

Legally Authorized Representatives in Clinical Trials

By Judy Katzen

The sickest patients need the best medical care, which might involve participation in a clinical study. By participating in clinical studies, they can also help improve the quality of care for future patients. However, these patients — who might be found in emergency rooms, critical care units, nursing homes, and other facilities — might not have the ability to give informed consent for themselves. In such cases, a "legally authorized representative" (LAR) might be able to give informed consent (or "permission") on their behalf. (This article does not address pediatric assent and parental permission, nor consent waivers or exceptions, e.g., in emergency situations. (See 21 CFR 50.23-24.)

The LAR's "right" to consent is an extension of the subject's right. Using "substituted judgment" based on "the best knowledge of the LAR," the LAR makes decisions as the subject would. When nothing is known about the subject's wishes (e.g., when the cognitive impairment has always existed), the LAR, usually a court-appointed guardian, acts in the subject's "best interests" to determine whether or not to give consent to participate in a clinical trial.

Obtaining informed consent from an LAR is just like obtaining it from the study subject, with the following additional steps:

- Modify the informed consent form to allow consent by LARs.
- Obtain institutional review board (IRB) approval for the use of LARs in the study by explaining the need for LARs and demonstrating safeguards to protect potential subjects.
- Determine that potential subjects do not have the decision-making capacity to give informed consent.

Modify the Informed Consent Form

If LAR consent is to be acceptable in a study, the informed consent form (ICF) must provide a place on the signature page for the LAR to sign. The IRB may also require a statement in the ICF to the effect that consent may be given by an LAR or, depending on the study, that consent by the LAR may be given while the subject is decisionally impaired, but upon change in that status, consent to continue in the study will be sought from the subject.

Obtain IRB Approval

Under 21 CFR 50, investigators are responsible for ensuring that informed consent is obtained in compliance with the regulations:

...no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. (CFR 50.20)

IRBs have broad discretion in setting requirements for ICFs, including whether a specific study allows for LAR consent, based on the following regulations:

An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations. (21 CFR 56.109(a))

IRB approval means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements. (21 CFR 56.102(m))

When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects. (21 CFR 56.111(b))

IRBs have approved the use of LARs for subjects with a broad range of chronic and acute psychological and neurological impairments. In critical care and similar settings, narcotics and sedatives can render potential subjects unable to provide informed consent during a narrow enrollment window.

Determine Decision-Making Capacity

Before a LAR can be identified, first determine whether a potential subject has the decision-making capacity to give voluntary informed consent. The answer may be far from obvious if the person is suffering from bipolar disease or moderate dementia. The National Institutes of Health (NIH) states, "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."^{1, 2} Such assessments must balance the ethical principles of autonomy and benevolence.

Identify the LAR

Provided state law allows for LARs for clinical research, the person represented can designate his or her LAR in advance of becoming decisionally impaired. However, if a decisionally impaired person has not already designated an LAR and the state has a statutory hierarchy of people who can serve as LAR, the site can identify the LAR for the person according to the hierarchy. If the first potential LAR identified is not available, willing and able to serve as LAR, the site can contact the next person in the hierarchy. If LARs are permitted and no hierarchy exists, a state court designates the LAR. The LAR laws of a given state might cover healthcare but not clinical trials, or they might limit the types of clinical trials for which an LAR can consent. The laws for emergency vs. non-emergency situations may vary. LAR laws vary by state and uncommon scenarios can arise, so a detailed LAR procedure reviewed by an attorney should be available.

According to federal regulations, a legally authorized representative is "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." (21 CFR 50.3(l), 45 CFR 46.102(c)) This definition sounds simple enough, but each state has its own rules, which can be complex. For example, the Commonwealth of Virginia states the following:³

"Legally authorized representative" means, in the following specified order of priority, (i) the parent or parents having custody of a prospective subject who is a minor, (ii) the agent appointed under an advance directive, as defined in § 54.1-

2982, executed by the prospective subject, provided the advance directive authorizes the agent to make decisions regarding the prospective subject's participation in human research, (iii) the legal guardian of a prospective subject, (iv) the spouse of the prospective subject, except where a suit for divorce has been filed and the divorce decree is not yet final, (v) an adult child of the prospective subject, (vi) a parent of the prospective subject when the subject is an adult, (vii) an adult brother or sister of the prospective subject or (viii) any person or judicial or other body authorized by law or regulation to consent on behalf of a prospective subject to such subject's participation in the particular human research.

For the purposes of this chapter, any person authorized by law or regulation to consent on behalf of a prospective subject to such subject's participation in the particular human research shall include an attorney in fact appointed under a durable power of attorney, to the extent the power grants the authority to make such a decision. The attorney in fact shall not be employed by the person, institution, or agency conducting the human research. No official or employee of the institution or agency conducting or authorizing the research shall be qualified to act as a legally authorized representative.

If two or more persons who qualify as legally authorized representatives and have equal decision-making priority under this chapter inform the principal investigator or attending physician that they disagree as to participation of the prospective subject in human research, the subject shall not be enrolled in the human research that is the subject of the consent.

Depending on the state, the statutory LAR hierarchy for consent for clinical research and clinical care may be the same. If the potential subject's residence and the site's location are in different states, the laws of the site's state govern. An advance directive or durable power of attorney executed in one state is probably effective in another state.

Obtain Consent from the LAR

Obtaining consent from an LAR involves several preliminary steps. First, contact the LAR. Second, ensure that the LAR understands his or her role and responsibilities. Third, obtain the LAR's agreement to serve as the LAR for the study subject. The LAR has the right to withhold consent without enduring the informed consent process, in which case his or her decision is final.

In trauma and other studies of acute conditions, it might be possible to identify and contact the LAR but impossible for the LAR to come to the hospital in time to enroll the patient in the study. For such studies, the IRB can approve the use of telephone consent. Telephone consent can be obtained with the following steps:

1. A physician (or nurse practitioner) overseeing care of the patient calls the LAR and explains the patient's condition. The physician informs the LAR about a potential trial that might be suitable for the patient.
2. If the LAR is interested, the physician tells the LAR that a member of the study team will call shortly.
3. A study team member calls, has a preliminary discussion with the LAR, and then asks if the LAR can receive a blank copy of the ICF on a fax machine or computer. (It might be necessary to use a courier service.)
4. The team member transmits the ICF and allows the LAR time to read it and print a copy.
5. At an agreed time, the team member calls the LAR to discuss the ICF material with another hospital employee on the line as witness.

6. If the LAR agrees to consent on behalf of the patient, the team member asks the LAR to sign and date (and not the time on) his or her copy, fax the signature page back (or scan and email it), and mail the original complete signed document, keeping a copy for him- or herself. If the site does not already have a copy of the patient's durable power of attorney or other LAR documentation, the team member asks the LAR to provide that documentation as well.
7. At the time of the call, the team member writes, "Phone Consent by [name and telephone number]" in the LAR signature area with the date (and time) on a copy of the ICF. The team member also completes the section for the person obtaining consent. The witness signs and dates the document. The team member then writes a standard informed consent progress note.
8. If required by the ICF, the investigator signs the copy of the ICF signed by the LAR.
9. The copy signed by the LAR and investigator, the copy signed by the team member and witness, and the signature page faxed by the LAR are all placed in the study binder with the progress note.
10. The team member mails a copy of the ICF signed by the LAR and the investigator to the LAR.

If it is unclear whether LAR consent is ethical or legally valid, consult with the IRB and site attorneys before proceeding.

Continuing Consent

If a subject enrolls in a study based on the consent of an LAR and subsequently becomes competent, obtain informed consent again, this time from the subject. In the opposite case, if a competent subject becomes incompetent during the study, re-obtain consent from the LAR to preserve the subject's right of withdrawal. If the IRB has not approved the use of LARs, withdraw the subject or obtain IRB approval for the subject, explaining how continuing participation will benefit, or at least not harm, the subject.

The NIH guidance, "Research Involving Individuals with Questionable Capacity to Consent: Points to Consider," states:¹

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... 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. 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 is protected in the HHS and FDA regulations. See 45 CFR 46.116(a)(8) and 21 CFR 50.25(a)(8), respectively.

References

1. "Research Involving Individuals with Questionable Capacity to Consent: Points to Consider" Accessed 1/24/11 at http://grants.nih.gov/grants/policy/questionablecapacity.htm#_ftn11
2. Assessing Competence to Consent to Treatment: A Guide for Physicians and Other Health Professionals, Thomas Grisso and Paul S. Appelbaum, Oxford University Press, 1998
3. 2006 Virginia Code – Title 32.1 – HEALTH, accessed 1/24/11 at <http://law.justia.com/virginia/codes/2006/toc3201000/toc3201000.html>

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