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Laurie M. Flynn

Ronald S. Honberg

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ACHIEVING PROPER BALANCE IN RESEARCH WITH DECISIONALLY-INCAPACITATED SUBJECTS: NAMI'S¹ PERSPECTIVES ON THE WORKING GROUP'S PROPOSAL

LAURIE M. FLYNN*

RONALD S. HONBERG, J.D., M.ED.**

I. INTRODUCTION

Helen B., 32 years old, suffers from severe schizophrenia. Although she is a bright, engaging individual, her brain disorder has had a profoundly negative impact on her life. She has been hospitalized on a number of occasions and has experienced frequent periods of homelessness. The public mental health system in her community has never provided her with the consistent treatment and services she needs to maintain her stability. Often, she must wait for weeks to get appointments at the local community mental health center, meaning that she sometimes goes for long periods without any medication at all. As her symptoms worsen, she has difficulty maintaining her apartment or keeping appointments, usually leading to evictions and the termination of mental health services because she is deemed "uncooperative."

Several years ago, through the help of a friend, Helen learned about a research program involving the study of an experimental drug for the treatment of schizophrenia. She was initially leery about entering a research program. She had been involved in one before which she thought was a treatment protocol but which turned out to be a study of the structure and biochemistry of the brain. Nevertheless, she decided to seek entry into the study because she was desperate to find treatment that could help her.

Before beginning the study, Helen met with the lead researcher and a social worker to discuss the study. They described the design of the study to her, including the potential benefits of the experimental medication and the potential side effects. It was further explained to her that the study had been reviewed and approved by an institutional review board (IRB). She was given a long, complicated informed consent document to read and sign. Although Helen did not understand all of the information on the document, her desire to

1. National Alliance for the Mentally Ill ("NAMI") is a national, grassroots advocacy organization comprised of 140,000 members who are persons with severe mental illnesses and family members.

* Executive Director, NAMI

** Director of Legal Affairs, NAMI

find a medication that worked for her was very strong, and she signed the document.

During Phase I of the study, Helen was hospitalized so that the effects of Haldol, the neuroleptic medication she was taking at the time she entered the study, could be entirely "washed out" of her system. Since she was on no medication at all for about four weeks, her auditory hallucinations, delusions, and other symptoms of her schizophrenia worsened. After four weeks, still on an inpatient basis, she began a course of "new medication," which turned out to be placebo. During this period, her symptoms remained quite severe.

After four more weeks, she was placed on the experimental medication. Fortunately, after a few days on this medication, her hallucinations and delusions subsided significantly. This improvement continued for several weeks, with few adverse side effects, at which time she was released into the community. She continued to receive the medication for two years as an outpatient following completion of the inpatient phase of the study. During this period, she completed a training program, found a part-time job, and maintained an independent apartment in the community.

Unfortunately, after two years, funding for the study terminated. Since the Food and Drug Administration (FDA) had not yet approved the drug, it was still considered to be experimental, and therefore, Medicaid would not pay for it. Helen was right back where she had started, trying to find appropriate treatment and a support system that would enable her to maintain her stability.

Severe mental illnesses such as schizophrenia, manic-depressive illness, major depression and others, can be devastating for those who suffer from them. These illnesses, now understood to be disorders of the brain, cause immense suffering and correlate significantly with homelessness, joblessness, involvement with criminal justice systems, and suicide.² Historically, there were few effective treatments for diseases like schizophrenia, and people who suffered from these brain disorders were usually relegated to the back wards of public institutions, out of the public sight, and therefore out of mind.³ However, recent breakthroughs in understanding the etiology, nature, and treatments of these disorders offer renewed hope that people with these disorders will be able to live meaningful, productive lives in their communities.

2. See generally, E.F. TORREY ET AL., NATIONAL ALLIANCE FOR THE MENTALLY ILL AND PUBLIC CITIZENS HEALTH RESEARCH GROUP, CRIMINALIZING THE MENTALLY ILL: THE ABUSE OF JAILS AS MENTAL HOSPITALS (1992); FEDERAL TASK FORCE ON HOMELESSNESS AND SEVERE MENTAL ILLNESS, OUTCASTS ON MAIN STREET (1992); NATIONAL INSTITUTE ON DISABILITY AND REHABILITATION RESEARCH, STRATEGIES TO SECURE AND MAINTAIN EMPLOYMENT FOR PEOPLE WITH LONG-TERM MENTAL ILLNESS (VOL. 1, 1992); A.WROBLESKI, SUICIDE: WHY? (1995).

3. See generally GERALD N. GROB, THE MAD AMONG US (1994).

These breakthroughs have occurred through biomedical research. Although we do not yet understand exactly what causes schizophrenia and other brain disorders, new treatments have been developed which control or even alleviate the most devastating symptoms of these disorders for many people.⁴ These remarkable advances would not have occurred without the participation of individuals suffering from severe mental illnesses as human subjects in research. These individuals are truly heroes in the struggle to better understand, treat, and eventually even eradicate these devastating brain disorders.

Nevertheless, there are often considerable risks associated with the participation of individuals as human subjects in research on severe mental illnesses.⁵ Individuals participating in research protocols that evaluate the efficacy and safety of potential new medications for severe mental illnesses may not directly benefit from their participation in such research, and infrequently may experience negative consequences from such participation.⁶ Moreover, brain disorders such as schizophrenia are often characterized by fluctuations in the mental or cognitive capacities of those who suffer from them.⁷ This means that some individuals with these disorders, who participate as human

4. For example, "a typical anti-psychotic medication such as clozapine (Clozaril), risperidone (Risperdal), and olanzapine (Zyprexa) have achieved promising results in successfully alleviating the most florid symptoms of schizophrenia. See e.g., NATIONAL ALLIANCE FOR THE MENTALLY ILL, UNDERSTANDING SCHIZOPHRENIA: WHAT YOU NEED TO KNOW ABOUT THIS MEDICAL ILLNESS at 6 (1996) [hereinafter NAMI]. Similarly, lithium successfully controls the most debilitating symptoms of manic-depressive illness in approximately 80% of all recipients, and fluoxetine (Prozac), sertraline (Zoloft) and paroxetine (Paxil) are quite effective in treating major depression. See, e.g., NATIONAL ALLIANCE FOR THE MENTALLY ILL, UNDERSTANDING MAJOR DEPRESSION: WHAT YOU NEED TO KNOW ABOUT THIS MEDICAL ILLNESS at 10 (1996); F.K. GOODWIN AND K.R. JAMISON, MANIC-DEPRESSIVE ILLNESS (1990).

5. While we limit our discussion in this article to research on severe mental illnesses, the points made conceivably could apply to research involving human subjects who suffer from Alzheimer's disease, autism, Huntington's disease and other brain disorders which can impact on the capacity of these individuals to understand the nature of the research or make informed decisions about their participation in research.

6. For example, although biomedical research facilitated the discovery and approval of clozaril as a breakthrough medication for the treatment of schizophrenia, a small number of people who participated in research protocols studying clozaril developed agranulocytosis. See e.g., J. Kane et al., *Clozapine for the Treatment-Resistant Schizophrenic: A Double-Blind Comparison with Chlorpromazine*, 45 ARCHIVES GEN. PSYCHIATRY 789 (Sept. 1988). Agranulocytosis is a potentially deadly side effect of clozaril characterized by a sudden decrease in white blood cells resulting in rapid death if the drug is not immediately withdrawn. See *id.* at 790. This side effect, and the importance of regularly monitoring the white blood cell counts of clozaril patients, was discovered only after the deaths of several individuals participating as human subjects in clozaril studies. See *id.*

7. See *id.* at 789-90.

subjects in biomedical research, may not always be capable of understanding the nature of specific research protocols or the potential benefits and risks associated with these protocols.⁸

Helen's story illustrates both the potentially dramatic benefits of research participation for people with severe mental illnesses and the extreme vulnerability of those who participate as human subjects in such research. Her experiences give rise to a number of complex ethical questions. Examples follow:

- *Should people with impaired capacity to provide informed consent be allowed to participate in research as human subjects? If yes, what types of research?*
- *Should research protocols using persons with brain disorders as human subjects include formalized procedures for evaluating the capacity of these subjects? If yes, who should be responsible for conducting these assessments?*
- *What can be done to ensure that informed consent is elicited from research participants (or their legally authorized representatives) in a manner which best ensures that they understand the nature, potential risks, and benefits of the research?*
- *What responsibility do IRBs have to ensure that procedures are developed and implemented for protecting the well being of research subjects whose capacity for informed decision making may be impaired?*
- *What is the dividing line between research and clinical treatment for people who enter into protocols involving the study of experimental medications?*
- *Is it ethical to administer placebo to research subjects who agree to participate in research with the expectation that they will have access to experimental treatments?*
- *What obligations exist, if any, after funding for research is terminated, to continue people on experimental medications that help them?*

According to the National Institute of Mental Health (NIMH), it funds more than seventy-five percent of all biomedical research on severe mental illness.⁹ All federally funded research on severe mental illnesses is subject to federal regulations governing protections of human subjects in research.¹⁰ However, these regulations (hereinafter referenced as "the Common Rule") do not adequately address most of the issues raised above. These rules provide general guide-

8. See NAMI, UNDERSTANDING SCHIZOPHRENIA, *supra* note 4, at 2-4.

9. See *id.*

10. 45 C.F.R. §§ 46.101-404 (1996).

lines for obtaining informed consent from research participants.¹¹ The federal regulations also assign significant responsibilities to IRBs to evaluate and monitor research proposals to ensure that they comport with the requirements set forth in the rules.¹² However, although the regulations identify "persons with mental disabilities" as a vulnerable population, they do not set forth specific guidelines or requirements for protecting the rights and welfare of research participants with these disorders.¹³ Hence, research investigators and local IRBs have generally assumed these responsibilities on an ad hoc basis.

Recently, concerns have arisen that not all IRBs effectively monitor the well-being of vulnerable research subjects with brain disorders.¹⁴ Particular attention has been focused on a case involving a research protocol on severe mental illness at the UCLA Neuropsychiatric Research Institute of the University of California, Los Angeles (UCLA).¹⁵ In this case, a former research subject at the Neuropsychiatric Institute and his family alleged that researchers failed to properly inform research subjects and their families about potential risks associated with the particular protocol.¹⁶ One aspect of this protocol involved withdrawing individuals from psychotropic medications to study the relationship between drug withdrawal and psychiatric relapse. The former research subject and his family claimed that they were never informed of the true purpose of the protocol, or the risks associated with withdrawal from medication.¹⁷ Because of this, they alleged, he experienced homelessness, long-term psychiatric deterioration, and extreme suffering. It was also alleged that at least one

11. *See id.*

12. *See id.*

13. The guidelines contained in the Common Rule were very much influenced by a 1978 report issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. THE NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS IN BIOMEDICAL AND BEHAVIORAL RESEARCH, NATIONAL INSTITUTES OF HEALTH, THE BELMONT REPORT (GPO 887-809, 1979). The *Belmont Report* identified four distinct groups of vulnerable populations. These populations were (1) pregnant women and fetuses; (2) children; (3) prisoners; and (4) persons with mental disabilities. *Id.* However, while the Common Rule contains special protections for the first three populations, it is virtually silent concerning special protections for individuals whose decisionmaking capabilities may, due to mental or cognitive disorders, be impaired. *See id.*; *see also*, Adil E. Shamoo, *Our Responsibilities Toward Persons with Mental Illness as Human Subjects in Research*, 5 J. CAL. ALLIANCE MENTALLY ILL 14 (1994).

14. *See* J. Horowitz, *For the Sake of Science: When Tony Lamadrid, a Schizophrenic Patient and Research Subject at UCLA, Committed Suicide, It Set Off a National Debate: What Is Acceptable in Human Experimentation and Who Decides?*, L.A. TIMES MAG., Sept. 11, 1994, at 16.

15. *See id.*

16. *See id.*

17. *See id.*

participant in the protocol committed suicide after similarly being withdrawn from psychotropic medication.¹⁸

After an investigation, the Office for Protection From Research Risks (OPRR) issued a report which concluded that the IRB-approved informed consent documents for UCLA's Schizophrenic Disorders research failed to comply with informed consent requirements set forth in the regulations of the Department of Health and Human Services (HHS).¹⁹ Moreover, OPRR found that UCLA's IRB had been deficient in monitoring informed consent documents and procedures.²⁰

We do not believe that the problems raised in the UCLA case are typical of all (or even many) research protocols for severe mental illnesses. The experiences of members of NAMI strongly suggest that most research on severe mental illnesses be conducted ethically, with procedures in place to monitor the well being of vulnerable subjects. However, the UCLA case raises several important questions. First, can steps be taken to better ensure that research subjects and their involved families adequately understand the nature, purposes, and procedures involved in research protocols? Second, are there limits on the types of research which should be conducted on individuals who may lack capacity to provide informed consent?

The Maryland Attorney General's working group was formed specifically to address questions like these.²¹ The group's mission is to develop recommendations that strike an appropriate balance between the need to proceed with vitally important biomedical research and the equally important need to develop adequate protections for vulnerable individuals with brain disorders who participate as human subjects in this research. In the remainder of this article, we will focus on certain aspects of the group's draft recommendations, with particular emphasis on issues of concern to consumers and families.

II. SHOULD RESEARCH BE CONDUCTED ON DECISIONALLY- INCAPACITATED SUBJECTS AT ALL?

Helen's case may be a typical illustration of the dilemma facing researchers trying to communicate information about specific re-

18. *See id.*

19. Office for Protection From Research Risks Division of Human Subject Protections (OPRR), Evaluation of Human Subject Research Protections in Schizophrenia Research Conducted by the University of California Los Angeles 16-17 (May 11, 1994).

20. *See id.* at 21.

21. The authors of this article wish to express their appreciation of the efforts of Jack Schwartz, Chief Counsel, Opinions and Advice, whose leadership has been the driving force in facilitating the development of the working group's proposal.

search protocols to research participants with brain disorders. Arguably, Helen was capable of providing informed consent at the beginning of the protocol. As the protocol progressed and her psychiatric symptoms worsened, serious questions arose about whether she remained capable of providing informed consent.

In some cases, it may be far clearer in the beginning of research that specific research subjects may lack capacity to understand the fundamental nature of the research or to provide informed consent to participate in the research. The question then arises as to whether it is *ever* appropriate to use incapacitated research subjects.

Under the Nuremberg Code,²² developed in 1947, the answer was clearly no.²³ The Code established that the "voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent."²⁴ Under this approach, research on decisionally-incapacitated subjects would not be permissible under any circumstances.

The Nuremberg Code was written as a reaction to revelations of cruel and sadistic experiments conducted by Nazi scientists on subjects with mental retardation and other mental disabilities under the rubric of "medical research."²⁵ However, with the passage of time, there was increased concern that the strict prohibitions contained in the Nuremberg Code may have been unduly restrictive of legitimate and humane research.²⁶ Over time, the necessity of more specific guidelines to govern biomedical research became increasingly apparent.²⁷

Subsequent declarations or rules for protecting human subjects participating in research have not contained the strict prohibitions contained in the Nuremberg Code. For example, the Helsinki Code of 1964²⁸ allowed for proxy consent or even a complete waiver of con-

22. The Nuremberg Code (1947), *reprinted in* Jessica W. Berg, *Legal and Ethical Complexities of Consent with Cognitively Impaired Research Subjects*, 24 J. L. MED. & ETHICS 18, 18-19 (1996).

23. *Id.*

24. *Id.*

25. See Irene Stith-Coleman, CRS Report for Congress: Protection of Human Subjects in Research at 2 (Feb. 28, 1994) (unpublished Congressional Research Service report to Congress).

26. See *id.*

27. See *id.* at 4.

28. WORLD MEDICAL ASSOCIATION, DECLARATION OF HELSINKI: RECOMMENDATIONS GUIDING MEDICAL DOCTORS IN BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1964) *reprinted in* GEORGE J. ANNAS & MICHAEL A. GRODIN, *THE NAZI DOCTORS & THE NUREMBERG CODE* 331-33 (1992).

sent if in the subject's best interests.²⁹ The Helsinki Code established a distinction between "therapeutic" and "non-therapeutic" research.³⁰ While requiring informed consent "in situations where [a patient's] illness results in cognitive impairments."³¹

The federal Common Rule requires that informed consent be obtained from all research subjects, or their legally authorized representatives, regardless of whether the research is classified as therapeutic or non-therapeutic.³² However, as stated earlier in this article, the Common Rule does not set forth specific guidelines for obtaining informed consent and protecting the rights and well-being of research subjects with mental illnesses or other brain disorders.

Many people with severe mental illnesses participate in research protocols in hopes of finding treatments that work for them. Standard treatments for brain disorders such as schizophrenia, manic-depressive illness, and major depression do not work for some people. In other cases, standard medications may alleviate the most devastating symptoms of the disorders but may also produce unpleasant or even harmful side effects. As in Helen's example, entry into a research protocol may represent a desperate effort to find a treatment that alleviates the extreme suffering characteristic of these disorders.

The existence of a hard and fast rule prohibiting research using decisionally-incapacitated individuals as subjects would have the effect of barring those who are most severely ill from participating in research which may alleviate their suffering and provide them with significant benefits. This, in our opinion, would be unjust and unnecessary. At the same time, the lack of specific rules establishing guidelines for when and how research may be conducted on decisionally-incapacitated individuals creates the potential for problems like those that occurred in the UCLA case. An ad hoc approach to evaluating research protocols involving the participation of decisionally-incapacitated individuals does not, we believe, serve the best interests of consumers or of the research community.

The working group's recommendations³³ represent, in our view, a judicious approach to determining when research using decisionally-incapacitated individuals as subjects is appropriate. The working

29. *Id.*; see also Berg, *supra* note 22, at 19.

30. See Berg, *supra* note 22.

31. *Id.*

32. 45 C.F.R. § 46.116 (1996).

33. Jack Schwartz, Office of the Md Att'y Gen., Third Report of the Maryland Attorney General Working Group (August, 1997) (the Third Report is reprinted in Appendix B to this issue of the *Journal of Health Care Law & Policy*) [hereinafter Third Report].

group's proposal would allow for the participation of decisionally-incapacitated individuals in certain types of research, with safeguards in place to protect these individuals from a violation of their civil rights or from harm.

The proposal attempts to retain as much autonomy as possible in research subjects, while at the same time allowing research to proceed under certain circumstances when individuals lack the capacity to provide informed consent. The proposal seeks to achieve this balance by (a) relying significantly, but not exclusively, for substitute decision-making on individuals specified as "research agents" or "health care agents" in advance directives developed by decisionally-incapacitated individuals (presumably, during periods of capacity),³⁴ and (b) relying heavily (in most, but not all cases) on direct evidence of the wishes of decisionally-incapacitated individuals pursuant to advance directives of other written or verbal representations.³⁵

"Research agents" and "health care" agents respectively have the greatest authority for substitute decision-making under the working group's proposal, because they have been specifically designated by the decisionally-incapacitated individual to make decisions regarding participation on his/her behalf.³⁶ "Surrogates" and "proxy decision-makers" respectively have less authority because they are not similarly appointed by the individual, and may not, in fact, even be known to the individual.³⁷

34. *See id.*

35. *See id.*

36. *Id.* at A-6 (§ 20-502(t) of the draft legislation; (defining research agents as individuals who are designated by decisionally-incapacitated individuals to make research decisions on their behalf). "Health care agents" are similarly designated to make health care decisions, pursuant to the Maryland Health Care Decisions Act. MD. CODE ANN. HEALTH-GEN. I § 5-601(c) (1994) (defining a health care "Agent" as "an adult appointed by the declarant under an advance directive made in accordance with the provisions of this subtitle to make health care decisions for the declarant"). A declarant is further defined in this section in subtitle 6(g) as "a competent individual who makes an advance directive while capable of making and communicating an informed decision." *Id.* at § 5-601(g).

37. Third Report, *supra* note 33, at A-6 (§ 20-502(u) of the draft legislation; (defining surrogate as "a disinterested adult who is neither a research agent nor a health care agent but who is authorized by the Health Care Decisions Act to make health care decisions for an individual, under the conditions specified in Section 5-605 of this article"). Of course, as discussed elsewhere in this article, the provision of health care treatment is not the same as research. *See supra* note 6. It could, therefore, be argued that surrogates should have no authority to make decisions pertaining to research. "Proxy decision maker" is defined in the working group's proposal as:

A disinterested adult who is not a health care agent, research agent, or surrogate for a decisionally incapacitated individual and who is designated by an IRB to consider whether to give informed consent, pursuant to sections 20-513(e) and

It should be noted that the working group's proposal also seeks to protect decisionally-incapacitated research subjects by sharply limiting the circumstances in which someone other than the individual him/herself may consent to participate to research which is considered to be non-therapeutic. In such instances, the higher the potential risks of the research, the more limited the circumstances in which substitute consent may be provided. For example, only research agents may provide informed consent for participation in research which is "more than a minor increment over minimal risk, with no direct medical benefit", and then only if "the research is unambiguously included in the individual's advance directive authorizing research participation."³⁸

We have two concerns about this aspect of the working group's proposal. First, the heavy reliance on advance directives (both for designating "agents" and for evidence of the individual's specific wishes regarding research) could have the effect of excluding from potentially beneficial research those decisionally-incapacitated individuals who do not have the wherewithal or sophistication to develop these documents. For example, Helen (in the above example) might be excluded from participation (or ongoing participation) in the protocol if she does not know how to go about executing an advance directive. To prevent this anomalous situation from occurring, the group may wish to consider accepting alternative ways in which the individual wishes of decisionally-incapacitated individuals can be documented, for example, evidence from family members.

Second, we are concerned that the working group's formulation of those who are authorized to act on behalf of decisionally-incapacitated individuals is lacking one important element. Families are frequently in the best position to understand the wishes of their decisionally-incapacitated family member and to therefore act on their behalf. However, families are notably absent from those who are authorized to provide substitute consent in the proposal. Since advance directives are in their infancy and are not yet being widely utilized by people with severe mental illnesses and other brain disorders, the absence of family members from the decision-making hierarchy

20-514(e), for a decisionally incapacitated individual who had executed an advance directive authorizing research participation.

Third Report, *supra* note 33, at A-5 (§ 20-502(q) of the draft legislation). These individuals are authorized to act on behalf of decisionally-incapacitated individuals only for "direct medical benefit" research or research which is classified by the IRB as "minimal risk, no direct medical benefit." *Id.* at A-5 (§ 20-502(q) of the draft legislation).

38. *Id.* at A-22 (§ 20-516(b)(1)(i) of the draft legislation).

means that individuals who may not really know the decisionally-incapacitated person may frequently be called upon to act on behalf of those individuals.³⁹

III. SUBJECT ASSENT

Recently, the Appellate Division of the New York State Supreme Court struck down New York Office of Mental Health regulations governing psychiatric research involving "more than minimum risk" patients in state run facilities who are incapable of providing informed consent. In *T.D. v. New York State Office of Mental Health*⁴⁰ the court raised the issue of the surrogate consent procedures set forth in the regulations.⁴¹

One aspect of these procedures which the court found particularly troublesome was that there were no express provisions in the New York State regulations requiring that patients be informed that they had been found decisionally-incapacitated or that surrogate consent procedures were being exercised.⁴² In fact, the court noted that it was possible under the regulations to commence research on the patient without ever informing the individual that he/she was participating in research.⁴³ As indicated in the language of the case, the working group acknowledges,

In that event, neither the determination of lack of capacity itself nor the decisions of the surrogate are reviewable at the patient's request. Indeed, given the lack of a notice require-

39. However, it should be noted that family members could conceivably be specified as "research agents" or "health care agents" by the decisionally-incapacitated individual. See *id.* at A-6 (§ 20-502(t) of the draft legislation). Family members could also be appointed as legal guardians. See *id.* at A-15 to A-16 (§ 20-512 of the draft legislation). The working group's proposal specifies that guardians must be consulted prior to enrollment of individuals in any kind of research. See *id.*

40. *T.D. v. New York State Office of Mental Health*, 650 N.Y.S.2d 173 (N.Y. App. Div. 1996), *appeal dismissed by* 680 N.E.2d 617 (N.Y. 1997), *leave to appeal granted by* 684 N.E.2d 281 (N.Y. 1997), *and appeal dismissed by* 1997 WL 785461 (N.Y. Dec. 22, 1997).

41. *Id.* at 190. Under these regulations, once an individual was determined to lack capacity to consent to research, surrogate consent could be obtained from "an individual appointed pursuant to a duly executed durable power of attorney; . . . or an individual designated by the patient to consent or withhold consent to the patient's participation." *Id.* at 188 (quoting N.Y. Comp. Codes R. & Regs. tit. 14 § 527.10(e)(2)(iii) (1996)). If the patient designated no person, surrogate consent could be obtained from the patient's spouse, parent, adult child, adult sibling, guardian, or a committee of the person authorized to consent to research. *Id.* at 188 (citing N.Y. Comp. Codes R. & Regs. tit. 14 § 527.10(e)(2)(iv) (1996)). If none of these options were available, surrogate consent could be obtained from "a close friend" of the patient or a court of competent jurisdiction. *Id.*

42. See *T.D.*, 650 N.Y.S.2d at 187.

43. See *id.*

ment, the patient may not even be informed of either determination and may not even be aware he or she is involved in research.⁴⁴

The working group's proposal contains two important requirements, which, if adopted, will hopefully prevent the concerns articulated by the *T.D.* court from occurring in Maryland. First, it requires investigators to tell decisionally-incapacitated individuals, prior to commencing the research, that they are being asked to participate in research.⁴⁵ It also requires researchers to provide these individuals with the name of the legally-authorized representative who has consented to their participation in the research.⁴⁶

Second, it requires investigators to obtain the *assent* of "any decisionally-incapacitated individual who is capable of giving assent prior to commencing the research."⁴⁷ Finally, the proposal emphasizes that investigators may not involve individuals in research or actions related to research if the individual expresses disagreement or refuses to participate.⁴⁸

IV. THE ASSESSMENT OF CAPACITY

Since the Common Rule does not address the issue of decisional incapacity, it also does not provide guidelines to researchers about procedures to follow in assessing the capacity of research subjects. The working group's proposal similarly does not address this issue.⁴⁹

While we have not seen specific data on the subject, it is entirely possible that, in some instances, responsibility for determining the capacity of individual research participants with severe mental illnesses or other brain disorders may fall on principal investigators themselves, or on others directly involved in the research.

In view of potential conflicts of interest, it is not advisable for those directly involved in research to assume the responsibility of mak-

44. *See id.*, at 190.

45. *See* Third Report, *supra* note 33 at A-15 (§ 20-511(a)(i) of the draft legislation).

46. *See id.* (§ 20-511(a)(ii) of the draft legislation).

47. *Id.* at A-15 (§ 20-511(b) of the draft legislation). The concept of assent has evolved from the field of research on Alzheimer's disease. *See generally* RUTH DUKOFF & TREY SUNDERLAND, DURABLE POWER OF ATTORNEY AND INFORMED CONSENT WITH ALZHEIMER'S DISEASE PATIENTS: A CLINICAL STUDY (1996). Assent is described as a combination of verbal agreement and non-verbal behavior. *See generally id.*

48. Third Report, *supra* note 33, at A-15 (§ 20-511(c) (i), (ii) of the draft legislation).

49. The working group is aware of the lack of specific guidelines for conducting capacity assessments and may take up this issue at some point in the future.

ing capacity determinations.⁵⁰ Rather, we believe that someone not directly involved in the research should make capacity determinations. This, we believe, will better ensure that such determinations are made objectively by outside experts who do not have direct interests in the course or outcomes of the research protocols.⁵¹

V. THE IMPORTANT ROLE OF IRBs

Even more so than under the Common Rule, the working group's proposal would vest significant responsibilities in local IRBs for evaluating, monitoring and overseeing research protocols involving the participation of decisionally-incapacitated individuals.⁵² In the working group's proposal, the responsibilities of IRBs include the following:

- determining if a particular protocol involving the participation or potential participation of decisionally-incapacitated individuals presents a reasonable prospect of direct medical benefit to the group of subjects as a whole,⁵³

50. We believe that most researchers are highly scrupulous and concerned about the well being of research subjects. However, there may, in some instances, be incentives for researchers not to be vigilant in monitoring the capacity of vulnerable research participants or in failing to determine that certain individuals lack capacity, if such determinations will delay or interfere with the course of the research protocol. On the opposite side of the spectrum, the Court, in *T.D.*, expressed concerns that the regulations in that state governing research on institutionalized patients in New York State facilities may create incentives for potential subjects to be found lacking in decisional capacity. *T.D. v. New York State Office of Mental Health* 650 N.Y.S. 2d 173 (N.Y. App. Div. 1996), *appeal dismissed by* 680 N.E.2d 617 (N.Y. 1997), *leave to appeal granted by* 684 N.E.2d 281 (N.Y. 1997), *and appeal dismissed by* 1997 WL 785461 (N.Y. Dec. 22, 1997). "Once a patient is deemed incapable, his or her ability to have an objection or continued participation honored is severely . . . curtailed by provisions allowing for override of the objection." *Id.* at 187.

51. In 1995, the NAMI Board of Directors adopted comprehensive policy concerning protections for individuals who participate as human subjects in research. One section of this policy addresses capacity determinations.

Research participants should be carefully evaluated before and throughout the research for their capacity to comprehend information and their capacity to consent to continued participation in the research. The determination of competence shall be made by someone other than the principal investigator or others involved in the research.

National Alliance for the Mentally Ill, *Standards for Protecting the Well-Being of Individuals Participating in Research*, NAMI PUBLIC POLICY PLATFORM, (2d ed., 1997) (a copy of these standards is reprinted in the Appendix to this article).

52. See Third Report, *supra* note 33, at A-9 to A-13 (§ 20-505 to 509 of the draft legislation).

53. *Id.* at A-11 (§ 20-507(a)(1)(i) of the draft legislation).

- determining the adequacy of safeguards developed to protect the rights and welfare of decisionally-incapacitated subjects,⁵⁴
- ensuring that legally-authorized representatives of individual decisionally-incapacitated research participants are provided with information which "fairly describe[s] the risks and benefits of research participation,"⁵⁵ and
- determining whether research presenting no reasonable prospect of direct medical benefit to a group of research subjects should be classified as "minimal risk," "a minor increase over minimal risk," or "more than a minor increase over minimal risk."⁵⁶

One shortcoming of the working group's proposal is that it doesn't address the training of IRBs or the composition of IRB membership. As discussed earlier in this article, OPRR took the IRB at the UCLA Medical Center to task for failing to adequately monitor the informed consent procedures and well-being of vulnerable individuals participating in the drug washout trial.⁵⁷ Other experts have expressed concern about the ineffectiveness of certain IRBs.⁵⁸ For example, the notable bioethicist, Jay Katz, has expressed concerns about the ability of local IRBs to maintain the expertise necessary to effectively carry out their important functions.⁵⁹ He has also articulated concerns about inherent conflicts of interest, which he believes, have the potential to hamper the ability of these Boards to objectively and impartially protect the rights and welfare of research subjects:

The majority of IRB members are on the faculty of the institutions to which the investigators belong. They not only share similar interests and objectives but they also know, when sitting in judgment of a research protocol, that their proposals may soon be subjected to similar scrutiny. Thus, particularly in the murky area of informed consent, it is unlikely that members of IRBs will hold investigators to a standard of disclosure and consent that would protect the subjects of research if doing so would place impediments on the conduct of research and, in turn, affect the well-being of their colleagues in decisive ways.⁶⁰

54. *Id.* at A-10 (§ 20-506(2) of the draft legislation).

55. *Id.* at A-11 (§ 20-507(a)(2) of the draft legislation).

56. *Id.* (§ 20-507(b)(1) of the draft legislation).

57. *See supra* notes 19-20 and accompanying text.

58. *See, e.g., Jay Katz, Human Experimentation and Human Rights*, 38 *ST. LOUIS U. L.J.* 7, 40-41 (1993).

59. *Id.*

60. *Id.*

We recommend that the working group consider the following three options for enhancing the ability of IRBs to effectively carry out their important responsibilities to protect the rights and welfare of decisionally-incapacitated research subjects:

(1) *Members of IRBs evaluating research on severe mental illnesses and other brain disorders should receive specialized training about these disorders and the needs of people who suffer from them. Persons with brain disorders and family members should be integrally involved in the development, provision, and evaluation of this training.*

IRBs at large, university-based research settings may be called upon to evaluate research protocols in a number of dissimilar areas. For example, in one sitting, an IRB may evaluate a protocol on cancer or heart disease followed by a protocol on schizophrenia. Yet, members of IRBs may not be sufficiently well-versed about schizophrenia and the daily problems experienced by persons suffering from this brain disorder to adequately evaluate potential risks and problems inherent in the design.

The training of IRBs on severe mental illnesses should include more than just clinical information about these disorders. The training should also encompass information about the impact of these disorders on the lives of those who suffer from them, so that IRBs are sufficiently aware of the importance of designing studies which minimize suffering and maximize supports for participants.

(2) *IRBs, which regularly review human subject research on severe mental illnesses and other brain disorders, should include consumers and family members who have direct and personal experience with these brain disorders.*

The Common Rule urges that “consideration shall be given to the inclusion [on IRBs] of one or more individuals who are knowledgeable about and experienced in working with these subjects” and who regularly review research involving vulnerable subjects.⁶¹ We believe that the working group’s proposal should go further and *require* the inclusion of individuals who have personally experienced severe mental illnesses as consumers or family members. Without impugning the motivations of individuals whose IRB membership is based on professional expertise, the working group’s proposal should recognize that consumers and family members, by virtue of their personal experiences, are more likely to focus on those aspects of research designs which may impact (positively or negatively) on the well-being of vulnerable research subjects.

61. 45 C.F.R. § 46.107 (emphasis added)

(3) *At least one member of all IRBs evaluating and overseeing research on severe mental illnesses or other brain disorders should be responsible for functioning as a research advocate or ombudsperson on behalf of those individuals. Investigators, as part of their informed consent responsibilities, must disclose the role, identity and means for communicating with the research ombudsperson to decisionally-incapacitated individuals and their legally authorized representatives.*

Although IRBs play a crucial role in overseeing research and in monitoring the well-being of vulnerable research subjects, members of these boards may have little or no contact with individuals who participate in research protocols. Moreover, research subjects, particularly those who are decisionally-incapacitated, may not even know about the existence of the IRB or the role of the IRB.⁶² The research ombudsperson will be responsible for responding to concerns raised by decisionally-incapacitated research participants or their legally authorized representatives.

VI. CONCLUSION

Research represents the best hope we have for eradicating the suffering associated with severe brain disorders such as schizophrenia, manic-depressive illness, and others. By the same token, constraints and limitations on the way that research is conducted means that not all individuals will derive direct benefits from their participation in research, and some individuals may, in fact, be harmed. The federal regulations which govern the provision of most research on brain disorders unfortunately do not set forth requirements for protecting the rights and welfare of extremely vulnerable, decisionally-incapacitated research subjects. The proposal developed by the Maryland Attorney General's Research Working Group reflects the desire of its members to develop standards which will better protect these vulnerable research subjects, while not compromising the ability to conduct vitally important research. Although the proposal may still require fine-tuning or modifications, it currently represents a significant step towards achieving this elusive balance.

62. See e.g., *T.D. v. New York State Office of Mental Health*, 650 N.Y.S.2d 173, 189-90 (N.Y. App. Div. 1996), *appeal dismissed* by 680 N.E.2d 617 (N.Y. 1997), *leave to appeal granted* by 684 N.E.2d 281 (N.Y. 1997), and *appeal dismissed* by 1997 WL 785461 (N.Y. Dec. 22, 1997).

APPENDIX

POLICIES ON STRENGTHENED STANDARDS FOR PROTECTION OF
INDIVIDUALS WITH SEVERE MENTAL ILLNESSES WHO PARTICIPATE AS
HUMAN SUBJECTS IN RESEARCH.

(Adopted by the NAMI Board of Directors, 2/4/95)

1. NAMI accepts the critical necessity for research using human subjects, acknowledges the important contribution of persons who become human subjects, and affirms that all such research should be conducted in accordance with the highest medical, ethical and scientific standards.
2. National standards to govern voluntary consent, comprehensive exchange of information, and related protections of persons with cognitive impairments who become research subjects must be developed, in which the interests of persons who become human subjects, families and other caregivers are included.
- 3(A). Participants in research and their involved family members must be fully and continuously informed, orally and in writing, about all aspects of the research throughout the process. Research investigators must provide information in a clear, accessible manner to ensure that participants and their involved families fully understand the nature, risks and benefits of the research.
- 3(B). The consent protocol must provide information, which is clear and understandable on an individual basis for each participant and their family members. The consent protocol must provide information on the purposes and scale of the research, what is hoped to be learned and prospects for success, potential benefits and potential risks to the individual (including options for treatment other than participation in research, since research is not the same as treatment). The consent protocol should also contain information concerning the function of the Institutional Review Board (IRB), the identity of the IRB Administrator, the address and telephone number of the IRB administrator and other information, as appropriate.
- 3(C). Whenever consent is given by someone other than the research participant, the participant and involved family members must receive information on the same basis as the person actually giving consent.

4. Research participants should be carefully evaluated before and throughout the research for their capacity to comprehend information and their capacity to consent to continued participation in the research. The determination of competence shall be made by someone other than the principal investigator or others involved in the research. Except for research protocols approved by the Institutional Review Board (IRB) as minimal risk, whenever it is determined that the subject is not able to continue to provide consent, consent to continue participation in the research shall be sought from families or others legally entrusted to act in the participant's best interests.
5. Institutional Review Boards which regularly review research proposals on severe mental illnesses must include consumers and family members who have direct and personal experience with severe mental illness.
6. Members of IRBs approving research on individuals with severe mental illness must receive specialized training about mental illness and other cognitive impairments and the needs of individuals who experience these disorders. Persons with severe mental illness and members of their families must be integrally involved in the development, provision and evaluation of this training.
7. Without penalty, a research participant is free to withdraw consent at any time, with or without a stated reason. Any time a participant terminates participation, regardless of reason, investigators will make every effort to ensure that linkages to appropriate services occurs, with follow-up to assist that participant to establish contact with appropriate service providers and/or care-givers. If a participant disappears or terminates their continued consent, the investigator shall contact his/her family or others designated to receive notification and information.
8. When participation by an individual in a research protocol is completed, participants and/or their families are entitled to be informed of results as soon as this information is available, to have the opportunity to receive feedback concerning their individual participation in the protocol, to critique the protocol, and to provide input concerning possible additional research.
9. All participants in research protocols involving the assessment of new medications will be provided with opportunities by the investigator for a trial on the medication being studied, so

long as other research on the new medication has demonstrated potential safety and efficacy.

10. All individuals who have benefited from the administration of experimental medications in research will be provided continual access to the medication by the investigator without cost until a source of third party payment is found.