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***Research Involving Persons with Questionable Decisionmaking Capacity:
A Draft Report of the Human Subjects Subcommittee
National Bioethics Advisory Commission****

Please note, highlighted sections reflect changes/additions from the earlier version.

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Appendix

Chapter One: RESEARCH AND PERSONS WITH QUESTIONABLE DECISIONMAKING CAPACITY

[N.B.: Major changes in this draft are in **bold**.--J.M.]

The Purpose of this Report

Biomedical research with the participation of human subjects plays an important role in the advancement of modern medical science. Over the past several decades there has been a growing awareness of the ethical issues associated with human subjects research, and mechanisms have been established to help ensure that studies involving human beings meets appropriate standards. Additional protections have been provided for populations that are regarded as particularly vulnerable and unable to give informed consent to research participation, with specific provision for children, fetuses, and prisoners. Persons with questionable decision making ability, such as those who suffer from psychiatric or neurologic disorders, have not been brought within the ambit of specific additional protections. The purpose of this report is to consider ways in which ethically acceptable research can be conducted with those whose decisional capacity is in doubt, whether specific additional protections are needed, and, if so, what they should be and how they should be imposed.

As will be elaborated in this report, there are special difficulties in decision making concerning research with those whose capacity is questionable, difficulties that help to create a compelling case for special protections. Persons in this population may have fluctuating capacity to engage in discussions concerning their treatment, which can complicate efforts to respect their right to decide about their care. Many of the conditions

underlying impaired decision making are medical problems that manifest themselves in behavior, making them hard to understand and causing discomfort in others. Persons with psychiatric and neurologic diseases have therefore been stigmatized, and efforts to improve their medical treatment have been marginalized. Those who are hospitalized in psychiatric units are liable to particular forms of vulnerability by virtue of the dynamics of that environment. Confusion about the goals of an intervention can easily be created when the physician caring for the patient is also a researcher, as is often the case. Because mechanisms for funding appropriate treatment are seriously wanting, many people do not have adequate access to health care outside the research context, though research is not necessarily intended to provide them with direct benefit. Many of the diseases being studied cause great suffering and there are at best few satisfactory treatments, but some of the research methodologies are controversial.

Issues arising out of research involving persons with questionable capacity are likely to become more prevalent in the near future. Medical science has recently made great strides in the understanding of underlying biological and chemical processes that figure in conditions that impair cognitive function, illnesses that afflict millions of Americans. This population represents significant growth potential for the pharmaceutical industry and an opportunity for research centers to expand their programs. In the United States, the blurry lines between private industry, government, and academia present a favorable atmosphere for scientific development, but they also present a challenge for a regulatory scheme intended to protect individuals while also permitting research and product development to flourish.

The combination of these and other factors creates a synergy that calls for special attention from the professions and institutions that engage in research involving persons with decisional impairments. For historical reasons that will be described in this report, previous efforts to establish specific protections for persons with decisional impairments have failed. The failure to take action cannot be laid at the blame of any particular professional group or set of institutions, but is a reflection of social attitudes and of a lack of consensus about how protections should be applied to those with psychiatric and neurological diseases. Our society has a moral obligation to remedy those failures for the sake of those who are directly affected and for their loved ones, so that treatment can be improved and important research can be continued.

Research Involving Persons With Questionable Capacity

The recent debate about research with **questionable decisionmaking capacity** has been stimulated by several incidents, including the tragic suicide of a former experimental subject in California and a court battle in New York State. Several tensions are inherent in the current controversy. Foremost among these tensions is that those who suffer from these diseases, and their loved ones, 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 are used in research and causing still greater suffering. In spite of this disagreement, much can be done to ameliorate the apparent conflict between the impetus to continue promising lines of research and 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 protection against research risks and access to

research benefits. But calls for protection and access can both be mere slogans that mask underlying problems. One 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 psychiatric **or neurologic** diseases.

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 and legal constraints of research so long as it is intended to be responsive 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”¹ trial of a medication approved for other purposes 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 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 treatment do apply, and the patient must give an informed consent to the innovative procedure that is to be attempted.

Calls for access to health care are also complicated by the fact that the “benefits” of being a research subject may easily be exaggerated, because clinical studies often are not only uncertain in their potential benefits, but may actually be designed to obtain information about questions

¹ **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.**

other than therapeutic efficacy. Further, the 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.

Perhaps most important, the need for improved access to health care 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 important ethical questions. 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."² 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 were not aware of important elements of the research.³ Considering the special complexities of research involving those whose decisional capacity is questionable, the radiation advisory committee's concerns must be at least as strongly applied to studies involving this population.

Principles that Should Guide Research

Surely protection from abusive research and access to potentially beneficial research are

² Advisory Committee on Human Radiation Experiments, The Human Radiation Experiments (New York: Oxford University Press, 1995), p. 456.

³Id., p.....

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 used in biomedical and behavioral research are treated with respect. This has been the underlying philosophy of more than three decades of continual improvement in the human research system, 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 questionable capacity** in research.

It must be acknowledged, however, that the purpose of medical research is to improve understanding of the mechanisms of disease and their means of prevention and treatment. There is no denying that our society is deeply committed to continuing this enterprise, from which so many of us have benefited. Often in the expansion of scientific knowledge there can be no reliable substitute for a human subject, including the study of diseases that manifest themselves partly by altering human subjectivity, such as depression or delusion.

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 anyone who is a subject of research, **in addition to any individual motivations**, is engaged in a form of public service for which there may be no direct or tangible reward. In the Commission's view, this inescapable fact argues decisively for the maintenance of a system of protection for all research subjects. Such protections **must never be less stringent for research subjects whose ability to be fully informed and freely consent** is lacking or in doubt **than it is for others**. This proposition is already well recognized in the case of pediatric research.

Of course, all persons suffering from an illness are at risk for impaired decision making due to physiologic and psychological stress. Health care professionals 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 situation and alternatives objectively than those who are well.⁴ **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 temptations to use them in research more than others. Another recognized precept of ethical research is that the burdens as well as the benefits of scientific projects should be distributed throughout the society. Some of **our** recommendations apply to ensuring that those whose **decisional capacity is questionable** 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

⁴Eric Cassell

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.

And in spite of the National Commission's work, those with **questionable decisional capacity** are not as well recognized in current federal regulations as other vulnerable subject populations.

It is time to elaborate on the foundation laid by the National Commission with regard to research involving **persons with questionable** decisionmaking capacity.

The Nature of Disorders that Affect Decisionmaking Ability

Persons with questionable decisionmaking capacity are not necessarily decisionally impaired, much less decisionally incapable. Rather, the observations that call decisionmaking ability into question may trigger a clinical assessment that could lead to a determination that decisional capacity is impaired. A number of disorders can affect decisionmaking capacity.

Material to be added.

Obstacles to Informed Consent

The ability or capacity to consent to being a research subjects is a critical consideration in ethical research. Every effort must be made 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 is to have all the information one would need to make an informed decision about being a subject. There is an affirmative obligation to help those with less ability to understand the relevant information about the research before they may be enrolled. It is generally agreed that those who lack the ability to decide about being in research may only be included under certain conditions.

Among these conditions are **an inability to do the research with subjects whose capacity to make decisions is not impaired**, a reasonable level of risk in light of potential benefits, and the importance of the research.

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 decisionmaking. It is important not to confuse the fact that decisionmaking abilities are limited for many people with the diverse ways in which it is limited. Appreciating and recognizing this diversity will help in the design of an ethically sensitive recruitment and research process.

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. 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. 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. Persons with limited capacity are in some way able to object or assent, as in the case of more advanced Alzheimer's. 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 only a framework for the different ways the problems can manifest themselves. Among those whose capacity fluctuates or is limited, one cannot "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 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 research is in turn designed to maximize their ability to participate in the decision to enter or to continue to be part of a study.

Finally, there are environmental factors that affect decision making capacity. All of us feel more "empowered" and in control in some 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. This insight can be critical in helping the individual achieve as high a degree of self-determination as possible.

The Possibility of Benefit

As has been mentioned, many research studies do not offer any direct prospect of benefit to the subjects. 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 benefit 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 experience no direct medical benefit, though they may enjoy financial compensation or the altruistic satisfaction that comes from their service.

Many studies do involve procedures or maneuvers that could be of benefit to the subjects, but it is often not easy for the researchers to know whether they would be better than nothing (as in the case of a placebo study), or whether they would be better than the standard treatment. Indeed, a researcher should not be sure one way or the other, because scientific uncertainty is an important justification for doing the experiment in the first place. **Nevertheless, even when there is justifiable uncertainty about which treatment is better (when the relevant scientific community is said to be in “equipoise”)**, 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 scientists must think. Especially when one is sick, 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 *aparticular* person some good, he or she 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 future 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, however, that the desire for a treatment may overwhelm the ability to assess the likelihood of benefit 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” may be especially intense in those whose decision making is impaired. But clinical trials are not normally therapeutic opportunities, and patient-subjects may feel betrayed or abandoned when their study participation comes to an end.

Special Ethical Issues in Research with Decisionally Impaired Subjects

Research involving decisionally impaired subjects must take into account ethical issues beyond those having to do with consent and risk and benefit, issues that are of special relevance to this population. The subjective nature of many disorders that impair decisionmaking can make the evaluation of interventions thought to confer benefit uniquely difficult. 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. Therefore clinical investigators working with these populations may have to factor more individualized judgments into their projections of risk and benefit than may be the case for other researchers.

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 neurologic and psychiatric disorders, and the fact that many stricken individuals are refractory to

treatment, make many of us uncomfortable. Many primary health care professionals are relatively unfamiliar with the signs of these illnesses or the 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 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 financing the treatment of many of these conditions continues to suffer in relation to diseases that seem to fit more easily into a “somatic” framework. Both public and private insurance mechanisms often fail to provide reasonable support for the kinds of intervention that may be required, a problem that is further aggravated among the mentally ill who tend to be among our poorer citizens. Without adequate access to mental health care and lacking in financial resources, these people 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 this sort of situation, those who might succumb to what has been called the therapeutic misconception about research, must be carefully guarded against.

Though the vast majority of biomedical scientists are dedicated to improving the lives of those suffering from terrible afflictions, it must also be acknowledged **that there are substantial material as well as psychological rewards associated with a successful research career.** The reward system among scientists has become more complex in recent years. While at one time government grants might have been the main source of support among academic researchers, private industry has come to occupy a more important role in the economy of

science. The pressures associated with professional advancement through publication have also not lessened, all trends that encourage subject recruitment. Most clinical investigators **are caring and humane and** treat their patient-subjects responsibly. Nevertheless, the evolving human research environment requires adjustments in regulatory processes and specifications of ethical practices so that, so far as possible, misunderstanding of societal expectations can be avoided.

It has already been noted that those who struggle with diseases that impair their decision making 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 of disenrolling 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 decision making capacity. Although there are certain clear cases, including those who are fully capable and those who are wholly without capacity, persons with fluctuating and limited capacity present serious problems of assessment. When can those whose capacity is impaired in these senses be said to be able to decide about being in research? In a society that treasures personal freedom this question goes to the very heart of our political philosophy and must therefore be treated with utmost care.

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 caretakers like family members and close friends has implications that range from the medical to the psychological to the economic. This is particularly true in a system such as ours, with its 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.”⁵

To be sure, communication with informal caregivers raises important issues of patient confidentiality, but recent bioethical theory has rarely been sensitive to the underlying interpersonal support mechanisms of family and close friends that are so important to those with long-term illness. On the contrary, much theorizing has in effect worked against recognizing and involving others in the ethical research process. The critical role of self-determination in human

⁵Patricia Backlar, “Ethics in Community Mental Health Care: Confidentiality and Common Sense,” Community Mental Health Journal 32(6):513-517, 1996, p. 517.

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. Social 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 Biomedical Research

As never before, research in the basic biological sciences and in their clinical application holds out the prospect of improved treatment for those who suffer from neurologic and psychiatric disease.

Material to be added.

The Heavy Responsibilities of Clinical Investigators

The clinical investigator is the key player in our system of human subjects research. Many of the central issues in this report -- standards for decisional capacity, assessment of risks and potential benefits, techniques for improving informed consent, recognizing the involvement of family members and friends -- in practice turn on the integrity, caring, and professionalism of the research physician. No matter how many regulations are put in place or guidelines written, and regardless of the intensity of scrutiny by IRB or other authorities, there can be no substitute for the researchers' commitment to ethically acceptable research.

It is often noted that there is no right to conduct research with human subjects, that

it is a privilege conferred to individuals who are prepared to undergo rigorous scrutiny of their proposed studies. 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 medical therapist 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 bringing the research project to a successful conclusion are not always congruent.

Does the scientific importance of my work justify asking people to be in my research? 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 voluntary? Is he or she liable to a therapeutic misconception? All of these are critical questions the clinical investigator must ask, creating a moral burden that has few if any analogies elsewhere in our society. The scientist is expected to advance knowledge that can improve the human condition and at the same time to manage human research subjects with utmost care and respect.

There is much truth to the view that 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 an essential element of ethically acceptable research practices, it cannot be the only element. It is unfair to expect that the complex moral problems entailed by modern human subjects research can be resolved 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. At the end of the day, all of us are responsible for placing profound and sometimes conflicting expectations upon those who do research involving our fellow human beings, and all of us must take responsibility for the results of such a system.

Chapter Two: A BRIEF HISTORY OF ETHICAL ISSUES

Historic Controversies in Research With the Decisionally Impaired⁶

Debate about the propriety and necessity of research with **persons whose capacity is questionable** 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 those with decisional impairments 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 directed that medical research

⁶ 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. Much of the material in subsequent chapters has been adapted from a contract paper prepared by Rebecca Dresser for the National Bioethics Advisory Commission. Both were consultants for this report.

must have the human subject's consent.⁷

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.⁸ 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.⁹ Following the Neisser scandal, physicians in that part of the world must 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 for Physiology or Medicine, also conducted research with the decisionally impaired. 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 complex tasks they had learned, they seemed to be immune to anxiety and frustration,. Moniz theorized that the same may be true

⁷George J. Annas and Michael A. Grodin, The Nazi Doctors and the Nuremberg Code (New York: Oxford University Press, 1992), pp. 127-128.

⁸"Julius Wagner von Jauregg," Nobel Prize Winners, Tyler Wasson, ed. (New York: The H.W. Wasson Co., 1987), pp. 1092-1094.

⁹Id. at 1094.

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. 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.¹⁰

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, which reported to President Clinton in October 1995 on post-war government-sponsored studies of ionizing radiation.¹¹

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 the decisionally impaired did not often provoke general outrage: They were 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**

¹⁰ "Egas Moniz," Nobel Prize Winners, ed. Tyler Wasson (New York: The H.W. Wilson Co., 1987), pp. 723-725.

¹¹ Advisory Committee on Human Radiation Experiments, The Human Radiation Experiments (New York: Oxford University Press, 1995).

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 fairly 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?"¹²

Pressures to make new medications available to alleviate human suffering are also great when significant commercial possibilities are present. 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, the human research issue casts a shadow. The neuroleptic drugs unquestionably inaugurated a new era in the

¹² Gerald Grob, The Mad Among Us (Cambridge, Ma.: Harvard University Press, 1994), p. 181.

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.¹³ 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.¹⁴ 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.

Not all instances of ethically questionable research practices involving those who are decisionally impaired are intended to benefit the subjects, nor even are they intended to yield knowledge of the sources of the impairment that affects the 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 is

¹³ Phil Brown, Transfer of Care (Boston, Ma.: Routledge and Kegan Paul, 1985).

¹⁴ Public Law 87-781, 21 U.S.C. 355, 76 Stat. 780; amending Federal Food, Drug and Cosmetic Act.

included in research because he or she is readily available (i.e., considered to be less eligible for protection), especially if the subject is 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 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 PI had a secret contract with the Army Chemical Corps to conduct research on a mescaline derivative, methyl di-amphetamine (MDA). In mid- January 1953 Blauer was given several injections of various forms of mescaline. Following one of the injections Blauer went into convulsions and died 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.¹⁵

At around the time the Blauer case began, in the early 1950s, 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 a study 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 Wrentham. At

¹⁵*Barrett v. U.S.*, 660 F. Supp. 1291 (S.D.N.Y., 1987).

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. 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.”¹⁶ (emphasis in original)

Both the Blauer and Fernald-Wrenthem cases involved decisionally impaired subjects but 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. The degree and quality of consent to participation in these studied greatly varied.¹⁷

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 directly nor to contribute to knowledge about the condition that has caused their decisional

¹⁶ *Supra* note 8 at 504.

¹⁷David 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.

impairment: the Brooklyn Jewish Chronic Disease Hospital case in 1963, in which debilitated patients were injected with live cancer cells, apparently without their knowledge.¹⁸ 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.¹⁹

History of Regulatory Efforts

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

¹⁸Ruth R. Faden and Tom L. Beauchamp, A History and Theory of Informed Consent (New York: Oxford University Press, 1986), pp. 161-162.

¹⁹ Jay Katz, Experimentation with Human Beings (New York: Russell Sage Foundation, 1972), pp. 9-65.

It happened that Moses was also a member of the German Parliament from the Social Democratic Party. 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. 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.²⁰

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

²⁰Michael 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.

human experimentation.

In his memorandum, Alexander singled out the mentally ill as a population that should be given special protections.²¹ 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, and with the decisionally impaired.

The next major international research code clarified the situation. The World Medical 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."²² 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"

²¹ Id. at 135.

²²World Medical Association, Declaration of Helsinki, 277 JAMA 927 (1997).

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 reasonable medical alternative, and local law permits overriding the objection."²³

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 up for consideration, 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,"²⁴ and its 1978 "Report

²³ CIOMS/WHO, International Ethical Guidelines for Biomedical Research Involving Human Subjects 22 (1993).

²⁴ National Commission, Report and Recommendations, Research Involving Children (1977) [hereinafter Report on Children].

and Recommendations on Research Involving Those Institutionalized as Mentally Infirm,²⁵ 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 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.²⁶

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

²⁵ National Commission, Report and Recommendations, Research Involving Those Institutionalized as Mentally Infirm (1978) [hereinafter Report on Institutionalized Persons].

²⁶ Id. at 58.

hierarchy of research categories establishing more rigorous substantive and procedural standards for proposals presenting more than minimal risk to incapable subjects; and a mechanism for incapable subjects to provide input in the form of "assent" or objection to study participation, that is, a simple yes or no when questioned about willingness to be in a study.

Differences in the recommendations on children and institutionalized persons were based on the 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.²⁷ 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

²⁷ 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.

Services (DHHS) in June 1983.²⁸ The proposed regulations on persons institutionalized as mentally disabled were never adopted, however.²⁹

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.³⁰ 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.³¹

²⁸ Protection of Human Subjects, Additional DHHS Protections for Children Involved as Subjects in Research, 48 Fed. Reg. 9818 (Mar. 8, 1983).

²⁹ Protection of Human Subjects, Proposed Regulations on Research Involving Those Institutionalized as Mentally Disabled, 43 Fed. Reg. 53950 (Nov. 17, 1978).

³⁰ President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Implementing Human Research Regulations 23-29 (1983).

³¹ 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 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.

With the exception of the IMI recommendations, the 1981 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."³² The regulations do authorize IRBs to institute additional safeguards for research involving vulnerable groups, including the mentally disabled.³³ 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 (4) 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 knowledge for the benefit of persons with the same condition; and (2) "entails only minimal risk

³²Federal Policy for the Protection of Human Subjects; Notices and Rules 56 Fed. Reg. 28002-28032 (June 18, 1991).

³³Ibid.

and minimal burden for the individual concerned.¹⁶⁴

The Contemporary Debate

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,³⁵ 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.³⁶ 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."³⁷ The Rule allows an incapable individual's "legally authorized representative" to give valid consent to the individual's research participation,³⁸ but provides no definition of incapacity, no guidance on the identity or qualifications of a subject representative

³⁴ Council of Europe, Convention on Human Rights and Medicine (Nov. 1996). No further explanation is given concerning definitions of the terms minimal risk and minimal burden. States will be invited to ratify or otherwise respond to this document.

³⁵ Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28012 (1991).

³⁶ Sec. ____ .111 (a)(3) & (b).

³⁷ Sec. ____ .107(a).

³⁸ Sec. ____ .116

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 questionable 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."³⁹ Inquiries into studies involving medication withdrawal from persons diagnosed with schizophrenia also have raised questions about the adequacy of existing federal policy.⁴⁰

There is strong indirect evidence that IRBs are unlikely to compensate for the lack of specific regulations for research with the cognitively impaired by aggressive use of their 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. IRBs appear to have all they can handle to keep up with their paperwork, as privately funded research

³⁹ Final Report, *supra*, at 706-07.

⁴⁰ 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 and justification, and monitoring to avoid harm to subjects after studies were initiated).

has proliferated. 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.⁴¹

The lack of specific federal guidance on research with the decisionally impaired 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 restrictive regulations. Recent events in New York State illustrate the situation, as a state court has prohibited carrying out research of all New York State-sponsored greater-than-minimal-risk research that does not offer potential benefit in mental institutions that are operated or regulated by the state. The decision in the T.D. case, resulting 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.⁴² 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 decisionally impaired subjects.

The growing interest in research with the decisionally impaired stems partly from the most

⁴¹U.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).

⁴² 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).

recent well-publicized incident with this population, the suicide of a former subject in a “drug free” or “washout” study at UCLA.⁴³ The National Institutes of Health Office for Protection from Research Risks concluded that the study design was ethical but the informed consent form flawed.⁴⁴ Defenders of the research claim that patients are often taken off all medication to establish baseline following admission to inpatient units, while admitting that withdrawing psychotropic drugs poses the danger of relapse and must be carefully managed.⁴⁵

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 on mentally disabled persons 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 who may be decisionally impaired and has led to the creation of a number of specialized publications. Representatives of several of these groups 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 members of the public, it is persuaded that there is substantial public

⁴³Adil E. Shamoo and Timothy J. Keay, “Ethical Concerns about Relapse Studies,” Cambridge Quarterly of Healthcare Ethics 5:373-386, 1996.

⁴⁴Office 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.

⁴⁵ R.J. Beldessarini, “Chemotherapy.” In: A.M. Nicolai (ed.), Harvard Guide to Modern Psychiatry (Cambridge, Ma.: Harvard University Press, 1978), pp. 387-432.

concern about actual or potential failures to protect persons with questionable capacity from inappropriate research protocols. It also believes that many clinical investigators may feel uncertain 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 present system for the protection of human research subjects are warranted with regard to those who may suffer from decisional impairments.

The recommendations advanced in 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 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 with persons whose capacity to make decisions about participating in research may be impaired? -- 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 harm may be done to human beings in the name of science. The Nuremberg Code (which formed part of the opinion of the judges in the “Doctors’ Trial”), 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 controlling research is to protect potential subjects from harm by establishing barriers to ethically flawed research. The result has been the establishment of a system of prior review of research protocols aimed at weeding out those that would expose subjects to risks that are judged to be excessive in light of the potential benefits.

In recent years, however, challenges have been raised to that objective, as some have argued that another goal -- ensuring access to experimental treatments -- also should shape 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 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. Those who lack such capacity, or whose capacity is questionable, may thus be excluded from research. Under the “protection model” such exclusion may seem appropriate, as the underlying premise is that it is better to protect subjects from being harmed, even at the cost of slowing down scientific investigation. Conversely, under the “access model,” barriers to research with decisionally impaired subjects are suspect because they prevent some people from obtaining the benefits that such research could 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 Impairments⁴⁶

⁴⁶Although older children and adolescents are not specifically discussed 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.

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 it is seen as one of the basic means of protecting people from research risks. **The threshold concept that qualifies an individual for participation in the informed consent process is decision making 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, task-specific concept, whereas competence suggests a more global sense that may not be necessary when a discrete decision needs to be made.**

Individuals whose capacity to make decisions is merely questionable 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.” As we have noted, impairments can result from a variety of causes, including cognitive difficulties as well as constraints on **personal** freedom due to institutionalization, dependency upon those who provide one’s treatment, **or other causes.** Whenever such factors are sufficient to impair a person’s ability to make the decision in **question** -- that is, whether to enroll in a research project, in light of its potential risks, benefits, and so forth -- the person lacks the capacity to make a voluntary, informed choice and hence cannot participate in research according to the standard requirements.

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.⁴⁷ 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. **But there are other forms of decisional impairment that are normally more temporary, such as the transitory side-effects of treatment, but that might also call for planning for research participation.**

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 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 those with persons who may be

⁴⁷The 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).

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 also requires a sociological 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 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 conditions 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 this population, including clinical investigators and IRBs, enrich their appreciation of the importance of context in the consent process and, therefore, in ethically acceptable research.

Immaturity and Decisional Incapacity

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 of human subjects research 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 (such as fetuses and children) or biologically defined populations (such as pregnant women) or even socially defined groups (such as prisoners). If those who are decisionally impaired are to be identified as in need of special treatment under research regulations, they must be carefully distinguished from other special populations.

Although persons with decisional impairments 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 questionable capacity. At the very least, this state of affairs argues for special protections for persons with decisional impairments, especially considering the additional social, financial, and interpersonal factors that make some psychiatric and neurologic disorders so burdensome. A stronger version of this position would be that there should be a single set of rules for minors who are unable to give consent (with the important exception of mature minors who may be able to consent to specific protocols), and those who are decisionally impaired

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

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 assumptions that may be far from obvious.⁴⁸

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

⁴⁸Thomas 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.

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 very low. But the selection of a threshold of decisional ability is not wholly a political one, as it must be justified by the individual's ability to satisfy certain benchmarks. One such benchmark is the ability to understand the implications of one choice or another for his or her 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 periods of lucidity along with cycles of mania and depression.

Determining the proper standards and procedures to govern capacity assessment poses a major challenge in formulating policy on research involving subjects with mental disabilities. Persons with mental disabilities vary widely in their ability to engage in independent decisionmaking. Persons with psychiatric disorders may retain such capacity, possess it intermittently, or be permanently unable to make decisions for themselves. Individuals with dementia 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.⁴⁹

Incorrect capacity determinations are problematic 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.

Conversely, a judgment that an incapable person is capable leaves that individual unprotected and vulnerable to exploitation by others.⁵⁰ The presence of many marginal cases among members of the relevant populations triggers concern about the adequacy of subject capacity assessments.

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 may be too willing to label prospective subjects capable when this will advance their research objectives.⁵¹

Existing federal policy fails to provide guidance to investigators and IRBs on the appropriate substantive and procedural standards applicable to capacity determinations in research

⁴⁹ 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).

⁵⁰ 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*].

⁵¹ 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"); 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").

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.⁵² Most of the commentary supports more systematic and specific federal direction on capacity assessment.⁵³ Greater guidance is needed on defining decisional capacity in the research context, and procedures for assessing such capacity.

Procedures for Capacity Assessment and Information Disclosure

Existing federal regulations acknowledge that mentally disabled persons may be vulnerable to undue influence or coercion, but leave the adoption of special safeguards up to individual IRBs. The regulations also fail to provide guidance on the process that should govern capacity assessments 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 the researcher's initial assessment." This flexibility, together with the absence of "appropriate and

⁵² Bonnie, *supra*, at 109.

⁵³ E.g., *id.*

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.⁵⁴ This decision raises questions about the constitutional status of the existing federal regulations as well, since they closely resemble the invalidated New York regulations.⁵⁵

A variety of approaches to capacity assessment is endorsed in the literature on research involving adults with cognitive impairment. Most 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.⁵⁶ **Evaluating decisional capacity is not as straightforward a task as might be inferred from philosophical discussions of capacity. Any assessment tool measures capacity indirectly through manifest performance, and our capacities do not always measure up to their 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 capacity. The problem is**

⁵⁴ T.D. v. N.Y. State Office of Mental Health, 650 N.Y.S.2d 173 (App. Div. 1996).

⁵⁵ See Capron, Incapacitated Research, Hastings Center Rep. Mar.-Apr. 1997, at 25.

New York's highest court has agreed to hear plaintiff's appeal of T.D. Plaintiffs argue that the intermediate appellate court's decision should apply to all research involving greater than minimal risk (including studies presenting a prospect of direct benefit) and to federally-funded research. The appeal will involve the court in a direct evaluation of the existing federal policy.

⁵⁶ E.g., Bonnie, *supra*; Melnick et al., *supra*.

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.⁵⁷ 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 opposition to this proposal reportedly was one reason the regulations never became final.

More recent commentary includes a spectrum of views on the need for an independent consent auditor. Some echo the National Commission's view that a requirement for an independent evaluator becomes increasingly justified as net research risks to subjects increase. A Canadian group took this position in its recent recommendations on dementia research.⁵⁸

⁵⁷ 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.

⁵⁸ Keyserlingk, et al., supra.

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.⁵⁹

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."⁶⁰ In testimony before the National Bioethics Advisory Commission, representatives of Citizens for Responsible Care in Psychiatry and Research recommended that "[a]n independent psychiatrist ... determine the capacity of [the] potential participant to comprehend the risks and benefits of enrolling in the proposed research study."⁶¹ 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

⁵⁹ Id. at 343-44. See also Melnick, et al., *supra*.

⁶⁰ Orr, Guidelines for the Use of Placebo Controls in Clinical Trials of Psychopharmacologic Agents, 47 *Psych. Services* 1262 (1996).

⁶¹ Shamoo & Sharev, Unethical Use of Persons With Mental Illness in High Risk Research Experiments, 2 *BioLaw S*:23 (1997).

advancement of general knowledge is the primary goal of the project at hand.⁶²

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 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.⁶³

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

⁶² 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.

⁶³ Bein, *supra*, at 748-49.

because such a system would be too responsive to institutional interests.⁶⁴

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 specialists, or concurrent consent by a family member."⁶⁵

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.⁶⁶ 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."⁶⁷ On the other hand, the presence of a caregiving relative could in some cases put pressure on subjects to enter a research study.⁶⁸

⁶⁴ Id. at 762.

⁶⁵ Bonnie, *supra*, at 110.

⁶⁶ 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").

⁶⁷ Karlawish & Sachs, *Research on the Cognitively Impaired: Lessons and Warnings from the Emergency Research Debate*, 45 *J. Am. Geriatrics Soc'y* 474, 477 (1997).

⁶⁸ Id.

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 systematic and rigorous inquiry.⁶⁹

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. A creative suggestion is for investigators to ask representatives of the affected population to critique drafts of information materials prior to their actual research use.⁷⁰

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

⁶⁹ 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)).

⁷⁰ Melnick, et al., *supra*.

official relationship."⁷¹ 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.

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."⁷² 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."⁷³

There is consensus that decisional capacity requires a certain level of cognitive ability.

⁷¹ World Medical Association, *supra*.

⁷² 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).

⁷³ Melnick, et al., Clinical Research in Senile Dementia of the Alzheimer Type, 32 *J. Am. Geriatrics Soc'y* 531, 533 (1984).

Less agreement exists on whether subjects should be judged incapable if they lack affective appreciation of the choice before them. In a recent article, Carl Elliott argues that some depressed persons "might realize that a protocol involves risks, but simply not *care* about the risks," or "as a result of their depression, may even *want* to take risks." (emphasis in original)⁷⁴ 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."⁷⁵

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.⁷⁶ Instead, investigators must present the specific material relevant to that project and evaluate the prospective subject's ability to understand and appreciate that information.⁷⁷

⁷⁴ Elliot, *Caring About Risks*, 54 *Arch. Gen. Psych.* 113 (1997).

⁷⁵ 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).

⁷⁶ 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).

⁷⁷ 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

Some commentators endorse a "sliding-scale" approach to decisional capacity in the research setting. This approach demands an increasing level of understanding and appreciation as study risks increase and potential benefits to subjects decrease.⁷⁸ 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."⁷⁹

Besides being informed, a decision to enter research should be voluntary. The Nuremberg Code provides descriptive characteristics of a voluntary decision.⁸⁰ 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

participation; (4) the procedures to be performed and which, if any, are experimental; (5) reasonably foreseeable risks and discomforts; (6) reasonably expected benefits to subjects or others; (7) alternatives, including treatment, that could benefit the individual more than research participation; (8) the level of confidentiality protecting any identifiable information recorded on the subject; (9) whether compensation and medical treatment will be available for injuries resulting from research; (10) the identity of the person(s) to notify if the subject has questions or suspects research-related injury; and (11) that participation is voluntary, refusal will not be penalized, and participation may cease at any time without penalty. 56 Fed. Reg. sec. ____116(a). Additional information must be disclosed and understood when relevant to a particular study, such as any additional costs subjects may incur as a result of study participation. *Id.* at sec. ____116(b).

⁷⁸ 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).

⁷⁹ Sachs, et al., *supra*, at 410.

⁸⁰ See p. 5, above.

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."⁸¹

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.⁸² 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.⁸³ Some 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.⁸⁴

⁸¹ Belmont Report, *supra*, at 6.

⁸² Bonnie, *supra*; Levine, Proposed Regulations, *supra*.

⁸³ Relatives may view research participation as improving their own chances for avoiding conditions that appear genetically-linked or as a means to reduce their caregiving burdens. Keyserlingk, et al., Proposed Guidelines for the Participation of Persons With Dementia as Research Subjects, 38 *Perspect. Biol. Med.* 319 (1995).

⁸⁴ 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).

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.⁸⁵ The matter of legally authorized representations will be considered later in this report.

⁸⁵ Appelbaum, Drug-Free Research, *supra*.

Chapter Four: THE ROLE OF INFORMED CONSENT

Research Decisions for Persons Incapable of Independent Choice

Many persons diagnosed with mentally disabling conditions may be unable to make truly informed decisions on research participation. Others may become incapable while they are participating in a study. In these circumstances, if they are potential subjects, persons other than the incapable individual must make the choice for or against that individual's research involvement. Decisions on the permissible conditions for enrolling and retaining incapable subjects must be made at the policy level, as well as by IRBs and the subject's personal representative.

Existing federal policy is largely silent on these matters. According to the Common Rule, the risks presented by any proposal to involve human subjects must be reduced to the minimum necessary to obtain the desired data, and must be "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."⁸⁶ No additional limits or criteria for evaluating permissible risk in research involving incapable subjects are included in the Rule. Special DHHS regulations establish such conditions for research involving children, but research involving incapable adults is governed solely by the Common Rule's general provisions.

Existing federal policy also gives little direction on who should act as the incapable subject's personal representative in making decisions on research participation. The Common Rule simply provides that "[i]nformed consent will be sought from each prospective subject or the

⁸⁶ Sec. ____ .111(a).

subject's legally authorized representative.⁸⁷ The Rule fails to address the desirable qualifications of a representative or the substantive criteria that should guide that person's choices. The Belmont Report simply states that third party decisionmakers "should be those who are most likely to understand the incompetent subject's situation and act in that person's best interest."⁸⁸

Improvements in current policy will require attention to five areas: permissible levels of risk in research involving incapable subjects; selection of an incapable subject's representative; substantive criteria governing the subject representative's decisionmaking; the incapable subject's assent or objection to research participation; and the incapable subject's preferences while capable. Although these areas are discussed in separate sections of this report, they are significantly related, and are likely to be combined in any policy revision. Before these matters are treated, however, attention must be paid to the logically prior questions whether research should in principle be permitted with those who are decisionally impaired or incapacitated or whether no protections can justify such research.

Should the individual's informed consent always be required for research participation?

The subject's informed and voluntary consent is the strongest basis for enrollment in a research study. Certain persons diagnosed with psychiatric disorders, developmental disabilities, dementia, and other conditions associated with mental disability possess the necessary cognitive abilities and are sufficiently independent of others to provide informed and voluntary consent. Many others, however, are not. A basic moral and policy question is whether these individuals should ever be involved in research.

⁸⁷ Sec. ____ .111(4).

⁸⁸ Belmont Report, *supra*, at 6.

We have noted that the first sentence of the Nuremberg Code states that “[t]he voluntary consent of the human subject is absolutely essential.” Adequate consent requires the subject's: (1) "legal capacity to consent"; (2) ability "to exercise free power of choice without the intervention of any element of force, fraud, deceit, duress, or over-reaching, or other ulterior form of constraint or coercion"; and (3) sufficient knowledge and comprehension of the elements of the subject matter involved," including "the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment."⁸⁹ Absent from the Code is any provision authorizing surrogate consent to research on behalf of subjects incapable of producing a decision that meets these criteria.

We have also seen that later research codes and policies have rejected the Nuremberg Code's apparent position that informed and voluntary consent is an absolute prerequisite to a human subject's research participation. Two justifications are offered for this rejection. One rests on an interpretation of the Code in light of its historical origins. The Code was formulated in response to the Nazi experiments conducted on competent subjects without their consent. The judges issuing the Code may not have intended to take a specific position on research involving decisionally impaired or incapable subjects.⁹⁰ The second justification for rejecting a ban on research involving impaired or incapable subjects is based on moral considerations. Because new

⁸⁹ United States v. Karl Brandt, reprinted in Katz, *Experimentation with Human Beings* 292, 305 (1972).

⁹⁰ McCormick, *Proxy Consent in the Experimentation Situation*, 18 *Perspect. Biol. & Med.* 2 (Autumn, 1974).

treatments must eventually be tested in persons suffering from the relevant condition, a policy totally excluding incapable subjects from research would preclude the development of improved treatment for persons with serious psychiatric disorders, dementia, and other mentally debilitating conditions.

As the field of medical ethics has grown some distinguished commentators have continued to defend the view that no research is permissible without the subject's informed consent. They point out that scientific progress is morally optional, while respect for human beings and their self-determination is not. Yet research with **younger children and other populations unable to give valid informed** consent has continued and flourished in the half century since Nuremberg. These practices have been justified by seeking what many regard as the moral equivalent of subject consent, including parental permission and subject assent where feasible. As we have noted, a further justification is that significant benefits to many individuals would have to be foregone if the consent requirement were strictly interpreted, but few have found strict interpretation of the consent requirement to be morally obligatory. Various standards and procedures have been established to protect the well-being of subjects. It is also often noted that, since treatment of individuals for disease must continue, far more harm would be done through the widespread clinical use of modalities that had not been subjected to controlled study.

Moreover, though the consent standard is imposed as an expression of respect for personal autonomy, and especially regarding bodily integrity, even that standard may be superseded when the need is compelling and there is a favorable balance of burdens and benefits. The need for public health programs such as vaccinations is one example of this phenomenon, as is scientific progress in research on more effective preventive medication.

A related justification for limits to the consent standard appeals to intergenerational justice: Those who benefit from today's medical science have gained from the sacrifices of yesterday's research subjects, and in enjoying the fruits of those past sacrifices acquire some obligations to the future.

Instead of **prohibiting research**, conditions have been placed on research with those who cannot give their own consent. If research with **younger** children and others who lack decision making capacity can be ethically acceptable, then presumably research with the decisionally impaired, who may have **fluctuating** decision making capacity, can also be done in a way that is ethically acceptable. Foremost among the conditions that may be imposed on research with those who are decisionally impaired or incapacitated is the gradually higher level of scrutiny that is accorded research proposals as the risk-benefit ratio becomes less favorable. Conditions may be imposed concerning not only acceptable levels of risk, but also through recruitment and selection of subjects, study design, consent processes, and independent monitoring. Later in this report we will examine some of these conditions.

Should those who are at risk of loss of decisional capacity, or those who already decisionally incapacitated, be excluded from research?

Considering the inherent limitations of measures intended to enable the incapacitated research subject to continue to have a voice in his or her treatment, it may be argued that those who are at greatest risk of decisional incapacity should simply be excluded from research. Were the assessment of risk for loss of decisional capacity required prior to enrollment in a study, the remaining subjects would be those who are less likely to require the application of additional protections, though these devices might still be a condition of study participation.

There are several objections to a rule-out procedure based on the prospect of a potential subject's losing decision making capacity. First, although the prospect of decisional incapacity is often clear, especially in progressive diseases or when a patient is going to be heavily medicated, in many cases the loss of capacity is not so predictable. Second, however one weighs the importance of advancing medical knowledge, prohibiting research on those most likely to lose capacity would create a significant obstacle to the study of some diseases in their most debilitating stages. Third, some research may be concerned with determining at what dosage a drug impairs cognitive function, an issue that could be of great importance to preventing future patients from losing their decision making ability. Fourth, a blanket exclusion of all patients whose conditions might tend toward a decisional incapacity later on would stigmatize a large number of persons with regard to their current cognitive powers.

Nonetheless, the idea that ethical problems raised by incapacity should be avoided if possible has intuitive force. One approach could be to require that a research project begin by enrolling those least likely to lose their decision making ability during the study period, and that the selection of at-risk subjects be justified by the particular goals of the study.⁹¹ A different approach would look again to the risk-benefit ratio, excluding prospective subjects from certain studies depending on their likely ability to make future decisions, as well as the anticipated level of risk.

One way to avoid the practical and philosophical problems with justifying research with those who are no longer able to consent would be to exclude such individuals from being part of research. A wholesale exclusion from research of those who lack decision making ability would

⁹¹Paul Appelbaum

square with the letter of the Nuremberg Code, but several subsequent ethics guidelines (including those of the Helsinki declarations of the World Medical Association and the Council for International Organizations of Medical Science) have endorsed research with those unable to consent under certain conditions. Recent scholarship indicates that even the Nuremberg Code itself was not intended to refer to clinical research with those who are ill, but to research with normal subjects.⁹² Further, there are not only positive moral goods to be achieved by research and evils to be avoided, there are various protections that may be brought to bear to help ensure the ethical propriety of the research. In general, it is thought that ethical research with human subjects who cannot give informed consent can be and has been conducted, especially if some form of advance directive or surrogate decision making arrangement is in place, and if care is taken in the way subjects are recruited and monitored.

Furthermore, though it is controversial, the recently authorized exception to informed consent requirements for certain emergency research is a greater departure from the Code's voluntary consent requirement than any contemplated herein concerning research with those who are decisionally incapacitated. A primary consideration in the creation of the narrow exception to the federal rules was the need for improvements in the care of emergent, life-threatening conditions.⁹³ A similar argument can be mounted on behalf of the improved treatment of those who have lost decision making ability under non-emergent circumstances.

⁹²Jonathan D. Moreno, "Reassessing the Influence of the Nuremberg Code in American Medical Ethics," Journal of Contemporary Health Law and Policy, 12(347-360):1997.

⁹³U.S. Food and Drug Administration, *Protection of Human Subjects; Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research; Final Rules*, 61 Fed. Reg. 51497-51531 (October 2, 1996).

The Commission was impressed that the former research subjects and their family members who testified were virtually unanimous in the belief that research involving those who are decisionally impaired should continue. In spite of some quite serious grievances, these committed individuals wanted medical science to bring its resources to bear on the afflictions themselves, but under conditions that exhibit greater sensitivity and respect for those who bear the burdens of illness while also involving them in studies that may lead to more promising therapies for others.

In the final analysis, however, neither previous statements of research ethics by authoritative bodies, nor prevailing conditions in the research environment, argue for broad exclusionary policies. Instead, this report will concentrate on the question of what additional protections should be provided for persons with decisional impairments who participate in research.

Individualizing Informed Consent

It is a commonplace in discussions about modern medical ethics that the preferred conception of informed consent as a cooperative process between subject and investigator has in practice given way to informed consent as the ritualized signing of a form. Lost opportunities to educate patients and their families about the implications of the medical alternatives before them and to gain their active involvement in the endeavor are rightly bemoaned. Not only physician-patient encounters concerning standard therapies, but even the more highly regulated research context is liable to the problem of a meaningless, bureaucratic “consent.”

Further aggravating the tendency described is the advent of multi-site clinical trials. Research projects involving a number of institutions come along with their own consent form, and

it is not always clear to what extent a participating site is permitted modify the consent form in order to be responsive to local circumstances. As a result, the informed consent ritual can become even more sterile and irrelevant.

In particular, several of those testifying before the Commission noted that, in many research projects, descriptions of risk and benefit are quite abstract, amounting to a laundry list of possibilities. Consent discussions and forms often fail to provide the potential subject and his or her informal caregivers with practical information about what they might experience in the course of a clinical trial. In some instances the problem may simply be one of using more specific language, but in other instances information may need to be individualized to the particular potential subject.

The Commission believes that the provision of usable information to individuals and their families and friends about what they might expect in the course of a study is of the essence in ethical research. Elaborate legislation or regulation should not be required to institute improvements in this area, and considerations such as efficiency in subject recruitment must not supersede it. For all potential subjects, and especially for those with decisional impairments and their loved ones, individualized information is central to research that truly engages participants as full partners in research.

Chapter Five: RISKS AND BENEFITS IN RESEARCH INVOLVING
DECISIONALLY IMPAIRED SUBJECTS

Balancing Risks and Expected Benefits in Research Involving Decisionally Impaired Subjects

If research involving persons with decisional impairments is to be permitted, a primary issue is the balance of risks and benefits that may be acceptable. 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."⁹⁴ 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 decisionally incapable subjects.

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.⁹⁵ 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

⁹⁴ Sec. ____ .111(a).

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

examinations or tests."⁹⁶

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 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. **If a study presents no more than minimal risk it may also be approved under an expedited review procedure**

If a study presenting more than minimal risk offers no prospect of direct benefit to child subjects, 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 that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations"; 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

⁹⁶ Sec. ____ .102(I).

accordance with sound ethical principles.⁹⁷

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

Defining Risks in Research Involving Decisionally Impaired Subjects

Impaired subjects 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."⁹⁸ 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 incapable adults suggests that review committees should consider "physical, social, psychological,

⁹⁷ 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, "Myotblast Transfer in Duchenne Muscular Dystrophy," August 13, 1991). The latter proposal has never been re-submitted. (Personal communication, Michael Carome, Office for Protections from Research Risks, November 3, 1997.)

⁹⁸ Keyserlingk, et al., *supra*, at 326.

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."⁹⁹ 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."¹⁰⁰

Evaluating risks to impaired subjects 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."¹⁰¹ 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.¹⁰²

Because of this special vulnerability to harm and discomfort, risk evaluation should incorporate reliable knowledge on the range of anticipated reactions subjects may have to study procedures. Though conceding that precise risk and benefit assessments rarely are attainable, the Belmont Report states, "the idea of systematic, nonarbitrary analysis of risks and benefits should

⁹⁹ Id. at 326-27.

¹⁰⁰ Berg, *supra*, at 24.

¹⁰¹ Keyserlingk, et al., *supra*, at 324.

¹⁰² Report on Institutionalized Persons, *supra*, at 8-9.

be emulated as far as possible."¹⁰³ 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."¹⁰⁴

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."¹⁰⁵ 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 acceptable in research as well.¹⁰⁶

¹⁰³ Belmont Report, *supra*, at 7.

¹⁰⁴ Report on Children, *supra*, at 8-9.

¹⁰⁵ Keyserlingk, et al., *supra*, at 329.

¹⁰⁶ 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

In contrast to the minimal risk concept's reference to the life and medical experiences of ordinary persons, the DHHS regulations' 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.¹⁰⁷ 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 majority of National Commission members 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 are more accustomed to the procedure. One 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

themselves." Report on Children, *supra*, at 137.

¹⁰⁷ 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.

health problems.¹⁰⁸

Commentators have criticized both the Common Rule's "minimal risk" definition, and the DHHS regulations' term "minor increase over minimal risk." Loretta Kopelman provides 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 child subject.¹⁰⁹

¹⁰⁸ Report on Children, *supra*, at 146 (dissenting statement of Commissioner Turtle).

¹⁰⁹ 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

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.¹¹⁰ 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.¹¹¹ 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."¹¹²

Difficulties with the minimal risk standard may partly have to do 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.

General, *supra*, at 4.

¹¹⁰ Janofsky & Starfield, *Assessment of Risk in Research on Children*, 98 *J. Pediatrics* 842 (1981).

¹¹¹ See Tauer, *The NIH Trials of Growth Hormone for Short Stature*, *IRB*, May-June 1994, at 1.

¹¹² Keyserlingk, et al., *supra*, at 326.

If this was the intention of the drafters of the regulations, it is not at all clear in the current Common Rule.

In July 1977 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...”¹¹³ 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.”¹⁴

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. A study classified as minimal risk at one institution could be classified as higher risk at another. Also needed is more discussion and clarification of acceptable risk in research involving incapable adults whose health problems expose them to risks in the 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.

¹¹³Tri-Council Working Group, “Code of Ethical Conduct for Research Involving Humans,” July 1977, p. 13.

¹¹⁴Id. at 14.

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 maneuvers, 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.¹¹⁵

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."¹¹⁶ 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."¹¹⁷ The draft legislation also prohibits

¹¹⁵ 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.

¹¹⁶ DeRenzo, *supra*, at 540.

¹¹⁷ Office of Maryland Attorney General, *supra*, at 7.

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."¹¹⁸

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.¹¹⁹ 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.¹²⁰ 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 for the Study of Ethical Problems in Biomedical and Behavioral Research 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

¹¹⁸ Id.

¹¹⁹ Keyserlingk, et al., *supra*, at 330.

¹²⁰ Id. at 330.

biopsies of the gastrointestinal tract.¹²¹ Taking these examples, a spinal tap might be more than minimal risk for patient-subject who is decisionally impaired, but not for a normal, healthy subject, while drawing venous blood might be minimal risk for all subjects.

One of this report's recommendations will concern clarifying definitions of minimal risk and greater than minimal risk. But whatever short-term refinements can be made in the lexicon of the current regulatory framework, in the long run the ambiguity about the meaning of minimal risk must be resolved. Besides the specific recommendations that are made in this report, the concept of research-related risk is one to which the NBAC will need to return in its subsequent work.

Defining Benefits in Research Involving Decisionally Impaired Subjects

Research involving impaired adults may 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.¹²² 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

¹²¹Harry 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.

¹²² Keyserlingk, et al., supra, at 327.

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.¹²³

According to the Commission, "[t]o be considered 'direct,' the possibility of benefit to the subject must be fairly immediate [and t]he expectation of success should be well-founded scientifically."¹²⁴

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.¹²⁵

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

¹²³ Report on Institutionalized Persons, *supra*, at 31.

¹²⁴ *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.

¹²⁵ Keyserlingk, et al., *supra*, at 327. This group notes that currently direct benefits to subjects in dementia research are limited to symptom control. There may be disagreement on whether research with the potential to extend life for someone in the later stages of a progressive dementia ought to be seen as offering the prospect of direct benefit to subjects.

benefits."¹²⁶ 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."¹²⁷ 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 subjects and their representatives.¹²⁸

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,¹²⁹ 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.¹³⁰

The court's response supports at minimum a need to scrutinize investigators'

¹²⁶ Report on Institutionalized Persons, *supra*, at 31.

¹²⁷ Keyserlingk, et al., *supra*, at 327.

¹²⁸ 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.

¹²⁹ 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.

¹³⁰ *Id.*

characterizations of research offering potential direct benefit to subjects.¹³¹ 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 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."¹³²

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

Proposed policies on research involving impaired or incapable adults generally require a balancing of risks and potential benefits to determine when such research is acceptable. Most proposals take the position that incapable adults 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

¹³¹ Capron, *supra*.

¹³² Melnick, et al., *supra*, at 535.

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.

Research presenting more than low risk to subjects is generally classified into one of two categories. The first category is research offering subjects a reasonable prospect of direct benefit. Though the moral justification for such 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 many normal volunteers, as well as some who are ill, agree 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 irresistible. 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 suffice to persuade a decisionally impaired person to enroll. The person who is decisionally impaired can too easily be moved into a submissive position (as can many of the rest of us), especially if the secondary rewards are substantial. 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.¹³³ This position is adopted in current DHHS regulations on research involving children.¹³⁴ It is also endorsed in most of the

¹³³ 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).

¹³⁴ See pp. 52-54, above.

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)."¹³⁵

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."¹³⁶ The NIH Clinical Center permits greater than minimal risk research offering a prospect of direct subject benefit with

¹³⁵ American College of Physicians, *supra*, at 845. A limited exception is permitted for incapable individuals who consented to higher risk through an advance directive.

¹³⁶ 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. 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.

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."¹³⁷

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 directive¹³⁸ or after review and approval at the national level, through a process resembling that set forth in the current regulations governing research involving children.¹³⁹ 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.

¹³⁷ NIH Clinical Center, *supra*.

¹³⁸ 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.

¹³⁹ 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).

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."¹⁴⁰ Supporters of this position contend that when these documents were created, "it was presumably well understood that a price of that prohibition would be that some important research could not proceed, some research answers would be delayed, and some promising therapies and preventive measures would for the time being remain untested and unavailable."¹⁴¹ Some writers explicitly label this stance the most ethically defensible position.¹⁴²

A position paper representing federally funded Alzheimer Disease Centers 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."¹⁴³ This group also believes that a national review process is not necessarily the

¹⁴⁰ Keyserlingk, et al., *supra*, at 334.

¹⁴¹ *Id.*

¹⁴² *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").

¹⁴³ 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.

best way to decide whether to permit research presenting no potential direct 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."¹⁴⁴

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. In particular, it should be noted that the distinction between a minor increase over minimal risk and a greater than minor increase over minimal risk cannot easily be applied to this population, considering the psychological implications of interventions for those who may not understand their purpose and context. Neither is it clear that a national panel to

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).

¹⁴⁴ 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.

review particular kinds of research or individual proposals is necessary to provide suitable protections, nor that such a body will be in a position to evaluate needs arising from local institutional conditions. Rather, any research that involves more than minimal risk and no direct benefit to impaired subjects should be required to be accompanied by certain additional arrangements, including an independent monitoring procedure.

Maintaining Acceptable Risk-Expected Benefit Ratios in the Research Process

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."¹⁴⁵ Commentators also refer to the importance of monitoring.¹⁴⁶ The major question is how to implement this task. A central issue is whether, and

¹⁴⁵ Sec. ____ .111(a)(6).

¹⁴⁶ 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").

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 University of California at Los Angeles (UCLA), the U.S. Office of 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."¹⁴⁷ The institution was directed to submit to federal officials a proposal on creating and operating the monitoring boards.

Detailed provisions on monitoring are included in Loma Linda University IRB guidelines on psychopharmacology research in which placebos are administered. Investigators must specify how often subjects will be assessed for deterioration or improvement during studies. 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.¹⁴⁸

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,

¹⁴⁷ Office of Protection from Research Risks, *supra*, at 27.

¹⁴⁸ Orr, *supra*, at 1263.

if such action appears in the subject's best interest."¹⁴⁹ The Maryland draft legislation directs subject representatives to "take reasonable steps to learn whether the experience of the individual in the research is consistent with the expectations of the legally authorized representative at the time that consent was granted."¹⁵⁰

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.¹⁵¹ 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.¹⁵² A place for independent monitoring is included among the Commission's recommendations.

Chapter Six: ADVANCE DIRECTIVES AND SURROGATE DECISIONMAKING

The Incapable Subject's Research Preferences

¹⁴⁹ Belmont Report, *supra*, at 6.

¹⁵⁰ Office of Maryland Attorney General, *supra*, at 16.

¹⁵¹ 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.

¹⁵² See Shamo & 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).

At some times or under some circumstances decisionally impaired persons are incapable of given valid consent to research participation. According to the Belmont Report, 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."¹⁵³ 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."¹⁵⁴

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.

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

¹⁵³ Belmont Report, *supra*, at 6.

¹⁵⁴ Report on Institutionalized Persons, *supra*, at 9.

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 incapable individuals can provide assent as defined by the National Commission. Some persons may satisfy certain elements of the standard, but not all of them.¹⁵⁵ Should the physical or verbal indications of persons incapable of assent be considered in research 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."¹⁵⁶ According to the National Commission, "mere absence of objection" ought not be interpreted as assent.¹⁵⁷ The 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

¹⁵⁵ 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.

¹⁵⁶ Kapp, *supra*, at 34.

¹⁵⁷ Report on Mentally Disabled 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.

unsettled in the existing literature.

There is general agreement that the sole potential justification for imposing research interventions on actively resisting subjects would be to advance the goal of 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 not otherwise obtainable in the clinical setting.¹⁵⁸ Yet not all commentators agree that potential direct benefit should be sufficient to override the incapable subject's behavioral resistance 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."¹⁵⁹

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

¹⁵⁸ E.g., Berg, *supra*; High & Doole, *supra*; High, et al., *supra*; Melnick, et al., *supra*.

¹⁵⁹ Keyserlingk, et al., *supra*, at 342, quoting Melnick, et al., *supra*.

best a position in need of further debate."¹⁶⁰

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."¹⁶¹ 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.¹⁶²

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 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 she subsequently loses decisional capacity.

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 also seen as protective in that it can prevent a surrogate from authorizing an incapable subject's

¹⁶⁰ Id. at 342.

¹⁶¹ Office of the Maryland Attorney General, Second Report of the Attorney General's Research Working Group, (May, 1997).

¹⁶² T.D., 650 N.Y.S. 2d at 193.

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 1980s. 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.¹⁶³ 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.¹⁶⁴ Such proxies 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 proxy'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 for permitting higher risk research than is otherwise permitted for subjects lacking court-appointed family

¹⁶³ R. Levine, *Ethics and Regulation of Clinical Research* 270-74 (rev. ed. 1986).

¹⁶⁴ 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*.

guardians.¹⁶⁵

In 1989, the American College of Physicians (ACP) gave qualified endorsement to instruction and proxy mechanisms permitting competent persons to register advance consent to research. According to the ACP, investigators seeking advance consent would be required to disclose to the competent person the usual information on a study's purpose, methods, risks, and potential benefits. Moreover, the ACP recognized a need for 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.¹⁶⁶

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."¹⁶⁷

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

¹⁶⁵ Research presenting greater than minimal risk is not permitted for subjects lacking a DPA or court-appointed family guardian.

¹⁶⁶ American College of Physicians, *supra*, at 844.

¹⁶⁷ 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.

permitted for other incapable subjects. The position paper states that incapable subjects with informal proxies should not be involved in greater than minimal risk research offering no prospect of direct benefit. In contrast, subjects with advance directives may be involved in such studies, as long as the above limitations are observed.

Other groups and commentators have expressed general support for advance research decisionmaking without addressing the concept in detail.¹⁶⁸ 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 person 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."¹⁶⁹

¹⁶⁸ 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).

¹⁶⁹ 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.

Federal policy establishes stringent disclosure requirements for investigators recruiting competent persons for research. An individual considering whether to authorize future research 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."¹⁷⁰

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.¹⁷¹ 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 individual's agreed to in a directive.¹⁷² 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

¹⁷⁰ Keyserlingk, et al., *supra* at 347.

¹⁷¹ 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).

¹⁷² Berg, *supra*, at 22 (surrogate has responsibility to withdraw subject only if research or risk-benefit ratio changes substantially from what subject consented to).

obligation to respect the person's prior wishes is limited by the obligation to protect the person. The 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.¹⁷³

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."¹⁷⁴ 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.

A Canadian group addressing dementia research proposes that research directives should apply to studies offering no direct benefit to subjects only if the risk is minimal or a minor increase

¹⁷³ 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").

¹⁷⁴ Moorhouse & Weisstub, *supra*, at 134.

over minimal.¹⁷⁵ 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."¹⁷⁶

Berg supports full implementation of advance research instructions 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."¹⁷⁷ 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.¹⁷⁸ The new regulations allow research to proceed in the absence of consent by a subject or subject representative if a number of conditions are met. One such condition is that investigators cannot reasonably obtain prospective consent from competent

¹⁷⁵ Keyserlingk, et al., *supra*, at 351.

¹⁷⁶ *Id.*

¹⁷⁷ Berg, *supra*, at 22.

¹⁷⁸ *Supra* at 42.

individuals likely to be candidates for later study enrollment.¹⁷⁹

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.¹⁸⁰ 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."¹⁸¹ 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.¹⁸² The New York court decision invalidating regulations governing research at the state's mental health facilities also 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

¹⁷⁹ 21 C.F.R. sec. 50.24 (a)(2)(iii).

¹⁸⁰ 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.

¹⁸¹ *Id.*

¹⁸² *Id.*

incapable individuals" in studies posing greater than minimal risk and no prospect of therapeutic benefit.¹⁸³ 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.

The 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...."¹⁸⁴ 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 well.¹⁸⁵

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

¹⁸³ T.D., 650 N.Y.S. 2d at 177.

¹⁸⁴ Id. at 190.

¹⁸⁵ 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.

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.¹⁸⁶

The 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 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."¹⁸⁷ Thus, otherwise prohibited research risk is permitted based on the prior competent choice of a now incapable subject.

The draft 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

¹⁸⁶ Office of the Maryland Attorney General, *supra*.

¹⁸⁷ *Id.* at 15.

(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.¹⁸⁸

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, especially if rigorous standards for information disclosure are observed. 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.

The Incapable Subject's Representative

The Common Rule's use of the phrase "legally authorized representative" leaves many unanswered questions. State laws contain general 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

¹⁸⁸ Id. at 16.

research in various ways; a number of laws require guardians to obtain specific court authorization to make decisions on a ward's research participation.¹⁸⁹

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.¹⁹⁰ Thus, investigators and IRBs in jurisdictions with specific law governing the identity and authority of research decisionmakers for incapable subjects 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 may act as an incapable subject's surrogate decisionmaker 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 status, are the customary decisionmakers when the research participation of incapable adults is sought.

Should federal policy require formal legal guardianship? 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

¹⁸⁹ See Appendix for brief descriptions of existing state legislation.

¹⁹⁰ Common Rule, Sec. ____ .101(f).

of assent, and the research presents more than minimal risk to subjects.¹⁹¹

Later commentary questions whether formal legal proceedings are necessary to provide adequate protection for incapable subjects, particularly those not residing in an institutional setting. As one writer notes, IRBs requiring legal guardianship "to be on the safe side" could end up contributing to a deprivation of general decisionmaking rights of subjects.¹⁹² 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 as a research decisionmaker.

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 is to allow decisionally capable persons to authorize in advance a specific individual to make decisions on 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

¹⁹¹ National Commission, Report on Institutionalized Persons, *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).

¹⁹² 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").

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 her values and protect her welfare. Intramural research at the National Institutes of Health (NIH) Clinical Center is governed by a policy that encourages this approach.¹⁹³ The American College of Physicians and numerous others express support for use of these devices.¹⁹⁴ As a practical matter, however, it is unclear whether many individuals will be interested in or willing to complete such a document.¹⁹⁵ 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.¹⁹⁶

A third alternative is to regard state legislation authorizing family members to make

¹⁹³ 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 subjects may designate the Center's patient representative or a chaplain, or social worker not assigned to the research unit.

¹⁹⁴ American College of Physicians, *supra*. See also Kapp, *supra*; Melnick, et al., *supra*.

¹⁹⁵ See High & Doole, *supra*.

¹⁹⁶ NIH Clinical Center, *supra*.

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 decisionally incapacitated persons 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.¹⁹⁷ Others believe that these laws should not be interpreted so expansively and that amendments or new legislation would be required to provide explicit statutory authority for delegation of research decisionmaking to relatives.¹⁹⁸

The final possible option is to assign research 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.¹⁹⁹ This approach also is easy to administer; moreover, it apparently has been and continues to be a common practice in the actual research setting.²⁰⁰

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

¹⁹⁷ Bonnie, *supra*, at 110.

¹⁹⁸ Kapp, *supra*.

¹⁹⁹ 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").

²⁰⁰ Kapp, *supra*; High & Doole, *supra*.

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 (see below). New legislation authorizing relatives to make research decisions for incapable persons would require action by the states; such legislation would emerge slowly and in some states, not at all.

All of these alternatives also raise questions about the accuracy with which incapable subjects' values and preferences as competent persons will be expressed by formal or informal representatives.²⁰¹ 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."²⁰² 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.²⁰³

²⁰¹ 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").

²⁰² Keyserlingk, et al., *supra*, at 346.

²⁰³ 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

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 preferences and current interests.²⁰⁴ 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.²⁰⁵

An alternative or additional approach is to limit the authority of any third party to consent to research participation by an incapable subject. Three forms of substantive limitations are commonly endorsed. One is to allow guardians, proxies, and informal surrogates to give valid

subject's participation even though they thought the subject would consent if competent or the family members would enter such a study themselves.

²⁰⁴ 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).

²⁰⁵ 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).

consent to studies if the incapable subject assents or fails to object to initial or ongoing research participation. The second is to require that third parties make research decisions consistent with the incapable subject's prior instructions issued while competent. The third is to permit subject representatives to authorize the involvement of incapable subjects only in studies that meet certain risk-potential benefit standards. Many of the recommendations on research involving persons with mental disabilities apply each of these limits, but combine them in a variety of ways.

Chapter Seven: SPECIAL PROTECTIONS IN RESEARCH

A Framework of Special Protections

A sound case can be made for requiring special protections in research for persons with decisional impairments or whose capacity is at least questionable. A framework of special protections should include, at a minimum, the following elements: a reasonable generic limitation on recruitment of persons in this population into research; requirements concerning the participation of persons in this population (decisionally impaired or questionable capacity) in more than minimal risk, non-potentially beneficial research; requirements concerning the participation of persons in this population in more than minimal risk, potentially beneficial research; and other requirements suited to the study at hand that may be imposed by appropriate authorities, such as an IRB. This framework is represented in the recommendations in Chapter 8.

When Other Subjects are Available

Some “vulnerable” or “special” populations are currently accorded particular protections in the regulations to ensure that they are not unfairly burdened with involvement in research simply because they are easily available **or because their participation otherwise creates special ethical issues.** Thus, for example, prison research is limited to conditions that especially affect that population. **Considering that persons who are decisionally impaired or whose capacity is questionable may be affected by some of the complicating factors discussed in this report, sometimes including their ready availability in institutions,** their position bears earmarks of special vulnerability.

One important justification for involving those with decisional impairments in research is

the need for progress in the treatment of certain diseases. In order to thwart the temptation to engage them in research simply because they are more available than others, it may be appropriate **to prohibit research involving persons with decisional impairments when the knowledge can be obtained from volunteers capable of giving a valid informed consent**²⁰⁶ IRBs should not approve research involving persons with decisional impairments when alternatives are available.

There are several circumstances under which other subjects may not be available. For example, if the research bears directly on conditions that underlie the subject's decisional impairment, then there may be no other opportunity to learn how to improve diagnosis and treatment for the conditions. However, if the research involves new ways to protect against diseases that are also common among those who are capable of giving informed consent, then other individuals should be recruited as participants in the research.

Notification and dissent from research participation

Our society's social philosophy includes a strong presumption in favor of individual self-determination. Judgments about an individual's capacity will often have a measure of doubt. 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. Obviously under many circumstances it will not be possible for the individual to comprehend the information, but reasonable efforts should be made.

²⁰⁶ This position has been adopted in Canada. Tri-Council Working Group, "Code of Ethical Conduct for Research Involving Humans," July 1997, p.22.

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

This requirement would also apply 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 no individual be forced to serve as a research subject, or even apparently forced to do so, even when the research may be of direct benefit to the individual and when his or her decisional capacity is in doubt.

Greater than minimal risk, not potentially beneficial research

Some important research may not be done without the involvement of persons with decisional impairments. An example is the study of dopamine receptor function and schizophrenia, for which there are currently no suitable alternative models. Some individuals with impaired decisionmaking may be able to give informed consent at certain times during their illness, or may be able to execute an advance directive authorizing their participation in certain kinds of studies. The presence of a neurologic or psychiatric disorder should not a priori disqualify an individual from being permitted to volunteer if the research is important and no other subject population is suitable.

However, because there are non-trivial risks associated with study participation, and because there is a reasonable chance that the subject will lack decisionmaking capacity at some time during the research, special protections are in order. The subject should have

a legally authorized representative who can make decisions on the subject's behalf about continuing or stopping participation in the research, based on his or her understanding of the subject's wishes. In addition, 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 assigned to track the reaction of the subject to the study and be empowered to stop the subject's participation if it is no longer in the subject's best interests. IRBs may wish to impose other protections as well, some of which are discussed later in this chapter.

Greater than minimal risk, potentially beneficial research

Although this category of research appears to raise fewer ethical problems than non-potentially beneficial research, no one is obligated to participate in a study, even if it may be of direct benefit. Therefore, either the potential subject's informed consent should be obtained; or an advance directive authorizing research participation should be obtained; or the subject's legally authorized representative has given permission for research participation *and* the subject has been given the opportunity to dissent from participation.

The latter condition is intended to discourage investigators from waiting to recruit subjects until after they have lost decisional capacity, preferring to approach a representative. Even an apparent dissent by the subject must be honored, regardless of the subject's capacity at the time. Again, IRBs may wish to impose some of the additional protections discussed later in this chapter.

Substantive Research Advance Directives

Research advance directives are an important part of this basic framework of

special protections. Advance directives may be of two kinds: substantive or procedural As was described in the previous chapter, a substantive (or instruction) research advance directive specifies a research project or projects that an individual would be prepared to enter, should he or she become so impaired as to lose decisionmaking capacity. This kind of advance directive would be roughly equivalent to living wills for standard treatment.

The idea of a research advance directive appears to be consistent with our society's dominant philosophical beliefs about control over one's body and with other practices. Some argue that, just as individuals may donate their remains to medical schools and laboratories, so they should be permitted to commit themselves to a research project as living subjects while they still have the ability to do so. This argument seems to gain strength when the anticipated research participation holds some prospect of benefit to the incapacitated subject.

Many contend that it is exploitive to permit people who hope desperately for a return to lucidity and health to make a commitment to research involvement, often well in advance of the actual research intervention. They note that one's views about continued medical procedures may change as one's illness progresses, perhaps without the opportunity to review a research living will once it has been executed. Further, how can it be decided when the experimental involvement should cease, especially in studies that did not offer benefit to the subject in the first place?

In spite of these difficulties, the idea of an advance directive for research is nevertheless attractive because of its consistency with our other values, such as the protection and promotion of patient autonomy and the advancement of medical knowledge. Some conditions could be placed on such arrangements that would seem to make them more protective of the interests of

the incapable subject. For instance, research advance directives might only be valid when the research presents some prospect of patient benefit, and strict time limits could be imposed that require active renewal of the living will. Another option is to require the appointment of a legally authorized representative who could make a decision about stopping participation in the study, as a condition of validity of the advance directive for research.

There is another objection to research advance directives that is rather different from those that have already been mentioned and that also relates to the question of subject protection. The incapacitated patient may be aware of being subjected to various experimental procedures, but be unable to understand their significance or appreciate that they had been consented to in advance. A person with waxing and waning awareness, often highly medicated and perhaps physically restrained, could experience study procedures as quite disturbing, and even as a kind of torture. To minimize this possibility, careful protections would need to be constructed, including perhaps the advance appointment of an alternative decision maker who could order study participation to be stopped at the least sign of subject distress.

Federal regulations should recognize substantive research advance directives for research that has the potential to benefit the subject. In order for these regulations to have meaning states may need to introduce legislation amending their living will statutes, or in other cases to consider promulgating entirely new legislation. IRBs may of course impose additional constraints on such research, some of which were discussed in chapter five. Health care institutions and professional organizations will need to promote the use of research advance directives among the general public if they are to become an important part of the medical research enterprise.

In reality, however, few potential subjects will avail themselves of a substantive research

advance directive. Relatively few individuals be in a position to contemplate volunteering to be a subject in a certain research project well in advance of a period of incapacity, so it will also be the unusual case that permits advance recruitment to a particular study. Patients are more likely to identify decision makers in advance of an illness, should they lose decision making ability, and these authorized representatives could have a role in research participation decisions as well.

Procedural Advance Directives and Legally Authorized Representatives

A second of advance directive indicates the decisionmaking procedure to be followed in case the principal becomes incapacitated, rather than giving substantive instructions for treatment. In anticipation of a period of incapacity, many individuals have appointed others to make treatment decisions on their behalf. The authority to appoint such representatives, who are often called health care agents, has been recognized in the laws of many states, technically known as the “durable power-of-attorney for health care” (DPAHC). In general, the health care agent is obligated to make medical decisions that are in accord with the patient’s previously expressed wishes, or, if those wishes are unknown to the agent, consistent with the patient’s expressed values. Failing that, the health care agent should make decisions that advance the patient’s medical best interests.

We have seen that many have advocated extending this legal authority to enable the representative to make research participation decisions. There are several situations in which such an arrangement has practical appeal. Often individuals “fail” standard therapy but are incapable of deciding about trying to take advantage of a medication or device still under study. Or a person may not have anticipated becoming ill and, suddenly incapacitated, may have had no time to consider whether some experimental treatment might be preferable to a standard therapy.

Or an individual may become decisionally incapacitated in the course of medical care without having considered the next step in his or her treatment. Finally, some may find donating their body to a research project to be a highly desirable and satisfying way to exit, but, rather than leave this to chance, wish a representative to identify a worthwhile scientific effort taking place at the time of death.

In one important sense, the power to appoint a “research agent” is an expression of the patient’s self-determination, for which all sorts of provisions are currently made in the delivery of health care. If individuals are empowered to identify those whom they wish to speak for them in making decisions about recognized medical interventions, then why not extend this authority to emerging medical alternatives?

One important difference between reliance on health care agents in the standard treatment setting and in the research setting is that recognizing the authority to decide about someone else’s care seems to be more easily justifiable when there is good reason to believe that the intervention will be in that person’s interest. Experimental procedures or maneuvers are not undertaken with the primary goal of subject benefit, but rather are intended to help advance knowledge about the problem motivating the study. Allowing other persons to decide about making someone an experimental subject, even when the individual in question has authorized them to do so, is a qualitative departure from ordinary DPA arrangements. Such decisions may entail considerable risks with little likelihood of substantial benefit.

Though great deference is given to individual self-determination in our political system, there does seem to be a legitimate societal interest when a private arrangement may present significant harm to the individual initiating it, in the absence of a reasonable prospect of offsetting

advantages. Weighing against this societal interest is the possibility that greater medical knowledge may accrue to society in permitting these arrangements to go forward in spite of their risks. In some cases, the rejection of those who would make themselves available for research through an agent could significantly hamper studies of the condition that led to the person's current incapacity.

A balance might be struck by limiting the conditions under which the health care agent's authority would be valid. For instance, studies that present no prospect of direct benefit to the subject, but entail significant risk, could be ineligible for enrollment via a research DPA. Studies that entail minimal risk could be regarded as consistent with a patient's best medical interests and therefore permissible, even though they do not advance those interests.

Alternatively, a representative's decision could be subject to review to establish that it is consistent with what is known about the patient's wishes. But (short of intervention by a court of law), it is not at all clear how such a challenge could be warranted, especially if the patient leaves no written statement about his or her attitudes toward research. How should other responsible parties, like researchers and IRBs, assess whether the patient's representative, in enrolling the patient in research, is truly acting in accordance with the patient's wishes and values? Unlike treatment DPAs, one test that would have very limited applicability is the best interests of the patient. Because studies are not designed to satisfy individual subjects' medical interests (though that may be a happy by-product of a study), to say that a study is in a person's best interests, especially when that person no longer has capacity, is often going to be far-fetched. For many, this limitation on objective review of a representative's decisions is important enough to reject procedural arrangements.

In partial amelioration of this problem, at least from the standpoint of potential harms to subjects, a warning to representatives might be appropriate in some cases. For example, legally authorized representatives could be informed of the possibility that the research would add to the patient's risk of harm or discomfort. Were such information made part of the process, the difference between the expected course with and without research should be clearer to the layperson representing the decisionally incapacitated person.

Procedural advance directives like research DPAs offer at least two advantages over instruction or substantive research advance directives. The first is that they are far more flexible than statements about preferred or permissible interventions. The second advantage, and one especially pertinent to patients who suffer from some degree of decisional impairment, is that it may be much easier to designate a representative whom one trusts than to assess the relative risks and benefits of a research study. Thus, it may be argued, if one wishes to grant patients the right to research participation when they no longer have decision making capacity, then the approach that is most reliable concerning their expressed choice is probably the procedural one. However, it must be granted that there is little evidence for this argument, however intuitively plausible it may

Another objection to research advance directives is rather different from those already mentioned but it also relates to the question of subject protection. As has been mentioned, the disoriented patient-subject may feel imprisoned and forced to undergo procedures without understanding, even though they have been authorized by the legally authorized representative. This could be a terrifying, nightmarish experience for a decisionally impaired person. Although a procedural advance directive may reduce this risk, it remains a serious concern and may require

more than one protective mechanism for the impaired subject.

Legally Authorized Representatives and Research Participation Decisions

Legally authorized representatives appointed in advance by the patient (research health care agents) should be able to give permission for a patient who has lost capacity to be enrolled in research that is of potential direct benefit. In non-beneficial research a legally authorized representative should not be empowered to give permission for initiation of research participation, but should be available to decide whether it may continue or must cease. State durable power-of-attorney statutes may need to be amended to take into account this research-related function. In all cases the legally authorized representative's decisions must be based upon the patient-subject's wishes, so far as they are known, and then they should be based upon the patient-subject's best interests. In addition, IRBs have the prerogative to require various further protections and revuew mechanisms along the lines described in this report.

A Model Research Advance Directive (RAD)

Taking these and other considerations into account, it is possible to describe a model research advance directive (RAD). **This model could serve as the basis for states to develop their own legislation or regulations, suitably adjusted for local conditions.**

An RAD is similar to a more familiar treatment advance directive for someone with a psychiatric disorder. Such a document allows the principal to make plans should she become psychotic in the future and temporarily lose her capacity to make healthcare decisions. Because this is something the individual has experienced before she understands what works for her and what doesn't work for her, and whom she trusts to help her get through the psychotic episode.

Of course, the concept of a RAD applies to research, not therapy. But the potential

subject may assess the proposed research procedures, and whom she would want to speak for her, in light of her previous therapeutic experience. Persons with fluctuating capacity are also able realistically to project themselves beyond the period of incapacity, thus RADs for this population are not liable to the criticism that the person who competently approved them has disappeared forever once incapacitated. With certain crucial features in place, a RAD may be a way to furnish adequate protection for research subjects with fluctuating cognitive impairments. A RAD should allow for subject consent, the appointment of surrogate decisionmakers (should the subject lose decision making capacity while participating in the study), and spell out precise safeguards.

Two *caveats* apply to the Commission's model for this form of planning for research participation. First, RADs should be designed for immediate and specific research studies; they are not intended to provide anticipatory planning for future unknown protocols. Second, the design of a particular RAD should be joined with the informed consent process that is required before a subject may participate in a research study.

In order to engage in a research protocol, the subject must have the capacity to engage in anticipatory planning. A prospective research subject must be able to recognize and to grasp that her consent to participate in a future 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 some of her decisions may involve agreeing to medical procedures or treatment.

The model RAD requires the potential subject to identify a surrogate decision maker with qualifications we discuss below. The potential subject must understand that she has appointed a surrogate to make decisions concerning her research participation should she become unable

(while in the study) to make these decisions herself. She must further understand that the surrogate may never overrule her wish not to participate in the research or in any part of it, but may overrule her instructions to continue participation, under certain conditions. The potential subject must be aware that she has given the researchers permission to provide her surrogate decision maker and her private mental health care provider with information about her treatment. She should appreciate that, should her preferences change, she may alter her instructions at any time she has the capacity to do so, and that whenever she wishes, whether she has decisional capacity or not, she may cancel her RAD and withdraw from the study.

Because research is designed to test an hypothesis and is characterized by uncertainty in outcome, there is always the possibility of unanticipated circumstances occurring in a research study. Therefore, subjects who have fluctuating capacity should be required to appoint a surrogate decision maker, excluding a member of the study team. The surrogate could be an informal caregiver (a relative or close friend) or the potential subject's private mental healthcare provider (who is familiar with her symptoms that usually precede a period of incapacity). The surrogate will be authorized to overrule the subject's prior competently made instructions concerning study participation in order to prevent harm to the subject.

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 her surrogate decision maker and her private mental health care provider. The subject's refusal to participate in the study must be honored at all times, whatever her capacity and whatever her prior decisions may have been. The research team must also make adequate provision for aftercare should the

subject decompensate, become unable to cooperate, and drop out of the study.

During the course of the study the subject's private mental health care provider, who has no relationship with the research and is concerned only with her well-being and interests, must follow her treatment. The surrogate and the private mental health care provider should also work together closely during they study to ensure the subject's welfare.

States would presumably need to pass legislation or create new regulations recognizing legal arrangements like the RAD. Most jurisdictions already recognize the durable power-of-attorney for health care. In theory, the paperwork for appointment of a health care agent could be combined with that for the appintment of a research agent. One question is whether federal regulations should recognize research advance directives and take them into account in rules concerning subjects who may lose their decision making capacity before they can enter or complete a study.

"Natural" Surrogates and Research Participation Decisions

Even though the research agent concept is more likely to be utilized by patients interested in making an advance commitment to research participation than "living will" style research directives, it, too, will still not generate many subjects. Usually people who lose decision making capacity have not created an advance directive of any sort, research or clinical. Sometimes members of their family or other caretakers are identified as suitable surrogates in granting permission to enter them into research. But these "natural" surrogate arrangements have, at best, an uncertain legal standing. Regulations could recognize state legislation that established in the law what is now a matter of common practice by granting natura" surrogates (such as family members or close friends) a specific role in the research recruitment process for decisionally

impaired persons.

An obvious objection to such arrangements is that, unlike a representative appointed by the patient in advance, the surrogate's standing as a substitute decision maker may arise only from the law. To many the moral basis for the surrogate's authority appears inadequate, especially in the research context, because he or she has not been selected by the potential subject. According to many bioethicists surrogates are supposed to act on the patient's behalf in accordance with their "substituted judgement." But there is no guarantee that even a close relative is aware of the patient's preferences or values with respect to standard medical treatments, let alone research participation, or even that the surrogate will act on those preferences or values if they are known. A surrogate may only be able to decide based on the patient's medical best interests. A "medical best interests" standard will not apply to studies that offer no prospect of direct benefit to the subject.

However questionable the legal basis of this process, a large number of research subjects have been recruited through identification of a "natural" surrogate and restrictions on these measures would constitute a severe blow to a great deal of research on diseases that involve cognitive disabilities. And many studies do hold out the prospect of direct benefit, including the use of new drugs and medical monitoring. One option would be to recognize in regulation the role of surrogates in research that involves only procedures that are potentially beneficial to the subject, or that entail no more than minimal risk.

Natural surrogates, including family members and close friends, should be considered to be legally authorized representatives for studies that are potentially of direct benefit to the patient-subject and for minimal risk research. The states will probably need to promulgate statutes that

grant such authority, including mechanisms for the identification of a suitable natural surrogate. IRBs may, again, impose further protections and review mechanisms if they wish.

Special Consent Requirements for Persons With Decisional Impairments in Research

To be found decisionally incapable and then enrolled in research according to alternative decision making arrangements is to have certain of one's rights curtailed, however justifiable the curtailment research 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.²⁰⁷ Such a notification process will often 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 a liberal, democratic society.

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 may be limited to those potential subjects who show any signs of consciousness. The notification would also enable the patient to assent to his or her research role, by no means a trivial recognition of individual dignity. A notification requirement should be added to the federal regulations

²⁰⁷ Another way to express this issue is whether the assent of incapable subjects should be required. Dresser, pp. 36-40.

concerning potential subjects found to lack decisional capacity.

Increased subject representation in the review and conduct of research is another commonly-endorsed strategy for improving research decisions affecting persons with mental disabilities. Representation is generally viewed as a means of enhancing the likelihood that decisions will be responsive to the interests of affected groups. 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. The current provision is advisory only; moreover, it refers to the involvement of expert professionals, not persons representing vulnerable subject groups.

After evaluating schizophrenia studies at UCLA, the OPRR directed the School of Medicine's IRB to "engage one or more subject representatives as IRB members who will assist the IRB in the review of issues related to the rights and welfare of subjects with severe psychiatric disorders."²⁰⁸ This requirement was imposed even though the IRB already had a psychiatrist and a psychologist as members.²⁰⁹

New federal policy creating an exception to informed consent requirements for certain research in the emergency setting directs IRBs approving such research to arrange for consultation "with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn."²¹⁰ The regulations also instruct IRBs to

²⁰⁸ Office of Protection from Research Risks, *supra*, at 21-22.

²⁰⁹ See also Shamoo & Sharev, *supra*, at S:29 (IRBs reviewing proposals to involve mentally disabled subjects should include at least two patient-representatives).

²¹⁰ 21 C.F.R. sec. 50.24 (a)(7).

ensure that plans for and results of such studies be disclosed to the relevant communities.²¹¹

Another development is the increased involvement of affected persons in the planning of clinical research on their conditions. The phenomenon first arose in the context of HIV research; it is now evident in other areas of clinical research as well.²¹² 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. Federal regulations should require IRBs to inquire whether studies drawing on populations of decisionally impaired or incapacitated persons have incorporated the views of representatives of these populations.

The consent auditor is one device that has frequently been suggested as an additional procedural protection in the recruitment of research subjects who may be decisionally impaired. The consent auditor, who is not a member of the study team but perhaps a member of the IRB or 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 will require a substantial investment by research institutions. The requirement may 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.

²¹¹ Id.

²¹² See Erikson, *Breast Cancer Activists Seek Voice in Research Decisions*, 269 *Science* 1508 (1995).

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 mechanisms conform with the spirit of informed consent as a process rather than a single event, and with the view of human research participants as collaborators 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. IRBs could attach a reconsent requirement to certain studies depending on their length and the condition of the individuals to be included, such as those with progressive neurological disorders.

Special Design Requirements for Persons With Decisional Impairments in Research

There is a general concern that 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 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 study participation 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 that involve the provocation of symptoms. Depending on the circumstances, IRBs should require a wraparound phase as part of the design of some studies.

Those 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. IRBs may 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 appears 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 be controlled by measures against standard therapy, in spite of the methodological shortcomings of such designs. A basis for excluding placebo arms in particular studies could be an individualized assessment that concludes that certain patients would be at high risk for relapse if their current therapeutic regimen was discontinued, that a "drug holiday" is not contemplated for this patient apart from enrollment in a study, and 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.

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 arrangements into account when evaluating research proposals. One regulatory option is to require investigators to explain how they propose to monitor subjects for symptom relapse in studies with a drug-free component that enroll decisionally impaired individuals with a history of psychiatric disorders.

The Costs of Special Protections

The kinds of special protections discussed in this report are not cost-free, but those costs must be viewed in the context of total financial resources invested in health care research, and in research involving human subjects in particular. Figures for the totality of such research in the United States, including funds from the private sector, are speculative. However, some sense of its scope may be gained from the fact that extramural research involving human subjects conducted by the National Institutes of Health in 1996 totaled \$5 billion dollars, which was given in 16,000 awards to 950 institutions. Intramural human subjects research at the NIH totaled an additional \$1 billion dollars.²¹³

Viewed in this light, it is hard to argue that some additional cost for special protections for human research subjects with decisional impairments would excessively burden the drug research and development system. For example, even if those protections were to result in a net additional cost of 10 million dollars to the NIH annually, this would amount to less than one quarter of one percent of the Institutes’ budget for human subjects research during 1996. Nor is it plausible that the small additional costs would present a

²¹³Gary Ellis, Director, Office for Protection from Research Risks, Personal communication to Emily Feinstein, National Bioethics Advisory Commission, 19 December 1997.

drag on the marketplace for important new pharmaceutical products, a market that includes millions of persons who suffer from neurologic or psychiatric diseases. Shall we say instead that it is not worth protecting 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 is not ethically unacceptable research; rather, the alternative is no research involving human subjects at all.

Chapter Eight: NBAC'S ROLE AND SUMMARY OF RECOMMENDATIONS

Moving Ahead in Research Involving Persons With Decisional Impairments

As has been shown in the first several chapters, this report stands in a long line of statements by governments and professional organizations that are relevant to the use of persons with decisional impairments in research. Each of these earlier efforts left a legacy of relevance 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 that 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 American 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 human subjects research under a common rubric whose key elements include informed consent and prior group review of research proposals.

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 that may be decisionally impaired due to a neurologic or psychiatric

disorder. Yet among the National Commission's reports pertaining to the protection of particular subject populations, this one has had the least influence over subsequent regulations.

Much has changed since the National Commission's report twenty years ago. There is a much greater sensitivity to the variety of conditions that can be associated with a decisional impairment, and a greater understanding of the ways that these conditions 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 individuals are involved in the research enterprise than ever before, and the research environment has become far more complex and involves a larger societal investment than ever, including a growing proportion from the private sector. The stigmatization and marginalization of those who suffer from conditions that put them at risk for decisional impairments, while by no means vanquished, shows signs of abating at least somewhat as an appreciation of the underlying biology of these conditions is gradually disseminated among the professional and lay public.

Under these conditions, it is hoped the legacy of this report in the line of its predecessors will be that of bringing persons with decisional impairments more fully and specifically within the ambit of additional protections that have been extended to other groups under the Common Rule. The new proposed protections must be accompanied by respect for all those engaged in research on these impairing conditions: clinical investigators, who are with rare exception skilled, compassionate, and dedicated to the alleviation of some of humanity's most terrible afflictions; informal caregivers, whose own

lives are often wholly absorbed in the tragedy that has befallen their loved one; and the person with decisional impairment, whose individuality must be protected and, where possible, promoted. Otherwise, research with human subjects can too easily come to symbolize the loss of our most prized values rather than their finest expression.

The Commission's Role

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 are consistent with achieving the important societal goals that have been identified. Many who are familiar with the current federal regulations concerning human subjects research complain that they are already unjustifiably complex and bureaucratic. Some of those engaged in research on conditions related to decisional impairment are fearful that further regulation affecting these populations will unnecessarily retard scientific progress and stigmatize individuals who may be suitable subjects.

But many others note that, in spite of the imperfections of the current regulations, the period since their enactment has been largely free of the sorts of large-scale controversies that helped give rise to them. It may also be urged that the issues discussed in this working paper illustrate some of the shortcomings of the Common Rule. The Commission was obliged to determine whether issues concerning the decisionally impaired in research are of such a magnitude that new regulations are required, or whether some or all of the reforms it believes are indicated could be advanced through another mechanism, such as a statement of recommendations for relevant parties.

In this spirit, our recommendations are divided into three categories: (1) proposals for new regulation, (2) suggestions for legislative changes at the state level, and (3) guidance to professionals who work with persons with decisional impairments **and IRBs and others responsible for human subjects protection.**

Recommendations

I. Regulation

A new sub-part of the current federal regulations should be added concerning research involving persons with decisional impairments. The new sub-part would address **research with those who have decisional impairments or incapacity when the research can be done with other subjects; greater than minimal risk, potentially beneficial research involving persons with decisional impairments or those with questionable decisional capacity; greater than minimal risk, non-potentially beneficial research involving persons with decisional impairments or those with questionable decisional capacity; the role of “natural surrogates”; notification of those who have been determined to be decisionally incapacitated and for whom a decision has been made to enroll them in research; and examples of minimal risk and greater than minimal risk interventions in research with those lacking decisional capacity. The new subpart would also include requirements on representation in research planning, involving subjects’ families in their care, and the context of research.**

[Notes to NBAC members:

1. In the following recommendations, this draft does not establish specific requirements for

minimal risk research. Whether such requirements should be established may turn partly on the question whether “minimal risk” should be relativized to all persons or to those who are potential research subjects.

2. This draft also does not distinguish between research that is a minor increment over minimal risk and research that is more than a minor increment over minimal risk. If the members wish new amendments to the regulations that track this distinction they may wish to consider a more highly articulated hierarchy of protections, perhaps drawing from the menu discussed in this draft. Alternatively, NBAC could choose to leave such decisions to IRBs, having established the “floor” of protections that appear in this draft for the several research categories mentioned.]

*1. Research with those who have decisional impairments or incapacity **when the research can be done with other subjects** .*

IRBs should not approve any research of this kind.

2. Notification of those who who have been determined to be decisionally incapacitated and for whom a decision has been made to enroll them in research.

IRBs should determine that the investigator has established a notification procedure for all such potential subjects who are conscious. **Any apparent dissent from participation must be honored regardless of the capacity of the potential subject.**

3. Greater than minimal risk, non-potentially beneficial research involving persons with

decisional impairments or those with questionable decisional capacity.

An IRB may approve this category of research only if the potential subject has given informed consent or, if incapable, has executed an advance directive specifically authorizing research of the kind represented in this study. In either case the IRB must ensure that there is a procedure for identifying a legally authorized representative who can make decisions about continuing or stopping the subject's participation in the research. The IRB must also ensure that there is an independent health professional monitor assigned to track the reaction of the subject to the study, who can stop the subject's participation. The IRB may wish to institute additional requirements as described in the section on Guidance below.

4. Greater than minimal risk, potentially beneficial research involving persons with decisional impairments or those with questionable decisional capacity.

An IRB may approve this category of research only if the potential subject has given informed consent and has executed an advance directive specifically authorizing the research; or the subject's legally authorized representative has given permission for the subject's participation in the research. The IRB may also wish to institute additional requirements as described in the section on Guidance below.

5. The role of "natural surrogates."

Family members and other close friends should be considered to be legally authorized representatives for studies that are potentially of direct benefit to the patient-subject.

6. Examples of minimal risk and greater than minimal risk interventions in research with those lacking decisional capacity.

The regulations should include examples of minimal risk and greater than minimal risk interventions to guide IRBs in approving proposals involving this population. Examples of minimal risk interventions with persons in this 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 this population are sternal and spinal punctures, bone marrow and muscle biopsies, intravenous and intrarterial transfusions, positron emission tomography, endoscopy and biopsies of the gastrointestinal tract.

7. Representation in research planning.

Investigators should be required to describe whether, and in what ways, studies including persons with decisional impairments have incorporated the views of representatives of this population.

8. The family's role.

All professionals whose expertise embraces research involving those who are decisionally impaired or incapable should find ways to recognize family caretakers as part of the healthcare team, including sharing information with them. Professional organizations should open discussions about methods to advance this goal that are consistent with the ethical obligation of patient confidentiality.

9. The context of research.

IRBs should consider whether the context of proposed research would tend to undermine the ability of decisionally impaired subjects to provide an informed consent, due to their psycho-social vulnerability or the prospect of a therapeutic misconception. Elements of a context that could be cause for concern include dependence on the institution as an in-patient or for continuing care, or a dual role played by the potential subject’s physician as a member of the research team (whether as principle investigator, recruiter, or simply as a source of names of potential subjects). In such cases the IRB may require that the study incorporate additional protections, such as a consent auditor.

II. Suggestions for State Legislation

States should consider amending their current statutes, promulgating new legislation, or creating new regulations concerning research living wills and legally authorized representatives, including both research durable powers-of-attorney and “natural surrogates,” along the lines that have been recommended for recognition in the federal regulations. In making these arrangements states may be guided by the model research advance directive (RAD) described in Chapter Seven of this report.

III. Guidance

IRBs must err on the side of caution in approving research with decisionally incapable subjects, and those at risk of loss of capacity. A range of alternatives is available, not limited to those discussed in this report, among them:

Informed consent procedures -- IRBs may require investigators to identify an independent

consent auditor to attend and approve of the informed consent process with subjects known to be decisionally impaired.

Determinations of incapacity -- Independent psychiatrists may be required to certify a potential subject's loss of decisionmaking capacity.

Monitoring -- IRBs may wish to supplement health care agents and legally authorized representatives by requiring that an independent health care professional be available to monitor the responses of subjects to placebo or experimental therapy and to recommend that participation be stopped if participation is no longer consistent with the subject's medical interests.

Washout studies -- Studies designed to provoke psychiatric symptoms through "drug holidays" may be required to begin with those patients who have the most modest history of symptoms, that the selection of higher risk subjects be justified, or even that some subjects be excluded based on their likelihood of future incapacity. IRBs may also require that an independent psychiatrist be appointed to assess subjects periodically and determine whether they should be removed from the study if participation is no longer consistent with the subject's medical interests.

Wraparound studies -- Placebo studies that may lead to confusion about their therapeutic value could be required to conclude with a treatment arm for those in the placebo group.

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 may require that investigators assess each potential subject and amend the form as needed.

Summary of Recommended Framework

1. Threshold limitation

No research is permissible with persons who are decisionally impaired or whose capacity is questionable when the research can be done with other subjects. (This requirement does not apply to observational and epidemiologic studies with anonymized data.)

2. Generic requirement

Persons who have been determined to be decisionally incapacitated for whom a decision has been made to enroll them in research, and are conscious, must be notified of that determination and decision; *any apparent dissent from participation must be honored regardless of capacity.*

(This requirement does not apply to observational and epidemiologic studies with anonymized data.)

3. Additional consent requirements

| Risk | Minimal | Greater than Minimal |
|---------------------------|---------|---|
| Benefit to the Subject | | |
| Potential | X | informed consent <i>or</i> advance directive authorizing this kind of research <i>or</i> legally authorized rep. has given permission |
| None | X | informed consent <i>or</i> advance directive authorizing this kind of research <u><i>and</i></u> legally authorized rep. available to continue or stop <i>and</i> |

health care prof^{al}. monitor

4. Discretionary requirements

At their discretion, IRBs may impose further requirements on any proposal, including further consent procedures, study design limitations, data monitoring committees, additional prior review procedures, etc.