Research Involving Individuals With Questionable Capacity To Consent: NIH Points To Consider[1] November 2009

I. INTRODUCTION

The National Institutes of Health (NIH) is committed (1) to helping investigators carry out clinical research in an ethical manner and (2) to protecting the rights and welfare of research subjects while advancing scientific knowledge and treatment opportunities. The purpose of this document is to provide investigators and institutional review boards (IRBs) with points to consider (a) in fulfilling ethical and Federal regulatory requirements[2] to ensure the protection of the rights and welfare of research subjects who—due to impairments in their capacity to give informed consent—may be vulnerable to coercion or undue influence and (b) in maintaining appropriate awareness of the ethical challenges associated with research involving this vulnerable population. Impaired decision-making capacity need not prevent participation in research, but additional scrutiny and safeguards are warranted for research involving individuals with such impairments.

Scope

For purposes of this document, the term "consent capacity" describes an adult's ability to understand information relevant to making an informed, voluntary decision to participate in research. Several kinds of information are relevant to such decisions—including the purpose of the study, its experimental nature, risks and anticipated benefits, the right to withdraw, alternatives to participation, confidentiality protections, and the safeguards used to minimize risks.

A wide variety of diseases, disorders, conditions, and injuries can affect a person's ability to understand such information, to weigh the advantages and disadvantages of participation in research, and to reach an informed decision regarding study participation.[3] Consent capacity can be impaired—for example—by mental disorders, neurological disorders such as stroke or dementia, metabolic impairments, psychoactive medications, substance abuse, and head trauma.

[1]This document was first issued in 1999. It was developed through a consultation with a broad array of experts on clinical research, bioethics, mental health, substance abuse, and age-related conditions. Representatives from professional and lay advocacy communities, former research subjects and institutional review board (IRB) members, and others concerned about clinical research and human subject protections also provided valuable perspectives. The document was updated in 2007-2009 under the auspices of the National Institutes of Health (NIH) Clinical Research Policy Analysis and Coordination Program and through the efforts of a Trans-NIH Bioethics Committee working group composed of representatives from the following NIH Institutes: National Heart, Lung, and Blood Institute, National Institute on Aging, National Institute of Alcohol Abuse and Alcoholism, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute on Drug Abuse, National Institute of Mental Health, and National Institute of Neurological Disorders and Stroke.

[2] For example, the document draws upon sections 46.111(a)(3), (a)(4), and (b) of the Department of Health and Human Services (HHS) regulations for the Protection of Human Subjects (45 CFR part 46) and the FDA regulations at 21 CFR 56.111(b).

[3]An individual's capacity to provide truly informed consent can be affected by other types of vulnerability—such as poverty and deficits in education. The focus of this document is subjects who may lack the capacity to reach informed decisions regarding consent to research for reasons such as diminished cognitive functioning rather than these other types of vulnerability.

It is important to recognize that, in some situations, these conditions may produce substantial impairment of capacity, while in other situations they may not affect an individual's understanding of key informed consent elements. In research involving such conditions, it is important to consider and determine whether a prospective subject's diminished decision-making capacity affects his or her capability to provide informed consent.[4] Assessing consent capacity may involve asking prospective subjects to describe facets of the research—such as the purpose of the study, the components that are experimental, the study's associated risks and anticipated benefits, and the voluntary nature of, and alternatives to, study participation.

Consent capacity varies along a continuum and depends in part on the complexity of the decision facing the individual. In this context, the more complex the study, the harder it may be to understand the relevant consent issues. For example, it is possible that a given individual at a given time may have sufficient capacity to consent to a simple research evaluation, but he or she may be incapable of consenting to participate in a complex research study.[5]

In making decisions about research participation, the complexity relates to a variety of factors—including study design, risks, anticipated direct and indirect benefits, and the safeguards used to minimize risks.[6] The determination of whether a prospective subject is capable of providing informed consent is based on a consideration of relevant study factors and an individual's consent capacity.

Importance of Research on Conditions and Diseases That Cause Impaired Decision-Making Capacity

A great deal of important clinical research is aimed at addressing diseases, disorders, conditions, and injuries of the brain and body that can affect cognition, mental acuity, awareness, and decision-making capacity. Excluding persons who may have impaired consent capacity from participation in such research can significantly delay attempts to answer important scientific questions that could lead to new treatments and better diagnostic, predictive, and preventive strategies. While involving individuals with such conditions in clinical research can be ethically challenging—because these disorders can affect the ability to provide informed consent—enrolling subjects with such disorders is crucial to the development of new treatments and diagnostic and preventive strategies.

It is important to remember that the ethical principle of equitable subject selection does not require research participation to be limited to the least impaired individuals. Studying only the mildest or earliest cases of a disease can be important, but such research is not likely to provide insights about the development of more severe symptoms and associated disabilities that may include impaired decision-making capacity. The biological mechanisms by which disease symptoms worsen need to be studied to improve diagnosis and treatment.

[4] While this document focuses on research into conditions that cause consent capacity impairments, the considerations and protections outlined here may also be relevant to the participation of individuals with questionable capacity to consent in any research.

[5] Rosenstein DL. (2004). Decision-Making Capacity and Disaster Research. *Journal of Traumatic Stress*. 17(5):373-381.

[6] Drane JF. (1984). Competency To Give an Informed Consent: A Model for Making Clinical Assessments. *JAMA*. 252(7):925-7.

By advancing scientific knowledge of the condition or disorder, research that does not directly benefit the individual subject can be of benefit to family members, other people at-risk for or with the condition, and society as a whole. For example, research focusing on understanding the pathophysiologic, genetic, and biochemical bases of disease may have no direct medical benefit to study subjects but will likely advance knowledge—and may lead to new strategies to diagnose, treat, and prevent disease.

In evaluating which studies should be approved and what additional safeguards and monitoring may be needed, IRBs should pay particular attention to the disorder under study, the study population, and human subjects protections. An IRB may decide that additional efforts are needed to enhance a prospective subject's ability to provide informed consent. Efforts that have been shown to improve comprehension of the elements of consent are discussed in Part III.

Current Regulatory Framework

The *Belmont Report*, part of the foundation for the current U.S. Federal regulations for the conduct of research involving human subjects, highlights respect for persons as one of the basic ethical principles for research involving human subjects, and—in the case of individuals who do not have the capacity to exercise their autonomy—respect for persons requires affording appropriate protections.[7] Two sets of Federal regulations are directly applicable to the conduct of research involving human subjects that is funded by HHS and/or that involves a product regulated by the Food and Drug Administration (FDA)—the Federal Policy for the Protection of Human Subjects, which is codified by HHS at 45 CFR part 46, subpart A, also called the Common Rule,[8] and the FDA regulations at 21 CFR parts 50 and 56.

The Common Rule and the FDA regulations call for the equitable selection of subjects and provision of additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence—such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.[9] HHS has promulgated additional regulations in subparts B, C, and D for research involving, respectively, pregnant women, fetuses, and neonates; prisoners; and children.[10] While research involving "mentally disabled persons" has not been subject to additional regulations in a special subpart of the HHS regulations, IRBs and the research community have nevertheless developed a broad array of additional safeguards for subjects who may be vulnerable to coercion or undue influence due to an impaired capacity to provide informed consent.

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[7] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm.

[8] The regulation is called the "Common Rule" because it has been adopted across the Federal government: Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Commerce, Consumer Product Safety Commission, International Development Cooperation Agency, Agency for International Development, Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veterans Affairs, Environmental Protection Agency, HHS, National Science Foundation, Department of Transportation, Central Intelligence Agency, and Department of Homeland Security (adopted in 2006). See 56 Federal Register 28025 (June 18, 1991).

[9] 45 CFR 46.111(a)(3) and (b) and 21 CFR 56.111(a) and (b), respectively.

[10] 45 CFR part 46, subparts B, C, and D, respectively.

State or local law may also be relevant to the conduct of research involving individuals with impaired consent capacity, and some institutions or IRBs may have additional policies that need to be followed.

II. ISSUES FOR CONSIDERATION

In order for individuals with impaired consent capacity to be ethically enrolled in research, investigators and IRBs should consider ways to enhance these subjects' understanding of information relevant to the consent process, doing this in a manner consistent with the Common Rule and the ethical principles outlined in the Belmont Report. Because individuals with impaired capacity to consent may be vulnerable to coercion or undue influence, investigators and IRBs should be guided by ethical principles—such as respect for persons and equitable selection of research subjects—and they should weigh the need for additional safeguards to ensure the voluntariness of study participation.

In some cases, enrolling individuals with impaired consent capacity in research may necessitate the involvement of a legally authorized representative (LAR).[11] When an LAR is acting on behalf of the prospective subject, IRBs should consider the most appropriate methods to present information to both the LAR and the subject about the study and its risks and anticipated benefits.

Assessing Consent Capacity

It is important to take prospective subjects' abilities, impairments, and needs into account when considering whether to invite them to participate in research. Well-validated and practical methods to assess consent capacity exist and are continuing to be developed. The NIH and others support research addressing improved consent and assessment in populations with diminished capacity.[12]

In past years, there was considerable debate about which abilities or types of knowledge should be evaluated and how such evaluations should be conducted. More recently, there has been an effort to develop a more practical and direct approach. Instead of trying to quantify the cognitive and other abilities that might relate to decision-making capacity, some methods now involve questions about consent-related aspects of the particular study being considered.[13] This is one of the reasons why the term "consent capacity" is used in this document rather than "decision-making capacity."

Trends in Consent Capacity Assessments

Early versions of consent capacity evaluations tended to include questions focused on various cognitive abilities. Using some of these instruments required special training and considerable time to administer, making them impractical for screening purposes.

[11] For additional information on LARs, see Part III of this document.

[12] For more information, see http://grants.nih.gov/grants/policy/ethics_research.htm.

[13] Jeste DV et al. (2007). A New Brief Instrument For Assessing Decisional Capacity for Clinical Research. *Arch Gen Psychiatry* 64(8):966-74.

In recent years, findings from research into consent capacity have helped pinpoint more useful and discerning questions to employ. These insights have allowed for the development of shorter assessment instruments that are simpler to administer but maintain the sensitivity of longer instruments.[14] As a result, the utility of these new instruments has been enhanced while their validity as screening devices has been maintained. Researchers are also investigating which assessments are best for which populations and what appropriate cut-off scores should be. There is no clear consensus as to which instruments are most effective in assessing consent capacity, and while these instruments are still considered useful, additional research and improvements to assessment techniques are needed.[15,16,17,18]

Practices that focus on consent capacity can include a discussion of the proposed research project with a prospective subject—e.g., during the consent process—followed by a series of questions to assess the person's understanding of key issues. Such questions might relate, for example, to the purpose of the research and the foreseeable risks and anticipated benefits of study participation. Other questions might explore the prospective subject's understanding of the voluntary nature of research and the elements of consent—including the right to be informed about appropriate alternative procedures or courses of treatment that may be available.

When To Assess Consent Capacity

Other important issues for investigators and IRBs to consider in developing and reviewing protocols relate to determining which prospective subjects should be assessed for consent capacity and how the assessment should be performed. If the study's inclusion criteria and recruitment plan include individuals with disorders commonly associated with decision-making impairments, some form of screening may be useful. After assessing study risks, anticipated benefits, complexity, availability of LARs, and patient characteristics, the IRB's next step would be to determine which additional safeguards would be appropriate.

Considerations for Recruitment Plans

In research involving individuals with questionable consent capacity, IRBs and investigators may consider a recruitment plan that sets out how the assessment of consent capacity will be handled. For example, the plan could involve an informal screening at the start of the consent discussion with a prospective subject, relying on investigator experience and simple questions to determine which prospective subjects may have problems understanding consent-related issues.

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[14] Id.
[15] Id.
[16] Palmer BW et al. (2005). Assessment of Capacity To Consent to Research Among Older Persons with Schizophrenia, Alzheimer Disease, or Diabetes Mellitus: Comparison of a 3-Item Questionnaire with a Comprehensive Standardized Capacity Instrument. *Arch Gen Psychiatry*. 62(7):726-33.
[17] Dunn LB et al. (2006). Assessing Decisional Capacity for Clinical Research or Treatment: A Review of Instruments. *Am J Psychiatry*. 163(8):1323-34.
[18] Sturman ED. (2005) The Capacity To Consent to Treatment and Research: A Review of Standardized Assessment Tools. *Clinical Psychology Review*. 25:954-974.

This initial screening may also involve more targeted assessment following the consent discussion. Prospective subjects may be asked to describe risks, anticipated benefits, alternatives, research purpose, and/or voluntariness issues, or they may be asked to answer specific questions about these areas. If these initial screening steps indicate that the subject has adequate consent capacity, those administering the consent process could document that the subject understood the key issues.

If, after the initial screening, an individual is still considered to possibly have impaired consent capacity, the prospective subject could be asked to undergo a more formal capacity assessment. The application of various educational techniques could be considered at any point in this process, to enhance the comprehension and consent capacity of prospective subjects. The prospective subject's consent would not be sought unless he or she demonstrates an adequate level of understanding.

The recruitment plan could also indicate whether individuals judged to have impaired consent capacity through an assessment method will be excluded from study participation or provided additional information and assessed further before being entered into a study, or whether consent will be required from an LAR instead. When a prospective subject is found to be incapable of consenting to a given research study, he or she could be ethically enrolled in research with the consent of an LAR or an advance directive, as permissible by state or other applicable law—if one had been executed.

Consent as an Ongoing Process

Consent capacity can be affected by disorders with progressive or fluctuating courses. In cases where a subject's cognitive condition is expected to deteriorate or fluctuate, it may make sense to re-evaluate consent capacity—and, as appropriate, strategies for consent enhancement—at several intervals during the study, especially in long-term studies that may involve multiple phases. In addition, such changes in clinical status may affect, for example, the risk/benefit considerations, appropriate alternatives to study participation, and need for additional safeguards or monitoring.

When consent capacity could diminish during the course of a study, it may be most appropriate to transition to LAR consent and decision-making. In these cases, involving at the start of the study an individual who could serve as an LAR later on may be most prudent.

For individuals with conditions that bring about fluctuating levels of consent capacity, it is important to consider the timing of the assessment and consent; it may make sense to time the initial consent carefully to avoid periods when prospective subjects may be experiencing heightened impairments—e.g., an individual with schizophrenia who is refusing medication or acute drug intoxication.

In all cases, respecting a subject's right to withdrawal from a research study is a continuation of the initial consent process, and consideration should be given to ensuring that diminished capacity does not limit this right. HHS and FDA regulations protect the right to discontinue participation in HHS-funded or FDA-regulated research at any time without penalty or loss of benefits to which the subject is otherwise entitled. See 45 CFR 46.116(a)(8) and 21 CFR 50.25(a)(8), respectively.

Responsibilities of Investigators

Principal investigators and other members of the research team bear primary responsibility for protecting research subjects and ensuring that their participation in the research is based on an adequate understanding of the study. Investigators can enhance a subject's understanding of his or her role in the research through ongoing educational efforts.

Research findings now suggest that certain educational approaches can significantly improve understanding among subjects with impaired consent capacity.[19] It is important for investigators to propose methods to screen for consent capacity impairments and to be aware of approaches that are useful in enhancing the subject's understanding of the information needed to give informed consent.

As noted previously, some institutions or IRBs have additional policies for the conduct of research involving individuals with questionable consent capacity. Investigators should be aware of and follow all relevant policies in advance of commencing research.

Membership and Responsibilities of IRBs

Membership

An IRB that regularly reviews research involving vulnerable subjects—such as those with impaired consent capacity—is required by HHS and FDA regulations to consider whether one or more individuals who are knowledgeable about or experienced in working with such subjects should be included in the review of the protocol.[20] Options for ensuring that the IRB is equipped to review studies involving this population of vulnerable subjects might be to involve the following individuals:

- professionals with the appropriate background, knowledge, and experience in working with individuals with impaired consent capacity
- representatives of patient advocacy groups
- experts in the assessment of consent capacity, and/or
- experts on the scientific and ethical issues relevant to studies involving vulnerable populations

[19] See footnotes 22, 23, 24.
[20] See 45 CFR 46.107 and 21 CFR 56.107.

There may be instances when the review of a research study might benefit from external input and consultation. For example, when there are significant questions about the risks and benefits, uncertainties about the study design, or concerns about the protocol, it may be helpful for the IRB to consult with outside experts in the review of research to provide a broader view of the ethical acceptability of the research. Such a consultation process could involve medical/scientific experts, ethics experts, legal experts, patient advocates, and/or representatives from the community of potential subjects to be involved in the research. This consultation would enable the IRB to gather additional information and perspectives in carrying out its review and oversight responsibilities.

Responsibilities

When IRBs review protocols that study conditions that can result in impaired decision-making capacity, they are required to consider whether additional safeguards are needed.[21, 22] Safeguards can increase on a sliding scale according to the IRB's best judgment. By considering proposed studies on a case-by-case basis, protections can be provided that are proportional to the expected severity of consent capacity impairment in prospective subjects, magnitude of experimental risk, anticipated benefits to the subject and/or society, complexity of the study design, and other relevant factors.

As study risks and subject consent incapacity increase, additional IRB scrutiny may be needed. It is important to have provisions for additional safeguards in place prior to involving individuals with impaired consent capacity in research.

Therapeutic Misconception and Conflicting Roles

One of the key ethical challenges in informed consent is to ensure that subjects understand the difference between research and treatment—including the study investigator's focus on producing generalizable knowledge rather than providing clinical care. While this ethical challenge exists across the spectrum of clinical research and is often referred to as the "therapeutic misconception," it can be heightened in research involving subjects with consent capacity impairments. It is, therefore, especially critical in this field for the informed consent process and documents to be very clear about these differences.

The description of the clinical study can be a particular source of confusion, so special attention to the wording of the study purpose and precision about experimental procedures is especially important. Another critical point that needs to be addressed clearly is whether study participation will have any effect on access to clinical care.

[21] When some or all of the subjects—including those with cognitive limitations—are likely to be vulnerable to coercion or undue influence, the IRB must be sure that additional safeguards have been included in the study to protect the rights and welfare of these subjects {45 CFR 46.111 (b) and 21 CFR56.111 (b)}.
[22] See 45 CFR 46.111(b) and 21 CFR 56.111(b).

III. ADDITIONAL SAFEGUARDS

A case-by-case approach involving an assessment of each study proposal's risks and anticipated benefits—as well as subjects' consent capacity—has been used by IRBs to review protocols and guide considerations about the need for additional safeguards. Applying this flexible approach allows for the consideration of several complex factors and a weighing of these factors in relation to a given subject's consent capacity.

Relevant factors include a prospective subject's consent capacity, the study's risks, anticipated direct and indirect benefits, the complexity of the protocol, and the provision of additional safeguards.[23] The case-by-case analysis generally leads to the conclusion that a higher level of consent capacity and provision of additional safeguards would be expected in more complex protocols with greater degrees of risk.[24]

This type of review process, which is based on the framework set forth in Subpart A of the HHS regulations and in FDA regulations on IRBs, is generally a more flexible and comprehensive type of analysis than processes that rely on predetermined categorical criteria, e.g., a risk-based approach modeled after the HHS and FDA regulations governing research involving children.[25]

The additional safeguards described below may be useful to investigators designing and carrying out studies involving subjects with consent capacity impairments and to IRB members as they evaluate research proposals. While these practices could be effective in other areas of clinical research, they are particularly important in studies involving potentially vulnerable subjects. The NIH and others are continuing to support research to validate and refine these techniques.

Consent or Study Monitors

Involving someone independent of the study—e.g., an unaffiliated clinician—to serve as a monitor of the consent process or the entire study may be appropriate for some studies. A monitor can be appointed to be present when investigators invite individuals with impaired consent capacity to participate in a research study. In addition, when reviewing research involving individuals with impaired consent capacity, IRBs can explore the value of an independent monitor. Alternatively, an IRB can decide to observe aspects of the study process itself—such as recruitment, consent capacity assessment, informed consent, and debriefing of research subjects (and/or their family/LAR).

Assessing Capacity To Consent

As discussed in Part II, instruments to assess consent capacity can be useful in deciding whether an individual has sufficient capacity to consent to research. While one universally accepted assessment does not currently exist, several instruments are available to assist in determinations of consent capacity.

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[23] Chen DT, et al. (2002) Enrolling Decisionally Impaired Adults in Clinical Research. *Medical Care*. 40(9) Supplement:V20-V29.

[24] See footnote 6.

[25] 45 CFR part 46, subpart D, and 21 CFR part 50, subpart D, respectively.

Use of Information/Educational Techniques

The way in which information about the study is conveyed to prospective subjects can enhance consent capacity. The following are some techniques that have been shown to be effective:

- Presentation of initial consent: Studies have shown that simplification and repetition of consent information as well as multimedia presentation have improved subject understanding. In addition, oral consent in combination with written consent rather than written consent only has been shown to lead to greater understanding.[26]

- Educational techniques that can be used during consent process to improve understanding: Other techniques of presenting consent information have been shown to improve subject understanding. Designing a step-wise consent process and providing additional information as needed can improve understanding[27] and allow for additional education during the consent process to further enhance comprehension. Interactive questioning during the consent process has been shown to increase post-consent subject understanding; this has the added benefits of highlighting important elements for the subject to focus on—ensuring understanding of earlier material to allow understanding of subsequent information and assessing subject understanding during the process to allow for appropriate explanation throughout the process.[28] Two other techniques that have shown to result in enhanced understanding are additional subject education[29] and repetition of misunderstood information[30].

- Continuous dissemination of information: Communication between members of the research team and subjects and their families throughout the course of the research study is a key to successful research participation. It is important to keep in mind that informed consent is an ongoing process that should continue throughout the course of the study. Such efforts to ensure that subjects remain informed are important, particularly if changes occur in the study, or findings from other studies alter the risks, anticipated benefits, or alternatives to participation. In addition to developing clear, well written consent documents, it is helpful for the research team to encourage subjects and family members to ask questions whenever they are uncertain or confused about study procedures. Study summaries describing relevant phases of the study and ethical safeguards can be prepared to supplement information in the informed consent document. When provided on a regular basis, such materials which may be subject to review and approval by the IRB, can enhance subject understanding.

[26] Eyler LT, Jeste DV. (2006) Enhancing the Informed Consent Process: A Conceptual Overview. *Behav Sci Law*. 24:553-68.
[27] Ibid.
[28] Eyler LT, et al. (2005) A Preliminary Study of Interactive Questioning Methods To Assess and Improve Understanding of Informed Consent Among Patients with Schizophrenia. *Schizophrenia Research*. 75: 193-8.
[29] Lapid MI, et al. (2003) Decisional Capacity of Severely Depressed Patients Requiring Electroconvulsive Therapy. *J ECT*. 19(2):67-72.
[30] Palmer BW, Jeste DV. (2006) Relationship of Individual Cognitive Abilities to Specific Components of Decisional Capacity Among Middle-Aged and Older Patients with Schizophrenia. *Schizophrenia Bulletin*. 32(1):98-106.

Waiting Periods

Prospective subjects with consent capacity impairments may need to take more time to decide whether to participate in the study. Before seeking the subject's formal written consent, it may be helpful to provide information incrementally and to build in a waiting period after the initial screening interview. A two-step informed consent process would facilitate family conferencing and consultation and allow more time to weigh the pros and cons of study participation.

Legally Authorized Representatives and Advance Directives

The HHS and FDA regulations provide for the use of LAR consent as an alternative to a subject's consent.[31,32, 33] State law may define when an LAR may be appointed and who may serve in this capacity on behalf of another. Executing a Durable Power of Attorney (DPA) for health care (which is an authorization that one person gives to another to act on his or her behalf) is one method to identify an LAR. Alternatively, many states have statutes to clarify when family members—and in which hierarchical order—may serve as LARs.

In most jurisdictions, LAR appointment processes are not specific to the research setting, and institutions rely on the laws governing the use of LARs for clinical care. It is important to note that some family members may not necessarily be considered LARs under applicable state law. IRBs may wish to consult with legal counsel when determining who can serve as an LAR for subjects of proposed research.

When LARs are involved, their role should be documented, and—after the elements of consent have been reviewed—their consent should be recorded in the informed consent document in the same manner as if the subject were giving consent directly. In addition to receiving information about the study, it is important for LARs to be informed about the role of an LAR and provided information about the health status of the research subject.

Prospective subjects with impaired consent capacity may still have the capacity to use a DPA to designate an LAR. Under these circumstances, involving an independent expert to assess the LAR's knowledge and understanding and the appropriateness of the selection is an additional measure that could be taken.

LARs who make research decisions on the basis of *substituted judgment* should be guided by their knowledge of the beliefs, views, and preferences of the subject. Basing decisions on a substituted judgment standard is considered preferable from an ethical standpoint because it is consistent with the principles of respect for persons and autonomy which are central to informed consent. In the absence of knowledge of subject values, the *best interest* standard is typically used in making decisions on behalf of the subject.

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[31] 45 CFR 46.116, and 21 CFR 50.20(a), respectively.

[32] A *legally authorized representative* (LAR) is defined in both HHS and FDA regulations as 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 procedure(s) involved in the research (45 CFR 46.102(c) and 21 CFR 50.3(1), respectively).

[33] The Office for Human Research Protections' Frequently Asked Questions on Informed Consent includes questions and answers on LARs at http://www.hhs.gov/ohrp/informconsfaq.html#q19.

While there are some data from studies suggesting that LARs who make clinical care decisions are not always able to predict patient treatment preferences,[34] in the research setting the substituted-judgment approach is still favored over the best-interest standard. In situations where LARs make consent decisions on behalf of prospective subjects, the autonomy of the subjects is further respected by seeking their assent for participation and by honoring their objection to participation or, subsequently, a desire to withdraw.

Given that surrogates, even when they are very close family members, may have difficulty predicting patient treatment preferences,[35] it may make sense to include an evidence standard for substituted judgment in the research context. For example, as the risk-to-benefit profile becomes less favorable to the patient (i.e., less benefit and more risk), there should be more evidence that the patient's preferences are being predicted correctly.

When the risks are low, or the research offers the prospect of direct benefit to the patient, study enrollment would be acceptable based on an LAR's permission unless there is good reason to think that the patient would have opposed the decision. For riskier research that offers no prospect of direct benefit to the patient, there should be increasing positive evidence that participation is what the subject would wish. When this level of evidence is not met, the LAR should use the best-interest standard. One way these higher evidence standards could be met is if individuals discussed and documented their preferences regarding research participation while they are still able to do so—such as through a living will or other advance directive.

Where state or other applicable law permits, an advance directive—which often specifies preferred clinical treatment—can be used in the research setting to identify the types of research in which an individual would or would not be willing to participate or to provide the LAR with explicit information about an individual's wishes regarding research participation.[36]

IV. CONCLUSION

In clinical research, varying degrees of research risk and consent capacity call for a careful review of research procedures and safeguards. Additional protections may be highly advisable in certain circumstances. It is essential for researchers and IRBs to strive for a balance that (1) maximizes anticipated benefits and scientific opportunities, (2) recognizes and extends individual autonomy, and (3) minimizes risks associated with scientific inquiry.

[34] Wendler D, Prasad K. (2001) Core Safeguards for Clinical Research with Adults Who Are Unable to Consent. *Arch Intern Med*. 135:514-523.
[35] Id.
[36] Policy and Communications Bulletin, NIH Clinical Center, Medical Administrative Series 92-7: Advance Directives.