Guidelines on Research Involving Human Subjects*
Part 2: Implementing Ethical Responsibilities

Introduction

The Medical Research Council of Canada (MRC) holds that the highest possible sensitivity and moral standards must be applied to all research. In its continuing concern, the Council in March of 1984 established a Standing Committee on Ethics in Experimentation. Council's first request of this multi-disciplinary group was to review the adequacy and currency of the 1978 MRC Guidelines for the protection of human subjects in research.

A Working Group on Research involving Human Subjects met between February and September 1985 to prepare a draft document designed to raise and deal with the essential issues which the Standing Committee should consider in its report to the Council. The Standing Committee on Ethics in Experimentation then used this draft as a basis for a discussion document.

In the course of the review by both committees, advice was sought from some who worked with the 1978 Guidelines, as well as from Canadian and foreign experts. Thirty-five guests accepted invitations to meet with the Working Group or the Standing Committee. Other granting agencies, as well as many health-related bodies and institutions were consulted. Individual and institutional submissions were invited from across Canada, and approximately 750 written submissions were received, including 500 from outside the research community. Meetings of the Standing Committee were open to the media to encourage public interest and input.

Council circulated this discussion document in November 1986 to approximately 2,000 persons, including all who had written to Council on this issue. Approximately 120 letters of comment were received and analysed by the Standing Committee in preparing its final report to MRC.

The Medical Research Council of Canada accepted this report as MRC's Guidelines on Research Involving Human Subjects, and requires all research which it funds to be in compliance with these Guidelines.

The primary aim of these Guidelines is to define the Medical Research Council's expectations of the research community in any research involving human subjects funded by the MRC. Council's first Guidelines were published in 1978 as *MRC Report No. 6, Ethics in Human Experimentation*. This document has become an integral part of the ethical review process in many institutions in Canada. The 1978 Guidelines are being superseded because of the need periodically to update all ethical statements and to guide the review of new research developments.

Ethics are principles of right conduct, guiding what ought to be done. Although they may reflect enduring moral values, ethics are not static but evolve with time and public perception. Because the issues at the interface between science and society are so important, the public must be involved. Hence, the audience for the MRC statement of research ethics includes lay members of committees considering the ethics of research proposals and the increasingly interested public beyond. These Guidelines aim as well to stimulate discussion and understanding of human research ethics, and to encourage further development of ethical awareness in both the research community and the broader public.

The purpose of the guidelines therefore, is not to tell those responsible for making the ethical judgements on research proposals what decisions they must reach. Their purpose is rather to sensitize and guide decision makers on the range of perception they should bring to bear and to describe the processes of decision making that must be observed.

The MRC Standing Committee on Ethics in Experimentation, as well as the Working Group, examined requirements for the ethical review in a number of institutions across Canada. This included procedures and practices for the assessment and surveillance of human experimentation. The Committee also considered ethical control in other jurisdictions. As a result of the Committee's research and deliberations, and consideration of the submissions of the public and the research community at meetings over a two-year period, the procedures recommended to Council are more stringent than those in the 1978 Guidelines.

Responsibilities for the proper conduct of human experimentation lies with all who are involved in the research, but most particularly with the researcher and the local REB. The MRC must ensure that public funds are spent only on research that is ethically acceptable.

Responsibilities

A. The Researcher

Researchers have the initial and continuing duty to ensure the ethical conduct of all aspects on their research. The researcher must identify and bring to the attention of the Research Ethics Board (REB) any factors which might raise concerns, both as part of the process of obtaining approval from the REB, and also as the research proceeds. It follows that, in every case, the researcher responsible must be clearly identified and unequivocally take on responsibility for the proper conduct of the entire research team.

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B. The Institution

The institution within which the researcher works has the major responsibility to ensure that the research meets the ethical standards of society. Although researchers apply to MRC for grants, the funds are administered through the institution, which acts as trustee. The terms of the trust include not only management of accounts, but also active responsibility for initial and ongoing conformity to proper standards. The Committee reaffirms the role of REBs in undertaking the institution's responsibility for the ethics of research undertaken with MRC support.

C. The Medical Research Centre

The MRC has assumed responsibility for providing guidance in research involving human subjects and for ensuring that its funds are used only within acceptable standards. This is achieved through guidelines and by fostering awareness of ethical issues relating to research involving human subjects. The Committee is of the opinion that in discharging its public trust, the MRC must monitor local procedures and practices in ethics review.

Procedures

A. The Institution

The primary responsibility for decisions on the ethics of research, carried out within the institution or by its staff, should continue to be delegated to Research Ethics Boards (REBs). The Committee has concluded that the REB should be established under the authority of the President or Principal of a university, or a comparable chief executive officer of a non-university institution. This person must give the REB a clear mandate for review of all protocols for research involving human subjects. Also, the REBs relationship to other committees concerned with ethical matters, for example, to professional, teaching or other related bodies, must be defined. The President, Principal, or their equivalents, should give the REB full authority for ethics review.

The REB should be a standing body which meets regularly. Its membership must be defined, and it should turn over periodically so as to blend experience with fresh perceptions. In addition, the workload of each REB should be sufficient to assure an experienced Board, but not so large that attention to necessary detail suffers. Therefore, in large institutions, more than one REB linked through some central system may be formed. A multiplicity of small local REBs should be avoided.

A.1. Composition of the Research Ethics Board

The Standing Committee is cognizant of the fact that there is wide variation in the organization and composition of REBs. The Standing Committee believes, however, that the guidelines should outline minimal expectations for an REB, such as we describe here. This proposed composition is intended to be illustrative.

The Community

The values of the particular community are the matrix of ethical review. The REB must contain members who can reflect community values. Lay members affiliated with a hospital or university board are often suitable, but the board should ideally include non-affiliated individuals. Community bodies may assist in the selection of such members.

Relevant Specialists

The REB should contain at least one specialist in the relevant discipline of the research. The specialist may be a permanent member of the REB or an *ad hoc* member.

A clinical psychologist or other mental-health expert may also aid in assessing the subject's capacity to understand the protocol and exercise a free choice.

Scientists with a broad understanding of research design and of research in the areas usually considered by the REB should sit on the board.

Nurses shouyld be represented on an REB which deals with clinical research.

Other disciplines

Bioethicists, philosophers or theologians will also contribute greatly to the work of an REB.

Since common law and legislation often impinge directly on the decisions an REB will need to take, the Committee regards the presence of a lawyer as desirable. The lawyer should not sit to represent the institution, but to provide legal expertise.

The committee recognizes that REB members undertake a major responsibility on behalf of the public, and that considerable demands are made upon their time. Service for two to three years, and a high rate of attendance at meetings, are necessary to develop and use the needed expertise.

A.2. Submission of Projects for REB Review

Evaluation by an REB of a research protocol is the major step through which the community can be certain that its values are respected. A document addressing the ethical aspects of a specific research protocol may be very different from one seeking research funds, particularly when the grant application sets out a program of research lasting for a number of years. Therefore, it should not be assumed that the research grant application is always suitable for ethics review, and the REB should require a document tailored to its needs.

The Standing Committee notes with approval the efforts which have been made in some institutions to provide guidance through specific questions or checklists on the material needed for review, and encourages Council to establish broad standards across the country. The materials submitted should include at least the following considerations:

The scientific validity of the proposed research

The documents submitted to the REB should provide, for the specific experiments proposed, sufficient scientific information about such factors as the current state of knowledge, the re-

search design and the methodology, to enable the REB to satisfy itself that the proposed research is scientifically valid.

The appropriateness of performing the experiments on human subjects
Applicable information derived from previous experiments with animals or with human subjects should be described and the need for the proposed experiments on human subjects should be justified.

The risks to subjects of the proposed research
All procedures that could possibly cause harm to the subject must be fully and precisely described. Any known risks arising from these procedures should be made clear, and potential risks should also be assessed as far a possible. Possible alternatives protocols should be discussed in order to demonstrate that the one selected minimizes risks. Procedures for preservation of confidentiality must be specified, as must the precautions taken to ensure medical surveillance when subjects are to be placed under stress.

Potential research subjects
The persons to be approached as potential research subjects should be described. This requirement has special significance for research that is not directed to a specific disease and in which the investigator may wish to approach, for reasons of convenience, groups like prisoners, students, employees, or others, in whom free choice is compromised.

Care should be taken that the group of potential research subjects is not already being overtaxed by other research projects.

Procedures for informed choice
Procedures for approaching potential subjects for the research should be described in detail. The description should identify persons who will seek their approval and any others who will be present during the obtaining of consent.

The document should also include a statement of the criteria to be used in selecting the individuals from a general group. The description should also include details of the information to be given to the potential subjects, including any written material to be used in connection, for example, with surveys to be conducted by mail. Where proxy consent is to be obtained on behalf of those unable to consent for themselves, the procedures to be used and the proxies to be approached must be specified.

The consent form must be provided as part of the research protocol. This form should contain statements of the aims of the project, of the procedures the subjects will undergo, and of the risks inherent in those procedures. The form should also contain statements of other relevant factors, including side effects of proposed drugs or treatments, which a reasonable person might be expected to consider before giving consent. The form should describe the areas of uncertainty in the research, including the statement that the procedures are experimental and that the subject may not benefit from the research. There should also be a statement that the subject may withdraw from the project at any time for whatever reason, and with no prejudice.

A.3. Accountability of the Ivestigator to the Research Ethics Board

The approval of an REB for a specific protocol is based on the exact and detailed information available to it. The REB may require changes to the protocol as a condition of acceptance. The investigator is then bound to act in accord with the statements made in the submission as approved. If changes are desired in any detail that pertains to the subjects of the experiment, the investigator should seek the further approval of the REB prior to implementing them. The investigator should also immediately report to the REB any apparent risks beyond those predicted and, if necessary, suspend the experiment pending clarification.

A.4. The Operation of the Research Ethics Board

Certain procedures are necessary if an REB is to meet its responsibilities to the institution and to the MRC.

The Standing Committee is certain that regularly-scheduled meetings are needed for the REB to discharge its duties, and that prior circulation of agenda material, with sufficient time to prepare for the meeting, is essential. The REB may allow its chairman to make interim decisions between meetings in certain areas, subject to ratification by the full board. Some committees may delegate some decisions to the chair, with the protocol circulated for discussion at the initiative of members.

The Standing Committee recommends that the REB establish, with the President, Principal, or other equivalent institution head to whom it reports, requirements for attendance at meetings, a quorum, and the majority needed for approval of a project. The chairman should conduct the meetings so that all points of view are fully addressed by the REB.

The REB chairman or secretary may identify projects needing external appraisals by scientists or others, and arrange for the reviews to be done. Their reports should form part of the documentation submitted in advance to the REB.

An REB need not be supported by an extensive secretariat, but it is important that minutes be kept. These should capture the issues raised and the assessments made, as well as the undertakings given and facts asserted as relevant to the study. The assurances by researchers to the REB may be critical to the assessment that the proposal can be ethically conducted. Since crucial points and undertakings may not be expressed elsewhere, the documentation of the terms and understandings upon which approval was given should include the minutes of the REB. Further, a record of the REB deliberations is valuable for circulation to interested parties, such as other REBs in the same institution or in other centres in a multi-centre trial, government agencies responsible for licencing a drug, or the MRC.

A.5. Continuing Review

The Standing Committee believes that the REB and MRC

should ensure that the actual implementation and conduct of the project continue to meet the standards of ethics agreed to among the researcher, REB, and the MRC.

As part of its initial discussion on ethics, the REB should determine whether audit or review is necessary in each case. If so, the procedures should be set by the REB as one of the conditions of approval. If no ethics audit or review is deemed necessary, the reasons should be given. The plan may provide for inspection of the means by which information is given to prospective subjects, or for an independent assessment of how much those thus informed understand what they have been told.

At a minimum, researchers should be required to provide an annual update on the status of any project for which the REB has given approval. This information should indicate any changes that may have occurred in scientific knowledge or in the design of the study, as wll as the progress of the study. For specific protocols, the REB should also be able to require more frequent or rigorous review.

Once REB approval has been given, the researcher must immediately inform the REB of any new information that might alter the ethical basis for continuing the research program.

It is expected, however, that the institution's monitoring will be more active than simply seeking investigators' assurances. Research officers, or members cognizant of ethical concerns, may be required to maintain scrutiny by periodic review of the research and of the factors involved in the ethics approval. The actual form of this monitoring will vary with the specific research protocols. In certain cases, specialists from outside the institution might be asked to act as monitors.

Investigators' applications to REBs should be contersigned by heads of departments or others with senior administrative responsibility. Notification of ethics approval, including minutes of REB meetings and amendments to the original protocols, should be relayed to such officers, thus placing them on notice of commitments made and accepted. Their institutional obligations in the management of their departments and personnel will help ensure compliance with these conditions.

The costs of this monitoring may transcend financial aspects, to include time taken from the monitor's other activities. Monitoring may also strain professional and personal relationships between colleagues or provide increased opportunities for a breach in confidentiality of information about research subjects and premature release of scientific or commercial information.

The Committee believes that reseachers and institutions should bear the costs of this day-to-day monitoring, which are largely similar to monitoring practices already well accepted in the health professions and commercially-sponsored research. The human costs of monitoring can often be reduced through mutual understanding of ethical duty and public interest. Monitors must be impressed with their own ethical responsibilities in accepting the task, and department heads must recognize their institutional duties to arrange adequate monitoring. Investigators must recognize that monitoring is intended to assist them in meeting commitments they have made in the cause of good cause science and good ethics.

Finally, it must be stated that the Standing Committee does not believe that appropriate attitudes in research can be ensured by these intensified procedures of monitoring alone. A high standard of ethics results not from policing but from human awareness and personal integrity.

B. The Medical Research Council

B.1. Review of Applications

Applications to MRC for research funds are reviewed by Grants Review Committees which report to Council. Scientists are asked to judge the scientific merit of the research proposed, the funding required and the duration of support.

Review of the ethics of the research proposal is also an essential part of the grants review process. However, the opportunity for review is limited. The applications, which are written primarily to address scientific issues, and which are limited in length, cannot fully address specific questions of ethics, and therefore are not ideally suited to ethics review. Also, many applications request long-term funding and cover many individual prospective experiments.

The Standing Committee believes that the grants review process should continue to review, to the extent that it is able, the ethics of the grant application, as well as the science. Also, the MRC should transfer back to the researchers and the REB any comments by the Grants Committee on the ethical aspects of the application, whether or not MRC funds the research, as this information may be of value to the REB and the applicant.

B.2. MRC Support of REBs

In support of the ethics review process, the Committee recommends that the MRC encourage ongoing information exchange and education concerning issues in the ethics of research with human subjects. One mechanism envisaged is the support of workshops intended especially for REB members and researchers. Another mechanism is regular communication between MRC and members of REBs and others interested in the ethics of research. This communication could provide a steady flow of information and would also afford the opportunity for the REB to learn how others are handling similar problems. Such educational means are necessary to deal with issues not explicitly covered in the Guidelines, either because of the degree of specificity or because of new developments in research.

The Standing Committee is certain that the Medical Research Council must establish mechanisms, perhaps with other agencies, to ensure the effective functioning of the local REBs on which it depends for review of the ethical aspects of research involving human subjects. While these Guidelines place the primary responsibility on the REBs, the Standing Committee is strongly of the opinion that public accountability demands that MRC monitor the functioning of the REBs which review the work that it funds.