

Chapter 2

Research Ethics for Clinical Researchers

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Abstract

This chapter describes the history of the development of modern research ethics. The governance of research ethics is discussed and varies according to geographical location. However, the guidelines used for research ethics review are very similar across a wide variety of jurisdictions. The paramount importance of protecting the privacy and confidentiality of research participants is discussed at length. Particular emphasis is placed on the process of informed consent, and step-by-step practical guidelines are described. The issue of research in vulnerable populations is touched upon and guidelines are provided. Practical advice is provided for researchers to guide their interactions with research ethics boards. Issues related to scientific misconduct and research fraud are not dealt with in this paper.

Key words Ethics, Informed consent, Privacy, Confidentiality, Inclusiveness, Protection of human research participants, Vulnerable populations, Risk–benefit assessment, Tri Council Policy Statement (TCPS)

1 Research Ethics Development

One of the earliest guides for the ethical conduct of research on humans was provided by Virchow in the Berlin Code of 1900 [1]. The code outlined the requirement for informed consent, excluded participation of minors and those incompetent, and allowed research only under the direction of the institute’s medical director. As with most codes for the ethical conduct of research, the Berlin Code arose from the public outcry over unethical research. In this case a “treatment” for syphilis, consisting of serum from “recovering” syphilis patients, was administered to prostitutes without their knowledge or consent resulting in the spread of syphilis among the prostitutes and their clients [1].

The Nuremberg Code (1949; [2]) was conceived by the prosecution as part of the case against physicians conducting “research” under the Nazi regime in Germany after World War II [3]. The Code describes the “legal, ethical and moral” basis on which research could be conducted in humans and served as the basis by which to decide whether research conducted by the

defendants met an acceptable public standard. The Nuremberg Code became part of the verdict of the war crimes trial and was later signed by the 51 charter members of the United Nations [3]. An expanded document, the Helsinki Declaration, derived from the Nuremberg Code, but outlining in detail the conduct of acceptable biomedical research was approved by the World Medical Association in 1964 [4].

It should be understood that although the principles and conduct of human research had been to some extent codified, there remained no generalized requirement for mandatory ethical review for research on humans. No systematic process was in place to ensure independent and impartial review to judge whether a research project was ethically sound. It was simply left to the investigator to see that the research was designed and executed in an acceptable manner. However, landmark publications by Pappworth (1965; [5]) and Beecher (1966; [6]) documented numerous studies in the UK and the USA that failed to meet such standards. Standards of consent and protection of vulnerable populations were repeatedly violated in the most egregious manner. Beecher felt that ethical conduct should not be decided by a board or panel, but instead was the responsibility of the investigator. However, public awareness and outrage over the Tuskegee study led to an outcry for action that went beyond the investigator [7]. The Tuskegee study, which started in 1930 and continued until its termination in 1972, employed deception, enticement, and unwarranted medical invasiveness while following the natural course of syphilis in 400 African American males who were consciously denied access to medical treatment. Despite concerns raised within the US Public Health Service, review by the Center for Disease Control in 1969 allowed the study to continue. The unethical conduct in human research documented by Beecher and revealed in the Tuskegee study led to passage of the National Research Act in 1974 [8] which institutionalized mandatory ethical review for all biomedical and behavioral research on humans and set the stage for the Belmont Report [8].

Unlike the previous ethical codes, the Belmont Report (1979; [8]) established a set of ethical principles underpinning the regulatory framework for research on humans. The principles are Respect for Persons, Beneficence, and Justice. Respect for Persons recognizes that humans are autonomous agents and as such must give informed consent to participate in research. Moreover, their privacy must be respected and whatever data is collected from their participation must be held in a confidential manner. Members of vulnerable populations, e.g., children and the institutionalized, require additional measures to ensure their protection. Humans must not be considered the means to an end, i.e., the generation of research results. Beneficence obligates the investigator to design research so as to maximize the benefits and minimize harms. For each study the risks and the benefits must be evaluated and risks

must be justified by potential benefits. Justice requires the fair treatment of participants. Those who are likely to share in the potential benefits of the research should equally share in the risks. Vulnerability should not be exploited to provide a pool of research participants, nor should vulnerability exclude a group that might benefit from the research. It is important to appreciate that a particular research design may bring these principles into conflict and that no principle trumps another in the ethical review process.

2 Governance

Ensuring an unbiased evaluation of ethical acceptability requires a governance structure that minimizes real and perceived conflicts of interest by the investigator, the institution, and members of the ethics review committee. Human participants are the means by which research results are generated and as such may be exploited by: (1) the investigator interested in achieving financial gain or career advancement; (2) the institution which may gain status, overhead funding, or a share in patents and other intellectual property arising from the research enterprise; and (3) members of the review body which may have personal or financial interest in the research outcome. Unfortunately, examples of such exploitation at the level of the investigator, institution, and review committee are readily available.

Canadian Research Ethics Boards (Institutional Review Boards, US; Research Ethics Committees, UK) require members with scientific expertise commensurate with the research under review (unscientific research is by definition unethical), expertise in bioethics and relevant law, and representation by the community, the group that is the beneficiary of research in the widest sense. Review committees must follow nationally or internationally accepted regulations or guidelines for the conduct of human research, e.g., Good Clinical Practice [9], Tri-Council Policy Statement (TCPS; Canada; [10]), and Common Rule (US; [11]). As well, institutions must have policies in place to assure independence of the ethical review process. The ethics review body must have written policies and standard operating procedures outlining the detailed operations of the review process and supporting infrastructure and to ensure procedures for research oversight and continuing or ongoing ethical review are in place.

3 Privacy and Confidentiality

Research participants have a right to expect that their privacy will be protected and that data collected will be maintained in a confidential manner by the investigator and study personnel.

Clearly maximum protection is provided when data is collected anonymously, e.g., a survey is completed without disclosing personal information or demographic data that would allow identification of the participant. Collecting identifiable data should be justified in relation to the expected benefits of the study. Once collected the identifier should be coded and only the coded identifier should be stored with the data. The file containing identifiers should be stored in a password protected file or locked file cabinet in a locked room. Access to identifiers should be strictly limited to study personnel on a need to know basis. Retention of identifiable data should be limited in time consistent with institutional policies on research integrity. Long-term retention of such data requires justification. Assurance regarding protection of privacy and confidentiality should be outlined in the consent form or as part of the consent process. Moreover, when confidentiality cannot be maintained, as in a focus group setting, or when privacy is clearly compromised in those cases where facial photographs are published to describe a genetic or medical condition, this must be emphasized in the consent form.

Public concerns with issues of privacy and confidentiality have resulted in extensive legislation guiding the use and dissemination of personal information and in particular the use of personal health information [12]. Investigators and ethics review committees must be aware of this legislation and how it may impact research. Moreover, in many jurisdictions ethics review committees have the authority to grant approval for the use of personal health information in the absence of informed consent when such use can be justified by the nature of the research or the feasibility of obtaining consent is in question or poses additional risks.

4 Composition of a Research Ethics Board

GCP [9] outlines guidelines for the minimum required membership for a research ethics board. It states that the IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

1. At least five members.
2. At least one member whose primary area of interest is in a nonscientific area.
3. At least one member who is independent of the institution/trial site.

5 How a Research Ethics Board Functions

As well as being aware of the composition of the REB, applicants should also have some appreciation as to how their local REB functions. Applications are screened by the cochair and those considered to be of minimal risk are triaged for expedited review by one board member and cochair. If approval is recommended, this is brought to the full REB for ratification only. No further review occurs. If expedited review identifies important ethical issues, then the proposal goes to the full board for review.

In situations in which more than minimal risk is involved, the application goes to the full board for review. One member is assigned the task of detailed review and presentation. The primary reviewer receives the detailed protocol, if available. All members of the board read each application and all applications are discussed at the board meetings which in our institution occur every 2 weeks. Decisions are generally arrived at by consensus, although a vote is taken for the record. Questions are communicated to the researcher. In cases where resolution of the issues proves difficult, the researcher may be invited to present in person to the board. This is generally not required and the majority of applications are approved in a timely fashion. If a proposal is not approved, the researcher has the right of appeal to a duly constituted independent appeals committee.

6 Balancing Risks and Benefits

One of the most important tasks of a research ethics board is deciding if the benefits of a proposed research project outweigh potential risks. In situations where more than minimal risk is involved, more intense scrutiny of the research is required including a scholarly review of the proposed research. In Canada the TCPS defines minimal risk as “If potential subjects can reasonably be expected to regard the probability and magnitude of possible harms implied by participation in the research to be no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research then the research can be regarded as within the range of minimal risk.”

Scholarly review is generally done in the setting of peer review. This poses significant logistical problems for research ethics boards. A true peer review process is time-consuming and could impede timely review and approval of research proposals. There are several approaches to this issue. In large institutions a separate peer review process may be in place. This does delay the timeframe of ethical review. Sometimes funding for the proposal is already secured and comments from a granting agency peer review panel may be available.

More commonly the research ethics board is sufficiently expert and diverse to provide a reasonable assessment of the scientific validity of a research proposal. This review is critically dependent on the quality and clarity of the submission provided by the researcher. Comments on scientific validity are often perceived by researchers as beyond the purview of a research ethics board. However, in situations where more than minimal risk is involved, a research ethics board has the obligation to assess the scientific validity of the proposed research.

A final decision on the risk–benefit ratio of a research proposal involves a review of the quality of the proposal, the likely side effects of the proposed intervention and the potential benefits to participants. Ultimately it is a judgment call of an appropriately constituted research ethics board. In situations where doubt arises, a formal presentation by the researcher to the ethics board may be helpful.

7 Informed Consent

Free and informed consent is a cornerstone of ethical research involving human subjects. It begins with the initial contact and must be sustained until the end of the involvement of the subjects in the research project. Free and informed consent is an iterative process whereby research subjects are informed in understandable terms about the details of the proposed research. While each organization is likely to have their own informed consent template a template developed in Newfoundland and Labrador in Canada [13] provides a practical guide to developing an informed consent document for a clinical trial and addresses the key important questions. This type of approach could easily be modified for other types of research designs.

What is a clinical trial?

This section should address how a clinical trial differs from normal clinical care. It should address the concept of randomization and the possible applicability of the results of the clinical trial to others with a clinical condition similar to the subjects.

Do I have to take part in this clinical trial?

This section needs to stress the voluntary nature of participation in a research project and an assurance of normal clinical care should the subject decide not to participate.

Will this trial help me?

For randomization to be ethical the response here has to be one indicating that benefit is uncertain.

Why is this trial being done?

This section should provide, in lay terms, the rationale for the research question.

What is being tested?

Has the intervention been approved by the appropriate regulatory authorities or is this trial a step towards that approval process. Has the intervention been tested in animals and what, in lay terms was found? Has the intervention been tested in humans? How many were studied and what was shown?

Why am I being asked to take part?

This should include a statement as to how a particular individual was flagged for possible inclusion in the study. This should provide an assurance to the potential participant that their autonomy and privacy has been protected during this process.

Who can take part in this trial?

This should clearly list the inclusion and exclusion criteria in understandable terms and must mirror those criteria outlined in the more detailed protocol.

How long will I be in the trial?

The research participant must be made aware of the overall duration of participation in the study. The amount of time involved in participating in trial activities must be explicitly stated.

How many people will take part in this trial?

Describe whether this is a single-center or multicenter study. If the latter is the case, indicate the number of local and overall participants.

How is this trial being done?

This section should provide a detailed but understandable description of the research methodology. This should include details of randomization and blinding as well as detailed description of what the experimental and control arms entail. Details regarding proposed blood and tissue collection should be described. Clearly describe anything involved in the trial which is not part of standard clinical care.

What about birth control and pregnancy?

Most organizations have standard wording addressing these issues. This should include what is known of the risks of the intervention and what birth control measures (for both the research subject and any sexual partners) are necessary for inclusion in the study. There will often be uncertainty about possible teratogenic effects or effects on breastfeeding babies. In the absence of information it should be assumed that the possibility of such effects exists and individuals should be advised appropriately.

Are there risks to the trial?

Possible adverse effects of the intervention should be listed and grouped according to frequency. Risks of any other procedures being performed as a result of participation in the study must be outlined (e.g., additional radiation exposure as a consequence of imaging procedures that are part of the study and would not be done if normal clinical care applied.) Occasionally certain questions on questionnaires may be distressing or uncomfortable for participants. Subjects should be given the option not to answer

such questions. If certain questions have a high likelihood of causing distress, appropriate support services, such as counseling, need to be in place and should be referred to in this section.

Are there other choices?

It must be clearly stated that the subject does not have to participate in the trial and a description of what other treatments are available should be provided. It should also be stated that once enrolled in the trial simultaneous enrollment in another clinical trial is not permissible.

What are my responsibilities?

It is important to point out that research participants should comply with the research protocol, report any changes in health status and provide updated information on the use of other medications.

Can I be taken out of the trial without my consent?

Research participants can be removed from a trial at the discretion of the investigator if he/she feels they are not complying with instructions or if their continued participation is harmful because of side effects or deterioration in their health status. The participant must be informed of the reason for withdrawal from the trial in the event that this happens.

What about new information?

If new information becomes available that may affect the participant's health status or willingness to continue in the study, this must be discussed with the participant.

Will it cost me anything?

Information regarding costs to the participant of being in the trial must be discussed. Reimbursement for expenses may be available and the participant must be made aware of this. If payment of participants is planned, this must be outlined. Payments that constitute an inducement to participate or exposure to excessive risk are not allowed by research ethics boards. Provisions for payment for treatment of or compensation for research related injuries must be addressed in this section of the consent form. If information from the study results in a patented product of commercial value, the participant will not usually receive any financial benefit. This should be made clear to participants.

What about my right to privacy?

Research participants should be assured of privacy and confidentiality. Outside agencies may be privy to private and confidential information for the purposes of audit or licensing. They are expected to observe strict confidentiality when examining the data. The participant must be informed of who will have access to their data. The duration of data storage must be specified. In the case of clinical trials this is generally 25 years after completion of data collection. Details of how the data will be stored and what steps will be taken to ensure secure and confidential storage must be provided. Information on how confidentiality will be assured for any

blood or tissue collected must be specifically addressed and will vary depending on the study objectives and the nature of the blood and tissue being stored.

What if I want to quit the study?

Explain the procedure for withdrawal to the participant. Not uncommonly data collected up to the point of withdrawal will be retained and may be used in data analysis to ensure validity of the study. If this is the case, this must be disclosed to the research participant. If the participant has already agreed to blood or tissue storage for future use, he/she must be given the option to withdraw or affirm such an agreement at this point.

What will happen to my sample after the trial is over?

If the sample is to be destroyed, this should be specified. If it is to be used for future research, the sample may be coded to allow future linkage or it may be anonymized in which case future linkage to the participant will not be possible. The participant must be informed and provide consent for either option. If genetic material is to be used for future research, the participant must be informed if the possibility of re-contact is involved and consent to same. The participant may also wish to specify the types of future research that he/she would consent to (e.g., an individual might consent to future use of their DNA for a specific disease and not necessarily for unrestricted use for any research purpose). Studies involving future use of research samples are normally considered sub-studies and require a separate consent form to be signed addressing the issues outlined here.

Declaration of financial interest: If the investigator has a financial interest in conducting the trial, this should be declared. If no financial interest is involved, this should be stated.

What about questions or problems?

If the participant has questions about the trial or has a medical concern, he/she should be provided with contact information for the local principal investigator and study co-coordinator. If a medical concern arises outside normal work hours, details of the process in place to contact help should be provided.

If the participant has questions about their rights or concerns with the way in which the study is being conducted, appropriate contact information should be provided. The contact in this case will vary in different jurisdictions. It will often be through the office of the research ethics board.

The signature page

The signature page should include a statement that the participant has had an ample opportunity to discuss the proposed research, that they understand the proposed research and have had their questions answered satisfactorily. It should indicate that they have been informed of who may access their research records and should indicate that they have the right to withdraw at any time subject to the conditions outlined in the consent form.

The form must be signed by the participant, an independent witness, the principal investigator and the individual who has performed the consent discussion (if not the principal investigator). The signature of the next of kin/legal guardian must be provided for certain types of research (e.g., research involving unemancipated minors and incompetent adults). If the consent form requires translation into another language, the signature of the translator is also required.

8 Inclusiveness in Research

Historically certain groups of individuals have been underrepresented and sometimes deliberately excluded from research. Such groups have included women, the elderly, children and incompetent adults. This list is not exhaustive and the reasons for exclusion of such groups are complex and varied and beyond the scope of this chapter. This issue has been specifically addressed by the Canadian TCPS in Section 5 [13] as follows:

Where research is designed to survey a number of living research subjects because of their involvement in generic activities (e.g., in many areas of health research, or in some social science research such as studies of child poverty or of access to legal clinics) that are not specific to particular identifiable groups, researchers shall not exclude prospective or actual research subjects on the basis of such attributes as culture, religion, race, mental or physical disability, sexual orientation, ethnicity, sex or age, unless there is a valid reason for doing so.

This statement is based on the principle of distributive justice. Its premise is that it is unethical to exclude individuals from participation in potentially beneficial research. Obviously the protection of these individuals from harm by inclusion in research is equally important. Indeed because some of these groups include potentially vulnerable populations protection from harm and providing fully informed consent does present some unique challenges. For the purposes of this chapter we will confine discussion to two vulnerable groups commonly involved in research: children and incompetent adults.

Often in incompetent adults the incompetence is caused by the disease which requires study. In this case the research cannot be done in a less vulnerable population and the intervention under study may directly benefit participants and others with the same disease. Consent is usually obtained from a proxy in this case, usually the next of kin or legal guardian, who is expected to act in the best interest of the individual participant. When studying incompetent adults it is important to recognize and establish that there are many types of specific competencies. While the individual being studied

may not be competent to understand all of the intricacies of the study and the informed consent process they may be perfectly competent to refuse a painful procedure (e.g., needle stick) as part of the study.

Research in adults may not be generalizable to children for a variety of biological, developmental and psychosocial reasons. Quite often the disease being studied is more prevalent in or exclusive to children. Again proxy consent is required for minors with the exception of emancipated minors. However, children beyond a certain age are capable of understanding many of the issues involved and should be involved in the informed consent process and asked to give assent to any proposed research. In certain cases during the course of a study children may reach the age where legal consent is possible. If not incompetent for other reasons, they should then be asked to sign the informed consent document on their own behalf.

9 Practical Tips for Researchers Applying to Research Ethics Boards

- Familiarize yourself with the research ethical guidelines that are used in your jurisdiction.
- Satisfy yourself that the research question is important and the research design is sound.
- Do not cut and paste from the protocol into the ethics application. Summarize the protocol so that it can be easily read by all members of the research ethics board. Remember in most jurisdictions one member of the board is assigned to read the entire protocol and summarize for the other members.
- Identify upfront what you think the ethical issues may be and present these in your application.
- If you have a particular concern, get some advice prior to submission from an appropriate member of the ethics board.
- Ensure that all sections on the form are complete and that the submission is signed.
- If the research requires a consent form, spend time on preparing it at a readable level. Most boards will index this against a certain educational level. Computer programs are available to assess readability level.
- Remember the primary function of the research ethics board is to protect human subjects involved in research. Boards have an ethical obligation to facilitate sound ethical research while fulfilling this function. Interpret any comments or questions from the board with these two concepts in mind.

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