Assent Is Not Just for Children:

Requirements and Best Practices for Assent in Clinical Research

Informed consent requires that prospective participants receive sufficient information about a research study and that they have the capacity to decide about their voluntary participation.[1] Paul Appelbaum defines capacity as the ability to understand the information provided, understand the consequences of a decision, make a decision and communicate a choice.[2] For those who do not have the capacity to provide consent, the challenge for the research community is how to balance the inclusion of these individuals in research with the requirement to protect those who may be vulnerable to coercion or undue influence.[3] In adults, significant numbers of clinical trials are exploring treatments for conditions that are causes of impaired decision-making capacity including neurologic diseases and psychiatric illnesses raising ethical considerations for the inclusion and the protection of these individuals in research.

In this paper we highlight the importance of asking prospective participants, who do not have the capacity to provide consent, for their assent to participate in research. We review the current regulatory and ethical framework for assent of both adults lacking capacity and children and offer strategies for engaging these potential participants in the assent process.

Is Assent Required of Adults Who Lack the Capacity to Consent? An Ethical Framework

Assent is the affirmative agreement to participate in research from a person who has some ability to understand but is unable to provide legally-effective consent.[4] While the United States regulations for human participant research require assent from children who cannot provide consent due to their age, they do not explicitly mandate obtaining assent from adults who lack the capacity to provide consent. Nevertheless, besides the obvious parallel for assent with children, there is support for this requirement in multiple regulatory frameworks, including the guiding principles of the Belmont Report[5] and US Food and Drug Administration (FDA) guidance on informed consent.[6]

The Belmont Report provides three basic ethical principles to guide human participants research.[7] These principles are Respect for Persons, Beneficence, and Justice. The first principle of Respect for Persons advocates for two ethical convictions, "first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection." The second conviction is addressed by requiring consent be obtained from a legally authorized representative (LAR) whenever an adult participant lacks capacity to consent. The first ethical conviction is not subsumed by the second; that is, respect is not limited to legally effective consent and decisional capacity is not a binary attribute. Participants without full capacity may fall along a spectrum of capacity and awareness and deserve the respect of engagement as they are able.

Like consent, assent is an ongoing process that may evolve over time. If a participant who was unable to be consulted for assent at the time of enrollment later regains some cognitive ability, the study team should attempt to obtain assent when the participant can be consulted.

The FDA states the following in a guidance document[8] on informed consent:

"Institutional Review Boards (IRBs) and investigators should carefully consider whether the inclusion in research of individuals who lack capacity is ethically appropriate and scientifically necessary. Whenever individuals with impaired consent capacity (partial, fluctuating, or complete) are or may be enrolled in clinical studies, ethical and procedural challenges arise. Considerations that may help address these challenges, and provide additional safeguards include:

Assessing whether individuals who cannot provide legally effective consent on their own behalf may nonetheless be able to provide some form of oral agreement (e.g., assent) at the outset of the study and, as appropriate, throughout the course of the research (e.g., for subjects with progressive disorders), and how such oral agreement would be documented. In such a circumstance, an LAR would need to provide documented written consent."

Therefore, the requirement for obtaining assent from adult participants who lack the capacity to provide consent is not formally established in federal regulations. However, in order to ensure a participant's autonomy is respected, WCG IRB requires investigators to obtain assent whenever a participant is unable to provide consent for themselves, but they are capable of being reasonably consulted.

The IRB is responsible for determining the appropriate method for obtaining assent and documenting assent. A separate assent form is not recommended for adult participants. Instead, WCG IRB generally recommends documentation of the verbal assent process by including the signature of the person obtaining assent and the date assent was verbally obtained on the informed consent document, which will also be signed by the LAR providing consent.

Is Assent Required of Children? A Study-by-Study Determination

US federal regulations[9] require that the IRB determine that adequate provisions are made for the assent of children when the IRB judges the children are capable of assent. Regulations[10] define "children" as persons "who have not attained the legal age for treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research is being conducted." Thus, the age of consent is determined by state or other local laws. In cases where a child is participating in research, the agreement of the parent(s) (or legal guardian) is referred to as "parental permission"[11] rather than consent.

The capacity to make voluntary, informed decisions evolves throughout childhood and adolescence and varies among individuals of the same age. The goal of the assent process is to involve children in discussions and decisions about research participation to the extent they are capable.

The IRB is required to determine whether assent will be required on a study-by-study basis. The IRB must consider several factors, including the characteristics of the patient population (developmental status and capacity, medical history, and amount of experience with the medical system, etc.) and the potential for direct benefit to the

participants resulting from study participation. The IRB may waive the requirement for assent in situations where the intervention may be important to the health or wellbeing of the participant, or in situations where the child is not capable of assent given their cognitive and emotional maturity and psychological state.

The Assent Process: What is Required?

While the federal regulations require the assent of the child for certain kinds of research, these regulations do not elaborate on the specific elements of assent. In his essay on the ethical dimensions of research involving children (written in 1995 but still applicable today), William Bartholome[12] identified the following elements of assent to guide the assent process.

According to Bartholome the investigator should:

1. Help the child "achieve a developmentally appropriate understanding of the nature of [their] condition."
2. Disclose to the child "the nature of the proposed intervention and what [they are] likely to experience."
3. Assess the child's understanding of the information provided.
4. Secure "the child's willingness to accept the proposed intervention."

When research involves younger children, the investigator should focus on providing basic information about what will happen, and on responding to questions and concerns. For older children and teenagers, the assent process may be similar to the consent process for adults, especially if the teenagers have chronic illnesses and experience with medical procedures. In some cases, a prospective participant may feel more comfortable asking the research team questions without their parent present.

How is Assent Documented?

The regulations do not provide a set age threshold for assent and place responsibility on the IRB to decide whether to require an assent form so the requirement for assent forms and documentation of assent may vary across IRBs.

Assent requires that participants have a basic understanding of what might be asked of them, and what might happen. The information appropriate to the individual child's cognitive level and situation may vary widely across studies and between children. For that reason, the individual assent discussion is more important than what, if any, forms are used. Whether documenting an assent discussion on the consent form/parental permission form, or using an assent form, the basic elements of consent should be addressed at the level appropriate for the child. If the sponsor or the researchers wish to use an assent form, the form should be appropriate for the likely capabilities of the children enrolled considering their age, physical and cognitive condition (which may be impacted by the disease being studied), and situation (such as where the assent discussion would occur).

The IRB uses guidance from both the FDA and Office for Human Research Protections (OHRP) to make their determinations for the requirements of documentation of assent:

FDA recommends:

"Older children may be well acquainted with signing documents through prior experience with testing, licensing and/or other

procedures normally encountered in their lives. Signing a form to give their assent for research would not be perceived as unusual and would be reasonable. Younger children, however, may never have had the experience of signing a document. For these children requiring a signature may not be appropriate, and some other technique to verify assent could be used. For example, a third party may verify, by signature, that the assent of the child was obtained."[13] From this guidance, the IRB may determine no assent form is required and documentation that the assent process occurred is appropriate. For research that enrolls children across a large range of ages (e.g., from infant to adolescent), it may be appropriate to have different versions of the assent form written in a language tailored to the participant's level of cognitive development. Because the ability of each participant may vary even among children of the same age, it is preferable to have these assent forms written for different levels of development rather than specific age ranges.

OHRP notes that:

"…the IRB has the discretion to decide what form of documentation is required for a study; but offers the following as guidance: If adolescents are involved in research where a consent form would have been used if the subjects were adults, it would generally be appropriate to use a similar form to document an adolescent's assent. If young children are involved who are as yet unable to read, documentation should take a form that is appropriate for the purpose of recording that assent took place. The IRB may also decide that documentation of assent is not warranted."[14]

Assent: General Best Practices

While researchers and IRBs focus much attention on the documentation of assent, research suggests that assent is most effective when it occurs as an ongoing/iterative process as opposed to the one-time act of signing of a written document.[15] When possible, prospective participants should be given time to think about whether they want to enroll in the study. They should also be afforded the opportunity to speak with others before making a decision. Discussions should allow sufficient time for questions and further explanations. These discussions may take place over several visits.

In general, the practices that apply to informed consent also apply to the practice of assent:

Assent should still be obtained, even when the requirement for signature documentation of consent for adult participants has been waived, although assent may be verbal.

If the informed consent or parental permission document is updated with new information during the study, any assent documents should also be appropriately updated, and a "re-assent" discussion should occur whenever a "re-consent" discussion would occur.

Conclusions

The need to improve conditions that are causes of impaired decision-making capacity including neurologic diseases, psychiatric illnesses, or diseases that affect children highlights the importance of developing effective strategies to ensure both the inclusion and the protection of these individuals in research.

The guiding principles of the Belmont Report, and FDA guidance on informed consent recognise the importance of obtaining assent in the informed consent process. Assent should be sought in a manner that considers the participant's age, cognitive development, and capacity to make decisions. This will ensure the participant is involved in the consenting process to the extent they are able, thereby respecting their rights and autonomy.

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