

**REPORT  
ON CONTROL MECHANISMS  
FOR CLINICAL RESEARCH IN QUEBEC**

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**ACKNOWLEDGMENTS**

## ACKNOWLEDGMENTS

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The Committee sincerely thanks Dr. Anne-Marie Duguet, a physician at *Hôpital Purpan* of Toulouse who allowed the President of the Committee to attend in Toulouse a session of the *Committee for the Protection of Biomedical Research Subjects* in the Midi-Pyrénées region as well as Mr. Jean Michaud, Judge at the *Cour de Cassation* of France and Vice-President of the *National Ethics Committee* who kindly met with the President of the Committee and Mr. Gérard Mémeteau, Professor at the Faculty of Law at *Université de Poitiers*.

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## **TERMS OF REFERENCE**

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On June 17, 1994, Madame Lucienne Robillard, at that time Quebec Minister of Health and Social Services, announced the creation of a Committee of Experts entrusted with the specific mandate to review the control process and evaluation mechanisms of clinical research activities conducted in healthcare institutions in Quebec. According to the terms of the mandate, the Committee was called upon to:

- 1.** Establish a picture of the control mechanisms pertaining to clinical research conducted in Quebec healthcare institutions;
- 2.** Analyze the control measures as relates to their relevance and effectiveness in ensuring the quality of research activities and guaranteeing the safety of patients who participate in research projects;
- 3.** Clarify the sharing of responsibilities within healthcare institutions involved in clinical research activities, the manner in which they carry out these responsibilities and identify the control mechanisms now in place;
- 4.** Propose improvements to the current mechanisms presently in place based on an analysis of those existing in Quebec, those found in other Canadian provinces, as well as in other countries.

Following this, the Committee was entrusted with making recommendations to the Minister of Health and Social Services concerning Article 21 of the *Civil Code of Quebec* with respect to experimentation on incapable persons of full age and minors.

The Committee as constituted by the Minister of Health and Social Services did not have the status of a Commission of Inquiry set up to examine instances of fraud or scientific misconduct, nor to investigate any particular case of scientific misconduct.

However, the Committee was always attentive to the practices and situations existing in clinical research activities that have a potential to **negatively effect the integrity of** research activities, to undermine the trust in research activities and to compromise the freedom and safety of research subjects.

In addition, the Committee paid particular attention to the evaluation mechanisms of research projects, in particular to the scientific, ethical and financial evaluation actually taking place, in order to better understand the current practices and make suggestions to improve their functioning.

The Committee's operating budget was \$29,900. This amount includes the three members' honoraria, travel expenses and the report's costs of production. One must note the important benevolent work provided by the Committee's members in the realization of their mandate.

# **FOREWORD**

## **FOREWORD**

Recent events that have occurred in the field of clinical research in Quebec have cast a certain discredit on the scientific community and have threatened the trust the public is entitled to have in biomedical research which, if conducted properly, leads to the advancement of knowledge and the betterment of a population's welfare. These events have also raised doubts in the ability of the healthcare sector in Quebec to ensure the integrity of research activities.

The scientific community and the healthcare sector in Quebec cannot allow an unhealthy climate to prevail in research activities giving the impression that the research community takes advantage of those who, in good faith, accept to participate in a research project.

It is crucial that the scientific community and the healthcare sector be able to guarantee the public that all clinical research activities conducted in Quebec remain of excellent quality and that the integrity of those who agree to participate in a research project is protected. This is necessary in order to maintain the trust that the public must have in research activities conducted in the healthcare sector. To achieve this goal, it is essential that the mechanisms for implementation of these guarantees not only exist but also function efficiently.

Presently, there are a number of mechanisms that ensure the scientific quality of research activities. For several years now, one has witnessed an intensification of the controls pertaining to the integrity of data generated within research projects as well as to the validity of the ensuing results, notably by agencies financing research activities. For some, the controls now in place in the field of biomedical research are sufficient since they far exceed those needed to ensure the quality of research activities. Given the large sums of money invested in research, one can understand the compelling interests of these agencies of ensuring that their investment is not jeopardized by research activities poorly carried out.

One may however fear that the imposition of new control mechanisms could further hinder the carrying out of research activities and could constrain investigators in reporting more frequently to too many entities throughout the research process. This apprehension is one of which the Committee members are aware of. Nevertheless, there is a need to implement mechanisms that are likely to ensure an adequate evaluation of research activities at each stage of their development, taking into account not only the scientific aspect of the activities but also their ethical and financial aspects, the latter two having received less attention than required.

In the opinion of the Committee members, - an opinion supported by many of those interviewed as well as by the Committee members' personal experience -, the time has come to review the mechanisms for evaluation of research activities carried out in Quebec. This effort is required to reassure the public in general and those who could eventually be asked to participate in a research project of the integrity and quality of research activities. Its purpose is not to uncover fraudulent conducts or cases of scientific misconduct.

That said, the Committee members wish to underline the fact that in their opinion, research activities which are carried out in Quebec in the health sector are, in general, of excellent quality. The problematic situations and practices exposed in the present report do not reflect a widespread phenomenon. They have been underlined in order to raise the awareness of those concerned by research activities to incidents that might compromise the integrity of research and infringe upon the dignity owed to those who agree to participate in a research project. Furthermore, these situations and practices emphasize the need to rely on adequate evaluation mechanisms in the field of clinical research.

The evaluation mechanisms proposed in the present report are primarily aimed at reinforcing the quality of research activities and preserving an equitable use of resources in the field of clinical research, bearing in mind the utmost consideration one must have for those who participate in research projects. The quality of research activities must continue to be fundamentally based on the competence and honesty of investigators, the physical and financial infrastructure at their disposal for carrying out research, as well as on the generous and voluntary contribution of those persons who accept to participate in research projects.

# **INTRODUCTION**

## INTRODUCTION

In the healthcare sector, biomedical research plays an essential and determinative role in the improvement of a population's health and well-being. It is through research that we can achieve real and substantive progress in the diagnosis and treatment of illnesses such as cancer, heart and respiratory ailments, childhood diseases and degenerative diseases of the nervous system, to name only a few.

The acquisition of new knowledge in the area of healthcare also depends on investigators wishing to further their understanding of the human body and its reactions to the effect of various experimental treatments. Furthermore, the discovery and the safe and sound implementation of new technologies as well as of new approaches in the diagnosis and treatment of illnesses rely heavily on research subjects, healthy or ill, willing to permit the testing of research hypotheses aimed at solving health problems.

For scientific progress to be acceptable in a society such as ours, the research activities upon which it is founded must be carried out with the utmost consideration for research subjects who make their body available to science. This implies that, at all times, research activities be conducted in accordance with recognized values and accepted standards.

As for clinical research, we have until now **presumed** that research activities were always carried out with integrity, fairness, efficiency, safety and efficacy. It is necessary today, if we wish to maintain confidence in clinical research activities, to **assure** ourselves that these activities are carried out in a well-defined environment that guarantees the existence of conditions ensuring quality.

In order to assure ourselves that clinical research is conducted properly and that research subjects are fully protected, it is necessary to develop control mechanisms based on a continual evaluation of research activities in its clinical, scientific, ethical and financial aspects, rather than strictly relying upon the denunciation of obvious scientific misconduct.

Surely, one should be able to detect particular cases of scientific misconduct through proper investigative mechanisms. However, this should not constitute the backbone of a surveillance system that would monitor how people involved in research activities assume their responsibilities.

If we wish to ensure that research activities are carried out in a manner leading to the best possible results, it is necessary that these activities conform to certain guidelines that bear on the performance of research activities as well as on their evaluation.

In general, one should expect clinical research activities carried out in a healthcare context to be guided by the following criteria: **Rigor, Efficiency and Equity.**

**RIGOR** demands that research projects be devised in a manner that allows the validation or refutation of the research question on which a research project is based. It requires that investigators and their research team scrupulously follow the approved research protocol so as to avoid compromising the validity of the results. It implies that investigators and their research team adhere at all times to the standards of good clinical practice.

**EFFICIENCY** demands that the scientific community in its entirety act in such a way as to optimize scientific breakthroughs in all areas of scientific research. It requires that there be more cooperation and greater coordination in carrying out research activities. It implies that the data collected be shared so as to provide new insight in a given area of scientific research and take advantage of a larger number of participants in research projects.

**EQUITY** demands that there be an equal distribution of constraints, both human and financial, inherent to clinical research. It requires that one not use the resources of a healthcare institution in an ill-considered manner while carrying out clinical research activities. It implies that the contribution of the different participants in research, subjects, investigators, institutions and sponsors be appropriately recognized.

In addition, the proper conduct of clinical research activities requires that they be managed according to the following values: **Benevolence, Integrity and Accountability**.

**BENEVOLENCE** demands that investigators and members of their research team act at all times in the best interest of those individuals who have agreed to participate in a research project. It requires that they never sacrifice the well-being of these individuals for their own personal interest. It implies that they make it a point of honor to remain at all times attentive to the fluctuating health conditions of research subjects so as to minimize all threats to their dignity as well as to their integrity.

**INTEGRITY** demands that investigators and members of their research team act at all times with honesty. It requires that they refrain from taking advantage of the good faith of individuals who have agreed to become research subjects and that they respect their freedom to participate in, or to withdraw from, a research project. It also requires that they never falsify the risks, data or results of research activities.

**ACCOUNTABILITY** demands that the investigator personally answer for the integrity and quality of the research activities under his direction. It requires that an investigator oversee the conduct of his research activities to ensure that they conform to accepted standards. It also requires that the healthcare institution, responsible for the well-being of patients, supervise the proper carrying out of research activities.

As well, in the opinion of the Committee members, the evaluation mechanisms pertaining to research activities need to be conceived in such a way as to take into account the following factors: **Efficiency, Credibility and Suitability**.

**EFFICIENCY** demands that the methods of evaluation pertaining to research activities be organized in a way so as to accelerate the approval process of research projects without compromising the quality of the evaluation. It implies that the human, organizational and financial resources required for the proper functioning of the evaluation process be made available to those responsible for the evaluation of research projects. It requires that the investigators cooperate actively with the evaluation process.

**CREDIBILITY** demands that competent persons perform the evaluations. It requires that these activities involve people having different backgrounds. It implies updating the skills and maintaining the competence of those people involved in the evaluation process.

**SUITABILITY** demands that the evaluation mechanisms utilized respect the culture of the milieu in which they are being implemented without compromising their efficiency. It requires that the mechanisms be appropriately adapted to different types of research that may exist in a given environment.

Moreover, in the opinion of the Committee members, methods of evaluation must take into account the following fundamental values: **Consistency, Transparency and Vigilance.**

**CONSISTENCY** demands that a regulatory framework be adopted as a point of reference and standard of measure for evaluation activities in clinical research. Furthermore, it requires that everyone abide by the rules contained in the approved regulatory framework. It implies that continuity be ensured with respect to the evaluation activities that have been instituted.

**TRANSPARENCY** demands that the evaluation procedures not be carried out in secrecy. It requires that the evaluation mechanisms and criteria applicable to research activities be clearly identified and known to all participants, patients, investigators, healthcare institutions and sponsors alike. It requires that the research milieu agree to periodic external review regarding the functioning of existing control mechanisms pertaining to the scientific, ethical and financial dimensions of research activities.

**VIGILANCE** demands a follow-up of research activities so as to assess their ongoing conformity to the scientific, ethical, legal and financial requirements agreed upon. It requires that healthcare institutions develop the appropriate mechanisms to assure adequate follow up.

The Committee members are aware that control mechanisms pertaining to research activities exist at various levels. Nonetheless, the Committee members believe, on the basis of their consultations and of different opinions expressed to them, that the research sector is presently in need of a review of its different modes of evaluation of research activities and that existing modes of evaluation and control mechanisms can be substantially improved.

That having been said, it is clear that there are neither easy solutions nor quick fixes to accomplish that which must be done in order to maintain the high quality of research activities and ensure the respect for research subjects. It is unrealistic to believe one can achieve these two last objectives without the commitment of proper human and financial resources.

In that respect, it would be extremely easy for the scientific community and healthcare institutions to find ways to evade the issues and find excuses to disclaim the responsibilities that are incumbent upon them concerning the evaluation of clinical research activities. Will they be able to meet the expressed expectations? Will they have the courage and willingness to institute what must be? Will they be able to wisely use the monies at their disposal to allow for proper evaluation of research activities in all their dimensions? Time will tell!

**Chapter 1**  
**STRATEGY AND METHODOLOGY**

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<b>Chapter 1 - STRATEGY AND METHODOLOGY</b>
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In order to address the prevailing situation concerning control mechanisms for clinical research in healthcare institutions, as well as to analyze control mechanisms established to ensure the probity of research activities and guarantee the safety of research subjects, the Committee members established a strategy (A) and a methodology (B) enabling them to attain the aforementioned objectives.

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**A.**

**STRATEGY**

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The means by which the Committee members achieved the objectives described previously consisted of consultations with people and organizations concerned with clinical research, as well as the examination of various texts related to the existing clinical research practices.

**1.**

**CONSULTATIONS**

The Committee members believed it essential to consult the research milieu to obtain from those directly implicated on a daily basis in research, their opinion as to the existing problems and the solutions that should be envisaged.

At various healthcare institutions in Quebec, the Committee members met persons directly concerned with research activities, such as research directors, investigators, administrative assistants and nursing personnel. They also met with representatives of different organizations, such as the College of physicians and the Quebec Hospital Association whose responsibilities involve overseeing professional or institutional practice, as well as with representatives of various interest groups.

**2.**

**DOCUMENTATION**

It appeared important to the Committee members to gather and study a number of documents bearing on the current rules governing clinical research on the North American continent and in Europe.

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**B.**

**METHODOLOGY**

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At the outset of this study, the Committee members met several times to develop the methodology that would allow them to best accomplish their mandate. They identified individuals and organizations that it would be appropriate to meet, with the objective of obtaining information on the current situation from people involved with clinical research in Quebec. In addition, they developed a questionnaire to be sent to those healthcare institutions.

**1.**

**QUESTIONNAIRES**

To understand the control mechanisms presently used in the field of clinical research in the most complete possible manner, the Committee members developed a questionnaire containing one hundred and fifty four (154) questions. This questionnaire was developed taking into account

the personal experiences of the three Committee members as well as the contents of a questionnaire developed by the *National Council on Bioethics in Research on Human Subjects*, which conducted a poll involving a number of research ethics committees.

The questionnaire was divided into nine (9) sections, as follows:

1. Research projects;
2. Research centres;
3. Scientific committee;
4. Ethics committee;
5. Council of Physicians, Council of Nurses, Multidisciplinary Council;
6. Board of Directors;
7. General Management;
8. Investigators;
9. Patients.

The questionnaire was sent to eighteen (18) healthcare institutions in Quebec. The selection of these institutions was made following discussions amongst the Committee members. The sample obtained reflects a balanced participation between:

- Francophone and Anglophone healthcare institutions;
- institutions treating children and those treating adults;
- general hospitals and psychiatric institutions;
- institutions situated not only in Montreal and Quebec City, but also elsewhere in Quebec.

The healthcare institutions selected were the following:

1. Royal Victoria Hospital;
2. Sir Mortimer B. Davis Jewish General Hospital;
3. Douglas Hospital;
4. Hôpital Notre-Dame;
5. Hôpital Ste-Justine;
6. St. Mary's Hospital;
7. Hôpital St-Luc;
8. Hôpital d'Youville;
9. Hôpital de Chicoutimi;
10. Hôtel-Dieu de Québec;
11. Hôtel-Dieu de St-Jérôme;
12. Institut de cardiologie de Montréal;
13. Institut Philippe-Pinel de Montréal;
14. Centre hospitalier Robert Giffard;
15. Centre hospitalier de l'Université Laval;
16. Centre hospitalier de l'Université de Sherbrooke;
17. Centre hospitalier régional de l'Outaouais;
18. Centre hospitalier régional de Lanaudière.

All eighteen healthcare institutions that received the questionnaire responded. Two institutions reported that they did not conduct any research.

## 2.

## MEMOIRS

Moreover, the Committee members requested certain groups to forward them a written memoir expressing their opinions on the types of control mechanisms they considered would be capable of guaranteeing excellence in the field of clinical research and offering adequate protection to research subjects, two elements of prime concern to the Committee members.

The following organizations submitted memoirs to the Committee:

- The Quebec Cancer Foundation;
- The Provincial Patients' Committee;
- The Quebec Heart Disease Foundation.

The *Quebec Cancer Foundation* memoir addresses the following four issues: the information given to patients, professional training, the isolation of investigators, and Research Ethics Boards.

As for the information provided to patients, the *Quebec Cancer Foundation* suggests that the documentation presented to a prospective subject and his or her next-of-kin be drafted in common and plain language, and that the research ethics committees of healthcare institutions work with the institution's physician-investigators to develop new mechanisms to provide information to patients.

The *Quebec Cancer Foundation* suggests that training and continuing education be offered on an annual basis in the form of a compulsory seminar. It also proposes that participation certificates or certificates of competence in clinical trials be issued to acknowledge this training. In addition, it recommends that *The College of Physicians of Quebec* expand its mandate in continuing medical education to include clinical research, and that it be responsible for this education.

As regards the isolation of investigators, the *Quebec Cancer Foundation* recommends that networks of investigators be created in Quebec to overcome the scattering of human resources in clinical research and to supervise research quality in a more predictable manner. It suggests that the *Minister of Health and Social Services* issue reasonable and sensible guidelines with regards to clinical research and facilitate the emergence of a coordinated structure similar to that in existence in other Canadian provinces. Furthermore, it proposes that the *Fonds de recherche en santé du Québec* give priority to research groups and encourage the creation of surveillance networks.

Finally, the *Quebec Cancer Foundation* suggests that the Research Ethics Boards of each institution be more carefully constituted, that it be rendered permanent and that its decisions be considered final.

In its memoir entitled "*Responsibility and Transparency as Essential Elements in Clinical Research*", the *Provincial Patients' Committee*, following analysis of the difficulties uncovered by the Poisson affair, studies the control mechanisms presently existing in Quebec with respect to experimentation in the healthcare field. It examined informed consent: the cornerstone of experimentation on human subjects. It studies the nature of information that should be provided to subjects during and after experimentation. Finally, the memoir concludes by underscoring the importance of rendering investigators fully responsible for their activities and of informing the public at large about human research.

The *Provincial Patients' Committee* is of the opinion that to ensure the protection of research subjects and to provide adequate control over research projects conducted in healthcare institutions, the *Ministry of Health and Social Services* should establish a precise framework for Research Ethics Boards to follow.

In addition, according to the *Provincial Patients' Committee*, there must be clear and precise guidelines developed by the *Minister of Health and Social Services* concerning the content and presentation of consent forms as well as the different modalities associated with it.

The *Provincial Patients' Committee* also proposes that the *Minister of Health and Social Services* issue clear directives regarding research in healthcare institutions, requiring that research subjects be provided with all the information to which they are entitled through all stages of a project. It also considers it important that the *Minister of Health and Social Services* enact regulations requiring institutions to rapidly implement measures for investigators involved in experimentation to be rendered accountable for their actions.

Finally, in order to protect those who are solicited to participate in research projects, the *Provincial Patients' Committee* proposes that the *Minister of Health and Social Services* enact regulations so that healthcare institutions provide the general public with adequate information with respect to human experimentation.

The memoir presented by the *Heart Disease Foundation of Quebec* deals essentially with those practices that ensure the scientific quality of research projects funded by the *Foundation* and the adequacy of incurred expenses.

For the *Foundation*, the quality controls applied to research projects they fund rest, firstly, on the peer review evaluation made by the granting organization at the time of submission of the initial request or at the time of renewal of a grant application and, secondly, on the assessment made by editorial committees of scientific journals at the time research results are submitted for publication. Peer review committees, whose members come from across Canada, evaluate requests for grants made to the *Foundation*. The results of the evaluations are then transmitted to scientific committees who act as consultants at the provincial level. They in turn, submit to the provincial boards of directors a budget for each project that takes into account the scientific rating of the research project and the available funds.

According to the *Heart Disease Foundation of Quebec*, the health research network in Quebec is equipped with control mechanisms, which along with the peer review committees of the *Foundation* guarantee the scientific quality and validity of research projects funded by the *Foundation* as well as the appropriateness of incurred expenses.

In addition, according to the Foundation, the fact that medical research is increasingly exercised in a context of multi-professional teams, which includes investigators, healthcare personnel and medical students, provides an additional quality control mechanism.

### 3.

### ***VISITS AND MEETINGS***

After analyzing the questionnaires' results, the Committee members deemed it appropriate to meet professionals and administrators involved with clinical research in a number of healthcare institutions.

The Committee members visited the following institutions:

1. Hôpital St-Luc;
2. St. Mary's Hospital;
3. Royal Victoria Hospital;
4. Hôpital Notre-Dame;
5. Hôpital Ste-Justine;
6. Hôpital D'Youville;
7. Douglas Hospital;
8. Sir Mortimer B. Davis Jewish General Hospital;
9. Hôtel-Dieu de Québec;
10. Institut de cardiologie de Montréal;
11. Centre hospitalier de l'Université Laval;
12. Centre hospitalier de l'Université de Sherbrooke;
13. Centre hospitalier Robert-Giffard.

During these visits, the Committee members were able to discuss various problems encountered in the evaluation and follow-up of research projects as well as the protection of research subjects.

The visits conducted by the Committee members alerted those present to the potential problems related to clinical research, the necessity of revising existing controls and developing a regulatory framework that would help ensure the growth of research, while protecting those directly involved in research activities, namely, research subjects, healthcare institutions and research personnel.

The Committee members also met with representatives of various professional groups or organizations, those being:

1. The College of Physicians of Quebec;
2. The Order of Nurses of Quebec;
3. The Quebec Health Research Fund;
4. The Quebec Hospital Association;
5. The Ministry of Health and Social Services of Quebec;
6. The Association of Research Centers Administrators of Quebec;
7. The Quebec Association of Pharmacists working in Healthcare institutions;
8. The Public Curator of Quebec;
9. The Office for Research Integrity (Washington, D.C.).

Furthermore, the Committee members met with different groups particularly interested in certain aspects of clinical research including a group of students in bioethics at the *Université de Montréal* and a group of ethicists from *McGill University*. In the course of this study, they also met individually with persons directly involved in research in Canada, the United States and Europe.

#### 4.

#### PROPOSALS

The consultations, which the Committee members initiated, as well as the various memoirs presented to them, enabled the Committee to establish a clear picture of the difficulties experienced in different clinical research environments. The Committee members relied upon those observations to propose a series of concrete steps to improve the conditions under which clinical research is conducted and the mechanisms for evaluation of research activities.

The Committee's proposals are of three different types. Firstly, they bear, at the local level, on the development and adoption of a regulatory framework, which would be comprised of a series of measures capable of guaranteeing the integrity of research and ensuring the protection of research subjects. Secondly, they deal, at a provincial level, with the creation of a permanent structure responsible for overseeing the control mechanisms instituted in healthcare institutions. Thirdly, they deal with a series of proposed actions needed to maintain the quality of research activities conducted in Quebec.

Concerning the adoption of a regulatory framework, the Committee members hope that every Quebec healthcare institution will retain the most pertinent elements proposed in this report that are applicable to its particular milieu. Moreover, the consultation process initiated by the Committee had the advantage of shedding some light on and triggering a sense of awareness of the potential problems that can occur in conducting research activities in the health sector.

With respect to the creation of a provincial permanent structure, the Committee members not only feel it to be helpful but essential in view of the present situation. It would allow the healthcare network to fully and efficiently take charge of its responsibilities with respect to the evaluation of biomedical research activities and would avoid its dependence on external agencies for the assessment of the quality and integrity of biomedical research activities carried out in Quebec.

Finally, the Committee members believe that the proposed actions aimed at the scientific and research community would offer an effective framework for clinical research activities in Quebec.

## **Chapter 2**

# **THE SPHERE OF CLINICAL RESEARCH**

## Chapter 2 - THE SPHERE OF CLINICAL RESEARCH

The Committee members felt it essential, prior to addressing the fundamental question of the present report, - the evaluation of control mechanisms in clinical research -, to describe certain elements critical to understanding the pertinence of the observations and recommendations which will subsequently be proposed.

Thus, it was important to the Committee members to draw a brief, albeit necessarily incomplete, picture of the sphere of clinical research. This description will depict the field of clinical research (A), the framework that shapes it (B), the context within which it develops (C), and the funding modes that it enjoys (D).

### A. THE FIELD OF CLINICAL RESEARCH

In its *Guidelines concerning Research on Human Subjects*, the *Medical Research Council of Canada* states that the term "research" refers to "the acquisition of information on people by intervention or other means, the acquisition derived from that being necessary for the immediate well-being of the individual person".

Despite the accuracy of this definition, it seemed important to the Committee members to clarify the scope of clinical research and the ways the healthcare sector defines a scientific activity which aims at verifying a research hypothesis using tested methodology or gathering data in order to elucidate scientific questions.

These explanations are important in the context where one uses numerous terms and different expressions to describe research activities conducted in the healthcare sector. Terms and expressions such as research, experimentation, experience, study trial, innovative therapy, experimental therapy, innovative care, medical research, biomedical research, therapeutic research, experimental research, biomedical experimentation, medical experimentation, therapeutic experimentation, pure and simple experimentation, etc., need to be defined, allowing for the fact that each of these terms are capable of carrying a semantic content which will vary depending on the person using them and the context in which they are applied.

For the moment, we will limit ourselves to the definition of the nature of clinical research in comparison to other types of health research by defining the different types of scientific activities that are included and by identifying the different developmental phases of a drug in pharmacological research.

#### 1. 1. THE NATURE OF CLINICAL RESEARCH

Various types of research exist in the area of health. These are clearly described in the three-year plan (1993-1996) of the *Quebec Health Research Fund*, which establishes eight different categories of research:

1. Fundamental research;
2. Clinical research;
3. Epidemiological research;

4. Operational research;
5. Organizational research;
6. Evaluative research;
7. Research on health services;
8. Applied research.

Although the present report deals strictly with clinical research, the Committee members believe that certain observations and recommendations formulated in this report could be applied in other areas of health research.

The document of the *Quebec Health Research Fund* defines health research as "the study of physiopathological processes, of the etiology of an illness or of an abnormality, but also of the diagnostic and therapeutic methods in order to improve, to specify the prognosis and to favour the autonomy of individuals. This research relies on human subjects".

Within the context of the present report, **clinical research** is that branch of health-related research which experiments on human subjects to validate a research hypothesis by applying rigorous scientific methodology or to analyze data which raise questions or which requires further clarification. The expression **biomedical research** refers to all research activities conducted in the health sector. It does not limit itself to fundamental research as was suggested by the *Quebec Health Research Fund*. Finally, **pharmacological research** relates to the development of new drugs or new applications of drugs already in use.

## 2. THE TYPES OF CLINICAL RESEARCH

The scientific activities specific to clinical research can be divided into various types. Each carries their particular characteristics and requires specific training for those pursuing them. Proper identification of these types is essential as they impact on the type of research conducted by an investigator. The five identifiable types of research are as follows:

### ***Type I***

**Type I** activities are investigative in nature and rely on methodologies applied in the social and human sciences. They deal with healthy or ill populations. The only specific data used are those gathered in a prospective or retrospective manner. This type of research mainly raises questions related to confidentiality and the appropriateness of inclusion and exclusion criteria in the definition of the studied populations.

### ***Type II***

**Type II** activities are biological in nature. These activities are carried on ill persons for the purpose of studying or modifying prospectively diagnostic methods, treatment strategies or methods of investigation. This type of research exposes research subjects to randomization in cohorts. It may involve undesirable and unforeseeable side effects. These activities should be carefully monitored.

### ***Type III***

**Type III** activities are biological in nature. They involve research activities associated with the study of human organic substances, such as cells and tissues obtained from healthy or ill subjects, but where the analysis will bear no clinical impact on an individual. The problems encountered in this type of research pertain primarily to confidentiality and consent. The samples obtained must at the outset be of use to the tests required for diagnostic purposes. In

the case of fetal tissue, specific problems arise. Similarly, problems arise with the preservation of DNA, of genetic material such as sperm and ova, or of tissue culture cells preserved for future use. Numerous ethical issues surround these different practices.

#### ***Type IV***

**Type IV** activities are also of a biological nature. They involve the study of human organic substances such as cells and tissues removed from sick patients. The study results suggest a potential modification of clinical practices. These activities are meant to give rise to new treatments that must be scrupulously analyzed.

#### ***Type V***

**Type V** activities involve biological research conducted on animal or cellular models of human diseases. These studies raise issues related to the use of animals; in particular, their upkeep, their quality of life, the numbers required for an experiment and possible substitutes.

### **3. THE PHASES OF PHARMACOLOGICAL RESEARCH**

In the field of clinical research, pharmacological research occupies an important place. The unique aspects of this research deal primarily with the different phases in the development of a chemical substance. One can group these into four distinct categories. Laboratory research and research on animals precede these four phases. The latter are well described in "Therapeutic Trials, their Use"<sup>1</sup> which we reproduce here. Each of these phases poses particular ethical questions, which are important to mention.

#### ***Phase I***

**Phase I** studies are usually carried out on a small number of healthy volunteers and last approximately one year. These studies on drug tolerance determine the maximum tolerated dosage. The choice of the initial dose is based on the toxicological data from animals, subsequent doses being progressively increased under high levels of surveillance, both clinical and biological. These studies are also conducted to evaluate the pharmacokinetics of the product. Lastly, these studies precede the determination of doses to be administered to Phase II research subjects.

#### ***Phase II***

**Phase II** studies are carried out on several dozen patients over a period of one to two years. The objective of these studies is to determine the pharmacological effectiveness of the product (proof of the hypothesis) to ascertain the optimal doses for Phase III studies. These studies are undertaken in an environment favoring optimal testing of a molecule.

In fact, certain Phase II trials apply double-blind techniques using a placebo control. They involve short-term treatment associated with simple indications. These trials allow, on the one hand, the study of certain medication interactions and observation of the most frequently undesirable side-effects while, on the other hand, allowing for further pharmacokinetic research, for example, as in cases of renal insufficiency.

#### ***Phase III***

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<sup>1</sup>Gilles Bouvenot, Comment on devient médicament" in Essais Thérapeutiques. Mode d'emploi. Paris IN5ERM 1990, pp. 6-7.

**Phase III** studies are primarily comparative trials lasting several years. They are conducted on a larger number of patients. The principle of comparative trials is based on the randomization of treatment and the use of double-blind techniques. Phase III studies permit the evaluation of the efficacy of a molecule in a clinical setting and the determination of its tolerance level.

#### ***Phase IV***

**Phase IV** studies usually follow marketing of the product and are conducted in the first few years following its release. They allow further understanding of the drug with respect to its safety and a more precise assessment pertaining to the conditions of its clinical applications and dosage efficacy. **Phase IV** also serves to detect rare but at times serious side effects left unobserved in previous phases. **Phase IV** studies can also lead to the discovery of new therapeutic indications.

### **4. BENEFITS AND RISKS LINKED TO RESEARCH**

It is readily accepted that clinical research, to the extent that it is well managed, contributes to the advancement of health care. At the same time it carries potential hazards for those who participate as research subjects.

#### **a) The Real Benefits**

One can assert that without the multiple research projects involving human beings conducted with the goal of furthering the knowledge of the functioning of the human body, the mode of action of various drugs on it, and the efficacy of various medical devices and parts implanted into it, health care could not have progressed to its present day status.

Clinical research, essential as it is, not only maintains but also improves the quality of care and the treatments offered to patients. It not only contributes to the advancement of diagnostic and therapeutic techniques but also influences decisions concerning prevention, the development of health policies, etc.

Thanks to clinical research, one is able to compare new methods of treatment with traditional ones, to maintain a constant concern for the quality and efficacy of treatments, to develop awareness for the limits of health care interventions and to allow the emergence of new therapeutic techniques. Without ongoing activity of this nature, the efficacy of health care procedures would be prevented from progressing. Healthcare intervention would become less and less capable of meeting the real needs of the population.

Clinical research furthermore raises the awareness of members of the medical profession, nursing personnel and other healthcare workers to the problems experienced by their patients. Clinical research allows a practical and early transposition of breakthroughs made in the field of fundamental research. Patients thus benefit from early breakthroughs. Clinical research makes those involved in fundamental research more acutely aware of the importance of finding solutions to specific health care problems. It acts therefore as a bridge between the evolving fundamental and clinical research and the patients in need of healthcare.

For research personnel, clinical research, when well managed, allows a continual updating of knowledge and of diagnostic and therapeutic techniques as well as an enhancement and deepening of scientific knowledge. It also facilitates inter-specialty cooperation and the

recruitment of highly qualified medical and paramedical personnel interested in the progress of science.

For healthcare institutions, research activities often allow early access to technology otherwise unavailable without having to expend the initial acquisition costs. Research activities allow a more exacting evaluation of new technology than that provided by the manufacturer's promotional literature or by expertise acquired in other clinical settings. Furthermore, research activities attract additional personnel (physicians, technicians, nurses) offering the opportunity of a more far-ranging recognition.

Clinical research naturally attracts additional financial resources for hospitals. Healthcare institutions and research centers are able to acquire or renew high technology equipment directly from the funds received by way of research grants or contracts. These extra financial resources allow for improvement in the delivery of health care.

For university teaching hospitals, research activities represent a major factor in the promotion of quality healthcare and teaching. In general, research offers the opportunity for teaching hospitals to successfully fulfill their mission of transmitting knowledge to new generations of physicians, investigators, clinicians or scientists. Scientific research acts to expose students not only to the scientific knowledge required to practice their profession, but also to the process that allows the acquisition of this knowledge. These activities must be well designed and motivated by a concern for quality.

In spite of the multiple benefits that the population derives from research activities, one must not forget the risks inherent to such activities, the side effects and inconveniences to which subjects are exposed when they accept to participate in a research project. If it is true that many research subjects derive immediate benefit from their participation in a research project, it is also true that a number of them will not derive a single benefit. The only benefit they might enjoy, not a negligible one at that, is of knowing that they have contributed to the advancement of knowledge aimed at improving the quality of life of their fellow-citizens.

## **b) The Potential Dangers**

It is widely recognized that participation in a research project is not a trivial act. As outlined forcefully by the *Medical Research Council of Canada* in its *Guidelines for Research in Human Subjects*, "the damages which can be caused are numerous and are not limited to harm to the body. They also involve the loss of dignity and self-esteem, guilt and remorse, or the feeling of having been exploited and humiliated."<sup>2</sup>

A number of research projects in the biomedical sphere carry significant risks of organic complications and side-effects for the participating subjects. These risks can arise from the interruption of regular intake of a medication, the administration of an experimental medication, the subjection to an invasive or experimental technique as part of the project.

Such risks are also attributable to the structure of certain research protocols, particularly those where techniques of randomization are applied, where placebo groups exist, and where neither

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<sup>2</sup>Medical Research Council of Canada. Guidelines for Research on Human Subjects, 1987, op. cit. note 2, p. 7.

the investigator nor the patient know the nature of the product being administered (double-blind studies).

Research subjects must be informed that they are running a risk, as minimal as it may be, of compromising their chances of maintaining or obtaining insurance coverage. One cannot presume how an insurer would react when learning that one of his insured, victim of a heart attack, has become an invalid following a complication, such as a cerebral hemorrhage, attributable to his participation in a research project. Would the insurer not object to a claim for loss of income when the subject had not informed the insurer of a risk of which he should have been made aware?

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## **B. THE FRAMEWORK OF CLINICAL RESEARCH**

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To further understand the conditions within which research is carried out, it is important to examine the operational as well as the regulatory frameworks within which it functions.

### **1. THE OPERATIONAL FRAMEWORK**

The description of the operational framework requires at the outset that one examine first the role played by those involved in research activities and thereafter, the environment in which research activities are conducted.

#### **a) The Persons Involved**

One must understand that clinical research constitutes an essential step in the process of acquiring new knowledge and developing new diagnostic and therapeutic techniques. The achievement of these two objectives can only be attained through the participation of research subjects (i) and through the involvement of healthcare professionals particularly interested in conducting research (ii).

##### **(1) Research Subjects**

In Quebec, as elsewhere, biomedical research would be seriously handicapped if it could not rely on the thousands of people in good or poor health who yearly agree to participate in research projects which aim at improving healthcare. Without them, sustained progress in clinical research and, as a consequence, in healthcare, would be limited.

The human being who accepts to participate in a research project is usually called a **research subject** nowadays rather than a **subject of experimentation**. With the evolution of time, he or she may eventually become a **study subject**.

In its *Guidelines for Research on Human Subjects*, the *Medical Research Council of Canada* defines a research subject as a "human being who directly assumes the risk of research."<sup>3</sup> This succinct definition is invaluable in pointing out unequivocally the burden borne by research subjects for the benefit of biomedical science.

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<sup>3</sup>Medical Research Council of Canada, *Guidelines for Research on Human Subjects*, 1987, op. cit., note 2, p. 7.

The research subject is called upon to bear the consequences, positive as well as negative, of scientific development, usually without compensation, recognition or gratification, except for the satisfaction of having contributed to scientific progress. This is the case when the individual is capable of appraising the situation, which is not the case, for example, with young children or incompetent persons.

Furthermore, in the opinion of the Committee members, it is not quite accurate to say that a person "participates" in a research project. It is more appropriate to say that the person "gives his or her consent", agreeing to put him or herself, his or her body, or a body part at the disposal of the investigator so that the latter can utilize it in the hopes of proving a research hypothesis or obtaining data capable of furthering scientific knowledge.

Benefiting from the fact that a person has agreed to place himself or herself in the hands of an investigator, the latter can test on a human organism the efficacy or safety of a substance or technique, of a therapeutic regimen, or of the properties of medical devices, without the person necessarily deriving any benefit from his or her participation in such research and without being informed of the results of the research.

Persons asked to participate in a research project may be healthy subjects or ill subjects.

#### **\* *The Healthy Volunteer***

A healthy subject or volunteer is a person who, without displaying any particular pathology, agrees to participate in a research project.

Usually healthy subjects are called upon to participate in a research project of a pharmacological nature only during Phase I or II of their development, those phases aimed at determining levels of a drug's toxicity and efficacy. They may also be involved in Phase III trials as control groups.

One may question the motives that compel healthy people to participate in research projects from which they themselves cannot derive any therapeutic benefit. Indeed, by participating in such projects, they agree to expose themselves to certain risks, no matter how timid, which may affect their health or well-being. Moreover, according to the legislation in force in Quebec, enrollment in an experiment may not give rise to any financial reward other than the payment of an indemnity as compensation for the loss and inconveniences suffered on account of an individual's participation.

In certain cases, the amount of the compensation can be so attractive that it constitutes an inducement to participate in a research project. This is especially true if the risks and inconveniences to which a person would be exposed appear minimal. Whatever the situation, the conditions surrounding these experiments must be particularly strict to ensure maximum safety and minimal inconveniences.

#### **\* *The Unhealthy Subject***

The development of new diagnostic and treatment methods in relation to a specific disease requires that the product or technique under study be tested on patients afflicted with that disease. In drug trials, resorting to ill subjects usually occurs during Phases II, III or IV studies, phases during which the object is to test the effectiveness, the safety and the superiority of one drug or product over another.

Altruism generally motivates ill patients to participate in a research project. At times, one can observe in them a certain naivety and often the hope that their participation in the research project will benefit them in some way, which is far from always being the case.

It is also worth mentioning that patients are often *a priori* inclined, even enthusiastic to participate in a research project, especially when it is their treating physician who assumes responsibility for the project. In many cases, they feel indebted to their treating physician for having saved their lives or for having improved their condition. Not only do they wish not to disappoint a physician who has done so much for them, but also they equally believe that they owe the latter something. They also do not wish to feel guilty for refusing to participate in a research project and may fear that refusal on their part would spoil their future relations or influence the quality of care they will receive.

The patient who accepts to participate in a research project agrees to conform himself to the project's requirements, that is, the visits, tests, examinations or interventions it entails. This involves a burden that the person assumes, enticed by the hope of gaining immediate benefit or by the desire to help others suffering from similar health problems. Furthermore, it must be noted that a patient exposes himself to a certain number of risks and inconveniences associated with the research project. These range from a simple headache all the way to cardiac arrest leading to death; they also include discomforts and side-effects such as nausea, visual problems or skin rashes.

Thus, it is important that the person who volunteers as a research subject be fully and honestly informed of the real benefits that he may personally gain from it as well as of the experimental aspects and specific risks of the project.

## **(2) Research Staff**

Clinical research is fundamentally the result of teamwork. Within a healthcare institution, this necessarily implies the involvement of various healthcare professionals, each of whom performs a specific task. Research personnel can be regrouped into three categories: investigators, research assistants, and students. Among investigators, different statuses exist.

It is important to clearly define the roles and responsibilities assumed by each member of these different groups of research personnel so as to define the expectations placed on each group.

### **\* The Investigator**

In clinical research, each research project is carried out under the supervision of an investigator, who is responsible not only for the quality and integrity of the research activities conducted under his authority, but also for the safety and general well-being of persons who participate in the project.

The investigator is directly accountable to the organization that grants or finances his research activities, with respect to the progress of the project and the allocation and expenditure of funds. The investigator also answers to the Research Ethics Board of the healthcare institution for the overall conduct of his research projects; to the director of the research center concerning the scientific and administrative aspects of his activities and finally, to the Director of Finance for the utilization of the research funds obtained.

Often, it is the investigator, not the healthcare institution, which is responsible for the hiring and firing of research personnel. According to the rules of good clinical practice, it is the investigator who must ensure the competence of his or her collaborators as well as the support personnel participating in the realization of the research project. This means that an investigator must not hire support personnel who do not have the necessary training for carrying out the research project, even if this means having to support additional costs to hire more competent personnel.

#### **\* *Research Assistants***

The realization of a research project in accordance with an established protocol requires that clinical investigators call upon specialized personnel responsible for the many interactions with patients: appointments, patients' recall, measurements, data collection, questionnaires, follow-up of treatment compliance, entering of data in manual or computerized data banks, compiling of data, etc.

Research assistants are often nursing professionals. These persons are at the heart of the research activities and research results depend greatly on the quality of their work. Moreover, they are often the first people to detect a health problem that may arise with a patient involved in a research project.

It is important that the responsibilities given to research assistants in a research project be in accordance with the training they possess. The quality of the research as well as the safety of subjects who participate in a research project depends upon this.

At the present time, this category of personnel is not usually unionized and has no job security. They are subjected to the uncertainties of obtaining grants and research contracts as well as to the authority of the hiring investigator.

#### **\* *Students***

When research projects are carried out in university hospitals, students may be called upon to participate in these projects. It is important that the principal investigator be fully aware of the nature of their participation and precisely delimits its extent. It is also important that the authorities responsible for the evaluation of research projects be informed of the extent and type of their participation.

### **b) *Research Environments***

Nowadays, clinical research is conducted not only in healthcare institutions, but also in private offices and within pharmaceutical laboratories. As a general rule, it is easier to draw a clear picture of research activities carried out in healthcare institutions than of those carried out in private offices or in pharmaceutical laboratories.

#### **(1) *Research in Healthcare institutions***

Clinical research projects in Quebec are mainly carried out in healthcare institutions. These offer not only an unparalleled infrastructure but also easy access to a pool of subjects required for carrying out clinical research activities.

Within many healthcare institutions, investigators form part of a structure called the «assembly of investigators», which fulfills various functions. Part of its mandate consists in advising on

research activities being carried out within the healthcare institution. It also adopts policies that serve as guidelines in conducting research activities. In healthcare institutions where a research center exists, the structure is also consulted with respect to the nomination of the Research Director.

Within many institutions, one can find a research institute or center<sup>4</sup> that is financed in part by a special program of the FRSQ (*Fonds de la recherche en santé du Québec*).<sup>5</sup> Such an institute or research center does not necessarily encompass all of the research activities conducted within a healthcare institution.

The Committee members were able to determine that, despite the existence of a research institute or centre in a healthcare institution, a number of research projects were carried out within various departments without the institute or center being necessarily informed of their existence. This is not without causing problems for the coordination of research activities within a healthcare institution. In healthcare institutions where there is no institute or research center, research groups or teams working within different departments usually carry out research activities.

For several years now, certain healthcare institutions have made their Research Institute or Centre a corporate body distinct from its parent-institution, which is managed by its own Board of Directors. The Director General, the Research Director as well as several investigators belonging to that healthcare institution serve as members of that Board. This structure seems more prevalent in healthcare institutions with a large volume of research activities. Such an independent structure serves to facilitate the expansion of research activities and the development of a mega-center.

As a rule, research conducted within a healthcare institution are governed by the policies and regulations adopted by either the institution itself or by the University with which the institution is affiliated. These policies and regulations are derived from the standards put forth by granting or funding agencies, such as the *Medical Research Council of Canada* or the *National Institutes of Health* (NIH).

From the results of the survey conducted amongst healthcare institutions, research projects are usually subjected to peer review that focuses on the scientific validity of the project and to an ethical review.<sup>6</sup> In cases where research activities do not conform to the established norms contained in the regulations, the investigator is exposed to administrative sanctions that may affect his investigator status.

As a general rule, the healthcare institution where the research project is carried out administers the research funds granted to an investigator. It appears from the consultations held by the Committee that at times, part of the funds end up in a financial institution external to the healthcare institution. Thus, the investigator himself or a management company that he has formed and of which he is a stockholder, exercises authority over the account.

Finally, it is worthwhile to note that for several years now, a significant number of research projects call upon investigators from different healthcare institutions to simultaneously contribute

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<sup>4</sup>See Appendix 3 of the present report.

<sup>5</sup>See, *Fonds de la Recherche en santé du Québec, Plan triennal 1993-1996*, op. cit., note 3, pp. 10 ff.

<sup>6</sup>See, in this respect, Appendix 3 of the present report.

to the validation of the same research hypothesis by using cohorts of subjects enrolled in the same research protocol. These are called multicenter trials.

## **(2) *Research outside Healthcare institutions***

Although the Committee members, due to the limits of their mandate, were not able to establish the actual scope of this phenomenon, it appears from consultations that a certain number of research activities are carried out in Quebec outside of a hospital environment. Physicians who are otherwise members of the Council of Physicians, Dentists and Pharmacists of a healthcare institution often conduct these in private offices. Pharmaceutical companies often sponsor research projects carried out in private offices. They are more often than not conducted to demonstrate the superiority of one product over another.

With respect to this type of research activity, a physician is asked to prescribe to his patients the drug that is being tested by the pharmaceutical company funding the research project. The patients are then required to return for a control visit, the cost of which is often passed on to the public health insurance regime. Subsequently, the physician investigator is required to complete a questionnaire to be returned to the company sponsoring the research project. The physician is then paid an honorarium for each completed and returned questionnaire.

Research projects carried out in private offices raise certain questions. These projects do not appear to be subjected to any particular regulatory framework. It is hoped that all the requirements essential to ensure the integrity of the research projects and the protection of patients are being met; however, this cannot be proven nor guaranteed for lack of specific information on how these research projects are carried out.

Indeed, since these research projects are carried out in private practice and not in healthcare institutions, it is less than certain that they undergo any peer review for scientific evaluation prior to their undertaking or review by an Ethics Board. Furthermore, the management of funds for research projects carried out in private offices is assumed in principle by the investigator who deposits the secured funds in a commercial or personal account. The investigator is accountable strictly to the body sponsoring his research project and to no one else.

The patients recruited for these research projects are often patients admitted to a healthcare institution for treatment to which the principal investigator is attached. In such cases, patients participating in these research projects might have the false impression that the research project is endorsed by the healthcare institution, the latter not even being aware of the existence of such projects.

If a problem of any kind should arise, the healthcare institution could be implicated, even though it has not been involved in the project. It is important that those responsible in a healthcare institution for overseeing research activities be empowered to terminate problematic research activities, primarily by freezing research funds, an impossible task if these same funds are managed outside the healthcare institution.

Moreover, a significant number of Phase I and Phase II drug research is carried out in pharmaceutical laboratories. With respect to these research projects, there is little knowledge of the conditions under which they are carried out. These projects may be less well regulated than those conducted within healthcare institutions.

2.

**THE REGULATORY FRAMEWORK**

Unlike the situation in France,<sup>7</sup> for example, in Quebec there is neither specific legislation nor regulations defining fully the standards that persons involved in research on human subjects should follow. However, a number of legal provisions<sup>8</sup> dealing with the capacity of a person to participate in a research project, the criteria to be respected as well as the conditions under which human tissue or other organic substances may be removed from a person for research purposes in the course of healthcare do exist.

There are also certain guidelines defining the ethical aspects of research on human subjects.<sup>9</sup> In addition, beyond existing legal rules and guidelines, one can find a number of standards adopted in other countries that bear on the conduct of clinical research in Quebec.<sup>10</sup> Finally there also exist precise and detailed clinical standards that have been established to govern clinical research activities.

In the course of the Committee's consultations, the latter was able to discern that many people engaged in research activities were not knowledgeable about these regulations and standards. This raises questions as to whether certain practices conform to established regulations and standards promulgated either by local legislation, or by local or foreign governmental agencies.

Recommendation no 1

*In the opinion of the Committee members, persons who work in the field of clinical research, whatever their status might be, must have adequate knowledge of the legislation, regulations, and other standards that regulate clinical research.*

Standards  
regulating  
clinical  
research

This having been said, it is not the intention of the Committee to present here a detailed analysis of the different laws and regulations that might apply in Quebec to the field of clinical research, but simply to make known the main features. A detailed analysis of these texts should be undertaken in the event that the legislator wishes to adopt further regulation of biomedical research in Quebec.

a)

**The Clinical Framework**

In the area of healthcare, clinical research is regulated by a set of precise rules developed by the scientific community, the goal of which is essentially to guarantee the validity of research results

<sup>7</sup>Code of Public Health, Book II bis, which includes the law No. 88-1138 of December 20, 1988, the so-called Huriet-Sérusclat law, modified by law no. 90-86 of January 23, 1990 and decree no. 90-872 of September 27, 1990.

<sup>8</sup>Quebec Civil Code, Arts. 20 to 26.

<sup>9</sup>Medical Research Council of Canada, Guidelines concerning research on human subjects, op. cit, note 2.

<sup>10</sup>Nuremberg Code 1945. World Medical Association, Helsinki Declaration, 1964. Public Health Service Act (USA), Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects.

and ensure the safety of subjects who agree to participate in a research project. These rules take into account the ethical imperatives, which must be followed in carrying out research activities, particularly those contained in the *Helsinki Declaration of the World Medical Association*.

These regulations were developed to prevent research activities which have no scientific value and thus of no scientific application and which represents a waste of time and money while exposing research subjects to unnecessary risks from being conducted. Secondly, they express the need to respect those who agree to participate in research projects and to ensure their safety.

It is important, in the context of the present report, to examine, however briefly, the means used by the scientific community to ensure the validity of research results and the safety of subjects. These means are clearly described in the various texts outlining the standards of Good Clinical Practice. With respect to these texts, one can make the following assertions as concerns the obtaining of valid results and the protection of research subjects.

The validity of research results rests, first of all, upon the quality of the research protocol, which must be elaborated prior to the start of the research itself. At a minimum, this document, the cornerstone of a research project, must contain the following elements:

- a) the objective of the project;
- b) the scientific value of the project;
- c) the need to use human subjects;
- d) the measures to be taken;
- e) the methods to be used;
- f) the nature and gravity of the risks and inconveniences to which subjects participating in the project could be exposed;
- g) the type of information that will be provided to the research subject;
- h) a review of the relevant literature.

Secondly, it relies on the investigator's adherence to Good Clinical Practices as developed by the scientific community and approved by various recognized organizations.<sup>11</sup> Good Clinical Practices precisely define the conditions which investigators are obliged to follow in the process of carrying out research. It defines the responsibilities of the sponsor, the healthcare institution and the investigator with regard to the good conduct of a research activity and outlines their obligations to the research subject.

Thirdly, it rests on a sophisticated inspection system (Audit) of research activities, which aims to ensure that the investigator follows in all respects the requirements of the research protocol. As a general rule, the audit allows the identification of all irregularities as well as all deficiencies in the conduct of research activities. It rests essentially on an on-site visit by persons whose mission it is to examine various technical elements of the research activity. Multiple techniques are used including analysis of research records, comparison with the corresponding clinical records and verification of entries into the data collection forms. Assurance of patients' safety

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<sup>11</sup>Refer to World Health Organization. Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products, 1993. See also Canadian Health and Welfare Branch of Health Protection, Drug Division. Directives of the Drug Division. Clinical Research, 1989. Ottawa, Products and Services of Canada, 1989, Revised April 1992. European Economic Community, European Guidelines for Good Clinical Practice, 1990.

benefits from audits carried out periodically within healthcare institutions to verify conformity of research activities to the approved protocols.

Moreover, in the case of multicenter trials, additional surveillance methods are applied. These projects usually provide for the creation of different committees such as a Steering Committee and a Safety Monitoring Committee. The first oversees the carrying out of the study while the second examines all adverse events reported in the course of a study to identify if the reported event is related to the research protocol and if so, to stop the continuation of the research project if it is felt that the complication rate exceeds the acceptable rate established by the Committee.

On the other hand, aware that research activities carry some risks for the research subject and some uncertainties on the part of the investigator, the scientific community has defined within the rules governing Good Clinical Practices, a set of standards aimed at ensuring the safety of persons who agree to participate in a research project.<sup>12</sup>

In concrete terms, these methods depend on the strict observance of the research protocol, the overseeing of the research subjects throughout the research project and the follow-up procedures, and the reporting and evaluation of all untoward events which occur during the project to determine if these are associated with the research project and if so, whether it is appropriate to terminate the project.

The safety of patients depends on the competence and expertise of the investigator and the members of his research team. It relies on the information the investigator has concerning the potential danger of the drug, and the techniques or methods applied in the course of a research project. Finally, it depends on the ability of the personnel of the healthcare institution where the research is carried out to deal with all complications that may arise in the course of the research project.

As a whole, one should not question the necessity for strictness and effectiveness of control mechanisms in clinical research that exist to ensure the validity of results and to detect irregularities which can arise even when in certain cases, the audit procedure failed to identify these irregularities. It must be stressed that in the presence of these controls, it is in the interest of the investigators to be beyond reproach in the conduct of research activities, since disastrous repercussions for the investigator can result from non-adherence to existing standards and rules.

Indeed, the discovery of irregularities, even if minor, such as the inversion of calendar dates on a form, or the entry of a weight measure in pounds rather than kilograms can, at worst, cast doubt on the validity of a study where such an irregularity could affect a previous excellent rating. Moreover, the discovery of major irregularities can signal the interruption of a research project and lead to an inquiry into the conduct of the investigator.

**b)**

## **The Ethical Framework**

In Canada, in the field of clinical research, the *Guidelines for Research on Human Subjects*, developed by the *Medical Research Council* in 1987, now under revision, serve as a point of

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<sup>12</sup>Medical Research Council of Canada, Guidelines for Research on Human Subjects, 1987, op. cit., note 2, p. 7.

reference for the ethical aspects of biomedical research.<sup>13</sup> They are essentially an update of the document entitled *Ethical Aspects of Research Using Human Subjects* published in 1978 by the same Council.<sup>14</sup>

Any Quebec investigator requesting funding from the *Medical Research Council* for a research project is required to follow these guidelines.<sup>15</sup> Although they do not have the force of law, the non-adherence to these guidelines will bring to an end the financial support awarded by *The Medical Research Council* for the research activities conducted by the investigator and could lead to a withdrawal of the funding previously granted.

Although the Council's guidelines define "the expectation of the *Medical Research Council* toward the research community as a whole, when research funded by the *Medical Research Council* deals with research on human subjects"<sup>16</sup>, they also serve as a measure for the majority of clinical research activities conducted in Canada. Thus they form part of the Directives issued by the *Drug Bureau* of the *Health Protection Branch of Health and Welfare Canada*, and are used to guide all clinical research associated with the development of new drugs.<sup>17</sup>

Other points of reference in ethical matters are the *Nuremberg Code* and the *Helsinki Declaration*. These two texts still constitute the main foundation for ethical regulations in clinical research.

The *Nuremberg Code*, promulgated in 1947, establishes the requirement that one cannot be submitted to an "experiment" without having given a free and informed consent. This essential requirement was modified in the *Declaration of Helsinki*, which legitimizes the participation of those who cannot personally give a free, and informed consent to a research project as long as certain conditions are fulfilled.

The *Helsinki Declaration*, adopted in 1964 by the *World Medical Health Association* and revised several times since, is made up of a series of recommendations aimed at guiding physicians throughout the world in research involving human subjects. The text of the *Declaration* requires primarily that a research project be submitted for «examination, commentary and advice» to an independent committee without any links to the investigator and the sponsor of the project.<sup>18</sup>

In Canada, the *Medical Research Council* in its 1987 *Guidelines* restates this requirement. In Quebec, it is a condition to be met by investigators requesting grants from the *Fonds de la recherche en santé du Québec* (FRSQ).<sup>19</sup> In the United States, it is contained in the regulations published in the Federal Register. Furthermore, one cannot ignore the principles and guidelines

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<sup>13</sup>Medical Research Council of Canada, Guidelines for Research on Human Subjects, 1987, op. cit., note 2.

<sup>13</sup>Medical Research Council of Canada, The Ethics of Experimentation on Humans, 1978, Canada, Supplies and Services Canada, 1978. 64 pp.

\*\*\*\*Medical Research Council of Canada. Guidelines for Research on Human Subjects, op. cit., note 2, p. iii.

<sup>16</sup>Idem, p. xi.

<sup>17</sup>Health and Welfare Canada, Director General for Health Protection, Bureau of Drugs. Guidelines of the Bureau of Drugs. Clinical Research, op. cit, note 15.

<sup>18</sup>Helsinki Declaration, Section II, art. 2.

<sup>19</sup>Fonds de la recherche en santé du Québec. Bulletin. Program of Scholarships and Grants 1995-1996. Montréal, Fonds de la recherche en santé du Québec, 1994, p. 14.

found in different texts that set out universal ethical imperatives, such as in the United States, the *Belmont Report*<sup>20</sup> as well as in those issued by the *Council for International Organizations of Medical Sciences*. (CIOMS).<sup>21</sup> Finally, it should be pointed out that, in Canada, the *National Council on Bioethics in Human Research* (NCBRH), now the *National Council on Ethics in Human Research* (NCEHR) publishes various points of view and reports on specific issues. They aim to guide Research Ethics Boards in their decision-making process.

### c) The Legal Framework

In Quebec, clinical research is subjected to regulations developed not only by the provincial legislature but also by the Canadian Parliament and the American Congress. It is appropriate here to briefly look at these regulations.

In Quebec, clinical research is primarily governed by the *Quebec Civil Code*, which contains specific rules dealing with experimentation and research. These rules are found in Articles 20 to 26 of the *Quebec Civil Code*. They define the conditions to be followed when enrolling a person in a research project. The rules differ when dealing with a competent adult, a minor or an individual who is unable to give a valid consent.

An adult can participate in a research project provided that the investigator obtains consent in writing,<sup>22</sup> that the consent be informed and freely given and that the risk incurred is not disproportionate to the benefit that can reasonably be anticipated.<sup>23</sup>

An adult who cannot give a free and informed consent, or a minor, can be enrolled in a research project provided the investigators obtain in writing,<sup>24</sup> the informed and freely given consent of the legal representative (tutor, curator, or mandatary, spouse or next of kind in an emergency situation) or of the person having parental authority, provided there are no objections on the part of the minor or adult if they are able to understand the nature of the procedure, and the project does not carry any serious risk to the subject's health.<sup>25</sup>

Obtaining free and enlightened consent from a person implies that the investigator has given the former all pertinent information, thus allowing the person to decide in full understanding, and that the investigator did not exercise any pressure on the subject so as to make him consent against his will.

As a general rule, information considered to be pertinent is transcribed on an "Information Sheet" also called the "Consent Form". *The Quebec Civil Code* does not specify the exact nature of the information to be provided as do ethical norms elsewhere.

In clinical research, it is now accepted that the person who is solicited to participate in a research project must be informed of all the risks of complications and of side-effects related to his

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<sup>20</sup>National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (USA). *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects*, 1978.

<sup>21</sup>Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, 1993.

<sup>22</sup>Quebec Civil Code, Art. 24.

<sup>23</sup>Quebec Civil Code, Art. 20.

<sup>24</sup>Quebec Civil Code, Art. 24.

<sup>25</sup>Quebec Civil Code, Art. 21.

participation in the experimental protocol. This rule is different from that currently applied in clinical care where the physician is obliged to divulge only the most serious and frequent risks and side-effects.

The determination of the risks to which a subject might be exposed by participating in a research project has no precise criteria for their evaluation. Since the absence of a serious risk to the health of an incompetent adult or minor and the presence of a risk proportional to the benefit that one could reasonably expect from the project is not defined *a priori*, it is the responsibility of Research Ethics Boards to assess these risks. The same situation applies to innovative therapy, where the legislator has not defined this term except to state that innovative therapy does not constitute experimentation.

The specific measures contained in *The Quebec Civil Code* are not the only body of regulations governing clinical research in Quebec. It is important also to consider those provisions of *The Quebec Civil Code* that generally govern any intervention on the integrity of the human person,<sup>26</sup> as well as interference with his privacy.<sup>27</sup> One must also refer to the pertinent authors<sup>28</sup> and court rulings<sup>29</sup> to fully understand its actual application.

In an incidental manner, the *Act on Health and Social Services of Quebec*,<sup>30</sup> the *Act on Access to Documents of Public Institutions and on Protection of Personal Information*<sup>31</sup> as well as the *Act on the Protection of Personal Information in the Private Sector*<sup>32</sup> are called upon to govern certain aspects of clinical research, namely the access to a person's research data and the respect of his private life.

When a research project involves use of an *Investigational New Drug (IND)*, the *Canadian Food and Drugs Act*<sup>33</sup> as well as the regulations supporting it governs the investigator's research activities.

When a research project is financed by an American agency such as the *National Institutes of Health (NIH)* or a company with headquarters in the United States, investigators must follow the regulations issued by the *Public Health Service Act* and contained in the *United States Code of Federal Regulations*.<sup>34</sup> These very detailed regulations require that an *Institutional Review Board (IRB)*, the membership of which is defined in the Federal Code approve of all research projects funded by American agencies or companies. In Quebec, since the IRB structure does not exist, for research projects funded by American agencies or companies, Research Ethics

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<sup>26</sup>Quebec Civil Code, arts. 10-18 and Charter of the Rights and Liberties of the Person, L. R. Q. c. C-12, Art. 1.

<sup>27</sup>Quebec Civil Code, Arts. 35-41 and Charter of Rights and Liberties of the Person, L. R. Q. c. C-12., Art. 5.

<sup>28</sup>See, for example, Mireille D.-Castelli and Marlène Cadorette, L'expérimentation biomédicale et l'inviolabilité de la personne: autodétermination ou protection de l'intégrité physique, in (1994) 25 R. G. D. 173-216 and Edith Deleury and Dominique Goubau, Le droit des personnes physiques. Cowansville, Les Éditions Yvon Blais Inc., 1994, pp. 120-124.

<sup>29</sup>Weiss vs. Salomon, [1989]. R. J. Q. 731 (C. S.).

<sup>30</sup>L.R.Q. c. S-4.2.

<sup>31</sup>L.R.Q. c. A-2.1.

<sup>32</sup>L. R. Q. c. P-39.1.

<sup>33</sup>L. R. C. 1985, c. F-27.

<sup>34</sup>Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects.

Boards of institutions or universities approve research projects conducted within healthcare institutions.

The *Federal Code of Regulations* also outlines the information that must be provided to persons asked to participate in a research project and describes the conditions under which informed consent must be sought.

The consent forms used in international multi-center trials originating in the United States are governed by the applicable American regulations. As these regulations are not always in tune with the legal and healthcare realities in Canada, there is cause for some concern.

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## C. THE CONTEXT OF CLINICAL RESEARCH

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Nowadays, clinical research activities are carried out in an environment of heightened competition and limited resources. While acknowledging that competition favors excellence and rationalizing resources maximizes output, it is important to realize that these two elements aggravate the risk of potential lapses that jeopardize the integrity of a project or the safety of research subjects.

This risk is amplified by conflicts of interests, which may arise in some situations, in particular where research activities are carried out, for the most part, in the context of care given to patients. In this type of context, it can be sometimes difficult to isolate the research components from the purely therapeutic ones.

### 1. A HIGHLY COMPETITIVE CONTEXT

In the field of clinical research, fierce competition exists not only between investigators, but also between sponsors funding research projects and between healthcare institutions supporting research activities.

#### a) The Investigator

Intense competition prevails amongst investigators applying for research grants from funding agencies such as the *Medical Research Council of Canada*, the *Fonds de la recherche en santé du Québec*, as well as the many private foundations. Presently, since these agencies are able to finance only a small number of grant applications, meritorious applications will sometimes not receive financial support.

In this regard, it must be understood that when an investigator has not obtained a grant, this may signify the end of his research career and perhaps the loss of his clinical or academic status, of a certain public notoriety or of his recognition within the scientific community, the loss of financial gain or of the possibility of purchasing specialized equipment for his department or for his research laboratory.

In such an environment, investigators are increasingly compelled to look to industry for funding. They hope to develop a lasting professional relationship based on mutual trust and perhaps a business relationship, which would allow investigators, once a project financed by industry has

been completed, to finance their own research projects with surpluses transferred from the industry project.

Whatever the context, it appears that the desire to succeed can lead to certain lapses as the past has shown. The taking of liberties with a research protocol can seem trivial. In reality, they are not as trivial as one might like to believe (the Poisson affair). Furthermore, the desire to be the first to discover a miracle drug can, at worst, lead to dishonest behavior in order to deprive a colleague of the fruits of research (the Gallo affair). Finally, the need to develop a marketable product can lead to lapses in conduct of the research protocol and in the carrying out of a research activity.

### **b) The Healthcare institution**

Competition also exists between healthcare institutions looking to obtain research funds to further stimulate the care given to their patients, to satisfy the demands of medical personnel involved in research activities, or to increase their reputation and enhance their visibility vis-à-vis other healthcare institutions. The potential benefits generated by research projects can lead healthcare institutions to lack critical judgment in the evaluation of research activities.

To maintain their competitive status relative to other healthcare institutions, be they in Quebec or elsewhere, certain institutions might not charge certain costs, such as those of a patient's hospitalization for research purposes, simply because other healthcare institutions holding similar activities do not charge such costs either. Also, as was pointed out to the Committee during its consultations, in order to maximize the chances of obtaining a research contract, some healthcare institutions choose not to assess these costs which are then necessarily borne by the public health care system.

### **c) The Sponsor**

Competition also exists amongst pharmaceutical companies. The market for drugs is very lucrative, and the discovery of a new molecule, of a new use of a molecule, or the proof that a molecule is more effective than another can guarantee substantial financial gains. The marketing of a new molecule or the demonstration of superiority of one molecule over another can represent a substantially larger market share for the sponsor.

To achieve this, the sponsor must invest significant amounts of money in the different phases of biomedical research: fundamental research on the molecule, pre-clinical trials, clinical trials, and post-market research following commercialization.

It should be emphasized that for some illnesses for which there is no known cure, a frantic race to be the first to discover and market a product that will be regarded as a therapeutic breakthrough represents the ultimate moment of fame and glory. Cancer and AIDS are good examples. In such a context, it is not surprising that the financial stakes involved might lead to an incomplete or biased presentation of the facts and results.

## **2. THE SETTING FOR POTENTIAL CONFLICTS OF INTERESTS**

In the field of clinical research as elsewhere, situations of potential conflict of interests do exist. The investigator is often at the core of these situations in cases where he is the treating

physician, when he is a stockholder in a private company doing business in the area of clinical research or when he is acting as a consultant for a pharmaceutical company.

**a) The Double Status of Investigator and Treating Physician**

It is not unusual, where clinical research activities are carried out within a healthcare institution, that the investigator is also the treating physician of patients enrolled in a research project, or that the treating physician acts as co-investigator in a research project. This double status certainly facilitates the recruitment of research subjects while creating situations conducive to serious conflicts of interests.

The statement of the Law Reform Commission of Canada concerning the role of investigators is pertinent: "The role of the investigator or the scientist is to rigorously follow the protocol, to remain neutral with regard to the results obtained. The loyalty of the investigator is essentially to the experiment itself. When he experiments on human subjects to prove or disprove his hypothesis, it is therefore not the well-being of the subject which is his principal concern but the scientific success of the project."<sup>35</sup> Therefore, the well-being of the patient is given a lower priority and can thus become secondary. The physician can be tempted to withhold the best treatment his patient could be receiving and may even be inclined to offer experimental treatment, from which he, in his capacity of investigator, could benefit.

**b) The Double Status of Investigator and Stockholder**

It is equally possible for an investigator to be a shareholder in a drug company for which he is conducting research. Holding a financial interest in the research project he is carrying out and in the validation of the research hypothesis can tempt an investigator to give priority to his research project to the detriment of his patient's best interest. As an example, he may be less likely to stop a research project testing a molecule carrying higher risks and side-effects than one already proven.

**c) The Double Status of Investigator and Consultant**

Some investigators are approached to become consultants to pharmaceutical companies that finance their research projects. They are hired to evaluate research projects that the company would eventually like to carry out in a healthcare institution; here again, the investigator's critical judgment could be affected by the existence of conflicting interests.

**d) The Double Status of Evaluator and Consultant**

Some scientists and physicians act as consultants to a pharmaceutical company while sitting on a Research Ethics Board or while involved in the evaluation of research projects. This can give rise to situations of conflict of interests and to distortions of the evaluation process. Special attention must be given to potential situations of conflict of interests involving persons assigned to evaluate the scientific, financial and ethical aspects of research projects.

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<sup>35</sup>Law Reform Commission of Canada, Biomedical Experimentation on Human Subjects. Ottawa Supplies and Services Canada, 1989, pp. 4-5.

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### **3. AN ENVIRONMENT OF LIMITED RESOURCES**

Nowadays, clinical research is carried out in an environment of rationalization, even of rationing of healthcare resources. Cutbacks in hospital budgets can have significant impact on the quality of care given to patients who, moreover, always seem to expect as much, if not more, from their healthcare system.

Resource rationalization can increase the temptation to use research funds to compensate for operating deficits or to reduce the impact of budget cutbacks on the quality of care. One cannot ignore the fact that a healthcare institution may use surpluses generated by a research project for worthwhile purposes, unrelated to research activities.

As well, in the context of decreasing resources, research projects could be called upon to bear the entire costs that they generate, even in those healthcare institutions where research is part of the healthcare institution's missions and where it would be justifiably expected for that establishment to financially support research activities.

On the other hand, the undeclared use of a healthcare institution's resources to finance research activities violates the principle of equity that must govern the utilization of healthcare resources unless proper compensation is provided.

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## **D. THE FUNDING OF CLINICAL RESEARCH**

Clinical research relies on two main sources of financing: research grants and research contracts. In the course of their work, the Committee members focused on these two different funding sources to determine the type of evaluation they were subjected to and to assess if the control mechanisms actually in place would ensure the integrity of research activities and the protection of research subjects. The Committee found that the approval process for research projects emanating from the industry differed from that used for research projects funded through grants.

### **1. RESEARCH GRANTS**

In biomedical research, many projects are financed by public agencies such as, in the United States, *The National Institutes of Health* (NIH), in Canada, the *Canadian Medical Research Council* (MRC) and in Quebec, the *Fonds de la recherche en santé du Québec* (FRSQ). As well, funds may originate from private agencies such as *The Quebec Cancer Foundation*, *The Heart Disease Foundation*, and *The Canadian Cancer Society*, to name only three. These agencies evaluate grant applications submitted by investigators.

Obtaining a research grant obeys to a very formal process. The investigator who wishes to obtain funding from one of these agencies must present an application that meets the agency's pre-established criteria. He must also present a detailed breakdown of the costs associated with the personnel, equipment and supplies needed to carry out the project. The lack of a detailed budget renders an application inadmissible for all practical purposes. The proposed budget does not contain, except in particular cases, any honorarium for the investigator.

Once the investigator completes an application, the local authorities (the head of the Department, the Research Director or the Research Center Director, the Scientific Committee, if one exists, and/or the Chief Executive Officer) must approve it. It must also be assessed by the healthcare institution's Research Ethics Board so as to validate its scientific and ethical value. Then, the application is forwarded to the appropriate agency, which submits the research project to a committee of peers, whose primary duty is the evaluation of its scientific value and validity.

It is estimated that only 15% of grant applications are accepted. Some are rejected on merit, others due to insufficiency of funds. It is possible, even if a project is accepted, that the funds allocated will be less than those requested. In such a case, the investigator must either look for other sources of funding or reduce the costs of his research project without weakening the scientific value of the research project.

Research projects funded by grants thus undergo a double evaluation: first at a local level, where the scientific, financial and ethical aspects are considered; second, at the granting agency level, where the financial and scientific aspects are subjected to peer review.

Some research projects whose scientific content has been accepted locally are rejected by the granting agency not for lack of funds, but for inadequate scientific design. This raises doubts on the quality of the scientific review done at the local level. It raises even greater concern with respect to research projects financed through research contracts considering the fact that this double level of evaluation does not exist for all intents or purposes.

## **2.**

## **RESEARCH CONTRACTS**

In Quebec, research in the field of healthcare relies more than ever on the private sector for funding. Over the years, public granting agencies have seen their budgets frozen or reduced. One notices an expansion of financial arrangements by which an investigator or a healthcare institution undertakes to carry out a research project for the benefit of a sponsor.

These arrangements are defined in a formal way in a research contract (Clinical Trial Agreement). The contract outlines the respective obligations of the parties to the agreement, the funds the sponsor will provide to carry out the research project as well as the conditions under which the funds will be paid.

The usual case involves a sponsor who wishes to test the properties of a molecule and retains the services of a physician to act as clinical investigator. Above all, the reputation of the physician and that of the healthcare institution where he practices are taken into account. The contribution of the healthcare institution, albeit essential, is secondary: if it cannot provide the needed infrastructure to support the research project, the research may not be funded or the investigator, with the agreement of the sponsor, may move the research installations elsewhere.

In general, the negotiations between the sponsor and the investigator are confidential. In that respect, the Committee members observed that at present, since the healthcare institution is not always party to the negotiations, it is often times confronted with a *«fait accompli»* thereby deprived of the possibility of modifying the research contract.

On the other hand, during negotiations held between an investigator and a sponsor, it is possible that the investigator, because of his prestige, his expertise and his negotiating skills, as well as the reputation of the healthcare institution where the research will be carried out, can obtain

particularly advantageous conditions for himself and the healthcare institution, especially with respect to the funds allocated to the project.

For example, the investigator can, without submitting a detailed budget, request the payment of a given sum per patient, which may differ from that paid to a less well-known or less talented investigator, or one who is affiliated to another healthcare institution. The particular conditions from which the investigator will benefit depend upon the sponsor's preference for one investigator over another in carrying out the project.

As well, an investigator may be an unskilled negotiator or unable to impose his own conditions on the pharmaceutical company that approached him. In such a case, the funds provided to the investigator by the company may not cover the real costs of the project.

If the funds turn out to be insufficient because of an inadequate evaluation of the real costs, the project could incur a deficit. The deficit may be absorbed either by resorting to other research funds of the investigator, to the research center's budget, or the healthcare institution's budget. From the replies to the questionnaire sent to the healthcare institutions surveyed, it appears that five out of sixteen institutions have acknowledged being responsible for budgetary overruns.

In the course of their consultations, the Committee members were informed of the existence of private non-profit corporations created by healthcare institutions with a two-fold mandate: firstly, to offer investigators the services of a negotiating agent who, in return for a percentage of the funds obtained, will assist the investigator in his negotiations with the pharmaceutical company concerning the conditions under which the research project will be carried out; and secondly, to help the healthcare institution solicit research projects which might eventually be conducted within that establishment.

The funds, which a sponsor agrees to pay, are often assessed on a per capita basis. A lump sum is agreed upon for each participating research subject. This is the amount of money that the sponsor will pay for each measurement made in the course of the research project for each participating subject. The per capita sum is increased by a percentage to cover the indirect costs associated with the project, and an honorarium may be paid to the investigator for each subject recruited. The total amount allocated for carrying out the research project equals the cost per subject multiplied by the expected number of subjects recruited.

In such a context, both the investigator and the healthcare institution have little input as to the total amount to be paid to the investigator. The budget must be adjusted to take into account the amounts awarded to the investigators, which do not necessarily match the real costs incurred by the healthcare institution. Those can hypothetically be more or less than the monies received. In the first case, the healthcare institution or the investigator runs a deficit, and in the second case, the investigator ends up with a surplus.

In Quebec, research contracts are partly governed by a circular adopted by the *Ministry of Health and Social Services* detailing how to calculate the inherent costs of a research project financed by industry, primarily manufacturers of medical or pharmaceutical products. The existing circular states that in order to cover overhead costs, the research center of a healthcare institution must require the payment of an amount equal to 18% of the project's costs. In addition to the 18%, an additional 2% is required to meet the institution's expenses related to the use of its facilities.

Usually, the administration of an investigator's funds, whether originating from a grant or contract, is entrusted or delegated to a healthcare institution where the research is carried out. In healthcare institutions with a research center, research funds are usually managed by an administrative assistant whose functions include approving the incurred expenses and the disbursement of funds throughout the course of the research project.

There is little doubt that research projects financed by industry undergo serious scientific evaluation. However, according to some statements made to the Committee, it seems that in industry-funded projects, it can be more difficult to ascertain undesirable side-effects of the substance being tested.

There is no choice but to rely on the expertise of the investigator responsible for carrying out the research project. He is expected to demonstrate a capacity for critical discernment with respect to the scientific validity of any research project. The final analysis of the scientific validity of a research project rests mainly with local bodies and their decision for all practical purposes is final and without appeal.

**Chapter 3**  
**PROBLEMATIC SITUATIONS AND PRACTICES**

## Chapter 3 - PROBLEMATIC SITUATIONS AND PRACTICES

In the course of their consultations, the Committee members were able to identify a certain number of situations and practices which could, if not subjected to serious and periodic control, compromise the quality and integrity of clinical research as well as the respect for those who agree to participate in research projects.

Some of these difficulties emerged from the analysis of the responses to the questionnaires that had been sent to a number of healthcare institutions. The remainder became apparent during the meetings held with various groups closely associated with clinical research.

The Committee proposes at this stage to proceed with a critical analysis of these situations and practices. It seems appropriate to examine them more closely, since they constitute potential dangers likely to discredit the conduct of research activities and investigators involved in these activities and to compromise the freedom of choice, safety and dignity of research subjects. These situations and practices have been grouped under the following headings:

- A.** Research Projects;
- B.** Research Subjects and Research Personnel;
- C.** Research Environment and Research Data;
- D.** Research Ethics Committees.

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### **A. RESEARCH PROJECTS**

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With respect to research projects, the problematic areas identified relate essentially to research contracts, research protocols and research budgets.

#### **1. RESEARCH CONTRACTS**

Problematic areas regarding research contracts pertain to the evaluation of the real costs of the research project and the planned disbursement of the approved funds.

##### **a) Cost Evaluation**

In principle, the monies allocated in virtue of a research contract should reflect the real cost of carrying out the project. Usually, these costs should be determined after consultation with the healthcare institution's different departments where the research will take place, such as the pharmacy for projects involving drug trials, nursing, laboratories, etc. At the present time, this is not a general practice.

Indeed, on the basis of their consultations and of the completed questionnaires, the Committee members can affirm that the costs inherent in carrying out a research project are not always adequately evaluated and that, in many healthcare institutions, a number of research projects are approved without a full breakdown of the real costs of such projects being provided.

This may lead to questioning the ability of certain investigators and even of certain healthcare institutions to evaluate the true costs inherent to a research project. Many healthcare institutions have yet to adopt a set of precise regulations that promulgate that the acceptance of a research project is conditional upon presentation of a complete and detailed breakdown of direct and indirect costs. This cost breakdown is to be supported by a stringent analysis of the resources to be used, the tests and measures to be performed and the investigative procedures to be carried out by the healthcare institution.

One explanation for the existence of this situation is that the requirements of cost breakdown impose an additional and undesired workload upon the investigator and the healthcare institution. It is thus tacitly agreed that a detailed cost breakdown is not required, in the hope that when the time comes, the research project's real costs will be discretely ignored. It should be pointed out that even with standard treatments, determining the real costs is not without difficulty. However, this should not preclude one from trying to estimate the real costs of a research project.

## Recommendation no 2

*In the opinion of the Committee, a rigorous evaluation of the real costs incurred by a research project must be made before the research contract is signed so as to ensure that the real costs are not higher than those anticipated.*

Real cost  
evaluation

### b) **Methods of Payment**

In general, research contracts provide for a payment schedule with respect to the funds allocated to the investigator. As a whole, two types of fund disbursements exist.

The research contract may state that the disbursement schedule will be contingent upon patient enrollment. For example, the contract can stipulate that amount X be paid following the recruitment of the 10th patient, amount Y following the 20th, and finally, amount Z to be disbursed at the time of the project's completion.

A research contract may otherwise stipulate a disbursement schedule based on the different stages of the research project, for example, amount X to be paid at the onset of the project, amount Y halfway through the project, and amount Z at the time the project's completion, as long as the recruited subjects do not withdraw from the study until its termination. In themselves, these methods are not illegal or unwarranted. However, they do raise important ethical questions.

In the first case, one can imagine the strained relationship that might arise between the investigator and the recruiting agent, often a nurse, if recruitment falls behind the anticipated enrollment projections, and, as a result of a shortfall of research subjects, cash inflow stops while research expenses are still being incurred. The investigator, faced with a budget deficit, can be pressured by the administrator of the research funds to redress the situation as soon as possible.

In turn, the investigator may pressure the recruiting agent to accelerate patient enrollment, informing the agent that his wages are paid out of the research project and that the research account is in deficit; an unpleasant situation for the investigator, the Director of Research, or for the managerial staff of the healthcare institution. The recruiting agent will be urged to rapidly make up for the deficit by being more persuasive towards the prospective research subjects. He may, in order to comply with the investigator's request, become less explicit in disclosing the risks and real side-effects associated with a research project.

On the other hand, in the second case, given that final payment is contingent on patients not withdrawing from the research project, it is not unlikely that, should a subject wish to withdraw from the project, an attempt would be made to encourage him to maintain his participation in the project, even though the consent form allows him to withdraw at any time without suffering any sanctions.

The Committee is aware that it might be considered unrealistic to wish to modify the payment practices as currently applied by industry and which, themselves, are not reprehensible. However, such methods can lead to ethical breaches in research, notably with respect to the recruitment of research subjects.

### Recommendation no 3

*In the opinion of the Committee, it is imperative that the members of a Research Ethics Board be aware of the planned disbursement schedule of research funds as outlined in the research contract so as to be able to verify its impact on the recruitment of research subjects and their freedom of choice to participate in or withdraw from a research protocol.*

Impact of the Disbursement of research funds on the recruitment of research subjects

In this context, members of a Research Ethics Board ought to be informed as to the detailed contents of a research contract in order to assess its possible repercussions on research activities. According to the information obtained from the Committee's consultations, Research Ethics Boards rarely have access to the research contracts or its contents.

## 2.

3.

**RESEARCH PROTOCOLS**

During their consultations, the Committee members were able to identify a certain number of problematic issues concerning the content of research protocols, their approval and their follow-up, as well as the storage of trial drugs.

a) **Protocol Formulation**

The information provided to those responsible for evaluating a research protocol in a healthcare institution must be as complete as possible for them to correctly determine the project's acceptability in its scientific, ethical, legal and financial dimensions.

As such, the sponsor or the promoter of a research project is expected to provide all relevant information in his possession considered essential to an adequate evaluation of the project. One cannot over-emphasize the need for transparency on the part of the sponsor and the investigator. This entails that they submit in the documentation presented to the Research Ethics Board results from previous studies that have uncovered risks of complications associated with the research project.

In the course of the Committee's consultations, it was brought to its attention that the documentation provided to correctly and properly evaluate a research project in its scientific, ethical, legal and financial aspects was most often inadequate. It was therefore difficult for those entrusted with the evaluation of a research project to fully assess the value and validity of a research project, to adequately assess its real scientific interest and the nature of the risks to which a person participating in the project is exposed.

Without implying bad faith, it is understandable that risks and complications occurring in previous research projects might not be mentioned or be minimized under the guise of uncertainty concerning the occurrence rate or their relevance to the project under consideration. The complications and risks may be kept confidential for reasons of industrial security or the weakness of previous results.

Recommendation no 4

*In the opinion of the Committee, neither the sponsor nor the principal investigator should withhold information essential to a rigorous and methodical evaluation of the scientific and ethical aspects of a research project, especially in cases where the fundamental respect of persons asked to participate in a research project is at stake.*

Withholding  
of  
information  
by a sponsor  
or an  
investigator

This being said, a Research Ethics Board has few means at its disposal to ensure that it receives all the relevant information related to research projects originating from outside the healthcare institution. The Committee must trust the investigator and the sponsor. This trust cannot be blind and it must be maintained with utmost vigilance.

Those responsible for the evaluation of any one of the aspects of a research project must not hesitate to request further clarification prior to the approval of a research project, if not satisfied with the documentation submitted or the information provided. In failing to do so, they seriously neglect their duties towards individuals who trust them above all, to ensure that the integrity and life of subjects will not be put unduly at risk in the course of a research project.

In the course of their consultations, the Committee members were unable to determine the extent to which the sponsors or promoters of research projects take into account the ethical and legal requirements applicable in a given environment in the development of research projects. This aspect is particularly important in multi-center trials, especially those with an international scope, as it can influence the conditions under which a research project will be conducted. Those responsible for the evaluation of a research project must take this element into consideration in the course of their evaluation.

In relation to multi-center research projects, it was brought to the attention of the Committee that members of Research Ethics Boards often do not know the identity of the members of the Water and Safety Monitoring Board, and even less so the pre-established criteria permitting it to terminate a study, such as for example, the number of deaths tolerated and the number of acceptable complications.

### Recommendation no 5

*In the opinion of the Committee, the members of a Research Ethics Board must be aware, if not of the identity of the members of the Water and Safety Monitoring Board, at least of the pre-established criteria permitting it to terminate a research project. The REC members must also have at their disposal the information needed to contact the Water and Safety Monitoring Board members at all times.*

The REB's  
relationship  
with  
the Water and  
Safety  
Monitoring  
Board

#### b) Approval of Protocols

In principle, all biomedical research projects conducted within a healthcare institution must receive the approval of a Research Ethics Board prior to their implementation.

Following consultations made by the Committee, it appears that some healthcare institutions are unable to account for the number of research projects being conducted within the establishment at any given time. No register of research projects, either computerized or manual, exists within many healthcare institutions.

Furthermore, some research projects may be conducted within healthcare institutions without having been approved by the establishment's Research Ethics Board. One would therefore be unable to ascertain the scientific validity or the ethical value of those research projects, much less determine if they are safe.

Recommendation no 6

*In the opinion of the Committee, it is critical that all research projects conducted within a healthcare institution be clearly identified, adequately evaluated and submitted for approval to the Research Ethics Board of the healthcare institution.*

Approval of  
research  
projects by  
Research  
Ethics  
Boards  
(REBs)

In addition, on many occasions during these consultations, many decried the slowness and cumbersome nature of the approval process for research protocols by Research Ethics Boards. In one instance in particular, it was emphasized that prior to the start of a research project, the project had to be reviewed by a scientific committee, approved by the Research Ethics Board, then accepted by the establishment's Council of Physicians, Dentists and Pharmacists, as well as by the Research Center Board of Directors before its final approval by the healthcare institution's Board of Directors. Many also complained about the length of the Research Ethics Boards' meetings.

The length of the meetings, as well as the slowness and cumbersome nature of the approval process can be due to a number of factors, including a lack of organization in the functioning of the Research Ethics Board, a lack of leadership on the part of a Chairman of the Board during meetings, or a possible need for the Board to review in detail aspects which were overlooked by the scientific committee, or by scientific evaluators who might have been too hasty. Moreover, the volume of documentation associated with a project that the Board must review may be too extensive or inadequate or incomplete. Finally, the length of meetings can be due to a lack of preparation on the part of Board members who did not read the relevant documentation before the meeting.

Although the Committee members did not try to establish the proportion in which each of these factors contributes to the dissatisfaction with the approval process found in many settings, they nonetheless believe that one must investigate the causes at the root of this dissatisfaction and review the functioning of Research Ethics Boards.

Recommendation no 7

*In the opinion of the Committee, serious questioning of the way in which Research Ethics Boards function ought to take place in order to render them more efficient, while at the same time removing irritants that can lead to inadequate evaluation.*

Mode of  
functioning  
of Research  
Ethics  
Boards

An increase in the number of bodies or levels of approval will not enhance the quality of research projects or the protection of research subjects. Instead, it is through the application of a more rigorous and transparent evaluative process, which calls upon competent individuals that these goals will be achieved.

In addition, from the responses to the questionnaire sent to healthcare institutions, a significant number of research projects and consent forms were initially rejected or revised. The temporary or final rejection of a research project is obviously irritating to the investigator. Not only must he re-evaluate certain aspects of the research project to satisfy the Board's requirements, but also he must endure delays in the implementation of his research project.

In many cases, it may be that some problems stem from the investigator preparing alone the documentation that is to be submitted to the Research Ethics Board. Despite the presence of directives defining the nature of the documents to be submitted to the Research Ethics Board and the deadlines that must be met, rarely are there formal directives on the content of these documents, particularly on how the information within a consent form should be presented.

Recommendation no 8

*In the opinion of the Committee, the requirements of Research Ethics Boards concerning the content of the documentation that should be submitted to it must be precisely defined. Ideally, someone should meet with the investigator before he formally submits his research project for approval to review the content and if need be, to suggest appropriate modifications.*

Requirements  
of REBs on the  
documentation  
submitted to it

The rejection of a research project or the request for a major modification of a basic component of the project is irritating for members of a Research Ethics Board. In many cases, precious time is lost in discussing the non-compliance of the research project with basic ethical norms or in trying to clarify certain nebulous aspects in the proposal, the methodology, the consent form, or the real costs of the project.

A variety of reasons may lead a Research Ethics Board to reject a research project. The Board may disagree with the inclusion or exclusion criteria, deeming that certain subjects may incur unacceptable risks. The Board might also feel that the risks to which research subjects are exposed are excessive because of the frequency of their occurrence or their severity. In addition, it may be felt that the scientific design of a research project would not provide an answer to the hypothesis formulated or to the objective sought.

It is inevitable that rejection of a research project may represent serious consequences for an investigator or a healthcare institution. A definitive rejection of a research project can mean a loss -- at times quite significant -- of income for the investigator. Such would be the case if a Research Ethics Board rejected for cause a research project which guaranteed to an investigator the payment of \$3,000 per patient in a study providing for the recruitment of 100 patients. It is possible to anticipate the uneasiness of a Research Ethics Board in rejecting such a project. One can also imagine the potential discomfort felt by a member of a Research Ethics Board towards an investigator who is also a colleague should he choose not to approve an unacceptable research project, knowing the harm it will cause his colleague.

In multi-center trials, rejection or modification by a healthcare institution's Research Ethics Board of a project otherwise accepted by all other institutions is a problem. The investigator who submitted the research project can question the Board's competence to correctly evaluate a research project that other ethics committees have already accepted. The pressures exercised upon the committee can cause it to reconsider its initial decision - which may be perfectly valid - simply because it is the only one objecting to the project. To what extent can a Research Ethics Board insist that the scientific design be modified if the members feel that it shows flaws that could affect the safety of research subjects? To what extent can a Research Ethics Board ask for changes in the consent form or information sheet if these are felt to be inadequate or some clauses considered too ambiguous or incomprehensible?

As a general rule, it is not appropriate for a Research Ethics Board to impose modifications to the scientific design of a multi-center trial. The only possibility available to the Board is to inform the centre or investigator responsible for the multi-center project of the modifications it would like to see integrated in the research project as a result of its evaluation. Eventually, the Research Ethics Board can only accept or reject the research project with the consequences the rejection may have on the investigator and on the healthcare institution. One can understand the reluctance of a Research Ethics Board to reject such a research project and imagine the criticism that may follow given the fact that other Research Ethics Boards have approved the project without changes.

It must be recalled that those responsible for the evaluation of a multi-center trial - or other type of projects- must not hesitate to reject a research project or ask that it be modified if they believe that it might jeopardize the safety of those who have agreed to participate in it.

### c) Protocol Follow-Up

In general, despite the exposure of certain research scandals by the media, the follow-up regarding the scientific quality of research activities conducted in healthcare institutions in Quebec is relatively well assured by those organizations providing research funds. On the other hand, healthcare institutions seem less well organized to ensure the follow-up of research activities once a Research Ethics Board has approved a research project.

Thus, regarding the scientific aspects of a research project, one relies essentially on the external evaluation conducted by the funding agencies and on the supervision exercised locally by the healthcare institution which, one expects and hopes, will denounce any scientific misconduct. Regarding the financial aspects, the person responsible for the research account in part controls this. As for the general costs generated by a research activity, these appear not to be always clearly defined. Finally, regarding the ethical aspects, one must deplore the poor follow-up that exists, notably in relation to the respect of research subjects' rights.

Presently, few if any Research Ethics Boards exercise an adequate follow-up of research projects they have approved. This fact stands out not only from the consultations conducted by the Committee members and the responses to the questionnaire sent to various Quebec healthcare institutions, but also from the study on the functioning of Research Ethics Boards in Canadian medical faculties carried out by the *National Council of Biomedical Research on Human Subjects*.<sup>36</sup> One must note that left to themselves, the scientific and healthcare sectors have yet to strictly comply with the *Medical Research Council Guidelines*<sup>37</sup> eight years after their publication.

Furthermore, few Research Ethics Boards can state that the consent forms they have approved with or without modification are actually the ones used by the investigator or that the forms remain unaltered following their approval by the committee. Few Boards can attest to the fact that the consent given by a research subject was fully informed and freely given. Few Boards can describe the circumstances under which participation in a research project was sought and whether the patient's freedom to participate or not was respected. Few Boards can attest to whether enrollment of research subjects took place before or after the date of approval of the research project by the Research Ethics Board.

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<sup>36</sup>Communiqué CNBRH, vol. 6., nr. 1, Winter 1995, p. 26. On reads: "Comme ...CER" [get quote].

<sup>37</sup>Medical Research Council of Canada, Guidelines for Research on Human Subjects, 1987, op. cit., note 2, p. 52.

Few Boards can vouch that they were informed of all of the complications that arose in the course of a research project. Few boards can say whether the apprehended risks or side-effects did occur. In most cases, it is therefore impossible for them to revise, on the basis of new information, their stand on projects already approved. Furthermore, they are often not in a position to know about disastrous situations that could have happened and the recurrence of which could have been prevented. Finally, few committees are aware of the outcome of projects approved by them and the publications resulting from them.

Recommendation no 9

*In the opinion of the Committee, Research Ethics Boards must ensure proper follow-up of research projects they have approved and must exercise constant vigilance with regards to the protection and safety of persons who have agreed to participate in a research project.*

REBs'  
involvement  
in the  
follow-up of  
research  
projects

Amongst the explanations offered for the prevailing situation are lack of funds and lack of time. One must realize that members of Research Ethics Boards often work on a volunteer basis and that the evaluation of research projects is time-consuming. In addition, one must acknowledge that if the follow-up process is to be serious and effective, Research Ethics Boards must be allocated the proper financial support to accomplish their mandate. The Committee members feel that lack of time or funds should not serve as excuses for not ensuring proper follow-up.

The 1987 *MRC Guidelines* requested that Research Ethics Boards keep a close watch over research projects from beginning to end, to ensure that they would be carried out in conformity with the ethical standards agreed upon by the investigator, the Research Ethics Board, and *The Medical Research Council of Canada*.<sup>38</sup> In addition, it was recommended that control be exercised through periodic examination of the research activity itself and factors considered during the approval process.<sup>39</sup>

Quite obviously, the absence of adequate follow-up prevents institutional Research Ethics Boards from fully carrying out their duties, notably to protect those persons who have agreed to participate in a research project. The present system functions on the principle of unconditional trust in the integrity and honesty of the investigator and his research team.

Without wishing to cast doubt upon the good faith of investigators in their relationship with persons who agree to participate in research projects, it is likely possible that the context within which research projects are conducted offer occasions to transgress, even slightly, established standards, and of taking liberties with the research protocol, thus possibly jeopardizing the welfare of research subjects.

<sup>38</sup>Medical Research Council of Canada, *Guidelines*, op. cit., note 2, p. 52.

<sup>39</sup>Ibid.

The latter observation should not be construed as accusing the scientific community of improper behavior while conducting research projects. It is made simply to highlight certain behaviors that can threaten the proper conduct of research activities. Besides, the MRC Guidelines establish that proper control over research activities conducted within a healthcare institution "cannot limit itself to obtaining guarantees from investigators."<sup>40</sup>

Therefore, it is proper that follow-up of research projects be undertaken once they have been approved by the establishment's Research Ethics Board. In principle, responsibility for follow-up of research projects is incumbent upon the establishment's Research Ethics Board whose primary mandate is to ensure the safety of research subjects.

### Recommendation no 10

*In the opinion of the Committee, hospital management must provide its Research Ethics Board with the human and financial resources required to ensure adequate follow-up of research projects.*

REBs' human and financial resources for follow-up

The follow-up cannot itself be limited to an analysis of reports submitted by the investigator or to incident reports. It must include interviews with patients recruited as research subjects and an examination of research records to ensure observance of the research protocol.

#### d) Storage of Trial Drugs

In the course of their consultations, the Committee was made aware of certain important practical problems in the management of experimental drugs.

It appears that, unlike other drugs, so-called investigational new drugs (IND) may not be under the immediate control of the pharmacy department, but of the investigator who often dispenses the drugs himself, when it is not administered by a member of his research team (nurse, secretary). These drugs are often kept in the investigator's office or in the research centre under sub-optimal conditions or conditions which might not permit adequate control of the medication and which might also allow dosage errors.

Admittedly, experiments using INDs are carried out under the close scrutiny and tight controls of *Health Canada*. However, these controls alone are insufficient to ensure the safety of patients involved in research protocols associated with such drugs. Indeed, especially in double-blind randomized clinical trials and trials using placebos, it is of the utmost importance to ascertain for each individual the appropriate dosage.

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<sup>40</sup>Ibid.

Furthermore, at times, the patient's medical record contains no indication as to the possible administration of an experimental drug to the patient. This information may be only recorded in the research file, which is often not available in emergency situations. It is essential that the patient's medical record contain all information, including the patient's participation in one or more research projects and the medications, if any, administered.

Besides the medical archives department, the pharmacy department ought to keep relevant information with respect to experimental drugs to be administered to a patient in order to cope with complications that a patient might encounter at any hour of the day, any day of the week, wherever the patient may be. The ideal mechanism would be to establish a drug profile for each patient participating in a research project and to render this drug profile available at all times through the pharmacy department.

Obviously, a pharmacist is more than competent to evaluate the risks pertaining to the administration of an experimental drug in a hospital environment. Furthermore, the pharmacy department has the expertise required for the preparation of drugs in accordance with existing standards and is best able to deal with complications that might affect a patient during an experimental drug trial.

#### Recommendation no 11

*In the opinion of the Committee, experimental drugs must be subjected to the same hospital controls as those of prescribed medications in order to protect patients to whom such drugs are being administered; also, the pharmacy department should have all material information concerning experimental drugs administered to a patient.*

Subjection  
of  
INDs  
to  
controls

#### 4.

#### RESEARCH BUDGETS

In principle, healthcare research should be self-financing. Healthcare institutions' operating budgets should not be used to finance research activities unless the healthcare establishment's authorities have otherwise agreed upon some form of compensation. Similarly, research funds should not pay for patient care unless otherwise agreed upon.

From the various consultations held by the Committee, it appears that problems exist as to the management of research funds. Furthermore, it seems that the utilization of research funds can give rise to doubtful practices.

#### a) Management of Research Funds

In the course of their consultations, the Committee members were made aware of the fact that, on occasion, research funds awarded to research projects conducted in a healthcare institution were managed outside the establishment by private financial institutions. It seems that this practice is more widespread than had been initially believed.

Indeed, there are obvious advantages for an investigator to manage his research funds himself. He is then not accountable to the healthcare institution, nor is he subjected to the financial guidelines adopted by the Ministry of Health and Social Services. He enjoys great latitude in the way the funds are utilized and is able to keep the interest generated by his research funds. In case of scientific misconduct, he stands a lesser risk of seeing his funds frozen by the institution.

The behaviour described above carries some serious drawbacks. When an account is in the investigator's name, the money deposited in the account can be considered professional income, and as such taxable. Creating a management company or a research corporation can circumvent this. This practice however prevents effective control over the utilization of the funds and does not allow verification of whether the funds were used for personal ends to the detriment of the research project.

An investigator who carries out research by utilizing the resources of a healthcare institution and who recruits his subjects within a healthcare institution should never be allowed to manage himself the funds allocated to a research project outside the establishment. The Committee members feel it is improper for an investigator to open his own bank account, thereby avoiding institutional control over his research funds. An investigator should be required to declare annually to the establishment research the activities that are carried out outside the establishment and to specify the way in which the funds obtained for such activities are managed.

Both healthcare institutions and sponsors must take a clear stand to discourage this practice managing research funds outside a healthcare institution. Above all, it is important that research funds be managed openly to avoid, beyond doubt, even the suspicion of misuse of research funds.

## Recommendation no 12

*In the opinion of the Committee, all research funds directed towards the financing of research activities carried out by an investigator having at its disposal the resources and the clientele of a healthcare institution must be managed by the healthcare institution where the research project is carried out. As a rule, a T5 form ought to be issued for all honoraria paid out to investigators performing research activities.*

Management of  
research funds

Some healthcare institutions do not have a policy requiring separate accounting for each research project. Usually, an account is opened for each investigator and not for each research project. All the funds an investigator obtains are deposited in the same account, whatever the source of funding or the research project. This practice raises questions with respect to the costs that should be charged to a research project and the financial audit of research accounts.

## Recommendation no 13

*In the opinion of the Committee, as soon as funds are provided to an investigator for a specific research project, an account or sub-account should be opened within the healthcare institution for the deposit of these funds.*

Opening of  
research funds  
accounts

**b) The Utilization of Research Funds**

In the course of the meetings held by the Committee members with different persons associated with healthcare research, it was made clear that a practice of double-billing related to research projects funded by the industry existed. Without making generalizations, it is nonetheless certain that the system in place to account for research expenditures, although not leading directly to such practice, permits it to exist. Thus, it is possible that research contracts provide for the payment of an honorarium for the performance of a specific medical act necessary to prove a research hypothesis. In theory, this payment should cover the cost of medical care provided by the physician, the latter being the investigator or someone else. Committee members were informed that in practice, it was possible for a physician who carries out a medical act provided for in a research protocol to bill the cost of the act to the *Régie de l'Assurance-Maladie du Québec* while the investigator who did not perform the act, retains the money in his research account or has it paid to him as an honorarium.

To the extent that two physicians participating in the same research project pool their professional revenues under a group practice arrangement, it is possible for the group to financially benefit from both the research honorarium and the honorarium paid by the *Régie d'Assurance-Maladie du Québec*.

A research project should never be an opportunity for an investigator, or the group practice to which he belongs, to profit from double-billing practices. It seems inconceivable to the Committee members that when a professional act which is considered a research act, the cost which ought to normally be covered by the research project requiring it, is also be billed to the *Régie d'Assurance-Maladie du Québec*.

Recommendation no **14**

*In the opinion of the Committee, the practice of double-billing in clinical research is unacceptable and dissuasive mechanisms should be instituted in order to counter double billing practices.*

Dissuasive  
mechanisms to  
counter  
double-billing  
practices

In addition, an investigator should never reward a member of his staff for recruiting research subjects. This is contrary to professional ethics. Financial reward must not serve as a motivational tool in recruiting research subjects. All practices of this nature must be reported to and stopped by the person responsible for ensuring the integrity of research activities.

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## **B. RESEARCH SUBJECTS AND RESEARCH PERSONNEL**

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In the course of their consultations and following the study of the questionnaires completed by the healthcare institutions surveyed, the Committee members were able to identify a set of problems related to research subjects and research personnel.

### **1. THE RESEARCH SUBJECTS**

The Committee members were able to identify three types of problems concerning research subjects. These relate to the recruitment of research subjects, the obtaining of their consent and the payment of an indemnity when they are victims of a complication related to the research project.

#### **a) Recruitment**

In principle, patients solicited to participate in a research project are free to participate or not. According to the *Medical Research Council of Canada*, "the offer made to a potential research subject must be made in a manner that allows him to exercise his freedom of choice ... It goes without saying that one cannot exercise upon him undue pressure."<sup>41</sup> In spite of this statement at the present time, very few means if any exist to verify if this rule is truly respected in healthcare institutions where research activities involving human subjects are carried out. Only those in charge of recruitment and the research subjects themselves are truly able to comment on recruiting practices.

In the course of their consultations, the Committee members were able to observe, for example, that Research Ethics Boards, as a general rule, have no knowledge of how research subjects are recruited, once a research project has been approved, and a consent form accepted. No follow-up exists. One has to rely on the investigator's good faith and that of his research personnel.

Obviously this situation should be remedied and the recruiting practices affecting research subjects open to examination to ensure that, during the recruiting process, persuasion and not coercion is used.

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<sup>41</sup>Medical Research Council of Canada. **Guidelines Concerning Research on Human Subjects.** op. cit. Note 2, p. 23.

Recommendation no 15

*In the opinion of the Committee, healthcare institutions where research activities are conducted should examine how the recruitment of research subjects is carried out (number of subjects solicited, number of subjects enrolled) and verify if the recruiting practices in force respect the principle of freedom of choice to participate in or to withdraw from a research project at all times.*

Studies on  
recruitment  
practices of  
research  
subjects

In light of the consultations they conducted and their personal experiences, the Committee members can affirm that, for a research subject, the freedom to participate or not in a research project and to withdraw at any time without prejudice to him is often relative.

This statement should not be interpreted as raising doubts as to the good faith of people who are involved in the recruitment of patients. It nevertheless underlines the fact that these people can find themselves in situations where they can unduly affect the willingness of a patient to participate or not in a research project. Given the importance of the principle of freedom of participation, one must be aware of these problematic aspects.

People in charge of recruiting and enrolling people in research projects must be particularly gifted if they are to recruit **anyone**. Without research subjects, there is no research project. Thus a patient who is too well informed and too aware of the risks he would be exposing himself to if he participated in a research project may be inclined to say, «No, thank you!» Therefore, it is necessary, - and this is a normal component of any recruiting process, - that those in charge of recruiting subjects use, as has already been noted, all of their recruitment abilities.

Given that the investigator is required by the research protocol to recruit a certain number of subjects presenting a specific profile within a given time frame, he can feel pressed to recruit as quickly as possible the number of subjects required by the protocol knowing that he cannot afford to compromise his contribution to the research project by not recruiting the required number of subjects. This constraint can lead the investigator to try to meet the protocol requirements at all costs, even if this means breaching the rules governing the recruitment of research subjects.

The recruitment of healthy subjects and at times, of ill subjects is often made by means of advertisements.<sup>42</sup> It goes without saying that these advertisements must be sufficiently attractive to entice someone in good health or mildly ill to expose himself to the inconveniences often associated with the participation in research project.

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<sup>42</sup>See in this respect the advertisement reproduced in the appendix.

In reality, it seems that the payment of compensation for the losses and inconveniences related to one's participation in a research project must serve as the enticement since the *Civil Code of Quebec* prohibits any financial reward.

In this regard, the Committee members were informed of certain practices where the proposed compensation appears to be a disguised financial reward.

In the private sector compensation practices exist which are ethically unacceptable and which reveal a dark side of research subject recruitment strategies. Thus, the indication, on a leaflet soliciting participation of patients in a research project, that the study drug will be provided to them free of charge and that an amount of \$100 will be paid to them at the end of the fourth visit to cover travel expenses is obviously an enticement for patients to complete the research study, since compensation will only be offered at the completion of the study.<sup>43</sup> Patients ending their participation in the research project after the second visit might not be compensated for their traveling expenses. On the other hand, the offer to compensate a patient for the inconveniences associated with his participation in a research project on the basis of an hourly rate of \$25, for example, might be construed as disguised remuneration.

As demonstrated in the past<sup>44</sup>, it is also possible that certain aspects of a research project, especially those related to the risks and discomforts it involves, are concealed in order to facilitate enrollment. This is contrary to fully informed consent and the respect that one should have for those who agree to participate in a research project.

With respect to the recruitment of ill subjects, it is important to underline that they are to a certain extent, individuals dependent on the healthcare environment in which they find themselves. Various elements brought to the attention of the Committee members attest to this reality.

Some persons solicited to participate in a research project may feel honoured to receive such an opportunity. Others seem ready to accept just about anything proposed to them in the hope however slim the chances, of improving their condition. They are even more willing to participate in a research project when the investigator is also their treating physician in whom they have blind faith.

The investigator who is also the treating physician of a patient is better positioned to recruit research subjects. The relationship of trust that he has established with his patient and the dependency that the patient might have developed towards him, might lead a person being recruited to more readily accept being enrolled in a research project regardless of its nature.

On the other hand, a patient will be more inclined to accept to participate in a research project when assured that his participation in the project will result in enhanced care.

One cannot ignore the fact that individuals solicited to participate in research projects in the course of therapeutic care are more vulnerable to seduction and manipulation especially if the research study is presented to them as a therapeutic option more promising than usual care.

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<sup>43</sup>See in this regard the advertisement reproduced in the appendix.

<sup>44</sup> See, for example, in Canada, *Halushka vs. University of Saskatchewan* (1965) 53 DLR (2d) 436.

In settings where the recruitment of research subjects is done not by the investigator, but by a member of his research personnel, for example a nurse, other problems can arise. In such a case, since the investigator usually hires the nurse, she is placed in a delicate situation. Thus, if a recruitment shortfall occurs, the nurse runs the risk of being reprimanded and perhaps replaced.

Thus, it was made known during the committee's consultations, that the recruiting agent cannot be considered as the guardian angel or watchdog for the person whose participation in a research project is being sought. On the contrary, the recruiting agent will more often be inclined to coerce a patient to participate and to insist if he hesitates or refuses.

In such a context, it is important that the Research Ethics Committee of a healthcare institution ensure that consent given by patients is effectively free and informed. Currently, although a Research Ethics Committee has some control over the first element of consent being the body that determines the content of consent forms, it has little or no control over the second element, that of knowing and ensuring that the consent is free of all undue pressure.

An example of undue pressure in the obtaining of free and informed consent from a patient as reported to the Committee members is when a patient is informed that because of delays within the healthcare system, certain tests or examinations could not be done immediately unless he agreed to participate in the proposed research project.

Moreover, a patient's right to withdraw from a research project at all times, which is the fundamental corollary of a patient's freedom to participate in a research project, can be illusory in a context where the investigator can incur a financial loss resulting from such withdrawal. One can imagine an investigator tempted to reassure a patient having expressed the desire to withdraw near the completion of a research project, knowing full well the financial consequences of the withdrawal. It is then a matter of the investigator protecting the financial survival of the research project.

## **b) Consent**

The obtaining of free and informed consent, either from the prospective research subject or from a proper legal representative, is a *sine qua non* condition for the enrollment of research subjects in clinical trials.

The person solicited to participate in a research project must be fully informed of all aspects of the project, notably its nature, the tests and examinations to be performed, the medical interventions to which he will have to submit, the risks, discomforts and side-effects which may occur as well as the potential benefits that he might gain by participating in the project.

From their consultations and own experience, the Committee members were able to establish that obtaining free and informed consent from a prospective research subject could pose problems. Thus, providing an overwhelming amount of information to someone or making him aware of the real dangers and side-effects inherent to a research project can cause a potential subject to refuse an offer to participate in a research project.

On the other hand, many patients, having experienced the side-effects of a test or an intervention, pointed out that if they had known initially what the test or intervention really entailed, they would never have agreed to participate in the research project.

Obtaining free and informed consent in an emergency situation poses serious ethical questions. It is far from certain that a person admitted in a state of shock or otherwise barely conscious in the emergency ward or intensive care unit of a healthcare institution can truly consent to participate in a research project. Given the fact that as the law presently stands, the consent of the legal representative or of the next-of-kin is required if an individual is not able to express his wishes or give an informed consent, one can wonder how such a consent which has to be given in writing can be obtained in due time if the legal representative or the next-of-fin is not present.

There is a risk that the ethical requirement obliging an investigator to obtain under all circumstances the free and informed consent of a potential research subject, or that of the subject's legal representative or next-of-kind, will be overlooked. Can one tolerate or accept, for the sake of scientific progress, that a research activity, however important, be conducted in violation of a person's right to personal integrity and freedom of choice? The answer is plainly no.

### Recommendation no 16

*In the opinion of the Committee, one may never enroll a potential research subject in a clinical trial without having obtained beforehand his free and informed consent or that of his legal representative or next-of-kin. If such consent cannot be obtained in due time, the potential research subject may not be enrolled in the research project, no matter how valuable the research project may be from a scientific point of view.*

Enrollment of  
research  
subjects

The Committee members were able to observe that the content of information leaflets or consent forms also poses problems. As a general rule, the writing and formulation of the information leaflet is the responsibility of either the investigator or the sponsor. A number of these leaflets are written in an abstruse<sup>45</sup> and recondite<sup>46</sup> style to common mortals, most notably those who are called upon to participate in a research project.

It is surprising and discouraging to see how little effort is expended at times by sponsors and investigators in the conception of information leaflets or consent form, so as to allow a patient recruited for a research project to easily and clearly understand the consequences of his enrollment in the research project.

<sup>45</sup>Whose difficulty repels the spirit. Le Petit Robert I.

<sup>46</sup>Hard to understand. Le Petit Robert I.

One cannot but be concerned by the lack of effort sometimes shown by sponsors and investigators to help prospective research subjects truly understand what their participation in a research project entails. It is also questionable whether the freedom of choice and the right to integrity of research subjects are truly respected by those who draft information leaflets or consent forms.

It is also quite troubling to note that if investigators and sponsors of research projects were not required to submit consent forms to a Research Ethics Committee for review and approval, many consent forms would lack clarity and would not give a research subject a true understanding of what his participation in the research project entails.

It is therefore important that Research Ethics Committees pay special attention to the content of the consent forms submitted to ensure that all the relevant information appears and that they are presented in a manner and style which would allow the prospective research subject to understand the true consequences of his participation in any given research project. If it appears that the information which is found in a consent form is incomplete or inadequate, a Research Ethics Committee should require that the necessary changes be made to it.

In a multi-center trial, a sponsor may be reluctant to see consent forms vary from one site to another, or a healthcare institution changing the content of an information leaflet which appears to be deficient. Thus, in the case of a legal challenge based on an absence of adequate information, one can surmise, for example, how a court would react if it was proven that the research subject was not provided with the proper information about the risks associated with the research project.

One can imagine the situation in which a sponsor, investigator or healthcare institution might find themselves if this person was able to support his case by showing that the information leaflet approved in another healthcare institution was more complete and more explicit regarding certain risks. It thus seems appropriate to suggest that there be discussions conducted with representatives from the pharmaceutical industry who often provide the original consent forms, so that they can begin to standardize and clarify certain clauses which appear in consent forms used in multi-center trials.

### Recommendation no 17

*In the opinion of the Committee, formal meetings between representatives from industry, research centers and Research Ethics Committees ought to take place to address issues specific to multi-center trials with the aim of developing precise recommendations as to the type of information which should appear on a mandatory basis on consent forms in Quebec as in the rest of Canada.*

Type of  
information  
on consent  
forms

c)

d)

Compensation

In principle, to the extent that a person who agrees to participate in a research project has been fully informed of the risks and complications associated with the project, and has accepted them, that person will assume the consequences associated with the occurrence of a risk insofar as the occurrence cannot be linked to any negligence or carelessness on the part of the investigator or a member of his team.<sup>47</sup>

**The research subject, who is victim of a complication arising in the course of a research project**, runs the risk of never being informed whether the complication he suffered was the direct result of his participation in the research project, or was due to the negligence or the carelessness on the part of the investigator or a member of his team.

In the course of a research project, whether it be a multi-center trial or not, it is the responsibility of the investigator to establish, according to his professional judgment, whether a complication is or is not linked to the research strategy or methodology, even in double-blind projects where the physician is unaware of the specific group of subjects to which the person who has experienced the complication belongs.

In multi-center trials, it is the responsibility of the Data and Safety Monitoring Board, specifically created to monitor the safety aspects of a trial, to decide from the information made available to it by the investigators, and based on its knowledge of the group to which the victim of the complication belongs, if the complication can or should be attributable in a significant manner to a particular facet of the research protocol. We say in a «significant manner» because it is possible that the Data and Safety Monitoring Committee might be of the opinion that the complication is only a fortuitous event, and that a larger number of complications is necessary to establish a statistical correlation between the scientific design of the project and the complication that has been observed.

It is important to understand that Data and Safety Monitoring Boards usually determine criteria indicating the number of complications required to establish a statistically valid correlation at the onset of a research project. Thus, even in the presence of a serious complication such as death, a Board may not automatically interrupt the study. It will do so only if it is convinced that the complication can be linked to the scientific design and has occurred to a statistically significant degree. As the Committee members were able to observe, dozens of deaths are sometimes required before one can establish a valid correlation between the scientific design and the complications observed.

To the extent that a patient suffers a complication, it can be difficult to distinguish whether the complication is related to the illness or to the research project. Moreover, the illness may mask the reality and make it impossible to establish the true cause of the complication. In such a situation, it is difficult to know if the occurrence of the complication is due to the negligence or to carelessness of the investigator or a member of his team.

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<sup>47</sup>See, in this case, the case **Weiss vs. Salomon** [1989] R.J.Q. 731 (C.S.).

It can be difficult, first of all, to establish a valid statistical relationship between a complication or a group of complications and the scientific design and secondly, to determine if the complication that occurred might not be the result of negligence or carelessness on the part of the investigator or a member of his team, a determination which could give rise to possible legal action on the part of the victim of such a complication.

The temptation exists for an investigator not to inform a research subject of the true nature of a complication where the latter might be attributed to negligence or carelessness. Deprived of that information, a person having suffered a complication will not be able to exercise his right to seek compensation.

In Quebec, there does not exist any legal obligation on the part of a sponsor, a healthcare institution or an investigator to compensate a person who, in the course of a research project, is victim of a complication which injures him. A sponsor, a healthcare institution or an investigator will only have to compensate the person victim of a complication if the latter is able to prove that the injury suffered was caused by the negligent conduct of the former.

This situation is very different from the one existing in France<sup>48</sup>. There, sponsors of research projects are required to carry insurance covering their civil liability. In addition, with respect to research projects which do not provide any direct benefit to the individual, sponsors are liable without the victim having to prove fault. However, in cases where the research project carries a direct benefit for the individual, they must answer for the damages sustained by the research subject, unless they can prove that the damage occurred without any fault on their part. One could consider the possibility of initiating such a change in Quebec.

Occasionally, one finds in consent forms indications, often unclear, that the subject could be compensated for healthcare costs incurred from a complication arising from the subject's participation in a research project. The Committee members deplore the lack of clear policies and texts concerning the costs a sponsor is prepared to bear should a complication related to one's participation in a research project occur.

The cost of medical and hospital care arising from the occurrence of a complication in the course of a research project is presently assumed by the public care system, whether the complication is linked to the research subject's illness or to the research project.

At the present time, in Quebec, it is thus the public healthcare system which assumes the cost of treatment of every complication which a patient experiences in the course of a research project. What are the actual figures of these costs? Nobody can truly say. Whatever the overall cost incurred by the state, it is likely not negligible. Short of suggesting that these costs should be accounted for and recovered by the state, the Committee members stress the importance of recognizing the State's contribution to research in that respect.

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<sup>48</sup>Code de la Santé Publique, Art. R. 209-7.

Recommendation no 18

*In the opinion of the Committee, those recruited to participate in a research project sponsored by the industry must be fully informed as to the financial compensation that they would be entitled to receive in the event of the occurrence of an untoward complication associated with the research project.*

Extent of financial compensation for complications arising in the course of a research project

2.

**RESEARCH PERSONNEL**

If one wishes to ensure the quality and integrity of research which is carried out in Quebec in the healthcare sector, as well as to guarantee the dignity and security of people who participate in research projects, it is important that research activities be carried out by professionals adequately trained so as to ensure that clinical research is not a mere business operation, but a necessary activity in the improvement of any healthcare system and in the enhancement of the quality of care.

In this respect, the Committee members were able to identify two sets of problems. The first relates to the training of those involved in clinical research activities, notably the training of support personnel. The second concerns the setting up of corporations by investigators.

a) **Training Programs**

At the present time, the training of investigators is in large part assured by training programs and research fellowships.<sup>49</sup> Those who benefit from these programs and fellowships are as a general rule individuals who wish to establish a career in research. However, research in the healthcare field does not rest only with career investigators. It also calls upon an important number of clinicians who may not have received any specific training in research, and whose research activities intermingle with their clinical activities. Directly implicated with the provision of health care, these professionals carry added responsibilities due to their dual role as caregiver and investigator. Research in the healthcare sector also calls upon an equally important number of investigators with no clinical training, nurses, clerks and technicians. These people make up the research support staff.

In light of the Committee's consultations, it appears that in some healthcare institutions, the support staff assigned to a research project had not received the basic training, which would permit it to then assume their role in a research project. This lack of training affected the staff's ability to critically analyze the research project and to report irregularities or breaches of protocol.

<sup>49</sup>See for this Fonds de la Recherche en Santé au Québec. Plan Triennal 1993-1996, op. cit. Note 3.

It was made known to the Committee members by the Office for Research Integrity (U.S.A.), an agency whose mandate is to undertake inquiries into accusations of scientific misconduct, that one of the reasons for occurrences of scientific misconduct could be directly related to the lack of proper technical and ethical training. Without such training, healthcare professionals acting as research agents become simple executants who blindly follow the protocol's requirements and are unable to react when problematic situations arise.

There is no doubt that, at the present time, in many healthcare institutions, important deficiencies exist in the training of support staff involved in both clinical and fundamental research activities. It is important that these deficiencies be corrected. It is not only the quality of research which is at stake, but also its integrity, as well as the safety of people who participate in research projects.

### Recommendation no 19

*In the opinion of the Committee, the level of clinical training of research personnel ought to be thorough enough to enable it to detect possible irregularities that might arise in the course of a research project. In addition, knowledge of the scientific process should be sufficiently mastered by such personnel so that any breach in the integrity of the process becomes immediately apparent.*

Training  
of  
research  
personnel  
with respect  
to research  
activities

The training of research personnel is no simple matter when one considers that there are approximately 65,000 professional nurses in Quebec. Evidently, one cannot expect to be able to train everyone in the near future, considering, amongst other things, that not all of them will be called upon to assist in research activities. It is important, therefore, to develop in the short term continuing education activities which will increase the skills of research personnel and develop their sense of judgment with respect to the research activities in which they are involved.

### Recommendation no 20

*In the opinion of the Committee, the "Fonds de recherche en santé du Québec" ought to assume a leadership role in the development of the knowledge base required for the training of research personnel; in cooperation with universities and colleges, the FRSQ ought to develop training programs in "Good Clinical Practices" for those involved in research activities.*

Leadership  
role of the  
FRSQ in the  
development  
of training  
programs in  
Good  
Clinical Practices  
(GCP)

Recommendation no 21

*In the opinion of the Committee, professional orders, together with universities and colleges, ought to include in their academic curriculum specific courses on the requirements of scientific research.*

Teaching  
of the  
requirements  
of scientific  
research

In addition, the Committee members were able to ascertain a lack of ethical training and knowledge on the part of those involved in clinical research activities. To the extent that one considers that legitimate research must be carried out in conformity with recognized scientific and ethical criteria, one must recognize the necessity of increasing the level of knowledge of ethical standards applicable to clinical research.

Recommendation no 22

*In the opinion of the Committee, in the same way that standards defining "Good Clinical Practices" and "Good Laboratory Practices" were developed, standards defining «Good Ethical Practices» ought to be developed so that the research personnel in healthcare institutions as well as members of research ethics committees be adequately trained in ethical matters.*

Development  
of  
"Good  
Ethical  
Practices"

b) **INCORPORATION**

Nowadays, not only do we find many research centres that are incorporated, but also a growing numbers of research investigators who have set-up their own management companies or research corporations. This trend is seemingly encouraged by many. In the course of their consultations, the Committee members were not able to fully assess the extent of this trend. However, they wish to express their concern in this regard since it could lead to excessive commercialization of research activities and the creation of an environment motivated more by financial goals than scientific progress.

There is reason for concern when a pharmaceutical company enters into a contractual agreement for the carrying out of a research project with a numbered company set up by an investigator who is, not only the sole shareholder of the company, but also one of its employees. This investigator's self-owned company could also enter into a contractual agreement with a research center having a corporate status or with the healthcare institution where it plans to carry out its research project, or even, with patients of the establishment who would then become suppliers of services.

There is potential for conflicts of interest when the investigator acts as a broker for a company which he controls in the recruitment of research subjects needed for a research project. This is heightened if the investigator is also the treating physician of the person recruited.

It is understandable that in Quebec as elsewhere, for clinical research to flourish, there is a need to establish partnerships and rely on a degree of entrepreneurship to allow research to develop and jobs to be created in a competitive environment. That every investigator in Quebec should create his own business or his own management company is an assertion that cannot be made lightly.

These initiatives should never affect the transparency which must exist in the conduct and evaluation of research activities or the investigator's responsibility for his own research activities. In no case should an investigator evade his responsibilities by hiding behind the corporate veil of a company he has set up. If for certain people research represents a business, persons engaged in research activities must avoid positions of conflicts of interest, and by so doing, avoid discrediting research and diverting it from its main goal, which is the improvement of the population's health.

### Recommendation no 23

*In the opinion of the Committee, investigators should not be induced to incorporate themselves while pursuing research activities. Personal accountability ought to be maintained vis-à-vis those who participate in research projects.*

Personal  
accountability  
of  
investigators

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## C. RESEARCH MILIEUS AND RESEARCH PERSONNEL

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With respect to research activities carried out in Quebec, one can pinpoint problems related to the milieu where the research is carried out and to the data gathered from research subjects.

### 1. RESEARCH MILIEUS

The Committee members were able to identify a number of problems pertaining to research conducted within a hospital setting as well as research carried out in a private office.

a) **Research within a Healthcare institution**

Research activities poorly designed, poorly organized and poorly managed, have the potential to cause more harm than good to those who require healthcare and to institutions which provide it. Thus, there is a risk when research costs are inadequately identified at the outset that the healthcare institution will support unexpected costs from its operating budget. It must be underlined that clinical research should never use the establishment's resources without fair compensation in some other way.

One must be aware of the fact that research activities take place in a therapeutic context and most often are an integral part of clinical activities. This can be a problem since it is difficult to isolate healthcare from clinical research. It is especially true when the research activity becomes part of a treatment plan.

It is important to understand that research activities and clinical care activities are geared towards different goals, however complementary they may be. Research activities aim at increasing knowledge. This can be achieved irrespective of the immediate mission of a healthcare institution. Even though clinical research activities are often carried out in a healthcare context, the goal of these activities is not the provision of healthcare but the testing of a research hypothesis. Theoretically, clinical research could run counter to the mission of a healthcare institution or even appear to compete with it. In any case, it is important that research activities and healthcare activities not be detrimental one to the other, but remain complementary.

Research imperatives as well as the additional resources at the disposal of the treating physician who conducts research activities, can contribute to the development of a two-tiered regime of care, as reported to the Committee members. This two-tiered system facilitates access for research subjects to certain services, the cost of which is absorbed by the research project.

It must also be emphasized that when a research project is financially supported by industry, the investigator might find himself in a subservient position to the sponsor. His clinical judgment as to the therapeutic needs of his patients may be negatively influenced and his impartiality altered in the interpretation of diagnostic and therapeutic findings.

There are also very real dangers for research to be used as a springboard for the introduction of unnecessary technologies in healthcare institutions. In a context of intense competition and high performance in healthcare institutions where research is carried out, research could potentially become a factory process, and the patients who agree to participate in research projects research material.

Recommendation no **24**

*In the opinion of the Committee, to preserve the integrity of research activities in healthcare institutions as well as the credibility of investigators involved in such activities, appropriate control mechanisms for the evaluation of research activities ought to be developed.*

Appropriate  
control  
mechanisms

Significantly, the scientific community at large already insists that organizations granting or financing research activities exert strict control over the conduct of such activities so as to protect their investment. The time has come to extend these controls to other dimensions of clinical research.

## b) Research in Private Offices

In the course of their mandate, the Committee members were not able to specifically investigate problems associated with the carrying out of research activities in physicians' offices or clinics. However, during the many consultations held by the Committee members, many people expressed concern at the way in which research in private offices was carried out.

Many raised doubts about the scientific quality of research activities carried out in private offices and the absence of any ethical evaluation; others emphasized the lack of follow-up of research activities carried out in private offices, aside from the follow-up that sponsors of such projects exercise as to the validity of the data gathered. The integrity and the safety of persons who have agreed to participate in such projects seems to be overlooked in many instances.

The Committee members were particularly concerned about how little knowledge was available on research projects carried out in private offices or private clinics, in particular, the ways in which these projects ensure the protection of research subjects.

### Recommendation no 25

*In the opinion of the Committee, the Ministry of Health and Social Services should assess how clinical research activities which are carried out outside healthcare institutions.*

Research  
carried out  
outside  
healthcare  
institutions

## 2.

## RESEARCH DATA

The creation of a research record distinct from the hospital record, as well as computerized data banks related to research projects raise many questions as to the protection of a research subject's private life. The same holds true with respect to the conservation of tissues removed from a research subject's body in the course of clinical care. The consultations undertaken by the Committee members permitted the identification of a number of problematic situations.

## a) Research Records

It should be remembered that research records are distinct from hospital records.<sup>50</sup> In principle, research records are subjected to the same confidentiality rules as hospital records.<sup>51</sup> It appears

<sup>50</sup>See, in this respect, The Regulation on the Organization and Administration of Institutions, R. R. Q. 1981, c. S-5, r. 3.01, Art. 50.

<sup>51</sup>See, for that, Medical Research Council of Canada Guidelines, op. cit., Note 2, page 39.

from the consultations held by the Committee, that research records are handled differently from hospital records. They are not necessarily under the immediate control of the hospital's archivist. They are found in different locations, such as the investigator's home, a hospital ward or the research centre.

### Recommendation no 26

*In the opinion of the Committee, there should be an in depth revision of the management of research records so that they may provide the same guarantees of confidentiality as hospital records do. In this respect, healthcare institutions ought to adopt an internal policy with regards to the creation and conservation of research records, in order to protect the privacy of research subjects.*

Assurance of confidentiality of research records and hospital records

Privacy of research subjects

As well, it appears that research subjects are not always informed of the existence of a research record pertaining to them nor of its content. They are not made aware of how long the record will be kept and who might have access to it. Normally, this information should appear on the consent form signed by a research subject.

Research subjects are rarely told that other investigators might have access to their medical or research records, for research and teaching purposes, without their knowledge. Furthermore, they are almost never told that investigators can obtain, without their knowledge, information from third parties, such as the Régie de l'Assurance-Maladie du Québec, for follow-up purposes.

### Recommendation no 27

*In the opinion of the Committee, research subjects must be fully informed of the identity of those who are likely to have access to their research records.*

Information related to research subjects with respect to their research records

#### b) Database

In the course of a research project, apart from the creation of a research record, it appears that databases, most often computerized, are established. These databases contain both nominative and personal data on each person who has agreed to participate in a research project. In this respect, it is important that investigators be made aware that the databases they create for the purposes of a research project are subject to legal requirements found in the law concerning

access to documents in public institutions and the protection of personal information<sup>52</sup> as well as the law concerning the protection of personal information in the private sector.<sup>53</sup>

It is equally important that those who agree to participate in a research project be made aware that data gathered by the investigator in the course of the research project can be computerized and made accessible to third parties without their knowledge.

### Recommendation no 28

*In the opinion of the Committee, healthcare institutions, if this has not already been done, ought to adopt an internal policy dealing with the creation, the conservation and the use of databases created by investigators for research purposes.*

Internal policy regarding the handling of information for research purposes

### c) Human Tissues

In the course of care, a patient often provides specimens required for the assessment of his health condition. Given the very sensitive nature of the information which can arise from the tests done, certain precautions must be taken to ensure the confidentiality of the information thus obtained.

Under the *Civil Code of Quebec*, substances removed from a person as part of the care he receives, cannot be used for research purposes, unless the person concerned or his legal representative has consented to their utilization.<sup>54</sup> This measure exists so as to ensure one's right to privacy and to prevent third parties from obtaining information on an individual without his knowledge.

Today, this measure, originally conceived to protect patients while permitting the advancement of medical knowledge, seriously handicaps the pursuit of certain medical activities, particularly epidemiological studies. The rigidity of the present regulation makes it impossible for an investigator to analyze a blood sample, for example, to study the prevalence of HIV virus in the population without having obtained a patient's prior consent. The fact that the investigator has no knowledge of the identity of the person having provided the specimen does not legitimize its use for research purposes.

In the course of their consultations, the Committee members were informed of this problem and of the difficulties encountered in conducting epidemiological research, which does not require that the identity of the person who has provided the sample be known to the investigator.

### Recommendation no 29

<sup>52</sup>L. R. Q., c. A-2.1.

<sup>53</sup>L. R. Q., c. P-39.1.

<sup>54</sup>Quebec Civil Code, Art. 23.

*In the opinion of the Committee, to the extent that the identity of a patient cannot be known to an investigator and where no relation can be established between the substance removed and the patient, an investigator could use the substance, even in the absence of the patient's consent, on the condition that the research project be approved by a Research Ethics Committee which will have ensured that the anonymity of the donor is protected.*

The use of human specimen

REBs' assurance of the subject's anonymity

In order to circumvent the present difficulties, consent forms now being used at the time of the patient's admission to a healthcare institution, should be modified so that a patient may authorize the use of substances removed from his body for research purposes on the condition that his identity remain unknown to the investigator.

Whatever the case, caution in this area is of the utmost importance. There already exist in Quebec situations where a professional can access personal data on a patient for research purposes without the latter's knowledge. One should not allow information obtained from the analysis of biomedical substances to be collected by third parties without the patient being made aware of such unless his identity is adequately protected.

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## D.

## RESEARCH ETHICS COMMITTEES

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Research Ethics Committees are called upon to play a determining role in the evaluation of research projects carried out in the healthcare sector. In principle, no research project can be undertaken unless such a committee has give its approval.<sup>55</sup> According to the answers to the questionnaire sent to various healthcare institutions, a Research Ehtics Committee existed in 15 healthcare institutions out of the 16 surveyed.<sup>56</sup>

At the present time, according to the Committee members, there are three different types of problems affecting Research Ethics Committees. These concern the membership of Research Ethics Committees, the training of their members and the role of such committees.

### 1.

### THE MEMBERSHIP OF COMMITTEES

In principle, Research Ethics Committees should be composed of people having different backgrounds and with different types of expertise. In this regard, *The Medical Research Council of Canada*, in its Guidelines states that "community values are the baseline of ethical evaluation

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<sup>55</sup> See, in this respect, Groupe de Recherche en Éthique Médicale (GREM), Les Comités d'Éthique au Québec. Guide des Ressources en Centres Hospitaliers. Québec, Ministère de la Santé et des Services Sociaux, 1991, p. 13.

<sup>56</sup> See, for this purpose, Annexe 3 of the present report.

and as a consequence, it is important that the Research Ethics Committees be made up of members who embody these community values."<sup>57</sup>

A study conducted by the National Council on Bioethics in Human Research (NCBHR), now the National Council on Ethics in Human Research (NCEHR) showed important deficiencies in this area.<sup>58</sup> According to the study, only a minority of Research Ethics Committees in Canada meet the membership requirements set by organizations called upon to define ethical standards guaranteeing the legitimacy of research activities involving human subjects.

In Canada, a large majority of Research Ethics Committees were found to be made up of scientists who, for the most part, have no specific training in ethics. The Council's report clearly shows that in a number of committees, "there is no lay representation, a primary role of which is the promotion of the research subjects' interest"<sup>59</sup>. In addition, the Council's report emphasizes the fact that "in an endeavour to provide a review of the quality of the science being considered, there has been some sacrifice of the viewpoint of the research subject concerning the risks and benefits of the research."<sup>60</sup> A large part of the problem stems from the premise that if it is not good science, it is not ethical, a premise which cannot be challenged. Given this premise, the ethical evaluation of a research project will first seek to assess its scientific validity. Thus, it must be carried out by people who have a scientific background. However, these same people, who are often investigators themselves and who have not always received ethical training, are asked to evaluate the other ethical aspects of a research project and to ensure the follow-up of these projects once they have been approved.

On the basis of these observations, one can reasonably wonder if Research Ethics Committees such as those existing today in Quebec as well as in the rest of Canada, are always able, owing to their structure, to carry out their mandate and to fully protect those who agree to participate in a research project.

In the course of its consultations, the Committee members were made aware of various situations which could impede the evaluation process of research projects submitted to a Research Ethics Committee.

It is a fact that the majority of people sitting on Research Ethics Committees work in the same healthcare institution. In principle, each member should be free to express his own views and each should have the opportunity to voice disagreement with respect to a research project. In practice, this is not always the case. A person employed by a healthcare institution might find it difficult to freely express himself on a given subject, knowing the repercussions which can arise if, due to his comments, the research project is not approved or is modified by the Research Ethics Committee.

One also cannot ignore the fact that it can be difficult for working colleagues to speak up when evaluating a research project, knowing what could happen in the future to their own research proposals. As well, an investigator involved in group practice will balk at the idea of criticizing a

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<sup>57</sup>Canadian Council for Medical Research, Guidelines concerning Research on Human Subjects, op. cit., note 2, p. 47.

<sup>58</sup>National Council on Bioethics in Research on Human Subjects. Protect and Promote the Subject of Human Research: An Examination of the function of ethics committees for research in Faculties of Medicine in Canada, loc. cit., note 1, p. 2.

<sup>59</sup>Idem, p. 21.

<sup>60</sup>Ibidem.

partner's research proposal, in view of the financial repercussions befalling on himself and his associates.

Finally, it is also conceivable that people employed by a healthcare institution who sit on a Research Ethics Committee are not exempt from constraints limiting their freedom of action, especially when they work under the direct authority of the investigator who has hired them.

Thus, it is appropriate to ask "Should Research Ethics Committees continue to be made up in majority, by scientists, physicians and investigators, and employees of the healthcare institution where the research is carried out?"<sup>61</sup>

The Committee members do not question the good faith of healthcare and research staff who sit on a Research Ethics Committee. They wish to stress that given the potential conflicts of interest related to the ethical evaluation of research projects, it remains a problem for Research Ethics Committees to be composed of people coming from the healthcare institution where the research project is to be carried out.

As well, it is deplorable that, despite the passing of time and the literature on the subject, one does not yet see in place the structures needed to assure the general public that the ethical evaluation of research projects is more than just a scientific affair, but that it calls upon people having different backgrounds.

### Recommendation no 30

*In the opinion of the Committee, Boards of Directors in healthcare institutions where clinical research activities are carried out must review the composition of the membership of Research Ethics Committees in order to ensure greater participation of individuals from outside the healthcare institution.*

Representation on REBs and underlying criteria pertaining to their composition

## 2.

### **TRAINING OF COMMITTEE MEMBERS**

From the answers to questionnaires sent to different healthcare institutions, it appears that members of many Research Ethics Committees did not have any specific training in ethics, and only in seven institutions were some members ethicists, or at least experienced in this discipline. Only seven of the sixteen healthcare institutions surveyed reported that members of the Research Ethics Committee attended training sessions.

<sup>61</sup>See, in this sense, Groupe de Recherche en Éthique Médicale (GREM), op. cit., note 60, p. 15.

These observations are similar to those of the study conducted by the National Council on Bioethics and Human Research. According to the results of that study, Research Ethics Committees are more inclined to be knowledgeable in science than in ethics.<sup>62</sup> This is unacceptable; it is comparable to having a scientific evaluation carried out by a majority of people without proper scientific training. Ethics is not simply a question of common sense nor is it something that is necessarily part of human knowledge; training is required.

### Recommendation no 31

*In the opinion of the Committee, training and continuing education in ethics must be proposed to members of Research Ethics Committees in order to allow them to fulfill their mandate.*

Continuing education in ethics

Role of REBs

### 3. THE MANDATE OF RESEARCH ETHICS COMMITTEES

In principle, a Research Ethics Committee's primary function is to ensure that the research project submitted to it for approval satisfies all the standard research ethics requirements. It also performs a second function, that of ensuring that these requirements are fulfilled throughout the conduct of the research project. In all instances, it is the responsibility of the Research Ethics Committee to ensure that the freedom, dignity, integrity and private life of every individual who participates in a research project is protected.

From the answers to the questionnaires sent to different healthcare institution, few Research Ethics Committees seemed able to ascertain if persons who participated in research projects were well protected in the various dimensions mentioned above. Due to the lack of proper financial and human resources, many committees were not able to carry out their mandate adequately. This raises serious doubts as to the real protection offered to those who agree to become research subjects. Furthermore, considering the fact that many research ethics committees do not follow, as to their composition, the minimal standards set by various organizations called upon to govern the conditions in which clinical research is carried out and that in many respects, the ethical training of research ethics committee members is deficient, one can again question the ability of research ethics committees to adequately fulfill their mandate to provide adequate protection to those who agree to be part of a research project.

One can also question the ability of research ethics committees created by virtue of Article 21 of the *Civil Code of Quebec* to adequately report to the *Minister of Health and Social Services* on the scientific validity and the ethical value of a research project involving incompetent persons and/or minors.

### Recommendation no 32

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<sup>62</sup>National Council of Bioethics on Research in Human Subjects, *Protect and Promote the Subject of Human Research: an examination of the function of ethics committees for research in Faculties of Medicine in Canada*, loc. cit., note 1, p. 21.

*In the opinion of the Committee, Boards of Directors of healthcare institutions sponsoring research activities must ascertain the ability of their Research Ethics Committee to efficiently fulfill their mandate.*

Assurance of  
competency  
of the REC

If a Research Ethics Committee cannot adequately fulfill its mandate due to a lack of resources, it might be appropriate to appoint an ombudsman, either on a full-time or on a part-time basis, to monitor research activities carried out in a healthcare institution, and more specifically, to ensure the well-being of persons who agree to participate in a research project, as well as ensuring that their rights are protected.

**Chapter 4**  
**THE EVALUATION MECHANISMS**

## CHAPTER 4 - THE EVALUATION MECHANISMS

Increasing control measures do not constitute the only means or way of guaranteeing proper implementation of research activities<sup>63</sup>. It is however important that the healthcare system which favors the proper development of research activities put into place evaluation mechanisms that are effective, efficient and fair to ensure the quality and integrity of research as well as the protection of research subjects.

### Recommendation no 33

*In the opinion of the Committee, control measures in the field of clinical research should rest first and foremost on the continual evaluation of the quality of research activities rather than on the sporadic identification of cases of scientific misconduct.*

Continual  
evaluation of  
the quality of  
research

There already exist in the scientific community various mechanisms that control the quality and scientific integrity of research. One can cite here, as an example, the control exercised by organizations who either finance or subsidize research projects or research activities of an investigator. In attempting to enhance control measures, the danger exists that many unnecessary mechanisms and levels of control of research activities could be put in place. The efficiency of evaluation measures may be compromised and investigators may be inclined to evade the control measures put into place.

This does not in any way affect the obligation to come up with control mechanisms which ensure the scientific quality, the financial equity and the ethical value of a research project. This is necessary if one wishes to ensure the quality and integrity of research activities carried out in Quebec, to maximize the outcomes while at the same time guaranteeing that research subjects are protected and research costs correctly evaluated.<sup>64</sup>

<sup>63</sup>Medical Research Council of Canada, Guidelines for Human Research, 1987, op. cit. Note 2, p. 53.

<sup>64</sup>See in this sense Groupe de Recherche en Éthique Médicale (GREM), op. cit. note 60, p. 13.

Recommendation no 34

*In the opinion of the Committee, in order to ensure the quality and integrity of research activities, the proper evaluation of the costs involved and the protection of research subjects, each research project carried out in a healthcare institution ought to be subjected to a financial, scientific and ethical evaluation. This can be part of a single evaluation process or in separate processes if need be.*

Financial,  
scientific  
and ethical  
evaluations

Evaluation  
process

The evaluations described above must take place for all research activities for which a healthcare institution is responsible. Thus, if a research project is conducted outside of a healthcare institution, to the extent that the person responsible for the research activity is not only a member of the Council of Physicians, Dentists and Pharmacists, or of the Council of Nurses of that establishment, but also makes use of the establishment's resources or recruits patients who are treated there, he must submit his research project to the evaluation process of the institution. This measure, which can appear tedious, is required to ensure transparency and guarantee the integrity of the healthcare institution whose resources are put to use, and whose patients are called upon to participate in a research project.

Furthermore, since the ethical evaluation takes into account certain financial and scientific factors, the evaluation process must follow a certain logic if it is to remain efficient.

Recommendation no 35

*In the opinion of the Committee, the financial and scientific evaluations of a research project must precede in all instances its ethical evaluation. In addition, it is essential that these three evaluations be performed by competent individuals in each of these three areas.*

Evaluation  
process

It is appropriate then to analyze the evaluation process of a research project through its three main components: scientific, financial, and ethical. For each of these components, the analysis will focus on the evaluation structure, process, parameters and applications. In addition, the question of scientific misconduct will be analyzed separately.

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**A.**

**THE SCIENTIFIC EVALUATION**

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The scientific evaluation of a research project is of major importance. It must be conducted even when the project has already been the object of an external evaluation. Thus the Committee members believe that even if a project has previously been the object of a scientific evaluation in another healthcare institution, this should not preclude the healthcare institution from thoroughly reevaluating the scientific validity of the project. This measure represents an additional guarantee with respect to the validity and scientific value of a research project as well as its appropriateness and its impact on the healthcare institution.

**1.**

**THE EVALUATION STRUCTURES**

In the course of their consultations, the Committee members were able to observe that there existed several structures and various methods of evaluation of the scientific aspect of a research project.

Thus, in certain milieus, the scientific evaluation is entrusted to evaluators chosen for their competence in a particular area. In other milieus, the scientific evaluation of a project is done by a scientific committee, consisting mainly of peers or employees of the healthcare institution. In this latter case, outside experts may validate certain aspects of the research projects when the scientific committee itself lacks the required expertise. Finally, in certain milieus the scientific evaluation of a research protocol is done by the Research Ethics Board of the healthcare institution which evaluates both its scientific and its ethical aspects.

The Medical Research Council of Canada has expressed the opinion that it is not appropriate to dissociate the study of the scientific aspect from that of the ethical aspect. According to the Council, a single committee must be responsible for the evaluation of these two aspects, that being the Research Ethics Board.<sup>65</sup> The Council's opinion is based on the premise that since a proper ethical evaluation requires a risks and benefits assessment, the Research Ethics Board must, in order to carry out its function to the fullest extent, be able to determine if the research protocol is scientifically valid and, when necessary, to consult external specialists in order to do so.

The Committee members consider that there is no sacred way of proceeding. They believe that one and the same committee, namely the Research Ethics Board, can simultaneously examine these two aspects, as long as it takes the proper steps to truly ensure the scientific value of a research project and can call upon external experts to compensate, should the case arise, for the board's lack of expertise.

In some instances, a rigorous analysis of a research project is better served by the existence of two distinct reviews. It is important, therefore, that good coordination exists between these two entities and that both benefit from the appropriate documentation so as to be able to evaluate every aspect of the research project. Whichever structure is used, it is important that the scientific evaluation of a research project be as transparent as possible and it is certainly appropriate to consider the participation of external evaluators in the examination of the scientific value and validity of a research project.

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<sup>65</sup>Medical Research Council of Canada, *Guidelines for Research on Human Subjects*, 1, 1987, op. cit., Note 2, p. 15.

Recommendation no 36

*In the opinion of the Committee, there exist different modes and structures of evaluation of the scientific components of a research project. In all instances, the latter must guarantee that the scientific value of a research project will be thoroughly and rigorously evaluated.*

Evaluation of scientific aspects

Recommendation no 37

*In the opinion of the Committee, it is essential that investigators, who are not associated with the healthcare institution where the research project is conducted, be permanently involved in the scientific evaluation of research projects either by sitting on an evaluating body or through a written evaluation. This external scientific participation adds transparency to the evaluation process.*

Presence of external evaluators in the review process

2.

**THE EVALUATION PROCESS**

In evaluating the scientific aspects of a research project, it is important that the entity performing the evaluation be provided with all the information necessary to judge the pertinence of the research project and the validity of the scientific design. The research protocol submitted for approval must therefore contain enough information for one to be able to adequately evaluate the project's purpose, the hypothesis that the investigator wishes to test, the strategy and methodology which the investigator will use to validate his hypothesis, and the risks and side-effects to which the research subjects will be exposed.

A written account of the deliberations pertaining to the research project must be submitted for each project. The written account must indicate if the project has been approved, with or without modifications, and if present, specifying them. On the other hand, if the research project is not approved, the written account should indicate the reasons for its non approval. The written account must indicate if the approval was unanimous or not, and the period of time covered by the approval.

Upon completion of the evaluation, an attestation that the research project has been approved by the body responsible for the scientific evaluation should be kept on file.

**3.**

***THE EVALUATION PARAMETERS***

A research project is considered of scientific value only if the proposed scientific design presents all of the essential elements for the investigator to validate the hypothesis which constitutes the basis of the research proposed.

When evaluating the scientific aspect of a research project, the entity responsible for the scientific evaluation must also inquire as to the appropriateness of the measures to be used to validate the proposed hypothesis. If these measures appear to be deficient, the investigator must be informed of these deficiencies and must make the necessary modifications, even if the scientific design may have previously been approved in another healthcare institution. Furthermore, it is important for the entity responsible for the scientific evaluation to examine the adequacy of the statistical analysis necessary to validate the results.

The scientific evaluation of a research project also must be concerned with the nature and appropriateness of the inclusion and exclusion criteria found in the research project. They must be able to ensure that the applicable criteria will allow the investigator to recruit a sufficient number of research subjects to successfully complete his research project, having regard to the particular context of the establishment where the research project will be carried out. It would be unethical for a research project to begin without the assurance that the required number of subjects will be recruited. In multicenter trials, they must also inquire about the conditions which will lead to the interruption of a research project.

Finally, those responsible for the evaluation of the scientific aspects of a research project must pay special attention to the potential risks and possible side-effects to which research subjects can be exposed and the eventual benefits which they could derive from their participation in the research project. They must ensure that the risks pertaining to the research project are reasonable and that research subjects are well informed about the frequency and severity of these risks.

**4.**

***THE MODALITIES OF IMPLEMENTATION***

Those responsible for evaluating the scientific aspect of a project, have the right, even in the case of a multicenter trial, to propose modifications to the research design if it appears to them that the research strategy, the research methodology, and the safety of research subjects are inadequate. Although this might displease certain sponsors or initiators of research projects, the entity responsible for the evaluation of a research project should never approve a project which does not meet the scientific requirements needed for its completion. If the scientific design submitted for approval does not meet these requirements, the sponsor or the initiator of the project must be asked to make the necessary changes. If they are not made, the demand for approval should be rejected.

The evaluation of the validity of a hypothesis or of the quality of a study can also be made midway in a project. It is then important, if one wishes to control the quality and integrity of the study's results, and as such, its scientific validity, that those responsible for the evaluation be able to access all available raw data generated in the course of the research project. This data is essential to support the scientific analysis required for the demonstration of the research hypothesis or to gain better knowledge of a given problem.

It is essential, then, that this data be kept intact. It is incumbent upon the healthcare institution in which the research is conducted to take the necessary measures so that the data obtained in the course of a research project remain accessible to those responsible for ensuring the integrity of research activities, notably the director of the research center, or the person responsible for the scientific evaluation of the project.

In addition, it is appropriate that each publication of research results correspond to a file containing the raw data and relevant analyses supporting the results. This file should remain accessible at all times for verification by the healthcare institution of the quality of the scientific information originating from the research activity. A copy of the copyright agreement if available should appear in the file. It falls upon the Director of the Research Center or the person responsible for research activities in an establishment to verify at random the content of publication files once the article has been submitted for publication.

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## **B. THE FINANCIAL EVALUATION**

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Every research project carries a variety of costs. These are related to the hiring of personnel, the execution of laboratory tests and analyses, the purchase of supplies, the payment of various expenses, such as telephone, photocopies, meetings, and so forth. These costs are real and cannot be ignored, whether they are accounted for or not.

The Committee members recognize that the evaluation of such costs is difficult but they do not believe that healthcare institutions should be exempted from carrying out the evaluation process and calling upon people who have the relevant expertise to do it.

### Recommendation no 38

*In the opinion of the Committee, each healthcare institution hosting clinical research must establish a procedure permitting a detailed financial evaluation of every research project and the precise cost breakdown engendered by each research act.*

Financial  
analysis and  
cost  
breakdown  
procedure

The procedure should give investigators instructions on how to evaluate costs engendered by the research project and whom to contact so as to properly evaluate the different financial components of the research project.

### **1. THE EVALUATION STRUCTURE**

The Committee members were able to determine, from their consultations and from the answers to the questionnaire sent to different healthcare establishments, that a permanent structure established for the evaluation of the costs associated with a research project did not always exist. This evaluation was sometimes done by the investigator himself; at times, it was conducted in conjunction with the Director of Financial Services or by an employee of the research center. In other instances, no evaluation was carried out before the completion of the research project.

Recommendation no 39

*In the opinion of the Committee, within a healthcare institutions hosting research activities, a structure entrusted with the evaluation of the financial aspects of research projects ought to be instituted. If the creation of such a structure is not warranted, a person specifically designated to evaluate the costs associated with a research project should be appointed.*

Composition of body or designation of a person entrusted with review of the financial aspects

In healthcare institutions where the creation of a committee might be found useful or necessary, the committee should be composed of individuals having different professional backgrounds such as the Finance Department, Pharmacy, Laboratories, Nursing, Professional Services and the Research Center, if one exists.

In any case, it is important that the evaluation of the costs of a research project be undertaken by competent individuals, knowledgeable both with regard to the true costs associated with a research project and hospital procedures. These individuals should be able to evaluate the financial impact that the research activities could have upon the institutional infrastructure. The direct involvement of healthcare staff is not only desirable but necessary.

**2.**

**THE EVALUATION PROCESS**

The evaluation of the financial aspects of a research project should occur before the project starts and the contract is signed. The structure responsible for the financial evaluation of a research project should, above all, ensure that the regulations governing costs that apply to a research project are adhered to. It should also assure itself that those who are responsible for the financial management of research projects and those who carry them out are aware of the grant or of the research contract content so as to understand all the possible financial repercussions that a research project may have on both the investigator and the healthcare institution.

The Research Center's Director, the Research Director, or any person designated by them should develop a form outlining the direct and indirect costs of a research project. This form should be completed before the project is submitted to those responsible for the scientific evaluation and for the Research Ethics Committee. The Board of Directors of a healthcare institution could adopt a bylaw stating that every research project must have a detailed estimate of costs submitted on an appropriate form before it can be approved by the proper authority.

When studying the application of any project which is the object of a grant application, the structure responsible for its financial evaluation should have, not only the grant application but also the operating budget, at its disposal. The grant application should be submitted to the entity responsible for the financial evaluation before the request is sent to the granting agency.

Furthermore, it is crucial that the entity responsible within a healthcare institution for the evaluation of the costs a research project be informed of the grant application's fate. If the grant application is rejected, in principle, the research should not take place, unless the investigator is able to find another source of financing and re-submits the project for evaluation. If it is accepted, it is important that the person responsible for the financial evaluation of research projects be informed of the extent of funding by the granting agency. If it appears that certain cuts have been made to the operating budget, the entity responsible for the financial evaluation of research projects should undertake to re-evaluate the budget with the investigator and determine how to make up for budgetary cuts.

When negotiating research contracts, the entity responsible for the financial evaluation of research projects must have a copy of the research contract which the sponsor and the investigator intend to sign. Special attention should be brought to bear not only on the amounts of money that the sponsor agrees to pay the investigator for carrying out the research project, but also on the guarantees offered to the healthcare institution and the investigator in terms of financial compensation should litigation arise from the conduct of the research project.

The entity responsible for the financial evaluation should be able to request that modifications be made to the contract's content if the contract does not meet the healthcare institution's budgetary requirements. In addition, it must also ensure itself that the contract meets the requirements found in the new directives issued by the Ministry of Health and Social Services, requiring that a 18% overhead charge be added to cover indirect research costs as well as a 2% overhead charge to cover indirect costs to the healthcare institution. It should ensure that these costs are correctly calculated.

The results of the financial analysis of a research project should be put in writing. The written evaluation should be sent to the investigator, to the Research Ethics Committee, as well as to the Research Center's Director, if there is one, or to the person who is responsible for research activities. The written evaluation should state that the research project either conforms or does not conform to the budgetary regulations and requirements of the healthcare institution.

#### Recommendation no 40

*In the opinion of the Committee, prior to the start of any research project in a healthcare institution, the structure responsible for the financial review of research projects should issue a written attestation indicating that the financial review of the project was conducted and that the project meets or does not meet the healthcare institution's financial requirements.*

Issuance of statements attesting to financial conformity by an evaluating body

This attestation could serve as a reference point in the audit process of research activities by an external auditor. It should also mention if those responsible for the financial evaluation had access to the research grant application or the research contract at the time of the evaluation the research project's financial aspects.

Every research contract should be signed by the General Manager of the healthcare institution or a representative and by the Research Center's Director or the Research Director once the

entity responsible for the financial evaluation of research projects has provided them with an attestation of conformity to the budgetary requirements of the healthcare institution.

3.

**THE EVALUATION PARAMETERS**

The financial evaluation of a research project must comprise a thorough cost analysis related to the carrying out of the research project as well as the potential financial impact of the project on the healthcare institution's resources.

In evaluating the costs of a research project, the entity performing the evaluation must ensure that the hospital, through its operating budget, does not subsidize the research activity by way of indirect or hidden costs.

Where a research project requires the administration of a medication, a pharmacist should always participate in the cost analysis. If the project requires additional days of hospitalization, these costs should be accounted for.

Thus, it is important that the entity responsible for the financial evaluation of research projects specifically identify those acts which can be ascribed to the research project (research procedures) in contrast to those arising from standard care (therapeutic acts) which the patient would have received in any event.

Recommendation no 41

*In the opinion of the Committee, whenever a healthcare act is required to prove a research hypothesis, it must unequivocally be considered as a research act, and so, even if it is medically required by the research subject's medical condition. The cost of this act must therefore appear as a research cost in the research project budget.*

Billing of  
therapeutic  
acts within a  
research  
project

It is important to point out that with respect to research grants, the costs scale is generally well known by those who fill out the grant application. It is altogether different with respect to research contracts.

Moreover, the entity responsible for the financial evaluation of research projects should require that a detailed evaluation of the costs incurred by research subjects for their participation in a research project be clearly identified and that the evaluation be submitted to that entity.

In cases where a research project requires the administration of a drug, a pharmacist should participate in the cost assessment. Furthermore, if a research project requires additional days of hospitalisation, the additional costs should be taken into account.

**4.**

**THE IMPLEMENTATION MODALITIES**

The effectiveness of a process designed to evaluate and control the financial components of a research project depends to a large extent on the goodwill of investigators and the sustained vigilance of administrators. This vigilance must apply beyond the initial cost evaluation if one is to ensure that the budget is adhered to as initially accepted.

The initial approval of a research project's budget represents only one aspect of the financial controls that healthcare institutions must exercise on the management of research funds. A periodic follow-up of research expenses ought to be made so as to ascribe to the proper research project the relevant costs, and thus avoid budget overruns or inappropriate allocation of research costs.

The investigator remains the primary person accountable for the funds which have been allocated for carrying out the research project. However, it falls upon the healthcare institution to recover costs incurred by it in relation to the research project.

The inherent costs related to a research project can be recovered by the healthcare institution, by way of a lump sum or on a unit cost basis. In the first case, the portion of the budget pertaining to certain clearly identified services rendered by the healthcare institution will be debited from the research project account according to modalities agreed upon by the investigator and the healthcare institution. In the second case, each procedure specified in the research protocol shall be identified when performed. This implies the existence of some identification mechanism, for example stamping, which will permit this act to be identified as a procedure part of a particular research project.

From a practical point of view, the Committee members believe that each investigator should be allocated a specific account number and that each research project be the object of a sub-account. This accounting procedure would permit transparency with regard to the use of research funds and the proper accounting of research costs.

At the time of completion of a research project, the principal investigator must submit to those responsible for the carrying out of clinical research activities a financial report which specifies how the research costs were identified as well as the surplus or deficit incurred by the research account for that particular research project. A positive balance could, according to the practices in force in the healthcare institution, be kept in the investigator's research account to be used to finance future research projects, or could be made available to the investigator's department head, with the agreement of the investigator, in order to sustain research activities carried on in the department.

In the course of its evaluation, the entity responsible for the financial evaluation of research projects must inquire as to how the research funds will be managed. In particular, it is important for it to ascertain if the funds will be managed outside the healthcare institution, and if those funds, including the investigator's fees, are to be deposited in financial institutions, such as banks and trust companies.

It is important that every budgetary component of a project, including the investigator's fees, be clearly identified and that the healthcare institution be responsible for every financial operation executed in relation to a research account. To ensure maximal transparency in the management of research funds, it is appropriate to discourage the practice where a sponsor

directly pays an investigator for his services, bypassing the research account. At the end of each fiscal year, an investigator should receive an income tax form showing honoraria paid to him in relation to his research activities.

Recommendation no 42

*In the opinion of the Committee, all research funds should be managed by the healthcare institution hosting a research project. This measure not only ensures proper management of research funds, but also avoids the misappropriation of funds by an investigator. It also allows the Research Director or the Director of a research center to freeze research funds in cases of professional misconduct.*

Management  
of research  
funds

C.

ETHICAL EVALUATION

To be accepted, it is not enough that a research project meet the scientific requirements as to value and validity as well as the financial requirements of the healthcare institution. It must, in addition, meet clearly defined ethical requirements. According to the Medical Research Council of Canada, ethics in the area of biomedicine refers to "the body of principles governing good conduct; it defines what must be done."<sup>66</sup> It conveys the values that must govern one's behaviour.

In Quebec, the evaluation of the ethical components of a research project is in principle the responsibility of a Research Ethics Board (REB). According to the Medical Research Council of Canada, "the evaluation of a research project by a Research Ethics Committee is the principal means that allows society to guarantee the respect of these values."<sup>67</sup>

Research Ethics Boards therefore play a determining role in the approval of research projects in clinical research. In fact, Research Ethics Boards have the authority or power to approve or reject a research project. They ultimately decide if a research project will be carried out in a healthcare institution. It is they who decide upon the ethical value of any research project. They are the cornerstone for the protection of research subjects. It is the Research Ethics Boards who must ensure that all the requirements of an ethical nature are met and that the integrity, privacy, freedom, safety and dignity of those who agree to participate in a research project are fully protected.

Given the central role that a Research Ethics Board plays in the field of clinical research, such a committee should never be regarded as a rubber-stamp body whose main role is to blindly ratify decisions already taken by others.

<sup>66</sup> Medical Research Council of Canada, Guidelines Concerning Ethics for Human Research, 1987, op. cit., note 2, p. xi.

<sup>67</sup>Ibid., p. 48.

Recommendation no 43

*In the opinion of the Committee, in view of the responsibilities given to Research Ethics Boards for the approval of research projects, healthcare institutions hosting research activities ought to create a Research Ethics Board that are both credible and efficient.*

Establishment  
of credible  
and efficient  
REBs

1.

**THE EVALUATION STRUCTURE**

In principle, a research project cannot begin before having received the approval of a Research Ethics Board.<sup>68</sup> Strictly speaking, this is not a legal requirement but one found in international codes of ethics, and in the regulations adopted by government agencies who provide funding for research activities.

It is the responsibility of every healthcare institution hosting clinical research to set up such a committee. The Committee members were made aware of the different modalities by which these boards are created. In the vast majority of cases, these committees are constituted by the Council of Physicians, Dentists and Pharmacists or by the Board of Directors of a healthcare institution.

Recommendation no 44

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<sup>68</sup>See, concerning this, Art. 21 of the Civil Code of Quebec which recognizes the need for the Ministry of Health and Social Services to obtain the advice from an Ethics Committee without which he cannot approve experimentation using minors or incapable adults.

*In the opinion of the Committee, Research Ethics Boards ought to be created by the Board of Directors of healthcare institutions hosting research activities and not by its Council of Physicians, Dentists and Pharmacists, or its Council of Nurses, or its Multidisciplinary Council. In addition, Research Ethics Boards ought to report directly to the Board of Directors.*

Creation of REBs and their reporting to the Board of Directors

Given the fact that healthcare institutions are wholly responsible for research activities carried out within their institution, it is appropriate that it be the Board of Directors to whom Research Ethics Boards should report. At the present time, not all research activities carried out in a healthcare institution are of a medical nature. Some clinical research activities are also carried out in disciplines other than medicine, such as nursing or physiotherapy. In such a context, it is inappropriate to give one council the sole prerogative of constituting the Research Ethics Board within a healthcare institution. Furthermore, the Board of Directors by virtue of its structural links to these bodies can consult with those directly concerned with clinical research.

#### Recommendation no 45

*In the opinion of the Committee, the members of a Research Ethics Board should be appointed by the Board of Directors of a healthcare institution upon the recommendation of various internal bodies such as the Council of Physicians, Dentists and Pharmacists, the Council of Nurses, the Multidisciplinary Council, as well as from external bodies such as the affiliated university, or the Patients' Committee, to name only a few.*

Appointment procedure of REBs' members

In addition, it is important that those who sit on Research Ethics Committees not be exposed to situations where, because of the position that they hold within the healthcare institution, they could be the object of subtle pressures in carrying out their functions as members of the Research Ethics Board. It is necessary to avoid all appearances of partiality or of conflict of interests which might cast doubt on the ability of Research Ethics Board members to analyze objectively the ethical value of a research project.

#### Recommendation no 46

*In the opinion of the Committee, in order to avoid all appearances of conflict of interest and to reduce the possibility of undue pressures on REB members, the Research Director, the Research Center's Director or the Scientific Director who might already be members of the scientific committee, should not at the same time be members of the Research Ethics Board.*

Avoidance of appearance of conflict of interest

That being said, each member of the Research Ethics Committee should declare all business ties with medical, technology or pharmaceutical companies, and abstain from the committee's deliberations each time the appearance of a conflict of interest may arise.

Furthermore, relying on the answers to the questionnaire sent to various healthcare institutions and the consultations of the Committee undertook, the membership of Research Ethics Boards varies greatly. In its 1987 Guidelines, the Medical Research Council of Canada proposed that the Research Ethics Board of a healthcare institution ought to count among its members a person having some expertise in the field in which the research is being carried out, a clinical psychologist, a scientist, a bioethicist, a philosopher or theologian, a lawyer or a jurist.

#### Recommendation no 47

*In the opinion of the Committee, Research Ethics Boards ought to be constituted of representatives from within and from outside the healthcare institution. In addition, the members recruited outside the healthcare institution should represent at least 40% of the Research Ethics Committee membership and be representative of the community at large. REB should include professionals having expertise in science and in law, as well as individuals with substantial clinical training.*

Composition of REBs'

Whatever the membership of a Research Ethics Board, its value comes primarily from the competence, credibility, dedication, and strength of character of the people forming it. Since Research Ethics Boards exist primarily to protect individuals who agree to participate in a research project, it is important for the Research Ethics Board's members, whatever their background, to have as their foremost concern the interest of those who are likely to participate in a research project and to be preoccupied primarily by their safety and comfort.

Within a Research Ethics Board, the chairman and the secretary play a key role. The chairman of the Research Ethics Board is the person in charge of presiding over the meetings. As such,

this individual controls the discussions that take place and determines the time allocated to the study of a research project and to the analysis of research reports. This position is of considerable importance. The secretary is often the person who is responsible for ensuring the administrative follow-up of a research project and bringing to the attention of the chairman all correspondence related to a research project.

To be a member of a Research Ethics Committee and more specifically to act as chairman or secretary takes a great deal of time and energy and requires a great deal of availability so as to ensure the continuous evaluation of research projects. In healthcare institutions where the volume of research activities is large, one cannot hold the office of chairman and secretary concurrently as there would be a risk that the duties incumbent upon the chairman and the secretary would be accomplished in an incomplete or superficial way.

Given the strategic importance of the function of chairman, one cannot overemphasize the necessity for the chairman to remain fully independent from any undue influence in the evaluation of a research project. He must not under any circumstances be in a position where he could become an object of intimidation.

### Recommendation no 48

*In the opinion of the Committee, the Chairman of the Research Ethics Committee must exhibit qualities such as dedication, wisdom, integrity, strength of character and impartiality. The position of Chairman should never be held by one who simultaneously holds an administrative function in a healthcare institution, such as President of a Council Research Director or Director of a department.*

Qualities  
attached to  
the REB's  
chairmanship

In making this proposition, the Committee members do not wish to question the integrity of those exercising administrative functions in a healthcare institution. However, the Committee members feel that for the chairman of a Research Ethics Committee to hold an administrative function can place him in a conflict of interest, and hamper his ability to accomplish his duties.

## 2.

## THE EVALUATION PROCESS

In certain milieus, the Research Ethics Board is called upon to evaluate both the scientific and the ethical aspects of research projects.<sup>69</sup> The Research Ethics Board must assess the validity of research hypotheses, the quality of the proposed methodology, and the relevancy of the expected results.

According to the Committee members, it is important in principle to analyze separately the ethical aspect and the scientific aspect of a research project. While it is true that separate evaluations

<sup>69</sup>Research Group in Medical Ethics (GREM), op. cit., note 60, p. 13.

can increase the time required for approval of a research project, it offers, to the extent that both evaluations are properly performed, better guarantees of protection with regards to research subjects. It is important, therefore for Research Ethics Boards to be able to rely on the contribution of scientists in understanding the technical features of a research project.

In addition, from the answers to the questionnaire sent to various healthcare institutions, the ethical evaluation of research projects is essentially an unpaid activity. On the whole, members of Research Ethics Boards are not remunerated for their work. Nonetheless, certain committees, whose workload is substantial, could in all fairness provide for honoraria to those sitting on these committees.

This having been said, one must recognize that the ethical evaluation of a research project is both difficult and complex. The first difficulty faced by one called upon to evaluate the ethical aspect of a research project arises from the documents themselves. It is not unusual for members of a Research Ethics Board to be faced with a large volume of documents which they are expected to read in order to assess the ethical value of the project, specifically whether it meets the recognized ethical standards as well as all of the legal requirements. Are these documents always read? It is hard to say without inquiring into this matter.

Due to the overabundance of documents submitted to Research Ethics Committees, one runs the risk of missing the important and pertinent elements, unless they are highlighted. Discouraged by the volume of work and by the absence of analytical indicators, committee members may only skim briefly through the documentation provided without identifying the data required to assess the project's ethical value. It is important therefore that they be provided with documents which, without being excessive, are sufficient to evaluate the relevant ethical issues of a research project.

Thus, members of Research Ethics Boards need to have available for assessment purposes a copy of the research protocol as well as a summary prepared by the investigator containing the following elements: a. object of the research; b. scientific justification of the project; c. nature of the risks, side-effects and inconveniences which research subjects may experience; d. recruitment strategy of research subjects; e. investigators' and research personnel's training related to the management of potential risks.

Furthermore, the members of a Research Ethics Board should have a copy of the minutes pertaining to the scientific evaluation of each research project. They should also be informed of the results of the financial evaluation of the research project.

Responsible for ensuring the safety of research subjects, Research Ethics Boards should not simply wait for the final results of a research project to be handed in. This is all the more true since it appears from the questionnaires sent to various healthcare institutions that submission of a final report on a project is not a formal requirement at this time. Members of a Research Ethics Boards must also identify the specific components of the follow-up required for each research project. These can include the frequency of the reports to be submitted, the adverse events which must be reported immediately and those which must be reported regularly.

## Recommendation no 49

*In the opinion of the Committee, the follow-up exercised by a Research Ethics Board on research activities should focus on the safety of research subjects and on their willingness to participate in a research project.*

Focus of the follow-up carried out by an REB

Finally, the functional dynamics of a Research Ethics Board must also be taken into consideration in order to appreciate the Research Ethics Board's ability to effectively fulfill its mandate. A Research Ethics Board should never become a rubber-stamping or ghost committee which does not evaluate a research project on its merits. There is a real danger in Research Ethics Boards operating in an expeditious manner, such that members are prevented from thoroughly discussing the key elements of a research protocol.

### Recommendation no 50

*In the opinion of the Committee, Research Ethics Boards should be provided with the necessary means permitting them to verify the outcome of their recommendations as well as gain knowledge of the complications, inconveniences and side-effects experienced by research subjects.*

REBs' means of verifying application of their recommendations and safety of research subjects

## 3. THE PARAMETERS OF EVALUATION

The ethical evaluation of a research project must be guided by the fundamental principle that to be ethically acceptable, it must be scientific valid. However, this cannot be the sole criteria for the evaluation of a project's ethical value since scientific expertise is in itself insufficient to guarantee all ethical aspects of a research project.

It is clear that a research protocol is not ethically valid if it is not likely to improve knowledge in a particular area, if it is not beneficial or if it does not have a potential social value.<sup>70</sup>

The evaluation of a research project's ethical aspects must include an analysis of its impact on the integrity, privacy and health of individuals who agree to become research subjects. This assessment must take into account the general and specific ethical standards which govern clinical research. It must also contain an analysis of a research project's adherence to existing legal rules.

It is imperative that members of a Research Ethics Board know the ethical standards which specifically apply to clinical research. They must also be aware of the law governing research

<sup>70</sup>Medical Research Council of Canada, Guidelines Concerning Research on Human Subjects, 1987, op. cit., note 2, p. 15.

activities in Quebec so as to properly assess research projects submitted to them. Significantly, investigators and sponsors are not always aware of the content of these regulations.

These regulations and standards provide only general indications as to the ethical value of a research project. For instance, with respect to persons of full age who participate in a research project, the statement that the risk incurred by them must not be disproportionate to the benefit that can be reasonably anticipated<sup>71</sup> remains overly general and subjective to the extent that the actual risk is not clearly identified and defined. In the case of minors and incompetent adults, the statement that the project must be free of any serious risk to their health<sup>72</sup> is ambiguous given that what constitutes a serious risk remains to be defined.

It would be interesting to survey members of Research Ethics Committees to gauge their views as to what elements and criteria should be incorporated in the ethical evaluation of a research project. For the members of this Committee, it is insufficient to define ethics as what should be done; it should be further defined by what needs to be done and whether and how it is done.

### Recommendation no 51

*In the opinion of the Committee, members of Research Ethics Boards must remain well informed of the regulations and standards underlying the ethical evaluation of a research project.*

Knowledge of legal rules and ethical standards relevant to the evaluation of research projects

Members of a Research Ethics Board must, in the evaluation of a research project, analyze in detail the nature of the risks, side-effects and inconveniences to which research subjects could be exposed.<sup>73</sup> They must inquire into the severity of these risks in relation to different facets of the scientific protocol. They must insist that the risks be described in clear and unambiguous terms in the information leaflet.

Furthermore, members of Research Ethics Boards must examine closely the exclusion and inclusion criteria of a research project not only to ensure that the persons who agree to participate in a research project are of a sufficient number to allow the investigator to obtain the required quota of subjects outlined in the research protocol, but that these subjects are not exposed to undue risks of injury. In this context, and as discussed previously, certain elements of the financial analysis that might influence recruitment of subjects are particularly relevant.

In evaluating the ethical aspects of a research project, particular attention ought to be given to the consent form, also referred to as the information leaflet. Members of a Research Ethics Board must ensure that this document contains the relevant information, and that the form that a research subject will be asked to sign is written in a clear and intelligible style. This is essential if the intention is to recruit subjects who are aware of what their participation entails. Members of Research Ethics Boards must also ensure that an ill person asked to participate in a research

<sup>71</sup>Civil Code of Quebec, art. 20.

<sup>72</sup>Civil Code of Quebec, art. 21.

<sup>73</sup>See, in this regard, Research Council of Medical Research in Canada. Ethics of human experimentation, 1978, op. cit., note 18, p. 17.

project is informed of the standard care in the treatment of his illness as well as the risks and side-effects associated with it so as to enable the subject to compare the standard procedure with the alternative treatment plan offered by the research project.

As well, Research Ethics Board members must ascertain how and by whom the recruitment of research subjects will be made and verify the period of time the research subject will have to assimilate the pertinent information before deciding whether or not to be part of a research project.

Finally, Research Ethics Board members must inquire about the modalities devised to ensure the confidentiality of data gathered in the course of the research project. They must ensure that the information leaflet fully informs research subjects as to the identity of the persons and organizations that will have access to their research record and to whom nominative information could be divulged.

#### 4. **THE MODALITIES OF IMPLEMENTATION**

An effective, efficient, and fair evaluation of the ethical aspects of a research project rests essentially on the personal values, strength, performance and credibility of those who make up the Research Ethics Board.

It is not appropriate to impose on Research Ethics Board individuals who have not received minimal training as to what is expected of them. According to the Committee members, many people are asked to be part of a Research Ethics Board and lack adequate preparation to efficiently assume the responsibilities flowing from their participation in the ethical evaluation of research projects. Information sessions must be offered on a continuing basis in Quebec to members of Research Ethics Boards.

### Recommendation no 52

*In the opinion of the Committee, continued education and appropriate training ought to be offered to persons called upon to sit on Research Ethics Committees. In this respect, the Committee members believe that the Quebec Hospital Association should assume leadership by initiating a training program aimed at assisting members of Research Ethics Boards in assuming their responsibilities.*

REBs'  
members  
continuing  
education

Training  
program  
initiated by  
AHQ

In addition, it is important to have people known for their integrity, competence, dedication, honesty and availability on research ethics committees. Disinterested persons should not sit on Research Ethics Boards. People who are members of Research Ethics Boards ought to have the courage to denounce, when necessary, attitudes and situations which appear unacceptable, and should resist any intimidation tactics which can occur occasionally during the discussion of research projects.

Research Ethics Boards' members must ensure the continued monitoring of research projects if they wish to maintain their credibility. Committees that do not assume those tasks are not fulfilling their duties. If they choose to ignore a project's outcome of a project and if they passively await an investigator's report, they are not fulfilling assuming their responsibilities.

Moreover, it is important that Research Ethics Committees be able to evaluate with promptness, effectiveness, and accuracy research projects which are submitted to them. The needed promptness and effectiveness may in reality be disrupted by poor functioning of the evaluation activities. If, for example, in institutions where separate bodies evaluate the scientific and the ethical aspects of a research project, the body responsible for the project's scientific evaluation provides incomplete assessment, it should not be held against the establishment's Research Ethics Board for taking more time to evaluate the project, as questions concerning its pertinence and validity still remain unresolved.

The costs engendered by the setting-up of adequate monitoring mechanisms could be paid for in various ways. In this respect, the Committee members believe that public and private organizations which fund research projects should see to it that part of a research project's budget be allocated for the evaluation and monitoring of those projects.

If the evaluation and monitoring of costs are not considered an integral part of a research project's assessment, one could consider that the 18% tax imposed on current research contracts may then be used in part to pay for the evaluation and monitoring costs of research projects. An alternate source of funding could be the interest generated by research funds, as well as the profits derived from a favorable exchange rate with respect to research projects funded in U.S. dollars.

### Recommendation no 53

*In the opinion of the Committee, costs related to the evaluation and the monitoring of research projects must be computed as an integral cost of the projects and be assumed by the healthcare institution through the 18% tax imposed on all research contracts.*

Costs related to the evaluation and monitoring of research projects

Still, the Committee members believe that a healthcare institution, whose intention it is to carry out research activities according to existing ethical standards, has no choice but to allot the necessary human and financial resources needed to fulfill its obligations towards those individuals who, through good will and altruism, agree to participate in research projects. At the present time, the consultations carried out by the Committee members show that in many

healthcare institutions, the resources needed for the proper functioning of Research Ethics Boards are inadequate.

Recommendation no 54

*In the opinion of the Committee, the Board of Directors of a healthcare institution hosting research activities must allocate to its Research Ethics Committee an annual operating budget allowing it to effectively fulfill its double mandate; that is, to ensure the quality and integrity of research activities as well as the respect and safety of research subjects.*

Allocation of financial resources to REBs

Whatever the budget allocated to a Research Ethics Board, it is a minimal requirement that the following resources be provided: office space for storage of the Board's archives; support staff for allowing proper keeping and handling of administrative files and meetings' records; a person responsible for the monitoring of research projects.

In healthcare institutions where the volume of research activities is extensive, it may be insufficient to rely on the administrative support of only one individual who who have the task not only of preparing documents to be studied by the Research Ethics Board, but also of ensuring proper follow-up of correspondence generated by a project.. Thus, it may be required that more than one person, according to the volume of research activities carried out in the establishment, be hired to ensure a permanent structure for the preparation and follow-up of research projects. These individuals would serve as liaison between the investigator and Research Ethics Board from the beginning to the end of a research project.

In concrete terms, the support staff should assure that, prior to submission of a research project to the Research Ethics Board, consent forms meet the agreed upon requirements as to content, form, and language. They should ensure that the files submitted to the Research Ethics Committee are complete so as not to delay the approval of research projects, due to the absence of vital information necessary for such evaluation.

Finally, these persons would monitor research projects, verifying from time to time whether the consent form used is the one approved by the Research Ethics Board and whether the conditions under which consent was obtained were respected. They would also report to the Research Ethics Board all problems of an ethical nature which might arise in the course of the research project.

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**D.**

**SCIENTIFIC MISCONDUCT**

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At the outset, it is appropriate to underline that scientific misconduct does not only entail falsification or fabrication of data generated in the course of a research project. More broadly speaking, scientific misconduct exists whenever an investigator or a member of his research

personnel knowingly or negligently deviates from good clinical practice and good ethical practice.

Scientific misconduct occurs when an investigator, by deception, leads a person to participate in a research project against his will, exposes him to undue risks given his state of health, or acting fraudulently, does not report an adverse event related to a research project or finally, misuses research funds. Scientific misconduct also occurs when an investigator appropriates for himself his colleagues' research findings, or unjustly omits to recognize a colleague's contribution to a scientific paper.

This having been said, one can affirm that in general, investigators who carry out research activities do so with honesty and integrity. Nonetheless, from time to time, some investigators will break rules and act in a manner that goes against established standards of conduct. For these investigators in particular, as well as for the institutions that support their research activities, and for the scientific community at large, the consequences of these misdemeanors are disastrous. The investigator who is found guilty of scientific misconduct runs the risk of being looked upon with contempt and of being deprived of his professional, institutional and university status. He may also be the object of judicial and disciplinary proceedings. Furthermore, he may be required to reimburse those organizations which have financed his research activities.

Moreover, the healthcare institution which has supported his research activities runs the risk of seeing its reputation tarnished, its administration put in doubt, and its patients' trust eroded. In addition, it risks being required, similar to the investigator, to repay monies given to it by granting agencies or sponsors, as the establishment is generally a co-signatory with the investigator. Finally, the scientific community itself runs the risk of being discredited by such events. The climate of trust essential to the proper carrying out and development of scientific activities will inevitably be altered.

One can understand, therefore, the necessity for any research milieu, for the healthcare sector and for all those who support research activities financially or otherwise, to be able to rely on efficient mechanisms aimed at identifying and remedying cases of scientific misconduct.

At the present time in Quebec, there is no permanent structure responsible for investigating allegations of scientific misconduct, and mandated to receive and handle information relating to a case of scientific misconduct. There is no Quebec equivalent to a body such as the *Office of Research Integrity* (ORI) in the U.S.A, which has the competence to investigate in Canada any allegation of scientific fraud associated with a research activity financially supported by a U.S. governmental agency or by an American company; nor is there a body similar to the *Office of Protection of Research Risk* (OPRR), also in the United States, which has the power to investigate in Canada any breach of American regulations with respect to research activities financially supported by U.S. governmental agencies or companies.

In Canada, there is no body specifically entrusted with the responsibility of investigating cases of scientific misconduct. The *Medical Research Council of Canada*, in conjunction with the *Natural Science and Engineering Research Council*, and the *Social Sciences and Humanities Research Council* have recently formulated policies which outline their expectations in the

matter of research integrity.<sup>74</sup> As well, the *Fonds de la recherche en santé du Québec* is in the process of developing a policy to regulate cases of scientific misconduct arising from the research activities which it supports.

The Committee members believe that it is important for a healthcare institution to develop the necessary mechanisms to handle questions of scientific misconduct that can arise in the course of research activities carried out within it.

Healthcare institutions which do not feel concerned by questions dealing with professional misconduct are seriously neglecting their responsibilities. Such an attitude reflects a lack of sensitivity towards a situation which, over and above the consequences for the subjects, can discredit them in the eyes of all, specifically in the eyes of healthcare personnel and patients. In addition, these institutions run the risk of being the object of an internal audit by an external regulatory body.

A healthcare institution is therefore entirely justified to take appropriate measures to prevent and detect cases of fraud or scientific misconduct with respect to research activities it carries out, without engaging in a unwarranted witch hunt. Furthermore, the responsibility that a healthcare institution has in this matter does not undermine the legitimate interests that other persons or organizations such as the university may have in investigating instances of scientific misconduct.

It is therefore appropriate to examine the measures which a healthcare institution should adopt to exercise its responsibilities.

## **1. THE DENUNCIATION OF MISCONDUCT**

As a general rule, if the evaluation and follow-up mechanisms operate adequately within the healthcare institution, it should be simple to detect cases of scientific misconduct. Cases of fabrication or falsification of data should, in principle, be uncovered, as well as such irregularities as tampering with a patient's signature or modifying a date.

However, in some cases, it may be difficult to identify certain instances of scientific misconduct, such as exposing a patient to undue risk, or obtaining consent by way of pressure or fraud. In the absence of appropriate evaluation and follow-up mechanisms, the denunciation or exposure of scientific or professional misconduct becomes the only method of dealing appropriately with such conduct.

It must be noted that for the person denouncing a case of scientific misconduct, such denunciation may carry dire consequences. Apart from the fact that the person's identity might eventually be exposed, - notwithstanding the confidentiality that should be maintained during an investigation of alleged misconduct -, the denunciation of irregularities committed in the course of a research project may lead to the abrupt interruption of the research project and the termination of that person's employment. It is therefore not surprising that so few cases of denunciation come to light.

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<sup>74</sup>Medical Research Council of Canada, Council of Research in Natural Science and Engineering in Canada, Council of Research in Social Science of Canada. *The Integrity of Research in Academic Work*, 1994.

In addition, caution must be taken when dealing with an allegation of scientific misconduct. Even when a denunciation is made in good faith, one cannot exclude the fact that such denunciation may be motivated by less than noble reasons.

Furthermore, the initiator of a denunciation may wish to preserve his anonymity. Anonymous denunciations cannot be ignored for they may be well founded or raise serious doubts as to the conduct of a research project. However, one must be aware of the fact that this type of denunciation often may be motivated by jealousy or unruly competition. The situation created by these denunciations is sensitive, and appropriate control mechanisms must be put into place to handle them.

## 2.

### **THE INVESTIGATIONAL STRUCTURE**

At present, neither the *Medical Research Council of Canada* nor the *Fonds de la recherche en santé du Québec* have formal mechanisms for investigating cases of fraud or scientific misconduct. These bodies rely on local structures to handle these problems. The only means at their disposal is to suspend the funding of research activities which are not conducted according to approved practices.

#### Recommendation no 55

*In the opinion of the Committee, the "Fonds de recherche en santé du Québec" (FRSQ) ought to be given the power to investigate, together with local authorities, all cases of scientific misconduct related to research activities which it funds.*

FRSQ's  
powers to  
investigate  
scientific  
misconduct

Furthermore, it appears from the responses to the committee's questionnaire sent to different healthcare institutions, that in nine institutions out of the sixteen surveyed, there was an absence of regulations, policies or directives governing scientific misconduct. In four of the sixteen institutions where such regulations, policies or directives existed, these had been enacted by the Board of Directors or the Research Center.

#### Recommendation no 56

*In the opinion of the Committee, healthcare institutions hosting research activities ought to implement a mechanism that will allow a person witnessing scientific misconduct to report it to a body entrusted with the power to investigate such misconduct and take proper action.*

The witnessing of scientific misconduct

Initiation of protective action by an investigative authority

This recommendation is similar to that expressed by the *Medical Research Council of Canada*, the *Natural Sciences and Engineering Research Council of Canada*, and the *Social Science and Humanities Research Council of Canada* which considers that "the responsibility to investigate allegations of misconduct by investigators, trainees or research personnel who receive funds from these organizations is incumbent upon the research institutions."<sup>75</sup>

### 3.

### **THE INVESTIGATION PROCESS**

When investigating an allegation of scientific misconduct, care must be taken not to tarnish the reputation of the person suspected of wrong-doing not to unnecessarily harm a career. The person is entitled to a fair hearing within a formal and confidential structure that will allow him to exonerate himself. As emphasized by the three Councils, one must remember that "all research can give rise to errors committed in good faith, to contradictory data, or to acceptable discrepancies in experimental protocol or in the interpretation of data."<sup>76</sup>

In addition, those in charge of investigating a case of scientific misconduct must identify the basis of the misconduct: is it an issue related to the scientific integrity of the project or to the conduct of the investigator towards another person? Furthermore, it is essential that in the course of the investigation the person suspected of wrong-doing be judged according to precise standards so as to be able to establish if he deviated from these standards. It is therefore important to clearly identify these standards.

In any case, one must be aware of the fact that there is a strong possibility that the investigation process will rapidly become judicialized due to the presence of attorneys responsible for ensuring that the professional accused of scientific misconduct is provided a full and complete defense.

### 4.

### **THE MODALITIES OF IMPLEMENTATION**

Depending on the volume of research activities carried on in a healthcare institution, one or more persons may be designated to whom an allegation of scientific misconduct can be reported. It is the responsibility of the Board of Directors of that healthcare institution to determine the role these people will play once informed of an allegation of scientific misconduct.

Recommendation no **57**

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<sup>75</sup>Medical Research Council of Canada, Council of Research in Natural Science and Engineering of Canada, Council of Research in Social Science in Canada. The Integrity of Research in Academic Work, 1994, op. cit., note 79, p. 2

<sup>76</sup>Idem, p. 1.

*In the opinion of the Committee, Boards of Directors of healthcare institutions must adopt specific regulations that deal with scientific misconduct following consultations with the Assembly of Investigators, where one exists, or the Research Director or the Research Center Director.*

Regulations dealing with scientific misconduct cases

Given that it is difficult for a healthcare professional to take the initiative of denouncing a colleague who may have acted inappropriately while conducting a research project, it is important to ensure the confidentiality of the examination process in cases of scientific misconduct.

Structures that truly ensure confidentiality will help protect an individual's reputation without paralyzing the examination process. A discreet internal inquiry revealing a real problem must lead to a larger investigation which should be conducted by peers from outside the particular institution.

Organizations supporting or financing research projects or research centers have an interest in being informed of any case of scientific misconduct arising out of activities which they support. Similarly, if the investigator holds a university appointment, it is appropriate for the university to be informed of any proven case of scientific misconduct involving one of its members.

In view of the multiplicity of bodies likely to have a legitimate interest in the investigation of a case of scientific misconduct, there is a danger of having multiple simultaneous investigations and there is a need to coordinate actions taken in this respect.

### Recommendation no 58

*In the opinion of the Committee, inquiries into scientific misconduct should be coordinated within a healthcare institution and the proper authorities should be able to apply appropriate sanctions in accordance with the existing administrative and disciplinary structures.*

Coordination of inquiries into scientific misconduct

**CHAPTER 5**

**THE BASIC PRINCIPLES**

**AND THE PROPOSED ACTIONS**

## Chapter 5 - THE BASIC PRINCIPLES AND THE PROPOSED ACTIONS

Having completed the analysis and evaluation of the current situation, it became obvious to the Committee members that it would not be enough to identify the evaluation mechanisms needed to effectively attain the objectives guaranteeing that research activities carried out in Quebec are of high quality, and that those who participate in research projects are well protected in all aspects of their being. It appears equally important to restate the principles which must guide the conduct of research activities and to develop concrete propositions that would help the scientific community and the healthcare sector to fulfill their responsibilities more efficiently in the field of biomedical research.

With respect to the guiding principles, the Committee members chose to highlight those which will promote an environment capable of ensuring the progress of knowledge and the protection of human beings. As for the actions that need to be taken, the Committee members propose various measures likely to guarantee the quality of research activities carried out in Quebec and the reliability of implemented control mechanisms.

### A.

### THE BASIC PRINCIPLES

As previously seen, clinical research is not scientifically valid unless it leads to a real increase in knowledge, oriented towards the improvement of a population's state of health. For this to occur, research must be carried out according to research protocols meant to enhance scientific knowledge. To ensure the validity of research results, research activities must be conducted according to the research protocol. Such conduct is also required to ensure the safety of persons participating in a research project.

But conducting research activities according to a research protocol is not enough. In addition, in order to be ethically acceptable, those conducting research must show a deep respect for the individuals who have agreed to be part of a research project.<sup>77</sup> This respect is necessary to prevent clinical research from transforming into an area where altruistic people are exploited by those motivated by fame and fortune. This respect for mankind is also necessary to preserve the dignity and protect the privacy of human research subjects. But it is not enough to show respect for people who participate in research projects. Clinical research must respect societal norms which identify the limits within which research must be carried out to remain acceptable in the eyes of the community. The standards reflect the values which have served to define the operating structures of healthcare research and outline the framework within which research must evolve and which it must not exceed without losing its legitimacy.

#### 1.

#### THE RESPECT OF RESEARCH PROTOCOLS

Research which is not scientifically valid is unacceptable. Therefore research cannot be undertaken unless it has a real scientific interest oriented towards the advancement of knowledge and the improvement of the quality of human life. It is important that a research

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<sup>77</sup>See, for this, Medical Research Council of Canada, *The Ethics of Experimentation on Human Subjects*, 1978, op. cit., note 18, p. 11.

protocol be conceived at the outset so that the design and methodology will promote the attainment of the proposed objective.

The observance of the scientific design is necessary to allow the validation or invalidation of the research hypothesis. Furthermore, the acquisition of new knowledge is only possible if the data generated in the course of a research project is of high quality.

#### a) **The Observance of the Scientific Design**

The research design is the cornerstone of any research protocol. In every clinical trial, one expects the investigator to scrupulously follow the content of the research protocol once it has been accepted and approved by the appropriate bodies. The observance of the research protocol is required to ensure the validity of the results and conclusions drawn from a research project. An investigator cannot take liberties with respect to a research design once approved.

The investigator who does not follow the requirements of a research protocol threatens the safety of those people who participate in a research project. The preservation of a research subject's integrity and safety must override an investigator's desire to complete his project at all costs. The investigator who does not follow the research design also runs the risk of facing administrative sanctions (freezing of funds), civil actions (civil liability suits) and criminal proceedings (fines and imprisonment).

The observance for the research design requires amongst other things:

1. that the investigator who thinks that modifications should be brought to a research design bring the matter up with those responsible for the design so that changes can be made and approved;
2. that the principal investigator of a research project inform the various entities responsible for the approval of the project, particularly the Research Ethics Committee, of any changes brought to the project and get approval before making the changes.

#### b) **The Quality of Data**

The data generated in the course of a research project constitutes the foundation upon which conclusions will eventually be drawn. The production of data of poor quality, whether incomplete or inaccurate, can lead to results that are inconclusive or false. It can also cause a waste of funds allocated for carrying out the research activity.

The investigator who deliberately and knowingly fabricates or falsifies data brings immense harm to the research and the scientific community. Undeniably, his contribution to the increase of knowledge and progress of science is compromised; the trust of those people who agreed to participate in the research project, and whose participation now appears to have been useless, is betrayed.

The gathering of sound data requires amongst other things:

1. that the investigator does everything possible to ensure that the data obtained is accurate and complete, and thus trustworthy;

2. that the investigator does not affect the validity of the data generated in the course of a research project by manipulating, falsifying or fabricating it;
3. that the investigator conforms to the establishment's policies pertaining to the safe-keeping of raw data generated in the course of a research activity;
4. that the investigator ascertain the accuracy of results obtained before they are published.

## 2. **RESPECT FOR RESEARCH SUBJECTS**

To respect research subjects generally implies the protection of their dignity and the adhesion to such values as self-determination, justice and consideration for others. With regard to clinical research, respect for research subjects implies preservation of their freedom to participate in a research project, the safeguarding of their integrity, and the protection of their privacy.

It must be acknowledged that the respect for research subjects may constitute an obstacle to the carrying out of certain research protocols. It can in certain cases constrain an investigator's ability to further develop research observations.

### a) **Preservation of Freedom of Choice**

In principle, an individual is free to participate or not in a research project. An individual is also free to withdraw at any time from a research project without justification. The freedom that a research subject enjoys is directly related to the information given by the research investigator.

The investigator seeking to obtain the participation of a person in a research project may be tempted to not reveal all that is known about the research project or hide certain information which if known, could lead the person to refuse to participate. It is imperative that the person solicited to participate in a research project be fully informed of what his participation entails.

The respect for the freedom of choice of research subjects requires, in particular:

1. that the investigator personally inform the person solicited to participate of the nature and objectives of the research project as well as of all that the project involves in relation to the study design, notably the examinations, tests and interventions which the person must undergo as well as the discomforts associated with them;
2. that the investigator inform the person solicited to participate of all the risks to life and health that the research project entails;
3. that the investigator allow the person solicited to participate a reasonable amount of time to understand the information contained in the consent form;
4. that the investigator or a member of the research staff should not exert undue pressure or make any misrepresentation to a prospective research subject or their legal representative in order to obtain their consent;

5. that whatever the circumstances, the investigator or a member of his research personnel should never hide information which if brought to the attention of the prospective research subject, would make the latter hesitate in giving consent or perhaps even refuse to participate.

The respect for the freedom of choice of research subjects requires in addition:

1. that the Research Ethics Board ensure that all pertinent information appear on the consent form given to the person asked to participate in a research project, or to his legal representative;
2. that the Research Ethics Board verify the conditions under which the consent of a research subject was obtained;
3. that the Research Ethics Board be informed of how the recruitment of research subjects will be undertaken;
4. that the research subject be informed of his right to withdraw at all times from the research project in which he is participating without any repercussions to the care which might ultimately be required.

**b) Protection of a Research Subject's Integrity**

In agreeing to participate in a research project, a research subject accepts in good faith the risk of experiencing more or less serious complications, as well as certain discomforts and inconveniences, without being assured of drawing any direct benefits from his participation in the research project.

Constant assurance of the safety of those who agree to participate in a research project must constitute the major concern of the organization financially supporting the research project, of the healthcare institution where the research is carried out as well as the investigator conducting the research project. The successful realization of a research project must never be achieved at the expense of the safety of research subjects. The desire to prove a research hypothesis whatever the cost must never prevail over the safety of a research subject. An investigator must not become overzealous or obsessively driven so as to jeopardize the health or life of a research subject.

Equally, the enthusiasm and optimism which may surround a research project must not cause an investigator to expose a research subject to undue risk, or lead a sponsor to conceal risks which need to be known to the investigator and the research subject so as to ensure the safety of the latter.

The safety of the research subject requires:

1. the the investigator inform the research subject of the symptoms which require attention and which could indicate complications arising from participation in the research project;

2. that the investigator or a member of the research staff should give the research subject a card indicating the research project's title, the investigator's identity, the research project's identification number and the telephone number of the person to be reached in case a problem should arise;
3. that the investigator or a member of the research staff must not cause undue risk to the person who participates in a research project;<sup>78</sup>
4. that the investigator must follow the evolution of the research subject's state of health in order to identify any undesirable effect associated with the study design;
5. that the investigator or the Research Ethics Board must interrupt a research project when it appears to be causing more harm than good.

The safety of research subjects further requires:

1. that the Research Ethics Board be informed as soon as possible of every adverse event which may arise in the course of a research project;
2. the Research Ethics Board should be informed immediately when a research project is interrupted for any reason whatsoever;
3. that the healthcare institution maintain a register of research projects as well as a register of research subjects which specifies the type of drug administered to a research subject part of a research project;
4. that the healthcare institution ensure that the consent form signed by the principal investigator is inserted in the research subject's medical record;
5. that a research subject's medical record specify the research project he is enrolled in and the method of gathering the data.

**c) Protection of privacy**

It is necessary to give a research subject every possible guarantee that their privacy will be protected<sup>79</sup> and that the data gathered will remain confidential. However, in no case, as emphasized by the *Medical Research Council of Canada* in its Guidelines, should one promise more than can be guaranteed.<sup>80</sup>

It would be inappropriate for a Research Ethics Board to approve a clause in a consent form stating that an organization will maintain confidential the information obtained on a person, without the assurance of such an undertaking.

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<sup>78</sup>See, for this, Medical Research Council of Canada, Guidelines on Research on Human Subjects, 1987, op. cit., note 2, p. 15 and The Ethics of Experimentation on Humans, 1978, op. cit., note 18, p. 16. See also The Helsinki Declaration, I. Basic Principles, Art. 4.

<sup>79</sup>Helsinki Declaration, art. 6.

<sup>80</sup>Medical Research Council of Canada, Guidelines Concerning Research on Human Subjects, 1987, op. cit., note 2, pp. 39-40.

The respect for a person's privacy requires, in particular:

1. that the research subject be clearly informed that a research record, separate from his hospital record, will be created, and that third parties may have access to this record without the knowledge of the subject;
2. that the research subject be clearly informed of the identity of those persons or bodies such as pharmaceutical and insurance companies, likely to have access to the research record;
3. that the research subject be clearly informed of the existence of any computerized database containing information gathered in the course of the research project which relates to the subject;
4. that the research subject be clearly informed of the information concerning him or her which may be sent to third parties, of the identity of these third parties as well as of the format, nominative or anonymous, of the transmitted data;
5. that the research subject be clearly informed of the possibility that those to whom nominative information is sent may create a file on him.

The respect for a person's privacy further requires:

1. that a Research Ethics Board verify with the bodies to whom nominative or any other type of information may be sent, of the use they intend to make of this information as well as of the possibility that the information may become part of a data bank;
2. that an establishment enact a policy on the content, management and storage of research records;
3. that an establishment ensure the confidentiality of the data gathered in the course of a research project;
4. that a healthcare institution require that every investigator declare to the person responsible for research activities within the healthcare institution the existence of any computerized data bank created in the course of a research project.

### 3. **THE RESPECT FOR EXISTING STANDARDS**

Clinical research is governed by a set of specific regulations and general principles contained in various texts which take the form of codes, declarations, and guidelines. Documents of particular significance are the Nuremberg Code, the Helsinki Declaration and the Guidelines of the Medical Research Council of Canada.

The regulations and principles contained in these documents are directly related to the standards of good practice in the field of biomedical research. These principles and regulations define the conditions according to which a research project can be considered acceptable, taking into account the existing scientific, ethical, and legal requirements.

Over and above these requirements, biomedical research is also governed by various laws and regulations which define those rules that must be observed to avoid acting illegally or illicitly. It is essential that the research personnel and not only the principal investigator be made aware of the general principles and of the legal and regulatory provisions which govern the participation of individuals in research projects.

The observance of established standards in the area of biomedical research requires:

1. that the principal investigator and the research personnel be aware of the standards governing good clinical practices and good laboratory practices;
2. that the investigator be aware of the ethical rules which govern scientific conduct in clinical research;
3. that the investigator be aware of the legal and regulatory provisions which govern the research activities which he undertakes.

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**B. THE SHARING OF RESPONSIBILITY**

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Prior to formulating recommendations for concrete action to ensure the quality and integrity of clinical research activities, as well as the respect and protection of research subjects, it is necessary to look at the responsibilities which fall upon the various actors in the field of biomedical research: (1) healthcare professionals, (2) healthcare institutions, and (3) bodies financially supporting research activities.

**1. HEALTHCARE PROFESSIONALS**

The responsibility associated with clinical research activities carried out in a given area depends first and foremost on the investigator and, by extension, on the research staff.<sup>81</sup>

The responsibility of each and every member of the project must be exercised on different levels: ensuring the safety of research personnel and research subjects; concern for the confidentiality, the quality and accuracy of data and of its interpretation; conformity to the protocol; publication of research results according to accepted standards.

The responsibility for clinical acts performed in the course of a research project falls at all times upon the treating physician, as well as on the other healthcare professionals. In cases where the treating physician is not the investigator, it is important that the treating physician fully assume his or her responsibilities with respect to patients who have agreed to participate in a research project.

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<sup>81</sup>See, in this regard, Medical Research Council of Canada, *The Ethics of Experimentation on Human*, 1978, op. cit., note 18. p. 35.

**2.**

**HEALTHCARE INSTITUTIONS**

Even though it is true that the investigator is responsible to the organization which financially supports the research activities for the quality and integrity of his research, it is nonetheless the obligation of the healthcare institution in which research projects are carried out to see that the research projects meet accepted standards governing biomedical research and that investigators comply with the regulations in force.<sup>82</sup>

The Committee members agree with the observations made by the authors of the 1978 document entitled The Ethics of Experimentation on Humans, that "...the best way to achieve high ethical standards is to leave the primary responsibility for these to healthcare institutions and to ensure that all those involved in research activities and in patient care are aware of the moral aspects of research involving human beings".<sup>83</sup>

This attitude is the only one which can really maintain the reputation of the healthcare institution and ensure the protection of patients recruited for different research projects. In the same way that investigators accept quality controls imposed upon them regularly by funding organizations, so must they accept institutional integrity controls.

In this context, the Board of Directors of a healthcare institution must take measures to ensure not only that research activities carried out in the establishment are well managed, but also that the safety of those who participate in research projects is well assured. Boards must put into place appropriate mechanisms in order to verify these elements at every stage of a research project.

A Board of Directors acts irresponsibly if it does not feel concerned by the research activities carried out within the establishment, and if it does not assume its responsibilities in this matter. Situations such as those brought to the attention of the Committee - where hospital administrators are unaware of the research process within their institution because those responsibilities have been delegated elsewhere - cannot be tolerated.

Mechanisms that have been put in place to ensure the quality and integrity of research activities, as well as the protection and respect of those who have agreed to participate in these research projects, must be known to be functioning adequately.

In every healthcare institution, it is the responsibility of senior management to assert that the resources of the establishment are neither used in an improper fashion in the conduct of research activities nor that they compromise the ordinary healthcare activities.

**3.**

**FUNDING AGENCIES**

In addition to the local bodies, it is incumbent on those bodies which financially support clinical research (industry, private foundations, governmental organizations) to ensure that the research protocol is adequate and safe and that the environment needed to induce good clinical practice exists with respect to the clinical research activities that they fund.

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<sup>82</sup>See, for this, Medical Research Council of Canada, The Ethics of Experimentation on Humans, 1978, op. cit., note 18, p. 14.

<sup>83</sup>Ibid.

Funding agencies must see to it that the appropriate verification mechanisms exist, and that they function efficiently with respect to the compliance of investigators to the requirements of research protocols.

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**C.**

**RECOMMENDATIONS**

In addition to providing an overview of the general principles that should apply in the field of biomedical research and identifying the responsibilities incumbent on those involved in research, the Committee members felt compelled to formulate concrete recommendations with regard to the organization and evaluation of research activities conducted in Quebec.

These recommendations should assist in achieving the two objectives pursued in clinical research, those of ensuring the quality and integrity of research activities and guaranteeing the respect and protection of those who agree to participate in a research project.

On the basis of these premises, the Committee members have conceived two sets of recommendations. First, the Committee members contend that healthcare institutions should adopt a regulatory framework to define the expectations and requirements concerning the evaluation and conduct of research activities. Secondly, the Committee members suggest that it is appropriate to develop a permanent structure to oversee and monitor the evaluation mechanisms pertaining to clinical research activities in healthcare institutions.

**1.**

**A REGULATORY FRAMEWORK**

Concerning the regulatory framework, it seems necessary to the Committee members for one to exist in each healthcare institution where research activities are carried out. The milieus consulted clearly recognized that, despite the existing evaluation structures, these have not been as effective as they should have been, and that there is a need to improve the controls without at the same time increasing the burdens.

By assisting healthcare institutions in developing a regulatory framework appropriate for the carrying out of clinical research activities in a transparent and coherent manner, the Committee members suggest that better protection can be extended to research subjects, and that the integrity of research activities can be better guaranteed.

The regulatory framework recommended for healthcare institutions where research activities are conducted, aims primarily at helping them to voluntarily develop evaluation mechanisms and operating mechanisms which will allow them to fully carry out their responsibilities.

The measures contained in the following regulatory framework can be adapted, completed and modified according to the needs and the specialties of each healthcare institution. They have the merit of presenting concretely certain actions specific to clinical research and to demystify poorly understood processes.

## Model of a Regulatory Framework

### Preamble

The healthcare institution where research activities are carried out is the principal body responsible for the organization and evaluation of research activities being carried out within.

In this respect, it is the responsibility of the Board of Directors of an institution to define in an appropriate regulatory framework, the conditions for conducting quality research activities, as well as the process of evaluation required to ensure its integrity.

### Chapter 1. Research Activities

1. A person responsible for research activities should be designated in all healthcare institutions where research activities are carried out.
2. All research activities which are carried out in a healthcare institution must meet the requirements of the present regulatory framework.
3. Research activities which originate outside a healthcare institution but which use the establishment's facilities or call upon people receiving care from the establishment, are subject to the control of the establishment.
4. In every health care establishment where research activities are carried out, an annual report on the evaluation, status and follow-up of research projects must be submitted to the Board of Directors. This report must specifically mention the nature of the research activities, listing them by categories of activities.
5. No research activity can be undertaken unless it is supported by a research protocol which defines specifically the project's objectives, the hypotheses to be proven, the procedures to be followed and the tests and statistical analyses to be done, as well as the identity of the research personnel.
6. A research protocol must state the inclusion and exclusion criteria, those for stopping the project, the risks and the side-effects to which a research subject could be exposed, as well as the examinations and the interventions which the research subject will be asked to undergo.

### Section A. Research Projects

7. Every research project must be evaluated by the institution where it is to be carried out, even if has been the object of a previous external evaluation, such that by a university or another institution.
8. No research project can begin without having successfully undergone the three evaluation processes hereafter prescribed, these being a financial, a scientific and an ethical evaluation, and without a written attestation to this effect being signed by the person responsible for research activities or the person who has been so designated.

9. Every clinical research project must be submitted to the head of the department concerned, before submission to the different bodies responsible for its evaluation.
10. The approval of a research project is not valid for a period of more than three years. A research project must be re-submitted in totality for approval at the end of three year period or whenever a significant complication arises, depending on which occurs first.
11. Any modification to the research protocol must be submitted to the bodies responsible for the scientific and financial evaluation of the research project, as well as to the Research Ethics Board for approval.
12. A register of research projects must be set up in each institution where research activities are carried out. This register must contain the following items: the project's title, the project's number, the principal investigator's name, the date of approval of the project, the date the project starts, the date the project ends, the total budget approved and the source of financing.

## Section B. Research Personnel

13. A research activity must be carried out under the responsibility of individuals accredited by the healthcare institution to carry out research activities and who have received the proper training.
14. The individuals who are involved in carrying out a research project, whatever their role, must be led by competent individuals, capable of passing adequate judgment on the conformity of research projects to established standards.
15. The responsibilities assumed by an investigator must be congruent with the investigator's training. They must be in accord with the type of activities of the research project with which the investigator is associated. It is the responsibility of the person responsible for overseeing research activities to verify conformity to this.
16. An investigator must declare annually, using the appropriate form, to the person responsible for overseeing research activities any association, whether as stockholder, consultant, or other, with a sponsor. The research ethics committee must have access to this information.
17. Every investigator must present an annual report on his clinical research activities in which he describes the status of each of his research project. This report must be accessible to those in charge of the scientific and ethical evaluation of research projects.
18. In the course of a clinical trial, a person may never receive payment for the recruitment of research subjects, nor receive a finder's fees.

## Section C. Research contracts

19. Every research contract must respect the standards contained in the the Ministry of Health and Social Services' circular concerning research contracts.
20. Every research contract must state the totality of the monies offered to the investigator, the institution or the patient, detail the sums contained in the contract as well as the costs of each of the examinations, tests, or interventions required by the research protocol.
21. The financial content of a research contract must be completely reviewed by the bodies responsible for evaluation before it can be signed by the sponsor.
22. A research contract cannot be signed between a sponsor, an establishment, and an investigator before those persons responsible for the scientific, financial, and ethical evaluations have provided an attestation of conformity to all requirements.
23. Research activities financed by a sponsor cannot lead to direct payment of an investigator if the investigator is also the treating physician of the person who agrees to participate in a research project.

## Section D. Research Subjects

24. Each institution where research activities are carried out must maintain a register of research subjects, which contains the name of the research subject, the identifying number of the research project to which he has given his consent, and the name of the investigator.
25. The person who has given consent to a research project must be given a card which contains the name, in both long and shortened form, of the research project, the name of the principal investigator, the telephone number to dial 24 hours a day in case of a problem.
26. When a research project uses experimental medication, the telephone number of the pharmacy must also appear on the card given to the subject.
27. Only people who have freely and in a well-informed manner agreed to participate in a research project can be enrolled in the research project.
28. A person who is asked to participate in a research project must be allowed sufficient time to decide if he will or will not participate in a reserach project.
29. The person asked to participate in a research project can require that the relevant information be directly provided by the investigator who is responsible for the conduct of the research project and not only from a member of the research personnel or staff.
30. The person asked to participate in a research project has the right to ask all relevant questions as concerns the carrying out of the research project, notably as concerns the duration of the project, the number of visits required, the tests and examinations which must be undergone and the risks of side-effects which he may experience.

31. The person who is asked to participate in a research project must be informed of his right to withdraw at all times from the research project without giving motives and without having ill effects of any kind.
32. In the case of a minor or of an incompetent adult, the consent of the holder of parental authority, tutor, curator, mandatory or of a recognized third party is required before the minor or the incompetent adult can be enrolled in a research project.
33. A person cannot participate simultaneously in more than one clinical research project of the same type, unless his participation involves only a simple collection of data for research purposes.
34. The information form given to a research subject must contain a clause indicating whether the sponsor has agreed or not to compensate the research subject in the event of an undesirable complication, specifically to offset the cost of health care within the care covered by the health insurance Régie which comes from an undesirable event.

## Section E. Research Funds

36. The funds allocated to a clinical research project must be used in conformity with the budget as presented and accepted by the body responsible for the financial evaluation of the projet. A change of more than 20% in the use of funds cannot be undertaken, except with the agreement of the Director of research, or of the Director of the research center, or his representative, as well as the person responsible for financial evaluation.
37. The funds allocated to a research project which is carried out at the level of a health care establishment must be managed by the health care establishment, or, eventually, or by the university with which it is affiliated. They cannot be administered by a private financial institution outside of the institution.
38. The person responsible for research has the authority to freeze the funds of an investigator when he has not respected the standards of the institution concerning the carrying out of research projects.
39. The payment of the investigator for clinical acts carried out in the course of a clinical research project must be funded by the research project. There cannot be parallel payment or additional payment.
40. In the case of research projects financed by a developer, the cost of clinical acts essential for proving the hypothesis of the project and required by the protocol, must be paid for by the research project.

## Chapter 2. Evaluation Mechanisms

41. The evaluation process must be made up of three distinct aspects, one scientific, one financial, and one ethical. In institutions where the volume of research activity is low, a single body can carry the three required evaluations. In others, the evaluation of the three aspects must involve three different bodies.
42. The process of evaluation must be known to investigators and regularly explained to personnel involved in the various research projects.

43. The Board of Directors of an institution must provide the human and financial resources necessary for the proper functioning of the evaluation process and the follow-up of the research project. It can, to this end, decree that a part of the 18% tax on research contracts be used to offset the cost of evaluation activities.
44. The evaluation activities for research projects must be managed by competent people, capable of passing an adequate judgment on the conformity of research projects to established standards.
45. The evaluation of a research project must include the use of evaluators from outside the establishment each time that the required expertise to carry out the evaluation is not available within the establishment.
46. The evaluation structure must permit the optimal evaluation of research projects, while avoiding an excessive bureaucratic burden and an undue delay in approvals. It is desirable to create sub-committees related to each of the evaluations areas or with respect to the different types of research activities.
47. All persons who participate in the evaluation process must declare annually in writing to the person responsible for research, using an appropriate form, all associations such as stockholder, consultant or other, with a developer. The Research Ethics Committee must have access to this information.
48. An investigator must abstain from participating in the decision of a body which evaluates a research project in which he participates in any manner whatsoever. He may, however, be himself called upon to present his research project to the body responsible for evaluation.
49. Detailed minutes of the discussions and recommendations related to the evaluation of a research project must be prepared after each evaluation meeting. The minutes must be saved by the secretary of the research.
50. A copy of all minutes must be sent to the president of each of the committees, as well as the person responsible for research in the establishment.
51. The people who participate in the evaluation of a research project must attend educational activities appropriate for the carrying out of their activities.

### **Section A. Scientific Evaluation**

52. Each research project carried out in a healthcare institution, as well as each research activity carried out within the framework of a research project, must be submitted for scientific evaluation.
53. Scientists from outside the institution must be involved in the scientific evaluation of a project in order to maximize the openness and minimize potential conflicts of interests.
54. A research project submitted for scientific evaluation must contain the necessary information for the people who make the evaluation to appreciate adequately the content and scientific value of the project, as well as its pertinence.

55. All research projects that do not lead to a valuable progress of knowledge must be considered unapprovable.
56. The people who participate in the scientific evaluation of a project must receive before the meeting the pertinent documentation for the evaluation of the project.
57. The number of research projects examined during one meeting for evaluation cannot be incompatible with careful work.
58. Those responsible for research activities in the establishment may never act as president of the scientific committee.
59. Research projects to be carried on incompetent adults or on minors, must be submitted to a scientific evaluation outside the institution by an expert in the area in which the research is based.

## Section B. Financial Evaluation

60. A financial evaluation must be made for each research project that is carried in the health care establishment.
61. Representatives of the administration, of directors concerned with the project (nursing, pharmacy, laboratories) and representatives of the research group must participate in the financial evaluation of a research project.
62. The financial evaluation must include identification of direct and indirect costs which make up the carrying out of the research project, so that the cost will not encroach invisibly upon the establishment budget.
63. The persons who participate in the financial evaluation must ensure that the institution recovers all the costs attached to carrying out a research project. If these costs cannot be well identified, a sum of money representing 1% to 10% of the project can be allocated to the benefit of the institution.

## Section C. Ethical Evaluation

64. A Research Ethics Board must be established in every institutions where research activities are carried out.
65. Sub-committees of evaluation reporting to the research ethics committee can be established when the volume or the diversity of types of research activities justify it.
66. The committee must be made up of representatives from patients, from people who have knowledge of law and of ethics, from various professional disciplines, as well as scientists able to explain the deliberations of the scientific committee and to clarify to the committee possible hidden aspects.
67. In institutions with a university affiliation, a university representative must sit on the committee. The presence of a member of the Board of Directors is highly encouraged.
68. The participation of people from outside the establishment is desirable in a ratio of 40% as a minimum.

69. The members of the research ethics committee must declare in writing to the president of the committee their affiliation or business connections with a person or a business likely to place them in a conflict of interest situation.
70. The director general, the director of professional services, and the director of the research center may not act as president of the research ethics committee.
71. Members of the research ethics committee must be present at 60% or more at the meetings of the ethics committee in the course of a given year, or lose their status as Committee members.
72. No meeting of the research ethics committee can be held unless there are at least two members present from outside the institution.
73. The committee must have knowledge of the scientific and financial evaluations during its deliberation. During the evaluation of a project, they must also have in hand a copy of the research protocol, or a fully-detailed summary, as well as a copy of the consent form or of the information bulletin. They must have a copy of the minutes of the scientific and financial evaluations.
74. The research ethics committee must have access to the research contract entered into between the institution, an investigator and the developer.
75. In the case of multi-center research, the committee must review in detail the proposed protocol, whether it has already been reviewed and accepted or not at other institutions.
76. In the case of a multi-center research, the investigator must attest to the ethics committee that no increased risk of mortality or morbidity has been detected, neither in the local population nor in the population at large who have participated in the project of research.
77. When a project is refused, the reasons for the refusal must be given to the investigator as well as to the person responsible for research activities.
78. The members of the research ethics committee must receive sufficient education to allow them to fully carry out their duties and this in a continuous manner.
79. The members of the research ethics committee from outside the institution can be paid for the services which they perform beyond that of their participation at the meetings of the ethics committee.
80. In order to improve and speed up the work of the ethics committee, it should be able to rely on the services of a qualified person whom an investigator can consult before presenting the research projects to the ethics committee. As well, this person can function to verify if all the necessary pieces of information for the evaluation of the research project are in the research dossier and if the information bulletin fulfills the requirements of the establishment. He can at the same time take over certain responsibilities for the follow-up.

## Section D. Follow-up

81. The ethics committee must identify the requirements for follow-up., especially as concerns the frequency of reports and the disclosures of undesirable side-effects.

82. When the volume of research activities justifies it, one or more persons can be designated to ensure the follow-up of research projects, specifically to ensure the quality of the research acts and their conformity with the decisions arising from the evaluations of the ethics, the financial evaluation, as well as regarding the overall respect of the research protocol.
83. The information bulletin must contain a clause by virtue of which the research subject accepts for a given period of time that a person who is mandated to ensure the follow-up will have access to his research record to verify if the investigator has conformed to the requirements established during the scientific evaluation and the ethical evaluation.
84. The person responsible for follow-up, must, through sampling, verify the carrying out of research projects, the quality of the process for obtaining and documenting data, as well as the quality of informed consent and the nature of the side-effects that happened to the persons participating in the research projects.
85. The research ethics committee must be informed, as soon as possible, of all possible major complications which arise in the course of a research project. The committee can request that the research project be examined anew.
86. The research ethics committee must receive from the investigator an annual report indicating to them what has occurred in the research project.

### **Chapter 3. Scientific Misconduct**

87. Each institution where research activities are carried out must have a policy on scientific misconduct. This policy must include the creation of a committee made up of one or more persons from outside the institution who are responsible for investigating all allegations of scientific misconduct.
88. The president of the committee must proceed in a preliminary and confidential manner, to a summary investigation of all allegations of scientific misconduct, of whatever nature they may be, which occur in relation with research activities of a member of the personnel of the institution. If the accusations seem to be at least partially justified, the president must refer the case to the committee.
89. If the committee judges that the allegation of scientific misconduct is well founded, it must immediately inform the authorities of the institution as well as the organizations which may be concerned in the case, specifically the university or the organization which provided the grant or financed the research activity.
90. The director of professional services of the institution must see that all patients involved in a research project are rapidly informed of a project's halt for reason of scientific misconduct and offer them the necessary support to answer their questions.

### **Section B. Permanent provincial structure**

91. It appears from the various consultations which the Committee members held that the various milieus involved in clinical research were not opposed to the existence of a structure responsible to evaluate regularly the way in which institutions carry out their functions of evaluation of the different aspects of research projects.

92. Some consider that the existence of such a structure would have the effect of increasing the quality of the standards. They deem, furthermore, that it must have real power so that its recommendations can be followed. For others, such a structure can play a determining role, not only as concerns the evaluation of control mechanisms, but also in the education and training for research.

Recommendation no 59

*In the opinion of the Committee members, the Ministry of Health and Social Services ought to consider the creation of a permanent Quebec structure with its main mission being to regularly evaluate the way in which healthcare institutions carry out their research activities as well as fulfill their functions in relation to the evaluation of these activities.*

The creation of a permanent structure in Quebec

Recommendation no 60

*In the opinion of the Committee members, the creation of a permanent structure is an essential adjunct to a healthy functioning of local mechanisms of evaluation for clinical research activities.*

Role of a permanent governing structure in conjunction with local mechanisms of control

93. The permanent structure which is being considered can take various forms. One can imagine the creation of an evaluative council on the model of the Conseil d'Évaluation des nouvelles technologies. One can equally imagine the creation of a more modest structure, such as a permanent committee, which does not require legislation to set it up. It could be a structure which gives accreditation to institutions for carrying out research activities for a period of three to five years. This accreditation would be based on the presence of an adequate regulatory structure, on the evaluation activities and on the appropriate follow-ups

94. The Committee members considered the possibility to give these responsibilities to an already structure such as the Fonds de la recherche en santé du Québec, of following up the local mechanisms of evaluation of clinical research activities. In light of the consultations which were held by the Committee members, and the American experience in this matter, experience which suggests strongly that one should avoid having the evaluating organization subject to a financing organization in order to avoid, if not conflicts of interests, at least the appearance of conflict of interests, it seems necessary that the new structure be independent of organisms which provide grants for research.

95. The structure as conceived must be made of people representing the community as well as the scientific milieu. These persons would come from different milieus (research, medicine, nursing, ethics, law, finance, and the public). Furthermore the evaluation activities of the permanent committee could be managed by teams of accreditors made up mainly of active investigators who would be sent to evaluate research projects on site in the establishment

and to evaluate on site the existing mechanisms to ensure adequate follow-up of research activities, in particular the protection of persons who give their consent to a research project.

96. One could see, for example, a team of three persons (investigator, administrator, ethicist who have had practical experience in clinical research) to visit an institution in order to analyze the pertinence of its regulatory structure and to verify how the institution carries out its responsibilities for the evaluation and follow-up of research projects.
97. The evaluation by the members of the team must start from concrete recommendations as to the required infrastructure for the institutions to carry out its functions as well as to the ways the establishment should function in carrying out the various evaluations. The Committee could, on this occasion, issue a certificate of conformity, or non-conformity, with respect to preestablished criteria that have been judged essential to guarantee a proper evaluation of research activities.
98. The Committee members are aware that some people may question the need to create such a structure, given that on the national level, there exists already a National Council of Bioethics of Research on Human Subjects, set up through an agreement between the Medical Research Council of Canada, Health and Welfare of Canada, and the Royal College of Physicians and Surgeons of Canada.
99. This Council's primary function is to develop guidelines in research calling upon human subjects, to advise research ethics committees on various problems they encounter in clinical research and to sensitize the scientific community and the public at large to the issues of research using human subjects. Among the means that the Council uses to accomplish its mandate, one must underline the workshops bearing on certain specific aspects of clinical research, the visit to research ethics committees, and the publication of a communiqué which describes the activities of the Council.
100. The Committee members in no way question the existence of this Council and the importance of its activities. Nonetheless, the Committee members feel that it is important, in the course of putting into place a global strategy to improve clinical research in Quebec, that a Quebec structure, with evaluative powers and recommendation powers, reporting directly to the Ministry of Health and Social Services, be created so that they can really ensure, here in Quebec, that each and every investigator, institution and developer assume their responsibilities in order to ensure the appropriate carrying out and the proper evaluation of research activities.

## Section C. Supporting Interventions

At the end of this analysis, the Committee members deemed important to suggest certain actions that could be taken, starting right now, to ensure the maintenance of quality research activities in Quebec, as well as to guarantee the respect and protection of people who give their consent by identifying the organizations who should take these actions.

### ***THE MINISTRY OF HEALTH AND SOCIAL SERVICES***

In the opinion of the Committee, the Ministry of Health and Social Services must consider putting into place a committee responsible for the periodic evaluation of mechanisms put in place in health institutions to ensure the integrity of research and the protection and respect of persons, and to organize along with the universities, educational activities in ethics of research for the members of ethics committees.

In the opinion of the Committee members, the Ministry of Health and Social Services must, in the framework of regulation of health and social services, impose upon health institutions where research activity is carried out, the creation of a register of research projects, and a register of research subjects. Furthermore, the regulation adopted by virtue of the Law on the services of health and social services must require the adoption of a regulation governing research activities carried out within a health establishment.

### ***THE MINISTRY OF JUSTICE***

In the opinion of the Committee, the Ministry of Justice must review the actual regulations governing clinical research in Quebec, with a view to bring them up to date with current practices, all the while ensuring the respect of human subjects in all its dimensions.

### ***LE FONDS DE RECHERCHE EN SANTÉ DU QUEBEC***

In the opinion of the Committee members, the research personnel in institutions where research is carried out, whether or not there exists a center of research, must receive obligatory specific information as concerns laboratory practices and good clinical practices, given by people competent in this matter. In the opinion of the members of the Committee, the Fonds de recherche en santé du Québec should take a leadership role in this matter.

### ***HEALTHCARE INSTITUTIONS***

In the opinion of the members of the Committee, the Board of Directors of an institution where clinical research is carried out must adopt a regulatory structure outlining the conditions within which research must be carried out in the institution and describing the evaluation mechanisms for the scientific, ethical and scientific aspects of the research projects.

In the opinion of the Committee members, the Board of Directors of an institution must name a member to sit on the research ethics committee of the institution.

In the opinion of the Committee members, the Council of Physicians, Dentists and Pharmacists of an institution where research activities are carried out must ensure that the clinical acts accomplished on patients who participate in research projects are evaluated.

### ***THE UNIVERSITIES***

In the opinion of the Committee members, universities in Quebec must be invited to collaborate, along with the Quebec Hospital Association and the permanent structure envisaged in this report to give educational sessions to members of ethics committees on a regular basis in order to ensure that they are regularly exposed all the major issues pertinent to their functioning on a Research Ethics Committee.

In the opinion of the Committee members, the universities must ensure that the university curriculum in health sciences is open to the sensitization and education of students to the specific requirements of health research.

### ***THE PROFESSIONAL ORDERS***

In the opinion of the Committee members, the Collège des médecins du Québec must see to it that its professional inspection service, during its professional inspection visits, pays attention not only to the medical records, but also to research records.

In the opinion of the Committee members, the Collège des médecins du Québec must develop and bring up to date guidelines for the carrying out of research activities.

In the opinion of the Committee members, the Collège des médecins du Québec must, along with the universities, ensure that the training of students in medicine include courses on the fundamentals and on the conditions for carrying out health research. In the opinion of the Committee members, the nursing include courses on carrying out health care research and the role of health care professionals in nursing in this process.

In the opinion of the Committee members, the Order of nurses should ensure that the professional service of inspection, during its professional inspection visits, pays attention not only to the nursing medical records, but also to the research records.

### ***QUEBEC HOSPITAL ASSOCIATION***

In the opinion of the Committee members, Research Ethics Committees members must undertake a specific education in research ethics. The Committee members believe that the Association des Hopitaux du Quebec, and the Quebec universities must assume leadership in this matter and develop a program of education for members of Research Ethics Committees, using persons known for their competence in the area. The program must contain both the theory and concrete methods used in the analysis of research protocols. The people who have taken these course should be given a note of attestation.

### ***THE PHARMACEUTICAL INDUSTRY***

In the opinion of the Committee members, the Canadian Association of Pharmaceutical Industry, which already has many permanent committees, such as the consulting committee for general policies, the committte for investigation of marketing practices, the committee for investigation of the price of non-generic medication, the committee for economic analysis in health care, must put in place a consulting committtee on research on human subjects in such a way as to create a forum where in a pro-active way, the multiples issues arising from this type of research, could be aired.

# CONCLUSION

## CONCLUSION

The problems encountered today in Quebec with respect to biomedical research are neither new nor exclusive to Quebec. In its 1987 Guidelines, the *Medical Research Council of Canada* identified a certain number of problems likely to arise in the field of biomedical research.

In 1990, the *National Council for Bioethics in Research on Human Subjects*, in the course of a workshop on the ethical problems encountered in clinical research involving pharmaceutical products, identified various deficiencies with respect to the training of clinical investigators in Canada, their remuneration, the training of members of research ethics committees and the obtaining of informed consent to mention only a few.<sup>1</sup>

In 1995, the same Council noted, following an investigation involving fifty-eight research ethics committees, that some major features contained in the *the Medical Research Council's* Guidelines were not always implemented, in particular those related to the composition of Research Ethics Boards, the follow-up of research projects, activities required to guarantee the protection of research subjects, as well as the integrity of research activities.

From the answers obtained from the questionnaire sent to eighteen healthcare institutions, and from the views expressed by various individuals or groups as well as different bodies or healthcare institutions, our own Committee was able to identify many deficiencies in the present evaluation process of research activities carried out in Quebec.

The various parties concerned with the proper carrying out of research activities and their proper evaluation should have taken appropriate measures to correct these observed deficiencies. The MRC Guidelines, considered as essential to give research activities their legitimacy, should have been scrupulously respected. This was only partly the case. Despite denunciations, despite urgings on many fundamental issues such as the follow-up of research activities and the composition of research ethics committees, a certain complacency if not, perhaps even indifference, seems to explain the observed inaction in these matters.

In the opinion of the Committee members, the recent events that occurred in Quebec in the field of biomedical research can be attributed to the inaction of the research sector and its various players as to what should be done to ensure the quality of research and the protection of research subjects. This can be explained mainly by the weaknesses of the evaluation mechanisms applied in the field of clinical research. The unfortunate events exposed by the media, which shook the research sector and the general public, represent part of the deficiencies existing in the present evaluation system of research activities when compared with the problems identified by the Committee members in the course of its consultations.

One cannot redress this situation in one day and one must show patience. But patience does have its limits, especially when the quality of research activities and the integrity of research subjects are jeopardized by the unwillingness to apply approved standards and to correct known deficiencies.

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<sup>1</sup> National Council on Bioethics in Research on Human Subjects, Ethical problems in clinical research related to pharmaceutical products, Minutes of a Workshop held in Ottawa, Canada, May 30 and 31, 1990, 18 p.

Energetic actions are needed now. If the actions taken, on a national or provincial level, are useful to define a body of standards and directives, the fact remains that healthcare institutions are responsible for the implementation of these standards and directives when dealing with the financial, scientific and ethical aspects of research activities.

Thus, today in Quebec, one must show greater rigor, transparency and care in the carrying out and the evaluation of research activities conducted in the healthcare sector. This is necessary, not really as we have said, to stem a wave of frauds, but to ensure that research conducted in Quebec is of excellent quality and that those who agree to participate in research projects are well protected in every dimension of their being, notably their freedom, their integrity, their privacy, and more broadly, their dignity.

Therefore, it is not sufficient to focus only on the elaboration of new guidelines or the revision of existing ones. One must ensure that these directives are applied and followed wherever research activities are carried out. This assurance must be given first and foremost by the investigators and the healthcare institutions themselves. It must also be guaranteed by private and public bodies, which financially support research activities. It must be confirmed, finally, by the existence of a regulatory framework which defines the responsibilities of each and every one involved in research activities and by an accreditation procedure.

Healthcare institutions must immediately take action so that clinical research activities are better regulated and that the evaluation procedures become more effective and be better supported. Some doubt could be cast on the willingness of the scientific community and of hospital administrations to set up a framework capable of ensuring the integrity of research activities and the protection of those who agree to participate in research projects if they do not take appropriate action.

There is no miracle solution to the problems mentioned. Vigilance must be intensified at all levels. The trust that can naturally be given to those who perform research activities must not slacken the vigilance which must exercise over research activities.

The Committee members readily acknowledge that some of the recommendations and suggestions which they have proposed may go against practices which presently exist in the field of clinical research. In accordance with the principles proclaimed in the introduction of this report, the members believe, nonetheless, that their recommendations offer the best guarantees to ensure that throughout Quebec, irrespective of the healthcare institution or of the investigator involved, clinical research activities are appropriately conducted and that those who agree to participate in research projects are well protected.

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**Chapter 5**  
**THE BASIC PRINCIPLES AND THE PROPOSED ACTIONS**

**TABLE 1**

TABLE 1

**A. THE TYPES OF HEALTH RESEARCH**

**Fundamental research**, generally defined as biomedical research, is the study, with the help of experimental methods, of the biological and biochemical processes and mechanisms of the human organism.

**Clinical research** is the study of physiopathological processes, the etiology of illness or an abnormality, but also **that** of diagnostic methods, of therapeutic means with the aim of improving, better defining the prognosis and **to further increasing** the autonomy of people. This research is carried out with the help of human subjects.

**Epidemiologic research** is the study of populations with the goal of determining the incidence, frequency and distribution of illness in relation of various factors. A number of these factors are biological factors, environmental factors, lifestyles, health care services and social conditions. The study of the effectiveness of methods used to control health problems or to predict the occurrence of illness are equally part of this research methodology.

**Operational research** is the detailed study of an integrated process with the aim of improving this process by applying formal modeling.

**Organizational research** studies the structures, the functioning and the use of resources of organizations, **the repartition of resources within an organization**, in order to improve the attainment of their mission and their objectives.

**Evaluative research** is the study of interventions in health care to determine the value of the results obtained.

**Research on healthcare services** study the degree that the objectives are obtained following the giving of services, **of attainment of the preestablished objectives following the offering of services** as well as the conditions and factors which led to or detracted from the achievement of these objectives, equally related to the provider as to the consumer.

The research on these services is different from evaluative research which studies **studying** the efficiency and

**Applied research** attempts to put into practice in the health care sector, theoretical models that come from other activity sectors and other research sectors.

Thus, applied research allows biomedical engineering, engineering, geography, law, sociology, psychology, and

Furthermore, other than health care research as such, there also exists research of a psycho-social nature concerned with other aspects of the human being and which is often pertinent to health. These are carried out mainly in sociology and demography.

Source: Fonds de la recherche en santé du Québec. Plan triennal 1993-1996.

**TABLE 2**

TABLE 2

**A. STATUS OF INVESTIGATORS**

**1. THE STATUS OF CLINICIAN INVESTIGATORS**

One acknowledges that a clinician investigator has three of the following four characteristics: the clinician investigator carries on research activities in an independent fashion; he receives research funds in his own name; he publishes in specialized literature; he trains students or residents in research.

This definition encompasses all disciplines and all methodologies. It includes investigators in biological sciences as well as human science and retains all those whose research activities have some impact on patients or on the distribution of health care. It requires adequate training in clinical research, even if it is not necessarily confirmed by a diploma. It must be remembered here that one does not simply act as an investigator, one becomes one. However, there are many ways to acquire what is necessary to become an investigator.

Since there is not a unique profile for a clinician investigator **assumes many profiles**, it is appropriate to describe several classical profiles of people identified as investigators in order to distinguish from others those which can be called such, and the responsibilities which devolve upon them. In this respect, it is appropriate to define the following profiles:

- i) the investigator not specifically trained in research;
- ii) the investigator trained in fundamental research;
- iii) the physician not specifically trained in clinical research;
- iv) the investigator who has specific training in clinical research.

**a) The investigator not specifically trained in research**

This type of investigator, who is not a physician, has not specifically trained in research. He is always engaged in nursing, inhalation therapy, or technicians. The responsibility of the research protocol is not theirs; they **simply** report to a company or to investigator colleagues.

Even though **Eventhough** they may sometimes be presented as such, these persons do not have the status of investigators. They are not responsible for the complications in protocols for the patients engaged in the research.

These people **investigators** cannot be responsible for the training of students and as a general rule, are not considered as such. These people who have not been trained to undertake them.

**b) The investigator trained in fundamental research**

This type of investigator, who is not a physician, has a formal academic training, or a training acquired by recognition organizational, evaluative, or even research on health care management.

In the hospital sector, this type of investigator works often in the framework of multidisciplinary teams made of people who require sophisticated measurements. They may or may not interact directly with research subjects and people patients who require requiring health care. They can therefore require specific additional training for participation in certain protocols of research on patients.

These investigators can be either **assume the role of** the principal investigator or the research assistant in the

**c) The physician not specifically trained in clinical research**

Furthermore, in clinical research, there are a number of physicians who have not been specifically trained in the field and have the privilege of co-authoring publications. They are generally a part work as of multidisciplinary teams, made up of other physician investigators. In this case, the responsibility for the protocol is often from devulged on external members outside (companies, colleagues).

As concerns this group of associate-investigators, formal training on the secondary effects and other risks of p expected expected events and side-effects must always be given to dispensed to them.

**d) The investigator who has adequate training in clinical research**

This type of investigator, who may or may not be a physician, is involved in research activities limited to his area of expertise. They may be direct students, obtain research fundings, author specific publications and are generally called upon to provide healthcare in the course of using research protocols.

All these people may be involved directly in research activities and their respective responsibility in carrying out

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