

Ethical issues in clinical research in neurology

Advancing knowledge and protecting human research subjects

The Ethics and Humanities Subcommittee of the American Academy of Neurology*

Neurology is evolving rapidly as research brings to light new knowledge about diseases of the nervous system and novel diagnostic and treatment options. An important ingredient in improving our understanding of neurologic diseases is the conduct of well-designed clinical research studies, including epidemiologic, genetic, and natural history studies, and clinical drug trials. However, some research involving people with neurologic diseases presents serious ethical and regulatory challenges.

As the Decade of the Brain progresses, it is appropriate to give attention not only to the scientific but also the ethical dimensions of neurologic diseases. We give a brief overview of some ethical and regulatory considerations concerning the protection of human subjects in neurologic research.

Ethical guidelines and federal regulations.

Biomedical and behavioral research funded or supported by the federal government, including the National Institutes of Health (NIH), is under the purview of regulations for the protection of human subjects (Title 45, Code of Federal Regulations, Part 46).¹ Also, in the United States, all clinical trials, regardless of the funding source, involving investigational drugs are under the regulatory purview of the Food and Drug Administration (FDA).² Both the FDA and the Department of Health and Human Services (DHHS) require that proposed clinical research undergo review by an Institutional Review Board (IRB) whose primary mandate is to protect the rights and safeguard the welfare of the subjects. In their deliberations, IRBs are expected to take into account the nature, content, and design of the research, ethical principles of the Belmont Report,³ and, when appropriate, the regulatory requirements of DHHS and the FDA.

IRBs are important because research investigators have an inherent conflict of interest. As health care professionals, they are dedicated to promoting the welfare of individual patients; as researchers,

they seek generalizable knowledge applicable to persons other than their individual patients. Because the second goal may come in conflict with the first, our society has decided by law that an objective review of human subjects research by a group of diverse individuals is most likely to protect human subjects and promote ethically sound research. Although the IRB system is not perfect, conscientious IRBs reassure the American public that the rights and welfare of human subjects are seriously considered by people who do not have a vested interest in the outcome of the research. It is through this process of research review and approval that investigators, research institutions, IRB members, and others are held publicly accountable for their decisions and actions.

Roles and responsibilities of research investigators.

An important, if not the most important, safeguard to the rights and welfare of human research subjects is knowledgeable, experienced clinical researchers. Particularly, the Principal Investigator's (PI) knowledge and skills are critical to the success of a particular research study. The PI has primary responsibility for the design of the study and for ensuring that it is conducted consistent with protocol and IRB requirements. He or she writes (or supervises the writing of) the protocol, submits it for review to the IRB, and ensures compliance with all IRB stipulations and decisions. Although institutions have varying requirements, protocols usually include a discussion of the human subjects protection issues that are relevant to the study and addresses, at a minimum, the risks to subjects; all procedures that are experimental; the anticipated benefits to subjects, if any; the anticipated number of subjects; the proposed consent document and consent process to be used; and appropriate safeguards if potentially vulnerable subjects are to be enrolled. Vulnerable subjects may include the elderly, prisoners, children, cognitively impaired individuals

*See the Appendix on page 595 for a list of Subcommittee members.

Approved by the Ethics and Humanities Subcommittee April 13, 1997.

Received October 20, 1997. Accepted in final form October 23, 1997.

Address correspondence and reprint requests to Dr. Alison Wichman, National Institutes of Health, Office of Human Subjects Research, Building 10, Room 1C116, Bethesda, MD 20892-1154.

(see below), and people who are economically or educationally disadvantaged or terminally or critically ill. Most research centers have policies and guidelines on the required content of research protocols and the responsibilities of research investigators.

Informed consent to research participation.

The ethical foundation for informed consent is the principle of respect for persons, which requires that research subjects be given the opportunity to choose what shall and shall not happen to them.³ Valid informed consent requires disclosure of relevant information about the research, comprehension of the information by the prospective subject, and his or her voluntary agreement, free of coercion and undue influence, to participation. Although few people disagree with the idea of informed consent, there is ongoing controversy about the nature and possibility of informed consent. Effective implementation in clinical research settings can be elusive, and neurologic researchers, because of the kinds of diseases they study, grapple with many problems associated with obtaining valid informed consent.

Much attention by IRBs and researchers has focused on written informed consent documents. This is understandable because complex regulatory requirements state that written consent should be obtained from research subjects, except in particular and uncommon circumstances. However, research on decision making shows that often consent documents are written at reading levels too high for many prospective research subjects and that retention and comprehension of information presented in written consent documents are poor, particularly when subjects are ill, educationally underprivileged, or when decisions by subjects about research participation must be made quickly.

Research and clinical experience suggest that some prospective research subjects do not consider written informed consent forms helpful in making decisions about research participation. Recognizing that new and innovative approaches need to be developed, the NIH has announced research grants to study the informed consent process in research involving individuals with mental disorders⁴ and to identify and validate methods for improving generally the informed consent process.⁵

Research involving vulnerable subjects. People who are relatively or absolutely incapable of protecting their own interests concerning participation in research are considered "vulnerable" research subjects.⁶ For example, people with dementia, stroke, toxic-metabolic or infectious encephalopathies, mental retardation, status epilepticus, and severe head trauma may have limited or no ability to provide informed consent to research participation. Ethical guidelines direct that research subjects with diminished autonomy are entitled to additional protection, and federal regulations provide specific additional protections for three groups of vulnerable subjects: pregnant women, fetuses, and research activities involving in vitro fertili-

zation; prisoners; and children. In addition, 45 CFR 46 requires that when prospective research subjects are likely to be vulnerable to coercion or undue influence, such as mentally disabled or sick persons or those who are economically or educationally disadvantaged, additional safeguards have been included in the study to protect the rights and welfare of these subjects.¹ However, regulations offer little practical guidance on what constitutes appropriate additional safeguards, leaving it up to local IRBs, in consultation with researchers and others, to provide specific appropriate safeguards in a particular research study.

When conducting research involving vulnerable research subjects, the scientific and ethical justifications must be particularly strong, and practical safeguards for these vulnerable human subjects, appropriate to the particular research study, must be implemented. Therefore, researchers studying vulnerable subjects are expected to provide, in the protocol justifications for the research, reasons why other (less vulnerable) subjects cannot be studied and identify what additional safeguards will be implemented to protect subjects' rights and safeguard their welfare.

Topics of special interest in neurologic research.

Research involving people with severe, progressive, or terminal diseases. Many ethical concerns arise when research subjects have serious, progressive neurologic diseases, particularly when they have failed standard treatments or have diseases for which there are no treatments. Although these sick people may have the intellectual capacity to give informed consent to research participation, sometimes the validity of the consent is questionable. Because of the severe restriction of their choices, out of desperation they may be willing to take serious risks even for a highly remote prospect of direct benefit.⁶ Although this is not necessarily inappropriate, researchers and IRBs must give careful attention to the informed consent process in research protocols studying terminally ill or very sick people.

The nature and severity of an illness has profound effects on research subjects' retention and understanding of information presented in research consent documents.⁷ When conducting research studies involving sick people, clinical researchers need to be aware that many prospective "research subjects" with life-threatening illnesses continue to view themselves primarily as "patients" seeking treatments. This attitude may be effective in helping an ill person cope with a serious disease, but it can lead to unrealistic and misinformed expectations when participating in research. This is particularly true when sick people participate in highly investigational research that has little prospect of benefiting them directly, such as phase 1 drug trials. Therefore, special care must be taken by researchers and others to ensure that potential subjects understand and appreciate how participation in the research may affect their daily lives.

Experienced physicians and researchers know that some patients will accede, on the basis of trust, to just about any medical requests their physicians make.⁸

Therefore, particular problems may arise when the researcher has a long-standing doctor-patient relationship with a person who also enrolls in his or her research protocol. Physicians and researchers must be vigilant about their relationships with these patients/subjects because the distinction between standard medical care and experimental treatment may become blurred. In such cases, researchers and IRBs may want to consider additional safeguards. For example, the IRB may request that an "uninterested" individual, such as a clinical neurologist not involved in the research, discuss with prospective subjects the research study and other clinical or research alternatives.

*Research involving people with cognitive impairments.*⁹ Some psychiatric illnesses, dementing diseases, and other illnesses involving the CNS compromise or eliminate a person's ability to provide valid informed consent, raising significant challenges to the performance of such research. When research subjects cannot give informed consent, regulations do allow consent to research participation by a "legally authorized representative." However, in particular research situations, it may not be clear who qualifies for this role, or the representative's knowledge of the subject's attitudes toward research participation may be limited. Informed consent is a necessary but not sufficient requirement for research participation, and therefore the ethical and legal challenges of such research go beyond concerns about informed consent. More generally, the question is how to provide appropriate protections for these vulnerable research subjects while at the same time promoting the conduct of much needed research. There is no national consensus on what constitutes appropriate safeguards, although over the last few years there have been some efforts to establish consistent guidelines. However, most researchers, IRBs, and research regulators agree that the extent of the protection afforded to research subjects should depend on the risk of harms and the likelihood, or not, of direct benefits to them. Therefore, when reviewing research involving cognitively impaired subjects, IRBs should take into account the nature, degree, and clinical course of the intellectual impairment; the risks, harms, and discomforts of research participation; and whether there is prospect of direct benefit to the individual subjects. For example, in research that exposes subjects to low risk or little discomfort, an IRB might decide that no additional safeguards are warranted beyond consent by subjects' authorized representatives. However, more stringent safeguards may be warranted for research exposing subjects to more than minimal risk, particularly when they do not stand to benefit directly from research participation. In fact, some state statutes prohibit such research. Where a state statute

does not exist, if an IRB was to approve such research, it might choose to monitor the study closely, require a consent monitor, or ask the researcher to implement educational activities for authorized representatives about their roles and responsibilities when making research-related decisions.

Institutions or research units that regularly conduct research involving cognitively impaired people should be encouraged to have policies or written guidelines concerning appropriate protections. Although the institution's IRB(s) and investigators must take into account the particular circumstances of each individual protocol, the existence of written policies or general guidelines appropriately demonstrates extra vigilance to the rights and welfare of these vulnerable research subjects.

Research in emergency circumstances. Research in emergency circumstances may include studies of cardiopulmonary arrest, head injury, status epilepticus, drug and alcohol intoxication, stroke and other cerebrovascular events, CNS infections, and shock/trauma. Valid informed consent can rarely be obtained from critically ill subjects and, in emergency circumstances, there may not be time to seek consent from their representatives. The issue of when, if ever, it is ethically permissible to conduct research without the informed consent of the subjects or their representatives has received much attention over the last few years. In October 1996, the FDA issued¹⁰ and the DHHS agreed to accept a new regulation that allows a waiver of informed consent by subjects or their representatives to participation in certain emergency research studies. The waiver applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition and when there is not time to seek the consent of subjects' representatives. FDA's approval of research conducted under the new rule is conditional on IRB approval. IRBs must fulfill a number of requirements, including consultation with members of communities in which the research will be conducted; public disclosure of plans for the research, its risks, and expected benefits; and, after completion of the research, public disclosure of the results. More details about the new regulation are reviewed elsewhere.¹¹

Research on genetic diseases. Genetic research raises complex ethical concerns depending on the type of research. For example, initial research efforts to identify a disease-specific gene often require pedigree studies that involve many individuals in families. In pedigree research, information about one subject may have direct implications for others, information flow may be increased among subjects raising concerns about confidentiality, and decisions about research participation may not be made independently. Researchers designing and IRBs reviewing pedigree studies need to consider the possible

effects and management of psychosocially potent personal genetic information. Researchers and IRBs must put into place procedures for recruiting subjects, obtaining informed consent, and storage and future use of information and samples. For example, attention should be paid to deposition of samples when the research ends or if a subject withdraws from the study and whether samples will be used in other related or unrelated research activities in the future. Other concerns include communication of potentially anxiety-provoking information to subjects and their family members (e.g., nonpaternity, identification of a disease-susceptible genotype), privacy and confidentiality protections (and their limitations), and subject withdrawal from the research. Research data may be collected that is of a sensitive nature (e.g., information about sexual attitudes, preferences, or practice or information related to alcohol or other substances of abuse) or that, if released, could be damaging to an individual's financial standing, employability, or reputation in the community. In these cases, researchers may want to seek a certificate of confidentiality (granted by the Public Health Service or appropriate NIH component) that grants protection from subpoena for personally identifiable research information.

The American Academy of Neurology has issued practice parameters on genetic testing in clinical practice that advise physicians ordering such tests to take into account several factors, including the predictive power of the test, pre- and post-test counseling, procedures for maintaining confidentiality, and possible adverse consequences of a positive test (e.g., stigmatization, loss of health insurance or employment).¹² Research on genetic testing includes many of these concerns and raises additional ones depending on whether the tests are under development or are already established as reliable. The four basic types of genetic testing are testing newborns (to detect serious genetic diseases), testing for carrier status (to identify people who may have a gene/chromosomal abnormality that might have serious implications for their children), prenatal testing (to detect gene/chromosomal abnormality in fetuses), and risk assessment testing ("presymptomatic" testing to determine the probability that a person will develop a genetically linked disease). IRBs and researchers are expected to give special attention to the ethical, social, and human subject protection issues presented by each type of research-related genetic testing.

The National Bioethics Advisory Commission (NBAC), formed in 1995 by Executive Order, has been charged with, among other tasks, consideration of and advice concerning ethical issues related to human subjects research, including issues in the management and use of genetic information. One of the major issues being considered currently by the genetics subcommittee of NBAC is the storage and future use of human samples for genetic testing. Its recommendations may have significant

impact on the research use of such samples and the management of genetics information in clinical and research settings.

Conclusion. Clinical research is critical to understanding and developing effective treatments of many serious neurologic diseases that currently lead to a diminished quality of life, much pain and suffering, or death for many people. Nevertheless, in the United States, overriding ethical and legal mandates require that all research involving people must be conducted in a way that protects their rights and safeguards their welfare. The overall quality of a research study is judged not only by the importance of the research question, its scientific design, and results but also by the particular attention paid to the ethical dimensions of the research, including the rights and welfare of the human subjects. Research involving people with neurologic diseases presents researchers with a wide array of scientific and ethical challenges. Neurologists can provide invaluable expertise and knowledge in helping to identify and offer effective, thoughtful approaches to the ethical components of their research activities.

Appendix

The following are the members of the Ethics and Humanities Subcommittee of the American Academy of Neurology: Alison Wichman, MD (principal author); James L. Bernat, MD; David Goldblatt, MD; Michael P. McQuillen, MD; Robert F. Nelson, MD; Thomas R. Pellegrino, MD; Russell Snyder, MD; and Robert M. Taylor, MD.

References

1. 45 Code of Federal Regulations Part 46. Department of Health and Human Services Regulations for the Protection of Human Subjects. Revised June 18, 1991.
2. 21 Code of Federal Regulations Parts 50 and 56. Food and Drug Administration Regulations for the Protection of Human Subjects. Revised June 18, 1991.
3. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles for the protection of human subjects of research. Washington, DC: Government Printing Office, April 18, 1979. U.S. Department of Health and Human Services publication GPO 887-809.
4. Public announcement (PA) 95-080, Informed consent in clinical mental health research. NIH Guide 1995 (July 2); Vol 24, No. 27.
5. Request for applications (RFA), Informed consent in research involving human participants. NIH Guide 1996 (September 27); Vol 25, No 32.
6. Levine RJ. Ethics and regulation of clinical research. New Haven, CT: Yale University Press; 1986.
7. Schaeffer MH, Krantz DS, Wichman A, Masur H, Reed E, Vinicky JK. The impact of disease severity on the informed consent process in clinical research. *Am J Med* 1996;100:261-268.
8. Beecher HK. Ethics and clinical research. *N Engl J Med* 1966; 271:1354-1360.
9. Wichman A, Sandler AL. Research involving subjects with dementia and other cognitive impairments. *Neurology* 1995; 45:1777-1778.
10. Protection of Human Subjects; informed consent and waiver of informed consent in emergency research; final rule. *Federal Register* 1996;61(October 2):51498-51531.
11. Wichman A, Sandler AL. Research involving critically ill subjects: new regulations, new challenges. *Neurology* 1997;48: 1151-1155.
12. Practice Committee Testing Task Force. Practice parameters: genetics testing alert. *Neurology* 1996;47:1343-1344.