Secretary's Advisory Committee on Human Research Protections (SACHRP)
Recommendations from the Subcommittee for the Inclusion of Individuals with Impaired Decision Making in Research (SIIIDR)

The following SIIIDR recommendations and preamble were approved by SACHRP at its March 27th, 2008, and March 4th, 2009 meetings:

Preamble to SIIIDR Recommendations

The Secretary's Advisory Committee on Human Research Protections (SACHRP) convened the Subcommittee on Inclusion of Individuals with Impaired Decision-making in Research (SIIIDR "*…to develop recommendations for consideration by SACHRP about whether guidance and/or additional regulations are needed for research involving individuals with impaired decision-making capacity*."

Impaired decision-making capacity or impaired consent capacity,[1] occurs in a wide range of disorders and conditions that affect large numbers of Americans, causing suffering, morbidity, and mortality on a large scale. For example, 5 million Americans are currently diagnosed with Alzheimer's disease, nearly 800,000 strokes occur in the U.S. each year, and 50,000 patients are admitted to intensive care units each day. As the U.S. population ages, these three conditions associated with impaired consent capacity will be even more prevalent. Traumatic brain injury, developmental disorders, intellectual disabilities, and serious mental illness are other common and devastating problems in which impaired consent capacity occurs. Current approaches to early detection, diagnosis, and treatment are inadequate, and there is a pressing need to advance therapeutics and understand basic mechanisms of disease and disease progression. Progress requires the inclusion of individuals with impaired consent capacity in research. A viable human protections oversight process must be equipped to meet the demands of research with the most impaired populations and must apply the highest ethical standards to research and research oversight.

It is noteworthy that despite over thirty years of federal oversight of human subject research in the United States, an understanding that these individuals are uniquely susceptible to exploitation and research related harm, and several high profile attempts to regulate in this area, research regulations and related guidance remain all but silent with regard to individuals who have impaired consent capacity. Without question, the field of human subject protections as a whole is better informed and has become increasingly professionalized over the last decade. However, is it equipped to oversee vitally important research involving some of the most impaired and vulnerable research participants? The core of the problem is the fact that the protections provided by free and informed consent are not available to individuals with impaired decision-making capacity, and consent provided by the LAR may not be ethically equivalent[2].

[1] Regarding terminology: We defined the term *consent capacity* in our Recommendation 1. We refer to individuals as having impaired consent capacity and at times as lacking consent capacity. The use of these and other terms, such as impaired decision-making, is not intended to describe different phenomena. The term research *participant* is used instead of the regulatory *subject* throughout the document, except where referring to regulatory language or specific terms of art. Research participant conveys a more equal and active role and was strongly favored by patient advocates.

[2] Further, approaches to surrogate-based consent reflected in state law often describe hierarchies of decision-makers, reflecting an understanding that some individuals may be better able to make decisions on behalf of the impaired individual.

The Common Rule requires that when individuals vulnerable to coercion or undue influence take part in research, "additional safeguards are included." Questions about the nature of required safeguard and to whom they should be applied are left unanswered by the Common Rule and related guidance. Few standards have emerged with regard to the consent process in general, and fewer still with regard to standards of capacity to consent, and the use of surrogate-based consent. Whether and in what fashion thresholds defining acceptable risk should be adapted for participants who are unable to consent for themselves has not been formally or uniformly addressed. At best, the field is characterized by a patchwork of IRB policies and research practices. Without a framework of regulations or guidance within which to conduct IRB review, it is evident that individuals may be unjustifiably called upon to take part in research, important ethical consideration may be missed, and valuable research may be hindered.

Another substantial shortcoming in the current federal oversight structure derives from the fact that federal rules point to state and local law to define who may provide consent for research on behalf of individuals with impaired consent capacity. Very few states specifically define legally authorized representatives (LARs) for research, and most state's laws are silent on the topic. Virtually no state laws address the many ethical issues that arise when LARs are involved in research decision-making, leaving it to IRBs and institutions to invent solutions. This shortcoming creates a legal and regulatory void and place investigators, institutions, and IRBs at risk for regulatory and/or state law violations. The resulting inconsistency and incompatibility among local rules does not serve the interest of contemporary scientific inquiry—inquiry that is commonly multi-institutional and multi-state. The field is left on its own to interpret "legally authorized representative" or to define LARs' responsibilities. This does not serve the interests of research participants or of science.

In fulfilling its charge, SIIIDR examined current practice and reviewed relevant empirical research on impaired decision-making, consent, and surrogate-based consent. Experts involved in the conduct and oversight of research with affected populations and those who advocate on behalf of such populations shared valuable data and perspectives with us at subcommittee and SACHRP meetings. SIIIDR studied the public comments provided to OHRP and the FDA pursuant to a Request for Information published in the Federal Register in September, 2007. We conducted a town hall meeting and workshops at a major national conference. Our membership itself reflected expertise in neurology, psychiatry, critical care medicine, research ethics, patient advocacy, law, and human subject protection. We encouraged and benefited from the active involvement of the ex-officio members of our subcommittee who represent the federal agencies that are signatory to the Common Rule. OHRP leadership and DHHS counsel educated SIIIDR on the regulatory and legal landscape and provided invaluable assistance. SACHRP provided ongoing input as we crafted and shared our approach and preliminary recommendations. Finally, SIIIDR carefully examined the body of work produced by predecessor committees; we aimed to learn from this history of failed efforts to regulate research involving individuals with impaired decision-making capacity.

SIIIDR's response to the question at the core of our charge is in the affirmative: new guidance and/or additional regulations are necessary to provide appropriate research protections for individuals who have impaired consent capacity. To this end, we have crafted a series of ten interdependent recommendations describing our priorities and best advice.

Recommendations 1 through 8 call for new guidance at this time rather than regulation. There are several reasons for this. First, guidance can be developed, disseminated, and influence practice in the field on a relatively short time frame. Second, guidance can promote the introduction of necessary safeguards with great flexibility, deferring when necessary to local

(IRB and institutional) considerations and expertise. In a clinical landscape as broad and varied as research with individuals who lack consent capacity, a less flexible approach might have the unwanted effect of limiting ethically sound and scientifically appropriate research. Finally, guidance can provide a potentially rich format within which to convey ethical priorities and capture clinical subtleties. By educating the field, guidance can drive good institutional policy and IRB practice. Guidance alone is not sufficient to address problems related to the regulation's reliance on local definitions of who may serve as a legally authorized representative. Therefore, recommendations 9 and 10 present options for a federal regulatory solution and consideration of model state legislation, respectively.

Current regulatory guidance is often regarded by the field as insufficiently educational, overly-fragmented, and difficult to access. It is SIIIDR's intent that guidance on this topic be developed and disseminated as a single, comprehensive resource document or pamphlet. The quality of IRB review and the conduct of research with individuals with impaired consent capacity can be improved with the development of clear, ethically and clinically informed and user-friendly guidance.

Throughout its work, SIIIDR acknowledged the extent to which the academic community feels over-regulated: a clear and consistent theme in responses to the OHRP/FDA Request for Information. We attempted to avoid being overly proscriptive when by allowing greater latitude for investigators, IRBs and institutions we could better serve the interests of research protections. Similarly, we sought to recognize the strength of our current, re-invigorated, better resourced, and better trained IRBs.

Individuals who have impaired consent capacity are uniquely vulnerable to exploitation and susceptible to harm, and SIIIDR's primary obligation was to enhance protections for those who are unable to protect themselves through the process of consent. This is an obligation we share with the community of researchers and professionals involved in research oversight. We believe our recommendations will move the field in the necessary direction.

Recommendation 1. Guidance should adopt the term "consent capacity" (following the working document developed by NIH) to denote the specific abilities necessary for a prospective research participant to understand and use information relevant to consent.

Recommendation 2. Guidance should provide information for institutions, IRBs and investigators on the nature of consent capacity and its impairment as it relates to research participation.

Specifically:

a**.** An individual's consent capacity is not simply present or absent; capacity is best understood as occurring along a continuum.

b. Impaired consent capacity occurs in a wide range of conditions and disease states. To respect the rights and welfare of all research participants, guidance should encourage the development of policies that acknowledge the many manifestations of impaired consent capacity and are not limited to consideration of specific disorders.

c. Consent capacity is task-specific and depends on the nature and complexity of the relevant decision-making process. Therefore, a judgment regarding an individual's capacity to consent may not be the same for all research studies.

d**.** In many individuals, impairment in capacity to consent is not a static phenomenon. During the course of a research study, a research participant's consent capacity may improve, fluctuate over time, or worsen with changes in the individual's underlying condition. Guidance should encourage policies on consent, the assessment of capacity, and the use of surrogate-based consent procedures to reflect this fact.

Recommendation 3. Guidance should address the implementation of appropriate safeguards related to the identification of individuals who may have impaired consent capacity. Such safeguards can be applied prior to participant enrollment, and as appropriate, throughout the course of research participation.

a. For all studies, investigators and research staff who obtain consent should consider each participant's capacity to consent to the research. In studies where the recruitment of individuals with impaired consent capacity is not anticipated, the judgment that prospective participants have the capacity to consent to the research can ordinarily be made informally during routine interactions with the participant during the consent process.

b. The method used to assess capacity, and when appropriate, the documentation of this assessment, should be tailored to the study population, the level of study risk, and the likelihood of the involvement of participants with impaired consent capacity.

(i) When it is anticipated that the research will include individuals who have impaired consent capacity, researchers should assess prospective participants' consent capacity and determine whether it is adequate to permit informed consent. This determination should be documented, when appropriate.

(ii) Formal methods such as questionnaires, structured instruments, or independent evaluators can be used to support or supplement the assessment of consent capacity by the researcher.

(iii) The likelihood of impaired consent capacity and the manifestations of that impairment will vary depending on the proposed study population and the setting in which the research is conducted. The choice of the method used to assess capacity must be informed by these clinical considerations.

(iv) The level of capacity required for consent will depend on the anticipated benefits from participation in the study, the degree to which the study protocol departs from ordinary practice or clinical care, and the magnitude of foreseeable risks associated with participation. These factors should be carefully considered in policy and practice.

(v) Investigators and research staff responsible for the consent process and consent capacity determinations should be appropriately qualified and trained.

c. Specific enhancements to the consent form and process may serve to improve a prospective participant's understanding and enable some individuals who otherwise lack consent capacity to make capable decisions. (Note: guidance may benefit from examples.) Consent enhancements should be adapted to the needs of the specific study and study population.

d. In making the determination as to methods to be used to ascertain consent capacity, it is important to note that more intensive approaches involve burdens for participants and researchers alike. Therefore, these should be reserved for those situations in which impairment is more likely to be present, anticipated benefits are fewer, and foreseeable risks are greater.

e. When changes in participants' consent capacity are anticipated or discovered during the course of a study, requirements for redisclosure of relevant information, reconsent, and reassessment of consent capacity should be considered. The frequency of any necessary reconsent procedures should be appropriate to the circumstances.

Recommendation 4. The inclusion of individuals who lack consent capacity presents unique ethical and procedural challenges to the IRB and to investigators. Consent to research by the legally authorized representative (LAR) stands in for the consent by the prospective research participant, but it is not fully equivalent to consent by the participant him or herself. Therefore, when the participant is unable to protect his or her interests through the process of consent, additional protections or safeguards at the level of IRB review are required. The following is intended to provide guidance to IRBs, institutions and investigators on additional considerations related to the approval of research under 45CFR46.111 when individuals who lack consent capacity are included in research.

Note: In some states and localities, applicable law defining the LAR further delineates the roles and responsibilities of the LAR and/or otherwise regulates IRB activities with regard to the inclusion of individuals who lack consent capacity. Institutions, IRBs, and investigators should familiarize themselves with applicable law. No recommendations presented are intended to preempt state or local authority.

a. **IRB Review Procedures:** IRBs should review and provide approval for the inclusion of individuals who lack consent capacity and for consent procedures to be followed by the LAR, as specified below:

(i) In determining level of review, IRBs should be especially mindful of any unique circumstances and susceptibilities of the proposed research participants. The serious medical, neurological, and psychiatric illnesses that give rise to impaired consent capacity may place participants at increased risk of harm and discomfort from research participation. Further, for participants who are unable to express discomfort, describe untoward effects or otherwise communicate their wishes once enrolled, research participation may involve added risk.

(ii) An IRB may determine that research that includes individuals who lack consent capacity may fulfill criteria for minimal risk and/or expedited review; the fact that a study includes individuals who lack consent capacity should not, in and of itself, mean that review by the convened IRB is required.

(iii) However, the expedited review of research involving such participants should be conducted by reviewers with appropriate expertise, as described below in point b. Membership and Reviewer Qualifications, and in accordance with well-defined, written policies and procedures for expedited review. These policies should describe requirements for consent by the LAR, and provide examples of additional safeguards required in the recruitment, identification, and approval of research with such individuals.

(iv) Minimal risk research that fulfills the requirement for waiver of informed consent[3] but will include individuals with impaired consent capacity may be reviewed by expedited review procedures without the additional requirements outlined in item a(iii), above.

b. **IRB Membership and Reviewer Qualifications:** 45 CFR46 requires that "**the IRB shall be sufficiently qualified** through the experience and expertise of its members." When an IRB reviews research involving research participants who lack consent capacity and consent will be provided by an LAR, convened review should involve at least one member or consultant knowledgeable about and experienced in working with the population. Information, experience, and expertise may be available to the IRB through its membership, consultants, and, as appropriate, requests for this information from the investigator. IRBs should give special consideration, as appropriate, to the involvement of the following types of individuals in the review process:

(i) Patients, former patients, patient advocates or family members or others who can represent the views and perspectives of the research participants;

(ii) Individuals with specific professional expertise related to the nature and consequences of impaired consent capacity in the study population;

(iii) Other individuals who can provide information relevant to the circumstances and context in which the participant and LAR will be recruited (e.g. the long term care facility, critical care unit, or mental health center);

[3] To fulfill criteria for waiver of consent, an IRB must demonstrate that "the research could not practicably be carried out without the waiver or alteration" (116(d)(3)). The fact that prospective participants are unable to provide consent, or that a legally authorized representative is not readily available, or that applicable law does not define an LAR for research purposes should not, in and of itself, serve to satisfy this criterion for lack of practicability. When a waiver of consent is not justifiable under 45CFR46.116(d) for research involving those with capacity to consent, a waiver would ordinarily not be applicable to research with individuals who lack consent capacity.

(iv) Individuals with expertise regarding applicable legal and regulatory requirements for consent to research by an LAR.

c. **Subject Selection: the Decision to Include Individuals who Lack Consent Capacity:** The decision to enroll individuals who lack consent capacity raises unique ethical challenges. Such individuals and their caregivers commonly experience substantial burdens related to the individual's illness and life circumstances. The individual's ability to consent to research is compromised or absent, and consent, when provided by the LAR, typically only approximates the prospective particpant's wishes or best interests. The Common Rule underscores the importance of equitable selection of subjects, recognizing the long history of incompetent adults in institutional settings who were exploited in research for reasons of convenience rather than either benefit to the population recruited or scientific necessity. The protection of prospective research participants who are unable to protect themselves through the consent process demands careful attention to both the rights and interests of the individual and the need to advance science and therapeutics for the most seriously ill. IRBs and investigators should carefully consider whether the inclusion of individuals who lack consent capacity in research is ethically appropriate and scientifically necessary. When research proposes to include individuals who lack consent capacity, each of the following should be considered:

(i) Investigators and IRBs should carefully consider the extent to which the research aims to improve the understanding, diagnosis, prevention or treatment of the disorders or conditions that are the cause of the incapacity.[4]
(ii) The study of related conditions, phenomena, or circumstances that commonly or uniquely affect the research participants may contribute in important ways to the current or future welfare of the study population[5] and therefore may also serve to justify their inclusion in research.
(iii) Review should consider the extent to which the scientific questions posed by the research are answerable in those who have capacity to consent. In general, "less burdened" groups should be studied first.
(iv) Factors such as participant availability, ease of recruitment or study cost should never alone justify the inclusion of individuals who lack consent capacity.
(v) The inclusion of individuals who lack capacity may be appropriate in research that offers therapeutic or other benefits to the individual participant when standard approaches are ineffective, unproven, or unsatisfactory.[6]

[4] It is important to note that multiple disorders or conditions may simultaneously contribute to impairment in consent capacity in particular participants or settings.

[5] Studies of problems that commonly complicate treatment in the critical care setting, for example, or are unique to this setting and cannot be studied in those with capacity may be appropriate. Similarly, studies of cognitive function and functional impairment in patients with developmental disabilities or post-traumatic brain injury may directly or indirectly contribute to the understanding of these conditions. Studies of family, social, educational or institutional processes involving individuals with impaired consent capacity may benefit these populations. Investigators should offer a scientific rationale to explain why such research questions could not be answered, or addressed first, in those with capacity, and IRBs should explicitly consider the adequacy of the rationale to justify research with this population.

[6] A clinical trial or other medical or socio-behavioral intervention may provide treatment for a disorder or benefits to participants that are unrelated to the causes or circumstances of impaired consent capacity. When standard approaches are ineffective, unproven or otherwise unsatisfactory to address the problem in

(vi) When individuals who lack consent capacity will be incidentally included in research because they are members of a larger group of prospective research participants, such as a cohort of clinic patients or a sample of the general population, the IRB should give careful consideration to the anticipated risks and potential benefits of the research as they might specifically affect those who lack consent capacity. Inclusion of those who lack consent capacity may be appropriate if the risk/benefit ratio is determined to be acceptable for these participants.

Recommendation 5. The approval of research under Subpart A requires an IRB to determine "that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." This regulatory language gives IRBs wide latitude in deciding when research offers a reasonable balance of risks to benefits, including circumstances when the benefits are in the form of scientific knowledge alone. Currently, no formal guidance addresses how IRBs are to interpret this criterion either for prospective research participants who have the capacity to consent, or those who do not. When a prospective participant has capacity, the process of informed consent respects the individual's autonomy and affords him or her additional protection.

Individuals who lack consent capacity, in contrast, are limited in expressing or unable to express their wishes. Consent provided on their behalf by a legally authorized representative (LAR) will only, and to a varying degree, approximate consent by the subject and may not provide equivalent protections. The criterion of reasonable risk is one that must reflect the non-equivalence of consent by the LAR, more so when the risks of research are greater and for research which does not offer a significant prospect of direct benefit.

When reviewing research with individuals with impaired consent capacity and with those who lack consent capacity, the IRB should consider the following:

a. The determination that the relationship of risks to benefits is reasonable requires a careful analysis by the IRB of several continuous variables, including the degree to which the research: introduces risk, presents a risk/benefit profile which departs from standard care, offers a prospect of benefit available only in the research, will yield knowledge that will benefit others, and the extent to which informed consent by an LAR can be considered equivalent to that of the research participants.
b. In weighing risks and benefits, IRBs and investigators should be especially mindful of the nature of the decision that the LAR will be asked to make. When a research participant is not providing informed consent, an important consideration relates to the degree to which the participant will be exposed to risks when the research provides him or her with no direct benefit but could serve to benefit others.
c. IRBs and investigators should recognize that different categories of LARs will stand in different relationships to the research participant and may not equally well fulfill the ethical requirements of informed consent.
d. Therefore, compared to research with individuals with consent capacity, it may be appropriate for an IRB to establish a lower threshold for allowable risk and require a more favorable risk/benefit ratio as a requirement for approval. This will serve to

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general or for individual participants, research that provides access to such benefits should be acceptable. A trial of an investigational anti-convulsant, for example, may reasonably include patients who lack capacity who have failed to respond to, or been unable to tolerate, existing therapies.

provide necessary additional protections.[7] It may be appropriate for an IRB to employ its standard risk-benefit considerations for studies that offer little or no prospect of direct benefit when the assessed risk of harm, discomfort or inconvenience is low.

e. IRBs should undertake a careful analysis of the anticipated direct benefits of research participation. The following should be considered:

   (i) Participation in research can serve to benefit the participant by offering assessment, diagnosis, treatment, or other (e.g., psychological, behavioral, interpersonal, or social) interventions or enhancements.
   (ii) In terms of the prospect of direct benefit, studies will vary from one another along a number of dimensions. These include the likelihood of direct personal benefit, the value of these benefits in relation to the same or similar benefits that exist outside the research,[8] and the extent to which subgroups of participants are not expected to benefit.[9]
   (iii) Financial compensation is not ordinarily considered a benefit of participation by IRBs in their risk/benefit analysis.

f. When the research involves risk at the higher end of the spectrum, IRB review should consider who will be consenting on behalf of the participants who lack consent capacity. The relationship of the prospective participant to the LAR and the responsibilities of the LAR will vary considerably based on the category of LAR, the individuals involved, and the research decision at hand. LARs will differ in whether they otherwise have been entrusted to make decisions on behalf of the prospective participants, in the extent to which they are familiar with the their wishes and attitudes, and in their ability to make a decision in the best interest of the participants. Specifically,

[7] 45CFR46.111(2) recognizes that some research is anticipated to provide little or no direct benefit to research participants but is anticipated to yield important scientific knowledge. It respects individual autonomy in allowing, within limits, for participants to assume the risks of research participation for altruistic or other reasons, even when the research offers no, or little, personal benefit. The limits (imposed by the IRB) relate to the requirement that IRBs weigh anticipated risks to research participants against anticipated benefits to society and determine what is "reasonable." In effect, in the interest of protecting research participants from research risk, the IRB decides when the relation of risk to scientific benefit is such that even an individual who is willing to participate should not be permitted to do so. When an individual's autonomy is compromised, the IRB will ordinarily recognize a greater need to protect the individual and establish a lower threshold of reasonable risk. There are, of course, circumstances in which it may not be necessary or appropriate for an IRB to alter its risk benefit analysis, for example, when all prospective participants have indicated by way of advance directives their willingness to participate in research of the sort under consideration, or when they suffer from otherwise untreatable and serious conditions.

[8] For example, a complex set of considerations arise in treatment research when standard approaches to care or commonly employed therapies are not "of proven efficacy." Enrollment in such research may therefore mean that the participant is forgoing routine—albeit untested—care in the interest of science. Other problems are posed by studies involving therapies that offer at best transient improvement for chronic conditions. Finally, and perhaps most complex, is when effective treatments exist but are not provided in the community or are not accessible for reasons of cost.

[9] A study of an intervention may offer unique benefit to some participants, but little or less value to participants who have previously failed the same or similar interventions, have not availed themselves of existing standard interventions, or are tolerating existing approaches. An IRB may determine that it is appropriate to approve the study for some participants, but not others, thereby optimizing benefit and reducing risk.

(i) The LAR for an incapable adult may have little or no experience in the required role and will have varying degrees of kinship or familiarity with prospective participants or their wishes with regard to research participation.
(ii) Some LARs may be appointed in advance by individuals to consent to research on their behalf; the subjects may have provided varying degrees of authority for the LAR, and enumerated their wishes, interests and instructions with different degrees of specificity.
(iii) LARs appointed through legally defined hierarchies for health decision-making or by a health care proxy or equivalent, are permitted to make decisions related to healthcare and, according to OHRP interpretation and barring state law to the contrary, by extension, to certain categories of research.
(iv) In the context of an individual's acute illness or chronic disability, next-of-kin or other caregivers may themselves evidence compromised ability to make a research decision.
(v) Some prospective research participants, for example, those with severe developmental disabilities, may never have been able to express wishes or attitudes with regard to research and altruistic behavior in general.
(vi) In some instances, an institution or government body may be authorized by law to provide consent for an incapable adult.

g. A careful consideration of the LAR's role in the consent process becomes increasingly important for research assessed as falling at the upper end of a continuum of risk and at the lower end of the direct benefit spectrum. For example:

(i) For certain types of research or research risk, an IRB may specify that only certain categories of surrogates may provide consent,[10] for example, those specified by advanced directives. In other cases, approval may require that consent be provided by LARs with closer kinship, those more familiar with the participants, and those who have already been in a care-giving relationship to them.
(ii) An IRB may require investigators and/or independent monitors to assess the ability of LARs to perform necessary duties.
(iii) An IRB may require that LARs be educated as to their roles and responsibilities during consent and, where applicable, throughout the course of the study.
(iv) An IRB may choose to limit or prohibit consent for certain categories of research by government or institutional authorities, require independent review, or put in place other safeguards.

h. In addition to the guidelines for subject selection specified previously, IRBs should develop written policies and procedures that define and limit research risk:

(i) Risk assessments by the IRB and investigator should carefully address the unique susceptibilities of the research participant to risk, the environment of the research and its impact on risk, and procedures to minimize risk.

[10] For example, if allowable under local law, patients with mild cognitive impairment recruited for a longitudinal study may appoint individuals to make decisions for them—assuming they retain the capacity to do so—if or when they lose consent capacity. They may also specify their interest in taking part in a research project or category of research. An IRB may determine that research that is otherwise not approvable (higher risk research with no direct benefit) is approvable when such LARs are available and are so informed.

(ii) IRBs will ordinarily establish a lower threshold for acceptable risk in studies in which consent is provided by an LAR than in studies in which consent is provided by the participant him or herself. Standards for upper limits of allowable risk should be developed and applied. IRBs developing these standards should consider the following:
    (a) In general, when the research offers little or no prospect of direct benefit, the probability and magnitude of harm or discomfort anticipated in the research (including, but not limited to, harm to physical, psychological, social or economic well-being and harms to dignity) should involve no more than a minor increase over minimal risk.
    (b) In exceptional circumstances, an IRB may consider the approval of research which offers little or no prospect of direct benefit and in which the risk of harm or discomfort anticipated in the research is moderate in terms of probability and magnitude.11 In such cases, the research must include safeguards appropriate to this degree of risk. Furthermore, the research must be of vital importance in the understanding, prevention or alleviation of a serious problem affecting the health or welfare of the study population.

Recommendation 6. Guidance to institutions, IRBs, and investigators should emphasize the value of self-determination for the research participant, even when consent capacity is impaired. While some participants, such as those with profound cognitive impairment, will not be able contribute to the consent decision, others may be able to remain actively involved in the decision to enroll and remain enrolled in the research, appoint a legally authorized representative (LAR), or define the limits of research participation. Individuals with impaired consent capacity should be included in the process of consent to the extent possible and consistent with their desires and abilities.

The IRB should consider the following during the process of review and approval:

a. When consent capacity is impaired, efforts to foster a meaningful dialogue about research participation during the consent process will often require special consideration of the time spent and methods used.
b. Specific modifications to the form and process of consent may serve to accommodate some individuals with impaired consent capacity and enable them to consent on their own behalf.
c. Common approaches, such as engaging individuals trusted by the prospective research participant during the consent process, and allocating additional time for decision-making, may be of special value.
d. When impairments in consent capacity may be amenable to intervention which may improve or enhance decision-making, such efforts should be undertaken.

[11] **It is SIIIDR's consensus that vitally important but ethically acceptable research would be prohibited by adopting "minor increase over minimal risk" as an upper limit of risk. To accommodate the variability in populations and research at issue, greater flexibility is necessary. The committee therefore recommends a "soft cap" reflected by our use of the term "moderate." This would allow research that introduces more than a minor increment above minimal risk when an IRB determines that appropriate safeguards are in place and the importance of the research justifies its approval. The subcommittee is not necessarily advocating the use of the term "moderate" in guidance.**

e. Except in circumstances of the most severe impairment, individuals should be informed that their capacity to consent has been judged to be impaired and that consent for research by an LAR is being considered.
f. In some cases, a prospective research participant who lacks consent capacity may be able to be involved in the decision to appoint an LAR or to express opinions with regard to the nature or extent of research participation; this involvement should be encouraged, when appropriate.
g. When consent will be provided by an LAR, the assent of the research participant should be sought at the outset and, as appropriate, throughout the course of research involvement, unless the participant is incapable of providing assent. Further:

    (i) As ability to express choice regarding participation will vary considerably depending on the study population, whether to require assent, and the requirements for assent, should be carefully considered by the IRB during review and approval.
    (ii) A definition of what constitutes "dissent" or unwillingness to take part may be an important consideration during IRB review, especially when prospective participants will have limited ability to communicate. For example, non-verbal communications or actions that indicate an unwillingness to take part in a research procedure should be considered a failure to assent or as a dissent to participate in that intervention.

Recommendation 7. While applicable law will define those who may serve as a legally authorized representative (LAR) for an individual who lacks consent capacity, guidance should address IRB and investigator responsibilities related to the selection and involvement of the LAR. Further, guidance should underscore the fact that the role of the LAR will in most circumstances extend beyond consent to the research participant's enrollment (e.g., to include on-going monitoring of the individual's participation). Therefore, guidance should serve to define the roles of the LAR in initial and ongoing research decision-making. Safeguards should reflect the unique nature of the task the LAR is being called upon to perform and should be tailored to study risk and benefit.

Specifically,

a. The process by which LARs will be identified and selected should be reviewed and approved by the IRB:

    (i) In some circumstances, it may be necessary for the investigator to assess the ability and willingness of the LAR to fulfill the required duties.
    (ii) IRBs and investigators should be cognizant of the potential for financial or other conflicts of interest on the part of LARs that may compromise their objectivity.
    (iii) Similarly, study compensation and other financial incentives may have unwanted effects on the objectivity of LAR decision-making and these potential effects should be carefully considered.

b. The expectations, obligations and authority of LARs should be reviewed by the IRB and communicated to the LARs by the investigator.

    (i) Where appropriate, the IRB may require an information sheet or other written material to assist LARs in understanding their roles.

(ii) LARs may benefit from guidance as to the basis (or standards) upon which their consent decisions are to be made.

c. In many studies, the role of LARs will extend beyond providing consent for study enrollment and may include observing the assent of the research participant, monitoring participant well-being, and providing re-consent.

(i) LARs should receive information about the research participant's status and well-being during the course of research participation. Investigator responsibilities in this regard should be defined.
(ii) During the course of a study, investigators should be required to provide important new information about study risks, benefits, and alternatives to LARs, as these may bear on the consent decision.
(iii) IRBs should consider when formal re-consent by LARs in a longitudinal study is a necessary safeguard.
(iv) In some instances IRBs may specify individuals other than LARs to perform monitoring or other research participant advocacy functions.

Recommendation 8. A legally authorized representative is defined at 45CFR 46.102 (c) 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 research." Guidance should provide additional information regarding the current HHS interpretation of "applicable law."

Specifically:

a. Laws defining who may provide consent to research for an individual who lacks consent capacity take many forms and vary widely among the states. Guidance should describe, with examples, those categories of laws upon which an institution or IRB may rely to determine who may serve as a legally authorized representative.
b. In states with laws or regulations that address consent to treatment but do not specifically consider consent to research, current OHRP interpretation permits consent to research by individuals authorized under laws that allow consent to the "procedures involved in the research." This interpretation should be further clarified with reference to specific examples of research that would or would not satisfy this interpretation.
c. Current OHRP interpretation is that, in the absence of applicable law, community or other standards (e.g. institutional policies, standards of care) which define hierarchies or individuals who may provide consent on behalf of someone who is unable to consent do not constitute applicable law and the individuals named are not considered legally authorized representatives. Effort should be made through guidance to insure that this interpretation is clearly disseminated to the research community.

Recommendation 9. The Subcommittee on the Inclusion of Individuals with Impaired Decision-making in Research (SIIIDR) recommends that HHS develop new regulations related to the inclusion of adults who lack consent capacity. This subpart will define a hierarchy of individuals who may provide consent on behalf of individuals who lack consent capacity when a legally authorized representative (LAR) for research is not defined in state or local law.

SIIIDR makes the following recommendations for consideration for inclusion in these regulations:

a. When an IRB approves the conduct of research under Subpart A and determines that it is appropriate for consent to research to be obtained from the LAR of adults who lack consent capacity:

    (i) Where applicable law exists to determine who is authorized to serve as an LAR to consent to an individual's participation in research, consent may only be obtained from an LAR in accordance with this law.
    (ii) In the absence of applicable law determining who is authorized to serve as an LAR to consent to a individual's participation in research, one of the persons listed below, in the following descending order of priority, shall be considered the prospective participant's LAR and may consent to participation on his or her behalf:

        (a) a person designated by the individual, while retaining the decisional capacity to do so, to make decisions for him/her regarding participation in research;
        (b) a person designated by the individual, while retaining the decisional capacity to do so, to make decisions for him/her regarding non-research health care decisions;
        (c) the individual's legal guardian with authority to make health care decisions for him or her;
        (d) the spouse, or if recognized by applicable law, the civil union partner or domestic partner;
        (e) an adult son or daughter;
        (f) a parent;
        (g) an adult brother or sister;
        (h) an adult who has exhibited special care and concern for the prospective research participant.

Recommendation 10. The Department of Health and Human Services should explore opportunities to promote the development and adoption by the states of specific and uniform legislation to enable consent by third parties for research activities involving individuals who lack consent capacity, and to ensure protection of human research participants in those circumstances.