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THE PROCESS OF INFORMED CONSENT

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Introduction

Every investigator and clinical research coordinator (CRC) should recognize the importance of obtaining valid and appropriate informed consent as an important protection of the rights and welfare of human subjects. Indeed, the very first principle of the Nuremberg Code[1], which represents the genesis of research ethics, states, "The voluntary consent of the human subject is absolutely essential." Obtainment of informed consent involves both the process which is the consent dialogue and the documentation of obtaining informed consent on the IRB-EC approved informed consent form (ICF). Unfortunately, the current HHS and FDA regulations which set the requirements for informed consent do not address the "process" in sufficient detail. These regulations simply state "an investigator shall seek … consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." [2, 3]

The lack of detail regarding the process of informed consent in both the regulations and in FDA/OHRP guidance is not surprising since these regulations were promulgated in 1981 and the informed consent requirements have never been revised or updated. On the other hand, there has been a remarkable evolution of medicine with its sophisticated healthcare technologies. Concomitantly, the field of research ethics has also evolved including emphasis on informed consent ethics as evidenced by a very extensive literature on this topic. Indeed, there have been many national and international working groups, as well as numerous ACRP conference sessions, devoted to identifying ways to improve informed consent including more attention paid to the consent process. Given the current length and complexity of ICFs, the need for research personnel to engage prospective subjects in an effective informed consent process has become critical.

One of the most advanced international guidelines on the informed consent process was put forth by the Council for International Organizations for Medical Sciences (CIOMS).[4] The Organization's commentary on Guideline 4 states "obtaining informed consent is a process that is begun when initial contact is made with a prospective subject and continues throughout the course of the study. By informing the prospective subjects, by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in doing so manifest respect for their dignity and autonomy. Each individual must be given as much time as is needed to reach a decision, including time for consultation with family

members or others." The CIOMS commentary further states "informing the individual subject must not be simply a ritual recitation of the contents of a written document. Rather, the investigator must convey the information…in language that suits the individual's level of understanding…the investigator must then ensure that the prospective subject has adequately understood the information."

The purpose of this ACRP guidance document is not to provide a literature review or summarize the recommendations of various working groups. Instead, the Association decided it would be helpful to our members if we provided short and focused guidance which describes how to best structure the informed consent process in accordance with best practices. In order to adhere to brevity, a description of the characteristics of the consent process will exclude recruitment and begin at the point at which prospective subjects have been presented with the IRB/EC approved ICF. While this document does not address parental permission or obtainment of "proxy" consent by use an adult subject's legally authorized representative (LAR), the guidance is equally applicable. Finally, assent of children is not addressed since this topic warrants its own focused guidance.

The previously mentioned CIOMS commentary will provide the basic premise upon which this guidance on the process of informed consent is built. The following are the characteristics of the process as it is carried out from the location of the initial consent dialogue to documentation of the subject's consent which represents the conclusion of the process. Since informed consent is necessarily an on-going process carried out throughout the subject's participation in the research, this extension of the process will also be addressed.

Environment

The environment where the process of consent is conducted should be determined by the type of research being conducted but there should always be a period where a private, confidential, and "safe" setting is afforded to facilitate a constructive dialogue between the prospective subject and the person(s) involved in obtaining consent. A physician's office or an examination room would likely be an appropriate location whereas a patient waiting room or a pre-op area would be examples of locations which may not be conducive to the obtainment of legally effective informed consent. Patients in these latter environments may exhibit stress associated with illness or procedural related anxieties (e.g., fear of pending surgery, cardiac catheterization, chemotherapy) which could compromise the process of consent.

Assessment of Capacity to Consent

All prospective subjects must have the cognitive ability to provide legally effective informed consent. Individuals who do not have such ability (i.e., decisionally impaired persons) can only be enrolled in research through consent of their legally authorized representative (LAR). If there is any concern about an individual's cognitive ability an appropriate assessment should be performed by a qualified individual. Different clinical specialties have specific standards for assessing cognitive capacity in very diverse patient groups. The standards of the clinical specialty area where the research will be conducted should generally be used for the assessment. The method for assessment of capacity to consent should be based upon the likely degree of cognitive or decisional impairment in the prospective subject population. In some cases, it would be appropriate to use more comprehensive assessment tools such as a neuropsychological evaluation and even utilize an independent assessor – one not affiliated with the researcher, research site or the research protocol. In other cases where there is not a need for a lengthy assessment, cognitive capacity can generally be determined by a series of simple questions.

Presentation of the Elements of Informed Consent

The required elements of informed consent should be presented and discussed with the prospective subject in a sequential manner utilizing the approved ICF as a guide. The presentation should be structured to facilitate a dialogue with reinforcement and elaboration of important information (e.g., the risks of the research). The person(s) involved in obtaining the subject's consent should constantly evaluate whether the process is achieving the goal which is obtainment of legally effective informed consent from the subject. In addition to paying attention to general signs of information receptivity, it is often helpful to ask open-ended questions in order to identify points of confusion which require clarification.

One of the difficulties that investigators and other research personnel often encounter, both during and after the informed consent process, is "therapeutic misconception" which can literally render informed consent invalid. Therapeutic misconception can be defined as the situation where a subject or their LAR either over-estimates the direct therapeutic benefits which may be gained by participation in the research and/or under-estimates the risks thereby compromising their ability to provide and/or maintain a voluntary and knowing informed consent. Research personnel who are

involved in the consent process should take all necessary steps to minimize the possibility that subjects will consent to participate in research because of therapeutic misconception.

There are many factors which promote therapeutic misconception such as the way the information is presented to the prospective subject and terms in the ICF (e.g., “new drug”; “treatment study”; “opportunity to participate”). In addition, physicians engaged in the informed consent process must remember that they are both a physician and an investigator. The prospective subject, in turn, should understand this dual role and that it can represent a potential conflict. Indeed, the issue of conflicting roles also applies to other health care personnel (e.g., RNs) who have both treatment and research-related responsibilities.

Use of a Delayed Consent Procedure

The amount of time allotted to the process of consent is dependent upon the nature and complexity of the research and the need to minimize the possibility of coercion or undue influence. In some research (e.g., complex or risky research) a delayed consent procedure should be used in order to afford the subject the opportunity to discuss participation in the research with family, friends, counselors, or other confidants before they sign the ICF. If the individual is uncomfortable or anxious about participating in the research they should be instructed to take the ICF home for further review and consideration before deciding whether or not to participate in the research.

Assessment of the Subject’s Comprehension

Investigators and other research personnel involved in obtaining informed consent have a legal and an ethical obligation to ensure that the prospective subject has sufficient knowledge and comprehension of all the elements of informed consent to enable him/her to make an informed and enlightened decision whether or not to participate in the research. The fact that an individual is prepared to sign the ICF and has no unanswered questions does not necessarily represent sufficient evidence of an adequate level of comprehension. Some investigators and CRCs, therefore, choose to determine the level of comprehension by questioning the individual concerning their understanding of the elements of informed consent. Alternatively, the prospective subject can be asked to explain in his/her own words their understanding of the research. In some cases computer technology is used to assess comprehension through the use of multiple choice tests. This method, however, is not commonly utilized.

Documentation of Informed Consent

Documentation of informed consent is the conclusion of the initial consent process. Whoever documents the obtainment of informed consent (i.e., signs the ICF) must be qualified to attest to the fact that the subject has provided legally effective informed consent. While a number of qualified research personnel can, and should, be involved in the process of consent, it should be remembered that the Principal Investigator (PI) is ultimately responsible for all aspects of the research including informed consent. Therefore, it is incumbent upon the PI to be involved in both the process and documentation of informed consent, particularly in studies involving investigational drugs or devices under an IDE. However, if the PI is unavailable, a sub-investigator with appropriate expertise who is also physician can serve as the PI's surrogate. In some studies, such as clinical trials of certain FDA-approved drugs or procedures involving minimal risk, it may be acceptable to have non-physicians (e.g. CCRCs) to both conduct the process and document the obtainment of informed consent.

The individual who assumes responsibility for documentation of informed consent and the consenting subject should sign and date the ICF, preferably in each other's presence. It is unacceptable for the person documenting consent to sign the ICF in advance of obtaining the subject's signature. Indeed, some PIs, out of an abundance of caution, require both the date and the time that the signatures were obtained. Finally it has become common practice for the ICF signature blanks to have an associated certification statement which represents the consent attestation.

Ongoing Consent

Compliance with regulations as well as ethical conduct of research requires that subjects be informed of new findings that may influence their continued participation in te research. In certain instances it is appropriate to actively seek continued permission/consent from subjects. A subject's preferences and interests may change over time, even in the absence of material changes in the research protocol. Indeed, some subjects forget they are participating in research which, in turn, perpetuates therapeutic misconception. Therefore, while regulations do not require re-consent, good ethics may. Depending upon the nature of the research and the subject population, the PI should ensure that written documentation of the re-consent is obtained at various intervals. In

other cases, documented verbal reaffirmation of the subject's willingness to continue participation in the research is sufficient.

Conclusion

Respect for persons demands that legally effective informed consent be obtained from subjects before they participate in research. Indeed, informed consent may be the most important protection of human subjects. Admittedly, there are a number of variables which affect the validity of consent and the process of consent can be both difficult and frustrating. Nevertheless, all research personnel should remember principle 1 of the Nuremberg Code: "The voluntary consent of the human subject is absolutely essential."

References

1. The Nuremberg Code; *"Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10",* Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.]

2. HHS regulations at 45 CFR 46.116; Protection of Human Subjects. Revised January 15, 2009; Effective July 14, 2009. 56 FR 28012, 28022, June 18, 1991 (unless otherwise noted).

3. FDA regulations at 21 CFR 50.20; Protection of Human Subjects (Informed Consent). 45 FR 36390, May 30, 1980 (unless otherwise noted).

International Ethical Guidelines for Biomedical Research Involving Human Subjects, prepared Council for International Organizations for Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO); Geneva, 2002.