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Chapter One:

RESEARCH INVOLVING SUBJECTS WITH MENTAL DISORDERS AFFECTING DECISIONMAKING CAPACITY

The Purpose of this Report

The use of human subjects in a wide variety of biomedical research protocols continues to play an essential role in the advancement of modern medical science and the enhancement of our ability to successfully treat various illnesses. Over the past several decades, however, there has been a growing awareness of the ethical issues associated with research protocols employing human subjects, and important new guidelines and mechanisms have been established to help ensure that studies involving human beings meet appropriate ethical standards designed to protect human subjects.[1] Moreover, 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.[2]

However, persons with psychiatric or neurologic disorders who may, as a consequence of their disease, have impaired capacity to make decisions, have not specifically been brought within

[1]In this report the Commission refers to persons who are participating in clinical research as the subjects of that research as "subjects," consistent with the language in current federal regulations.

[2]45 CFR 46, Subparts B, C, and D. June 18, 1991.

the ambit of these or other additional protections.[3] The purpose of this report is to consider ways in which ethically acceptable research can be conducted using human subjects who suffer from mental disorders that may have affected their decisionmaking capacity, whether specific 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 reflect upon the goals of research and appropriate protections for human subjects. As in all of NBAC's reports, this educational function is seen as an important part of our mission.

Research Involving Persons With Mental Disorders Affecting 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 perhaps anyone who is ill and vulnerable may be significantly less capable of making decisions than would be the case in other circumstances. But the persons with whom this report is especially concerned are those who may be candidates for involvement in a research protocol because they have a mental disorder that is being studied.

A point worthy of emphasis is that the mere diagnosis of a mental disorder does not imply

[3]Others, whose decisionmaking capacity is compromised by other factors, such as trauma (e.g., head injury) or physical illness (e.g., cancer or sepsis), will not be considered in this report. As a general rule, consent for research into their disease (e.g., cancer or sepsis) cannot be obtained from persons who lack the capacity for such autonomous consent.

a lack of decisionmaking capacity, or even that the ability to make a particular decision is impaired. Many persons who suffer from mental disorders are usually able to make decisions for themselves, such as the decision whether or not to participate in a research study. Rather, a diagnosed mental disorder is only one among many other factors that may be a reason to trigger an assessment of someone's decisionmaking capacity.

As will be explained in this report, there are special difficulties in designing ethically acceptable research protocols that employ human subjects with mental disorders whose decisionmaking capacity is impaired, difficulties that help to create a compelling case for some special protections. These conditions can complicate efforts to respect their right to decide about their care or their participation in a research project. Problems in determining the presence or absence of decisionmaking capacity are only one sort of difficulty in conducting ethically acceptable research involving persons with mental disorders.

Many of the conditions underlying impaired decisionmaking are the sort of psychiatric or neurologic conditions that manifest themselves in behaviors that make prospective subjects hard to understand and indeed often cause discomfort in others. As a result, persons with these disease have too often been stigmatized, and efforts to improve their medical treatment frequently have been marginalized. Those who are hospitalized in psychiatric units are liable to particular forms of vulnerability 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 them into a

research protocol. Finally, because mechanisms for funding appropriate treatment of these diseases are often seriously wanting, this population may be especially vulnerable as they typically do not have adequate access to health care outside the research context, even though research is not always intended to provide the subjects themselves with direct benefits.[4] Despite all this, many of the diseases from which this population suffers require study, and there are often few satisfactory treatments.

Medical science has recently made great strides in the understanding of underlying biological and chemical processes that figure in conditions that are associated with mental disorders that affect millions of Americans. As a result, issues regarding the appropriate design of research protocols involving persons with disorders that may affect decisionmaking capacity are likely to become both more prevalent and more important in the near future. The great needs of this population represent significant growth potential for the pharmaceutical industry and a valuable opportunity for research centers and all those dedicated to helping those with these disorders to expand their programs. In the United States, the increasingly important interactions between private industry, government, and academia present a favorable atmosphere for scientific development, but they also present a challenge for a regulatory framework intended to protect individuals while also permitting appropriate research and product development to flourish.

The combination of these and other factors creates a new imperative that calls for special

[4]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.

attention from the professions and those institutions that engage in research involving persons who may have decisional impairments. For historical reasons that will be described in this report, previous efforts to establish specific protections for persons with uncertain decisionmaking capacity have failed. These efforts have been hampered by social attitudes toward persons with uncertain decisionmaking capacity and of a lack of consensus about how protections should be applied to those at risk for psychiatric and neurological diseases. Our society has a moral obligation to address these issues for the sake of those who are directly affected and for those who care about them, so that important research can be continued and treatment can be improved.

The Recent Debate About Research Involving Persons With Mental Disorders

Several tensions are inherent in the current controversy. Foremost among these tensions is that those who suffer from these diseases, and those who care about them, desperately want medical science to find ways to improve their conditions, yet there is great disagreement about how this can be done without exploiting those who participate in research protocols and thus causing still greater suffering.[5] In spite of this disagreement, much can be done to ameliorate the apparent conflict between the impetus to continue promising lines of research and supporting the dignity and well-being of potential research subjects.

One way of expressing the dilemma, one that is familiar in academic writings on the ethics of research with human subjects, is that between the desire for adequate protection against

[5]Adil E. Shamoo, ed., Ethics in Neurobiological Research with Human Subjects (Gordon and Breach Publishers, 1997).

research risks and the desire to develop additional methods for dealing with a particular disorder. At the same time, calls for greater protection from research risks and greater knowledge about disease that comes with research can both be mere slogans that mask underlying problems. One such underlying problem is that many of the situations that give rise to calls for protection against abusive research are really problems of the clinical setting in which research may take place, such as insufficient attention to the emotional needs of persons afflicted with mental disorders whether or not they are research subjects.

Another complicating factor in efforts to protect human research subjects is the boundary between research and what is often called "innovative treatment." The latter is not subject to the same ethical or legal and regulatory constraints so long as it is intended to be responsive solely to the needs of an individual patient who has not responded to standard therapy, and the results are not to be presented as a scientific finding. For example, a patient whose physician recommends an "off-label"[6] trial of a medication approved for other purposes (as physicians are entitled to do as part of individualized treatment), is not a research subject unless the physician is engaged in the systematic collection of data about this use of the drug. In this kind of situation, certain existing regulatory requirements for ethically sound research, such as prior review of the procedure, do not apply. Nevertheless, the requirements of informed consent to an intended therapeutic

[6] 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. Recently some have argued that the privilege of "off-label" usage should be restricted.

treatment do apply, and the patient, or the patient's legally authorized representative, must give an informed consent to the innovative 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. Clinical studies often are not only uncertain in their potential benefits, but may actually be designed to obtain information about questions other than therapeutic efficacy. Further, the patient's 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 and that should be incorporated into the treatment of their patients.

Finally, the understandable desire to develop better treatment protocols should not obscure the fact that, even in recent years, some research protocols that have passed required review procedures and that have produced published data raise, in our opinion, important ethical concerns. In its review of research proposals involving human subjects and ionizing radiation that were approved and funded in fiscal years 1990 through 1993 by several federal agencies, the president's Advisory Committee on Human Radiation Experiments found that almost half of the studies reviewed that involved greater than minimal risk raised "serious or moderate concerns."[7] The Advisory Committee also surveyed hundreds of people who were ill but who retained decisional capacity and were currently participating in clinical trials, concluding that many of them

[7] Advisory Committee on Human Radiation Experiments, The Human Radiation Experiments (New York: Oxford University Press, 1995), p. 456.

were not aware of important and relevant elements of the research.[8] Considering the special complexities of research involving those whose decisional capacity may be affected by mental disorders, the radiation advisory committee's concerns must be at least as strongly applied to studies involving the special population that is the focus of this report.

[8]Id., pp. 459-481.

Values that Should Guide Research

Surely protection from abusive research and access to potentially beneficial research are both worthy goals and need not be incompatible. Without succumbing to a facile distinction between protection and access, an essential mission of a regulatory framework must be to help ensure that those who are employed as human subjects in biomedical and behavioral research protocols are treated with respect. This has been the underlying philosophy of more than three decades of continual improvement in the design of research protocols involving human subjects, much of which has involved gaining a more refined understanding of the meaning of respecting human subjects under specific circumstances. In that spirit, this report is partly an effort to advance public understanding of the meaning of respectful treatment of persons with mental disorders that may affect decisionmaking capacity who are participating in research protocols.

The purpose of medical research is to improve understanding of the mechanisms of disease and their means of prevention and treatment, and our society is deeply committed to continuing this enterprise, from which so many of us have benefited. It must also be acknowledged that in the expansion of this scientific knowledge often there is no reliable substitute for a human subject, and this is certainly true of the study of diseases that manifest themselves partly by altering human subjectivity or impair cognitive functioning, such as depression or delusional states.

If human beings must be involved as research subjects in order for important questions to be answered, then they must be treated with respect. Respectful treatment of human beings participating in research begins with the scientific quality of the research itself. 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. Soundness in design is a *sine qua non* for ethical research involving human subjects.

In reality, however, practice may deviate from a standard of excellence. The American people need to understand that, so long as any research is conducted involving human beings, there is a possibility that an individual will be harmed or wronged. 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 which may involve more than minimal risk and for which there may be no direct or tangible personal reward. This has led to the development of a system of protection 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.[9]

Of course, all persons suffering from an illness are at risk for impaired decision making due to physiologic and psychological 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' decision making ability can be respected and promoted. Indeed, the very fact of 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

[9]45 CFR 46, Subpart D, 1991.

situation and alternatives as objectively as those who are well.[10] 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 key to 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 decision making ability do not have the same opportunity to determine the extent of their research involvement as do the rest of us, care must be taken not to succumb to any temptations to employ members of this population in research when their participation is unnecessary. As a result, another recognized value underlying ethical research is that the burdens as well as the benefits of scientific projects should be distributed throughout the society. Some of the Commission's recommendations, therefore, are specifically designed to ensure that persons with mental disorders that may affect decisionmaking capacity are not exploited as a group of vulnerable persons.

These views about respect for persons, beneficence, and justice are squarely in the tradition established by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978). The National Commission's framework of ethical principles for the guidance of research with human subjects is no less valid today than it was nearly twenty years ago. Yet the environment of research, including the way it is conducted, its funding sources, and in many instances the complexity of the research itself, have changed.

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[10]Eric Cassell, Personal Communication, May 1998.

And in spite of the National Commission's excellent work, those with mental disorders that may affect decisionmaking capacity are not specifically recognized in current federal regulations. It is time to elaborate on the foundation laid by the National Commission and current regulations with regard to research involving persons with mental disorders.

The Nature of Mental Disorders that May Affect Decisionmaking Capacity

While there is 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 observations that call decisionmaking ability into question should trigger a clinical assessment that could lead to a determination that decisionmaking capacity 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 rise to the level at which a potential research subject would be considered unable to consent to research participation, although extra care in the informed consent process may be required. More advanced or severe forms of disorder, however, may render the subject incapable of independent choice. Thus, identification of a potential subject as suffering from a disorder that may impair mentation does not obviate the need for an individualized assessment of the person's decisionmaking abilities.

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 list highlights some of the major conditions that affect decisionmaking ability, although it 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 2-4% in the population over 65 years old to 20% or more in persons over 85 years old. [11] Dementias may also be caused by vascular infarcts of the brain, head trauma, HIV infection, and other neurological conditions, such as Parkinson's disease and Huntington's disease.

Study of decisionmaking impairment in persons with dementia has focused on Alzheimer's disease. Even patients with mild Alzheimer's dementia may evidence deficits in understanding relevant information and reasoning sufficient to call their capacities into question, although the choices they make about treatment and research may not differ at this point from non-impaired populations. As dementia progresses to the moderate stage, however, the range and magnitude of deficits expands, and many more persons fail even the simplest tests of decisionmaking capacity. [12] The co-occurrence of other disorders, such as delirium or depression, may exacerbate the impact of dementia on the ability to make decisions.

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

[12] Marson DC, Ingram KK, Cody HA, Harrell LE: Assessing the competency of patients with Alzheimer's disease under different legal standards. Archives of Neurology 52:949-954, 1995; Stanley B, Guido J, Stanley M, Shortell D: The elderly patient and informed consent. Journal of the American Medical Association 252:1302-1306, 1984.

Delirium

Like dementia, delirium involves alterations in cognition, but usually evolves over hours to days. Disturbances of consciousness and attention are prominent. Delirium is most often caused by systemic medical conditions, side-effects of medications, intoxication with or withdrawal from psychoactive agents, or toxins. [13] 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, the treatments being administered. [14] In contrast, other work suggests that serious medical illness that does not directly impair brain function, even when it results in hospitalization, is not likely, by itself, to result in limitations on decisionmaking abilities. [15]

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. [16] Many of its manifestations can be reduced with antipsychotic medication, but residual symptoms

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[13] American Psychiatric Association, DSM-IV, op. cit.
[14] Cohen LM, McCue JD, Green GM: Do clinical and formal assessment of the capacity of patients in the intensive care unit to make decisions agree? Archives of Internal Medicine 153:2481-2485, 1993.
[15] Appelbaum PS, Grisso T: Capacities of hospitalized, medically ill patients to consent to treatment. Psychosomatics 38:119-125, 1997.
[16] American Psychiatric Association, DSM-IV, op. cit.

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 understanding, appreciation, and reasoning. [17] 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. [18] Lack of insight into the presence of illness and need for treatment is common among persons with schizophrenia[19]; this may make it especially difficult for them to anticipate the consequences of their decisions 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. [20] Cognitive impairments may exist in information processing [21] and reasoning, [22] among other functions. It has also been suggested that decreased motivation to protect their interests may reduce depressed patients' abilities to make decisions,[23]

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[17] Grisso T, Appelbaum PS: The MacArthur Treatment Competence Study, III: Abilities of patients to consent to psychiatric and medical treatments. Law and Human Behavior 19:149-174, 1995.
[18] Rosenfeld B, Turkheimer E, Gardner W: Decision making in a schizophrenic population. Law and Human Behavior 16:651-662, 1992.
[19] Amador XF, Strauss DH, Yale SA, Gorman JM: Awareness of illness in schizophrenia. Schizophrenia Bulletin 17:113-132, 1991.
[20] American Psychiatric Association, DSM-IV, op. cit.
[21] Hartlarge S, Alloy LB, Vazquez C, Dykman B: Automatic and effortful processing in depression. Psychological Bulletin 113:247-278, 1993.
[22] Baker JE, Channon S: Reasoning in depression: impairment on a concept discr
nation learning task. Cognition and Emotion 9:579-597, 1995.
[23] Elliott C: Caring about risks: are severely depressed patients competent to consent to research? Archives of General Psychiatry 54:113-116, 1997.

and alter the nature of those decisions. [24] Less clear is the extent to which these consequences of depression impede decision making. One study suggested that hospitalized depressed patients may manifest problems roughly half as often as patients with schizophrenia, that is, in about one-quarter of cases. [25] 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 other conditions may also predispose to impaired decisional functions. *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 notorious for making poor decisions about money and personal affairs, and it is probable that this deficit extends into research decision making for some subset of this group. *Other psychotic disorders* involve some of the symptoms seen in schizophrenia, including delusions and hallucinations, and probably have some of the same consequences for decision making. *Substance use 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, and other mental functions.

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[24] Lee MA, Ganzini L: Depression in the elderly: effect on patient attitudes toward life-sustaining therapy. Journal of the American Geriatric Society 40:983-988, 1992.
[25] Grisso and Appelbaum, op. cit.

Informed Consent and Decision Impairments

The ability or capacity to consent in a fully informed manner to being a research subject is a critical consideration in ethical research. 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 fully capable 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 understand the relevant information about the research to be as fully informed as possible before they may be enrolled. 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, a reasonable level of risk in light of potential benefits.

Varieties of Decisionmaking Impairment

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 with the diverse ways in which it is limited. Appreciating and recognizing this diversity will help in the design of ethically sensitive recruitment procedures and research protocols.

There are at least four sorts of limitations in decisionmaking ability that need to be taken

into account in planning and executing research with this population that may lack adequate decisionmaking ability. 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 decision making 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, persons with limited capacity are in some way able to object or assent, as in the case of more advanced Alzheimer's. Fourth, persons who have lost the ability to make nearly any decision that involves any significant degree of reflection are decisionally incapable, as in the later stages of Alzheimer's and profound dementia.

These four sorts of decisional limitations -- fluctuating, prospective, limited, and complete -- provide an initial framework for the different ways the problem of decisionmaking capacity can manifest itself.[26] Among those whose capacity fluctuates or is limited, one cannot easily "read off" the precise nature of a decisional disability from these groupings. Some disorders entail limitations on decision making ability that are subtle and hard to identify, and even individuals who fit within a particular diagnostic category may exhibit their decision making limitations in different ways.

The situation is further complicated by the fact that two or more of these four categories

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

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 decision making 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 their ability to participate in the decision to enter or to continue to be part of a study, or to choose either not to enroll or to cease participation.

Finally, there are circumstantial factors that affect decision making capacity. All of us feel more "empowered" and in control in some social situations than we do in others, and some with whom we associate are more capable than others of enhancing the feeling that we are competent decision makers. Similarly, persons with neurological or psychiatric disorders may be more and less capable of making their own decisions, depending on the 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. This insight can be critical in helping the individual achieve as high a degree of self-determination as possible.

<u>The Possibility of Benefit</u>

Many research studies do not offer any reasonably expected and/or direct prospect of benefit to the human subjects involved. This may be because not enough is known about the way

a drug or device will function in human beings, or because the study is not designed to help find out about a potentially direct benefit to the subject but rather about how a person will react or how the drug or device will be affected by being in a human body. Sometimes an individual may experience benefit just from having his or her condition closely assessed or monitored by the study team, but that is not a benefit of the medication or mechanism that is being studied. Of course, healthy "normal" persons who volunteer to be in research may not expect a direct medical benefit, though they may receive limited financial compensation or the altruistic satisfaction that comes from this type of public service.

Many studies do involve interventions that could be of benefit to the subjects, but it is often not possible for the researchers to know whether these interventions would be better than nothing (as in the case of a placebo study), or whether they would be better than the currently available standard treatment. Indeed, if they were certain there would be no justification for doing the experiment in the first place. Nevertheless, even when there is justifiable uncertainty about which treatment if any is better (when the relevant scientific community is said to be in "equipoise"[27]), the investigator should have some reason to believe that the study might do some subjects some good, usually based on animal experiments or basic scientific knowledge or both.

It may be hard for anyone, let alone someone who has a decisional impairment, to appreciate the idea of equipoise, especially if they are unaccustomed to thinking in ways that

[27]Benjamin Freedman, Equipoise and the Ethics of Clinical Research, 317 New Eng. J. Med. 141 (1987).

scientists must think. When one is ill, it is all too easy to over-interpret a phrase like "some reason to believe that the study might do some subjects some good" as a prediction of benefit. But not only can the scientist in equipoise not predict that a study will do a *particular* person some good, they cannot even predict that it will benefit *any* subject. The only thing that can be promised is that a well-designed research study will advance knowledge and perhaps lead to benefits for patients.

Interest in access to potentially beneficial experimental treatment is not, of course, limited to persons with conditions that are 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 the balancing of risks and benefits from the drug or device being studied. The situation is further complicated when the caregiver is also the researcher. This "therapeutic illusion" or "therapeutic misconception"[28] may be especially intense in those whose decision making is impaired. Because many clinical trials are not primarily therapeutic opportunities, and patient-subjects may feel betrayed or abandoned when their study participation comes to an end.

Special Ethical Issues in Research with Persons with Mental Disorders

Research involving persons with mental disorders must take into account ethical issues

[28]Paul Appelbaum et al., *False hopes and best data: consent to research and the therapeutic misconception*, Hastings Cent. Rep. 17(2):20-4 (April 1987).

beyond those having to do with consent and risk and benefit, and deal also with issues that are of special relevance to this population. Currently, illnesses associated with decisional impairments often involve testing at a more primitive stage of drug development than is usually the case, because there are generally no animal models available for diseases with psychological or cognitive symptoms. The subjective nature of mental disorders may require researchers to factor more individualized judgments into their projections of risk and benefit than may be the case for other researchers in other fields.

Mental health care has a notoriously checkered history characterized by long periods of neglect, abuse, superstition and stigmatization. Sadly, 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 many of us uncomfortable. In addition, many primary health care professionals are relatively unfamiliar with the signs of these illnesses or the best treatment that is available for them, and many people 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.

Another factor that conditions research and therapy on illnesses associated with decisional impairments is that financial arrangements for treating many of these conditions continue to suffer compared to other diseases. Both public and private insurance mechanisms often fail to provide adequate support for the kinds of intervention that may be required. This problem is further

aggravated by the often resulting disadvantaged economic situation of many persons with mental disorders, who may have trouble completing education and training programs or in securing jobs due to their symptoms. As a consequence, there is a significant association between mental illness and poverty.[29] As many as half of homeless Americans are said to be suffering from schizophrenia.[30] Without adequate access to mental health care and lacking in financial resources, these people and their families may feel that research presents a rare opportunity for treatment. Again, a hope for cure can easily overwhelm an understanding of the remote likelihood of direct benefit, even among those of us who are not decisionally impaired. The ease of taking advantage of people in such a situation, (i.e., those who might succumb to the therapeutic misconception about research) must be carefully guarded against.

Although the vast majority of biomedical scientists are dedicated to improving the lives of those suffering from terrible afflictions, there are also substantial material as well as psychological rewards associated with a successful research career, a situation that creates the potential for some conflict. The reward system among scientists for research in general has become more complex in recent years. While at one time government grants might have been the main source of support among academic researchers, in some areas private industry has come to occupy a

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[29] Barker, P.R., Manderscheid, R.W., Hendershot, G.E., Jack, S.S., Schoenborn, C.A., & Goldstrom, I. (1992). Serious mental illness and disability in the adult household population: United States, 1989. In R.W. Manderscheid & M.A. Sonnenschein (Eds.), MENTAL HEALTH, UNITED STATES (DHHS Publication No. SMA 92-1942, pp. 255-261). Washington, D.C.: U.S. Government Printing Office.

[30] Cited in Peter Wyden, Conquering Schizophrenia (New York: Alfred A. Knopf, 1998).

more important role in the economy of science. Furthermore, the pressures associated with professional advancement through publication have also not lessened. Overall, these trends encourage the recruitment of human subjects. Although most clinical investigators are caring and humane and treat their patient-subjects responsibly, the evolving context of the research environment may require adjustments in regulatory processes and more particular specifications of ethical practices so that, so far as possible, ethically appropriate procedures are followed.

It has already been noted that those who struggle with diseases that impair their decisionmaking abilities are much like the rest of us when we are ill and vulnerable, but that in other respects people who have conditions that are known to be specifically associated with decisional impairments are especially vulnerable. For example, even having enrolled in a study with a reasonable understanding of the possibility of benefit, those struggling with psychiatric disease can easily feel dependent on the research institution and study personnel, engendering a fear that they will be released from the study and thereby losing all their professional support. As is so often the case, "voluntariness" is easy to require in regulations and guidelines but much harder to guarantee in the real life of those who are ill.

Finally, there is a basic difficulty that is central to deliberations on research involving those who are decisionally impaired: Our society has not decided what degree of impairment counts as a lack of decisionmaking capacity. Although there are certain clear cases, including those who are fully capable and those who are wholly without capacity, persons with fluctuating and/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 where the integrity and value of each individual is central to our political system, this question goes to the very heart of our political philosophy and must therefore be treated with utmost caution.

The Role of Informal Caregivers

In the blizzard of legal considerations and moral subtleties that swirl around the involvement of decisionally impaired persons in research, it is too easy to lose sight of the role of informal caregivers like family and friends in the care and support of persons who might be part of a study. The Commission 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.

The *de facto* role of uncompensated caregivers like family members and close friends has implications that range from the medical to the psychological to the economic. Our system has familiar inadequacies in its access to health care, especially in continuity of care, long-term care, and rehabilitation. Informal caregivers commonly complain that mental health professionals fail to include them as members of the team caring for the patient. In the words of Commission member Patricia Backlar, "currently mental health providers rarely share relevant information with the informal caregiver, nor do they ask families for information germane to treatment or legal

decisions."[31]

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 gainsaid. But within the autonomy-based framework of our society's regulatory philosophy there must also be a place for the actual roles of those with close emotional attachments to the potential subject. These individuals not only provide care and compassion for the patient-subject, they also experience the sequelae of the experimental project, both direct and indirect, through their long-term involvement with their loved one. These important social support networks must be integrated into the regulatory framework of research with those who are decisionally impaired far more actively and sensitively than has been done before.

The Promise of Research with Mental Disorders that May Cause Decisional Impairments

Psychiatric, neurological, and other mental disorders that may render persons decisionally impaired account for enormous morbidity, with its associated human and economic costs. Of the 10 leading causes of disability in the world, according to a recent World Health Organization

[31]Patricia Backlar, "Ethics in Community Mental Health Care: Confidentiality and Common Sense," Community Mental Health Journal 32(6):513-517, 1996, p. 517.

report, five were psychiatric conditions: unipolar depression, alcohol use, bipolar affective disorder, schizophrenia, and obsessive-compulsive disorder.[32] 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.[33] 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 benefits are enormous. 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.[34] Thus, every incentive exists to improve our understanding of disorders affecting brain function and to develop more effective treatments for them.

Research on these conditions falls into two broad categories: studies aimed at elucidating

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[32] World Health Organization: The Global Burden of Disease. Cambridge, MA, Harvard University Press, 1997.

[33] American Psychiatric Association: Opening Windows into the Future: Psychiatric Research in the 21st Century. Washington, DC, APA, 1997.

[34] Testimony of Steven Hyman, Director, National Institute of Mental Health, U.S. Senate Appropriations Subcommittee Hearings, 1997; Meltzer HY, Cola P, Way L, Thompson PA, Bastani B, Davies MA, Snitz B: Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. American Journal of Psychiatry 150:1630-1638, 1993.

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), fast magnetic resonance imaging (fMRI), single photon emission computer tomography (SPECT), and related devices facilitate identification of the anatomic location of brain areas involved in cognitive and affective functions. [35] 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.[36]

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.[37]

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[35] Andreasen NC, O'Leary DS, Arndt S: Neuroimaging and clinical neuroscience: basic issues and principles, in Oldham JM, Riba MB, Tasman A (eds.), American Psychiatric Press Review of Psychiatry, Vol. 12. Washington, DC, American Psychiatric Press, 1993.

[36] Baxter LR, Schwartz JM, Bergman, KS, Szuba MP, Guze BH, Mazziotta JC, Alazraki A, Selin CE, Ferng HK, Munford P, Phelps ME: Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Archives of General Psychiatry 49:681-689, 1992.

[37] American Psychiatric Association, Opening Windows, op.cit.

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 mechanisms of disease and on promising treatments must involve human subjects. Moreover, unless research is to be limited to the mildest forms of the disorders--which may differ substantively from more chronic or severe forms--persons whose decisionmaking capacities may be impaired are likely to be involved. From this reality flows the central dilemma of designing appropriate protections for persons with mental disorders who participate in such research protocols: Protection of subjects from harm must be balanced against the potential for benefit to the subjects themselves and to other persons with their disorders that may arise from their participation.

The Ethics of Study Design

There is considerable commentary on the ethical prerequisites for research involving human subjects, much of it represented in the Nuremberg Code and subsequent 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 way to obtain information that, all else being equal, would be preferable with regard to the level of risk entailed. 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 forgone if the

costs to individual subjects are too great.

Those who conduct research with human beings have the responsibility of designing studies which are both scientifically and ethically sound. While this principle may be self-evident, it has been suggested that 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.[38] Many granting and regulatory groups require that ethical research must be based on rigorous methodology and that scientific investigation must be conducted according to ethical principles. The short-hand expression, 'good science is a prerequisite for good ethics' is a helpful reminder,[39] but may not capture all of the nuances of what is morally required of high quality research design. Freedman helpfully captured the essence of this problem when he argued that scientific validity and scientific value are twin requirements for ethical research.[40] While all research should be expected to meet these requirements, studies that involve persons who are vulnerable would seem to require particular attention to these requirements. Research that is poorly designed expose individuals already at risk to the inconvenience of participation, and possibly to the specific risks of harm without any prospect of value from the knowledge to be gained, let alone any prospect of

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[38] Sutherland HJ, Meslin EM, Till JE. What's missing from current clinical trials guidelines? A framework for integrating ethics, science and community context. Journal of Clinical Ethics (Winter 1994); 5(4): 297-303.

[39]Rutstein, D., Human experimentation, A Guided Step into the Unknown, ed. W.A. Silverman, Oxford, OUP, 1986, p165.

[40]Freedman B. Scientific value and validity as ethical requirements for research: a proposed explication. IRB: A Review of Human Subjects research 9 (1987):7-10.

benefit. Deciding which design will best answer the research question, what procedures will be used, which subjects will be studied, are all question which have 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 opportunity costs associated with this choice. Further, the decision to pursue some hypotheses, and the experimental design that accompanies that decision, can have moral consequences of a very direct sort. A classic example is that of the World War II Manhattan Project scientists who hypothesized that the atomic pile would not go critical during a test run, thereby incinerating a substantial portion of Chicago.[41]

As has been the case for research with other populations, one of the controversial aspects of research involving persons with mental disorders concerns the basic design of the studies. There are, for example, concerns in some quarters regarding study designs that use drugs to stimulate behavioral or physiological manifestations of the disease under study. In "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 various interventions can be attempted and evaluated. The term "challenge study" refers to a general category of psychologic and pharmacologic provocations (Miller and Rosenstein, 1997, p. 403). Miller and Rosenstein list among these provocations: injection of intravenous amphetamine, inhaled carbon dioxide and the presentation of a phobic stimulus. The principal scientific rationale for conducting

[41] Rudner, R.,"The Scientist Qua Scientist Makes Value Judgments," *Philosophy of Science*, (Englewood Cliffs, New Jersey: Prentice Hall, 1966).

psychiatric symptom-provoking studies is "to learn more about the underlying pathophysiological mechanisms responsible for the symptomatic expression of psychiatric illnesses" (Miller and Rosenstein, 1997, p. 404).

There are several ethical issues which arise in challenge studies, and the Commission has heard testimony on this subject on several occasions by members of the public. Two concerns have emerged, both from the literature and from public testimony. The first concern is whether informed consent to participate in a study designed to provoke symptoms is possible to achieve. The second concern is whether the relationship between risks and potential benefits can ever justify enrolling individuals in such studies when the principal goal is to intentionally induce what would otherwise be considered a harmful or unwanted experience.

Another study design that has generated a good deal of concern and debate is that which entails a period without the medication that a patient has been prescribed for therapeutic purposes, a "drug holiday." Sometimes also called "washout" 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. 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, obviously there will be special ethical concerns for persons whose decision making capacity is fluctuating or absent at the time of study enrollment

Given that ethical guidelines and regulations are designed for use by IRBs, it is not surprising that when reviewed in detail, their focus tends to be on the requirement that there be scientific merit in the proposals.[42] It should be the case that scientific merit and ethical acceptability are jointly necessary for the conduct of an approval study involving human beings This view is obviously shared by many of those with responsibility for reviewing and approving research proposals: Indeed, members of institutional review boards often raise questions about alternative designs in human research, both among themselves and with investigators. A relevant question for this report is whether those sorts of discussions have been as common as they should be, both among IRB members and among 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. Many of the central issues in this report -- standards for decisional capacity, assessment of risks of harms and potential benefits, techniques for improving informed consent, recognizing the involvement of family members and friends -- turn on the integrity, caring, scientific quality, 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

[42] Sutherland HJ, Meslin EM, Till JE.. p. 297.

by IRB or other authorities, there can be no substitute for the researchers' and the research institution's ongoing commitment throughout the research process to ethically appropriate behavior. This is true not only as the research project is planned and protocols are developed, but throughout the trials themselves.

It is often noted that there is no right to conduct research with human subjects, that it is a privilege conferred to those individuals who are prepared to undergo rigorous scrutiny of their proposed studies and ongoing research trials. Nevertheless, it is a commonplace that medical scientists are under enormous pressure to find treatments for diseases that can cause much suffering. Under these conditions, the privilege of conducting human subjects research can slide too easily into the illicit notion that there is a social obligation for particular individuals to serve as research subjects.

In the United States the key role of the clinical investigator is still more heavily burdened by the fact that he or she usually is both a clinician and a medical researcher, actually playing two roles in relation to a single patient-subject. Although financial conflicts of interest are more concrete and familiar, arguably role conflict is a more pervasive and subtle problem in clinical research than financial conflict, for the goals of caring for the patient and of bringing the research project to a successful conclusion are not always completely congruent.

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? Does this patient have the capacity to decide about being in this study? Are the risks and potential benefits of study

participation acceptable for this patient? 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? All of these are critical questions the clinical investigator must consider carefully. The scientist is expected to advance knowledge that can improve the human condition and at the same time to treat human research subjects with 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 might they 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. Further, many research participants could not otherwise afford the highly specialized attention available in many protocols.

But involvement in a study should not be presented or perceived as a substitute for health care, and the research system must not become a supplement to a health care system that may not be accessible to many. 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 the primary goal of the latter is to provide medical assistance. Nor can the good intentions of most clinical investigators substitute for society's responsibility to ensure that reasonable protections are in place for those who are vulnerable, and should not be solely contingent on the good will of researchers.

Nevertheless, there is much truth to the view that in, as a practical matter, the only real

protection for human research subjects is the personal moral character of the medical scientist in whose hands are entrusted human lives. But while the clinical researcher's own morality may be a necessary element of ethically acceptable research practices, it is not alone sufficient. It would be unfair to expect that the complex moral problems arising from human subjects research can be resolved solely by individual clinicians, 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 no longer adequate to focus only on the individual in research communities.

The responsibility for insuring that the persons and rights of human subjects are protected should also to 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. This responsibility is not relieved by the approval of the investigator's research protocol by an IRB or other IRB functions as they are presently constituted.

The Structure of this Report

Four analytical chapters follow this one. The next chapter offers an account of the history of efforts to regulate research involving persons with mental disorders. It is followed by chapters on decisional impairment and incapacity; risks and potential benefits in research that includes persons with mental disorders; and informed consent, advance directives and surrogate decision making. In light of its analysis, the final chapter describes special protections recommended by

the Commission for research involving persons with mental disorders that may affect decisionmaking capacity.

The recommendations advanced at the end of this report are accompanied by an acute awareness of the already considerable burdens placed on dedicated clinical scientists and on research centers. Some of the recommendations may require a greater investment in arrangements designed to protect human research subjects, such as institutional review boards at the local level and the federal office charged with ensuring human subjects protections. But if important research to benefit our society is to flourish, 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.

Chapter Two: HISTORICAL AND CONTEMPORARY PERSPECTIVES

Historic Controversies[43]

Debate about the propriety and necessity of research with persons whose decisionmaking capacity may be affected by a mental disorder is not new, though historically these discussions have been couched in terms of particular conditions such as sexually transmitted diseases and schizophrenia. More recently, Alzheimer's disease research has emerged as a focus of concern. For at least one hundred years important scientific work has been touched by concerns about such research. This review of some prominent controversies is not presented as a general indictment of psychiatric or neurological research, or research in any field. It is intended, rather, as historical background that may help to explain how the current debate has come to pass, and how particular cases and concerns have stimulated attempts to regulate and reform research practices.

Research involving persons with mental disorders that affect decisionmaking capacity has sparked controversy since at least the turn of the century. In 1892, for example, a Prussian medical school professor had given blood serum from people with syphilis to four children and three young prostitutes. Dr. Albert Neisser was working on a syphilis vaccine, but failed to ask the permission of those he infected, or their legal guardians. When several contracted the disease, newspapers carried banner headlines about the scandal. In 1900 the Prussian government

[43] Much of the material in this chapter has been adapted from Jonathan D. Moreno, "Regulation of Research on the Decisionally Impaired: History and Gaps in the Current Regulatory System," which was presented at the conference "Conducting Research on the Decisionally Impaired," University of Maryland School of Law, May 28, 1997.

directed that medical research must have the human subject's consent.[44]

Viennese physician Julius Wagner von Jauregg was awarded the Nobel Prize for "Medicine or Physiology" in 1927 for his malaria therapy for general paresis, a condition that occurs during the tertiary phase of syphilis and can cause insanity, paralysis, and death. Von Jauregg experimented with the induction of fevers as a cure. He injected nine paralyzed patients with malaria, which was subsequently cured with quinine. The malaria-induced fevers were claimed to cure 85 percent of the patients.[45] Important as it was, Wagner von Jauregg's work was clouded by his questionable use of patients as research subjects. Like many whose use of human subjects may be challenged, von Jauregg had the reputation of a humane and dedicated physician. He was an ardent campaigner for laws to protect the insane from persecution and discrimination.[46] Following the Neisser scandal, physicians in that part of the world should have been well aware of problems in research ethics, but how these considerations might have affected Wagner von Jauregg's research design is not known.

Portuguese physician Egas Moniz, who won the Nobel Prize in 1949 also conducted research with persons whose decisionmaking capacity may have been affected by their condition. American physiologists had experimented with monkeys whose prefrontal lobes had been surgically removed. The monkeys no longer became upset when they made mistakes carrying out

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[44]George J. Annas and Michael A. Grodin, The Nazi Doctors and the Nuremberg Code (New York: Oxford University Press, 1992), pp. 127-128.

[45]"Julius Wagner von Jauregg," Nobel Prize Winners, Tyler Wasson, ed. (New York: The H.W. Wasson Co., 1987), pp. 1092-1094.

[46]Id. at 1094.

complex tasks they had learned, they seemed to be immune to anxiety and frustration,. Moniz theorized that the same may be true for severely anxious or aggressive mental patients. The operation did seem to cure at least some of the first 20 on whom it was tried.[47] Moniz supervised the performance of more than 100 "leukotomies" (later called lobotomies); he was too impaired by gout in his hands to perform the procedure himself. The technique was banned by the Portuguese government after psychiatrists who favored other treatments protested, but others adopted lobotomy, especially in the United States, and applied it widely.[48]

In retrospect, it is possible that physicians experimenting upon subjects afflicted with the disease being studied did not perceive themselves as bound by the same ethical constraints as those doing research with healthy, "normal" subjects. The theory that there has long been a different perception of the ethical constraints involved in doing research with the sick than with the healthy was also developed in another context by the federal Advisory Committee on Human Radiation Experiments.[49]

If this reconstruction of an historical assumption is correct -- even though people may not have been aware of the dichotomy of values at the time -- it may also help explain why certain very public experimental uses of persons whose decisionmaking may have been impaired did not

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[47] It is unknown what consent procedures were involved in Moniz's procedures. A requirement for consent to a surgical intervention, either from a patient or next of kin, was widely recognized in the United States at that time.

[48] "Egas Moniz," Nobel Prize Winners, ed. Tyler Wasson (New York: The H.W. Wilson Co., 1987), pp. 723-725.

[49] Advisory Committee on Human Radiation Experiments, The Human Radiation Experiments (New York: Oxford University Press, 1995).

often provoke general outrage: Apparently they were often considered less than fully eligible for normal protections and even experimental procedures conducted by physician-scientists were commonly assumed to fall within the then-privileged domain of doctor-patient relationships. Values such as telling patients the truth about their condition and upholding a patient's right to determine the goals of her or his own treatment were not widely recognized, even in principle, until quite recently. In such a climate physicians were far less constrained to be clear about the boundary between recognized and novel treatment than is the case today.

Several other innovative somatic therapies were introduced into psychiatry in the 1930s. "Shock therapy" could involve electrical impulses or drugs such as insulin to induce hypoglycemia or metrazol to induce convulsions. Contemporary psychiatrists were discomfited by the rush of these new and unproven drastic interventions, but they found themselves in a moral dilemma. As historian Gerald Grob has put it, they asked themselves whether physicians should "deploy experimental therapies on patients whose illness often impaired their mental faculties?" Finally, though, the pressure to find an effective treatment for the large numbers of chronic mental patients crowding hospitals in this heyday of institutionalization overwhelmed any concerns regarding informed consent, which seemed somewhat abstract. In Grob's words, "(I)f there was even a remote chance that an experimental therapy would aid them, should they be deprived of its use until more conclusive evidence was available?"[50]

[50] Gerald Grob, The Mad Among Us (Cambridge, Ma.: Harvard University Press, 1994), p. 181.

In the early 1950s there was a long-sought ray of hope for the medical treatment of mental disorders. Psychiatrists noticed that a class of tranquilizers seemed to ameliorate the symptoms of schizophrenia. But here, too, a shadow is cast by allegations of the inappropriate use of human subjects in these research protocols. The neuroleptic drugs unquestionably inaugurated a new era in the treatment of the mentally ill, and by the mid-1970s the deinstitutionalization policy they helped justify was well-established. Unfortunately, the new "psychoactive" medications also had serious side-effects with long-term use, a fact that had already been recognized by the 1960s.

Some commentators charged that the drug company that had marketed Thorazine, the first of these medications, conducted hasty clinical trials in its rush to bring the potentially lucrative new product to market.[51] These charges followed the thalidomide tragedy that resulted in the subsequent expansion of the U.S. Food and Drug Administration's (FDA's) authority, to include efficacy as well as toxicity in approving the sale of drugs.[52] But in the case of Thorazine, like thalidomide, the problem was not conducting overly aggressive clinical research, but just the opposite (though thalidomide's teratogenicity was so statistically infrequent that only a massive, large-scale study would have uncovered it). The alleged result was the wide prescription of a psychiatric medication whose long-term effects were not well understood, and which justified a drastically altered public policy, in effect a social and scientific experiment directed at the perennial problem of mental illness.

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[51] Phil Brown, Transfer of Care (Boston, Ma.: Routledge and Kegan Paul, 1985).

[52] Public Law 87-781, 21 U.S.C. 355, 76 Stat. 780; amending Federal Food, Drug and Cosmetic Act.

If this claim were sound it would imply a disrespectful attitude toward the individuals exposed to unproven drugs. But others argue that the source of disrespect was not the scientific community or the pharmaceutical industry but rather legislatures and naive advocates who garnered support for "deinstitutionalizaton," leading to undertreatment of individuals with psychotic symptoms and large numbers of homeless persons with mental illness. Under these conditions, the relatively positive results of studies using the new drugs in the 1950s made their introduction a compelling concern.[53]

Unfortunately, not all instances of ethically questionable research practices involving those who are decisionally impaired were intended to benefit the subjects, nor even were they 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 (i.e., considered to be less eligible for protection), especially if the subject was institutionalized. Two prominent illustrations of this scenario also occurred during the 1950s, though they were 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

[53]Steven E. Hyman to James F. Childress, "Critique of NBAC Working Paper," January 8, 1998, p. 1.

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-amphytemine (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 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 in compensation from the federal government.[54]

At around the time the Blauer case began, in the early 1950's, the Atomic Energy Commission (AEC) was helping to support studies that would demonstrate some of the peaceful uses of nuclear energy. In one such episode that came fully to light only a few years ago, the AEC co-sponsored with the Quaker Oats company study by MIT researchers of mineral uptake in the human body, using as a tracer minute amounts of radiation in breakfast cereal. Subjects included emotionally disturbed adolescent boys in Massachusetts institutions known as Fernald and Wrenthem. At Fernald, about which more is known than the other site in this study, parents were asked to consent for their boys to be in a special program called the "Science Club." They were not told the true purpose of the club, nor that tiny amounts of radiation would be ingested.

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

In its 1995 final report to the president, the Advisory Committee on Human Radiation Experiments found that government officials and biomedical professionals even *at that time* "should have recognized that when research offers *no prospect* of medical benefit, whether subjects are healthy or sick, research should not proceed without the person's consent."[55] (emphasis in original)

Both the Blauer and Fernald-Wrenthem cases involved decisionally impaired subjects but were part of research protocols that were neither intended to benefit the subjects nor designed to address the conditions that caused their impairments. Interestingly, both were also projects that were at least partly sponsored by national security agencies, a sector of government that had also used mental patients in research during the Second World War. Although the vast majority of wartime subjects were military personnel (mainly in mustard gas studies), conscientious objectors, prisoners, and psychotic patients were used in a malaria study and retarded subjects in dysentery vaccine experiments sponsored by the Committee on Medical Research, an arm of the Executive Office of the President.[56] Although the degree and quality of consent to participation in these studied greatly varied, many of the wartime subjects were voluntary, even enthusiastic, participants in research.

Among the more commonly-cited research ethics scandals there is one that also falls into the category of research with the decisionally impaired that is neither intended to benefit them

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[55] *Supra* note 8 at 504.

[56]David H. Rothman, Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making (New York: Basic Books, 1991), pp. 34-36.

directly nor to contribute to knowledge about the condition that has caused their decisional impairment: the Brooklyn Jewish Chronic Disease Hospital case in 1963, in which debilitated patients were injected with live cancer cells, apparently without their knowledge.[57] The study's purpose was to gather information on how the systems of patients with non-cancerous chronic conditions would respond to the presence of these transplanted cells. The investigators claimed to have obtained verbal consent of some sort from the subjects. They also defended the lack of documentation on the grounds that more dangerous procedures were performed without consent forms, and the lack of truth-telling because they did not want to frighten the patients. The principal investigator was censured by the New York State Board of Regents, which at that time was responsible for physician certification in the state.[58]

History of Regulatory Efforts

Most efforts to regulate the use of vulnerable human subjects have been stimulated by understandable concerns about the use of children as human subjects in research protocols, and to a lesser extent about the use of about pregnant women and fetuses and, later, prisoners. Nonetheless, prior to the 1970s there were some attempts to develop guidelines for the involvement of the decisionally impaired in various types of research protocols. One of these attempts occurred in Weimar Germany. In 1930, a doctor named Julius Moses reported that 75

[57]Ruth R. Faden and Tom L. Beauchamp, A History and Theory of Informed Consent (New York: Oxford University Press, 1986), pp. 161-162.

[58] Jay Katz, Experimentation with Human Beings (New York: Russell Sage Foundation, 1972), pp. 9-65.

children had died in Lubeck as a result of pediatricians' experimenting with tuberculosis vaccine. The German press was already highly critical of the powerful chemical manufacturers for using hospitals to test their new products. The scandal in Lubeck gave flesh to the accusations that people were being exploited (i.e., used without their consent) for potential profits.

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 resulting rules were far more comprehensive and sophisticated than anything introduced by any government until then, and compare quite favorably with modern regulations.[59] They included a requirement for consent from informed human subjects, with special protections for the mentally ill. These regulations were trampled by Hitler's regime, which used tens of thousands of concentration camp inmates in vicious experiments. 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 actions of the Hitler regime in the use of human experimental subjects, but the defense lawyers were able to call their legal status into question because they were not cited by international organizations monitoring health law in the 1930s and 1940s.[60]

However, the team that investigated the Nazi crimes did take note of the abuse of the

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[59]Hans-Martin Sass, "...." Journal of Medicine and Philosophy, 1992.

[60]Michael A. Grodin, "Historical Origins of the Nuremberg Code," in George J. Annas and Michael A. Grodin, eds., The Nazi Doctors and the Nuremberg Code (New York: Oxford University Press, 1992), pp. 129-31.

mentally ill in the context of the "T-4" or "euthanasia" program that led to the 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, and 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. This portion, which posterity knows as the Nuremberg Code, is the judges' attempt to set out the rules that should guide research protocols involving human subjects.

In his memorandum, Alexander singled out the mentally ill as a population that should be given special protections.[61] However, the judges did not include this item in their final draft. A possible explanation is that the judges did not wish to seem to be interfering in legitimate medical judgments about innovative treatment, but only to rule out non-beneficial and highly risky experiments with easily coerced populations of healthy subjects like prisoners. The Code's celebrated first line, "The voluntary consent of the human subject of research is absolutely essential," 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, as well as with the decisionally impaired.

The next major international research code clarified the situation. The World Medical

[61] Id. at 135.

Association's Declaration of Helsinki, first issued in 1964, provides for limited research involvement of incapable human subjects. The most recent version of the Declaration states, "[i]n the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation."[62] The Declaration divides research into two categories: "therapeutic" and "non-therapeutic." The Declaration appears to rule out the participation of incapable subjects in research that fails to offer them the possibility of direct benefit. When research has the advancement of knowledge for the benefit of others as its sole objective, the Declaration states, "[t]he subjects should be volunteers ...."

Two other recent documents also address research involving incapable human subjects. 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 "legal guardian or other duly authorized person" to authorize an incapable individual's research participation. The guidelines permit research involving incapable subjects only if "the degree of risk attached to interventions that are not intended to benefit the individual subject is low" and "interventions ... intended to provide therapeutic benefit are likely to be at least as advantageous to the individual as any alternative." Incapable subjects' objections to participation must be 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

[62]World Medical Association, Declaration of Helsinki, 277 JAMA 927 (1997).

reasonable medical alternative, and local law permits overriding the objection."[63]

When the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created in 1974, in the wake of the Tuskegee Syphilis Study scandal, the decisionally impaired were among the special populations that it intended to consider, partly because of the controversy about lobotomy. The National Commission's report on those who were carefully described as "institutionalized as mentally infirm" (IMI) came at the very end of its tenure. In its 1977 "Report and Recommendations on Research Involving Children,"[64] and its 1978 "Report and Recommendations on Research Involving Those Institutionalized as Mentally Infirm,"[65] the National Commission rejected both the Nuremberg Code's complete ban and the Helsinki Declaration's limitation on the involvement of incapable subjects. The members of the National Commission believed a less restrictive approach was justified to avoid harm to incapable persons as a group:

> since some research involving the mentally infirm cannot be undertaken with any other group, and since this research may yield significant knowledge about the causes and treatment of mental disabilities, it is necessary to consider the

[63] CIOMS/WHO, International Ethical Guidelines for Biomedical Research Involving Human Subjects 22 (1993).

[64] National Commission, Report and Recommendations, Research Involving Children (1977) [hereinafter Report on Children].

[65] National Commission, Report and Recommendations, Research Involving Those Institutionalized as Mentally Infirm (1978) [hereinafter Report on Institutionalized Persons].

> 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.[66]

The National Commission concluded that the dual goals of benefiting the class of 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. The National Commission's proposals regarding children and institutionalized persons with mental impairments were similar, though with some variation. The proposals had several elements in common: a requirement to justify the involvement of these subject groups rather than alternative less vulnerable subject populations; a hierarchy of research categories establishing more rigorous substantive and procedural standards for proposals presenting more than minimal risk to incapable subjects; and a mechanism for incapable subjects to provide input in the form of "assent" or objection to study participation, that is, a simple yes or no when questioned about willingness to be in a study.

Differences in the recommendations on children and institutionalized persons were based

[66] Id. at 58.

on the Commissioners' 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" presenting greater than minimal risk. Moreover, the members of the National Commission believed such auditors should be *required* in projects presenting no prospect of direct benefit and more than minimal risk to subjects. The National Commission's proposals also gave incapable adults more authority than children to block study participation.[67] Finally, because incapable adults usually lack the clear legal guardian that most children have, the Commission noted that in some cases a court-appointed guardian would be required to provide adequate authority for 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. The regulations on research involving children were adopted by the Department of Health and Human Services (DHHS) in June 1983.[68] The proposed regulations on persons institutionalized as

[67] The 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 presents a prospect of direct benefit to subjects not available outside the research context.

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

mentally disabled were never adopted, however.[69]

The Secretary of DHHS attributed the government's failure to issue final regulations on research involving institutionalized persons 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 Commission's recommendations.[70] Robert Levine blames the reported lack of consensus on DHEW's earlier failure to adhere to the Commission's recommendations. The agency's proposed regulations indicated that consent auditors might be mandatory for all research involving institutionalized mentally disabled persons. Moreover, they 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.[71]

With the exception of the Institutionalized as Mentally Infirm recommendations, the 1981

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

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

[71] Robert J. Levine, “Proposed Regulations for Research Involving Those Institutionalized as Mentally Infirm: A Consideration of Their Relevance in 1996,” IRB, Sept.-Oct. 1996, at 1. See also Richard Bonnie, “Research With Cognitively Impaired Subjects,” 54 Arch. Gen. Psych. 105, 107 (1997) (debate over proposed regulations provoked division between scientists concerned that safeguards, especially consent auditors and subject advocates, would significantly hinder research and advocates for mentally disabled persons, concerned about subjects' vulnerability). Bonnie also refers to opposition to special regulations for persons with mental illness on grounds that such an approach would foster negative stereotypes about such individuals.

DHHS rules largely followed from the National Commission's work. In 1991 these rules were codified for 17 federal agencies that conduct or sponsor research with human subjects and are now known as the "Common Rule."[72] The regulations do authorize IRBs to institute additional safeguards for research involving vulnerable groups, including the mentally disabled.[73] The safeguards could involve consultation with specialists concerning the risks and benefits of a procedure for this populations, or special monitoring of consent processes to ensure voluntariness. But it is not known how frequently IRBs actually implement such further conditions.

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." This document allows persons without the capacity to consent to be involved in research if *all* the following conditions are met: "the results of the research have the potential to produce real and direct benefit to his or her health"; "research of comparable effectiveness cannot be carried out on individuals capable of giving consent"; and participation is authorized by the incapable person's "representative or an authority or a person or body provided by law"; and the incapable person does not object to participation.

The document also 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

[72]Federal Policy for the Protection of Human Subjects; Notices and Rules, 56 Fed. Reg. 28002-28032 (June 18, 1991).

[73]Ibid.

knowledge for the benefit of persons with the same condition; and (2) "entails only minimal risk and minimal burden for the individual concerned."[74]

The Contemporary Debate

In the United States at this time, no special regulations govern research involving adults diagnosed with a condition characterized by mental impairment. Such research is governed by the Common Rule,[75] the general federal provisions governing human subjects research. A few Common Rule provisions address research involving persons with mental disabilities. The Rule identifies "mentally disabled persons" as a vulnerable population. Institutional review boards are directed to include "additional [unspecified] safeguards ... to protect the rights and welfare" of mentally disabled research subjects; IRBs are also advised to ensure that "subject selection is equitable," and that mentally disabled persons are not involved in research that could be conducted on a less vulnerable group.[76] 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."[77] The Rule allows an incapable individual's "legally

[74] Council of Europe, Convention on Human Rights and Medicine (Nov. 1996), Articles 6 and 17. 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.

[75] Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28012 (1991).

[76] Sec. ___.111 (a)(3) & (b).

[77] Sec. ___.107(a).

authorized representative" to give valid consent to the individual's research participation,[78] 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 benefits is acceptable.

In the 1980s and 1990s, numerous groups and individuals expressed dissatisfaction with gaps in the existing regulations. For example, the Advisory Committee on Human Radiation Experiments reviewed eight studies conducted in the early 1990s involving adult subjects with uncertain decisionmaking capacity. Four of these studies required subjects to undergo diagnostic imaging that offered them no prospect of direct benefit, and two appeared to present greater than minimal risk. Yet, as the Committee noted, "there was no discussion in the documents or consent form of the implications for the subjects of these potentially anxiety-provoking conditions. Nor was there discussion of the subjects' capacity to consent or evidence that appropriate surrogate decision makers had given permission for their participation."[79] Inquiries into studies involving medication withdrawal from persons diagnosed with schizophrenia also have raised questions about the adequacy of existing federal policy and the ethical acceptability of certain existing research protocols.[80]

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[78] Sec. ___.116

[79] Final Report, supra, at 706-07.

[80] Office for Protection from Research Risks, Evaluation of Human Subject Protections in Schizophrenia Research Conducted by the University of California, Los Angeles (1994). See also Shamoo & Keay, Ethical Concerns About Relapse Studies, 5 Camb. Q. Healthcare Ethics 373 (1996) (in review of 41 U.S. studies involving relapse published between 1966 and 1993, authors found frequent lack of attention to capacity assessment, subject or proxy consent, risk reduction

There appears to be strong indirect evidence that IRBs are unlikely to adequately compensate for the lack of specific regulations for research with persons with cognitive impairments by aggressive use of their existing discretionary authority. Observers of the local review process agree that, if anything, the IRB workload has greatly increased since the current regulatory system was first implemented. As research has proliferated IRBs appear to have all they can handle to keep up with their workload and mounting paperwork. Moreover, monitoring of a protocol's progress after approval is practically non-existent, apart from investigators' routine filing of annual progress reports. After the initial stages, local review has only minimal impact on actual research practices.[81]

The lack of more specific federal guidance on research involving persons with mental disorders that may affect their decisionmaking capacity has also meant that non-federally funded research has gone its own way, or rather at least 50 different ways. State laws and regulations in this area vary widely; most states have no rules that specifically apply to this group while some have quite restrictive regulations. Recent events in New York State illustrate the situation. The Supreme Court of New York prohibited carrying out all State-sponsored, greater-than-minimal-risk research that does not offer potential benefit to the subjects themselves in mental institutions that are operated or regulated by the state, unless the subjects can give valid informed consent.

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and justification, and monitoring to avoid harm to subjects after studies were initiated).

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

The court enforced restrictive research regulations as a result of a law suit that challenged the constitutionality of regulations promulgated by the New York State Office of Mental Health. The decision in the so-called T.D. case, which resulted from a suit brought by former patients and several advocacy organizations, came with harsh criticism of state practices, some administrative, some technical, and some constitutional in nature. Among other charges, the plaintiffs claimed that proper procedures were not in place for reviewing and monitoring research of this kind.[82] Ironically, the court limited its ruling to research that was not subject to federal regulations, under the apparent -- but, as previously mentioned erroneous -- impression that the federal regulations provide special protection for subjects with mental disorders that may affect their decisionmaking capacity.

The growing interest in research with this population stems partly from the most recent well-publicized incident with this population, the suicide of a former subject in a "drug free" or "washout" study at UCLA.[83] The National Institutes of Health Office for Protection from Research Risks (OPRR) concluded that the study design was ethical but the informed consent form flawed.[84] Defenders of the research claim that patients are often taken off all medication to establish various baseline measurements following admission to inpatient units, while admitting

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[82] T.D. vs New York State Office of Mental Health, New York City, No. 5136/91 (S.C., A.D., order issued 18 January 1996).

[83] Adil E. Shamoo and Timothy J. Keay, "Ethical Concerns about Relapse Studies," Cambridge Quarterly of Healthcare Ethics 5:373-386, 1996.

[84] Office for Protection from Research Risks Division of Human Subject Protections. Evaluation of Human Subject Protections in Schizophrenia Research Conducted by the University of California, Los Angeles. Los Angeles, University of California, 1994.

that withdrawing psychotropic drugs poses the danger of relapse and must be more carefully managed.[85]

The Role of the National Bioethics Advisory Commission

Dissatisfaction with the current regulatory system also has driven many organizations and individuals to propose additional provisions to govern research involving persons with mental disorders in general, as well as on particular subgroups, such as persons with dementia and persons diagnosed with particular psychiatric disorders. In recent years a network of former patients and concerned family members has grown around the topic of research involving persons with mental disorders that may affect their decisionmaking capacity and has led to the creation of a number of specialized publications. Representatives of several of these groups, including persons who were research subjects and their family members, were among those who have spoken before the Commission.

Although the Commission does not have the authority to investigate specific complaints that have been offered by some of those who testified, it is persuaded that there is substantial public concern about actual or potential failures to protect persons suffering from mental disorders from inappropriate research protocols. It also believes that many clinical investigators may feel unsure about how they should conduct themselves when working 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

[85] R.J. Beldessarini, "Chemotherapy." In: A.M. Nicolai (ed.), Harvard Guide to Modern Psychiatry (Cambridge, Ma.: Harvard University Press, 1978), pp. 387-432.

present system for the protection of human research subjects now appear to be warranted with regard to those who suffer from mental disorders that may affect decisionmaking capacity.

Chapter Three: DECISIONAL IMPAIRMENT AND INCAPACITY

The Centrality of Voluntary and Informed Choice

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 the premises underlying governmental and professional regulation of all research with human subjects. Ever since the horrific revelations in the trial of the Nazi doctors at Nuremberg, it has generally been accepted that some means of social control is necessary to minimize the possibility that ethically unjustified harms may be done to human beings in the service of scientific and medical advances. The Nuremberg Code and the regulatory structure that has grown up over the past thirty years in the United States proceed on the premise that the central objective in regulating human subjects research is to protect potential subjects from unjustified harms by establishing barriers to research protocols that do not meet accepted ethical standards. The result has been the establishment of a system of prior review of research protocols anchored in the scientific quality of the protocol itself and informed consent and aimed at weeding out those protocols that would expose subjects to inappropriate risks.

In recent years, however, challenges have been raised to these goals, as some have argued that another goal -- ensuring access of all groups to experimental treatments -- also should shape the social control of research. In this view, insistence upon obtaining the maximum benefit from research while minimizing the risk of harm to subjects unduly restricts the ability of some patients to obtain new medical interventions for their conditions, and hence regulatory requirements

should be adjusted to make it easier for people to become research subjects and to gain access to experimental interventions.

The tension between these two paradigms remains to be resolved. In the present context, however, what may be most noteworthy is that both rely on the voluntary and informed choice of the potential subjects of research. The Nuremberg Code makes such consent the first, essential requisite of ethical research; likewise the current demands for greater access rest on a model of patient self-determination. Thus, in either view, research protocols are not acceptable if subjects have not had the opportunity to be informed about the methods, objectives, and potential benefits and risks of research and to decide whether or not to participate in a free and uncoerced fashion.

Plainly, then, the capacity to participate in this process of informed decisionmaking lies at the heart of the present system of social control of biomedical and behavioral research. Under such a framework those who lack such capacity, or whose capacity is uncertain, may thus be excluded from research, and there would be no way to assess many new clinical approaches to the diseases from which they suffer. Under the "protection model" such exclusion may seem appropriate, as the underlying premise is that it is better to protect subjects (who may be unwilling participants) from being harmed, even at the cost of slowing down scientific investigation and medical advances. Conversely, under the "access model," barriers to research with persons with conditions that affect decisionmaking capacity are suspect because they prevent some people from obtaining the 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. From either perspective impaired decisionmaking capacity presents a pivotal problem.

Persistent Decisional Impairments

As noted above, voluntary, informed consent is commonly regarded as an essential feature of ethically and legally acceptable research. It embodies the respect for persons that is one of the foundational principles for all physician-patient interactions (and of our political system), and it is seen as one of the basic means of protecting people from unwarranted research risks. The threshold concept 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 carries a legal rather than a moral import. Capacity is also a functional concept, whereas competence carries a more global connotation.

Individuals whose capacity to make decisions is merely uncertain must be presumed capable until they are evaluated by a qualified professional. Following a proper assessment, a person who lacks the capacity to be an informed decisionmaker may be thought of as "decisionally impaired." Impairments can result from a variety of causes, including medical illnesses, cognitive difficulties as well as constraints on personal freedom due to institutionalization, dependency upon those who provide one's treatment, or other causes. The specific concern of this report, however, is with persons whose decisional impairments may be related to the presence of 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 are 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.[86] Rather, the impairments that raise the greatest concern are those that persist as a feature of a person's psychology. 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. Often these conditions are caused by (or, in medical parlance "secondary to") a progressive disease, an injury, a neurological impairment, or a psychiatric illness. 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 are relevant to these other factors that may affect decisionmaking capacity, but, again, our primary concern is with neurologic or psychiatric conditions and their

[86]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 (Oct. 2, 1996).

affect on the decisional capacity of potential research subjects.

It is neither ethically acceptable nor empirically accurate simply to presume that individuals with ongoing medical problems are decisionally impaired. Less obvious, it is also inappropriate to suppose that those who exhibit some decisionmaking deficit cannot be helped to attain a level of functioning that would enable them to be part of a valid consent process. Once these facts are appreciated they help make us aware of the special ethical obligations that are imposed on medical institutions and society in general when research with persons who may be decisionally impaired is contemplated.

Not only must psychological and medical factors be taken into account, but a full understanding of the nature of impaired decision making may also require a broader perspective. As has already been noted, even those of us who would not count as suffering from a decisional impairment may be disoriented when placed in a patient role, with all its attendant social inequalities and vulnerabilities. Persons with a tendency toward impaired decision making due to a mental disorder may experience the consequences of institutionalization in a still 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 of the consent. Such an appreciation may also provide practical insights that can improve the process, such as the use of peers (other persons with similar mental disorders who have already participated in the research) in the consent encounter or in drafting forms to render them more accessible. 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.

Immaturity and Decisional Incapacity[87]

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 decisionmaking, and assuming such an impairment is a form of prejudice toward older persons.

Therefore when we speak of decisional impairments in the context in research employing human subjects who suffer from mental disorders we intend an incapacity that is not part of normal growth and development. Senile dementia is not part and parcel 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 biologically defined populations (

[87]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.

pregnant women) or even certain socially defined groups (prisoners).[88] 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.

Although persons with mental disorders are not necessarily in the same moral position as young children, the fact that our society does impose special restrictions on research involving children, who are unable to make many decisions for themselves, also has moral implications for research involving those who have uncertain capacity. At the very least, this state of affairs argues for additional special protections for persons with mental disorders that may affect decisionmaking capacity, especially considering the other social, financial, and interpersonal factors that make some of these conditions so burdensome.

Impairment versus Incapacity

In practice, it is not usually hard to determine whether a person has the ability to make a decision or not. Findings of incapacity in a global sense are not usually very challenging or subject to much disagreement. Much more challenging (and the subject of numerous "hard cases" in the law) is determining whether someone with limited decisional capacity, a decisional impairment, nevertheless has sufficient capacity so that a particular choice should be respected

[88] 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.

Having a decisional impairment need not imply a particular social or legal status. Persons who are institutionalized may not be decisionally impaired and those who are not institutionalized may have impaired decisionmaking capacity. 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. As a functional term, decisional impairment is neutral with respect to other particular characteristics an individual may possess. Thomas Grisso and Paul Appelbaum note that what counts as impaired decisionmaking is partly determined by the standard of competence that is chosen. Among the several major standards for assessing decisional capacity related to treatment (understanding, appreciation, and reasoning), no single standard applies to all the patients that the others apply to. If more than one standard is used the result could be over-inclusive and therefore deprive a large number of people of their rights to make treatment decisions. Thus what counts as decisional capacity is dependent upon a subtle set of assumptions that are far from obvious.[89]

Even once the standard of capacity has been chosen, one must set the threshold that distinguishes those who meet the standard that has been selected from those who do not. Where to set the threshold of capacity is partly a decision that must be made 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 set

[89]Thomas Grisso and Paul S. Appelbaum, "Comparison of Standards for Assessing Patients' Capacities to Make Treatment Decisions," American Journal of Psychiatry 152:7(1033-1037), 1995.

very low. But the selection of a threshold of decisional ability certainly is not wholly a political one, as it must be justified by the individual's ability to satisfy certain benchmarks. One such benchmark is the ability to understand the implications of one choice or another for their future, another the ability to communicate a preference. In turn, a society's institutions must frame information and alternatives in a manner that is suitable for that individual's level of capacity.

Decisional impairment is not only a matter of the relevant standard and degree. Another quality of decisional impairment that is often encountered in the clinical setting is the waxing and waning fashion in which such impairments manifest themselves. The gradual loss of capacity due to a neurodegenerative disease is rarely a straight line, and psychiatric illnesses like bi-polar disease are notorious for their sometimes very substantial periods of lucidity along with cycles of mania and depression.

For all these reasons, and others, determining the proper standards and procedures to govern capacity assessment poses a major challenge in formulating policy on research involving subjects with mental disorders affecting decisionmaking capacity. As noted above, persons with such disorders vary widely in their ability to engage in independent decisionmaking. Persons with mental disorders may retain such capacity, 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 become intermittently and then permanently unable to make their own decisions. Some individuals with developmental disabilities are capable of making many choices for themselves; others completely lack such

capacity.[90]

Incorrect capacity determinations are problematic, therefore, because of their moral consequences. A judgment 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 -- all serious matters. Conversely, a judgment that an incapable person is capable leaves that individual unprotected and vulnerable to exploitation by others.[91] In addition, the presence of many marginal cases among members of the relevant populations triggers concern about the adequacy of our ability to make capacity assessments for many individuals. Although it is important to accord due respect to mentally disabled persons capable of autonomous choice, it is also important to recognize that investigators seeking to enroll subjects face conflicting interests, and perhaps some may be too willing to label prospective subjects capable when this will advance their research objectives.[92]

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

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

[92] See, e.g., Marson, et al., 45 J. Am. Geriatrics Soc'y 453, 455 (1997) ("researchers increasingly desire and encourage" patients with Alzheimer's disease to participate in research, but at the same time, "the progressive cognitive impairment characteristic of the disease relentlessly erodes decision-making capacity and makes AD patients vulnerable to coercion and exploitation"). See also Shamoo & Keay, supra, at 373 (1996) (expressing concern about researchers' assumptions of subject capacity, for example, in one study authors asserted that all twenty-eight acutely psychotic subjects with schizophrenia "were capable of informed consent and entered voluntarily." Note, however, that this does not imply that the first 28 such patients were all enrolled.)

Existing federal policy fails to provide guidance to investigators and IRBs on the appropriate substantive and procedural standards applicable to capacity determinations in research involving mentally disabled subjects. In the current situation, individual IRBs determine how investigators are to address these matters. The likely result is substantial variation in the criteria and safeguards applied to this form of research.[93] Some commentators support more systematic and specific federal direction on capacity assessment.[94] More guidance is needed not only for defining decisional capacity in the research context, but also for developing better procedures for assessing such capacity.

Procedures for Capacity Assessment and Information Disclosure

Shortcomings in the process of capacity assessment were cited in the T.D. case mentioned earlier, a recent New York appellate court decision invalidating state regulations governing nonfederally funded research involving incapable adult residents of facilities operated and licensed by the New York State Office of Mental Health. Plaintiffs in the case were involuntarily hospitalized individuals deemed incapable of making treatment decisions who feared they would also be labeled incapable of research decisionmaking and then "forced" to participate in greater-than-minimal risk studies.

The New York regulations gave the IRB "complete discretion in designating the individual or individuals who will make the assessment [of subject] capacity and who will thereafter review

[93] Bonnie, supra, at 109.
[94] E.g., id.

the researcher's initial assessment." This flexibility, together with the absence of "appropriate and specific provisions for notice to the potential subject that his or her capacity is being evaluated and for appropriate administrative and judicial review of a determination of capacity," contributed to the court's conclusion that the regulations violated the due process requirements of the New York State Constitution and the Fourteenth Amendment to the U.S. Constitution.[95] This decision raised questions about the constitutional status of the existing federal regulations as well, since they closely resemble the invalidated New York regulations. However, the New York State Court of Appeals has since concluded that the constitutional issues should not have been raised by the lower court, because the relief sought by the plaintiffs could be granted on more limited grounds. [96]

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.[97] Evaluating decisional capacity is even a 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 our peformance does not always reflect our

[95] T.D. v. N.Y. State Office of Mental Health, 650 N.Y.S.2d 173 (App. Div. 1996).
[96] See Capron, Incapacitated Research, Hastings Center Rep. Mar.-Apr. 1997, at 25.

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

capacity or potential. Many factors can inhibit performance, including anxiety or environmental conditions. 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, by whom, etc.), is so important.

Unlike the discrepancy between capacity and performance, a major point of contention that has been widely discussed is whether capacity assessment and information disclosure should be conducted by an individual not otherwise connected with the research project. The National Commission recommended that IRBs have discretion to require an independent "consent auditor" for projects presenting greater than minimal risk to persons institutionalized as mentally infirm. 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 subject's continued willingness to participate.[98] The Commission recommended that such auditors be required for projects presenting greater than minimal risk and no prospect of direct benefit to subjects. The DHEW regulations contemplated mandating auditors for all projects involving this subject population, but, as noted above, opposition to this proposal reportedly was one reason the regulations never became final.

[98] The Commission discussed the auditor's observation of ongoing research as a means to ensure continued assent, but the mechanism could also be adopted to monitor a capable subject's continued consent, especially if a decline in capacity is possible.

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 evaluators becomes increasingly justified as net research risks to subjects increase. A distinguished team of Canadian scholars took this position in its recent recommendations on dementia research.[99] 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." This 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 benefit to subjects, an independent assessor/monitor should be appointed.[100]

Others appear open to general use of outside observers and examiners. Recent guidelines adopted by the Loma Linda University IRB state, "[c]onsent observers who are independent of the investigator and of the institution will be required by the IRB in those conditions where the potential subject's decisionmaking capacity is suspect."[101] In testimony before the National Bioethics Advisory Commission, representatives of Citizens for Responsible Care in Psychiatry

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[99] Keyserlingk, et al., supra.

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

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

and Research recommended that "[a]n independent psychiatrist ... determine the capacity of [the] potential participant to comprehend the risks and benefits of enrolling in the proposed research study."[102] Recent articles also endorse the participation of a "special research educator" in the disclosure and decision process, particularly to ensure that prospective subjects understand that advancement of general knowledge is the primary goal of the project at hand.[103]

A 1991 article makes a strong case for an independent, federally-employed patient-advocate's involvement in capacity determinations, as well as in assisting and monitoring decisionmaking by family surrogates 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, 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

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

[103] DeRenzo, The Ethics of Involving Psychiatrically Impaired Persons in Research, IRB, Nov.-Dec. 1994. In a study of this approach, researchers found that the participation of a trained educator increased the comprehension of psychiatric patients asked to enroll in research. Appelbaum, et al., False Hopes and Best Data: Consent to Research and the Therapeutic Misconception, Hastings Center Rep., April 1987, at 20.

> members of vulnerable populations have been enlisted as subjects. Second, the interests of medical researchers in securing participation in the experiment often conflicts with their duties as treating physicians to inform, advise, and act in the best interests of their patients. Third, experimentation is inherently highly intrusive and dangerous, as the nature and magnitude of risks involved are largely unknown and unknowable.[104]

In contrast, Bein suggests that courts have not demanded such safeguards for decisions on life-sustaining treatment, based on an absence of the above features in the treatment setting. He also argues that an IRB-administered system of patient-advocates would provide inadequate oversight because such a system would be too responsive to institutional interests.[105]

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 consent interviews, second opinions, use of consent

[104] Bein, supra, at 748-49.
[105] Id. at 762.

specialists, or concurrent consent by a family member."[106]

Many groups advise the involvement of a trusted family member or friend in the disclosure and decisionmaking process. Capable subjects reportedly are often willing to permit such involvement. Dementia researchers frequently adopt a mechanism called "double" or "dual" informed consent when the capacities of prospective subjects are uncertain or fluctuating.[107] This approach has the virtue of providing a concerned back-up listener and questioner who "may help the cognitively impaired individual understand the research and exercise a meaningful informed consent."[108] 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.[109]

Another suggestion is to require the use of a two-part consent process. 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 retested. This process is likely to yield more accurate judgments of subject capacity than a less

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[106] Bonnie, supra, at 110.

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

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

[109] Id.

systematic and rigorous inquiry.[110]

Finally, numerous ideas have been offered to make information more accessible to subjects capable of exercising independent choice. Simple perceptual aids, such as increasing the type size of printed material, may enhance the ability of elderly subjects to comprehend the necessary information. Information can be delivered through videotape, slides, or pictorial presentations. Another interesting suggestion is for investigators to ask representatives of the affected population to critique drafts of information materials prior to their actual research use.[111]

The literature offers fewer suggestions for ensuring adequate voluntariness. The Helsinki Declaration 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 or him or her or may consent under duress." In these circumstances, "informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship."[112] To guard against pressure from family or other caregivers, someone should talk separately with consenting subjects on their reasons for participating. Again, the issue is whether a research team member, independent evaluator, or IRB representative should be given this responsibility.

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

[111] Melnick, et al., supra.

[112] World Medical Association, supra.

Substantive Requirements for Research Decisionmaking

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."[113] Subjects also should "comprehend the fact that the suggested intervention is in fact research (and is not intended to provide therapeutic benefit when that is the case)," and that they may decide against participation "without jeopardizing the care and concern of health care providers."[114]

There is consensus that decisional capacity requires a certain level of cognitive ability. Less agreement exists on whether subjects should be judged incapable if they lack affective appreciation of the choice before them. In a recent article, Carl Elliott argues that some depressed persons "might realize that a protocol involves risks, but simply not *care* about the

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[113] High, et al., Guidelines for Addressing Ethical and Legal Issues in Alzheimer Disease Research: A Position Paper, 8 Alzheimer Dis. Assoc. Disord. 66, 69 (Supp. 4, 1994).

In discussing decisional capacity in the research context, many writers also cite the President's Commission's requirements for treatment decisionmaking capacity: (1) possession of a set of values and goals; (2) ability to communicate and comprehend information; and (3) ability to reason and deliberate about the choice at hand. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Making Health Care Decisions: A Report on the Ethical and Legal Implications of Informed Consent in the Patient-Practitioner Relationship 60 (1982).

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

risks," or "as a result of their depression, may even *want* to take risks." (emphasis in original)[115] Elliott believes that judgments on a person's capacity to consent to research should take into account such emotional attitudes. He also proposes that subjects failing to exhibit a "minimal degree of concern for [their] welfare" should be deemed incapable of independent decisionmaking. Others oppose this position, contending that such an approach could yield 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 tolerate before we consider someone incompetent."[116]

It is generally agreed that a prospective subject's capacity to decide whether to participate in a particular research project cannot be determined through a general mental status assessment.[117] Instead, investigators must present the specific material relevant to that project and evaluate the prospective subject's understanding and appreciation that information.[118] In its 1998

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[115] Elliot, Caring About Risks, 54 Arch. Gen. Psych. 113 (1997).

[116] Appelbaum, Rethinking the Conduct of Psychiatric Research, 54 Arch. Gen. Psych. 117, 119 (1997). See also Hirschfeld, et al., Protecting Subjects and Fostering Research, 54 Arch. Gen. Psych. 121 (1997).

[117] High, et al., supra; Marson, Determining the Competency of Alzheimer Patients to Consent to Treatment and Research, 8 Alzheimer Disease and Assoc. Disord. 5 (Supp. 4, 1994).

[118] According to the Common Rule, prospective subjects should understand: (1) that the study involves research; (2) the purposes of the research; (3) the expected length of time of research participation; (4) the procedures to be performed and which, if any, are experimental; (5) reasonably foreseeable risks and discomforts; (6) reasonably expected benefits to subjects or others; (7) alternatives, including treatment, that could benefit the individual more than research participation; (8) the level of confidentiality protecting any identifiable information recorded on the subject; (9) whether compensation and medical treatment will be available for injuries resulting

report on "Research Involving Individuals with Questionable Capacity to Consent," a National Institutes of Health panel also concluded that "a key factor in potential participants' decision-making is their appreciation of how the study applies to them (in the context of their lives)."[119]

Like other commentators, the 1998 NIH panel endorsed a "sliding-scale" approach to decisional capacity in the research setting.[120] This approach demands an increasing level of understanding and appreciation as study risks increase and potential benefits to subjects decrease.[121] Similarly, some suggest that many prospective subjects incapable of independent research decisionmaking remain capable of selecting a research proxy, since "the decision-making capacity that is required to designate a proxy is far less than the capacity required to understand a detailed protocol."[122]

Besides being informed, a decision to enter research should be voluntary. The Nuremberg

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from research; (10) the identity of the person(s) to notify if the subject has questions or suspects research-related injury; and (11) that participation is voluntary, refusal will not be penalized, and participation may cease at any time without penalty. 56 Fed. Reg. sec. ___.116(a). Additional information must be disclosed and understood when relevant to a particular study, such as any additional costs subjects may incur as a result of study participation. Id. at sec. ___.116(b).

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

[120] Ibid.

[121] Elliott, Mentally Disabled and Mentally Ill Persons: Research Issues, in Encyclopedia of Bioethics 1760 (W. Reich ed., rev. ed. 1995); Appelbaum, Drug-Free Research in Schizophrenia: An Overview of the Controversy, IRB, Jan.-Feb. 1996, at 1; Annas & Glantz, Rules for Research in Nursing Homes, 315 New Eng. J. Med. 1157 (1986). See also Art Schafer,....., Journal of Medical Ethics (1982).

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

Code provides descriptive characteristics of a voluntary decision.[123] The National Commission's *Belmont Report* characterizes a voluntary decision as "free of coercion and undue influence." According to the 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 Report notes, an inducement that is not overly persuasive to most adults could unduly influence the judgment of vulnerable subjects. The Commissioners acknowledged that unjustifiable external influence 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."[124]

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 such pressures no matter where they reside.[125] Prospective subjects living in the community frequently rely heavily on the assistance of professionals and family members and may perceive research participation as essential to maintaining the approval of their caregivers.[126] Some

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[123] See p. 5, above.
[124] Belmont Report, supra, at 6.
[125] Bonnie, supra; Levine, Proposed Regulations, supra.
[126] Relatives may view research participation as improving their own chances for avoiding conditions that appear genetically-linked or as a means to reduce their caregiving burdens.

support also remains for providing special protections to persons in residential facilities, due to their near-complete dependence on the good will of the staff.[127]

A final element of decisional capacity, implicit in the above discussion, is the subject's ongoing ability to make a voluntary and informed choice 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. Studies involving subjects with fluctuating or declining decisional capacity must include mechanisms to ascertain and address this possibility, including provision for appointment of a representative for subjects who become incapable.[128] The matter of legally authorized representatives will be considered later in this report.

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

[127] Elliott, supra; High & Doole, Ethical and Legal Issues in Conducting Research Involving Elderly Subjects, 13 Beh. Sci. & L. 319 (1995). See also American College of Physicians, Cognitively Impaired Subjects, 111 Ann. Intern. Med. 843 (1989) (recommending that IRB "consider asking a committee composed mostly of representative residents of, for example, a nursing home, to review proposed research projects to be conducted at the facility).

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

Chapter Four: RISKS AND POTENTIAL BENEFITS IN RESEARCH INVOLVING PERSONS WITH DISORDERS THAT MAY AFFECT DECISIONMAKING CAPACITY

Balancing Risks and Potential Benefits

If research involving persons with mental disorders that may affect decisionmaking capacity is to be permitted, a central issue becomes the evaluation of risks and potential benefits. A well recognized principle is that research risks to human subjects must be justified by expected benefits to subjects, to others, or to both. The Common Rule directs IRBs to ensure that research risks are minimized and are "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[129] These provisions govern all research involving human subjects. Many commentators and organizations, as well as the international documents described earlier, favor placing additional constraints on acceptable risks in research involving persons with decisional impairments, including those whose mental disorders may affect their capacity to decide.

As we have noted, the National Commission proposed a research review framework in which greater substantive and procedural demands would be applied to research presenting relatively high risks to children and incapable individuals institutionalized as mentally infirm. The current DHHS regulations governing research involving children incorporate such a framework.[130]

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

[130] 45 C.F.R. sec. 46 (1991). See appendix for a copy of the regulations.

The regulations classify research using the somewhat controversial concept of "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."[131]

The DHHS regulations on research involving children permit IRBs to approve research presenting no more than minimal risk as long as requirements for parental permission and child assent are satisfied. Studies presenting greater than minimal risk must meet additional requirements. If a study in this greater than minimal risk category also offers a prospect of direct benefit to subjects, criteria for IRB approval include: a finding that the risk is justified by the prospective direct benefit; and a finding that the research presents at least as favorable a risk-expected benefit ratio for subjects as that presented by available alternatives in the clinical setting.

For greater than minimal risk research involving children, the regulations require incremental protections depending on whether or not a direct benefit to the subject is intended. If a direct benefit is intended then the IRB must also find that the risk is justified by the prospective direct benefit, and that the risk-benefit ratio of the research is no greater than available alternative treatments. If no direct benefit is intended, criteria for IRB approval include: a finding that the research presents a minor increase over minimal risk; a finding that "the intervention or procedure presents experiences to the subject that are reasonably commensurate with those inherent in their

[131] Sec. ___.102(I).

actual or expected medical, dental, psychological, social, or educational situations"; assent of the child and permission of the parents; and a finding that the study is likely to produce generalizable and vitally important information on the subjects' condition.

The regulations also 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.[132]

These regulations, the National Commission's recommendations on research involving children and institutionalized persons, and the literature on research involving impaired or incapable adults present the following policy matters for consideration: the appropriate definitions of risk and benefit to be adopted in policy on research involving impaired adult subjects; the appropriate limitations on risk for research involving this population; and the appropriate

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

procedures for ensuring that the chosen substantive standards are observed during the research process.

Defining Risks in Research Involving Persons With Disorders that May Affect Decisionmaking Capacity

Persons involved in research who may be impaired are vulnerable to a variety of possible harms when they participate in research. Risks "range from physical injury and pain at one extreme, to discomfort and inconvenience at the other, including at various points along the continuum such effects as frustration, dislocation, confusion, and shame."[133] The Common Rule's definition of minimal risk refers to "harm or discomfort," which seems clearly to include experiential burdens as well as health risks.

The most thorough published analysis on risks and potential benefits in research involving adults who lack decisionmaking capacity would suggest that review committees should consider "physical, social, psychological, and economic," risks, including "foregone benefits, ... violations of privacy, ... effects upon the subject's relationship with family members, [and] the new anxiety associated with being invited to participate in ... research before having come to terms with one's affliction."[134] Risk assessment also involves probability judgments: "[t]he quantification of risk involves an examination of both the degree or magnitude of harm that could occur and the possibility that such harm will occur."[135]

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[133] Keyserlingk, et al., supra, at 326.
[134] Id. at 326-27.
[135] Berg, supra, at 24.

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

> "It is commonly said that the benefits and risks must be balanced and shown to be in a favorable ratio. The metaphorical character of these terms draws attention to the difficult 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."[136]

Strictly speaking, risk assessment is a technique used to determine the nature, likelihood and acceptability of the risks of harm.[137] 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, 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.[138] For example, 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 assessment should be a value free determination limited only by the technical ability to derive probability estimates.[139] In contrast, the "subjectivist" school argues that the

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[136]Belmont, pg. 7.

[137] Wilson R, and Crouch EAC. Risk assessment and comparisons. Science 1987; 236:267-70.

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

[139] Haefle W. Benefit-risk tradeoffs in nuclear power generation. In Ashely H., Rudman R, Starr C. Eds. Energy and the Environment. New York: Pergammon Press, 1981.

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.[140] It would seem that both schools of thought ought to influence IRB decisionmaking, 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.

Evaluating risks to subjects with disorders that may affect decisionmaking capacity 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."[141] Similarly, as the National Commission observed, some subjects institutionalized as mentally infirm may "react more severely than normal persons" to routine medical or psychological examinations.[142] Because of this special vulnerability to harm and discomfort, risk evaluation should incorporate reliable knowledge on the range of anticipated reactions particular subjects may have to particular

[140] Schrader-Frechette, K. Values, scientific objectivity and risk analysis: five dilemmas, In Humber JM, and Almeder RF, eds. Quantitative Risk Assessment: Humana Press: Clifton, NJ, 1986: 149-70.

[141] Keyserlingk, et al., supra, at 324.

[142] Report on Institutionalized Persons, supra, at 8-9.

proposed study procedures.

Though conceding that precise risk and potential benefit assessments are rarely attainable, the *Belmont Report* states, "the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated as far as possible."[143] 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."[144]

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. Giving substance to these concepts poses difficulties, however.

The Common Rule's minimal risk definition is tied to the risks of ordinary life and medical care. The minimal risk concept is praised for its flexibility: "[i]t 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."[145] In addition, 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

[143] Belmont Report, supra, at 7.
[144] Report on Children, supra, at 8-9.
[145] Keyserlingk, et al., supra, at 329.

acceptable in research as well.[146]

In contrast to the minimal risk concept's reference to the life and medical experiences of ordinary persons, the concept of minor increase over minimal risk is tied to the prospective subject's individual situation. Because persons with psychiatric and other 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.[147] For subjects not accustomed to or in need of such medical interventions, however, the same study would present a higher level of risk.

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

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[146] 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 the Commission 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.

[147] 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.

are more accustomed to the procedure.[148] One National Commission member was highly critical of this approach, however, contending that it was wrong to take a more permissive approach to research risk in children with health problems than in than other children. He argued that the only morally defensible differential treatment of sick and healthy children would be one that was more permissive about research risks to healthy children than to children already burdened by their health problems.[149]

Commentators have criticized both the Common Rule's "minimal risk" definition, and the DHHS regulations' term "minor increase over minimal risk." Loretta Kopelman provides perhaps the most detailed critique. First, she finds the risks of ordinary life too vague a notion 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 with health problems who 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

[148]At its January 8, 1998 meeting, OPRR director Gary Ellis asked the members of the National Bioethics Advisory Commission to consider lumbar puncture as another example.

[149] Report on Children, supra, at 146 (dissenting statement of Commissioner Turtle).

child subject.[150]

A few empirical studies indicate that there is a substantial possibility of 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.[151] 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.[152] 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."[153]

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[150] Kopelman, Research Policy: Risk and Vulnerable Groups, in Encyclopedia of Bioethics 2291, 2294-95 (W. Reich ed., rev. ed. 1995); Kopelman, When Is the Risk Minimal Enough for Children to Be Research Subjects? in Children and Health Care: Moral and Social Issues 89-99 (Kopelman & Moskop eds., 1989). See also Berg, supra, at 24 (noting possible interpretations of minimal risk and concluding that "[i]t clearly does not mean only insignificant risk, but its exact scope is unclear").

The Maryland draft legislation adopts a definition of minimal risk similar to that in the Common Rule. It also refers to minor increase over minimal risk, which is defined as "the probability and magnitude of harm or discomfort anticipated in the research, including psychological harm and loss of dignity, are only slightly greater in and of themselves than those ordinarily encountered in the daily life of the potential research subjects or during the performance of routine physical or psychological examinations or tests." Office of the Maryland Attorney General, supra, at 4.

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

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

[153] Keyserlingk, et al., supra, at 326.

Difficulties with the minimal risk standard may partly have to with an historical confusion. Some contend that the drafters of the definition of minimal risk deliberately dropped the National Commission's reference to normal individuals, intending to make the relevant comparison point the risks ordinarily encountered by the prospective research subject. This approach would allow research risks to be classified as minimal if they were reasonably equivalent to those the subject encountered in ordinary life or routine medical care. For persons with mental disabilities 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 adopted 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...."[154] The 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."[155]

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[154] 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

[155]Id. at 14.

The text does not elaborate on the procedures that should accompany the cautious approach it counsels.

In sum, if policy on research involving incapable adults incorporates the concepts of minimal risk and minor increase over minimal risk without providing further guidance to investigators and IRBs, 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 special vulnerability of those subjects with respect that 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. Persons with impairments who are accustomed to certain procedures may experience fewer burdens when undergoing them for research purposes. Thus, it may be defensible to classify the risks to them as lower than they would be for someone unfamiliar with the procedures.

On the other hand, care should be taken in using the fact that an individual often undergoes medical procedures due to an illness as an excuse to perform even more such procedures for someone's else's convenience. 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.[156]

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. 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."[157] The Maryland draft legislation states that an IRB may not classify a study as presenting minimal risk if the study would expose incapable subjects to "a loss of dignity greater than that ordinarily experienced by individuals who are not decisionally incapacitated during the performance of routine physical or psychological examinations or tests."[158] The draft legislation also prohibits IRBs from applying the minimal risk or minor increase over minimal risk categories to studies exposing incapable subjects to possible "severe or prolonged pain or discomfort" or "deterioration in a medical condition."[159]

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[156] 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.

[157] DeRenzo, supra, at 540.

[158] Office of Maryland Attorney General, supra, at 7.

[159] Id.

Another document lists as minimal risk for dementia patients "routine observation, data collection, answering a questionnaire, epidemiological surveys, venapuncture, and blood sampling," as well as neuropsychological testing.[160] Though some reportedly classify lumbar punctures and bone marrow biopsies as presenting a minor increase over minimal risk, this document 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.[161] Finally, the document notes that repeated performance of procedures ordinarily qualifying as minimal risk could at some point create sufficient burdens to subjects to merit a higher risk classification.

In 1980, The President's Commission commissioned a paper on the Swedish system for compensation of subjects injured in research. That paper included a list of risk groups. The first and lowest risk group included sampling of venous blood administration of approved drugs in recommended doses, intravenous and intramuscular injections, skin biopsies. The next risk group included sternal and spinal punctures, intravenous and intraarterial infusions, muscle biopsies, and endoscopy and biopsies of the gastrointestinal tract.[162] Taking these examples, a spinal tap might be more than minimal risk for patient-subject who is decisionally impaired, but not for a normal,

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

[161] Id. at 330.

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

healthy subject, while drawing venous blood might be minimal risk for all subjects.

Although the philosophical debate about the meaning of minimal risk in research will surely persist, the meaning of minimal risk for persons in the population of concern in this report must be resolved. For persons with mental disorders that may affect decisionmaking capacity, 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. Therefore the risks associated with specific procedures to which the subjects would not be exposed were it not for their research participation should not be minimized 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 that may affect decisionmaking capacity cannot be done. Rather, it means that research procedures that would be minimal risk for a general population must be assessed in light of the specific research population. Research proposals should be more highly scrutinized if they involve persons with mental disorders that may affect decisionmaking capacity, and special conditions may be required, but on the whole we believe that the most valuable research can continue within such constraints. Further, theorized direct benefits of the research to the subjects cannot by themselves justify experimental interventions that present significant risks to a subject population. Even though there may be potential direct benefits of research participation to individuals, such

research cannot be justified by the possibility of benefit alone.

Defining Benefits in Research Involving Persons With Disorders that May Affect Decisionmaking Capacity

Research involving adults who may have decisionmaking impairments can yield three types of benefit: direct medical benefit to subjects, indirect medical benefit and financial benefit to subjects, and benefit to others. Direct benefit to subjects includes health improvements which may or may not be related to the disorder responsible for the subject's incapacity.[163] The National Commission stated that research offering potential 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.[164]

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

[163] Keyserlingk, et al., supra, at 327.
[164] Report on Institutionalized Persons, supra, at 31.

scientifically."[165] 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.[166]

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."[167] 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."[168] According to one group, indirect benefit may be acknowledged, but should not be assigned the same weight as direct benefit in research review and discussions with prospective

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[165] 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.

[166] 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.

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

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

subjects and their representatives.[169]

The T.D. decision criticized New York's failure to include a more precise definition of direct subject benefit in the regulations the court invalidated. The regulations referred to "direct benefit that is important to the general health or well being of the subject and is available only in the context of the research." Because otherwise applicable limitations and safeguards could be waived if a study offered potential direct benefit to subjects,[170] the court seemed to favor a narrow definition encompassing only expected benefits produced by the research procedure, related to the incapable subject's psychiatric condition, and reasonably equivalent to those provided by currently available treatments.[171]

The court's response supports at minimum a need to scrutinize investigators' characterizations of research offering potential direct benefit to subjects.[172] Such claims require careful scrutiny by IRBs and other reviewers. Specific definitions of direct and indirect benefit, and a statement on the relative significance of the two, could assist investigators and reviewers in evaluations of the benefits anticipated from particular studies. The decision also questions the

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[169] 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. The group characterized indirect benefits as "by nature difficult to predict with any accuracy and ... often very person-specific." Id. at 327.

[170] The regulations permitted the involvement of incapable subjects in greater than minimal risk research with the prospect of direct benefit without otherwise applicable requirements for an absence of subject objection and a finding that the study could not be conducted without the participation of incapable subjects. T.D., 650 N.Y.S. 2d at 187-88, 193.

[171] Id.

[172] Capron, supra.

justification for a policy adopting less rigorous limits and safeguards for studies offering prospective direct benefit to subjects, if direct benefit is defined as broadly as it was in the New York regulations.

Research benefit to others encompasses benefit to a subject's family or other caregivers, to persons with the same disorder as subjects, and to persons diagnosed with the disorder in the future. This category of research presents the greatest challenge for 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 the interests of the potential subject."[173]

Acceptable Risk-Anticipated Benefit Ratios in Research Involving Decisionally Impaired Subjects

Proposed policies on research involving adults who are decisionally impaired generally require a balancing of risks and potential benefits to determine when such research is acceptable. Most proposals take the position that adults who lack decisionmaking capacity may be involved in studies presenting little or no risk to them, 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 failing to offer subjects a reasonable prospect of direct benefit.

[173] Melnick, et al., supra, at 535.

Research presenting more than minimal risk to subjects is generally classified into one of two categories. The first category is research offering subjects a reasonable prospect of direct benefit. "Direct benefit" is understood to refer to health benefits for the person who is both a patient and a research subject, and does not refer to any other perceived benefits to the person such as heightening a sense of altruism or relief of boredom. Though the moral justification for directly beneficial research is enhanced by the potential for improving subjects' health or welfare, most proposals incorporate the view that limits on risk are still needed to provide adequate protection to impaired or incapable individuals.

There is continuing debate about the role of payment as an indirect benefit of research participation. Financial incentives for the subject are harder to sort into the categories of direct or indirect benefit. They are indirect in the strict sense that they do not stem from the research interventions themselves, but they may be quite salient in the subject's mind. A concern here is who actually receives and controls the funds, the subject himself or herself or a third party who authorizes research participation. In many cases it may be preferable to structure the payment mechanism so that it is received directly by the individual who is participating in research.

The principle that financial incentives should not exceed "reimbursement" for the subject's time and expenses, so as not to establish undue motivation to participate, is well established but not always easy to apply. The problem is 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 participation can provide important

social benefits. Payment must be great enough to justify their commitment of time and their submission to discomfort, but presumably not so great as to be an irresistible inducement. Similarly, some who are suffering from an illness 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, especially among those who are uninsured. Surely the care should meet a high standard considering the opportunity that the patient is providing to medical science, but the study conditions also should not exploit a patient's social and economic disadvantages.

Along these lines, the indirect benefits of study participation, ranging from monetary payment to a more attractive clinic setting to a sense of being accepted and valued by influential professionals, should not be of such magnitude that they put an undue influence on a decisionally impaired person to enroll. Because there can be no formula to determine exactly when in any given situation the indirect benefits are inappropriate inducements for some potential subjects, IRBs have a great burden in remaining sensitive to this issue in particular cases.

Greater Than Minimal Risk Research Offering 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 that available in the clinical setting.[174] This position is adopted

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

in current DHHS regulations on research involving children.[175] It is also endorsed in most of the proposals on incapable adults.

The American College of Physicians document allows 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)."[176]

The Maryland draft legislation deems "expected medical benefit" research permissible if an agent or surrogate, "after taking into account treatment alternatives outside of the research, ... concludes that participation is in the individual's medical best interest."[177] The NIH Clinical

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[175] See pp. 52-54, above.

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

[177] Office of Maryland Attorney General, supra, at 11.

Commentators take a similar position. See, e.g., Berg, supra, at 25 (approving this category of research if "no alternative treatment is available of at least equal value, and the experimental treatment is not available through any other source").

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

Center permits greater than minimal risk research offering a prospect of direct subject benefit with the consent of a DPA or court-appointed family guardian, following an ethics consultation to ensure that the third party decisionmaker 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."[178]

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.

[178] NIH Clinical Center, supra.

Greater Than Minimal Risk Research Offering No 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 directive[179] or after review and approval at the national level, through a process resembling that set forth in the current regulations governing research involving children.[180] The National Commission also recommended a national review process for studies that could not be approved under its other recommendations on research involving persons institutionalized as mentally infirm. Others see this position as either too liberal or too restrictive, however.

On 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 Helsinki Declaration's "conviction that vulnerable and unconsenting individuals should not be put at undue risk for the sake of patient groups or society."[181] Supporters of this position

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[179] Even in this case, 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 advance directive authorizing research participation." Office of Maryland Attorney General, supra, at 15. 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.

[180] 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).

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

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."[182] Some writers explicitly label this stance the most ethically defensible position.[183]

A position paper representing federally funded Alzheimer Disease Centers, however, adopts a somewhat different view: "[r]esearch 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."[184] 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

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[182] Id.

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

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

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

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

benefit and more than minimal risk to incapable subjects. They acknowledge that "there may be some advantages" to national review, but contend 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."[185]

In sum, there is a range of opinion on how federal policy should address risks to decisionally impaired or capable subjects in studies conducted solely for the benefit of others. The literature presents at least three options: (1) preserve the status quo and allow IRBs to determine acceptable risk levels; (2) require approval at the national level for studies exceeding a specific risk level; or (3) determine a risk level beyond which further specific protections are required.

The Commission does not believe that the status quo is acceptable, as there can be substantial variation among IRBs concerning what special protections must be adopted with regard to certain risk levels. We have already stated that experimental procedures or interventions that present minimal risk to a general population may present more than minimal risk for persons with mental disorders that may affect their decisionmaking capacity. Similarly, the distinction between a minor increase over minimal risk and a greater than minor increase over minimal risk requires special scrutiny when applied to this population, considering the psychological implications of interventions for those who may not understand their purpose and

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

context.

Independent Research Monitors

In the initial review process, IRBs evaluate a research proposal's risks and expected benefits based on predictions of subject response. In many cases, a range of responses among subjects will be predicted. In some cases, predictions may prove inaccurate as research progresses, for some or even all subjects. As a result, subjects' health status and experiences must be evaluated on an ongoing basis to ensure that subjects can be removed if risks become excessive. In particular, the assessment of potential harms and benefits should be individualized for the patient in question, taking into account the proposed subject's medical, psycho-social, and financial context.

The need for subject 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."[186] Commentators also refer to the importance of monitoring.[187] The major question is how to implement this task. A central issue is whether, and if so, when, monitoring should be conducted by a person independent of the research team.

After evaluating human subject protections in schizophrenia research conducted at the

[186] Sec. ___.111(a)(6).

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

University of California at Los Angeles (UCLA), the U.S. 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."[188] The institution was directed to submit to federal officials a proposal on creating and operating the monitoring boards.

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. Validated 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.[189]

Other documents 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."[190] The Maryland draft legislation directs

[188] Office of Protection from Research Risks, supra, at 27.
[189] Orr, supra, at 1263.
[190] Belmont Report, supra, at 6.

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."[191]

The general policy question is whether research team members and subject representatives can provide sufficient protection to impaired or incapable subjects. Research team members face a conflict between protecting subjects and maintaining the study population.[192] It is unlikely that subject representatives will be present during every part of an incapable subject's research involvement; in addition, laypersons might not recognize every indication of increased risk to subjects. IRBs require 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.[193] A place for independent monitoring is included among the Commission's recommendations.

[191] Office of Maryland Attorney General, supra, at 16.

[192] 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.

[193] 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).

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Chapter Five: INFORMED CONSENT, ADVANCE DIRECTIVES AND SURROGATE DECISION MAKING

Assent and Dissent

For all persons with decisionmaking capacity, informed consent is the touchstone of the ethical conduct of research. For those whose decisionmaking capacity is impaired, informed consent is the standard against which must be judged all efforts to obtain the ethical participation of individuals in research.

At some times or under some circumstances persons with mental disorders that may affect decisionmaking capacity are incapable of giving valid informed consent to research participation. Ethically acceptable research involving such persons may, nevertheless, be possible. According to the *Belmont Report*, for example, 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."[194] Consistent with this view, the National Commission recommended that under specified conditions, researchers should obtain assent to research participation from subjects incapable of independent decisionmaking. 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."[195]

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[194] Belmont Report, supra, at 6.
[195] Report on Institutionalized Persons, supra, at 12, 14-16.

Dissent also plays in important role in the involvement of 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 rule out research involvement unless the study offers the subject a prospect of direct benefit *and* a court specifically authorizes the subject's participation. The National Commission also stated that an objecting incapable subject should be involved in research presenting a prospect of direct benefit and more than minimal risk only when the benefit is available solely in the research context.[196]

The members of the National Commission recommended procedural mechanisms to ensure application of these substantive provisions. They stated that IRBs should have discretion to appoint an independent auditor to verify the subject's assent or lack of objection. They also recommended that independent auditors be required to monitor the incapable subject's initial and ongoing assent in research presenting more than minimal risk and no prospect of direct benefit to subjects; if subjects object at any time to this category of research, they should be removed from the study.

Not all individuals who lack decisional capacity can provide assent as defined by the National Commission, though some may satisfy certain elements of the standard.[197] Should the physical or verbal indications of persons incapable of assent be considered in research

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[197] 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.

decisionmaking? A related question is "whether the failure to actively object to participation in a protocol is enough to be interpreted as a tacit or implied form of assent or whether some more affirmative agreement is necessary."[198] According to the National Commission, "mere absence of objection" ought not be interpreted as assent.[199] The National Commission recommended requiring the consent of a subject's legal guardian to authorize more-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.

There is general agreement, however, that the sole potential justification for imposing research interventions on actively resisting subjects would be to advance the goal of their protection; that is, to provide a potential material health benefit unavailable outside 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 benefits

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[198] Kapp, supra, at 34.

[199] Report on Institutionalized Persons, supra, at 14.

What constitutes a recognizable objection is another question. Subjects might exhibit a transient unwillingness to participate, due to temporary fatigue or distraction. Should any sign of unwillingness suffice as grounds to remove the subject from research, or may the investigators be given another opportunity to seek the subject's cooperation? See Keyserlingk, supra, at 341 (should not assume that "transient lack of cooperation always signifies an objection"; instead, "[d]ecisions as to whether a patient is clearly or probably objecting will obviously be a matter of judgment"). A related issue is whether such judgments should be made by an investigator, independent evaluator, the subject's representative, or an IRB representative.

not otherwise obtainable in the clinical setting.[200] Yet not all commentators agree that potential direct 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."[201]

This group was "not fully persuaded" that potential therapeutic benefit provides ethical justification for compelling an objecting subject's research participation. In their view, this "is at best a position in need of further debate."[202] Draft legislation under consideration in Maryland would completely bar investigators from conducting research involving a decisionally incapable individual "who refuses to perform an action related to the research."[203]

Once part of a research study, subjects must always have the opportunity to withdraw at

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[200] E.g., Berg, supra; High & Doole, supra; High, et al., supra; Melnick, et al., supra.
[201] Keyserlingk, et al., supra, at 342, quoting Melnick, et al., supra.
[202] Id. at 342.
[203] Office of the Maryland Attorney General, Second Report of the Attorney General's Research Working Group, (May, 1997).

any time without prejudice and without regard to subject capacity. This is a basic tenet of ethical research with human subjects that was recognized in the Nuremberg Code. The lower court in the T.D. case labeled 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.[204] Although the constitutional portion of the judgment was set aside by the Court of Appeals, such a state of affairs would also be ethically objectionable according to the Nuremberg principle, among others, as well as legally suspect.

The Incapable Subject's Preferences While Competent

Various groups and individual commentators have explored the relevance of advance decisionmaking in the research context. Two types of research advance directives are discussed in the literature. Through an instruction or substantive directive, a competent person may consent to or refuse future research involvement during a future period of temporary or permanent incapacity. Through a proxy or procedural directive (also known as a research durable power-of-attorney), a competent individual may choose someone else as her research decisionmaker if they subsequently lose decisional capacity. Proxy or procedural directives will be considered later in this chapter.

As in the treatment area, advance research decisionmaking is supported as a means of extending respect to the autonomous choices of capable individuals. Advance decisionmaking is

[204] T.D., 650 N.Y.S. 2d at 193.

also seen as protective in that it can prevent a surrogate from authorizing an incapable subject's involvement in research the subject previously deemed unacceptable. The primary issues raised by research advance directives are: whether advance decisions can be adequately informed; how to safeguard the subject's right to withdraw from research; and whether advance choice is a morally defensible basis for permitting otherwise prohibited levels of risks and burdens in research involving incapable subjects.

The concept of advance research decisionmaking was initially discussed in the 1980's. In his volume on clinical research, Robert Levine discussed the "research living will" as an avenue for competent persons to authorize future research involvement while incompetent.[205] In 1987, the NIH Clinical Center adopted a policy in which persons "who are or will become cognitively impaired" are asked to complete a durable power of attorney (DPA) document appointing a proxy research decisionmaker.[206] Such decisionmakers 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 decisonmaker'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 Clinical Center policy deems a subject's prior exercise of choice an acceptable basis

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[205] R. Levine, Ethics and Regulation of Clinical Research 270-74 (2nd ed. 1986).

[206] 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.

for permitting higher risk research than is otherwise permitted for subjects lacking court-appointed family guardians.[207]

The terminology of "research advance directive" or "research living will" is somewhat confusing. Conventional living wills and other advance directives address the individual's preferences concerning recognized treatment, or identify the individual to be empowered to make treatment decisions, if the individual should lose decisionmaking capacity. However, research often concerns interventions that are not known to be effective or not generally considered to have therapeutic value, or interventions that are not intended to benefit the subjects at all, but only to gain information that may lead to improved treatment. Further, while advance directives appropriately address treatment preferences well before the time they may be implemented, the moral arguments that would support a public policy favoring advance consent to a research project are not as clear -- especially considering that in many instances the individual might be asked to authorize participation in a research project that does not even exist at the time. Under these circumstances a research advance directive is in effect a blank check permitting oneself to be used in a research project after the loss of decisionmaking capacity.

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

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

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.[208]

Accordingly, this group 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."[209]

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 position paper states that incapable subjects who have given only informal instructions to a surrogate decisionmaker about their research preferences should not be involved in greater than minimal risk research offering no prospect of direct benefit. In contrast, subjects with formal advance directives may be involved in such studies, as long as the

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

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

above limitations are observed.

Other groups and commentators have expressed general support for advance research decisionmaking without addressing the concept in detail.[210] Four articles published between 1994 and 1996 present more lengthy analyses of advance research directives and are discussed below.

In reviewing the advance directive's potential application to dementia research, Greg Sachs suggests it is unlikely that many individuals will prepare research directives. He notes that relatively few people make treatment directives, even though many fear overtreatment 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."[211]

Federal policy establishes stringent disclosure requirements for investigators recruiting competent persons for research. An individual considering whether to authorize future research

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[210] 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 decisionmaker; 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).

[211] 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.

participation ought to be informed about a prospective study as well. But problems in information delivery are posed by the time lapse between a capable individual's decision to enter a future study and the onset of actual participation. As a Canadian group points out, "[t]he research intervention, process, or technology may have evolved; the risk of harm may have increased beyond what was originally predicted; the patient's medical conditions, relationships, level of family support, and daily routine may have changed and deteriorated."[212]

In light of these possibilities, commentators agree that a third party decisionmaker should be appointed to withdraw the subject from a study if previously unrecognized risks and burdens become apparent.[213] They differ, however, on the standard third parties should apply when exercising the subject's right to withdraw from research the subject previously authorized.

Some writers favor withdrawal only when the factual circumstances become materially different from what the individuals agreed to in a directive.[214] 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

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[212] Keyserlingk, et al., supra at 347.

[213] 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 decisionmaker must have power to remove subject from study).

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

> function of the [third party decisionmaker] 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.[215]

This dispute is related to disagreement on the appropriate scope of a competent person's advance consent to research. Commentators are divided on whether policy should permit an incapable subject to be exposed to otherwise impermissible levels of research risks and burdens based on the subject's prior instructions. Moorhouse and Weisstub contend that directives should be restricted to authorizing research "with a negligible or less than substantial risk."[216] 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, Keyserlingk's group in Canada proposes that research directives should apply to studies offering no direct benefit to subjects only if the risk is minimal

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

An intermediate position is presented in Keyserlingk, et al., supra, at 352 (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 [decisionmaker] to be socially or morally unacceptable").

[216] Moorhouse & Weisstub, supra, at 134.

or a minor increase over minimal.[217] 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."[218]

Berg 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."[219] Conversely, when an advance directive refuses research participation, Berg suggests that the subject's refusal could be overridden if a study offers possible direct benefit unavailable in the clinical setting. She fails to explain why concern for the incapable subject's best interests justify disregarding a directive in one situation and not the other.

A few public policy developments are also relevant to this topic. In 1996, the Food and Drug Administration and NIH adopted new regulations governing research involving incapable subjects in the emergency setting.[220] The new regulations allow research to proceed in the

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[217] Keyserlingk, et al., supra, at 351.
[218] Id.
[219] Berg, supra, at 22.
[220] Supra at 42.

absence of consent by a subject or subject representative if a number of conditions are met. One condition is that investigators cannot reasonably obtain prospective consent from competent individuals likely to be candidates for later study enrollment.[221]

The regulations and agency comments do not address the rationale for or implementation issues raised by prospective consent. The commentary implies that the ordinary disclosure requirements for informed consent govern advance research decisionmaking.[222] 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."[223] 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.[224] As has been noted, this is a problem that applies to all advance directives for research participation.

The New York court decision invalidating regulations existing governing research at the

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[221] 21 C.F.R. sec. 50.24 (a)(2)(iii).

[222] The FDA's comments on the regulations include as examples of when "prior informed consent" could be used, "use of a surgical procedure with a known severe consequence; administration of a drug product with a known serious adverse reaction; identification of a population with a particular disease or condition who are at an extremely high risk for a serious event." 61 Fed. Reg. at 51511.

[223] Id.

[224] Id.

state's mental health facilities expressed support for prospective decisionmaking on research participation. In T.D., the appellate court took the position that without an incapable subject's previous consent or the consent of someone the subject specifically chose as her research decisionmaker, "[i]t may very well be that ... there is at present no constitutionally acceptable protocol for obtaining the participation of incapable individuals" in studies posing greater than minimal risk and no prospect of therapeutic benefit.[225] By implication, then, the court deemed advance consent or the consent of a specifically authorized research proxy a constitutionally adequate basis for an incapable subject's participation in research posing more than minimal risk and no prospect of direct benefit to subjects. As we have mentioned, however, on appeal the court's reference to constitutional issues was found to be unnecessary to decide the case at hand.

The original T.D. court's position was based on earlier New York decisions addressing surrogate decisionmaking on life-sustaining treatment for incapable patients. These decisions established a rule that "in the absence of specific legislation, and where there is no evidence of personal intent, a surrogate has no recognized right to decide ... that treatment should be withheld...."[226] Because "participation in studies involving greater than minimal risk exposes the subjects to possible harmful, and even fatal, side effects," the court determined that explicit legislation or the subject's prior expression of intent should be required in the research context as

[225] T.D., 650 N.Y.S. 2d at 177.
[226] Id. at 190.

well.[227]

The state of Maryland has initiated a third policy effort relevant to advance research decisionmaking. The draft legislation includes a framework for third party decisions on research for decisionally incapacitated persons. 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 authorized by statute to make health care decisions for an incapable person; or (4) a monitor designated by the IRB to act as a research decisionmaker for an incapable person.[228]

The Maryland draft gives greater 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 proposal to use a potential subject's appointed

[227] Id. at 191. This support for advance decisionmaking also reflects the judges' apparent view that requiring a prior choice shows respect for the competent person's right of self-determination and provides better protection of incapable subjects than the state's invalidated provisions on surrogate decisionmaking. The opinion fails to discuss how to ensure that advance decisions on research are adequately informed or how to implement the subject's right to withdraw from a study.

[228] Office of the Maryland Attorney General, supra.

representative to make research participation decisions will be considered in the next section.

The draft legislation also recognizes a limited role for instruction directives. A monitor may consent to an incapable individual's participation in research presenting minimal risk and no direct benefit if the individual's advance directive explicitly authorizes such participation. A research agent may permit an incapable subject to be involved in research presenting more than a minor increase over minimal risk only if "the research is unambiguously included in the individual's advance directive authorizing research participation."[229] Thus, otherwise prohibited research risk is permitted based on the prior competent choice of a now incapable subject.

The draft Maryland legislation does not discuss the study 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; and (2) withdraw consent if continued participation would, considering all relevant circumstances be detrimental to the well-being of the individual.[230]

In sum, advance research decisionmaking has been widely discussed in the literature and included in some recent policy initiatives. Numerous conceptual and practical questions remain unresolved, however. The number of persons willing to prepare research directives may be small,

[229] Id. at 15.
[230] Id. at 16.

especially if rigorous standards for information disclosure are observed. Further, investigators and IRBs face challenges in providing competent individuals with up-to-date information on 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.

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 the individual's views prior to the period of incapacity.[231]

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 phrase 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 contain general

[231]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.

provisions on the standards and procedures governing appointment of guardians for persons declared legally incompetent. Guardianship 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.

Relatively few states have laws specifically addressing the area of research decisionmaking by legal guardians. 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.[232]

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.[233] Thus, investigators and IRBs in jurisdictions with specific law 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 decisionmaker for a person who may lacks decisional capacity and may be involved in research.

The literature indicates that at present legal guardianship is rarely, if ever, mandated in the research setting. Instead, close family members, who may or may not have formal guardianship

[232] See Appendix for brief descriptions of existing state legislation.
[233] Common Rule, Sec. ___.101(f).

status, are the customary decisionmakers 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.[234]

Later commentary 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

[234] 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, 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 Dis. & Related Disord. 28 (Supp. 4, 1994).

side" could end up contributing to a deprivation of general decisionmaking rights of subjects.[235] 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 for making decisions regarding participation of their ward in research protocols.

Dissatisfaction with a requirement for legal guardianship has led to proposals of alternative mechanisms for granting authority to act as an incapable person's representative in research decisionmaking. One option, alluded to above, 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 (DPA) 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.

The primary advantage of the research DPA is the explicit authority granted by the subject, who presumably will choose someone likely to express their values and protect their welfare. Intramural research at the National Institutes of Health (NIH) Clinical Center is governed by a policy that encourages this approach.[236] The American College of Physicians and

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[235] 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").

[236] Fletcher & 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

numerous others express support for use of these devices.[237] As a practical matter, however, it is unclear whether many individuals will be interested in or willing to complete such a document.[238] Moreover, the device cannot be applied to the population of persons with mental disability who are currently incapable and not expected to recover capacity.

A second potential source of authority is an existing health care power of attorney. In this situation, the now-incapable subject previously exercised an autonomous choice to delegate medical decisionmaking to a particular person. The question is whether an individual's choice of a friend or relative to make treatment decisions in the event of incapacity is defensibly interpreted as an authorization for research decisionmaking as well. The NIH Clinical Center policy allows previously chosen health care proxies to make research decisions for subjects.[239]

A third alternative is to regard state legislation authorizing family members 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 relatives. Most reasonable would be to extend the laws' application to a close relative's decision regarding research offering potential health benefit to an incapable subject.[240] Others believe that these laws

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subjects may designate the Center's patient representative or a chaplain, or social worker not assigned to the research unit.

[237] American College of Physicians, supra. See also Kapp, supra; Melnick, et al., supra.

[238] See High & Doole, supra.

[239] NIH Clinical Center, supra.

[240] Bonnie, supra, at 110.

should not be interpreted so expansively and that amendments or new legislation would be required to provide explicit statutory authority for delegation of decisions regarding this participation to relatives.[241]

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.[242] This approach also is easy to administer; moreover, it apparently has been and continues to be a common practice in many actual research settings.[243]

Each of the above options presents advantages and drawbacks. Requiring judicial involvement raises the costs of research and does not necessarily advance respect for and protection of incapable persons. Requiring explicit durable powers of attorney for research poses practical difficulties, since relatively few persons have or can be expected to complete these documents. Another question is whether the power of DPAs to accept research risks to 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

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[241] Kapp, supra.

[242] 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").

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

incapable persons would require action by the states; such legislation would emerge slowly and in some states, not at all.

All of these alternatives also raise questions about the accuracy with which incapable subjects' values and preferences as competent persons will be expressed by formal or informal representatives.[244] The problem of potential conflicts of interest between subjects' interests and those of their representatives exist 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."[245] 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.[246]

One response to the above concerns is to conduct screening and education of subject representatives, with the goal of ascertaining inappropriate decisionmakers and enhancing the likelihood that representatives will make choices that adequately respect the subject's competent

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[244] 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").

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

[246] 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.

preferences and current interests.[247] Adopting a requirement for screening and training would raise the further question of whether this procedure should be conducted by a member of the research team, the IRB, or someone otherwise independent of the project.[248]

An alternative or additional approach is to limit the authority of any third party to consent to research participation for another. Three forms of substantive limitations 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

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[247] See, e.g., High & Doole, supra at 328 ("family members may be disqualified to serve as surrogates for a variety of reasons, including lack of capacity, inattention to the subject's well-being, self-interested motives, or unavailability"); American College of Physicians, supra, at 844 ("researchers must inform [proxies and surrogates] of the standards for decisionmaking").

Some concerns about the quality of third-party decisions are raised by empirical studies of parents consenting to their children's research participation. For example a recent study of 64 parents whose children had participated in a clinical trial found that only a small number recognized that drug trials are designed to test safety as well as efficacy, while the majority believed such trials posed either no risk or low risk. Fewer than half realized that they had the right to withdraw their children from the trial at any time. Harth & Thong, Parental Perceptions and Attitudes About Informed Consent in Clinical Research Involving Children, 41 Soc. Sci. Med. 1647 (1995).

[248] For contrasting views on this point, see Berg, supra, at 26 (investigator or IRB could prepare document for subject representatives on substantive standards for decisionmaking, and giving examples of how to apply them; in complex protocols, neutral educator could be assigned to explain relevant information) and Bein, supra, at 761 (independent, government-employed patient-advocate could present information to and advise family-surrogates on research decisions for incapable relatives; advocate questioning surrogate's "good faith or ability to make a proper decision" could initiate court proceedings to resolve whether incapable person should participate in study).

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 impaired decisionmaking capacity apply each of these limits, but combine them in a variety of ways.

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 a physician is available as an advisor for each research participant or their surrogate. This independent physician advisor should not be involved with the study and should have had a previous relationship with the potential subject. The physician advisor's role would be to help the potential subject and surrogate decide whether participation in a particular research protocol is a good choice for that person. For persons who are incapacitated and whose research participation is contemplated, the physician advisor could be an invaluable consultant to the legally authorized representative.

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

A comprehensive system involving an independent physician advisor for persons with mental disorders that may affect their decisionmaking capacity and who are potential research participants, or their legally authorized representatives, would thus be two-fold: For those individuals who have decisionmaking capacity at the time of enrollment in a study, an independent physician advisor for each subject would be available to consult with the 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, an independent physician would be available to advise a legally authorized representative whether or not to halt the subject's participation. In each instance the independent physician should have been previously acquainted with the potential subject.

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

[249]The Law Commission, "Mental Incapacity: Item 9 of the Fourth Programme of Law Reform: Mentally Incapacitated Adults" (London, England: House of Commons, 1995), p.101.

decisionmaking capacity. The last chapter presents the Commission's reasoned judgment about appropriate protections for this population and the justification for those recommended protections.

Chapter Six: SPECIAL PROTECTIONS IN RESEARCH

Moving Ahead in Research Involving Persons With Mental Disorders Affecting Decisionmaking Capacity

This report stands in a long line of statements, reports, and recommendations by governmental advisory groups and professional organizations that focused on research involving, as subjects, persons with disorders affecting decisionmaking capacity. Each of these earlier efforts has left a relevant and important legacy to this report. For example, the Nuremberg Code (1947) established the importance of voluntary consent to research participation. The Declaration of Helsinki of the World Medical Association (first issued in 1964) distinguished between research intended partly to be beneficial to the subject and research intended solely for others' benefit. The International Ethical Guidelines for Biomedical Research of the Council for International Organizations of Medical Sciences and the World Health Organization (1993) allows legal guardians to consent to low-risk and potentially beneficial research. Among the landmark United States documents, the National Commission (1978) proposed ethical principles that should govern all human subjects research, and protections for those institutionalized as mentally infirm that resembled their proposals for pediatric research, though only the latter were adopted in federal regulations. And the federal Common Rule (1991) 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 review of research proposals by Institutional Review Boards.

Among all these important precursors to this report, the National Commission's proposals concerning those institutionalized as mentally infirm speak most specifically to a group of persons who may have impaired decisionmaking capacity due to a neurologic or psychiatric disorder. Yet among the National Commission's reports pertaining to the protection of particular subject populations, this one was never adopted and has had the least influence over subsequent regulations and guidelines in the U.S.

Much has changed since the National Commission's report twenty years ago. There is a much greater sensitivity to the variety of disorders that can affect decisionmaking capacity, 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 and involves a larger societal investment than ever, including a larger role for the private sector. The stigmatization and marginalization of those who suffer from mental disorders that put them at risk for impaired decisionmaking, while by no means vanquished, show signs of abating at least somewhat as improved understanding of and empathy for those individuals and a new appreciation of the underlying biology of some of their conditions gradually increase among the professional and lay public.

In this context, NBAC hopes that the legacy of this report in the line of its predecessors will be to bring persons with mental disorders that may affect decisionmaking more

fully and specifically within the ambit of appropriate additional protections, such as those that have been extended to other 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 individuality must be protected and, where possible, promoted; clinical investigators, who are with rare exception skilled, compassionate, and dedicated to the alleviation of some of humanity's most terrible afflictions; and informal caregivers, whose own lives are often wholly absorbed in the tragedy that has befallen their loved one. In view of the ethical uncertainties many researchers have noted and the ethical problems some subjects and their families have identified, we believe that these proposed protections will facilitate progress in this area of research by engendering greater public trust and confidence that subjects' rights and interests are centrally important and fully respected.

The Costs of Special Protections

We do not believe that the additional costs of special protections for human research subjects with mental disorders that may affect their decisionmaking capacity would excessively burden the development of effective new treatments. Indeed, it is our responsibility to protect the interests of those without whom this research could not be done, those who are unable to give full informed consent and who may not themselves directly benefit from the research. The alternative to ethically acceptable research with human beings, or with certain groups of human

beings as subjects, is not ethically unacceptable research; rather, the alternative is no research involving these populations as human subjects at all.

A Framework of Special Protections

A cogent case can be made for requiring additional special protections in research for persons with mental disorders that affect their decisionmaking capacity. A framework of special protections should include, at a minimum, the following elements: (1) a mandate that IRBs consider protections that should be integrated into the very design of a given study; (2) a requirement for appropriate additional membership on IRBs for research involving persons with mental disorders that may effect decisionmaking capacity; (3) a limitation on recruitment of persons in this population into research; (4) requirements for notifying individuals that they have been determined to lack decisionmaking capacity and that they have been entered into a study; (5) a mandate that IRBs consider requiring additional protections for the consent process; (6) a requirement that any apparent dissent to research participation be honored (absolute subjects' rights to dissent to participation); (7) focused attention on risk assessment; (8) restrictions concerning the participation of persons in this population in more than minimal risk research that is potentially beneficial to subjects; (9) restrictions concerning the participation of persons in this population in more than minimal risk research that is not potentially beneficial to subjects; (10) provisions for research that involves persons with fluctuating capacity or prospective incapacity; (11) provisions for the rights and liabilities of legally authorized representatives of persons with

mental disorders that may affect decisionmaking capacity. Of course, these elements constitute a point of departure for the protections an IRB may require. IRBs should retain the ability to require protections beyond these when appropriate. This framework is represented in the discussion and the various recommendations that follow.

(1) Protections in Research Design

Those with serious illnesses can be exploited by being included in study arms from which it is known they will receive no benefit. One way to ameliorate this problem is to incorporate into study design a non-research or wraparound phase following the conclusion of the research period, one that provides the subject with some beneficial intervention independent of the study itself.[250] A problem with a wraparound phase is that it may shift the balance in the opposite and equally problematic direction by providing an inappropriate incentive to participate in studies in order to derive the benefits of a recognized therapeutic strategy without payment. On the other hand, wraparounds are suitable follow-ups to certain kinds of research, including those that involve the provocation of symptoms. In appropriate circumstances, IRBs should require a wraparound phase as part of the design of some studies.

Subjects who are included in experimental arms that involve receiving the study drug are also liable to unfair and exploitive treatment if results indicate that the drug is effective but there is no mechanism to continue those subjects on the medication when the study concludes. In such

[250] NBAC testimony

circumstances IRBs could condition study approval on the manufacturer's commitment to continue to supply the medication to research participants (including any subjects who did not receive it during the study, such as placebo or standard therapy controls), if it proves to be effective.

Many decisional impairments are associated with psychiatric disorders that can be managed symptomatically with neuroleptic medication. When a known risk of placebo is the return of symptoms, it may be argued that it is unethical to include a placebo arm. Thus, some contend that new drug investigations should use standard therapy as a control, in spite of the methodological shortcomings of such designs.[251] Among the possible grounds for excluding placebo arms in particular studies could be (1) an individualized assessment that certain patients would be at high risk for relapse if their current therapeutic regimen was discontinued; (2) that a drug holiday is not contemplated for these patients apart from enrollment in a study; or (3) that standard therapy is generally considered effective if not ideal. However, any change in human subjects regulations concerning permissible research design should presumably accommodate other federal requirements for drug approval.[252]

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. Presumably, under current regulations for vulnerable subjects IRBs should take such

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[252]Fn re FDA and other references

arrangements into account when evaluating research proposals.

(2) IRB Membership

The issues considered in this report are complex and as multi-faceted as the many and various research protocols that might assist medical progress on 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 is generally viewed as a good way to increase the likelihood that its decisions will be responsive to the interests of affected groups. More specifically, increased subject representation in the review and conduct of research is a commonly-endorsed strategy for improving research decisions affecting persons with mental disabilities. It is not surprising then that the Common Rule directs IRBs frequently reviewing research involving a vulnerable subject group to consider including as reviewers persons with knowledge of and experience working with the relevant subject group.[253] The current provision, however, is advisory only; moreover, it refers to the involvement of expert professionals, not persons representing vulnerable subject groups. Another development is the increased involvement of affected persons in the planning of clinical research on their conditions.

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

[253] 45 CFR 46.107(f)

members who will assist the IRB in the review of issues related to the rights and welfare of subjects with severe psychiatric disorders."[254] This requirement was imposed even though the IRB already had a psychiatrist and a psychologist as members.[255]

All IRBs that regularly consider proposals involving persons with disorders that affect decisionmaking capacity should include at least two members who are familiar with the concerns of this population, whether they are individuals from this population, family members, or representatives of advocacy organizations. IRBs for whom such proposals are not routine should obtain consultants in these categories. In this way the special issues of concern to this population are more likely to be represented in IRB deliberations and conveyed, as appropriate, to investigators. 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.

This phenomenon first arose in the context of HIV research, but it is now evident in other areas of clinical research as well.[256] It would be possible for federal policy on research involving persons with mental disabilities to promote the involvement of subject representatives in planning clinical studies of the relevant conditions.

(3) Appropriate Subject Recruitment

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

[255] See also Shamoo & Sharev, supra, at S:29 (IRBs reviewing proposals to involve mentally disabled subjects should include at least two patient-representatives).

[256] See Erikson, Breast Cancer Activists Seek Voice in Research Decisions, 269 Science 1508 (1995).

Some vulnerable or special populations currently receive additional protections in the regulations to ensure that they are not unfairly burdened with involvement in research simply because, for example, they may be more easily available, or because their participation otherwise creates special ethical issues. Thus, for example, research using prisoners as subjects is limited to conditions that especially affect that population. Considering that persons with mental disorders that affect decisionmaking capacity are likely to face some of the complicating and difficult factors discussed in this report, sometimes including their ready availability in institutions, or the feeling of helplessness they and/or their loved ones experience, their position bears earmarks of special vulnerability.

One important justification for research involving those with conditions that affect their decisionmaking is the need for progress in the treatment of just these conditions. However, because of the special vulnerability of this population, it is appropriate to prohibit research involving persons with impaired decisionmaking capacity as a result of their mental disorder when that research can be conducted perfectly well with other potential subjects.[257] 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 in

[257] This position has been adopted in Canada. Tri-Council Working Group, Code of Ethical Conduct for Research Involving Humans, July 1997, p.22.

the selection of research subjects each imply that IRBs should not approve research protocols involving persons with decisional impairments due to mental illness when the research does not require subjects with this type of disorder.

There are circumstances, however, under which other subjects without these special 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 using 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 decision making capacity should not be recruited.

Apart from the fact that sometimes persons with mental disorders whose decisionmaking capacity is not impaired are not appropriate subjects for a particular protocol, an individual with impaired decisionmaking capacity may have a life-threatening condition for which there is no satisfactory treatment. When the intervention is designed to ameliorate or potentially cure a life-threatening condition, then under current regulations these individuals may obtain the investigational treatment outside the proposed study on compassionate grounds.[258] Therefore, as a matter of justice, people whose best therapeutic alternative may be an innovative treatment can still have access to the intervention.

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(4) CapacityAssessment Notification

To be found decisionally incapable and then enrolled as a subject in a research protocol on the basis of alternative decision making arrangements is to have certain of one's rights curtailed, however justifiable the curtailment may be. Some argue that whenever an individual is found to be decisionally incapable the individual should be put on notice of this finding, especially when it could have important consequences for the individual's medical treatment, as in the case of enrollment as a subject in a research protocol.[259] Such a notification process sometimes might seem to be an empty ritual. Worse, a requirement that implies a duty to so inform those who are in an advanced stage of dementia prior to research involvement could well contribute to undermining health professionals' respect for the regulatory system. Nevertheless, to be unaware that one has been found decisionally incapable is to be deprived of the opportunity to seek review and perhaps of the right to judicial intervention. The implications of such a determination, including the loss of control over one's own person, are among the most serious one can imagine for members of a democratic society.[260]

Rather than require that all individuals who have been found to be decisionally incapacitated be informed of that finding prior to their enrollment in a study, such a rule should be limited to those potential subjects who show signs of consciousness. The notification would also

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[259] Another way to express this issue is whether the assent of incapable subjects should be required. Dresser, pp. 36-40.

[260] 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.

give the potential subject an opportunity to dissent from research participation, by no means a trivial recognition of individual dignity. A notification requirement should be added to the federal regulations concerning potential research subjects found to lack decisionmaking capacity.

For persons who are conscious but whose capacity may be questionable, the Commission noted earlier in this report the difficult problems involved in ascertaining whether a person's level of capacity is sufficient for the decision making task at hand, such as choosing a substantive treatment option or identifying a surrogate. NBAC's survey of the literature on the elements of capacity indicated that capacity assessment is an evolving field. Physicians responsible for determining decisionmaking capacity may therefore differ in the criteria and methods they use for this purpose. Considering again the implications for individual freedom that a finding of decisional incapacity may entail, it is appropriate that protocols involving the participation of individuals with questionable decisionmaking capacity satisfy IRBs concerning the methodology that will be employed in making capacity determinations. Further, it is highly desirable that the individual making the determination should be independent of the study team. These conclusions are reflected in our recommendations.

(5) Possible Additional Protections for the Consent Process

The use of a consent auditor has frequently 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

IRBor an institutional ethicist, witnesses the consent process and then either certifies the consent as valid, or informs the principal investigator that an individual is not able to give valid consent. IRBs could require consent auditors for potential subjects who have conditions associated with a decisional impairment. A system of audited consent would require a substantial investment by research institutions. However, 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 hold out the prospect of 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 disenroll from a study. A requirement for periodic reconsenting would help ensure that a patient's continued involvement is truly voluntary by giving permission to leave the study. Such a requirement would also provide the occasion to reassess decision making capacity, and it could 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 of human research participants as partners in the study process rather than as passive subjects.

Although reconsenting is another labor-intensive measure that would add to the cost and complexity of the human research system, a number of long-term studies already include such a procedure.[261] IRBs should consider attaching a reconsent requirement to certain studies based on

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their length and on the condition of the individuals to be included, such as those with progressive neurological disorders.

(6) Dissent from Participation in Research

Our society's social philosophy includes a strong presumption in favor of individual self-determination. Judgments about an individual's decisionmaking capacity will often have a measure of uncertainty. Therefore, anyone who is found to be decisionally incapable but is conscious or has periods of consciousness has a prima facie moral right to be told of a determination of incapacity, especially when it is linked to research participation that involves a degree of risk. Obviously under many circumstances it will not be possible for the individual to comprehend the information, but reasonable efforts should be made.

Most importantly, notification that he or she is to be part of a study also gives the individual an opportunity to dissent from participation. Even when decisionmaking capacity appears to be severely impaired, individual self-determination is more fundamental than any asserted duty to serve the public good as a research subject. Hence, even an apparent dissent by a potential or actual subject must be honored.

The requirement to honor any apparent objection to research participation applies 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 every effort be made to 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 noted that the right to refuse to participate in research is not dependent on establishing a right to choose to participate. The two are distinct and can be defended separately.

Possible Additional Protections

(7) Contemplation of Levels of Risk

One section of the current regulatory framework for federally funded research involving human subjects recognizes three categories of research expressed in terms of level of risk:[262] minimal risk, a minor increase over minimal risk, and more than a minor increase over minimal risk. The current regulations also stipulate a definition of minimal risk. The recommendations in this report adopt the current risk-related categories for research, but suggest that some examples of minimal risk and greater than minimal risk research be included in the regulations as good rules to follow due to the ambiguity of the concept of minimal risk.

However, the risk categories in the current regulations do not automatically apply to particular procedures, but must be applied contextually in light of specific study conditions. 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. Persons with mental disorders that

[262] §XX C.F.R. XX.406(a).

affect decisionmaking capacity may be unable to understand the rationale for an intervention that poses only a modest physical risk but due to the subject's mental state would possibly lead to considerable psychological distress. For example, repeated venapunctures (blood draws) that would be innocuous to many people could be quite disturbing to persons with certain mental disorders.

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 also 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, *a priori* categorization may not be sufficient.

As a consequence, clinical investigators who propose to work with persons with mental disorders affecting decisionmaking capacity must carefully articulate to IRBs the nature or their risk evaluation procedures for potential subjects. Even within the same protocol, the same intervention may entail different risk levels for different individuals depending on their particular condition. When the level of risk may be higher for some subjects than for others owing to lesser capacity, the determination of risk level for the entire subject group should err on the side of

caution. 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.

Some research involving persons with mental disorders that may affect decisionmaking capacity that is not otherwise approvable under our recommendations may have the potential for important scientific benefits for this population or may further understanding of their condition. In such cases only the Secretary of the Department of Health and Human Services (or his/her specifically designated alternate) should be able to approve such research and only after consultation with an expert panel to determine whether the research satisfies appropriate scientific and ethical standards.

(8) Greater than Minimal Risk Research that is Potentially Beneficial to Subjects

Some important research may not be done without the involvement of persons with disorders affecting decisionmaking capacity, 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.

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 neurologic or psychiatric disorder should not a priori disqualify an individual from being permitted to volunteer

if he or she has sufficient capacity to consent and other protections are in place. Moreover, an individual may be able to give consent to participate in a specific study in advance of an anticipated period of incapacity, which may be especially important for research that examines a physiologic state during such a period.

Yet no one is obligated to participate in a study, even if it may be of direct medical benefit to them. Therefore, in order for research in this category to go forward, either (1) the potential subject's informed consent must be obtained, or (2) the subject's legally authorized representative must have given permission for research participation *and* the subject must have been given the opportunity to dissent from participation. The legally authorized representative will be an individual designated under state law or institutional rules to make medical decisions on behalf of another individual. Again, even an apparent dissent by the subject must be honored, regardless of his or her capacity at the time. In all cases IRBs should consider whether to require some of the additional protections discussed later in this chapter.

(9) Greater than Minimal Risk Research that is Not Potentially Beneficial to Subjects

Research that involves persons with disorders that affect decisionmaking capacity but that is not of potential benefit to them may be conducted only with their informed consent. The presence of a neurologic or psychiatric disorder should not a priori disqualify an individual from being permitted to volunteer for a study relevant to his or her disorder that cannot be conducted on others if he or she has sufficient capacity to consent. As is the case for studies that present a

potential direct benefit, their consent to a particular study may sometimes be obtained in advance of a period of incapacity.

In addition, any such subject must have a legally authorized representative who can make decisions about continuing or stopping participation in the research on his or her behalf, based on the representative's understanding of the subject's wishes. Because the subject's 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 identified as available to advise the subject's representative about the subject's continued participation. Depending on the level of risk involved, IRBs should consider whether to introduce other protections as well, some of which are discussed later in this chapter, depending on the level of risk.

(10) Research Planning With Persons With Fluctuating Capacity or Prospective Incapacity

Ethically acceptable research involving persons with fluctuating capacity or who face the prospect of loss of capacity presents special challenges. To be part of an informed consent process, a potential research subject must be able to recognize and to grasp 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 discern that there is a difference between being a research subject and being a patient, and that the decision to participate may involve agreeing to additional medical procedures and/or treatment.

As the Commission understands it, anticipatory planning for research participatiion 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. Therefore, the anticipatory planning envisioned by the Commission is not a "blanket" consent to research participation.

For persons with fluctuating capacity and those who are at risk for loss of capacity during a study, the Commission'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. Because the very nature of all research is to test or to generate an hypothesis, it is characterized by uncertainty in outcome. Therefore, 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 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 anticipatory planning, the potential subject must understand that he or she has appointed a legally authorized representative as a surrogate to make decisions concerning research participation should the subject become unable (while in the study) to make these decisions. The subject must further understand that the surrogate may never overrule his or her 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 private mental 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 private mental health care provider. The research team must also make adequate provision for a reasonable amount of aftercare should the subject decompensate, become unable to cooperate, and drop out of the study.

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

(11) Legally Authorized Representatives and Research Decisions

This report has reviewed various proposals for extending the decisionmaking authority of individuals participating in research in anticipation of a period of incapacity. 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. And 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 identifying others they want to make important decisions on their behalf. These appointments, which may particularly include family members or close friends, should be recognized in state laws that firmly establish the status of legally authorized representative for research purposes.

However, individuals sometimes lose decisionmaking capacity before having an opportunity to appoint a surrogate who can function as a legally authorized representative. Nevertheless, for studies that have potential direct medical benefit for the patient-subject their legally authorized representative should be permitted to enter potential subjects into such studies, unless the potential subject apparently dissents.

While legally authorized representatives should be able to give permission for a patient who has lost capacity to be enrolled in research that offers potential direct medical benefit, their authority to enroll subjects should not extend to research that is not potentially beneficial and involves greater than minimal risk. For the latter type of research, legally authorized representatives should be available to decide whether a subject's participation may continue or

must cease, once started, but should not be empowered to initiate research participation.

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 they should be based upon the subject's best interests. These ordered criteria are widely recognized in current bioethical opinion.[263] In addition, IRBs should consider whether to require various further protections and review mechanisms along the lines described in this report.

[263] Buchanan and Brock

Recommendations

Recommendations for Different Decisionmakers

Not all of this report's recommendations are aimed at the development of new governmental regulation. 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 formal 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 disorders affecting decisionmaking capacity fear that further regulation will unnecessarily retard scientific progress and inappropriately stigmatize individuals who may be suitable research subjects.

In addition, many others note that, in spite of imperfections in current regulations, the period since their enactment has been largely free of the sorts of large-scale controversies that led to their initial enactment. Still others stress that the issues discussed in this report illustrate some of the shortcomings of the Common Rule. In this context, the Commission 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 indicated could be advanced through other mechanisms, such statements of principle, suggested professional guidance, or other educational materials for all relevant parties.

In this spirit, our recommendations fall into several categories: proposals for new federal regulations, proposals for legislation at the state level, and guidance to IRBs, to investigators, to other professionals who work with persons with disorders that affect decisionmaking capacity, and to any others responsible for human subjects protection.

Proposed Regulatory Requirements for IRB Protocol Review

In addition to the general regulations that already apply to all federally conducted and sponsored research, IRB deliberations and decisions about research involving subjects with mental disorders that may affect decisionmaking capacity should be governed by additional regulations. Specifically, a new sub-part should be added to the current federal regulations concerning greater than minimal risk research involving persons with mental disorders that may affect decisionmaking capacity. The new sub-part would address: (1) IRB membership; (2) limiting the enrollment of subjects with mental disorders that may affect their decisionmaking capacity to protocols where they are, in principle, necessary for the research;(3) the assessment of the potential subjects'

capacity to decide about participating in research; (4) notification of determination of incapacity and enrollment in research; (5) the duty to respect subjects' objection to participating in research; (6) investigator justification of the determination of a particular level of risk, informed consent procedures, and other protections; (7) examples of minimal risk and greater than minimal risk interventions in research in subjects with mental disorders that may affect decisionmaking capacity; (8) rules for greater than minimal risk, potentially beneficial research; (9) rules for greater than minimal risk research that is not potentially beneficial for this population.

IRBs should be clear that their first order of business is to protect human research subjects regardless of the research's potential benefits, including its potential for direct medical benefits to subjects. Moreover, as the risks of research participation increase without offsetting potential direct medical benefits to the subject, the intensity of consent processes and of other protections should increase.

1. IRB membership.

All IRBs that regularly consider proposals involving persons with mental disorders that may affect decisionmaking capacity 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 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. 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.

2. *Limiting subjects with mental disorders that may affect their decisionmaking capacity to protocols where their participation is necessary.*

An IRB should not approve research involving subjects with mental disorders that may affect decisionmaking capacity when such research can be done with other subjects.

3. *Assessing potential subjects' capacity to decide about participating in research.*

An IRB should not approve research protocols involving persons with mental disorders that may affect decisionmaking capacity unless it is satisfied that investigators will employ an adequate and 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.

4. *Notification of determination of incapacity and enrollment in research*

A conscious person who has been determined to lack capacity to consent to participate in a research protocol must be notified of that determination before permission can be sought from his or her legal authorized representative to enroll that person in the research, and must then be

notified if permission has been given to enroll him or her in the research.

5. *Subjects' objection to participating in research.*

Any apparent dissent by a subject from participation 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.

6. *Investigator justification of the determination of a level of risk, informed consent procedures, and other protections.*

Investigators must justify their determination of the level of risk entailed by research protocols involving persons with mental disorders that may affect decisionmaking capacity, as well as describe the special informed consent procedures to be developed and other appropriate protections, all of which must be appropriate in light of the level of risk posed by particular research interventions and explained in the protocol.

7. *Minimal risk and greater than minimal risk interventions in research involving human subjects with mental disorders that may affect decisionmaking capacity.*

The regulations should require investigators and IRB's to evaluate carefully the risk level

entailed by particular procedures in light of the specific conditions of the individuals who may be involved as subjects in the study. The risk level may be minimal, a minor increment over minimal, or more than a minor increment over minimal.

As guidance, the regulations should include examples of minimal risk and greater than minimal risk interventions for a general population. Examples of minimal risk interventions with persons in a general population are routine observation, data collection, answering a questionnaire, epidemiological surveys, venapuncture, intravenous and intramuscular injections, skin biopsies, blood sampling, and neuropsychological testing. Examples of greater than minimal risk interventions with persons in a general population are sternal and spinal punctures, bone marrow and muscle biopsies, intravenous and intraarterial transfusions, positron emission tomography, endoscopy and biopsies of the gastrointestinal tract.

8. *Greater than minimal risk, potentially beneficial research involving persons with disorders affecting decisionmaking capacity.*.

An IRB may approve this category of research only if the potential subject has given informed consent -- including as part of an advance planning process -- or the subject's legally authorized representative has given permission for the subject's participation in the research, and there is no apparent subject dissent. A legally authorized representative is an individual authorized under state law or previously approved and published institutional rules to make medical decisions on behalf of another individual. The IRB should also consider whether to

institute additional requirements as described in the section on Guidance below.

9. *Greater than minimal risk research that is not potentially beneficial involving persons with mental disorders affecting decisionmaking capacity*.

An IRB may approve this category of research only if the potential subject has given informed consent, including consent given as part of an advance planning process. In addition, the IRB must ensure that there is a procedure for identifying a legally authorized representative (someone authorized under state law or previously approved and published institutional rules to make medical decisions on behalf of another individual), to make decisions about continuing or stopping the subject's participation in the research. The potential subject may still have sufficient capacity to appoint a legally authorized representative, or may have appointed a representative prior to current incapacity. The IRB must also ensure that there is an independent physician advisor identified and available to counsel the subject or the subject's representative about enrolling or continuing in the study. The IRB should consider additional requirements as described in the section on Guidance below.

Guidance for IRBs: The Research Context

IRBs should consider whether the particular context of a proposed research protocol would tend to undermine the ability of persons with disorders affecting decisionmaking capacity to provide informed consent, due to their psycho-social vulnerability or the prospect of a therapeutic misconception. Features of a context that could be cause for concern include potential subjects' dependence on the institution as in-patients or for continuing care, or a 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). In such cases the IRB should consider requiring that the study incorporate additional protections, such as those listed below.

Informed consent procedures -- IRBs should consider requiring investigators to identify an independent consent auditor to attend and approve of the informed consent process with subjects known to be decisionally impaired.

Individualized consent -- IRBs should consider whether standardized consent forms are sufficient for certain studies or for certain populations, such as those with decisional impairments, and should consider whether to require investigators to assess each potential subject in order to amend the consent process and form as needed for these individual subjects.

Independent physician advisors-- IRBs should consider whether to supplement health care agents and legally authorized representatives by requiring that an independent physician advisor be available to counsel subjects and/or their legally authorized representatives in potentially beneficial research (this is already recommended for research that is not potentially beneficial).

Study design -- IRBs must require investigators to justify certain controversial study

designs -- e.g., challenge studies, studies involving drug holidays, certain placebo studies – in light of the risks presented to specific subjects. IRBs should also consider whether to require that an independent physician advisor be appointed to assess subjects periodically and to determine whether they should be removed from the study if their participation is no longer consistent with the their medical interests.

Wraparound studies -- Studies that may lead to confusion about their therapeutic value could be required to end with a treatment phase for subjects in non-treatment groups.

Recommendation to State Legislatures

The states should legislate a definition of a legally authorized representative for purposes of deciding on a subjects 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 individuals while competent.

Recommendation to Professionals and Organizations of Healthcare Professionals

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 Healthcare team, including sharing information with them. Professional organizations should open discussions about methods to advance this goal. Innovations in this area must, of course, be consistent with the ethical obligation of patient

confidentiality.

Recommendation to the National Institutes of Health

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

Recommendation to the Department of Health and Human Services

In protocols that promise significant scientific benefits for persons with mental disorders that may affect their decisionmaking capacity or significant increases in understanding their conditions, but that are otherwise unapprovable under the rules proposed in this report, the Secretary of the Department of Health and Human Services should be able to convene an expert panel to determine whether a specific research protocol is so promising that it meets all appropriate scientific and ethical standards and then to approve the research if approval is warranted.

Appendix 1:

Summary of **Proposed Regulatory Requirements for IRB** Protocol Review

For all research involving persons with disorders that affect decisionmaking capacity:

* IRB membership

All IRBs that regularly consider proposals involving persons with disorders affecting decisionmaking capacity should include at least two members who are familiar with the concerns of this population; other IRBs should have two consultants when protocols of this kind are being considered.

* Necessary use

An IRB should not approve research involving subjects with disorders affecting decisionmaking capacity when such research can**, in principle,** be done with other subjects.

* Risk determination

Investigators must justify in their protocols their determination of the **particular** level of risk entailed by **their** research involving persons with disorders affecting decisionmaking capacity, and informed consent procedures and other protections.

* Dissent

Any apparent dissent by a subject to participate in research (of any risk level) must be honored.

For research involving persons with disorders affecting decisionmaking capacity that entails greater than minimal risk:

* Assessing Decisionmaking Capacity

An IRB should not approve research **protocols** unless it is satisfied that **they will employ** an adequate and appropriate method**, administered** by a competent expert who is independent of the research team**,** to assess the potential subjects' capacity to decide whether to participate in the research.

* Notification

A conscious person who has been determined to lack capacity to consent to participate in a research protocol must be notified of that determination before permission **can be** sought from his or her surrogate decision maker to enroll th**at** person in the research**,** and must then be notified if permission has been given to enroll him or her in the research.

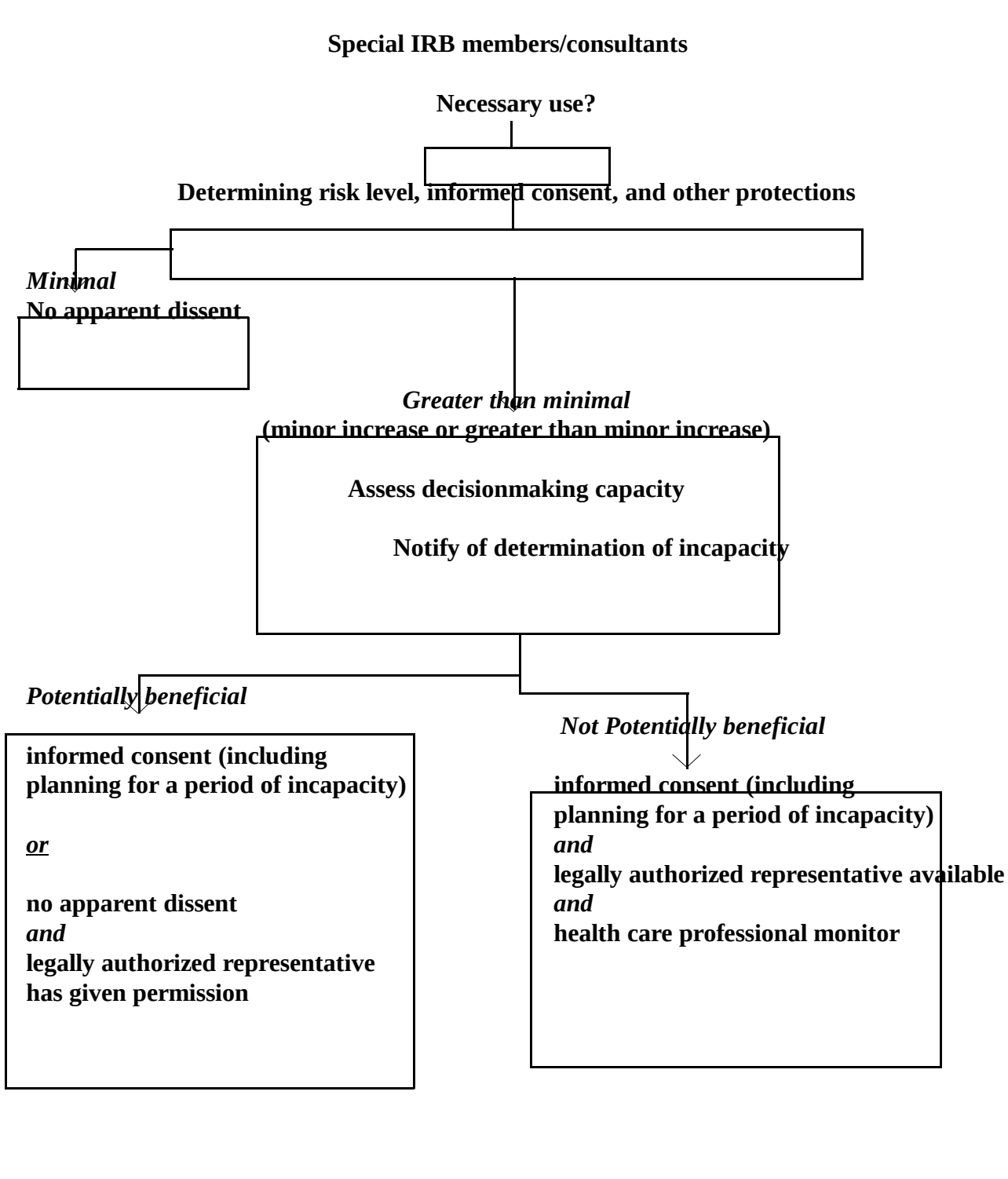
* Additional requirement for greater than minimal risk research that is potentially beneficial to the subject:

An IRB may approve this category of research only if the potential subject has given informed consent, or the subject's legally authorized representative has given permission for the subject's participation in the research and there is no apparent subject dissent.

* Additional requirement for greater than minimal risk research that is not potentially beneficial to the subject:

An IRB may approve this category of research only if the potential subject has given informed consent and a legally authorized representative and an independent physician adviser can be identified.

Appendix 2: Flow Chart Summary of Recommended Review Procedure


Special IRB members/consultants
Necessary use?
Determining risk level, informed consent, and other protections
Minimal
No apparent dissent
Greater than minimal
(minor increase or greater than minor increase)
Assess decisionmaking capacity
Notify of determination of incapacity
Potentially beneficial
Not Potentially beneficial
informed consent (including planning for a period of incapacity)
or
no apparent dissent
and
legally authorized representative has given permission
informed consent (including planning for a period of incapacity)
and
legally authorized representative available
and
health care professional monitor

Appendix 3: Glossary