# Proxy and Surrogate Consent in Geriatric Neuropsychiatric Research: Update and Recommendations

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**Objective:** The ethics of involving decisionally incapable adults in research will continue to grow in importance as more research is conducted to address the problems of decisionally impaired persons, especially elderly persons. The authors provide an updated discussion, critique, and recommendations regarding the need for clear legal and regulatory policy on this issue.

**Method:** The authors summarize and build on discussions of a workshop on proxy and surrogate consent in geriatric neuropsychiatric research sponsored by the Aging Research Consortium of the National Institute of Mental Health. They incorporate the views of various stakeholders present at the workshop as well as review recent federal and state initiatives, recent empirical research and media reports, and various commission reports and relevant regulations.

**Results:** Despite a wave of initiatives in the late 1990s to clarify policy, surrogate consent for research continues to be a murky legal area and incapable subjects in the United States still lack clear regulatory protection. There is evidence that conservative risk management strategies by institutional review boards and their institutions may severely restrict research with decisionally impaired subjects. A passive approach to this problem may no longer be feasible. A recent federal advisory report on human research protections and legislative initiatives in some states could begin to provide a blueprint for future policy making. Interim recommendations for various stakeholders are given.

**Conclusions:** It is imperative that the scientific community, patients and their advocates, and policy makers at all levels establish a constructive dialogue to clarify ethical and legal standards in the area of proxy and surrogate consent for research.

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Losing the ability to exercise one's power of choice can be an unfortunate consequence of illness. Conditions such as Alzheimer's disease and other neurodegenerative disorders, stroke, head trauma, severe medical illnesses, and certain severe psychiatric disorders can be especially devastating. Because current treatments for many of these conditions are only modestly effective, there is a clear need for further research. Yet the very factor that makes these illnesses so devastating creates significant ethical concerns and poses potential limits to research, because loss of decisional capacity among some persons with these conditions precludes obtaining their informed consent.

This ethically sensitive area has long been a source of controversy (1–3). The protection of decisionally impaired subjects and the regulation of research involving such persons may rely too heavily on the "diverse ethical senstivities of individual investigators and on ad hoc responses of particular institutional review boards" (2). A workshop (hereafter referred to as "NIMH workshop") entitled "Proxy and Surrogate Consent in Geriatric Neuropsychiatric Research: Informing the Debate" was convened under the sponsorship of the National Institute of Mental Health (NIMH) Aging Research Consortium on July 1, 2002, in Rockville, Maryland. The workshop participants constituted a diverse group, including patient advocates, research sponsors, federal and institutional regulators, researchers, clinicians, bioethicists, and legal experts.

This article summarizes and builds on the discussions of the NIMH workshop. In the first three sections, we elaborate on the ethical tensions, present a brief history, and lay out the current situation surrounding research with decisionally impaired subjects. We then (in the fourth section) discuss why this problem can no longer be avoided. In looking toward a lasting solution, we note in the fifth section that several interconnected ethical and procedural issues must be addressed. Although a comprehensive solution is unlikely in the near future, we make several suggestions for how such a solution might be sought (sixth section) and what steps may be taken in the interim by the various stakeholders (seventh section).

## Scientific Inquiry and Protection of Research Subjects

There is wide agreement that decisionally incapable persons should not be involved in research that can ade-

quately be performed with capable subjects (2, 4, 5). Unfortunately, there remains important research on conditions that cause decisional impairment that can only be conducted with persons who have significant impairment. Studies on the pathogenesis of a disease may require subjects with unequivocal diagnoses, which may mean that the patient's disease is advanced enough to cause significant decisional impairment; some of these studies can involve invasive procedures such as the use of an arterial or venous line for a positron emission tomography scan or lumbar puncture (6, 7). Studies that examine the effect of a disease—for instance, the psychosocial and functional effects of advancing Alzheimer's disease—will also involve impaired persons (8). Treatment studies targeting complications of advanced disease—for example, agitation and psychosis in Alzheimer's disease—of necessity will involve incapable subjects (9).

There is also a need for studies that focus on the most affected subgroups within a clinical population. For example, much of the functional morbidity of schizophrenia is secondary to the negative symptoms and cognitive impairments associated with the disease—two factors that also predict impaired decisional capacity (10, 11). Thus, performing research with only clearly capable persons with schizophrenia will leave unaddressed the clinical factors most in need of study.

Finally, the ethical tension inherent in research involving incapable subjects will continue to increase, given that some of the more innovative emerging approaches to treatment could involve unknown—but potentially significant—risks, such as therapies based on gene transfer, vaccine technologies, stem cell research, and other invasive technologies (12–14).

How should our society balance the need for scientific inquiry to develop effective treatments with the need to protect the rights and welfare of decisionally impaired research participants?

## A Brief History

The closest our society came to a national policy on this topic was a proposed regulation based on the 1978 report "Research Involving Those Institutionalized as Mentally Infirm" by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (15). The report specified the conditions under which incapacitated "mentally infirm" subjects may be enrolled in research and stated that court authorization—either directly through a court order or indirectly through the court's authorization of a guardian—was the only source of surrogate consent. The commission's report failed to garner consensus because of controversies surrounding the singling out of psychiatric inpatients for regulation of surrogate consent and because of the multiple regulatory procedures added to the original commission report (1, 2, 16).

It was not until the 1990s that another national debate took place, precipitated in large part by the case of *T. D. v. New York State Office of Mental Health* (17) and a University of California, Los Angeles, study on schizophrenia (18) eventually found to have deficient informed consent practices. A National Bioethics Advisory Commission report and reports of state-level efforts in New York and Maryland grew out of the 1990s debate (5, 19, 20). Although the three reports differed significantly from each other, they all departed from the National Commission's 1978 report in that they would have permitted surrogate consent without judicial proceedings, with limitations based on the risk-benefit profile of the study in question. None of these proposals have been adopted into public policy, and the regulation of research with decisionally impaired adults remains uncertain in most states. (We later discuss the recently amended California and Virginia laws that clarify and permit surrogate consent for research [21, 22].)

## Current Situation

### *Inadequacy of Current Regulations*

Although a literal reading of the Nuremberg Code would prohibit research with incapable subjects altogether (23), most prominent research ethics documents throughout the world would allow certain types of research involving such subjects (4). The U.S. federal regulations endorse the idea of informed consent by a legally authorized representative who is "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in research" (24, 25). The regulations do not go much beyond this mere idea of third-party consent.

Many experts believe that clearer protections for decisionally impaired research subjects are needed to address the shortcomings of current regulatory policy (1, 2, 5). First, the authorization of legally authorized representatives is left to the states, but the states often do not provide clear policy guidance. Previous reviews of state laws and regulations on proxy or surrogate consent for research have revealed tremendous heterogeneity (unpublished NIMH workshop presentation of E. Saks, 2002) and have concluded that "little, if any, state law directly addresses this issue" (26). There is evidence that researchers may not be aware of the applicable laws in their own states (27). Furthermore, most of the laws with some relevance to this issue single out institutionalized psychiatric patients for protection (26).

Second, even if a legally authorized representative is properly identified, the current regulations do not provide guidance on how institutional review boards are to oversee the involvement of the representative. For example, from the perspective of the federal regulations, it is currently permissible for a legally authorized representative to consent for a decisionally incapable person to partici-

pate in studies that are widely felt to be problematic, e.g., a study that has no anticipated benefit and presents a high risk of harm to the subject. Even in states that have specified a research consent process that includes identification of a legally authorized representative, a noteworthy gap in protections can result unless the state also has research regulations that provide a specific framework for risk-benefit analysis.

### *Current Practice*

These uncertainties in policy remain despite increasing research activity involving persons with decisional impairment. In 1978, when the National Commission wrote its report, we were approximately 15 years away from availability of even a modestly effective drug to treat some symptoms of Alzheimer's disease. Now, with some advances already having been made in the treatment of Alzheimer's disease, research with this patient population is increasing. However, decisional incapacity is common even in fairly mild Alzheimer's disease. In one group of Alzheimer's disease subjects with a mean Mini-Mental State Examination (MMSE) score of 23, more than 60% failed at least one standard of competence for research consent (28). It is therefore not surprising that a recent survey of the Alzheimer's Disease Cooperative Study centers found that most sites reported using proxy consent by family members (27).

## The Need to Revisit the Problem

The current U.S. regulations do not reflect the ethical consensus that specific protections are needed for decisionally impaired research subjects. Although the research community has resorted to ad hoc practices that seem to have worked satisfactorily, there are now indications that such approaches have limits.

### *Research Ethics as a Major Public Policy Issue*

Our society is currently undergoing a period of unprecedented and sustained focus on research ethics. With the current President's Council on Bioethics, created in 2001, we have had the longest period of activation of a national-level council on bioethics since the great wave of research ethics discussions of the 1970s and early 1980s (29). There have been several major dramatic events, including widespread national attention to the tragic deaths of two young research volunteers (30, 31) and the shutting down of research at some of the nation's most prominent institutions because of lapses in research ethics practices (31, 32). In 2000, the National Institutes of Health began requiring education in the protection of human research participants from all of its applicants for funding (33). Accreditation of institutional review boards is under way. For example, the Association for the Accreditation of Human Research Protection Programs (http://www.aahrpp.org), founded in 2001, offers such accreditation. A national debate on conflicts of interest in scientific research is occurring (34, 35). The media have given extensive coverage to lawsuits against investigators, institutional review boards, and their institutions (36). In short, our national concern over research ethics has matured into an abiding societal focus.

### *Specific Events Regarding Surrogate Consent*

Amid this heightened scrutiny of research ethics, the issue of surrogate consent is itself moving beyond an academic discussion to a debate over actual policy decisions with potentially broad implications. This trend has been highlighted by several events.

1. Clinical Antipsychotic Trials of Intervention Effectiveness is a large, NIMH-sponsored clinical trial that, in part, tests the relative effectiveness of antipsychotic medications for the management of behavioral symptoms in Alzheimer's disease (9). The selection criteria allow inclusion of persons with MMSE scores as low as 5. In one of the approximately 30 sites (a medical center in New York State), the institutional review board in 2001 refused to approve enrollment of any decisionally incapacitated persons with Alzheimer's disease.
2. At the University of California, Los Angeles, institutional review board members in 2001 questioned whether California law allows for proxy or surrogate consent for research. A review by the institution's legal counsel resulted in an institutional determination that the laws of California allowed only legal guardians to serve as proxy. Subsequently, in 2002, a moratorium was placed on all research based on surrogate consent at the University of California, Los Angeles (37). Yet, other University of California institutions have interpreted state law differently (38). After these events, the California Health and Safety Code was amended to allow surrogate consent for research (20).
3. The highest court in Maryland ruled in 2001 on lawsuits brought on behalf of children who had been involved in a research study comparing various lead abatement programs (39). Citing *T.D. v. New York State Office of Mental Health* extensively, the court stated, "in Maryland, a parent, appropriate relative, or other applicable surrogate cannot consent to the participation of a child or other person under legal disability in nontherapeutic research or other studies in which there is any risk of injury or damage to the health of the subject." Although the full implication of the decision is as yet unclear, the decision is an indication of how some courts may respond to involvement of incompetent subjects in research (3).
4. The Office for Human Research Protections of the U.S. Department of Health and Human Services (DHHS) has written many determination letters in the past few years directly commenting on various institutions' practice of surrogate consent in medical research (38, 40). Determination letters are sent to institutions by the Office for Human Research Protec-

tions in response to queries and concerns and serve as de facto policy documents for the nation's institutional review boards. These documents indicate that investigators are expected to rely on explicit, applicable legal sources for the authorization of surrogates (38, 40)—sources that may not exist in many states.

5. In response to the determination letter written by the Office for Human Research Protections (40), Vanderbilt University in 2002 suspended all research involving surrogate consent for adult subjects. Subsequently, a change in Tennessee Department of Health policy in July 2003 allowed some surrogate consent for research to resume (41).

In summary, the effect of the continuing uncertainties in policy can currently be seen in some of the most populous and research-intensive states. It is likely that a conservative risk management approach by institutional review boards and their institutions will become more prevalent.

Thus, not only is the current policy inadequate for research participants, it is paradoxically restricting important, uncontroversial research as well. The issue now seems to go beyond the classic tension between protection of human subjects and promotion of research; rather, the lack of clear guidance may adversely affect research subjects *and* socially beneficial scientific activities.

## Looking to the Future: Identifying the Obstacles

### *Potential Obstacles: Process and Content*

The major obstacles to a lasting policy on surrogate consent fall into two interacting domains. First, formulating a policy on third-party consent for research raises a host of other issues that are themselves not easy to solve. At minimum, some type of guidance is needed for questions regarding risk-benefit analysis, thresholds for initiating (and standards for conducting) capacity evaluations, and the role of subject assent and dissent, among others. Although these are questions without clear answers, they are best categorized as questions about research regulation, a domain traditionally overseen by the federal government.

Second, this complex set of interrelated questions becomes even more formidable to capture in a policy, given the federal deference to the states in defining who can serve as a legally authorized representative. This deference makes sense in view of the historical role of the states in determining law regarding surrogate-based decision making (for example, in the medical treatment context). However, because the idea of a legally authorized representative for research consent raises several related research ethics issues, as noted earlier, the states are forced to enter the unfamiliar territory of research regulation.

Both substantive and procedural challenges therefore exist in creating a lasting policy. In the remainder of this section, we summarize and build on some salient points for discussion that emerged during the NIMH workshop; the aim of the workshop was not to resolve these issues but to inform the debate surrounding them.

**Who can serve as a legally authorized representative?** Currently, many types of third-party decision makers exist in the medical treatment context, including legal guardians, proxies appointed by the affected parties in advance, and "nonassigned" de facto surrogates such as family members and other caregivers. Some state statutes allow research with some incompetent adults by means of very restrictive mechanisms, such as a court order or use of a legal guardian, while a few states allow a broader set of persons to give third-party consent (unpublished NIMH workshop presentation of E. Saks, 2002). But in the absence of explicit statutory authorization, the legal basis is unclear even for a guardian to consent to research that poses risk to the subject or deprives the subject of benefit.

From a practical point of view, the central issue is whether and how to permit families and other intimates to serve as de facto surrogate consenters. Advance directives for research participation may be useful in certain contexts (42), but they are unlikely to be workable for many other research studies (43). Also, while court-appointed guardians are often thought of as providing the highest level of protection for incapacitated persons, their practicability and ethical suitability are unclear. Few decisionally incapacitated persons have court-appointed guardians, and it is unrealistic to expect the court system to conduct a large volume of guardianship hearings for the sole purpose of allowing research participation. Further, unless the guardian is also a known intimate of the subject, it is unlikely that he or she will have a reasonable basis to decide what the subject would have wanted. In research, as in medical treatment settings, the substantive ethical-legal issue is as follows: to what extent can a nonassigned, de facto surrogate agent—usually a family member—serve as a legally authorized representative?

Since the time of the debate over the National Commission's proposals in the late 1970s and early 1980s, our society has undergone a significant evolution in clarifying the role of family members as surrogate decision makers in the medical treatment context (2), although research is not usually explicitly addressed. For some types of "therapeutic" research, laws that permit nonassigned surrogates to consent to medical procedures are sometimes put forward as permitting surrogate consent for research procedures. For example, this basis for permission seems to be within the bounds of interpretation allowed by the Office for Human Research Protections in some instances (40), as well as by other sources (5).

**What standard or procedure will legally authorized representatives use to make their decisions, and how will the institutional review board oversee such a practice?** Substituted judgment—that is, a surrogate basing his or her decision on what the potential subject would have wanted—is the standard that is, even if imper-

fect (44), most widely accepted (4, 16). The alternative standard of "best interests" of the potential subject is problematic for research consent, since the point of research participation may not be for direct health benefits to the subject, although it is possible that a promising treatment may be available only within a research protocol and therefore the best-interest standard could at times be relevant. The analysis of risks and potential benefits should guide the selection of approaches from a range of safeguards that should be at the disposal of institutional review boards. For instance, as the risk-benefit ratio increases, institutional review boards could institute a system that allows them to assess whether appropriate reasoning was used and an acceptable justification existed for a surrogate's decision.

Any policy on surrogate consent should note an important difference between the ethics of research involving children and the ethics of research with incapacitated adults, namely that it may be possible that some adults have expressed explicit opinions regarding their willingness to participate in research before becoming decisionally disabled, for example, by stating these opinions in a formal advance directive. New regulations should accommodate the possibility that advance directives may in some cases provide enough evidence of subjects' intent that they could serve as the basis for decisions to enter subjects into research involving greater than minimal risk, even when the likelihood of significant benefit is slim. Categorically excluding the moral voice of patients represented in their advance directives seems excessively paternalistic. However, because any research participant has the right to withdraw at any time, participation of an incompetent subject based on an advance directive must involve an advocate who can faithfully carry out the responsibility of withdrawing the subject when the risk-benefit ratio on which the original decision was based changes significantly (45).

Research into the congruence between patients' preferences in treatment or research and their surrogates' estimation of those preferences has yielded mixed results (46–49). A recent survey of 246 first-degree relatives of Alzheimer's disease patients (43) is informative in describing the complexity of potential subjects' preferences. The respondents were asked their research participation preferences in the event that they were to become incapacitated. Although a clear majority (80.9%) preferred to give advance instructions rather than have their family members decide (12.6%), 87.8% also responded that their family members may consent for them if no advance directive exists. Indeed, 80.1% would endorse their family's overriding an advance directive if the research were potentially beneficial for the respondent.

**Should a different, more "stringent," risk-benefit analysis be used by institutional review boards in reviewing protocols that propose to use legally authorized representatives?** This question represents one of the most important issues in formulating a policy for research that is based on surrogate consent. Such research must be conducted with extra safeguards because incapable subjects are less likely to be able to protect their interests. Thus, the current federal regulations for research involving children (50) require institutional review boards to engage in a more fine-grained risk-benefit analysis than do the regulations for research involving adults. Four categories of research are specified in the regulations guiding children's research: 1) research that does not involve greater than minimal risk, 2) research that involves greater than minimal risk but presents the prospect of direct benefit to the individual subjects, 3) research that involves greater than minimal risk and no prospect of direct benefit to individual subjects but that is likely to yield generalizable knowledge about the subject's disorder or condition, and 4) research otherwise not approvable (51). In contrast, the risk-benefit analysis for adult research is quite generic: the institutional review board needs to ensure that risks to subjects are "reasonable" in relation to any anticipated benefits *or* the importance of the knowledge to be gained (52).

For incapacitated adults, there is little controversy that research involving minimal risk is acceptable with surrogate consent, as is research involving anticipated direct benefit to the subject that is reasonable in relation to the risk (4). There is also agreement that if the proposed research involves procedures that are not tied to any anticipated benefit for the subjects, a more conservative risk-benefit analysis is necessary. The recent report from the National Human Research Protections Advisory Committee on this topic captures this emerging consensus (53). This report patterns the approach for incapacitated adults on the risk-benefit analysis described in the federal regulations for research involving children, but the report identifies three levels of risk instead of four. This approach is a significant departure from the recommendations of the National Bioethics Advisory Commission, but it is in agreement with the New York and Maryland proposals (as well as the framework of the National Commission's 1978 report). The National Human Research Protections Advisory Committee's report is significant for two other reasons. First, this committee, formed by former DHHS Secretary Donna Shalala, was advisory to the Office for Human Research Protections, and, thus, its report has national significance, even if it has not been adapted into regulations. Second, the writers of the report had the advantage of being able to review the considerable literature surrounding the National Bioethics Advisory Commission's work and the New York and Maryland proposals, and, thus, the report can be seen as a further step in the national dialogue on this issue.

**When should an institutional review board "trigger" a special set of protections for potential subjects, and how will it be decided that potential subjects need a capacity evaluation?** Protections, including evaluation, should be triggered not by a diagnosis but by credible evidence that in a particular protocol the researchers will likely encounter persons with decisional incapacity, no matter what the cause. Although the impulse to single out psychiatric patients as particularly vulnerable may have understandable sources, it is important to weigh whether the effect of restricting research with such populations does not in fact perpetuate their vulnerability. In this regard, the following statement from the National Human Research Protections Advisory Committee report is significant: "this report applies to all potential subjects in…research who lack decisional capacity for any reason, and is not limited to persons with mental illness"(53).

**What kind of capacity assessment should be required by institutional review boards?** The science of capacity assessments is relatively young (54–57). Although some standardized instruments have been used for research purposes, there is relatively little experience with specific protocols for capacity assessments. At least one large, multicenter clinical trial of treatments for schizophrenia is using a structured interview, the MacArthur Competence Assessment Tool—Clinical Research version (57), to assess the decisional capacity of potential subjects. Until more data are available, institutional review boards should be guided by principles and options rather than by a rigid set of guidelines based on as yet sparse data. Institutional review boards should require that as risks of research increase and the anticipated benefits decrease, the rigor and thoroughness of capacity evaluations should increase (58). Further, the threshold for capacity should vary according to the risk-benefit context. Finally, given the mounting evidence that persons with severe psychiatric conditions can improve their decision-making abilities (10, 11, 59, 60), the enhancement of the decisional abilities of potentially impaired subjects should be encouraged by institutional review boards.

**Who should perform capacity assessments?** In establishing who should perform capacity assessments, the same principle used to determine the kind of capacity assessment should be followed: as the risk becomes greater and the anticipated benefits decrease, the desirability of having an independent evaluator increases. A minimal definition of independence would be that the evaluator is independent of the research team. If an independent evaluation is mandated by an institutional review board, the costs for such evaluations should be seen by research sponsors as a legitimate part of research costs. Researchers should recognize the conflict involved in evaluating their own subjects for capacity, if their research entails some risk to subjects.

It is likely that structured, validated capacity evaluations will also have the effect of making such evaluations less prone to bias. This area will evolve as more data are generated to guide practice. Institutional review boards and investigators need policies that outline principles that can be adapted to and accommodate the emerging evidence base.

### *Other Related Questions*

The set of questions discussed in the previous section is not exhaustive of the ethical issues that need to be addressed in a policy on surrogate consent for research. For instance, there is controversy concerning how much independent oversight of research participation by incapable subjects is necessary, e.g., in the form of consent monitors, subject's advocates, or participation monitors. This and other issues may need further attention.

Finally, institutional review boards should remain flexible rather than lock in safeguards to broad risk-benefit categories. Even within broad risk-benefit categories, a wide range of risk levels may exist. Institutional review boards should identify various options within each risk-benefit category and then apply these options case by case, adapting their practice as they gain experience and as the evidence base develops.

## Dimensions of a Long-Term Solution

The designation of who can serve as a legally authorized representative has historically been the role of the states, while the oversight of human subjects research has been largely directed by federal guidelines. One logical solution would be for the states and the federal government each to address the domains with which they are most experienced. The federal government could adopt a new "Subpart E" for its current research regulations (Title 45, Section 46 of the Code of Federal Regulations), appropriately adapting the current regulations for research involving children (Subpart D). Each state then could make explicit its mechanism for designating a legally authorized representative. The advantage of this approach would be that each jurisdiction's strengths and historically accepted functions would be preserved. As for the sequence of events in achieving this goal, it may be better to develop first the federal guidelines on regulating research with decisionally impaired persons, for two reasons. First, a state attempting to clarify its process for authorization of legally authorized representatives may be forced to "reinvent the wheel" of research regulations for decisionally impaired persons, because questions about regulation of research based on consent of legally authorized representatives will inevitably arise. The recent failed efforts in New York and Maryland took on this comprehensive and complex task for this reason. Second, if a state simply passes a statute that addresses the use of legally authorized representatives without also supplying guidelines that cover the related ethical issues we outlined earlier, then, at least from a theoretical perspective, one could argue that inca-

pable adults would be even more vulnerable than they currently are.

In this regard, the recent National Human Research Protections Advisory Committee recommendations to the Office for Human Research Protections are significant. If these recommendations lead to creation of a "Subpart E" for Title 45, Section 46 of the Code of Federal Regulations, the enhanced regulation would provide a platform on which states could build their statutes to address the use of legally authorized representatives. The National Human Research Protections Advisory Committee report (53) states that its recommendations are limited in value unless the issue of legally authorized representatives is clarified: "[The Committee] strongly urges the states to consider and adopt" legislation for the appointment of legally authorized representatives for research consent and, most significantly, endorses the National Bioethics Advisory Commission recommendation of defining a legally authorized representative as "a person chosen by the subject, or…a relative or friend of the subject"—a definition that includes nonassigned surrogates.

At the state level, there are two possible approaches to enacting legally clear guidelines. One attractive approach would be the development of a model statute. For the model statute to be successful, it would need to be coupled with broad and effective backing by all of the stakeholders on this issue. Such a law should reflect a societal consensus and not just the views of groups with narrow interests. Because the scope of the proposed law would go beyond psychiatry, it would be important for such a coalition to address the general issue of research with decisionally impaired subjects rather than singling out psychiatric patients for inclusion or exclusion. Given the current lack of federal guidelines, the model statute would need to address not only a mechanism for authorizing a legally authorized representative but also the several related topics mentioned earlier in this article.

Another possible approach is for such a coalition to help individual states to clarify their existing regulations or laws. This process has occurred in California and Virginia and has led to amendment of the states' respective statutes regulating human subjects research (21, 22). The new statutes allow nonassigned surrogates to consent to research participation of incapable subjects. The California law specifies that the research must be related to the subject's condition, the subject must not express dissent or offer resistance, and the surrogate must have "reasonable knowledge" of the subject. Both laws appear to impose additional restrictions on research with decisionally incapable psychiatric inpatients. Unlike the California statute, the Virginia law imposes a "minor increase over minimal risk" limit as the maximum allowable risk for "nontherapeutic" research. It is noteworthy that, unlike their failed counterparts in New York and Maryland, the new California and Virginia statutes are brief and are focused primarily on the use of legally authorized representatives.

It is clear that a long-term, definitive solution is needed. It is less clear whether the affected parties currently have enough awareness and energy—or sufficient agreement—to form a truly effective coalition that can help forge a societal consensus on this issue. To take the neuropsychiatric research community as an example, some researchers may feel that focusing on this issue will increase, rather than decrease, opposition to research with decisionally impaired persons. Yet, a "don't ask, don't tell" approach may not be feasible in the long run, as the societal trend is to demand more, not less, accountability in research ethics.

## Steps for the Immediate Future

Although the framework used by the National Human Research Protections Advisory Committee and efforts in California and Virginia could serve as pathways toward a more definitive solution, for most investigators, research participants, and institutional review boards, no such solution will be available in the foreseeable future. Instead, an explicit risk management mentality is rapidly developing, and it is possible that the most conservative options will be chosen by institutional review boards and their institutions, i.e., halting all research with incapable subjects or relying only on guardians or other court-appointed decision makers.

This trend has several dangers. First, important, uncontroversial research could be restricted. Second, such unnecessarily burdensome restrictions will put pressure on investigators (and perhaps patients and family members as well) to find ways to preserve participation of persons at risk for decisional incapacity. The history of Alzheimer's disease research confirms that researchers, families, and patients, faced with a devastating illness and no effective treatment, will turn to alternative ethical solutions, sometimes running ahead of the law. Creating pressure to enroll questionably capable persons in research is worrisome, given that once a person is deemed competent to consent, no special safeguards are in place to protect the subject. In a recent survey of Alzheimer's Disease Cooperative Study centers, 14% (four sites) reported that their institutional review boards will not allow any type of proxy consent (27). It is interesting to note that three of these four sites reported that in clinical trials involving Alzheimer's disease patients with MMSE scores ranging from 13 to 26 inclusive, 85% to 100% of the subjects were capable of consenting to the clinical trial—a much higher range of percentages than for the sites that employed surrogate consent procedures.

Finally, although lawsuits from family members who have served as proxy agents for Alzheimer's disease studies are as yet unheard of, several contextual factors are in flux. For instance, innovative therapies that are being developed have unknown risks, as was shown in the trial of an Alzheimer's disease vaccine in which a number of participants developed encephalitis (12). As more effective

treatments for Alzheimer's disease are developed, the thorny question of using placebo-controlled efficacy trials will come increasingly to the fore.

Institutions whose mission is to promote knowledge that can decrease disease-related suffering must weigh their societal mission in light of the legal risks. In the absence of clear legal guidelines or when guidelines are at variance with widely accepted ethical opinion, it is left to institutional review boards, investigators, and their institutions to forge a thoughtful and informed policy. The following points for consideration may be useful in dealing with these continuing uncertainties:

- Researchers and institutions should be aware of the exact risk management issue they are facing. Each state has a different risk management situation, and it is the responsibility of the investigators, their institutional review boards, and their institutions to be aware of the local legal situation. Approaches that meet the legal standards for one jurisdiction may not automatically meet the standards of another. For example, it appears that from the federal regulatory perspective, an investigator may in some circumstances apply laws concerning surrogate decision making for medical procedures to "procedures" in research (40). However, there is no guarantee that states' courts will agree with such an interpretation.
- Individual institutional review boards and their institutions need to develop a thoughtful policy that is attentive to the considerable literature, including the numerous commission reports, that has been generated over the years on this topic. In this regard, the general framework adopted by the National Human Research Protections Advisory Committee (53) can be seen as a useful benchmark. The committee's recommendations for the most part capture important consensus points, and the framework adopted by the committee is derived from the currently applicable regulations governing research with children, a framework already quite familiar to institutional review boards.
- The institutional review board community should develop a model policy for research with decisionally impaired adults. Thoughtful policy documents based on the considerable expertise of institutional review board professionals have already been developed (61). Although a model policy for institutional review boards will not have the force of law, it could begin to provide a de facto national standard for institutions that is based on sound ethical reasoning and consensus.
- The stakeholders in this debate should be informed of the latest research available and should encourage further research to guide policy. Although ethical issues require careful normative analysis, the choice and implementation of ethics policies depend on good data. Questions that need further research include: How prevalent is surrogate-consent-based research, i.e., just how large an issue is this? What are the societally acceptable risk-benefit trade-offs in such research? How do surrogates make their decisions? How can capacity assessments be made both efficient and accurate? What are the normatively acceptable thresholds for competence judgments, and how can they be made transparent? What are the current perceptions and practices of institutional review boards regarding surrogate consent for research? What are the best ways to remediate decisional impairments? What are the costs and benefits of various approaches to oversight (e.g., consent monitors, independent competence assessments)? If research ethics is to remain an abiding public policy area, it will need to be guided by well-designed and informative research.

## Conclusions

Research involving older adults who are unable to consent for themselves, especially research that does not offer direct anticipated benefits to the participants, remains one of the most challenging areas for research ethics. The current regulations may not adequately protect decisionally impaired subjects, and they do not provide sufficient guidance to institutional review boards and investigators. These uncertainties in policy are beginning to have substantial negative effects on scientific inquiry. It is imperative that the scientific community (investigators and their institutions, as well as sponsors of research), patients and their advocates, and institutional, state, and federal research regulators come together to clarify the ethical and legal standards in this area.

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