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**International Council of Ophthalmology
Research Committee**

**Regulations and Ethical Considerations Related to
“Research,” Particularly When Investigations Involve
Human Subjects**

NOTE: “Research,” defined as the generation of new knowledge, with the intent of sharing it with others, is highly regulated in most countries. In the U.S., all such research is subject to regulations if it involves the use or analysis of any human data, even if it never entails direct contact with patients. Thus, if a study only employs chart reviews, or analyzes billing and abstracted data with or without personal identifiers, the study must receive approval by an authorized IRB (Institutional Review Board) prior to initiating the project. All human research projects also must inform the IRB at the time of ANY change in the research protocol, and must submit progress reports annually thereafter.

The background and fuller discussion of pertinent ethical and regulatory issues involved in human research, below, was prepared at the request of the ICO by Professor Nancy Kass of the Johns Hopkins Bloomberg School of Public Health.

When a researcher enrolls human beings into studies, various ethics guidelines, codes, and regulations must be followed. These guidelines are intended to ensure research is not too risky, that subjects join voluntarily, and that research benefits and burdens are fairly distributed across populations. Ethics codes and regulations often were drafted after research abuses came to public light, and government or professional bodies determined new oversight mechanisms might minimize such problems in the future.

The Nuremberg Code of 1948 is considered the first international code of research ethics (ohsr.od.nih.gov/guidelines/nuremberg.html). This Code was written in reaction to horrific experiments forced on concentration camp prisoners by Nazi doctors during World War II. Testimony at the war crimes tribunals described experiments submerging prisoners in ice cold water to see how long it was before hypothermia developed and injecting prisoners with live viruses to observe the effects. Not surprisingly, the first principle in the

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Nuremberg Code states that participation must be voluntary; ensuring the participant has sufficient information and his consent is voluntary is the “personal responsibility” of the investigator. The Code further states the experiment should be based on previous animal research and knowledge of the problem, it must be conducted by qualified persons, and the subject may stop participation at any time. The Code, however, had little impact on ethical norms. Most researchers considered the Nazi experiments so horrific, and so different from the research they did, that they assumed the Code had little relevance for them.

As more clinical research was conducted, physicians became aware of potential dual role conflicts when doctors enroll patients in research. In response, the World Medical Assembly drafted the Declaration of Helsinki (ohsr.od.nih.gov/guidelines/helsinki.html). The Declaration articulates many ethical requirements outlined in Nuremberg, such as informed consent and basing research on good science but also reminds doctors that, regardless of the importance of the research question, “the health of my patient will be my first consideration.” The Declaration is also the first code stating research not conducted in accordance with these ethical norms should not be published, regardless of scientific merit.

Within the United States, guidance and law changed in response to a series of research abuses that came to light in the 1960s and 1970s. The Willowbrook hepatitis study, in which some numbers of healthy children were fed concentrations of hepatitis, and a Hospital study, in which elderly, institutionalized residents were injected with live cancer cells, outraged the public. Dr. Henry Beecher, a professor at the Harvard Medical School, published a widely cited article in *the New England Journal of Medicine* cataloguing 22 experiments from recent, top medical journals, where he believed ethical problems had occurred such as substituting placebos for established treatment without telling patients and inappropriately targeting vulnerable populations.

Since examples came from the best medical journals, he suggested that the *norm* for U.S. medical research needed change. Finally, in 1972, the public learned the U.S. Public Health service had been conducting the “Tuskegee syphilis study” for 40 years. This study enrolled poor, black men with syphilis and led them to believe they were receiving free medical care, something they desperately wanted. Instead, government physicians did multiple tests on the men to track the natural history of syphilis over a lifetime. Even after antibiotics were developed in the 1940s, men were still not treated, without their knowledge. The study was abruptly stopped in 1972 and Congressional hearings held.

As a result, the National Commission for the Protection of Human Subjects was convened from 1974-1978, charged by Congress to identify ethics principles to guide human research; this resulted in the Commission’s landmark publication, *The Belmont Report*.

The Belmont Report (ohsr.od.nih.gov/guidelines/belmont.html) outlined three ethics principles that must be followed when conducting human research: respect for persons, beneficence, and justice. Respect for persons recognizes all human beings have value, and their ability to make autonomous, voluntary decisions should be respected. This happens in research through the informed consent process which requires not only voluntary decision making but also adequate information to make the decision. Valid informed consent requires disclosure of relevant information by the investigator, understanding of information by the participant, voluntariness of participation, and competence to make the decision. Many guides and laws further require study information be provided on an "informed consent form" to be signed by participants. Informed consent requires telling prospective subjects the activity is research, its purpose, the main procedures involved, risks, possible benefits, alternatives to participation, methods to protect confidentiality, and that joining is voluntary.

Beneficence requires researchers to examine the risks and benefits of research, to ensure risks are reasonable in relation to anticipated benefits, and to minimize risks as possible. Risks can be physical (side effects, medical harms), psychological (anxiety, emotional upset), social (stigma from others, often as a result of a confidentiality breach), or economic. Having valid research methods also is relevant to beneficence. If sample size is inadequate, if investigators are not properly trained, if literature is not properly reviewed, or if analytic techniques are flawed, the risks and burdens of study volunteers will be for little or no benefit and, thus, ethically may not be justified. Sound training in research methodology, thus, is not simply a scientific imperative; it is also an ethical one.

Justice is the ethics principle requiring research benefits and burdens to be equitably distributed across populations. Research cannot target vulnerable populations, prisoners, mentally disabled persons, or those in institutions unless it relates directly to them. Similarly, new experimental therapies thought to be promising cannot be tested only among the privileged and sophisticated who clamor for access.

When the U.S. Congress created the National Commission to outline ethics principles for research, they also passed a *law* for the first time related to ethics and human research. The 1974 U.S. Code of Federal Regulations (ohsr.od.nih.gov/guidelines/45cfr46.html) required federally funded health research to be reviewed by an Institutional Review Board (IRB), which, in turn had to ensure risks were minimized, sound procedures were used, informed consent was sought and documented, and populations were selected fairly.

Importantly, U.S. regulations apply to all federally funded research, whether the research is conducted in the U.S. or internationally. International research must be reviewed both at the investigator's U.S. home institution, and also in the host country where the research is conducted. According to the regulations, IRB review must occur both before the project starts, but also annually for a routine progress report, and also whenever ANY protocol change is made. Thus, adding

a new population, changing the number of blood draws, or changing the interview instrument, all require an IRB amendment. Projects in other countries that will receive any U.S. government funding must obtain a Federal Wide Assurance (www.hhs.gov/ohrp/assurances/assurances_index.html).

More recently, discussion emerged that research in developing countries raise additional and challenging ethics issues. The Council for the Organization of Medical Sciences (CIOMS), based in Geneva, drafted the CIOMS guidelines in 1992 to outline ethical norms for this context (www.cioms.ch/frame_guidelines_nov_2002.htm). Much CIOMS text is drawn directly from the Declaration of Helsinki, with new sections added to address issues relevant to resource poor settings, such as appropriate use of incentives and obligations to communities when the research is over. Growing numbers of countries now have their own laws that provide oversight for research that involves humans (www.hhs.gov/ohrp/international/HSPCompilation.pdf).

Research ethics training: Anyone receiving a grant from the U.S. National Institutes of Health or submitting a proposal to a U.S. authorized IRB is now required to demonstrate evidence of research ethics training. Moreover, international organizations and institutions are calling for access to more training in the ethics of research. Free and available materials on the ethics of research developed specifically for research in low-income countries were developed by Family Health International (www.fhi.org/en/RH/Training/trainmat/ethicscurr/index.htm). Their training also includes some “train the trainer” materials so host country investigators can provide workshops in research ethics for their colleagues.