

Informed Consent: A Pivotal Piece in a Trial

BY ARON SHAPIRO; INGRID LAPSA; DAVID WATERS-HONCU; AND ASHLEY LAFOND

When a patient appears to be eligible to participate in a clinical trial, it is necessary to obtain and document his or her informed consent before proceeding with any study-specific screening procedures. The informed consent process is the primary and among the most critical aspects of human participant protections in the entirety of clinical trial execution. The process itself involves four specific elements, all of which must be documented: disclosure and comprehension, the informational components; and competence and voluntary choice, the consent components.

INFORMED CONSENT PROCESS

Institutional review boards (IRBs)/ethics committees (ECs), clinical investigators, and sponsors of clinical research share joint responsibility for ensuring that the informed consent process is conducted properly and professionally, but the responsibility of actually obtaining informed consent is ultimately the investigator's alone. The US Food and Drug Administration (FDA) states: "Informed consent is more than just a signature on a form, it is a process of information exchange that may include, in addition to reading and signing the informed consent document, subject recruitment materials, verbal instructions, question/answer sessions and measures of subject understanding."¹ The tangible outcome of this process is the establishment of proper documentation to satisfy legal and regulatory requirements. The foundations, however, are central among the basic fundamentals of ethical conduct and research practice. These internationally accepted standards were first set forth in the 1964 Declaration of Helsinki and remain recognized to this day. From a practical perspective, the informed consent process is also a chance to launch good patient-practitioner communication and develop positive rapport with potential subjects. In sum, the consent process should serve as the basis for a meaningful exchange between the investigator and the subject.

INFORMED CONSENT ELEMENTS¹

Although the FDA does not explicitly require the clinical investigator to personally conduct the consent interviews, he or she is responsible for ensuring that proper informed consent is obtained from each subject before the subject is allowed to participate in a clinical study. The IRB-approved

informed consent form (ICF) used to document consent may be either of the following: a full, written document or a short form that states the relevant information has been presented orally to the subject. It is not uncommon to see a high frequency of these short forms used in retina studies because many potential subjects for these trials have severely compromised visual acuity. In this case, an impartial witness must be present during the informed consent discussion. After the ICF and any other IRB-approved supplemental information has been provided to, read by, and explained to the subject (and/or the subject's legally authorized representative) and the subject consents to participate, the subject is asked to sign and date the ICF. The witness should also sign and date the consent form to attest that the information in the consent form was accurately presented to the subject.

In the context of an investigational drug, biologic or device study, the ICF must also contain a statement that the study involves research; this differentiates it from consent forms used for standard medical procedures. Additionally, this must be supplemented by an explanation of the purpose of the study, an outline of the study visit schedule and procedures, the number of subjects expected to be enrolled in the study, and identification of any investigational products. It is important that the information be in terms that the subject can understand. Taking the time to thoroughly review terms or procedures that may be unfamiliar to the subject (e.g. randomization, placebo control, tonometry) are crucial to ensuring the subject is truly informed prior to giving his or her consent to participate. Additionally, it may help to clarify any concerns prior to the study and eliminate confusion or misunderstanding as the study commences.

Informed consent must be based on an objective presentation of the study and its main components—this includes both the risks and potential benefits. Thus, the ICF and consent discussion must describe both. Regarding potential benefits, some subjects may experience a personal benefit while others may not. At the very least, it is quite possible that the study that is taking place will help further research in that particular field and may help generations to come. Discussion of risks must detail those that are known as well as include a statement that there may be risks yet unknown. Foreseeable risks or side effects associated with participating may be based on outcomes of prior research or general

medical understanding. For example, in a study with intravitreal injections, complications seen in prior studies or potential side effects should be outlined in the ICF and also carefully explained to the subject. At the same time, it is the nature of research for unknown or unforeseeable risks to exist, and this is very important for patients to understand before deciding to participate in research. Keeping with this, subjects must also be made aware that they will be notified of any significant new findings that emerge during the course of the research that may be relevant to the subject's willingness to continue participation. Outlining both the risks and the potential benefits as part of the consent process supports a subject's ability to make an educated and well-informed decision regarding his or her participation in the study. As always, ensuring research subject safety is a pillar of any clinical trial, and the informed consent form must provide information regarding whether any compensation and/or medical treatments will be available if an injury occurs. The ICF should also clearly provide contact information for any pertinent study questions that the research subject may have and provide information on whom to contact in the event of a research-related injury.

Study-specific details are not the only components of informed consent. The consent form must also summarize any alternatives to entering the study so that the subject is made aware of any FDA-approved therapies or other available therapeutic options. For example, in a wet age-related macular degeneration study, the informed consent might make note of pegaptanib (Macugen, Eyetech), ranibizumab (Lucentis, Genentech), and verteporfin (Visudyne, QLT), the three FDA-approved drugs indicated for its treatment, and recommend that the subject discuss alternative treatments with the study doctor. If the study is registered with clinicaltrials.gov or any other registry, the ICF should direct patients to the database listing. Much like the potential risks and benefits, a patient's understanding of any therapeutic alternatives helps to ensure an informed decision.

Another important component of the informed consent concerns confidentiality of records. Informed consent forms should notify study subjects of the extent to which the confidentiality of their protected health information and any records identifying them will be maintained. Patients should be made aware that the FDA may inspect study records and that they do not have the option to keep their records from being reviewed. Very simply, it is imperative that the subjects be well aware of how their information will be used and disclosed prior to agreeing to participate in the study.

It should also be explained that there may be circumstances in which a patient's participation may be terminated by the investigator or sponsor, independent of the subject's desire to exit the study. Indeed, the subject's participation in a research study may be terminated at

any time. A terse statement relating that subjects could be removed from the study will not suffice; patients must understand the particular anticipated circumstances by which their participation may be terminated.

Patient autonomy throughout the consent process, and indeed the entire study, is an ethical cornerstone in conducting human research.² It should be emphasized and reiterated that participation in the study is voluntary and that the subject may decline to participate or to discontinue participation at any time. Each subject should be fully informed that he or she is permitted to withdraw consent to participate at any time, for any reason, and that he or she will not relinquish any rights by participating in a research study. Similarly, if the subject has any questions about the study at any time, he or she should be urged to contact the study doctor or staff personnel. The consent process is in place to ensure that potential subjects are provided with all information relevant to the study that they may use in determining whether they want to participate, and each subject must know that the decision to leave the study is available to them at each step along the way.

CONCLUSION

The informed consent process is a cornerstone of clinical research, and should be regarded as such. Be sure to engage in a continuous dialogue with subjects and maintain a sensitive awareness of any reservations that they may have towards participation in the trial. At times, the information being presented to the subject can be difficult to understand or even overwhelming and may require time to absorb and think about. Potential subjects should be encouraged to take information home and discuss their potential participation with family members or close friends in order to make a well-informed decision. And remember, informed consent may be documented with a signature on a form, but it does not begin or end there; the consent process continues throughout the entire study. It is your obligation as an investigator to ensure that each subject is informed throughout his or her involvement in the study, just as the subject maintains authority over his or her consent during the same period. In effect, a subject's choice to continue participating in a trial is an act of consent at every step of the way. ■

Aron Shapiro is Vice President of Retina at Ora, Inc., in Andover, MA. Ingrid Lapsa is a Manager of Quality Assurance; David Waters-Honcu is a Manager of Retina Clinical Operations; and Ashley Lafond is a medical writer at Ora, Inc.



1. A Guide to Informed Consent - Information Sheet Guidance for Institutional Review Boards and Clinical Investigators: Contents <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm>. Accessed June 13, 2011.

2. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. http://videocast.nih.gov/pdf/ohrp_belmont_report.pdf. Accessed July 18, 2011.