Over the last seven decades, federal lawmakers and regulators have developed an expansive set of informed consent requirements designed to protect individuals participating in clinical trials and to ensure that such trials meet ethical standards. Failure to satisfy all of these legal requirements can expose research sponsors, investigators, and even clinical trial sites to significant risk. Far beyond a one-action item on the to-do list, legally effective and compliant informed consent is an ongoing, dynamic process requiring that information about the clinical research be provided to the participant so that each individual can make an informed decision about his or her involvement in the trial. Because this is an ever-changing area of law – just this past spring the FDA released draft guidance on obtaining informed consent through text messaging and other electronic means – research sponsors, investigators, and clinical trial sites should periodically review their informed consent templates and processes to ensure continued compliance.

BACKGROUND

The Code requires obtaining voluntary consent from people in order to use them as test subjects.\(^3\) In the mid-1960s, the World Medical Association Declaration of Helsinki expanded this concept by requiring that such consent also be informed.\(^9\) The ethics principles developed under the Nuremberg Code and the Declaration of Helsinki serve as the basis for U.S. law currently governing informed consent in clinical research as well as many other state and local laws regarding the extent of information to be provided to participants in order for their consent to be legally effective.\(^6\)

**REQUIREMENTS OF INFORMED CONSENT**

Obtaining a patient’s informed consent is usually a multi-step process, including an initial meeting with the participant to review the consent form, giving him or her time to consider the form, confirming an understanding of the terms in a follow-up meeting, and updating the terms of the consent form throughout the trial as needed. Generally, the requirements for obtaining informed consent in clinical research are as follows:

1. The investigator is responsible for obtaining the informed consent prior to the person’s participation;\(^7\)
2. The consent must be legally effective;
3. The investigator must provide the prospective participant sufficient opportunity to consider whether to participate in the trial and minimize the possibility of coercion or undue influence;
4. The information given to the participant must be written in language understandable to him or her;\(^8\)
(5) The consent may not include exculpatory language through which the participant waives or appears to waive any legal rights or releases or appears to release the investigator, the sponsor, site or its agents from liability for negligence.9

While the trial sponsor and trial site typically negotiate the terms of the informed consent form for a clinical trial, an institutional review board (“IRB”) or independent ethics committee ultimately has final approval of what the consent form will look like, including its contents and allocations of risk.10 An IRB ensures that the information provided to participants in the informed consent contains all federally mandated elements, which include:

1. A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the person’s participation, a description of the procedures to be followed, and identification of any experimental procedures;
(2) A description of any reasonably foreseeable risks or discomforts to the participant;

(3) A description of any benefits to the participant or to others which may reasonably be expected from the research;

(4) Disclosure of appropriate alternative procedures or treatment, if any, that might be advantageous to the participant;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained and noting the possibility that the FDA may inspect the records;

(6) For research involving more than minimal risk, an explanation of any compensation or medical treatment for injury and, if offered, an explanation of treatment or where further information may be obtained;

(7) Contact information for (i) who can answer pertinent questions about the research and the participant’s rights, and (ii) who to contact in the event of a research-related injury;

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits earned, and that the participant may withdraw from the program at any time without penalty or loss of benefits earned; and

(9) A specific database statement that clinical trial information has been or will be submitted to a clinical trial registry databank.

An IRB may require that additional information be provided when, in the IRB’s judgment, the information would meaningfully add to the protection of the rights and welfare of participants.

Informed consent must be documented by a written form approved by the IRB and signed and dated by the participant at the time of consent. A copy of the form must also be given to the participant. The consent can either be (i) a written document that embodies all requisite elements (which may be read to the subject, but there must be adequate opportunity for the participant to read the form before signing), or (ii) a short form document stating that the required elements were presented orally to the participant in the presence of a witness, which is signed by the participant.

As a trial site, sponsor, or investigator, it is imperative to analyze other special considerations specific to the trial for purposes of obtaining consent.

One major issue to be carefully considered is whether the participant will be entitled to compensation for injuries.
and/or reimbursement for treatment costs associated with injuries incurred during the trial. If so, the consent should provide clear direction on who is responsible for such compensation or reimbursement, including whether the patient will be required to seek insurance reimbursement first.

Additionally, trial sites and sponsors should consider whether a local or central IRB will be used to review and approve the consent form and, when using a local IRB, identify the form selected. Determining the exact form to use can lead to a “battle of the templates” between the sponsor and site.

A third serious consideration is the inclusion of language to comply with (i) accreditation boards, such as the Association of Accreditation of Human Research Protection Programs, (ii) HIPAA, which has major implications as to how the participant’s protected health information may be used in the study, and (iii) the Medicare Secondary Payor Act, which affects the ability of the sponsor to receive protected health information it normally would not obtain and obligations to report to the Centers for Medicare and Medicaid.

**CONTINUING OBLIGATIONS DURING THE TRIAL**

Even after the trial has begun and research is well underway, it may be necessary to obtain informed consent on a continuous basis. A researcher is obligated to update participants on new information that may:

1. Be relevant to the participant’s willingness to continue in the trial;
2. Affect adversely the rights, safety, or well-being of participants;
3. Impact the trial’s methodology, procedures, or outcomes; and/or
4. Alter IRB approval for the study conduct.²¹

This gives the participant the opportunity to ask questions or to raise concerns and even to withdraw the consent that was previously given.²² Subsequent informed consent may also be necessary if there is an error creating
a possible adverse effect on any of the requisite elements of a valid consent (e.g., a researcher learns at a later date that the language used in the form was not understandable to the participant).23

An IRB will review the research at intervals appropriate to the degree of risk, but not less than once per year.24 Further, an IRB has authority to observe or have a third party observe the consent process and the research.25

LOOKING AHEAD: THE USE OF ELECTRONIC INFORMED CONSENT IN CLINICAL TRIALS

In March 2015, the FDA released a draft guidance covering the use of electronic media and processes to obtain informed consent for FDA-regulated clinical investigations of medical products, including drugs and biological products, medical devices, and combinations of such products for human use.26 This would enable investigators, sponsors, and IRBs to use electronic means, such as texts, podcasts, and interactive Web sites, to convey information related to the study and to obtain and document informed consent.27 Many believe the use of electronic informed consent allows for easier and faster communication with participants and better facilitates the participant’s ability to comprehend the information via interactive interfaces.28

The FDA’s guidance provides that electronic informed consent must still comply with all of the current federal regulations governing informed consent. In addition, it recommends four major considerations to implement an electronic informed consent process for sites and sponsors:

1. Protecting human participants;
2. Facilitating and improving people’s understanding of the information conveyed during the consent process to ensure an informed decision to enroll;
3. Ensuring appropriate documentation of the electronic consent; and
4. Ensuring data quality and integrity when consent is obtained electronically.29
The FDA has not yet published its final guidelines; however, all those involved in the realm of U.S. clinical trials should expect major advancements and new challenges in their interactions with participants during clinical investigations and the informed consent process if electronic informed consent is approved.

CONCLUSION

The complexities of the informed consent process in clinical investigations should not be discounted. Failure to comply with relevant requirements can result in administrative actions, civil or criminal penalties, and even affect the outcome of subsequent litigation involving the studied product. Although the FDA’s guidance may offer some relief in the future to ease and facilitate the process of obtaining informed consent, the number of requirements and elements necessary for that consent to be legally effective will not be changing any time soon.

1. For purposes of this article, any reference to “participant,” with regard to disclosures and consents means the participant or the participant’s legally authorized representative, as applicable.
2. 21 CFR 50.20 et seq.
4. Id.
6. 21 CFR 50.25(d).
7. The investigator does not have to conduct a consent interview but is ultimately responsible for obtaining the consent.
8. Understandable means that the information is presented in a language and at a reading level comprehensible to the person, including the explanation of scientific and medical terms. The investigator should avoid terms such as “fully explained” or “fully understand,” as the participant cannot genuinely claim to fully understand the clinical investigation.
9. 21 CFR 50.20. This does not mean a sponsor, investigator, or site has to compensate for injuries to the participant if the participant is negligent. Exceptions to these requirements are available upon certain investigator and physician certifications as to the existence of specific facts which make obtaining informed consent infeasible, where the U.S. President has waived consent for the administration of a new drug to an armed forces member, for emergency research, or where the IRB waives the consent requirements because it finds that the research presents no more than a minimal risk of harm to participants and involves no procedures for which written consent is normally required outside the research context. See 21 CFR 50.23, 50.24, 56.110.
11. This should amount to “sufficient information” and include pertinent alternatives such as, supporting care with no additional disease directed therapy; this should be more than a list but a full risk/benefit explanation may not be required.

12. Note that absolute confidentiality should not be promised or implied.

13. This does not mean the sponsor must pay for injuries; if the sponsor will not pay, the consent must include a statement to the effect of: “no funds have been set aside for medical treatment for injury; the cost will be billed to you or your insurance.” These do not waive a participant’s legal right to seek redress.

14. 21 CFR 50.25(a). Additionally, federal regulations also require that the consent disclose certain points and include other information based on the particular details of the study, for example any additional costs the subject could incur from participation in the research. 21 CFR 50.25(b).

15. 21 CFR 50.25(c). The database statement must read: “A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”


17. 21 CFR 50.27.

18. Id. Although not required, providing the signed version of the copy provided to the participant helps to protect investigators and sites.

19. 21 CFR 50.27. Where a short form consent is used, a copy of the consent, along with a written summary of the oral presentation, must be provided to the participant. The witness must sign both the short form consent and a copy of the summary. Furthermore, the person obtaining the consent must also sign a copy of the summary.

20. 21 CFR 50.50 et seq.


22. Id.

23. Id.


25. Id.


27. Id.

28. Id.

29. Id.