Bioethics for clinicians: 10. Research ethics

Education

Éducation

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Abstract

MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS raises complex ethical, legal and social issues. Investigators sometimes find that their obligations with respect to a research project come into conflict with their obligations to individual patients. The ethical conduct of research rests on 3 guiding principles: respect for persons, beneficence, and justice. Respect for persons underlies the duty to obtain informed consent from study participants. Beneficence demands a favourable balance between the potential benefits and harms of participation. Justice requires that vulnerable people not be exploited and that eligible candidates who may benefit from participation not be excluded without good cause. Studies must be designed in a way that ensures the validity of findings and must address questions of sufficient importance to justify the risks of participation. In any clinical trial there must be genuine uncertainty as to which treatment arm offers the most benefit, and placebo controls should not be used if effective standard therapies exist. Researchers have a responsibility to inform themselves about the ethical, legal and policy standards that govern their activities. When difficulties arise, they should consult the existing literature and seek the advice of experts in research ethics.

Résumé

LA RECHERCHE MÉDICALE PORTANT SUR DES SUJETS HUMAINS soulève des questions éthiques, juridiques et sociales complexes. Les chercheurs trouvent parfois que leurs obligations relatives à un projet de recherche entrent en conflit avec leurs obligations envers certains patients. La conduite déontologique de la recherche repose sur 3 grands principes : le respect de la personne, la bénignité et la justice. Le respect de la personne sous-tend l'obligation d'obtenir le consentement éclairé des participants à une étude. La bénignité impose un équilibre favorable entre les avantages et les préjudices éventuels de la participation. La justice oblige à ne pas exploiter les personnes vulnérables et à ne pas exclure sans raison les candidats admissibles qui pourraient bénéficier de la participation. Il faut concevoir les études de façon à assurer la validité des résultats. Elles doivent porter sur des questions suffisamment importantes pour justifier les risques que présente la participation. Dans toute étude clinique, il doit y avoir une incertitude véritable quant au mode de traitement qui offre le plus d'avantages, et il ne faut pas recourir au contrôle par placebo s'il existe des thérapies normalisées efficaces. Les chercheurs doivent s'informer au sujet des normes éthiques, légales et politiques qui régissent leurs activités. Lorsqu'il se présente des difficultés, ils devraient consulter les publications existantes et demander conseil à des experts en éthique de la recherche.

Dr. W is a family practitioner with a special interest in the treatment of HIV infection and AIDS. He receives a letter from the coordinator of a study to evaluate a promising new treatment for the prevention of HIV-related dementia. The letter invites Dr. W to submit the names of potentially eligible patients. He will be paid $100 for each name provided.

Dr. X, a psychiatrist in private practice, is approached by a pharmaceutical

company to assist with a clinical trial to test the efficacy of a new drug in the treatment of acute psychosis. The study will enrol acutely psychotic patients with no history of psychosis (or of treatment with antipsychotic drugs) through physicians' offices and emergency departments. Patients enrolled in the study will be randomly assigned to receive the new medication or a placebo and will remain in hospital for 8 weeks. During this time they will not be permitted to receive antipsychotic medications other than the study drug. Informed consent will be obtained from each participant or a proxy. Patients may be withdrawn from the study if their medical condition worsens substantially.

What is research ethics?

Research involving human subjects can raise difficult and important ethical and legal questions. The field of research ethics is devoted to the systematic analysis of such questions to ensure that study participants are protected and, ultimately, that clinical research is conducted in a way that serves the needs of such participants and of society as a whole.

Why is research ethics important?

Many of the ethical issues that arise in human experimentation — such as those surrounding informed consent, confidentiality and the physician's duty of care to the patient — overlap with ethical issues in clinical practice. Nevertheless, important differences exist between research activities and clinical practice. In clinical practice, the physician has a clear obligation to the patient; in research, this obligation remains but may come into conflict with other obligations — and incentives.[1] The researcher has an obligation to ensure that the study findings are valid and replicable, and this has implications for the design and execution of the study. For example, the study must be designed in such a way that the research question is answered reliably and efficiently; sufficient numbers of patients must be enrolled in a reasonable period; and study participants must comply with their allocated treatment. Substantial rewards can accrue to the successful completion of a research project, such as renewed funding, academic promotion, salary increases, respect from colleagues and, in some cases, fame. Unfortunately, in a number of research studies, including some conducted in Canada, the welfare of individual patients has been sacrificed to these competing interests.[2,3] Various ethical principles, legal requirements and policy statements have been formulated in an attempt to ensure that clinical research is conducted in accordance with the highest scientific and ethical standards.

Ethics

The predominant ethical framework for human experimentation was set out by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the Belmont Report.[4] This report articulated 3 guiding principles for research: respect for persons, beneficence, and justice. Respect for persons requires that the choices of autonomous individuals be respected and that people who are incapable of making their own choices be protected. This principle underlies the requirement to obtain informed consent from study participants and to maintain confidentiality on their behalf.[5] The principle of beneficence requires that participation in research be associated with a favourable balance of potential benefits and harms.[6] The principle of justice entails an equitable distribution of the burdens and benefits of research. Researchers must not exploit vulnerable people or exclude without good reason eligible candidates who may benefit from participation in a study.[7]

The principles set out in the Belmont Report do not, however, exhaust the ethical requirements for clinical research.[8] Conditions such as the following must also be met.

- A study must employ a *scientifically valid design* to answer the research question. Shoddy science is never ethical.[9,10]
- A study must address a *question of sufficient value* to justify the risk posed to participants. Exposing subjects even to low risk to answer a trivial question is unacceptable.[9]
- A study must be *conducted honestly*. It should be carried out as stated in the approved protocol, and research ethics boards have an obligation to ensure that this is the case.[11]
- Study findings must be *reported accurately and promptly*. Methods, results and conclusions must be reported completely and without exaggeration to allow practising clinicians to draw reasonable conclusions.[12,13] Whenever possible, study results should be reported quickly to allow physicians timely access to potentially important clinical information.[14]

Law

The researcher's duty to have informed consent from research subjects is established in law. The legal doctrine often described as "informed consent" is better understood as "informed choice," since a physician's legal duty is to inform the patient so that he or she may exercise *choice* — which does not always result in *consent*. The physician's duty to disclose information relevant to the choice that the patient is asked to make falls under an aspect of civil law: the law of negligence. A physician may

be found negligent if a patient's choice (including the choice to forgo treatment) is inadequately informed and results in harm.[15] Accordingly, patients who are invited to enter a study must be informed of, among other things, the nature and extent of the known risks of participation, the possibility that participation may present unknown risks, and the intended benefit of the study to participants and others. A subject's treatment in a trial without consent may be grounds for legal action on the basis of "unauthorized touching," which is dealt with in 2 domains: assault in criminal law, and battery in civil law.

The duty to ensure confidentiality is founded in the physician–patient contract, fiduciary duty and legislation. Confidentiality is a usually implicit term of the physician–patient contract (that is, the tacit agreement between physician and patient on the rendering of care), and its violation is therefore a basis for legal action against the physician. Increasingly, however, as physicians move from fee-for-service payment to salaries or other remuneration systems, confidentiality is addressed under the law of fiduciary duty.[16] Fiduciary duty — the highest standard of duty implied by law — requires that physicians disclose information about a patient only in the patient's best interests and that they avoid any conflict of interest in the disclosure of patient information (even if that information is contained in records physicians lawfully hold). Unauthorized disclosure is actionable as a breach of fiduciary duty. It may also violate a duty of confidentiality enacted in provincial legislation (which varies substantially from province to province). For example, the Civil Code of Quebec is so protective of patient information that anonymous epidemiologic studies may be unlawful without the consent of each person whose medical record is used.[17]

Policy

A number of international policies guide the conduct of research. Although the Nuremberg Code and the International Covenant on Civil and Political Rights remain important early statements,[18,19] the World Medical Association's Declaration of Helsinki, as amended most recently in October 1996, is probably the most influential document governing research world wide.[12] Many of the requirements set out under "Ethics" in this article reflect the Declaration of Helsinki. The Declaration highlights an important additional requirement: patients' participation in research should not put them at a disadvantage with respect to medical care.

Canadian researchers conducting studies funded by the US National Institutes of Health must do so in accordance with the regulations of the US Department of Health and Human Services.[20] Researchers conducting research in other countries should consult the guidelines of the Council for International Organizations of Medical Sciences.[21,22] Geneticists should consult the guidelines developed by the Human Genome Organization.[23]

Medical research in Canada, including studies conducted in the drug approval process, is governed by guidelines of the Medical Research Council (MRC) of Canada.[24,25] These guidelines define research as "the generation of data about persons, through intervention or otherwise, that goes beyond that necessary for the individual person's immediate well being."[24] Proposals for research involving human subjects must be submitted to a local research ethics board for review. Research that will not generate generalizable knowledge (e.g., quality assurance research for internal use and not intended for publication) is generally considered exempt from such review.

The Tri-Council Working Group, a collaboration of the MRC, the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada, is preparing the final version of its code of conduct for research involving humans. A draft document, released in March 1996, generated considerable interest and controversy.[26] It proposed important new standards with respect to research involving communities or "collectivities" (including a requirement to involve community members, where appropriate, in the design process) and the inclusion of women (including "potentially pregnant" and pregnant women) in clinical studies. It also proposed the clear prohibition of placebo-controlled studies when effective standard treatment exists. If the final version closely resembles the draft document in these respects, substantial changes in the conduct of research in Canada will ensue.

Empirical studies

Empirical studies have much to contribute to our understanding of informed consent and the risks and benefits of participation in research. For example, if the principle of respect for persons is to be upheld, it follows that research subjects must not only be *informed* of the purpose, nature, risks, benefits and alternatives associated with their participation but must also *understand* this information. But how well *do* research subjects understand information presented to them in the consent process? The answer seems to be "Not well at all."[27] Indeed, because of a phenomenon that Appelbaum and colleagues[28] refer to as "therapeutic misconception," patients commonly believe that experimental projects are tailored to optimize their individual care. In its final report, the White House Advisory Committee on Human Radiation Experiments detailed the results of a survey of 1900 research participants and concluded that serious deficiencies remain in the current system of protecting human subjects of research.[29]

Two lessons follow from the empirical studies on informed consent to participation in research. First, researchers need to establish and maintain effective strategies to ensure that research subjects comprehend the information they are given during the consent process. In an elegant review of this topic, Silva and Sorrell list a wide range of methods available to improve participants' understanding.[30] Second, although such additional measures are important, the empirical data highlight the inadequacy of consent alone to protect study participants. Consent is an important component of this protection, but a research study must present an acceptable balance of risks and benefits as well.[31]

Empirical studies on the risks and benefits of research participation have also made an important contribution to research ethics. For many years, participation in research was viewed as a risky endeavour, one from which people ought to be protected.[32] However, a number of studies in the late 1970s and early 1980s showed that the risks associated with study participation were, in reality, relatively small.[33] Indeed, recent empirical work in oncology suggests that cancer patients who participated in clinical trials received — apart from the specific study treatment — a *net benefit*, namely, improved survival.[34–37] If further study establishes conclusively that trial participation *in itself* is associated with a higher probability of benefit, it may be that prospective study participants should be informed of this fact.

How should I approach research ethics in practice?

Ethical issues in research must not be addressed by researchers as an afterthought. Ethical issues permeate research and must guide research design. What should be used as a control treatment? Who should be included or excluded from a study? How large should the sample be? All of these questions have an ethical component.[38] Researchers ought, therefore, to consider ethical issues from the first stages of planning.

What resources are available to researchers to guide them in ethical matters? Clearly, all Canadian physicians involved in research ought to be familiar with the key documents outlined earlier, particularly the MRC guidelines (and the Tri-Council guidelines when they become available). Though directed primarily toward an American audience, a number of excellent reference texts are available.[5,39] To our knowledge, the only peer-reviewed journal devoted exclusively to research ethics is *IRB: A Review of Human Subjects Research* — an excellent source for the researcher in an ethical quandary. Finally, and perhaps most important, clinicians should routinely consult with colleagues who have expertise in the ethics of research, including members of research ethics boards.

The cases

Dr. W is offered a financial reward if he will provide the names of patients to a third party who is coordinating a research study. Such "finders' fees" are ethically and legally objectionable.[40] Physicians act in breach of fiduciary duty and in conflict of interest if they use their professional knowledge of a patient's medical or other circumstances for their personal benefit. First, names may not be given to third parties without patient consent. A physician who believes that entry in a study may benefit an eligible patient should inform that patient and let the patient decide whether his or her name may be given to the investigator. Second, physicians must not accept a fee based on the number of names provided. If a physician is asked to consult patients' records or to do other searches, he or she may be remunerated for the time required to perform that service, whether or not any patients are identified and consent to participate.

Dr. X is invited to enrol his patients in a placebo-controlled study of a new antipsychotic drug. Is it ethical for him to recommend the study to his patients? No. As we have discussed, consent alone is an insufficient ethical basis for enrolling patients in a study: the study must present a favourable balance of benefits and harms. A physician may recommend participation in a study only if the treatments being studied are in a state of "clinical equipoise," that is, if there is "genuine uncertainty" within "the expert clinical community about the comparative merits of the alternatives to be tested."[41] In other words, genuine uncertainty must exist in the community of expert practitioners as to the preferred treatment.[41] When effective standard treatment exists for a disease, as it does for schizophrenia,[42] it is unethical (since placebo is an inferior "treatment") to expose patients to the risk of "treatment" with placebo alone. Practising physicians may be told that placebo controls are necessary in clinical research for scientific, ethical or regulatory reasons. Freedman and colleagues have reviewed these claims comprehensively and conclude that practitioners should regard them with scepticism.[43,44]

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