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Getting the Right Signatures on Informed Consent Documents

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LEARNING OBJECTIVE
After reading this article, participants should be able to define "impartial witness" and "legally authorized representative" (LAR) as they would be used in the informed consent process; demonstrate understanding of the roles of the impartial witness and the LAR, and in what situations they would participate in the informed consent process; and develop informed consent documents that appropriately specify which persons should sign the informed consent form, consistent with the protocol and the intended study population.

DISCLOSURES
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The process of informed consent to participate in clinical research, and documentation of that conversation, is usually straightforward; the study population includes adults who are capable and competent to make their own decisions, who speak the same language as the investigator and study team, and who can participate fully in the consent discussion and can document their agreement to participate in the study by signing an informed consent document written in the language they speak. Sometimes, though, either the consent process or the documentation of informed consent is more complex.

Complicating Consent

In some settings, the informed consent process may require the involvement of other persons. One example of another involved person is termed a "legally authorized representative" (LAR). Some guidelines use the term "legally acceptable representative,"[1] but the meaning is essentially the same.

An LAR is a person who is "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."[2] Increasingly, many protocols consider LARs as including parents and legal guardians of children who have not reached the age of majority to provide consent themselves. This practice can be confusing in studies that enroll both children and adults.

For the purposes of this article, the authors use LAR only in reference to situations in which potential adult study participants lack the capacity to consent.

A second example of an involved person is an impartial witness to the consent process. An impartial witness is defined by the International Conference on Harmonization (ICH) as "a person who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's [LAR] cannot read, and who reads the informed consent form and any other written information supplied to the subject."[3]

However, there are also regulatory references to witnesses found in U.S. Food and Drug Administration (FDA) and Department of Health and Human Services (HHS) regulations, various state-specific laws (e.g., as found in Virginia) requiring a witness signature in some human subject research, and local uses of a witness signature based on standard procedures. These uses may be very different from ICH, and the U.S. federal regulatory application of witness signatures does not define, nor do consent documents usually define, the purpose of the witness signature.

This article will focus on the ICH and U.S. federal regulatory application of the witness role. Examined in addition will be the fact that informed consent documents might request the signature of someone who is not involved in the consent process. For example, informed consent documents often have a space for the signature of the study's investigator, in addition to the signature of the person who actually conducted the consent discussion.

Whose Line is it, Anyway?

In the process of institutional review board (IRB) review, questions frequently arise when the informed consent document has signature lines for persons who would not be expected to participate in the consent process, based on the protocol information. Delays in IRB review may occur when the protocol and the consent document are apparently inconsistent in their respective intentions regarding the intended informed consent process or the study population. While this may sometimes seem to study sponsors to be a minor clarification, the implications of the potential enrollment of vulnerable subjects in research are significant in the IRB review process.

Ahead, we will take a closer look at the parties who may be involved in the consent process, including those who may be asked to sign the informed consent document, and at the specific settings in which consent should occur. We will also describe the need for careful review of the protocol's description of the intended subject population, the considerations of the IRB for vulnerability, and the informed consent document as part of the development of study-specific consent forms.

When Should LARs Provide Consent?

The inclusion of LARs in the informed consent process implies that potential study participants are expected to be incapable of providing consent on their own behalf. The corollary to this is that someone who would be the LAR (if the subject were not competent) cannot provide a valid consent on behalf of someone who is capable of providing consent for themselves. That is, though a wife would be the LAR for her husband should he become incapacitated, she cannot provide valid consent for her husband to participate in a research study if he is currently capable of making his own decisions about participation.

State laws determine who may serve as an LAR if there is no pre-existing documentation naming an LAR, and in what hierarchy persons should be considered (parent, spouse, adult children, etc.).

As noted previously, it is not uncommon for the signature spaces of a consent document to imply a consent process that is different from that which is described in the study protocol. For example, the eligibility criteria may state that "subjects must be able to agree with the requirements of the study and provide informed consent for participation," but the informed consent document submitted from the sponsor to the IRB with the protocol includes a signature space for an LAR, indicating the expectation that subjects may be enrolled who in fact cannot provide their own informed consent.

In many cases, it is probable that the LAR signature line was present on the template form used to draft the consent, and was never deleted when the consent was made study-specific. In other cases, the protocol eligibility criteria as described in the above example may conflict with other sections of the protocol describing overall quality and compliance standards for the study conduct, which states that "the subject or their Legally Authorized Representative" will sign the consent document. This type of conflict within the protocol must be resolved by the IRB before approving the research and the study documents supporting the consent process.

What Types of Studies Usually Need LARs?

The ICH Guideline for Good Clinical Practice and federal regulations in the United States recognize that decisionally impaired persons are a vulnerable population for whom additional protections are required.[4] As FDA regulations state in the criteria for IRB approval of research, "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."[5]

Inclusion of such subjects must be made thoughtfully and with specific consideration of the implications for issues pertaining to justice, respect for persons, and the potential benefits of the research. In addition, the IRB is expected to consider "… inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects…" as part of the review of research involving vulnerable persons.[6] Thus,

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consideration of issues pertaining to vulnerable populations requires experience by the IRB reviewing the protocol and attention to the "additional safeguards" that make the research ethical.

Many study protocols refer to the enrollment of decisionally impaired subjects, either intentionally or by implication, by referring to consent by the subject or LAR or by including the LAR signature space on the consent form. IRBs consider the implications of enrolling subjects who do not have the capacity to provide consent themselves very seriously. It is rare to encounter a research proposal that explicitly makes a case for enrolling subjects who lack capacity for consent, unless the disease or condition that causes that lack of capacity is the focus of the study (for example, a new investigational agent for the treatment of acute stroke).

A significant complicating factor in the potential enrollment of decisionally impaired study participants is the wide variety of presentations and etiology of lack of capacity. Conditions such as schizophrenia, brain injury, loss of consciousness due to acute trauma, and dementia such as found in Alzheimer's disease represent very different considerations regarding the prospect for regaining decisional capacity; however, all persons with such conditions deserve the same protections and additional safeguards afforded by the regulations and ethical considerations. IRBs must then consider two core principles that are generally recognized in the ethical literature as supporting the inclusion of this vulnerable population: scientific need and the prospect for direct benefit to those participating in the research.

The concept of *scientific need* asks the question whether the study objectives can reasonably be satisfied by enrolling the less vulnerable population that includes only those who are capable of providing consent. The applicable standard for the IRB's consideration for inclusion can be stated as enrolling those persons with the least degree of impairment that is compatible with the study goals. If there are adequate numbers of competent individuals available, there is little to be gained by including those who lack the ability to consent for themselves, unless the research is specifically intended to treat cognitive impairment.

Consider a large Phase III trial in diabetes comparing add-on therapy with standard of care to standard of care plus placebo. Studies have suggested that type 2 diabetes can increase the risks of Alzheimer's disease, vascular dementia, and other forms of dementia.[7,8] However, there is no scientific need to include those who actually have dementia in the typical diabetes trial—where the endpoints are better glucose control—given the widespread nature of the disease and availability of potential participants. However, if the study drug is intended to treat dementia, the narrative with respect to scientific need would be altered in a positive direction, due to the potential need to try the drug in the population in which it is intended to be used.

The concept of *direct benefit* is an aspect of additional protection for vulnerable populations in that there is justification for the prospect of risk associated with a study that is offset by the potential for direct benefit by participating in the research. The higher the potential risks of the research, the greater the anticipated benefit must be to justify inclusion of vulnerable persons. Thus, a drug with relatively few risks of a transitory nature can be justified by rather modest symptomatic relief. However, a drug with potentially serious and permanent risks must likely meet a higher standard for benefit that might include disease modification rather than mere relief of symptoms.

As an example of how to apply the above concept, a product aimed at treating moderate to severe Alzheimer's disease would likely first be tested in normal, healthy adults for safety, and then in those with less profound loss of mental acuity for reasonable signs of efficacy before being given to more severely ill participants.

What if the Capacity to Provide Consent May Change During the Study?

Some conditions involving mental capacity are expected to deteriorate over time. If a study is anticipated to run for several years or more in a population including mild-to-moderate Alzheimer's disease, best practices often dictate that individuals asked to take part in such research *identify* an LAR at the beginning of the consenting process in order to reduce unnecessary

withdrawal from the research and the loss of important data. Failure to identify this individual may leave investigators in a position of having to navigate arcane state laws and tricky family dynamics in order to identify an appropriate surrogate for consent. Although the identified LAR would not provide the consent for initial enrollment in the study—when the subject is still competent to make that decision—informed consent is an ongoing process, and the LAR would be asked to provide continuing agreement for participation should the subject become incapable later.

Conversely, some forms of diminished capacity can improve over time. An LAR may be needed for someone to be enrolled in research who may be temporarily incapacitated—for example, in studies involving patients with acute traumatic loss of consciousness or in a medically induced coma. In trials where the intended population may be in this situation, consent by an LAR is appropriate for enrollment, but such subjects must be re-consented in the event that they regain consciousness and the ability to consent.

When Should a Witness be Involved in the Consent Process?

If used, a witness is expected to ensure that the prospective subject was provided sufficient opportunity to consider study participation, that the possibility of coercion or undue influence was minimized, and that the subject or the subject's LAR understood the information provided to them. There are two situations defined in the regulations in which an impartial witness may be required in the informed consent process.

In the first situation, use of an impartial witness is necessary when either the subject or the subject's LAR speaks and understands English, but either cannot read and write, or is visually impaired such that changes to the consent document, such as increasing font size, are insufficient to allow the subject (or LAR) to read the document(s). In this case, the witness is expected to listen to the verbal presentation of the informed consent discussion, which must include all the required regulatory elements of informed consent. The witness is present to ensure that the potential subject appears to understand the information provided to him or her and has the opportunity to ask questions, and that the potential subject is freely consenting to participation in the research. The witness will then sign the consent form on the "witness" line, to document his or her confirmation of these facts.

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In the second situation, a witness is necessary when the informed consent process uses a "short form" informed consent document (a brief document containing the basic statements about the rights of research participants in a language that is understandable to the potential subject).[9] While short form documents are not frequently used in clinical research, they are permissible in situations in which the potential subject does not speak English (or the language in which the study is being conducted, if it is not English) and a full and complete translated informed consent document is not available.

As defined in the regulations,[10] a short form written consent document requires that there is a witness to the oral presentation. The IRB must approve a written summary of what is to be said to the subject or the LAR. Only the short form itself is to be signed by the subject or the LAR; however, the witness will sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary should be provided to the subject or the LAR in addition to a copy of the short form.

Neither FDA regulations nor HHS regulations define "witness" per se. FDA Guidance (FDA Information Sheets, A Guide to Informed Consent, "Illiterate English Speaking Subjects") indicates the expectation that the witness be an "impartial third party," but does not provide guidance on what constitutes impartiality. It is useful for any institution at which research is conducted to have a written definition or standard operating procedure that covers who may serve as a witness to an informed consent process.

Note that, since the witness should be independent of the trial, the witness cannot be another member of the study team, and should ideally not be someone who works closely with the study team (e.g., office staff). In larger institutions, a person of presumed neutrality, such as a chaplain or someone from another department, would be an appropriate choice.

In many cases, it is probable that the LAR signature line was present on the template form used to draft the consent, and was never deleted when the consent was made study-specific.

Although not prohibited, best practice often dictates that the witness not be a member of the potential subject's family, as it is may be difficult for them to be impartial about the decision regarding study participation. It is also not generally recommended that a family member act as translator when oral translation of informed consent information is needed, since they may not fully understand the medical information and may mistranslate information, and because they may incorporate their own thoughts into the discussion as the information is translated.

Thus, sites should be prepared to have staff who can serve as translators, especially if the need is frequently encountered, or to have a reliable translator service available. This is important as dialogue will continue *after* the initial consent process, or if the subject or LAR has questions that may require site contact outside planned visits.

Having a pre-defined policy will help minimize situations in which a witness has to be chosen quickly, or in which study-related site personnel are pulled in unprepared, or inappropriately, to serve as witnesses.

Further, many protocol inclusion criteria begin with a statement mentioning the "subject who has signed the consent form," or something similar to this. An illiterate or visually impaired subject can usually provide a "signature" (their "mark"—be it an X or thumbprint), and consent forms would also contain impartial witness lines to accommodate these subjects. However, many studies have diaries, dosing instructions, and questionnaires for subjects to complete. Sometimes these documents must be completed by the subject directly, but sometimes completion by someone on behalf of the subject is acceptable.

When no impartial witness lines are present on the consent form, the IRB may anticipate only literate or sighted readers are to be included, even though that is not the sponsor's intent. Therefore, the protocol eligibility criteria should address whether or not nonreaders will be enrolled, to facilitate the IRB's review.

When Should an Investigator's Signature Appear on the Consent Form?

According to the ICH Guideline for Good Clinical Practice, "Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's [LAR], and by the person who conducted the informed consent discussion."[11] The person who conducts the discussion is either the investigator for the study or a study staff member delegated by the investigator to conduct the consent process.

Sometimes, in addition to the space for the signature of the delegated person who conducted the informed consent process, there is also a space for the signature of the investigator. Presumably, a principal investigator is expected to sign the consent form in this space to indicate his or her awareness of the enrollment of the participant in circumstances when he or she was not the person who conducted the consent discussion.

There is no regulatory or best practice requirement for an investigator to sign the informed consent document, unless the investigator was the person who conducted the consent discussion—in which case, he/she would sign the form in that space. Although less frequently seen now, this practice seemed to be a trend for several years, and presumably was intended to document the oversight of the investigators and their knowledge of participants being enrolled in the study. However, asking investigators to provide a signature as verification of a discussion for which they were not present is not good evidence of oversight.

This practice also creates an additional potential issue of noncompliance; what if the study coordinator who conducted the discussion has signed the form but the investigator has not? What if the investigator signature is dated days, weeks, or even months after the consent discussion occurred, and well after the subject's study participation has begun? The routine addition of an investigator signature line seems to add nothing of value to the consenting process. The recommendation, therefore, is that investigators not be asked or required to sign a consent form, unless they were the person who conducted the consent discussion, in which case they would sign in that capacity.

Conclusion

Documentation of informed consent can involve many layers of complexity and is fraught with the potential for errors and confusion. The persons creating the protocol and documents for informed consent should ensure clear descriptions of the eligible population sought for the research, and should carefully review protocol and consent template language to ensure that it is appropriate in that specific setting and that documents are concordant. This requires evaluation of the research proposal's legitimate need to enroll persons who lack capacity to consent for themselves, and when it is neither necessary nor appropriate, to remove protocol language and consent signature lines for LARs.

Of course, in protocols where the intervention is intended to treat the cause of the incapacity to consent, or where there is a robust expectation of benefit for participants, inclusion of those incapable of consent is ethical and just. The issue of allowance of nonreaders is very different, in that these subjects have the capacity to consent for themselves. One can make the case that it is unethical to exclude this population, barring considerations of the necessity for reading to safely administer a study drug or satisfy study endpoints such as self-administered survey instruments.

When these decisions have been reached and the protocol language is clear, the IRB can easily find the correct documentation and the information required to make approval determinations. Adding signature lines that have no regulatory or ethical relevance to the research is an invitation for noncompliance. The result of this careful review is a more ethically sound study, with reduced timelines to initiation.

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