

## Research Involving Cognitively Impaired Adults

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Although the federal government funds research to improve the lives of critically ill adults and of the people who care for them, recent investigations show that it does not provide investigators with guidelines for ensuring that such research is on firm ethical grounds, especially in the case of cognitively impaired subjects.<sup>1-4</sup> Federal regulations for the protection of research participants, known as “the common rule,” require that research involving “vulnerable” subjects include “additional safeguards” (45 CFR 46.111) and that the investigator obtain informed consent from a “legally authorized representative” (45 CFR 46.116).<sup>5</sup> But the rule does not describe safeguards in detail, and most states have not addressed the question of who is legally authorized to provide consent. Proposed regulations to address these limitations have not been enacted.<sup>6-10</sup> In this article, I provide a framework for federal research regulations, state laws on proxy decision making, and institutional policies that I believe would help address this problem.

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### ASSENT, DISSENT, AND ADVANCE INFORMED CONSENT

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An investigator’s assessment of a person’s abilities to understand information about a study and to reason and make a choice on the basis of that information is essential evidence for the judgment of whether the person is competent to provide informed consent.<sup>11</sup> Protocols for studies that enroll cognitively impaired subjects should describe a procedure to assess these abilities. For example, the MacArthur Competence Assessment Tool for Clinical Research allows the investigator to fit the details of a protocol into open-ended questions that assess these abilities.<sup>12-14</sup>

In the case of a person who is not competent, there is a general consensus that the investigator should seek the person’s assent and respect his or her dissent, if the subject is capable of providing assent or dissent. Because there are no widely accepted standards for obtaining assent or dissent,<sup>15</sup> research protocols should indicate the kinds of performance on measures of decision-making ability that show that a person can assent or dissent. The informed-consent form should include a section to document these assessments — for example, a checklist to indicate whether the subject adequately understood key items required for assent.

If subjects can be recruited before a predictable loss of capacity occurs (e.g., before the administration of anesthesia), advance informed consent is an option.<sup>16</sup> In a recent study of pulmonary-artery catheterization to monitor fluid balance in the intensive care unit, the investigators used this approach.<sup>17</sup> When advance informed consent is obtained, investigators should also ask each subject to designate a person who will serve as his or her proxy during the course of the research. These practices are distinct from the often proposed but largely untested option of a research advance directive that stipulates a person’s preferences independently of an actual study.<sup>18</sup> With advance informed consent, the investigator recruits an eligible subject for a particular study before the onset of cognitive impairments but close enough to enrollment so that the informed-consent form presents information that is salient and relevant to the patient.

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### PROXY DECISION MAKING

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Recent controversies<sup>19</sup> and within-state differences in institutional interpretations of laws and cases<sup>20,21</sup> highlight the need for clear guidance on the identification of persons who are legally authorized to provide informed consent on behalf of incompetent adults, as specified by the common rule. States should enact laws that clarify the legal status of a family member to serve as a research proxy. Research regulations should help institutional review boards (IRBs) and investigators address the following ethical question: in the absence of a research advance directive that designates a proxy and guides that proxy, what is the justification for asking a proxy to provide informed consent on behalf of a noncompetent adult?

The legal approach to proxy decision making in the care of patients with permanent unconsciousness or terminal illness relies on obtaining informed consent from a family member, identified on the basis of a hierarchy of family relationships widely thought to reflect closeness, such as the spouse and then an adult child.<sup>22</sup> California recently passed a law that in my opinion is a good model for legislation on who can serve as a legally authorized representative for research decision making.<sup>23</sup>

In many instances, this hierarchy is also used to identify the person who is an ethically appropriate proxy for making decisions about participation in

research. But in some cases, the two proxy roles are not assumed by the same person. For example, an adult grandchild who has lived with, cared for, and made medical decisions with an adult who is no longer competent is arguably a more ethically appropriate choice as a proxy for providing informed consent to participate in research than the person's estranged child. A family member in such a caregiving role recognizes that the risks and benefits of research affect the caregiver as well as the subject.<sup>24</sup> Hence, the family member makes a decision that reflects an appreciation of how the risks of research can affect the patient. Research regulations should permit an IRB to require that the protocol identify the ethically appropriate research proxy. In instances in which a different person is the legally authorized research proxy, the investigator will need to obtain informed consent from both people.

The ethical guidelines for decision making by a research proxy should not uniformly require the proxy to make a substituted judgment — that is, choosing what the patient would choose if he or she were capable of choosing. A research proxy's violation of an adult's substituted judgment<sup>25</sup> is not as ethically problematic as it appears. Just as in clinical care, proxies cannot consistently make accurate substituted judgments for enrollment in research.<sup>26</sup> The claim that the person would want to enroll is as likely to be wrong as it is to be right. In addition, as with decisions about clinical care,<sup>27</sup> many potential subjects would grant their proxies leeway over an advance directive indicating their wish to participate in potentially beneficial research.<sup>28</sup> It would be reasonable to require that the informed-consent form instruct the proxy to base the decision on the potential subject's previous wishes and that if this information is not available — which is likely to be the case in most situations — to make the decision on the basis of the person's best interests.

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#### REASONABLE RESEARCH RISKS

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When is enrolling a noncompetent patient in research ever in his or her best interests? A competent adult has complete personal discretion in making this decision.<sup>29</sup> In most cases, a proxy for a noncompetent adult should not have the same degree of discretion.<sup>6-10</sup> The core ethical challenge is to define the limits on the kinds of research risks that the proxy can accept on behalf of a noncompetent subject.

Regulations governing pediatric research pro-

vide a model for these limits (45 CFR 46subpartD).<sup>5</sup> A proxy should be allowed to enroll a person if the IRB finds that the research is potentially beneficial or presents minimal risks and that the knowledge that may be gained would be important to the class of subjects.<sup>6-10</sup> These categories formalize the common rule's requirement that research risks be reasonable in relation to the potential benefits to the subjects and the importance of the results the research may yield (45 CFR 46.111[a][2]).<sup>5</sup>

But current and proposed research regulations do not clearly describe how to fit the risks and benefits of research into these categories or how to balance the risks against the potential benefits for the subjects and against the knowledge the research may produce.<sup>30,31</sup> Consider the study of two ventilator tidal volumes conducted by the Acute Respiratory Distress Syndrome Network.<sup>32</sup> The risks of the higher volume included barotrauma and stretch-induced lung injury. The risks of the lower volume included agitation, dyspnea, and atelectasis. These risks are certainly greater than minimal. How can proxy consent be permissible? On the other hand, participation in the study offered potential benefits to the subjects. Which risks are justified by these benefits?

A common approach is to compare all of the risks of the research with all of the potential benefits for the subjects. The judgment that the risks are reasonable in relation to the potential benefits — such as a shorter period of mechanical ventilation and a reduced risk of death — justifies the risks, even though they appear to be “greater than minimal.” This approach is intuitively appealing because it reflects clinical reasoning. But it fails to recognize that research typically includes procedures that are not intended to provide benefits for subjects. The risks associated with these procedures ought to be the focus of the minimal-risk assessment for proxy consent.

Suppose the trial included right-heart catheterization to assess the effect of the ventilator volume on cardiac performance and these data were gathered and analyzed in such a way that the treating clinician could not use them to affect patient care. Under these conditions, right-heart catheterization would not provide data that could potentially benefit the subject's care. But the risk assessment described above would weigh the risks of right-heart catheterization against the potential benefits of the ventilator settings. In other words, a risk of an intervention performed solely to obtain general-

izable knowledge (catheterization) would be justified by the potential benefits of another research intervention (use of the ventilator) — a situation that could exploit vulnerable subjects in the pursuit of knowledge.

To avoid this problem, a distinction should be made between risks that are justified by potential benefits for the subjects and risks that are not justified by those benefits. Current research regulations, including those governing pediatric research, do not clearly address these distinctions. The National Bioethics Advisory Commission has proposed a framework for risk assessment that does do so.<sup>30</sup> This framework recognizes that research has two distinct components.<sup>31</sup> One component consists of interventions that involve both risks and potential benefits for subjects (the ventilator setting). The other component consists of interventions that pose risks but offer no potential benefits for the subjects (right heart catheterization). A comprehensive assessment of a study's risks would be based on separate analyses of the risks of these two components. The risks posed by components with potential benefits are weighed only against those potential benefits. The risks posed by components that do not have potential benefits are weighed against the value of the knowledge that may be gained from the research.<sup>33,34</sup>

How great can these risks be? A useful guideline is the concept of minimal risk: "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46.102[i]).<sup>5</sup> There has been considerable confusion about how to apply this definition, because it does not specify the comparison group to be used.<sup>35</sup> Options include the subjects themselves (i.e., the risks they encounter in their daily lives), the general public, and healthy persons.<sup>30</sup>

Because risk assessment is highly contextual, the regulations should not identify a single comparison group but should make it clear that the decision about what risks are minimal will differ according to the group selected for comparison. The subjects of the research are persons who have serious risks because of their illness. The risks for healthy persons are considerably smaller, and those for the general public lie somewhere in between. The choice of a comparison group should reflect the principle of justice. Vulnerable subjects must not be exposed to

excessive research risks, without the possibility of benefit, in the pursuit of scientific progress.<sup>36</sup>

The two-component model of risk assessment will help IRBs judge whether the risks of research are reasonable with respect to two factors: the potential benefits, if any, for the subjects and the importance of the results the research may yield (45 CFR 46.111[a][2]).<sup>5</sup> Proxy consent is permissible if the risks posed by the components of the research that do not offer potential benefits for the subjects are no more than minimal and are justified by the importance of the knowledge to be gained. This is a more straightforward application of the concept of minimal risk than the use of increments, such as "a minor increment above minimal risk."

In my view, most studies of critical care that enroll noncompetent subjects would probably pass the two-component assessment. Components without potential benefits, such as obtaining additional blood specimens from an arterial line that is already in place as part of clinical care, present risks that are no greater than those posed by routine medical care and tests. In other words, these risks are minimal. They are justified by the importance of the knowledge anticipated from the research. The risks posed by components with potential benefits, such as the use of one of two ventilator settings, are justified by the state of equipoise: the expert consensus that the interventions being compared are within the standard of care and that equilibrium exists in the balance between risks and benefits in the intervention and control groups.<sup>31,37</sup>

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## CONCLUSIONS

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Until regulations exist for research that involves critically ill and other cognitively impaired adults, federal investigations will be inevitable, slowing and even halting the progress of valuable research. Informed-consent practices should be systematic and documented, a process already required by some medical journals.<sup>38</sup> Proxy consent is permissible when the risks of the research that are not justified by its potential benefits for the subjects are no more than minimal and are justified by the importance of the knowledge to be gained from the research. This approach differs from the regulations governing pediatric research, but it addresses the shortcomings and ambiguities of those regulations. State laws should identify legally authorized research proxies, and the regulations should permit IRBs to specify any additional conditions.

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