



# Cancer Research Center Hotline

## The Informed Consent Process in Cancer Research Studies

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The protection of human beings who take part in research studies is of paramount importance. The federal government has taken the lead role in establishing policies and procedures to ensure human subjects protection and safety.

Current regulations have roots in the past. In 1947, the Nuremberg Code was established after 23 physicians were convicted of performing inhumane experiments on Nazi prisoners during World War II. This Code is a set of standards for physicians and scientists who conduct research on human subjects. The first principle of the Code states that voluntary consent is "absolutely essential". It also emphasizes that consent should be based on the knowledge and understanding of the proposed procedures and treatment and the possible risks.<sup>1</sup>

The Declaration of Helsinki, written by the World Health Organization in 1964, was targeted at medical research involving human subjects. It outlined the specific topic, which should be addressed during the informed consent process. Subjects had to be informed, preferably in writing, of the aims and methods of research; anticipated benefits and risks of the study; and right of the individual to refuse participation and to withdraw from the study at any time.<sup>3</sup>

Following a revision to the Helsinki Declaration, on July 12, 1974, the National Research Act (NRA) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical & Behavioral Research. This commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines to follow to assure that research is conducted in accordance with these principles. As a result, the Belmont Report was developed.

Through the Belmont Report, the NRA dictated that all studies using human subjects in research be reviewed by an institutional review board (IRB) before grants could be funded. Issued in 1976, this report summarized the basic ethical principles for research. It currently serves as a guideline for any ethical issues that occur when doing research with human subjects.<sup>4</sup>

The Office of Human Research Protection (OHRP), a branch of the National Institute of Health (NIH), is delegated by the Secretary of Health and Human Services (HHS) to administer programs for institutional protection of human subjects. The Code of Federal Regulations (45 CFR 46) is for the protection of human subjects and is used as a guideline for all regulatory issues. It is evident that the Belmont Report, Federal and state regulations, along with ethical and moral considerations, have shaped the informed consent process.<sup>5</sup>

The process of obtaining proper informed consent has been the topic of increased attention in recent years. Not only clinical researchers, but ethicists, lawyers, and social scientists have all become involved in a constant debate regarding the informed consent process. The practice of obtaining informed consent differs from country to country and physician to physician in particular institutions. The most formalized and standardized regulations can be found in the United States.<sup>1</sup>

Informed consent is defined by the Department of Health and Human Services as "the knowing consent of an individual or his legally authorized representative so situated as to be able to exercise free power of choice without inducement or any element of force, fraud, deceit, distress, or any other form of constraint or coercion."<sup>6</sup> The Food and Drug Administration (FDA) mandates eight basic elements of informed consent: research procedures, risks and discomforts, benefits, alternative treatments, compensation, confidentiality, the voluntary nature of subject participation, and contacts.<sup>5</sup>

The consent form is merely the documentation of informed consent and does not, in and of itself, constitute informed consent. The fact that a subject signed a consent form does not mean that he/she understood what was being agreed to or truly gave their voluntary consent. One problem with informed consent is information overload, which can cause increased stress, confusion, and impaired decision-making. Potential participants who have information overload cannot sort out what is important from what is not important. The average person can juggle only three to five pieces of information at one time; potential participants must process a huge amount of information.<sup>9</sup>

Prior to participating in a clinical trial or any research study, investigators are required to provide subjects with information so that they can make an informed decision about participating in a study before the study is initiated. Informed consent implies that subjects have been given complete information about the study, that they comprehend the explanations, and that they are volunteering to participate in the study based upon this understanding. They must also understand they can withdraw from the study at any time. The informed consent document is only one part of an ongoing process of informed consent that starts before a participant goes on study, and continues throughout study participation and often through follow-up.<sup>7</sup>

Many people who are being recruited for clinical trials and other cancer research studies are sick; they may be stressed, depressed, and fearful. A 1996 study showed how disease severity affects informed consent understanding. Healthy volunteers remembered the most about risks and side effects, while severely ill patients in phase I studies remembered the least.<sup>9,10</sup>

Appelbaum et al found that many subjects thought the research project would benefit them, despite what they were told and read in their consents.<sup>9,12</sup> Gotay found in a large prostate cancer prevention study, that many men did not remember the consent process. The results of a questionnaire mailed to the healthy participants indicated that the informed consent process must be reinforced throughout the study in order to maintain compliance.<sup>11</sup>

The informed consent process should include a dialogue between investigators and potential research participants. Potential participants should be allowed to review the consent form and ask questions. Although potential participants are encouraged to ask ques-

tions, many people are afraid to ask questions because they do not know what to ask or they do not want to appear dumb. To avoid this, the subjects should take the consent documents home to read and write their questions on the consent form. They should be encouraged to highlight areas they do not understand. When the subjects return with the consent form, the investigator should answer all questions and concerns that the potential participants have, to ensure that the rights of the participant are protected.

The National Cancer Institute's (NCI) mission has always included the ethical conduct of cancer clinical trials with an emphasis on informed consent. Though consent forms are supposed to help subjects make well-informed decisions, because of concerns over meeting legal requirements, the consent forms in NCI-sponsored clinical trials have become very complex, very long, and very difficult to read and understand.

In late 1995, a working group of experts, which included IRB members, clinical investigators, nurses, patient advocates, lawyers, ethicists, communication experts, members of the pharmaceutical industry, and staff from OHRP, FDA, and NCI met to discuss problems with the informed consent process.<sup>7</sup> This group of experts, named the Comprehensive Working Group, was asked to recommend improvements to the informed consent and quality of consent forms. The group worked diligently for over two years.

In September 1998, the Comprehensive Working Group published a template called Recommendations for Developing Informed Consent Documents for Cancer Clinical Trials.<sup>8</sup>

The general recommendations included suggestions about formatting, readability and specific elements of informed consent. The group also suggested writing consents at an eighth grade reading level. However, even at a sixth grade reading level, a consent form is difficult to understand because most people are not familiar with research procedures. The recommendations have been supported by a letter from OHRP, a Special Award for Plain Speaking in Government from Vice President Gore's National Partnership to Re-Invent Government in 2000, and an NIH award for Plain Speaking in 2001.<sup>7</sup>

Now, more than a half a century since the Nuremberg trials, new ethical issues have appeared on the horizon of medical research. In particular, consent issues with children have surfaced. Children are considered a vulnerable population at risk for exploitation; therefore, they are given special protection in clinical research.<sup>13</sup> At the same time, research on children is sorely needed to understand more about pediatric diseases and improve health care for children. Both parental agreement plus a child's "assent" are needed for a child to participate in research.

In Hawaii, before research studies are initiated, the University and/or hospital IRB(s) review each study's design and consent procedures and forms. An IRB is comprised of men and women, who have the professional competency necessary to review specific research activities. Each IRB must include at least one member whose primary concerns are in scientific areas, one member in a nonscientific area, and at least one member who is a community person not affiliated with the institution.<sup>5</sup> The IRB is responsible for safeguarding the rights and welfare of human subjects in research. This includes complying with federal and local regulations and ethical principles.

If an IRB regularly reviews research that involves vulnerable subjects, such as children, prisoners, pregnant women, or handi-

capped or mentally disabled persons, one or more individuals must be included on the board who are knowledgeable and experienced in working with these subjects.

In summary, informed consent is a process, not a single event. It requires health professionals to have expert knowledge and good communication skills. With the complexity of cancer research, such as potential short- and long-term toxicities of treatment, it requires investigators to continue the process throughout the study.

## References

1. Aaronson NK, Zittoun R. Informed consent and cancer clinical trials. *Psychosocial Aspects of Oncology* (Edited by Holland JC and Zittoun R): 117-120. Springer, Berlin, 1990.
2. Faden R, Beauchamp T. *A history and theory of informed consent*. New York: Oxford University Press, 1986.
3. Grady C. Ethical issues in clinical trials. *Seminars Oncology Nursing*, 7(4): 288-96, 1991 Nov.
4. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report*, 1979.
5. U S Department of Health and Human Services. 45 Code of Federal Regulations 46, 1991.
6. Department of Health and Human Services: Protection of Human Subjects: Informed Consent. Washington DC, Federal Register, January 27, 1981, part 1X.
7. Flach, J. Developing informed consent documents. *SoCRA Source* 2002; 31: 19-21.
8. Comprehensive Working Group on Informed Consent in Cancer Clinical Trials. Recommendations for the development of informed consent documents for cancer clinical trials, 1998.
9. Hochhauser M. The informed consent, how literate is your research participant? and "therapeutic misconception". *SoCRA Source* 2002: 34-37.
10. Schaeffer MH, Krantz PS, Wichman A, Masur H, Reed E, Vinicky JK. The impact of disease severity on the informed consent process in clinical research. *American Journal of Medicine*; 1996; 100 (3): 261-268.
11. Gotay C. Perceptions of informed consent by participants in a prostate cancer prevention study. *Cancer Epidemiology, Biomarkers and Prevention*; October 2001, 16: 1097-1099.
12. Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: Consent to research and the therapeutic misconception. *Hastings Center Rep* 1987; 17: 20-24.
13. Simar MR and Johnson V. Pediatric informed consent, challenges for investigators. *July 2002*; 11 (7): 46-54.

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