EXECUTIVE SUMMARY

Regulations and Guidelines

The Nuremberg Code outlines the earliest published set of ethical guidelines for biomedical research. It was part of the 1948 judgment in the trial of Nazi physicians who conducted experiments on prisoners during World War II. The Nuremberg Code includes an absolute requirement for the informed consent of the subject for research participation. The Nuremberg Code also requires that experiments be scientifically valid, and that the risks are justified by the potential benefits to society in the form of generalizable knowledge.

The World Medical Association published the Declaration of Helsinki in 1964, and it has been revised on eight occasions since then. The Declaration of Helsinki articulates basic ethical principles and guidelines for human subjects research. The Declaration of Helsinki recognizes that not all potential subjects have the capacity for making decisions about research participation, so it allows the enrolment of incapacitated subjects with the consent of a substitute decision-maker. The second revision of the Declaration of Helsinki in 1975 included one of the first regulatory requirements for the review of research proposals by a research ethics board (REB) to assure a study's compliance with basic ethical principles and guidelines. Research funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada is subject to the Tri-Council Policy Statement (TCPS). Institutions that receive funds from these agencies also apply the TCPS to the REB review of research funded by other sources. The TCPS lays out requirements for REB composition and function, informed consent, subject selection, analysis of harms and benefits, and protections for vulnerable subjects.

Basic Principles

The ethical guidelines and regulations that have been developed over the past 50 years reflect a set of basic ethical principles: respect for persons, beneficence and justice.

Respect for persons: Autonomy, informed consent and protecting vulnerable subjects

The principle of respect for persons describes two separate moral requirements. First, capable individuals should be treated as autonomous agents. Second, those with diminished autonomy require additional protections.

Practically, this means that the choices of capable individuals must be respected. This is the source of the requirement that subjects give their informed consent for research participation. Deceiving a person, withholding information or ignoring an individual’s wishes is disrespectful to that individual. The TCPS lays out the information that must be disclosed to potential subjects during the consent process. These disclosure requirements will often be formalized by institutional REBs.

Some individuals may have diminished autonomy. The TCPS recognizes that respecting these individuals requires extending them additional protections. The extent of the necessary protections depends on the subjects’ degree of vulnerability, and on the risk of harm and likelihood of benefit.

Beneficence: The analysis of risks and potential benefits

The principle of beneficence describes the requirement to protect, as far as possible, the well-being of research subjects. This means the avoidance of deliberate harm, and maximizing the potential benefits while minimizing risks.

Clinical research includes both therapeutic procedures and non-therapeutic procedures. Therapeutic procedures offer the possibility of direct benefit to the subject. Non-therapeutic procedures, by definition, do not offer benefit, but are used to gather data and answer the scientific question of the study. The risks and potential benefits of therapeutic and non-therapeutic procedures should be considered separately (Figure 1).

Therapeutic procedures must be roughly consistent with competent medical care in terms of an overall assessment of the
risks and potential benefits to subjects and of uncertainty.6 Therapeutic procedures must satisfy the requirement of clinical equipoise. Clinical equipoise requires that, at the start of a trial, there is a state of honest, professional disagreement as to the preferred treatment in the community of expert clinicians. Clinical equipoise ensures that subjects will not knowingly be disadvantaged by randomization to either arm of the clinical trial.7

One practical implication of these ethical requirements for therapeutic procedures is that the use of placebo controls is only justifiable if no effective treatment exists for the condition under study, or if there is no acceptable therapeutic option.6,8

The risks of non-therapeutic procedures must be first be minimized as far as possible within a sound scientific design. For example, unused serum collected for clinical purposes may be used to measure biochemical markers rather than subjecting the subjects to additional blood draws. Second, the risks of non-therapeutic procedures must be reasonable in relation to the importance of the scientific knowledge that is expected to be gained.

**Justice: Fairness in subject selection**

The principle of justice entails a fair distribution of the burden of research risks, and an assurance that the benefits of research will similarly be fairly distributed.

Practically, the principle of justice forbids the use of populations of convenience for research. Subjects who are easily accessible because they are hospitalized or institutionalized already bear significant burdens because of their medical conditions. Burdening these populations with research risks is just only if the class of subjects will benefit from the research. Basic science or physiological research that offers no benefit to these subjects is permissible only if it is related their medical condition. Otherwise, a less vulnerable subject population, such as healthy volunteers, is more appropriate.

The principle of justice requires that the burdens and benefits of research be fairly distributed. For both scientific and ethical reasons, clinical research must include subjects who suffer from the medical condition under investigation. Conversely, the exclusion of particular groups of subjects (e.g., women, children, the elderly) without scientific justification may deprive these groups of valuable evidence as to the efficacy of a particular therapy.

**Special Populations**

Certain subjects, by virtue of diminished capacity or the seriousness of their medical condition, are considered more vulnerable than others. The principle of respect for persons requires vulnerable subjects to be extended additional protections.

**Children**

Early in life, children are not capable of making informed decisions about research participation. Because of this lack of capacity, children constitute a vulnerable population and are entitled to additional protections. A parent or guardian is responsible for making decisions regarding research participation that are in the child’s best interests.

If possible, it is necessary to seek the assent of the child prior to enrolling him/her in a research study. Assent refers to a child’s agreement to participate in a study, after the child has discussed the risks and potential benefits with parents, investigators and others. The US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has established 7 years as an appropriate age at which to involve children in discussions about study participation and seek their assent for participation.9 However, the capacity to assent or dissent will vary between children and should be assessed individually. Another protection is a limit on the degree of permissible research risks. The TCPS requires that research on incompetent individuals (such as children) pose no more than minimal risk without the possibility of direct benefit (article 2.5).3 “Minimal risk” refers to the risks associated with daily life, including routine physical examinations or tests.

**Incapacitated adults**

Adults may lack or lose the capacity to make decisions about research participation because of injuries or acute or chronic illnesses. The TCPS lays out the protections that are owed to incapable adult research subjects in Canada (articles 2.5–2.7).1 Incapacitated adults may only be enrolled as research subjects when the research addresses a health concern that is directly relevant to those individuals. The participation of incapacitated adults must be authorized by a substitute decision-maker who is not part of the research team. The research must pose no more than minimal risk, unless the research risks are justified by the potential direct benefits. These protections are identical to those offered to pediatric research subjects. Subjects enrolled in research with the consent of an authorized third party, who understand relevant features of the research, must give their assent to research
participation. Failure to obtain a subject’s assent shall preclude that subject’s participation.

**Emergency health situations**

The TCPS includes a provision for a waiver of informed consent for emergency research when a subject is incapacitated and no substitute decision-maker is available (article 2.8).³ The TCPS requires that the research cannot be practicably done without the waiver and that current treatments for the problem under study are unsatisfactory. The risk of harm must be “…not greater than that involved in standard efficacious care, or it is clearly justified by the direct benefits to the subject.”

**Privacy and confidentiality**

Privacy refers to an individual’s control of access to him/herself, including the right to keep personal information private. Confidentiality refers to a physician or researcher’s responsibility to protect a subject’s privacy.¹⁰ It is a risk of research participation that personal information may be inadvertently disclosed to unauthorized individuals. Steps must be taken to assure that the privacy of subjects’ health information is protected.

Medical research, particularly epidemiologic research, often requires the review of medical records. Provided that steps are taken to safeguard the privacy of medical records, including the anonymization of information retrieved from medical records, the risks to individual subjects from examination of their medical records is minimal. Consent for review of medical records is typically not required for epidemiologic research, provided that privacy safeguards are in place. If, however, the data gleaned from medical records contain identifying information, or if individual patients may be identifiable through published reports of the research, then consent for the use of medical records may be required (TCPS articles 3.2–3.3).³

**Research in developing countries**

There have been concerns that studies performed by investigators from developed countries using subjects from developing countries with a greater disease prevalence may place an unjust burden on those subjects. This problem was particularly highlighted in the 1990s with HIV/AIDS treatment and prevention trials in Africa and southeast Asia.²⁴, ²⁵

The US National Bioethics Advisory Commission, the Council of International Organizations of Medical Science, the World Health Organization, UNESCO and UNAIDS have all issued ethical guidelines for research in developing countries.¹¹–¹⁶ Common themes in these documents include the requirements for proper scientific design; scientific and ethical review of proposed studies, with input from local authorities or ethics boards; voluntary, informed consent from all adult participants; and appropriate care for subjects during and after the trial, particularly for any harms that result from study participation.¹¹ A study performed in a developing country can only be justified if the findings will be relevant to that country’s people. In other words, the study should be responsive to the needs of the population under study.²⁴

**Research ethics and the law**

Canadian Federal legislation does not specifically address the conduct of biomedical research. Only Québec has specific provincial legislation. The Civil code of Québec contains sections pertaining to biomedical research that investigators in this province should be aware of.¹⁷ Rulings in tort law in Saskatchewan and Quebec have set out specific requirements for consent for research participation.

The rulings in Halushka v. The University of Saskatchewan¹⁸ and Weiss v. Solomon¹⁹, ²⁰ explicitly state that the standard for disclosure of pertinent information in the informed consent process is higher for research than for medical practice. In research with no intended benefit to the subject, investigators are required to provide a “full and frank” disclosure of all risks, no matter how rare.³ The TCPS requires disclosure of all reasonably foreseeable harms during consent discussions (article 2.4).³

**Conflicts of interest**

Investigators owe a duty of care to patients who are enrolled in their clinical trials.²¹ Investigators whose studies are funded by external sources (e.g., granting agencies, private foundations, biopharmaceutical companies) may find themselves in a conflict of interest: their duty toward their subjects may be at odds with the agenda of a study sponsor. This may particularly be the case if the investigator is contractually obligated to disclose only those study results that are satisfactory to the sponsor. In some
instances, confidentiality agreements between investigators and sponsors have acted as a barrier to informing research subjects of risks that have been discovered as clinical trials have progressed. The International Committee of Medical Journal Editors has condemned research contracts that prohibit investigators from independently reviewing and publishing the results of sponsored studies. Medical journals require authors to fully disclose any potential financial or personal conflicts of interest. The Canadian Institutes of Health Research requires that the institutions it funds develop policies for the identification, disclosure and management of potential conflicts of interests. The TCPS requires investigators to disclose to subjects, at the time of study enrolment, any potential conflicts of interest (article 4.1A).

Figure 1. The ethical analysis of benefits and harms in research by the REB. (Previously published in Nature Medicine 2004; 10: 570–3).

References

Further Reading and Resources

- Collins A. In the sleep room: The story of CIA brainwashing experiments in Canada. Toronto: Key Porter Books; 1988.


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