aware of important and relevant elements of the research.⁹ Considering the special complexities of research involving those whose decisional capacity may be affected by mental disorders, ACHRE’s concerns must be at least as strongly applied.

As NBAC’s predecessor, ACHRE provided a basis for further consideration of suitable conditions for involving in research those persons whose decisional capacity might be impaired. However, the deliberations that produced NBAC’s report were not stimulated by a perceived crisis in the participation of persons from this population in clinical studies, but by the recognition of substantial confusion about the principles and procedures that should govern such research. While we heard powerful testimony from members of the public and the professions at NBAC meetings, and received materials and information describing the strengths and weaknesses of the system of human subjects protection, NBAC did not rely on these as evidence of the need to “fix a broken system.” We were informed by this input, and grateful for it, but our rationale 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.
closing one of the possible gaps perceived to exist in human subjects research protection.\textsuperscript{10}

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

\textsuperscript{11}Office for Protection from Research Risks, “Evaluation of Human Subject Protections in Schizophrenia Research Conducted by the University of California, Los Angeles” (1994). 
\textsuperscript{12}National Institutes of Health Panel Report, Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards, February 27, 1998 
\textsuperscript{14}The New York Department of Health Working Group. 
\textsuperscript{15}Council of Europe. Convention on Human Rights and Medicine, November 1996. 
\textsuperscript{17}CIOMS, Guidelines on Research Involving Human Subject, 1993. 
\textsuperscript{22}John C. Fletcher & Alison Whitman, A New Consent Policy for Research with Impaired Human Subjects, 23 Psychopharmacology BULL. 382 (1987). 
a critical mass was developing, and it afforded NBAC the opportunity to review and consider these issues in the context of its responsibility to advise the President through the National Science and Technology Council.

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

NBAC was also mindful of worries that have been expressed about the ability of IRBs at some large research centers to actually monitor, as necessary, approved research proposals.

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

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

29 Berg.
Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity

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

Although this volume is titled the Diagnostic and Statistical Manual of Mental Disorders:

\[30\]Wichman, op. cit. p. 104.
Mental Disorders, the term mental disorder unfortunately implies a
distinction between “mental” disorders and “physical” disorders that is a
reductionistic anachronism of mind/body dualism. A compelling
literature documents that there is much “physical” in “mental” disorders
and much “mental” in “physical” disorders. The problem raised by the
term “mental” disorders has been much clearer than its solution, and,
unfortunately, the term persists in the title of DSM-IV because we have
not found an appropriate substitute.  

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

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

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

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31American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, p. xxi, hereinafter
DSM-IV.
to label persons—our intention is to describe and explain a set of appropriate concerns regarding research involving certain persons and to propose ways to ensure that both appropriate protection and important science proceeds. Indeed, this is the basis for the DSM-IV. The measures to protect these individuals are designed for those who are vulnerable \textit{when they are vulnerable} to intended or unintended coercion and exploitation; but we fully appreciate that these measures can only be successful when they do not, as a consequence, discriminate against those persons who may have a mental disorder, but who do not now, or who may never have decisional impairment of the kind that would limit their ability to decide whether or not to participate in research. The persons about whom this report is especially concerned are those who may be considered for research protocols because it is their particular mental disorder that is being studied.

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

Clearly, special difficulties arise in designing ethically acceptable research protocols that involve human subjects with mental disorders whose decisionmaking capacity and, therefore, their ability to give informed consent may be impaired. Such medical conditions can complicate efforts to respect the rights of human subjects involved in a research project, especially when the research design is such that the subjects themselves will receive no direct benefits.\footnote{For example, some drug research is intended only to determine at what dosage the medication under study will cause a person to become ill, or how rapidly the drug is excreted from the body.} Problems in determining the presence or absence of appropriate decisionmaking capacity, however, are only one
sort of difficulty in conducting ethically acceptable research involving persons with mental disorders.

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

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

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

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

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

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34Department of Health and Human Services, Office of the Inspector General, “Institutional Review Boards:
desperately want medical science to find ways to improve their conditions. On the other hand, there is disagreement about how this can be done without exploiting those with mental disorders who participate in research protocols, thus causing them still greater suffering. As we elaborate in this chapter, several factors combine to make some persons with mental disorders especially vulnerable: they may have impaired capacity to consent due to the condition being studied; they are often dependent for care upon researchers who may also be their physicians; many mental disorders remain resistant to available therapies; and persons with mental disorders tend, principally as a result of the disorder itself, to be more economically disadvantaged than other adults. We believe, however, that despite these tensions and special factors, much can be done to ameliorate the apparent conflict between the impetus to continue promising lines of research and the ethical imperative to support the dignity and well-being of research subjects.

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

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

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

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

Values that Should Guide Research

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

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\(^{36}\text{Physicians who are licensed to practice medicine are permitted to prescribe medications for therapeutic purposes other than those for which the medication has been tested and approved for manufacture and sale.}\)
design of research protocols have evolved from the underlying philosophy that regulatory frameworks are established to ensure that human subjects in biomedical and behavioral research protocols are treated with respect. Over time, researchers have refined their understanding of what it means to respect human subjects involved in research protocols, and this report is partly an effort to share that knowledge with the public.

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

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

Even with the best research designs, however, research protocols can rarely eliminate all risks. The American people need to understand that despite these measures, as long as research is conducted involving human beings, there is a possibility that subjects will be harmed or wronged despite best efforts to protect them. Thus, in addition to any individual motivations, anyone who serves as a subject in a research protocol is engaged in a form of public service that may involve risk and for which there may be no direct or tangible personal reward. The unavoidable element of risk has mandated protections for all research subjects, and clearly such protections must never be less stringent for research subjects whose ability to be fully informed
and to freely consent is lacking or in doubt than it is for others. This proposition is already well recognized in the case of pediatric research.\(^\text{37}\)

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

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

Justice is relevant to the selection of subjects of research at two levels:

the social and the individual. Individual justice in the selection of


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

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

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

The Nature of Mental Disorders That May Affect Decisionmaking Capacity

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

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

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

**Dementia**

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

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

**Delirium**

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

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42American Psychiatric Association, DSM-IV, op. cit.
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. 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. 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. Lack of insight into the presence of illness and need for treatment is common among persons with schizophrenia. This may make it especially difficult for them to anticipate the consequences of their decisions on participation in research as they relate to the risk of future relapse.

Depression

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

Some Other Disorders

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

49 American Psychiatric Association, DSM-IV, op. cit.
54 Grisso and Appelbaum, op. cit.
involve some of the symptoms seen in schizophrenia, including delusions and hallucinations, and may have some of the same consequences for decision making. Substance abuse disorders, for example, including use of alcohol and illegal drugs, result in states of intoxication and withdrawal that resemble delirium in their effects on attention, cognition, other mental functions, and, consequently, decision making. There also can be some decisional impairments associated with drug abuse and addiction outside the circumstances of intoxication and certain forms of withdrawal. However, it is important to emphasize that the diagnosis of substance abuse disorders does not imply that decisionmaking capacity is impaired.

Informed Consent and Decisional Impairments

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

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

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

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

\textsuperscript{56}National Commission, The \textit{Belmont Report}, p. 4.
These four sorts of decisional limitations—fluctuating, prospective, limited, and complete—provide an initial framework both for the different ways the problem of decisionmaking capacity can manifest itself and for the design of appropriate protections. Among those whose capacity fluctuates or is limited, one cannot easily pinpoint the precise nature of a decisional disability from these groupings. Some disorders entail limitations on decisionmaking ability that are subtle and hard to identify, and even individuals who fit within a particular diagnostic category may exhibit their decisionmaking limitations in different ways.

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

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

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57 These categories do not apply to children, whose decisional limitations are developmentally appropriate and which are not a result or symptom of an illness.
can be critical in helping the individual achieve as high a degree of self-determination
as possible.

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

Other Additional Ethical Issues in Research with Persons with Mental Disorders

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

Limitations on Drug Development

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

Subjective Experience of Disorders

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

Problems in Mental Health Care

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

Access to Care

Another factor that affects research and therapy on illnesses associated with decisional impairments is that financial resources for treating many of these conditions continue to suffer compared to other diseases. Both public and private insurance policies often fail to provide adequate support for the kinds of intervention that may be required. This problem is further aggravated by the disadvantaged economic situation of many persons with mental disorders, since many may have trouble completing education and training programs or in securing or retaining employment due to their symptoms. As a result, they are often not well connected to social support networks,
especially if the onset of the disorder occurs early in life. For all these reasons, there is a significant association between mental illness and poverty. According to a study published in 1992, 21 percent of adults with serious mental illness fall below the poverty threshold, as compared with 9 percent of the general adult population.\(^{58}\) As many as half of homeless Americans are said to be suffering from schizophrenia.\(^{59}\) Moreover, the widespread lack of understanding regarding the nature and implications of these disorders itself serves independently of financial issues as a barrier to appropriate care. In any case, without adequate access to mental health services and other social supports and lacking in financial resources, these people and their families may feel that their participation in a research protocol presents a rare opportunity for treatment. Their hope can thus easily overwhelm their understanding of the various risks and the sometimes remote likelihood of direct benefit, even among those who are not decisionally impaired. Researchers and investigators must scrupulously avoid taking advantage of people who might expect therapeutic effects from their research participation.

**Formal and Informal Caregiving**

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


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

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

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

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60Herbert Pardes, Columbia University, July 31, 1998
share relevant information with the informal caregiver, nor do they ask families for information germane to treatment or legal decisions.”

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

The Possibility of Direct Benefit

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

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

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

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

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

The Promise of Research on Mental Disorders

Mental disorders that may render persons decisionally impaired account for an
enormous amount of illness and human and economic costs. Of the 10 leading causes
of disability in the world, according to a recent World Health Organization report, 5
were psychiatric conditions: unipolar depression, alcohol use, bipolar affective
disorder, schizophrenia, and obsessive-compulsive disorder. It has been estimated
that direct and indirect costs of mental illness and substance abuse in the United States
totaled more than $313 billion dollars in 1990. Alzheimer’s disease now afflicts
approximately 4 million people in this country and, with the number of persons over
65 years of age expected to double by the year 2030, the resulting morbidity can be
expected to grow proportionately.

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

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

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

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

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

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

The Ethics of Study Design

There is considerable commentary on the ethical prerequisites for research
involving human subjects, and much of it is represented in the Nuremberg Code and
subsequent professional, national, and international codes and guidelines for research.
These considerations include whether the importance of the study is great enough to
justify the potential harms to which human subjects are exposed, and whether there is
any other reasonably effective way to obtain information that would reduce the level
of risk entailed to the subjects involved. As well, there is a widely accepted view in the
ethics of human subjects research, particularly since World War II, that some
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
Clearly, those who conduct research with human beings have a responsibility to
design studies which are both scientifically and ethically sound. Nonetheless, in some
contexts, scientific and ethical considerations are not always seen as jointly necessary
features of high-quality research design. For example, textbooks on research methods
and clinical trials rarely integrate ethical guidance with scientific guidance. At the
same time, many granting and regulatory groups recognize that ethical research must
meet the requirements of scientific validity and importance and that scientific
investigations using human subjects must be conducted according to ethical principles.
The shorthand expression “good science is a prerequisite for good ethics” is a helpful
reminder, but may not capture all of the nuances of what is morally required for
designing of high-quality research involving human subjects. Freedman helpfully
captured the essence of this problem when he argued that scientific validity and
scientific value are among the important requirements for ethical research. While all
research should be expected to meet these requirements, studies that involve
vulnerable persons would seem to require particular attention to these requirements.
Deciding which design will best answer the research question, what procedures will be
used, which subjects will be studied, are all questions that require both scientific and
ethical justifications. Philosophers of science have long pointed out that even the
selection of one hypothesis over another has moral implications, insofar as there are
opportunity costs associated with this choice. Further, the decision to pursue some
hypotheses, and the experimental design that accompanies that decision, can have
direct moral consequences.

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University Press, 1986).
73 Freedman B., “Scientific value and validity as ethical requirements for research: a proposed explication.” IRB: A
As has been the case for research with other populations, one of the controversial aspects of research involving persons with mental disorders concerns the ethical acceptability of the basic designs of some studies. There are, for example, significant concerns in some quarters regarding study designs that use drugs to stimulate behavioral or physiological manifestations of the disease under study. The term “challenge study” refers to a general category of psychologic and pharmacologic provocations.\textsuperscript{74} Miller and Rosenstein list among these provocations injection of intravenous amphetamine, inhalation of carbon dioxide, and presentation of a phobic stimulus. The principal scientific rationale for conducting psychiatric symptom-provoking studies is “to learn more about the underlying pathophysiological mechanisms responsible for the symptomatic expression of psychiatric illnesses.”\textsuperscript{75} In these “challenge” or “symptom-provocation” studies, the goal is to generate these disease manifestations in a controlled setting so that they can be more fully understood and so that future appropriate interventions can be designed, attempted, and evaluated.

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

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

\textsuperscript{74}Miller and Rosenstein, 1997, p. 403
\textsuperscript{75}Miller and Rosenstein, 1997, p. 404
studies, this design often seeks to return the individual to a medication-free “baseline” state so that behavior can be assessed or new drugs introduced without the confounding factor of other substances already in the person’s system. In other protocols of this type a beneficial drug may be withdrawn for purposes of determining, for example, the appropriate length of the drug therapy. Of particular concern are washout studies in which treatment is suddenly or very rapidly withdrawn. Given that existing regulations require that subjects be informed of the consequences of their decision to withdraw from the study, and what the procedures are for the orderly termination of a study, it is appropriate to draw attention to this issue. Often the washout and challenge approaches are combined in a single study.

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

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

45 CFR 46.116(b)(4).
that there be scientific merit in the proposals. As noted previously, however, both scientific and ethical merit are jointly necessary for conducting human subject research. “Washout” studies, “challenge” studies, and placebo-controlled studies done with subjects who are the focus of this report require special attention to appropriate ethical constraints, both from IRB members and from researchers who work with persons with mental disorders.

The Responsibilities of Clinical Investigators

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

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

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

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

The ethically responsible scientist is expected to carry the dual burden to advance knowledge that can improve the human condition and at the same time to recognize the absolute imperative to treat human research subjects with the utmost care and respect.

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

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

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

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

The Structure of This Report

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

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

In making these recommendations, we are acutely aware of the already
considerable burdens placed upon dedicated clinical scientists and research centers.
Some of our recommendations will undoubtedly require a greater investment of
resources to enhance the protection of human research subjects. These new
investments will be required to support better IRBs at the local level, those federal
offices charged with ensuring compliance with federal regulations regarding human
subjects protections, and NIH and other research agencies. But if important research
that will benefit our society is to flourish as we hope it will, it may only do so in an
environment that adheres in the strictest possible manner to the values and rights that
are so central to our society. It is our view that in the long term such investments will
increase support for updated biomedical research.
Debate about the propriety and necessity of research involving persons whose decisionmaking capacity may be affected by a mental disorder is not new. Historically, many of these discussions have been couched in the context of particular conditions such as sexually transmitted diseases and schizophrenia. More recently, research with subjects affected by Alzheimer’s disease has emerged as a focus of concern. There is, however, an important history in which significant experiments involving human subjects with mental disorders raised sufficient concern to have an impact on contemporary approaches to the public oversight of research in this area. Like other areas of medicine, psychiatry and neurology were not immune to cases of unethical research, including research conducted by very distinguished scientists. Unfortunately, not all instances of ethically questionable research practices involving those who are decisionally impaired were intended to benefit the subjects, nor even intended to yield knowledge of the sources of the impairment that affected the particular subject population. Rather, they may have an entirely unrelated purpose, such as determining the effects of an agent on the human body, or the body’s effect on the agent. In these cases, the decisionally impaired subject was included in research because he or she was readily available, especially if the subject was institutionalized.

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One illustration of this scenario occurred during the 1950s, although it became generally known only much later. In 1952, Harold Blauer was 42 years old and employed as a tennis pro at Manhattan’s Hudson River Club. Apparently despondent over a divorce from his wife, with whom he had two young daughters, Blauer checked himself into Bellevue Hospital. He was diagnosed with clinical depression and transferred to the Psychiatric Institute, a New York State facility staffed by Columbia University faculty. Unbeknownst to Blauer, the researcher had a secret contract with the Army Chemical Corps to conduct research on a mescaline derivative, methyldi-amphetamine (MDA). In mid-January 1953, Blauer was given several injections of various forms of mescaline. Following one of the injections Blauer went into convulsions and died some hours later. The Army and New York State arranged a cover-up of the actual circumstances of Blauer’s death and split an $18,000 payment to his widow and two young children. Over two decades later, after the true story finally came to light, a court awarded Blauer’s daughters $750,000 as compensation from the Federal Government. This case and others make up part of the history that ultimately led to the development of the federal regulations for the protection of human subjects. In what follows below, we review some of the international and then U.S. efforts to regulate the involvement of vulnerable persons in research.

History of International Regulatory Efforts

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

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87 For an extended discussion of this and other historical examples, see Moreno, op. cit.
develop guidelines for the involvement of the decisionally impaired in research protocols.

The Nuremberg Code

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

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

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

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

\textsuperscript{90}Grodin M.A., op cite.
extermination of many psychiatric patients and was, in effect, a rehearsal for the mass
murders in the concentration camps. The chief medical advisor to the Nuremberg
judges, Leo Alexander, unraveled the horrific story of the camp experiments from the
records of SS Chief Heinrich Himmler, records that made the Nuremberg prosecutions
possible. Near the end of the trial, Alexander wrote a memorandum to the judges,
portions of which were incorporated into their decision. That portion, which posterity
knows as the Nuremberg Code, embodies the judges’ attempt to set out the rules that
should guide research protocols involving human subjects.

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

The Declaration of Helsinki

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

91Id. at 135.
legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation." The Declaration divides research into two categories: "therapeutic" and "nontherapeutic," and appears to rule out the participation of incapable subjects in research that fails to offer them the possibility of direct medical benefit. When research has as its sole objective the advancement of knowledge to benefit others, the Declaration states, "[t]he subjects should be volunteers. . . ." Most codes of research ethics following in the Helsinki tradition tended to adopt the therapeutic/nontherapeutic distinction, one which Levine has appropriately criticized as confusing and illogical. In recent years, however, this distinction has slowly been abandoned. NBAC’s view, discussed more fully below, is that research involving humans will, in practice, present certain risks of harm to particular individuals but, at the same time, can be considered to fall either in the class of research protocols that hold out the prospect of direct medical benefit to individual subjects, or the alternative class that does not hold out such a prospect of benefit.

**CIOMS Guidelines**

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

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93 Levine RJ. Ethics and Regulation of Clinical Research, 1986, p. 8-10.
respected; the sole exception would be the rare case in which "an investigational
intervention is intended to be of therapeutic benefit to a subject, . . . there is no
reasonable medical alternative, and local law permits overriding the objection."94

The Council of Europe

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

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

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

Regulatory Efforts in the United States

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

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

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

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

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

\textsuperscript{99}Id. at 58.
Differences in the recommendations on children and institutionalized persons were based on the National Commission’s recognition that some adults institutionalized as mentally infirm retain the ability to give an informed and voluntary decision. Because of concerns about the vulnerability of institutionalized persons, however, the National Commission recommended that IRBs be given discretion to appoint "an auditor to observe and assure the adequacy of the consent process for research" that presents greater-than-minimal risk. Moreover, the National Commission believed such auditors should be required in projects presenting no prospect of direct benefit and more-than-minimal risk to subjects. Their proposals also gave incapable adults more authority than children to block study participation. Finally, because incapable adults usually lack the legal guardian that most children have, the National Commission noted that in some cases a court-appointed guardian would be required to authorize research participation.

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

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100 The National Commission required explicit court authorization to involve an objecting institutionalized person in research. In contrast, the group recommended that parents be permitted to authorize research over a child's objection if the study presented a prospect of direct benefit to subjects not available outside the research context.
Robert Levine blames the reported lack of consensus on DHEW’s earlier failure to adhere to the National Commission's recommendations.\textsuperscript{104} DHEW’s proposed regulations indicated that consent auditors might be mandatory for all research involving institutionalized mentally disabled persons, and suggested that the authorization of an additional person assigned the role of independent advocate might be necessary before an incapable person could become a research subject. During the public comment period, many respondents objected to these additional procedural requirements, presumably on the belief that they were unnecessary and overly burdensome to research.\textsuperscript{105}

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

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

\textsuperscript{105} Ibid.
\textsuperscript{107} Ibid.
\textsuperscript{108} The recent NIH Panel Report indicated that IRBs regularly exercise this authority, Panel Report, p. XX.
instead under the Common Rule, the general federal provisions governing human
subjects research. However, a few Common Rule provisions do address research
involving persons with mental disabilities. First, the Rule identifies "mentally disabled
persons" as a vulnerable population, and directs institutional review boards to include
"additional [unspecified] safeguards . . . to protect the rights and welfare" of mentally
disabled research subjects. The Common Rule also advises IRBs to ensure that
"subject selection is equitable," and that mentally disabled persons are not targeted for
involvement in research that could be conducted on a less vulnerable group.109 Finally,
"[i]f an IRB regularly reviews research that involves a vulnerable category of subjects,
such as . . . mentally disabled persons, consideration should be given to the inclusion
of one or more individuals who are knowledgeable about and experienced in working
with these subjects."110 The Common Rule allows an incapable individual's "legally
authorized representative" to give valid consent to the individual's research
participation,111 but provides no definition of incapacity, no guidance on the identity or
qualifications of a subject representative beyond "legally authorized," and no guidance
on what ratio of risks to potential benefits is acceptable.

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

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109 Sec. ___.111 (a)(3) & (b).
110 Sec. ___.107(a).
111 Sec. ___.116
was there discussion of the subjects' capacity to consent or evidence that appropriate surrogate decision makers had given permission for their participation."\textsuperscript{112} Inquiries into studies involving rapid medication withdrawal from persons diagnosed with schizophrenia have also raised questions about the adequacy of current federal policy and the ethical acceptability of certain existing research protocols.\textsuperscript{113}

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

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

\textsuperscript{112}ACHRE Final Report, supra, at 706-07.
widely; most states have no rules that specifically apply to research involving this population while some states have quite restrictive regulations. Several states currently prohibit certain types of research on persons with mental disorders, research which presents greater than minimal risk and subjects are not likely to benefit.\textsuperscript{116} This suggests that both IRBs and researchers may have trouble identifying (and thus following) the procedures and standards that are requisite to ethical and legal investigations involving persons with mental disorders, even in states that have attempted to provide the badly needed guidance.

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

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\item[-] \textsuperscript{116}Those states are Alaska See, e.g. ALASKA STAT. § 47.30.830 (Michie 1996) (prohibiting experimental research on state mental health patients that involve 'any significant risk of physical or psychologic 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)
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with respect to participation in greater than minimal risk research by minors and persons who lacked the capacity to give informed consent. In 1995, the trial court invalidated the regulations on the grounds that the Office of Mental Health lacked statutory authority to adopt them. The next year, the intermediate appellate court in New York agreed with the trial court's conclusion but added a far more wide-ranging critique of the regulations, opining that they violated constitutional due process rights and substantive protections granted these research subjects under New York's statutory and common law. Finally, however, New York's highest court narrowed the judicial holding to the original decision of the trial court.

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

The Role of NBAC

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

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119 690 N.E.2d 1259 (N.Y. 1997). 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.”
121 Executive Order 12975. Sec 5(a).
review is a result of the confluence of many developments including certain historical
and contemporary cases in which protection of subjects appears not to have been
adequate; the perceived gap that exists in the federal regulatory system established for
the protection of human subjects, and our desire to ensure that important research that
maximizes the opportunity to develop treatments for these disorders is able to proceed.
We are persuaded that there is substantial public concern about actual or potential
failures to protect persons suffering from mental disorders from inappropriate research
protocols. We also believe that many clinical investigators may feel unsure about how
they should conduct themselves when carrying out research with this population, and
that authorities in New York, Maryland, and elsewhere have indicated a sense of
unease about the lack of federal guidance. With those considerations in mind, certain
elaborations of the present system for the protection of human research subjects now
appear to be warranted with regard to those who suffer from mental disorders.
Chapter Three: INFORMED CONSENT AND LIMITATIONS ON DECISIONMAKING CAPACITY

The Centrality of Voluntary and Informed Consent

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

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

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

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

Plainly, then, the capacity to participate in this process of informed decision making is a requirement of but not the total corpus of the present system of public oversight of biomedical and behavioral research. Under a strict protection model, those who lack such capacity, or whose capacity is uncertain, may be excluded from participation as subjects in research, and there would be no way to assess the promising new clinical approaches to the diseases from which they suffer. Such exclusion may seem appropriate; according to this view, the underlying principle is that it is better to protect subjects (who may be unwilling participants) from harm, even at the cost of slowing the progress of scientific investigation and medical advances. The additional cost, and the obvious dilemma presented by the strict protection standard, is that research leading to therapies for those disorders that—as a manifestation of those disorders themselves—would be halted in the absence of subject consent.
Conversely, under the “access model,” a total barrier to research for persons with mental disorders is suspect precisely because it would prevent some people from obtaining the potential benefits that such research might offer them, either directly as a result of participating in the research or indirectly as a result of the improved understanding of their illness and of methods for treating it that may result from the research in question. From either perspective, impaired decisionmaking capacity is a pivotal issue that must be addressed.

Persistent Decisional Impairments

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

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

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

Some of the discussion and recommendations in this report may be relevant to these
other factors that may affect decisionmaking capacity but, again, our primary concern
is with the effect of conditions on the decisional capacity of potential research
subjects.

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

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124 The ethical problems of conducting research in emergency settings, in the face of the acute loss of
decisionmaking capacity that often accompanies admission to a hospital emergency room, has recently been the
subject of new federal regulation. The regulations promulgated by the Food and Drug Administration in 1996
permit a narrow exception of the informed consent requirement for emergency research involving serious
conditions for which there is no proven satisfactory standard treatment. Department of Health and Human
Services, Food and Drug Administration, Protection of Human Subjects; Informed Consent, 61 Fed. Reg. 51498
cannot be helped to attain a level of functioning that would enable them to be part of a valid consent process. Once we recognize these facts, we become more aware of the special ethical obligations that are imposed on scientific investigators and institutions sponsoring, carrying out research and society in general when research with persons who may be decisionally impaired is contemplated.

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

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

Therefore, when we speak of decisional impairments in the context of research involving human subjects who suffer from mental disorders, we mean an incapacity that is not part of normal growth and development. For example, senile dementia is not part of normal aging, and schizophrenia is a biologically based disease. These are examples of conditions that deviate from regular developmental patterns and are not captured under regulatory categories intended to address periods in the life cycle (fetuses and children) or certain defined groups (e.g., pregnant women or prisoners).

If those who are decisionally impaired are to be identified as in need of special treatment under research regulations, they must be carefully distinguished from other special populations.

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

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

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

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

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

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

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

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

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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.

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

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

\(^{132}\)Saks, Ibid.
\(^{133}\)National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The \textit{Belmont Report}: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1979) [hereinafter \textit{Belmont Report}].
\(^{135}\)Bonnie, supra, at 109.
systematic and specific federal direction on capacity assessment, not only for defining decisional capacity in the research context but also for developing better procedures for assessing such capacity.

E.g., id.
Procedures for Capacity Assessment and Information Disclosure

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

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

\textsuperscript{137}E.g., Bonnie, supra; Melnick et al., supra.
recommended that, “where appropriate,” IRBs should appoint a “consent auditor” for research involving those persons institutionalized as mentally infirm.\textsuperscript{139} IRBs would have this authority to determine whether a consent auditor would be appropriate, and how much authority the consent auditor would have. For example, in research involving greater than minimal risk without the prospect of direct benefit to the subjects, the National Commission recommended that the auditor would observe and verify the adequacy of the consent and assent process, and in appropriate cases observe the conduct of the study to ensure the subjects’ continued willingness to participate.\textsuperscript{140} The proposed DHEW regulations contemplated mandating auditors for all projects involving this subject population, but opposition to this proposal reportedly was one reason the regulations never became final.

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

\textsuperscript{139}National Commission. \textit{Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm}, pp. 8-20.

\textsuperscript{140}ibid. p. 15.

\textsuperscript{141}Keyserlingk, et al., supra.
benefit to subjects, Keyserlingk and his group argued that an independent
assessor/monitor should be appointed.\textsuperscript{142}

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

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

As with psychotropic medication and sterilization,

\textsuperscript{142}Id. at 343-44. See also Melnick, et al., supra.
\textsuperscript{143}Orr, Guidelines for the Use of Placebo Controls in Clinical Trials of Psychopharmacologic Agents, 47 Psych. Services 1262 (1996).
\textsuperscript{145}DeRenzo, The Ethics of Involving Psychiatrally 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.
several distinct features of experimentation suggest the need for special protections. First, the history of medical experimentation has been characterized by significant incidents of abuse, particularly where members of vulnerable populations have been enlisted as subjects. Second, the interest of medical researchers in securing participation in the experiment often conflicts with their duties as treating physicians to inform, advise, and act in the best interests of their patients. Third, experimentation is inherently highly intrusive and dangerous, as the nature and magnitude of risks involved are largely unknown and unknowable.\textsuperscript{146}

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

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

\textsuperscript{146}Bein, supra, at 747-48.
\textsuperscript{147}Id. at 762.
consent interviews, second opinions, use of consent specialists, or concurrent consent
by a family member."\textsuperscript{148}

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

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

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

\textsuperscript{148}Bonnie, supra, at 110.
\textsuperscript{149}High, 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").
\textsuperscript{150}Karlawish & Sachs, Research on the Cognitively Impaired: Lessons and Warnings from the Emergency
\textsuperscript{151}Id.
\textsuperscript{152}Ratzan, Technical Aspects of Obtaining Informed Consent from Persons with Senile Dementia of the
Alzheimer's Type, in Alzheimer's Dementia: Dilemmas in Clinical Research 123 (Melnick & Dubler eds., 1985)
to comprehend the necessary information. Information can be delivered through videotape, slides, or pictorial presentations. Another promising suggestion is for investigators to ask representatives of the affected population to critique drafts of information materials prior to their actual research use.153

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

Substantive Requirements for Research Decision Making

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

153 Melnick, et al., supra.
154 World Medical Association, supra.

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

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

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

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159 High, et al., supra; Marson, Determining the Competency of Alzheimer Patients to Consent to Treatment and Research, 8 Alzheimer Disease and Assoc. Disord. 5 (Supp. 4, 1994).
specific material relevant to that project and evaluate the prospective subject’s understanding and appreciation of that information. In its 1998 report on “Research Involving Individuals with Questionable Capacity to Consent,” a National Institutes of Health panel also concluded that “a key factor in potential participants’ decision-making is their appreciation of how the study applies to them (in the context of their lives).”

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

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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).


162Ibid.


164Sachs, et al., supra at 410.
as great as that which would be required to consent to participate in research: we
discuss this further in Chapter Four.

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

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

\textsuperscript{165}See p. 5, above.
\textsuperscript{166}Belmont Report, supra., at 6.
\textsuperscript{167}Bonnie, supra; Levine, Proposed Regulations, supra.
caregivers. On the other hand, there remains considerable support for retaining special protections to persons in residential facilities due to their near-complete dependence on the good will of the staff.

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

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

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169 Elliott, supra; High & Doole, Ethical and Legal Issues in Conducting Research Involving Elderly Subjects, 13 Beh. Sci. & L. 319 (1995). See also American College of Physicians, Cognitively Impaired Subjects, 111 Ann. Intern. Med. 843 (1989) (recommending that IRB "consider asking a committee composed mostly of representative residents of, for example, a nursing home, to review proposed research projects to be conducted at the facility). 
170 Appelbaum, Drug-Free Research, supra.
Chapter Four: ASSENT/DISSENT, ADVANCE PLANNING, AND SURROGATE DECISION MAKING

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

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

175 An empirical study found that many dementia patients incapable of independent decisionmaking were nevertheless "able to provide useful information on their values and preferences that was pertinent to making research enrollment decisions." Sachs, et al., supra, at 410.
necessary.” According to the National Commission, "mere absence of objection" ought not be interpreted as assent. The National Commission recommended requiring the consent of a subject's legal guardian to authorize greater-than-minimal-risk research involving nonobjecting subjects incapable of assent. Whether this situation might be adequately addressed through less formal procedural safeguards, or by imposing special limits on research risks, remains unsettled in the existing literature.

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

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

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

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176 Kapp, supra, at 34.
178 Report on Institutionalized Persons, supra at 7-10.
Yet not all commentators agree that potential direct medical benefit should be sufficient to override the resistance (whether verbal or behavioral) of persons lacking decisional capacity with regard to research participation.

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

Faced with an objection by a patient of impaired capacity, the justification advanced for nevertheless imposing the investigational intervention is that it holds out the prospect of direct (therapeutic) benefit. However, it is normally not legitimate to impose even established therapy on a patient refusing it. The case for proceeding may be stronger regarding the incompetent . . . patient who objects, but it is difficult to equate an intervention which is investigational in nature—whatever its potential for direct (therapeutic) benefit—with an intervention "which would be ordered in a purely therapeutic context."\(^\text{180}\)

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

\(^{179}\) E.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.
who expresses disagreement with or who refuses to perform an action related to the research.182

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

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

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

The Role of Advance Planning and Surrogate Decision Making

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

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

\(^{184}\) *T.D.* v. New York State Office of Mental Health et al, 650 N.Y.S. 2d at 193.
itself. Yet the patient's anticipatory decision, made prior to the biopsy, is no less an exercise of informed consent. This type of decision making about discrete, future clinical contingencies likewise occurs when a person fills out a living will, the original advance directive document. The typical living will is an instruction that specifies end-of-life interventions not be used in the event of a terminal prognosis. Despite the difficulty in meshing this kind of instruction with what is often a more complex clinical situation, a living will nevertheless can serve as a self-executing embodiment of the person's right to decide about these interventions.

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

The third type of anticipatory decision might be called a projection of personal relationships. Just as someone may entrust another with responsibility for financial matters during a potential period of future disability, a person may designate a decision maker for health care matters. The legal instrument by which this designation is accomplished, the durable power of attorney for health care, has become a familiar feature of the clinical landscape; a recent study found about a nine percent usage rate among residents of nursing homes in several states. Teno JM. “Changes in advance care planning in nursing homes before and after the Patient Self-Determination Act: report of a 10-state survey.” Journal of the American Geriatrics Society 45:939-944 (1997).
designation can be coupled with instructions or guidance about the choices that the proxy might face.

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

Informed Consent

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

Personal Values

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

Personal Relationships

A person may embody in an advance directive his or her choice of a decision maker concerning research participation. Because of the trust reposed in the person, a proxy named in a research advance directive ought to have authority to agree to research participation under circumstances closed to other decision makers.
This summary account of the role of advance decision making in research is not intended to gloss over several important issues: whether advance directives can be adequately informed; how to safeguard the subject's right to withdraw from research; and whether anticipatory decision making is a morally defensible basis for permitting otherwise prohibited levels of risk and burden in research involving incapable subjects. The concept of advance research decision making was initially discussed in the 1980s. In his volume on clinical research, Robert Levine discussed the "research living will" as an avenue for competent persons to authorize their future research involvement while incompetent. In 1987, the NIH Clinical Center adopted a policy, which is currently under review, in which persons "who are or will become cognitively impaired" are asked to complete a durable power of attorney (DPA) document appointing a surrogate research decision maker. Such decision makers may authorize an incapable subject's participation in research presenting greater-than-minimal risk to subjects. In such cases, an ethics consultation is conducted to verify the decision maker's capacity to understand information relevant to the research decision. If no DPA exists, the consent of a court-appointed family guardian is required. The NIH Clinical Center policy deems a subject's prior exercise of choice an acceptable basis for permitting higher-risk research than is otherwise permitted for decisionally incapable subjects lacking court-appointed family guardians.

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

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187 Subjects "not seriously impaired" are viewed as capable of completing a research DPA. If a prospective subject is "so seriously impaired as to be incapable of understanding the intent or meaning of the DPA process, a next of kin surrogate may be chosen by the physician." In addition, if a prospective subject has a previously completed health care DPA or a court-appointed guardian, no research DPA is sought. NIH Clinical Center, supra.
188 Research presenting greater-than-minimal risk is not permitted for subjects lacking a DPA or court-appointed family guardian.
would be required to disclose to the competent person the usual information on a study's purpose, methods, risks, and potential benefits. Moreover, the ACP recognized a need for more caution regarding advance research decisions than advance treatment decisions:

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

Accordingly, the ACP took the position that research advance directives "may be abrogated if it is later determined that the proposed research would unduly threaten the subject's welfare."\cite{Forexample}

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

\cite{AmericanCollegeofPhysicians}
\cite{Forexample}
with formal advance directives may be involved in such studies, as long as the above limitations are observed. We are sympathetic to this approach.

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

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

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

\textsuperscript{191}E.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).

\textsuperscript{192}Sachs, Advance Consent, supra. Sachs refers to unpublished survey data finding that while 16 of 21 ethicists expressed enthusiasm for advance research directives, only 8 out of 74 investigators agreed that directives would be a workable approach. In a different survey of healthy elderly persons, many respondents indicated they would be unwilling to complete "blank checks" authorizing participation in a wide range of future studies. Respondents were more positive about advance directives authorizing research offering a reasonable prospect of direct benefit, but only if interventions were restricted to the specific procedures, pain, and discomfort set forth in the document. Keyserlingk, et al., supra, at 347.

\textsuperscript{193}See, e.g., Moorhouse & Weisstub, Advance Directives for Research: Ethical Problems and Responses, 19 Int'l. J. L. & Psychiat. 107, at 135 ("in the event of the development of unforeseen risks, a change in the subject's condition, or an objection expressed by the incapable subject or a concerned third party," subject's surrogate decision maker must have power to remove subject from study).
standard that third parties should apply when exercising the subject’s right to withdraw from the research that the subject previously authorized.

Some favor withdrawal only when the factual circumstances become materially different from those to which the individuals agreed in directives.\textsuperscript{194} Others contend that withdrawal should also occur if it becomes apparent to others that research participation threatens the incapable subject's welfare. According to this position, a research proxy's or surrogate's obligation to respect the person's prior wishes is limited by the obligation to protect the person. The function of the [third party decision maker] is to promote what subjects think are their best interests, which necessarily excludes consenting to being intentionally harmed or to being unreasonably exposed to the risk of harm.\textsuperscript{195}

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

\textsuperscript{194}Berg, supra, at 22 (surrogate has responsibility to withdraw subject only if research or risk-benefit ratio changes substantially from what subject consented to).
\textsuperscript{195}Moorhouse & Weisstub, at 135. See also Shamoo & Sharev, supra, at S:29 (advance directives should not bind a subject to research participation).
\textsuperscript{196}Keyserlingk, supra, p. 352.
impermissible levels of research risks and burdens based on the subject's prior instructions. Moorhouse and Weisstub contend that directives should be restricted to authorizing research "with a negligible or less than substantial risk." Their position is based on the belief that capable individuals cannot predict with complete accuracy how they will experience research as incapable subjects. These authors also argue that the competent individual's freedom to volunteer for research to advance the interests of others is qualified by society's responsibility to protect vulnerable individuals from material harm.

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

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

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197 Moorhouse & Weisstub, supra, at 134.
198 Keyserlingk, et al., supra, at 351.
199 Id.
200 Berg, supra, at 22.
subject's best interests justifies disregarding his directive in one situation and not the other.

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

\(^{201}\) 21 CFR.50.24(a)(2)(iii). The DHHS Secretary, at the same time, waived the general requirements for informed consent under conditions that are almost identical to FDA regulations. See 61. Fed. Reg. 51531 (1996).

\(^{202}\) Id.

\(^{203}\) Id.
The State of Maryland has initiated a policy effort relevant to advance research decision making. The draft legislation includes a framework for third party decisions on research for decisionally incapacitated persons—i.e., research is permitted with consent of an incapable subject's "legally authorized representative." Unlike current federal policy, this proposal specifies who may fill this role. Subject representatives may be, in the following priority order: (1) a research agent designated in an advance directive for research; (2) a health care agent designated in an advance directive for treatment; (3) a surrogate—that is, a family member or close friend—authorized by statute to make health care decisions for an incapable person; or (4) a proxy decision maker designated by the IRB to act as a research decision maker for an incapable person.204

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

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

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204 Office of the Maryland Attorney General, supra, Parts VI, VII, VIII, & IX.
directive authorizing research participation.”\textsuperscript{205} Thus, otherwise prohibited research risk is permitted based on the prior competent choice of a now incapable subject.

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

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

(2) withdraw consent if:

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

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

(iii) considering all relevant circumstances, continued participation would be detrimental to the individual’s well-being.\textsuperscript{206}

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

\textsuperscript{205}Id. at A-32.
\textsuperscript{206}Id. at A-26.
very few persons prepare research directives and if rigorous standards for information
disclosure are observed. Further, even in the best circumstances, investigators and
IRBs face challenges in providing competent individuals with all the necessary
information about a future study. Finally, the literature reveals disagreement on the
significance policy should assign to the competent individual's preferences about
future research participation posing more-than-minimal risk to incapable subjects.

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

Representatives and Research Decision Making

Surrogate decision makers are frequently mentioned as one solution to ethical
problems of enrolling persons from certain vulnerable groups in research. In its recent
report on “Research Involving Individuals with Questionable Capacity to Consent,”
the 1998 NIH panel concluded that “Individuals with questionable capacity (or clear
incapacity) to consent may have a family member and/or legally authorized
representative serve as a surrogate, with this role documented during the consent process.” The panel further recommended that the surrogate’s research decisions should reflect, to the greatest extent possible, the individual’s views prior to the period of incapacity.\footnote{National Institutes of Health Panel Report, “Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs)” February 27, 1998, p. 3.}

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

As we have mentioned earlier, however, relatively few states have laws specifically addressing the area of research decision making by legal guardians or other allowable surrogates. Moreover, existing state legislation limits the involvement of incapable subjects in research in various ways; a number of laws require guardians to obtain specific court authorization to make decisions on a ward's participation in a research protocol. Several states currently prohibit certain types of research on persons with mental disorders, research which presents greater than minimal risk and from which subjects are not likely to benefit. Wichman notes that if an IRB were to approve
a study in a state which did not have such a statute, the IRB might choose to invoke
certain protections, including additional monitoring of the study, requiring a consent
auditor, or requiring educational activities for authorized representatives.\textsuperscript{208}

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

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

\textsuperscript{208} Ibid. pp. 94-95.
\textsuperscript{209} Common Rule, Sec. ___101(f).
\textsuperscript{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,
Subsequent commentary by others questions whether formal legal proceedings are necessary to provide adequate protection for subjects who lack capacity, particularly those not residing in an institutional setting. As one writer notes, IRBs requiring legal guardianship "to be on the safe side" could end up contributing to a deprivation of general decisionmaking rights of subjects. Moreover, the guardian appointment process ordinarily will not address research participation issues in any explicit way. In most cases, a judicial decision to confer guardianship status on a particular person is made without consideration of that person's suitability to make decisions regarding their ward's participation in research protocols.

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

211 Office 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").
others express support for use of these instruments. As a practical matter, however, it is unclear whether many individuals will be interested in or willing to complete such a DPAs. Moreover, the device cannot be applied to the population of persons with mental disorders who are currently incapable and not expected to recover capacity.

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

A third alternative is to recommend state legislation authorizing family members (and, in a few states, friends) to make certain treatment decisions on behalf of relatives as conferring authority for research decisions as well. It might be argued that such legislation embodies a recognition that important health-related decisions for persons lacking decisional capacity are properly assigned to appropriate relatives. Perhaps it would be reasonable to extend the law’s application to a statutory proxy’s decision regarding research offering potential health benefit to an incapable subject.

Others believe that these laws should not be interpreted so expansively and that

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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).
amendments or new legislation would be required to provide explicit statutory
authority for delegating to relatives decisions about the subject’s participation.\textsuperscript{217}

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

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

\textsuperscript{217}Kapp, supra.
\textsuperscript{218}This position is endorsed in policy guidelines adopted by Alzheimer Disease Centers in the U.S. See High, et al., ("[u]nless there is statutory or case law to the contrary, family members should be recognized as having surrogate authority without prerequisite appointment as guardians or proxies through the use of instruments such as durable powers of attorney").
\textsuperscript{219}Kapp, supra; High & Doole, supra.
All of these alternatives also raise questions about the accuracy with which incapable subjects' values and preferences as competent persons will be expressed by formal or informal representatives. The problem of potential conflicts of interest between subjects' interests and those of their representatives exists as well. Those most likely to act as representatives are family members, who may see the subject's research participation as an avenue "that may lighten the burden of caregiving or lead to treatment from which the family member may benefit." Two empirical studies found some family members willing to allow an incapable relative to be entered in a research study even though they thought the relative would refuse if competent. Some family members also stated they would allow an incapable relative to become a subject even though they would refuse to enroll in such a study themselves. At the same time, we recognize many of the potential advantages that such mechanisms might offer to permit important research to go forward. Moreover, we are satisfied that the argument for expanding the authority of the LAR is sound so long as the following components are in place, which we describe in more detail below: (1) a clear description of the role and authority of the LAR, (2) a description of certain protections that must be in place in order for an IRB to assure itself that the LAR is appropriately acting on behalf of the incapable persons, and (3) a commitment on behalf of both the public and research communities to carefully study and report on the experience of using LARs in this way.

The Authority of the LAR

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220 See Sachs, Advance Consent for Dementia Research, 8 Alzheimer Disease & Related Disord. 19 (Supp. 4 1994) ("I think it is fair to assume that most proxies [in the current consent process] know very little about their demented relative's preferences regarding research participation"). 221 Keyserlingk, et al., supra, at 346. 222 Sachs, et al., supra; Warren, et al., Informed Consent By Proxy, 315 New Eng. J. Med. 1124 (1986). There were also cases in which family members would not allow an incapable subject's participation even though they thought the subject would consent if competent or the family members would enter such a study themselves.
We recognize that there are two mechanisms by which a LAR can be involved. One option might be to allow individuals, while competent to designate their legally authorized representative, to give permission to enroll them in research. This scenario requires the designation of an individual whose authority is limited to research involvement. Given the paucity of experience with research-specific LARs in this country, we recognize the burden that might be created by recommending that only this method be used. Another option would be to permit existing DPAs (the many thousands of individuals who have already been appointed in this country to be health care decision makers for clinical decisions) to make certain research decisions. For both mechanisms, the authority of the LAR would need careful description.

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

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


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

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

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

(b) Requiring documentation that the subject and LAR understood the scope of the authority being granted to the LAR. Because of our concern that LARs may have some significant self interest in enrolling a now incapable person into a study, we would favor a process where the designation of an LAR was documented. The documentation we refer to here would enable IRBs to satisfy themselves that the now incapable subject and his LAR had reasonably understood the scope of the type of study being proposed. This places considerable emphasis on the degree to which the IRB is assured that the prospective subject (when competent) and his designated LAR understood the difference between research and therapy, and between research that imposes a greater than minimal risk which is with and without the prospect of direct benefit to the subject. As we note below for each of the two other protections listed, the value of this particular protection is in need of empirical testing and validation.
With regard to the standard by which substitute decisions are made, NBAC favors, in general, giving first priority to those decisions by LARs that approximate most closely the now incapable subject’s previously expressed preferences. In the absence of this information, LARs would be expected to make judgments which are consistent with the subject’s best interests. We are acutely aware of the difficulties this approach presents and explain our rationale in somewhat more detail in Chapter 5 below. Here we are only indicating our general view since it relates directly to the assignment of LARs and the protections associated with this. We would expect IRBs to carefully scrutinize LAR decisions on behalf of now incapable subjects: the greater the risk in the study, the more IRBs should require of the LAR that the substitute decision approximates the subject's preferences.

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

**Ongoing Evaluation of LARs**

We wish to emphasize that the protections listed above could provide the IRB some assurance that the LAR has been assigned in a legally and ethically valid way. However, we also believe that ongoing assessment of the LAR process would be of considerable value. IRBs intending to permit enrollment of a now incompetent subject on the basis of LAR decisions (regardless of how well documented this process might be) would be strongly encouraged to evaluate the effectiveness of LARs. Such evaluation may be considered as part of the procedural requirement that institutions utilize under the mechanisms of audit and disclosure, which we discuss in more detail below. We believe there would be considerable value having IRBs report on those studies involving greater than minimal risk research in which enrollment of decisionally incapable subjects with mental or brain disorders was authorized by an
LAR. We also wish to stress that in the absence of good empirical data about the effectiveness of the LAR mechanism in both permitting scientifically valuable research to go forward and, at the same time, ensuring appropriate protections from research harm, we cannot fully endorse it without reservation. Therefore, we would strongly encourage the research community, led by NIH (in view of its experience with research DPAs), to support research on the appropriate use of research DPAs. We would also encourage research which assesses the extent to which clinical DPAs can be extended to include research decision making.
Independent Professional Support for Subjects and Surrogates

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

One way to provide intellectual and emotional support to these individuals is by ensuring that an independent and appropriately skilled health care professional (e.g., physician, nurse, social worker) is available as an advisor for each research participant or their surrogate. This independent advisor should not be involved with the study and preferably should have had a previous relationship with the potential subject. Subjects, or their representatives if subjects lack capacity, should be able to choose their responsible health care professionals. The advisor’s role would be to help a potential subject and representative decide whether participation in a particular research protocol is a good choice for that subject. For persons who are incapacitated and whose research participation is contemplated, the health care professional could be an invaluable consultant to the legally authorized representative. Often this professional will be a physician; however, other professional caregivers may serve the same role—a nurse-clinician or a social worker, for example. The basic requirement is that such caregivers be familiar with the patient, understand the nature of the research protocol, not be part of the research team, and, if feasible, not part of the organization conducting the research. We would not expect, of course, that the health care professional be required for all research involving persons with mental disorders, but would be required where the patient lacks capacity to decide or is expected to lose capacity during the course of the study.
The British Law Commission recommended a similar system to the House of Commons in 1995, though their proposal applied only to individuals who lack capacity. They wrote: “In most cases the appropriate person to carry out an independent check [on research participation] will be a registered medical practitioner who is not involved in the research project. . . . The doctor who knows the person best, by virtue of having responsibility for his or her general medical care, will often be the best candidate.” The Maryland proposal assigns this responsibility to a “medically responsible clinician” if research involves withdrawing a group of decisionally incapacitated subjects from a standard treatment or otherwise presents more than minimal risk.  

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

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Chapter Five: THE ASSESSMENT OF RISK AND POTENTIAL BENEFIT

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

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

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225Sec. ___.111(a).
Defining and Assessing Risk

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

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

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

Minimal Risk and Greater than Minimal Risk

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

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231Sec. 102(i).
some of the added protections to protocols that they believe to be of greater than
minimal risk. This bar cannot of course be set for all time, because experience and
new knowledge will change how the research community, IRBs, and research subjects
perceive the acceptability of various research risks.

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

Like the current DHHS regulations on research involving children, many
proposals on research involving impaired or incapable adults employ the concepts of
minimal risk and minor increase over minimal risk. Indeed, we have received a
number of comments from the public suggesting that NBAC recommend grouping
research involving persons with mental disorders into three categories of risk: minimal
risk, minor increment over minimal risk, and greater than minimal risk (which we
understand to mean, risks greater than a minor increment over minimal risk). The
Common Rule does not specify that IRBs should (or be expected to) use three
categories of risk in making judgments about the acceptability of a set of risks in
relation to certain potential benefits, nor do the specific additional regulations relating
to pregnant women\textsuperscript{232} or to prisoners.\textsuperscript{233} Only the regulations pertaining specifically to
children describe three categories of risk.\textsuperscript{234} Giving real substance to these concepts, as
noted above, poses serious practical difficulties. The Common Rule's minimal risk
definition is tied to the risks of ordinary life and medical care encountered by the
population as a whole. The minimal risk concept often is praised for its flexibility: "It

\begin{footnotes}
\footnotetext[232]{45 CFR 46.201.}
\footnotetext[233]{45 CFR 46.301.}
\footnotetext[234]{45 CFR 46.401. In addition, the Department of Education independently adopted DHHS regulations pertaining
to children as of December 26, 1997. See 34 CFR 97.401.}
is inescapable and even desirable that determinations of risk level (and its acceptability when balanced with benefit consideration) are matters of judgment rather than detailed definition, judgments which are patient-specific, context-specific, and confirmed after consideration and debate from many points of view."

On the other hand, the concept's reference to "risks of everyday life" is supported as conveying a defensible normative judgment that the sorts of risks society deems acceptable in other contexts may be acceptable in research as well.

In contrast to the minimal risk concept's reference to the life and medical experiences of the overall population, the concept of minor increase over minimal risk is tied to the prospective subject's individual situation. Because persons with mental disorders undergo treatment and tests involving some discomfort and risk, a study presenting similar procedures and potential for harm may qualify as presenting a minor increase over minimal risk to them.

For subjects not accustomed to or in need of such medical interventions, however, the same study could present a higher level of risk.

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

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235 Keyserlingk, et al., supra, at 329.
236 Freedman, Fuks & Weijer, In Loco Parentis: Minimal Risk as an Ethical Threshold for Research Upon Children, Hastings Center Rep., Mar.-Apr. 1993, at 13, 17-18. According to the National Commission, "where no risk at all or no risk that departs from the risk normal to childhood (which NBAC calls 'minimal risk,') is evidenced, the research can ethically be offered and can ethically be accepted by parents and, at the appropriate age, by the children themselves." Report on Children, supra, at 137.
237 The DHHS regulations on children in research provide that studies may be approved as presenting a minor increase over minimal risk as long as the risks and experiences "are reasonably commensurate with those inherent in the child subjects' actual or anticipated medical or other situations."
venipuncture, which may be more stressful for healthy children than for children being
treated for a medical condition who are more accustomed to the procedure.

Commentators have criticized both the Common Rule's "minimal risk"
definition, and the category “minor increase over minimal risk” in the children’s
regulations. Loretta Kopelman provides perhaps the most detailed critique. First, she
finds the notion of “risks of ordinary life” too vague to provide a meaningful
comparison point for research risks. Ordinary life is filled with a variety of dangers,
she notes, but "[d]o we know the nature, probability, and magnitude of these
‘everyday’ hazards well enough to serve as a baseline to estimate research risk?"

Second, though the comparison to routine medical care furnishes helpful guidance
regarding minimal risk, it fails to clarify whether procedures such as "X rays,
bronchoscopy, spinal taps, or cardiac puncture," which clearly are not part of routine
medical care, could qualify as presenting a minor increase over minimal risk for
children whose health problems dictate they must undergo these risky and burdensome
procedures in the clinical setting. Kopelman argues that the phrase “minor increase
over minimal risk” should be replaced or supplemented by a clearly defined upper
limit on the risk IRBs may approve for any child subject.238

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

238 Kopelman, Research Policy: Risk and Vulnerable Groups, in Encyclopedia of Bioethics 2291, 2294-95 (W.
Reich ed., rev. ed. 1995); Kopelman, When Is the Risk Minimal Enough for Children to Be Research Subjects? in
Children and Health Care: Moral and Social Issues 89-99 (Kopelman & Moskop eds., 1989). See also Berg, supra,
at 24 (noting possible interpretations of minimal risk and concluding that “it clearly does not mean only
insignificant risk, but its exact scope is unclear”).
The Maryland draft legislation adopts a definition of minimal risk similar to that in the Common Rule. It also
refers to minor increase over minimal risk, which is defined as “the probability and magnitude of harm or
discomfort anticipated in the research, including psychological harm and loss of privacy or other aspects of
personal dignity, are only slightly greater in and of themselves than those ordinarily encountered in daily life or
during the performance of routine physical or psychological examinations or tests.” Office of the Maryland
Attorney General, supra at A-5.
intending to make the relevant comparison point out the risks ordinarily encountered
by the prospective research subject. This approach would allow classifying research
risks as minimal if they were reasonably equivalent to those the subject encountered in
ordinary life or routine medical care. Using this approach with persons with mental
disorders who face higher-than-average risks in everyday life and clinical care, a
research intervention could be classified as minimal risk for them, but classified as
more-than-minimal risk for healthy persons. If this was the intention of the drafters of
the regulations, it is not at all clear in the current Common Rule.

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

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

239 The Medical Research Council of Canada, The Natural Sciences and Engineering Research Council of Canada,
and The Social Sciences and Humanities Research Council of Canada, Code of Ethical Conduct for Research
Involving Humans (The Tri-Council Working Group, July 1997) p. 16
240 Id. at 14.
special vulnerability of those subjects with respect to those procedures might not be
taken into account. A procedure classified as minimal risk at one institution could be
classified as higher risk at another, or even from one study to another. Also needed is
more discussion and clarification of acceptable risk in research involving incapable
adults whose ongoing health problems expose them to risks in their everyday clinical
setting. Because some persons with mental disorders who are accustomed to certain
procedures may experience fewer burdens when undergoing them for research
purposes, some would argue that it may be defensible to classify the risks to them as
lower than would be the case for someone unfamiliar with the procedures.

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

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Prior exposure to procedures could actually increase the fear and anxiety for some incapable subjects. Incapable adults with memory impairment may not recall undergoing procedures; for them, each procedure will be experienced as a new one.
accomplishing the twin goals of providing protection for persons with mental disorders
while encouraging important research to go forward.

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

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.
245Ibid at A-17.
A list of minimal risk procedures for dementia patients includes "routine observation, data collection, answering a questionnaire, epidemiological surveys, venipuncture, and blood sampling," as well as neuropsychological testing. Though some reportedly classify lumbar punctures and bone marrow biopsies as presenting a minor increase over minimal risk, Keyserlingk suggests that such procedures may present "greater risks for some patients with dementia who are unable to understand or tolerate the pain or discomfort" accompanying the interventions.

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

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

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246 Keyserlingk, et al., supra, at 330.
247 Id. at 330.
Therefore, the risks associated with specific research procedures should not be underestimated by citing the subjects’ other experiences, including those in their everyday lives or those associated with their ongoing health care.

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

Assessing Risk

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

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250 Meslin EM. Protecting human subjects from harm through improved risk judgments. IRB. Jan/Feb 1990: 7-10.
assessment should be a value-free determination limited only by the technical ability to
derive probability estimates. In contrast, the "subjectivist" school argues that the
values of those who conduct the assessment, those who interpret the results, and those
who bear the risks should play a role in the overall assessment of risks. It would
seem to us that both schools of thought ought to influence IRB decision making, the
former because risk judgments should be empirically based insofar as possible, and the
latter because there are contributions that many who have an interest in research with
persons who have impaired decisionmaking capacity can make to these assessments
despite the lack of formal quantitative data.

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

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252 Schrader-Frechette, K. Values, scientific objectivity and risk analysis: five dilemmas, In Humber JM, and
254 Keyserlingk, et al., supra, at 324.
Because of this special vulnerability to harm and discomfort, risk assessment should incorporate reliable knowledge on the range of anticipated reactions particular subjects may have to particular proposed study procedures.

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Defining Benefits

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

Direct Medical Benefit

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

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256 Keyserlingk, et al., supra, at 327.
According to the National Commission, "[t]o be considered ‘direct,’ the possibility of benefit to the subject must be fairly immediate [and t]he expectation of success should be well-founded scientifically." A more recent statement on dementia research limits direct benefit to a short- or long-range improvement, or a slowing of a degenerative process, in the specific medical condition of the relevant subject, whether in the patient's condition of dementia, a medical symptom associated with dementia, or another physical or mental condition unrelated to dementia. Such direct benefits include those resulting from diagnostic and preventative measures. Investigators' assertions that research offers the prospect of direct benefit to subjects should be carefully scrutinized by IRBs and other reviewers. Unless the distinctions between direct and indirect benefits are identified, and their relative significance explored carefully, there is a danger that investigators may construe the concept of direct benefit too broadly.

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

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258 Id. at 13.

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

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

260 This problem was of concern to the intermediate appellate court in the T.D. litigation.
research protocol may offer potential direct benefits to individual participants, it
cannot be justified by the possibility of benefit alone.

Indirect Benefit to Subjects

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

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

The principle that financial incentives should not exceed “reimbursement” for
the subject’s time and expenses, so as not to establish undue motivation to participate,

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262 Keyserlingk, et al., supra, at 327.
263 Thus, indirect benefit ought not be deemed sufficient to enter an incapable subject in studies presenting more
than a "minor increment over minimal risk." Id. at 333-34. Keyserlingk, et al. characterized indirect benefits as "by
nature difficult to predict with any accuracy and . . . often very person-specific." Id. at 327.
is well established but not always easy to apply. The problem is a complex one because normal volunteers, as well as some who are ill, may agree, for example, to pharmaceutical testing as an important supplement to their income, if not their sole income source, and their main reason for participating. Remuneration must be appropriate to justify their commitment of time and their submission to discomfort, but presumably not so great as to take unreasonable risks. Similarly, some who are suffering from an illness, especially among those who are uninsured, may be tempted to join a study if it appears that the ancillary medical care will be superior to what he or she can obtain otherwise.

Research Benefit to Others

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

Balancing Risks and Potential Benefits

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

\(^{264}\)Melnick, et al., supra, at 535.
It is commonly said that the benefits and risks must be “balanced” and shown to be “in a favorable ratio.” The metaphorical character of these terms draws attention to the difficulty in making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible.265

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

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

265Belmont, pg. 7.
offer the prospect of benefit for some individuals; this is not identical with describing research as being “therapeutic” or, worse, with describing research that may not offer the prospect of benefit as being “nontherapeutic.”

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

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

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

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

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

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

The American College of Physicians and other groups take the position that
greater-than-minimal risk research offering incapable subjects no reasonable prospect
of direct benefit should be permitted only when authorized by a research advance
directive²⁷¹ or after review and approval at the national level, through a process
resembling that set forth in the current regulations governing research involving
children.²⁷² The National Commission also recommended a national review process for

questionable capacity to enter or remain in such trials. See Appelbaum, supra; Gilbert, et al., Neuroleptic
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.
²⁷⁰ NIH Clinical Center, supra.
²⁷¹ However, the ACP would rule out research that "would unduly threaten the subject's welfare." See pp. 41-42,
above.
The Maryland draft legislation would permit research presenting more than a minor increase over minimal risk
and no reasonable prospect of direct benefit only when subjects appointed a research agent and "the research is
unambiguously included in the [incapacitated] individual's research advance directive." Office of Maryland
Attorney General, supra, at A-32. Berg proposes that high risk research offering little or no prospect of direct
subject benefit should be prohibited unless there is clear evidence that a subject's competent preferences would
support participation. Berg, supra, at 28.
²⁷² American College of Physicians, supra, at 846. See also Melnick, et al., supra, at 535 (advising national ethics
review prior to any decision to permit studies in this category).
involving persons institutionalized as mentally infirm. However, others see this position as either too liberal or too restrictive. On the one hand, some favor an absolute prohibition on moderate- or high-risk research offering no benefit to subjects but great promise of benefit to others, based on the Nuremberg Code's and the Declaration of Helsinki’s conviction that vulnerable and unconsenting individuals should not be put at undue risk for the sake of patient groups or society. Supporters of this position contend that when these documents were created, "it was presumably well understood that a price of that prohibition would be that some important research could not proceed, some research answers would be delayed, and some promising therapies and preventive measures would for the time being remain untested and unavailable." Some writers explicitly label this stance the most ethically defensible position.

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

273 Keyserlingk, 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.

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

276 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 & Speryer-Ofenberg, Incompetent Persons as Research Subjects and the Ethics of Minimal Risk, 5 Camb. Q. Healthcare Ethics 362 (1996).
minimal risk to incapable subjects. It acknowledges that "there may be some advantages" to national review, but contends that "immediate and direct monitoring of such research and on-site assurance of its humane ethical conduct are at least as important as the process of evaluation and approval of any proposed research."  

Procedures for Evaluating and Monitoring Risks

**Special Review**

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

**Opportunities to Enhance IRB Education and Decision Making**

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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.

27745 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, “Mytoblast Transfer in Duchenne Muscular Dystrophy,” August 13, 1991). The latter proposal has never been resubmitted. (Personal communication, Michael Carome, Office for Protection from Research Risks, November 3, 1997.)
We have been mindful of the concern expressed by some that IRBs, limited to two categories of risk when making judgments about the acceptability of risks in relation to potential benefits, may be inclined to consider all projects involving greater than minimal risk as requiring the most comprehensive protections. In particular, we recognize the concern expressed by some that if research involving relatively benign interventions (such as PET scans or MRIs) were categorized as greater than minimal risk, this could result in burdensome restrictions that would either substantially delay or otherwise limit research. We believe, however, that the most appropriate way of addressing this issue is not to focus on an arbitrary line, which cannot be definitively established, but rather to focus attention on improving the quality of IRB judgments generally, and on the unavoidable responsibility of IRBs to not only ensure an appropriate balance between risk and benefit, but a balance between risks and protections. We believe that this presents a useful opportunity for enhancing IRB decision making. One possible strategy may be for IRBs individually and collectively to develop "research ethics case law."

The purpose of having a set of categories is to enable individuals (in this case, IRBs) to discriminate more precisely when making judgments about whether adequate protections are in place, and whether their judgment about risk in relation to the potential benefits is appropriate. But since risk will vary along a continuum that involves a number of factors, and since IRBs currently have the authority to require a variety of additional protections for persons involved as subjects (even on minimal risk research, should they so choose), we are not persuaded by the argument that an additional category of risk is needed to assist in these decisions. We would hasten to add, however, that by limiting the categories of research to two, we are not intending for IRBs who determine that research which poses greater than minimal risk should require all available protections, nor are we presuming that having several categories of risk might serve an important heuristic purpose for IRBs. Such stratification might
be a useful educational method for training new IRB members, or could be used to help determine how individual IRB members perceive risk.

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

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

Independent Research Monitors

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

281 Keyserlingk, et al., supra, at 326.
inaccurate as research progresses. As a result, subjects' health status and experiences must be evaluated on an ongoing basis to ensure that subjects can be removed from the protocol if risks become excessive. In particular, the assessment of potential harms and benefits should be individualized for the subject in question, placing the proposed subject’s medical, psychosocial, and financial situation in context.

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

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

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

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

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

285 Orr, supra, at 1263.
286 Belmont Report, supra, at 6.
287 Office of Maryland Attorney General, supra, at A-25.
288 In the UCLA schizophrenia research, subjects received clinical care from psychiatrists who also were
coinvestigators for the study. There was concern that such a conflict of interest could lead psychiatrists to be
insufficiently responsive to signs of possible relapse in patient-subjects.
will be present during every part of an incapable subject's research involvement, and lay persons might not recognize every indication of increased risk to subjects. In these circumstances, IRBs would benefit from guidance on potential approaches to monitoring harms and benefits to individual subjects and on criteria for determining when the involvement of an independent health care professional is needed.\textsuperscript{289} NBAC believes that, at certain risk levels in research using persons with mental disorders which may affect their decisionmaking capacity, independent monitoring is essential, and that such monitoring should be an ongoing process. Indeed, in our view, IRBs should expect investigators to describe in their research proposals how potential harms to subjects will be monitored.

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

\textsuperscript{289}See Shamoo & Sharev, supra, at S:29 (researchers and IRBs should be held accountable for monitoring to ensure welfare of subjects protected; physician not associated with research or institution where research conducted should help decide whether subjects' interests served by continued participation).
Chapter Six: MOVING AHEAD IN RESEARCH INVOLVING PERSONS WITH MENTAL DISORDERS: SUMMARY AND RECOMMENDATIONS

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

Much has changed since the National Commission’s report 20 years ago. There is a much greater sensitivity to the variety of mental disorders and an improved understanding of the ways that these disorders can be recognized and ameliorated. Both diagnostic techniques and treatment methodologies have progressed, sometimes in breathtaking ways, with the promise of still greater breakthroughs on the horizon. More research is being conducted than ever before, and the research environment has become far more complex, involving both a larger societal investment than ever and a
larger role for the private sector. While by no means vanquished, the stigmatization
and marginalization of those who suffer from mental disorders that put them at risk for
impaired decision making show signs of abating as improved understanding of and
empathy for those individuals, as well as a new appreciation of the underlying biology
and, increasingly, the genetic bases of some of their conditions,\textsuperscript{290} gradually increase
among the professional and lay communities.

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

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

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

\textsuperscript{290} See, for example, \textit{Journal of the American Medical Association}, August 19, 1998.
impede the development of new treatments. It is difficult to validate such claims because there is, to date, insufficient evidence to support or reject them. NBAC does not believe, however, that the additional protections recommended in this report should excessively burden or hamper the development of effective new treatments. Moreover, it is useful to be reminded that many share in the responsibility to protect the interests of those without whom this research could not be done—especially those who may be unable to give full informed consent and who may not themselves directly benefit from the research. In our view, all research involving human beings must satisfy appropriate ethical standards; otherwise, we should not conduct research with these human subjects at all. This imperative is especially acute for potentially vulnerable populations such as individuals with mental disorders.

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

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

Recommendations for New Regulations

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

Whatever one’s view of the current regulations, the period since their adoption
has been, in the judgment of some, largely free of the sorts of large-scale problems and
abuses that led to their initial promulgation. Others, however, stress that the issues
discussed in this report illustrate some of the shortcomings of the Common Rule. In
this context, NBAC was obliged to determine whether the outstanding issues and
problems in research involving persons with mental disorders that may affect their
decisionmaking capacity warrant new regulations and/or whether some or all of the
reforms it believes are required could be advanced through other mechanisms, such as
statements of principle by those individuals involved in reviewing, regulating, and
carrying out these projects; suggested changes in professional guidance; or other
educational materials for all relevant parties.
NBAC believes that, in addition to the general regulations that already apply to all research conducted or sponsored by the Federal Government or that is otherwise subject to federal regulation, IRB deliberations and decisions about research involving subjects with mental disorders that may affect decisionmaking capacity should be governed by specific additional regulations. We come to this conclusion because regulations provide one of the most important methods used in the United States to uniformly assure the protection of the rights and welfare of human subjects. Below we propose 14 recommendations directed at the regulation of IRBs. We recognize, of course, that regulation is not the only method. For this reason, we make a number of other recommendations apart from those directly affecting regulation.

Recommendations Directed at the Regulation of IRBs

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

IRB Membership

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

The issues considered in this report are as complex and as multifaceted as the
various research protocols designed to advance medical knowledge about mental
disorders that may affect decisionmaking capacity. At least some of these issues are
likely to arise in most protocols involving research subjects with such disorders. In
general, representation of the subject population on IRBs and the increased
involvement of affected persons in planning clinical research on their disorders are
generally viewed as good ways to increase the likelihood that the IRBs’ decisions will
be responsive in appropriate ways to the interests of affected groups. More
specifically, increased subject representation on IRBs and, therefore, in the review and
conduct of research, is now an increasingly common strategy for improving the design
of research protocols that involve persons with mental disabilities.\footnote{For example, the NIH Expert Panel also recommended that IRBs include “voting members representing patient advocate groups, family members, and others not affiliated with the research institution.” Expert Panel Report to the National Institutes of Health, \textit{Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs)}, p. 3 (February 1998).} It is for these
reasons that the Common Rule directs those IRBs that frequently review research
involving a vulnerable subject group to consider including as reviewers persons
knowledgeable about and experienced with working with the relevant subject group.\footnote{45 CFR 46.107(f).}

The current provision, however, is advisory only; moreover, it refers only to the
involvement of expert professionals, not to other persons also representing the
interests of vulnerable subject groups. On the other hand, the Department of
Education’s National Institute for Disability and Rehabilitative Research (NIDRR)
must comply with a regulation that, “If an [IRB] reviews research that purposefully
requires inclusion of children with disabilities or individuals with mental disabilities as
research subjects, the IRB must have at least one person primarily concerned with the
welfare of these research subjects.” This regulation was published on the same day in 1991 as the Common Rule.

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

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

Appropriate Subject Recruitment

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

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

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294 34 CFR 97.100.
295 Office for Protection from Research Risks, supra, at 21-22.
296 See also Shamoo & Hassner Sharav, supra, at 5:29 (IRBs reviewing proposals to involve mentally disabled subjects should include at least two patient-representatives).
their mental disorder. The principle we are invoking is one of fairness in the selection of subjects—persons should not be targeted to participate in research because they are administratively convenient or unusually accessible. These same individuals, were they able to consent, would be permitted, as any person would, to choose to enter a study unrelated to their condition. This recommendation is in line with current regulations, which provide additional protections to some potentially vulnerable populations to ensure that they are not unfairly burdened with involvement in research simply because, for example, they may be more easily available.

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

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

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

Assessing Potential Subjects’ Capacity to Decide About Participating in Research

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

Notification of Determination of Incapacity and Enrollment in Research

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

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

To be found decisionally incapable and then enrolled as a subject in a research protocol on the basis of alternative decisionmaking arrangements is to have certain rights curtailed, however justifiable the curtailment may be. Some argue that whenever an individual is found to be decisionally incapable, that individual should be so notified, especially when such a finding could have important consequences for his or her medical treatment—such as enrollment in a research protocol. Such a notification process might seem, at times, to be an empty ritual and, worse, to be a requirement that could well contribute to undermining health professionals’ respect for the regulatory system. Nevertheless, ethical treatment of human subjects demands this process be observed, for to fail to do so is to deprive the subject both of the right to seek review of the decision and of the right to possible judicial intervention.

Abrogating the subject’s autonomy in such a way is indefensible in a democratic society.

Dissent from Participation in Research

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

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

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

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

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

**Recommendation 7.** Investigators should be required to provide a detailed explanation of their assessment of risks and potential benefits, including the identification, estimation, and acceptability of the risks to the subjects. This assessment should include consideration of the particular procedures proposed and
their relationship to the specific conditions of the individuals who may be involved as study subjects.

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

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

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300 45 CFR 46.100.
it would for someone who fully understood the reason for the intervention. For example, repeated venipunctures (blood draws) that might be innocuous to many people could be quite disturbing to persons with limited understanding. Thus, a procedure that per se presents minimal risk could nonetheless be highly threatening to those who are unable to appreciate the procedure’s context or the nature of their current situation.

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

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

**Protections in Research Design**

**Recommendation 8.** Investigators should be required to provide a detailed justification of the research design they will use, including any efforts they will
utilize to reduce the risk in studies which are designed to provoke symptoms, to withdraw patients rapidly from therapies, or to randomize patients into placebo controls.

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

Subjects with serious illnesses are often more vulnerable than others to exploitation when they are involved in randomized clinical trials. While the study itself may be designed so as to hold out the prospect of benefit, and satisfies the condition of clinical equipoise described above, there will be instances in which the “drug arm” of a study turns out to be more beneficial to subjects than the placebo arm. One way to
ameliorate this problem is to incorporate into the study design a nonresearch or wraparound phase following the conclusion of the research period, one that provides the subject with some beneficial intervention independently of the study itself. However, using a wraparound phase may be problematic because it may shift the balance of protection in the opposite and equally problematic direction by providing an inappropriate incentive to participate in studies in order to derive the perceived benefits without having to pay for the drugs. However, wraparounds are suitable followups to certain kinds of research, including those that provoke symptoms. In appropriate circumstances, IRBs could require a wraparound phase as part of the overall study design.

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

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

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

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

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

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

**Recommendation 10.** An IRB may approve protocols in this category of research if the potential subjects are currently incapable of making a decision about participation, are of fluctuating capacity, or are likely to become incapable during the course of the study, when the following conditions occur: the potential subjects, when previously capable of making a decision about participation in research, have previously expressed their agreement to participate in a durable power of attorney document; the subjects have been notified of the assessment of their capacity, and have not objected to or otherwise dissented from participation; and the subject’s legally authorized representative has given permission for the subject to be enrolled in the study.
Recommendation 11. An IRB may approve protocols in this category of research if the potential subjects have never been capable of making a decision to participate, when the following conditions occur: the subjects have been notified of the assessment of their capacity, and have not objected to or otherwise dissented from participation; and the subject’s legally authorized representative has given permission for the subject to be enrolled in the study.

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

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

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

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

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

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

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

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

(b) a person with the capacity to give informed consent for participation in specified future research has given consent to do so in an advance directive; there has been no material change in the research protocol or the person’s situation (apart from loss of decisionmaking capacity) between the time that the advance directive was executed and the time that the research participation is actually to begin; and, in accordance with a state statute or, to the extent permitted by state law, previously approved and published institutional rules, a legally authorized representative is available to make decisions about continuing or stopping the person’s participation in the research;
(c) in accordance with a state statute or, to the extent permitted by state law, previously approved and published institutional rules, a person with the capacity to execute an advance directive has done so, designating a research proxy and describing the research in which the person is willing to participate; the particular research is within the description in the advance directive; the designated research proxy gives informed consent to the person’s participation; and the designated research proxy is available to make decisions about continuing or stopping the person’s participation in the research; or

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

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

Recommendation 13. An IRB may approve protocols in the category of research if the potential subjects have never been capable of making a decision to participate, when the following conditions occur: the subjects have been notified of the assessment of their capacity and have not objected to or otherwise dissented from participation; and the subject’s legally authorized representative has given permission for the subject to be enrolled in the study. In addition, the IRB must ensure that there is a responsible health care professional identified and available to counsel the subject and/or the subject’s LAR about enrolling, continuing to participate in, or withdrawing from a study. In these cases, the IRB should be
especially vigilant in requiring that the presence of a mental disorder should not automatically disqualify an individual from being permitted to volunteer for a study relevant to his or her disorder, if he has sufficient capacity to consent, that cannot be conducted on others. Research proposals involving persons with mental disorders, but which is not of potential benefit to these individuals, may be conducted only under certain circumstances. For persons assessed to have the capacity to decide whether they want to participate in such a study, their informed consent is required. For persons about whom there is some question as to whether their capacity may fluctuate (or be lost entirely) during the study, their participation would be permitted only with the permission of a legally authorized representative, whose authority we discussed previously but we reiterate below. Because the representative will not ordinarily have the training to make a judgment about the subject’s medical well-being, a health professional who is not a part of the study team should also be selected to advise the representative about the subject’s continued participation. Depending on the level of risk involved, IRBs should consider whether to introduce other protections as well.

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

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

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

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

In turn, the researchers must agree to discuss information about the research subject’s treatment (e.g., possibilities of decompensation, description of likely
symptoms, data about medications and potential side effects, and possible danger to
self or others) with the surrogate decision maker and responsible health care
professional. The research team must also make adequate provision for a thorough
diagnostic assessment of the subject’s current clinical status and develop an
appropriate continuing treatment plan should the subject decompensate, become
unable to cooperate, and drop out of the study.\textsuperscript{303}

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

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

\textsuperscript{303}This language was suggested in the public comment of Dr. Hermann Diesenhaus, July 31, 1998.
establish the status of legally authorized representative for research purposes. In order
to preserve the subject’s autonomy to the greatest extent possible, the legally
authorized representative’s decisions must be based upon the subject’s wishes, so far
as they are known; if the subject’s wishes are unknown, then these decisions should be
based upon the subject’s best interests.

Additional Guidance for IRBs

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

The Research Context

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

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

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

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

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304 An expert panel convened by NIH also notes that "repeated exposure to information in 'small doses' over time may greatly improve comprehension." Expert Panel Report to the National Institutes of Health, Research Involving Individuals with Questionable Capacity to Consent: Ethical Issues and Practical Considerations for Institutional Review Boards (IRBs) p14 (February 1998).
supported by the National Institute on Aging already include such a procedure. IRBs should consider attaching a reconsent requirement to certain studies based on their length, on their risks and benefits, and on the mental condition of potential subjects, such as those with progressive neurological disorders or fluctuating capacity.

Independent Health Care Professional Advisors

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

Voluntary Self-evaluation

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

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

Guidance for Institutions

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

Audit and Disclosure

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

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

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

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

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

Recommendation to State Legislatures

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

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

Recommendation to Professionals and Organizations of Health Care Professionals

**Recommendation 15. All professionals whose expertise embraces research involving those with disorders that may affect decisionmaking capacity should find ways to recognize family members, close friends, and other important caregivers as part of the health care team and to share appropriate information**
with them. Professional organizations should open discussions about methods to pursue this goal. Innovations in this area must, of course, be consistent with the ethical obligation of patient confidentiality.

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

Recommendations to the National Institutes of Health

Further Research on Informed Consent

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

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

Further Research on Advance Planning
Recommendation 18. The National Institutes of Health should support research on the appropriate use of research durable powers of attorney and other advance planning documents for use by persons with mental disorders.
Further Recommendations

Special Expert Panel

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

Mandatory Registry

Recommendation 20. The appropriate federal agency should establish a mandatory IRB registry. This registry would require that all institutions receiving federal funds for protocols involving human subjects to register annually. The agency housing the registry should have the authority to conduct audits of IRB records and procedures without cause. The auditing agency, with full compliance of federal agencies, should have the authority to review and publicly disclose the results of its findings. Information gathered under paragraph 1, above, should be published annually. All federal actions with respect to IRB compliance and conduct should also be published annually.
Appendix 2: Flow Chart Summary of Recommended Review Procedures for IRBs
Appendix 3: Title 45 CFR Part 46—Federal Policy for the Protection of Human Subjects (enclosed)