Attributes of Exemplary Research

A New Look at Informed Consent for Cancer Clinical Trials

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Informed consent is fundamental to the conduct of clinical trials. Firmly established in the Nuremberg Code and Belmont Report is the right of individuals to be given the opportunity to make informed choices about participation in research.^{1,2} In order to make the best choice for them, prospective participants need to be adequately informed and given the opportunity to ask questions and consult with relatives or friends without feeling pressured or rushed. This process, whereby a patient is informed about his or her disease and all available treatment options, must include a discussion of both the standard of care and emerging options available only through participation in research. If a patient expresses interest in the trial, then it is the responsibility of the clinician or research team member to review the known and possible risks, benefits, and requirements of participation.

History reminds us of the importance of obtaining informed consent for research. The story of Henrietta Lacks, a patient whose cancerous cells were used for medical research without her knowledge or consent, serves as a poignant reminder of scientific misconduct.³ It is no wonder that patients are sometimes suspicious of researchers asking for tissue or body fluids, and it is important for the research community to be humble and respectful when requesting such donations. When participation involves risks or exposure to experimental drugs or devices, the patient deserves a detailed outline regarding the purpose of the research and the anticipated personal consequences of participation.

This article, part of the *Journal of Oncology Practice* series on attributes of exemplary clinical trial sites, outlines the elements of an informed consent document and provides practical tips for conducting the informed consent process.⁴ A good conversation about clinical trials can solidify the relationship between patients with cancer and their physicians. Indeed, by helping patients understand the uncertainty about outcomes and the limitations of our body of knowledge, we can assist them in becoming actively engaged and involved in their own care.

Elements of the Informed Consent Document

The general requirements for any informed consent document in the United States are governed by the Code of Federal Regulations. Basic consent requirements include (and are not

limited to) a description of foreseeable risks, benefits, and alternative treatments and an explanation of procedures that will be performed. The document must also include a statement that the study involves research and an explanation about the purpose of the research. The document must make clear that participation in the study is voluntary and that participants may discontinue participation at any time. Research with human subjects that is funded by the United States Department of Health and Human Services cannot be conducted unless all requirements of the Code of Federal Regulations Title 45, Part 46 have been met (Figure 1).⁵ Alternatively, Code of Federal Regulations Title 21, Part 50 is applied to research regulated by the US Food and Drug Administration (FDA), including clinical research sponsored by pharmaceutical companies. Guidance regarding these requirements is available on the Web sites of both the Office for Human Research Protections and FDA.^{6,7}

The consent document must be written in a clear and logical manner that can be understood by a reasonable person. Readability can be assessed through the use of readability tests, which are available in most electronic word processor programs.⁸ Commonly, it is recommended that an informed consent document should be written at a sixth to eighth grade reading level, although some research suggests that a lower reading level might be more appropriate.^{9,10} The National Cancer Institute has developed recommendations for improving the readability of an informed consent document,¹¹ which include:

- Use words that are familiar to the reader.
- Define medical terminology.
- Reduce sentence and paragraph length.
- Sequence content logically.
- Highlight important points.
- Use a font size of at least 12 points.

Patient advocates can provide invaluable feedback regarding the readability of informed consent documents. If such colleagues are available, it is helpful to include them to assist the research staff in preparing the necessary documents. They can provide expert guidance to address common concerns and ensure that the document provides the right amount of detail desired by a reasonable person. Patient advocates also help research staff identify problems such as the use of jargon or inadequately defined medical terminology.

General Requirements for Informed Consent - Title 45 CFR, Part 46

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
- (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

- (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- (3) Any additional costs to the subject that may result from participation in the research;
- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
- (6) The approximate number of subjects involved in the study.

Figure 1. General requirements for informed consent, Title 45 Code of Federal Regulations, Part 46.

The institutional review board (IRB) plays an essential role verifying that an informed consent document is appropriate and includes all required elements. No federally funded or FDA-approved research involving human participants can be conducted in the United States without approval from an IRB.¹² In order to expedite the review process, it is best to review documents thoroughly before submission. Common mistakes include inconsistencies between the consent document and research protocol—such as inconsistent statements regarding the frequency and timing of research procedures—and missing elements required by the Code of Federal Regulations. An IRB will not approve an informed consent document unless all elements are appropriately included.

Informed Consent Process for Treatment Trials

Ideally, the process of obtaining consent for participation in a treatment trial is extensive and comprehensive. The process should address the patient's expectations and concerns and may require more than one visit. The degree of effort involved is hardly reflected by the signature obtained in the document procured during this process. At many sites, the physician introduces the concept of participation in a trial and then delegates the task of educating the patient to another member of the research team. Licensed health professionals such as research nurses, physician assistants, and nurse practitioners can provide information and answer questions and should be integrated into the consent process to improve efficiency and guarantee that all aspects are duly covered.¹³ Local IRBs

often require the consent process standard operating procedure to be written out, which the IRB then approves or disapproves.

Identifying prospective trial participants in advance of their office visit may save time and improve accrual. Being prepared to present all treatment options during the initial discussion and having research staff available to answer additional questions serve to improve the flow of information, facilitate communication, and may well produce a higher yield of enrollment into trials. Screening the charts a day or two in advance is a key element and an efficient technique for a practice committed to clinical research.

Important Considerations

The informed consent discussion must convey a realistic explanation regarding the patient's potential for personal benefit from participation. In the case of early-phase trials, there is often a limited expectation that the patient will personally benefit from participation. A study of patients enrolled on early-phase trials found high levels of unrealistic optimism, even among patients who properly understood the purpose of the trial.¹⁴

Regardless of potential personal benefit, the patient must also be educated about all potential risks associated with participation on the clinical trial, including possible adverse effects associated with the study agent and risks associated with protocol-required procedures. Patients also need to be given timely updates of new adverse events identified during the conduct of the trial, which often involves signing a new informed consent form. The patient also needs to be informed about their right to withdraw participation at any time and to be reassured that this will not affect his or her care.

Assessing a patient's level of comprehension is very important. After discussion with the patient, a member of the staff should document how the patient's comprehension was assessed. The same techniques that are used to gauge a patient's understanding of standard treatment can be used to assess understanding of a clinical trial. A few simple suggestions include watching the patient's body language and noting their verbal and nonverbal responses to the conversation. Is the patient engaged in the conversation? Are they asking good questions that indicate understanding about what is being said? Another technique is to ask the patient to summarize the take-home messages.¹⁵⁻¹⁷ This "teach-back" can be elicited quite easily with a prompt such as: "Please tell me what I have just said to you" or "What will you tell your son when he calls this evening?"

Another way to promote active patient discussion is by providing the patient a question prompt list regarding clinical trials. A question prompt list is a structured list of questions that can improve a patient's comprehension by promoting information seeking.¹⁸ The list of questions can help the patient identify components of the clinical trial that they do not understand and prompt the patient to seek clarification from their health care provider. Examples of questions in a prompt list developed by Brown et al¹⁸ include "Will there be adverse effects on the trial which I won't get on the standard treatment?" "Is this trial randomized?" and "What does that mean and why is it important?"

It is best to include family or another supportive adult in the conversation. Research regarding the informed consent process

has shown that family member opinions can greatly influence a patient's decision to enroll on a clinical trial.¹⁹ If a family member is unable to physically accompany the patient but wishes to participate, it is still possible to involve them through the use of audiotapes that record the conversation or speaker phones to allow participation and communication in real time. The patient should also be given contact information they can use to reach the research nurse or program manager and ask questions after having had an opportunity to debrief and review the information presented.

In recent years, we have made some progress in recognizing that language barriers may unfairly limit participation of immigrants or racial and ethnic minorities in cancer clinical trials. Major cancer centers and hospitals are required to have interpreters available to assist with language-discordant consultations, but such services are not always available in community settings. Remote consecutive interpretation via phone is increasingly used and provides accurate and efficient service. Use of family members or untrained staff as interpreters is considered suboptimal because they may lack the knowledge to interpret accurately and may deliberately omit important information in order to "protect" the patient from the harsh reality.²⁰⁻²² Finally, it is important to note that even native English speakers may have difficulty reading complex documents and understanding medical jargon. Clear and plain language, in and of itself, has therapeutic value.

Conclusion

Informed consent is fundamental to the conduct of any research involving human participants. This article, part of the series on attributes of exemplary clinical trial sites, reviews some of the required elements of the informed consent document and provides practical tips that can be used in practice. Properly conducting the informed consent process helps ensure that a patient makes an educated decision about participation in a research study. The process also informs the patient regarding the requirements associated with participation and the patient's right to withdraw from participation at any time.

Accepted for publication on May 22, 2011.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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DOI: 10.1200/JOP.2011.000347

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ASCO's EHR Social Networking Site

ASCO has developed a social networking site, where oncologists and their practice staff can connect and share information about the use of electronic health records (EHRs) in oncology practices. This Web site also serves as a platform for oncologists and EHR vendors to discuss the advancements, usability, and challenges that emerge in using EHRs in oncology offices. Become a member today!

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