Sheet 7: RESEARCH INVOLVING COGNITIVELY IMPAIRED SUBJECTS: A REVIEW OF SOME ETHICAL CONSIDERATIONS

1. INTRODUCTION

Illnesses causing cognitive impairment are a considerable health problem in the United States. These include Alzheimer's disease, Huntington's chorea, cerebrovascular disease, psychiatric disorders, chronic alcoholism, and AIDS dementia complex. For many years, investigators at the Warren G. Magnuson Clinical Center (CC) have conducted research involving cognitively impaired subjects in order to investigate the etiology and treatment of these diseases. However, dementing and psychiatric disorders may compromise or eliminate a research subject's ability to give informed consent to participation in research. Therefore, while research with intellectually impaired people generates valuable biomedical data, it also provides significant ethical challenges. How should institutions and investigators conducting research on cognitively impaired subjects balance the societal commitment to advance important scientific knowledge with the ethical obligation to protect the rights and welfare of human research subjects?

2. ADDITIONAL PROTECTION FOR COGNITIVELY IMPAIRED SUBJECTS

The Belmont Report articulates the ethical principles relevant to the conduct of all research with human subjects. One of these principles is that individuals should be treated as autonomous agents and that persons with diminished autonomy are entitled to protection. Cognitively impaired research subjects have diminished autonomy and may be limited in their ability to give informed consent and are thus entitled to additional protection. The ethical principles of The Belmont Report are incorporated into Federal Regulations for the Protection of Human Subjects (45 CFR 46). 45 CFR 46 charges Institutional Review Boards (IRBs) with protecting the rights and welfare of human subjects and grants them authority to review and approve all research activities involving human subjects, including those who are cognitively impaired. IRBs are given broad authority by 45 CFR 46 to insure that: "where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects" [45 CFR 46.111(b)]. Therefore, the IRB, in concert with the principal investigator, is responsible for providing specific additional safeguards appropriate to the research study under consideration.

3. CLINICAL CENTER POLICY REGARDING COGNITIVELY IMPAIRED SUBJECTS

In 1987, the CC adopted MAS Policy 87-4 entitled **"Consent Process in Research Involving Impaired Human Subjects."** In 1992, the Clinical Center added MAS Policy 92-7, "Advance Directives," which delineates NIH staff responsibilities and procedures for informing research subjects about advance directives. These policies provide guidance on specific additional safeguards for research subjects who are, or may become, cognitively impaired during their participation in clinical research. MAS Policy 87-4 is based on two key principles found in 45 CFR 46. **(1)** Protection should be proportionate to the risk involved, with the least protection required when research involves minimal risk**.** *Minimal risk "means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." [45*

CFR 46.102(i)]. **(2)** While the assent of vulnerable (cognitively impaired) subjects is necessary, it is not sufficient. More must be done to verify that subjects would do what they are being asked to do if they were able to make decisions for themselves.

When cognitive impairment is mild (early Alzheimer's disease), or can be predicted on the basis of diagnosis, the CC policy calls for prospective research subjects to appoint someone else to make decisions for them regarding their involvement in research if and when they become unable to do so. The major consideration in appointing a representative is that he or she (usually a family member or a close, trusted friend) knows the subject well enough to make decisions concerning research participation that the subject would make if able to do so. This appointment is executed by a CC Durable Power of Attorney (DPA). A DPA is an advance directive which is generally used in the United States for decision-making in (non-research) health care. However, NIH investigators have used the CC DPA successfully in the context of research decision-making.

The CC policy enumerates eight different research situations in which IRBs should require additional protections to the informed consent process (see **5**., below), based on: **(a)** the degree of intellectual impairment of the research subject, **(b)** the level of research risk of the study, and **(c)** whether or not the research offers prospect of benefit to the individual subject. These considerations determine whether the DPA or other approaches, including court-appointed guardianship, should be used in selecting a representative for the research subject.

When submitting research protocols that involve impaired or potentially impaired subjects, investigators are expected to describe which of the eight research situations apply to their studies, and request approval for use of the DPA or other appropriate measures as stipulated by the policy. The IRB will take this information into consideration in making a decision to: **(1)** approve the research, or **(2)** approve it contingent on certain changes or modifications, or **(3)** table it, or **(4)** disapprove the research. The CC policy provides guidance to IRBs and they are not required to follow it in an inflexible manner. For example, they may require additional safeguards, such as monitoring the recruitment of subjects and the assent/consent procedures.

4. CONCERNS REGARDING RESEARCH INVOLVING COGNITIVELY IMPAIRED SUBJECTS

A controversial issue in research institutions in the United States is whether it is ever ethically permissible to conduct research when all of these conditions apply: (1) there is no directive from the subject completed before cognitive impairment, (2) subjects are too intellectually impaired to give consent, (3) the research involves greater than minimal risk, and (4) offers no prospect of benefit to the individual subject (see **5.**, below Case 6). For example, such a situation exists when the wife of a severely demented man, who never expressed a desire to be involved in research, is asked to give permission for her husband to undergo a series of three PET scans solely for research purposes.

The American College of Physicians, in its position paper "Cognitively Impaired Subjects" (Annals of Internal Medicine, Vol. III, No. 10, November 1989, pages 843-848) takes the view that when all above conditions apply, research is rarely ethically permissible, but suggests that a national review body be available to review such research. Some institutions disallow such research altogether, but the CC policy allows

IRBs to approve it with special safeguards, one of which is court-ordered guardianship to assign a legally authorized representative to make research decisions for the subject. This has rarely been done at the NIH, and IRBs and investigators have generally chosen to limit their research activities to involve less severely impaired subjects and/or those with advance directives which provide evidence of their willingness to participate in research.

5. DESCRIPTION OF EIGHT CASE TYPES, CONSIDERATIONS OF LEVELS OF RESEARCH RISK AND IMPAIRMENT, AND THE ACTION(S) REQUIRED:

Case 1: The subject is capable of understanding the DPA, and the research risk is minimal. The DPA is executed, notification given, and research can proceed. Notification is done by sending copies of the signed and witnessed DPA forms to those designated on the carbons (IRB Chair, Institute Clinical Director, CC Bioethicist).

Case 2: The subject is incapable of understanding the DPA, and the research risk is minimal. The physician shall request an ethics consultation for the selection of a next-of-kin surrogate. After a positive consultation report, the substituted proxy consent of the relative can be obtained, and research can proceed.

Case 3: The subject is capable of understanding the DPA, and the research risk is greater than minimal but with a prospect of direct benefit to the subject. The physician shall request an ethics consultation to assure that the person appointed by the subject is capable of understanding the risks and benefits of the study. After the DPA is executed, notification shall occur, and research can proceed.

Case 4: The subject is capable of understanding the DPA, and the research risk is greater than minimal but with no prospect of benefit to the subject. The physician shall request an ethics consultation to assure that the person appointed by the subject is capable of understanding the purpose and risks of the study. After the DPA is executed, notification shall occur, and research can proceed.

Case 5: The subject is incapable of understanding the DPA, and the research risk is greater than minimal with a prospect of direct benefit to the subject. No court-appointed guardian exists, but family members desire the patient's participation in the research. The physician shall request an ethics consultation for the family members to assure their understanding of the risks and benefits and also of the CC's policy requiring court appointment of a guardian. Research shall not proceed until family members initiate court proceedings and a court-appointed guardian can give consent for the research.

Case 6: The subject is incapable of understanding the DPA, and the research risk is greater than minimal with no prospect of benefit to the subject. No court-appointed guardian exists, but family members desire the subject's participation in the research. The physician shall request an ethics consultation for the family members to assure their understanding of the risks and lack of benefit in this case. Research shall not proceed until family members initiate court proceedings and a court-appointed guardian can give consent for the research.

Case 7: The subject is incapable of understanding the DPA, and the

research risk is greater than minimal with a prospect of direct benefit to the subject. The subject does not have an intact family; i.e., no relatives are alive or able to act as surrogate decisionmakers. Research can proceed 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.

Case 8: The subject is incapable of understanding the DPA, and the research risk is greater than minimal with no benefit to the subject. The subject does not have an intact family or relatives. Research is prohibited in this case.

6. EVALUATION OF THE CLINICAL CENTER'S POLICY

In 1990, the Clinical Center's Bioethics Program conducted an evaluation of the CC policy regarding cognitively impaired research subjects. Investigators and nurses in the Institutes were given a questionnaire designed to elicit information on a wide range of issues related to the policy. Most respondents believed strongly that the policy is an important safeguard for research subjects and that it facilitates, rather than impedes, research with cognitively impaired subjects.

The Clinical Center has been a leader not only in advancing scientific knowledge about disorders which cause cognitive impairment, but also in addressing the ethical concerns that accompany such research. However, there remain a number of controversial ethical concerns associated with this kind of research and there will be more in the future as medical technology advances. Investigators and others should recognize that conducting research with human subjects is not a right but a privilege. At the NIH, the privilege is granted to investigators who, after thorough scrutiny by IRBs, can demonstrate that they intend to conduct important, high quality research that provides appropriate protections for human subjects.