

Practice Guide **THE PHYSICIAN AND CLINICAL RESEARCH** 2023



COLLÈGE DES MÉDECINS DU QUÉBEC

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Note: In this publication, the masculine gender is used without discriminatory intent and solely to facilitate reading.

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LIST OF MAIN ACRONYMS AND INITIALISMS

AI: Artificial intelligence C.C.Q.: Civil Code of Quebec CAI: Commission d'accès à l'information CCER: Comité central d'éthique de la recherche **CIHR:** Canadian Institutes of Health Research **CMPA:** Canadian Medical Protective Association **CTA:** Clinical Trial Application **CTA-As:** Clinical Trial Application - Amendments **DPS:** Director of Professional Services **DSMB:** Data and Safety Monitoring Boards FRQ: Fonds de recherche du Québec FRQS: Fonds de recherche du Québec - Santé GCP: Health Canada Good Clinical Practices **ICF:** Information and consent form MSSS: Ministère de la Santé et des Services sociaux **NOL:** No Objection Letter **REB:** Research ethics board RMGA: Réseau de médecine génétique appliquée TCPS 2: Tri-Council Policy Statement: Ethical Conduct

for Research Involving Humans

INTRODUCTION

The Collège des médecins du Québec (hereinafter the Collège), whose mission is to promote quality medicine for the protection of the public and contributing to the improvement of Quebecers' health, has long been involved in clinical research. In 2007, the Collège published a practice guide laying the general foundations of clinical research for physicians in Quebec.

Several years later, this guide now requires an update to address the new realities of clinical research encountered by physicians conducting (in whole or in part) or collaborating on a research activity in any form. By way of example, the sophistication and complexity of the regulatory framework; the increasing number of biobanks, specifically for genetic material; social media, big data, etc.

Research in general and more specifically clinical research are conducted in a perspective of common good and are generally of little personal benefit to the participants. That said, while it may be acceptable for individuals to take risks to advance knowledge, these risks should never outweigh the expected benefits of the research for the participant and for society.

Ensuring the protection of those participating in advancing knowledge for everyone's benefit is the responsibility of society as a whole.

For these reasons, all of the jurisdictions involved implemented the currently enforced regulatory framework decades ago.

It is possible that a physician who wants to contribute to advancing scientific medical knowledge could feel overwhelmed, if not discouraged, by the extent of knowledge and standards they must (or should) assimilate. While recognizing the importance of standards and restrictions, rather than drawing an exhaustive list, this guide aims to identify specific issues arising from clinical research, especially when the researcher is also the patient-participant's caregiver. The guide is intended to be pragmatic, with an educational and reflective focus on the roles and responsibilities of physicians in clinical research. The document begins by outlining the current context of clinical research and its regulatory framework, which is limiting but undoubtedly needed to foster public trust in research and its contributors. In particular, it addresses the risk of conflicts of interest inherent to the multiple roles assumed by physicians when conducting or collaborating on research.

The text then describes the scientific, financial, and ethical review process which all clinical research projects conducted in Quebec must undergo before the first participant can be recruited.

Several practical aspects are then presented to be taken into account when recruiting a participant and obtaining their consent to participate in a clinical research project, after duly informing them of not only the benefits, but also the disadvantages and risks of the project. Certain obligations to which physicians and all researchers are bound when conducting or collaborating on research are highlighted, from participant privacy, to record keeping of research files, to special duties concerning research with minors or persons of full age who are incapable of giving consent to participate in research.

Lastly, some issues specific to current clinical research are discussed, namely research in emergency health situations, genetic research, banks, secondary use of research data, and avenues for discussion about open data, big data, and artificial intelligence.

CONTEXT OF CLINICAL RESEARCH

1. DEFINING CLINICAL RESEARCH

Clinical research falls under several definitions. To provide a proper definition, we must first agree on what constitutes "research." *Tri-Council Policy Statement: The Ethical Conduct for Research Involving Humans* (TCPS 2) defines research as:

"an undertaking intended to extend knowledge through a disciplined inquiry or systematic investigation. The term "disciplined inquiry" refers to an inquiry that is conducted with the expectation that the method, results, and conclusions will be able to withstand the scrutiny of the relevant research community."¹

In 2004, the Canadian Institutes of Health Research (CIHR) designated clinical research quasi exhaustively as:

[*Translation*] "[research] that combines the findings of fundamental research conducted in scientific laboratories with the observations and theories of clinicians (...). It then defines the mechanisms of health and disease in humans (...), describes possible preventive, diagnostic, and therapeutic measures, and lastly assesses the effectiveness of such measures in improving health (...). It also emphasizes more rigorous comparisons between current approaches in diagnosis, treatment, and prevention, and develops new approaches to determine those that are safer and more effective. Contemporary clinical research benefits from utilizing powerful physiological, genomic, and proteomic markers that predict disease or provide individualized guidance on diagnosis and prognosis. Health systems and policies, and population health studies often compile new knowledge, which results from clinical research (...) and vice versa."²

Broader than clinical trials alone, clinical research includes research on the mechanisms of human health and disease, translational research, experimental and observational trials in prevention and treatment, research on health systems and services, as well as clinical studies in epidemiology. It should be noted that an increasing number of clinical trials include a genetic or genomic component and storage of data or samples in research banks. Moreover, it is expected that more and more clinical trials will be conducted virtually, with the introduction of digital health technologies at different stages of their protocols.³

3 National Academies of Sciences, Engineering, and Medicine (2019).

¹ TCPS 2 (2022), Chapter 2.

² CIHR (2004). This quote, translated into French in 2012, has not been traced in its original English form

Physicians can have diverse roles while working in clinical research. They may be the principal investigator, i.e. a researcher who leads the research team and, as such, ensures the research is carried out and is responsible for the behaviour of the research team members; or they may provide support for analysis, recruitment, evaluation, treatment, or follow-up of research participants. They may also act as a consultant or safety monitor on the clinical research project.⁴ While this wide spectrum obviously entails distinct obligations and responsibilities depending on their role in research, even the smallest of roles does not exempt them from respecting their fundamental obligations as a physician. When managing a patient participating in clinical research, the physician must exercise sound clinical judgment. They must not disregard any symptoms deserving of attention and must diligently investigate them as dictated by the participant's health status, regardless of the research protocol.

Learners also begin to participate in clinical research activities during their initial training, and even more so during specialized training.⁵ Their supervision must meet the safety requirements for the patients and the learners themselves.⁶

5 Some undergo specific training in research: Royal College Clinician Investigator Program (2 years), and College of Family Physicians of Canada Clinician Scholar program (1 year).

⁴ CMPA (2013) and (2016).

⁶ See the guide entitled *Role and Responsibilities of the Learner and the Supervisor* published by the Collège des médecins du Québec in 2016.

2. CURRENT CLINICAL RESEARCH

In recent years, the level of public funding has been increasingly limited for not only federal and provincial research,⁷ but also for Quebec universities,⁸ in turn exerting significant pressure on researchers in Quebec's universities and university centres to be more competitive and to even conduct commercial research. [Translation] "Excellence, as currently promoted by university institutions, is defined much more by research performance (itself assessed in quantitative and non-qualitative terms) than by the quality of teaching."9 In the teaching community, there is enormous pressure to publish research outcomes.¹⁰ A researcher's career advancement and reputation are closely related to not only the grants/sponsorships they obtain and the papers they publish, but also their findings. In Canada, the Canadian Institutes of Health Research (CIHR) recognizes that it is a difficult task to design, implement, and fund multi-centre clinical trials, and it deplores Canada losing its competitive hold in the field.¹¹ While the health sciences sector receives the lion's share of both public and private research funding,¹² in recent years it has been at the expense of fundamental research in favour of more industrial and marketable research. Moreover, it is important to note that the private sector disengaging from funding research has been observed across all research sectors, except the health sciences sector (31% of the budget is sourced from the private sector). The private sector invests in projects with the highest potential return on investment.13

These contextual elements have impacts clinical research: The increasingly on competitive environment complex and involves multidimensional and cross-border collaborations and partnerships.¹⁴ Physicians are increasingly turning to income-generating multi-centre pharmacology studies for which they are neither the primary investigators nor sponsors of the research themes,¹⁵ and reasonable concerns arise about the potential impact on the direction of clinical research. which neglects research that is minimally or not related to pharmaceutical and biotechnology industry interests (e.g. orphan diseases, child psychiatry, etc.).

Canada's Fundamental Science Review advisory panel (2017).

Racine St-Jacques J. et al. (2016) p. 22 8

Racine St-Jacques J. et al. (2016) p. 10.

¹⁰ McRae A.D. (2005). 11 CIHR (2017).

Racine St-Jacques J. et al. (2016) p. 6 and p. 7. From 2003-2004 to 2009-2010, 33% of funds were devoted to pure

and applied sciences, 39% to 46.5% to health sciences, while humanities and social sciences accounted for 12.5% to 17% of the budget.

¹³ *Ibid.*, p. 27, 29, 30. FRQ (2014). 14

Corvol, P. (2015).

Among these new partnerships, involving patients and families as partners in the research process is a positive step toward producing a new outlook for current clinical research. A transition to a more proactive role for patients is part of a partnership in which the physicians conducting the research activities and the patients are together contributing to planning these activities, in line with the priorities established by the patients. Research then becomes a unique opportunity to establish this partnership, with each party bringing their knowledge to the table: the physician's clinical knowledge.¹⁶

In conclusion, the increased complexity of the research environment produces new challenges that physicians must acknowledge. This complexity also gives rise to new opportunities, the development of new tools, and interdisciplinary research collaborations that will, despite these challenges, be considered valuable to the future of clinical research.

¹⁶ For example, Canada's Strategy for Patient-Oriented Research (SPOR) implemented by the CIHR, including the establishment of the <u>Quebec</u> <u>Strategy for Patient-Oriented Research (SPOR) Support Unit</u>, whose mission is to transform frontline clinical and organizational practices, and promote the integration of care and services through patient-oriented research. For the CIHR's ethical guidelines concerning patient-researcher collaborations, refer to CIHR (2020); for the ethical implications, refer to Martineau (2020).

3. THE HIGHLY STANDARDIZED FRAMEWORK OF CLINICAL RESEARCH

Research involving human subjects has resulted in (and still produces) a significant body of international and national standards.¹⁷ However, no Quebec or Canadian law currently regulates all aspects of research involving humans in a single document.

These standards are recorded in various acts, regulations, declarations, statements, action plans, guides, guidelines, and directives, and they refer to rules that are mostly general in nature. Some of these standards apply to all areas of research while others only apply to specific areas. Although the saying goes, "ignorance of the law is no excuse," it would be unrealistic to expect physicians engaged in research to be aware of every one of these standards. However, they should be familiar with the broad principles common to all applicable regulatory acts and keep abreast of new developments regarding specific provisions from Canadian and Quebec regulations that impact their practice.

Ethical review and the application of these standards are entrusted to research ethics boards (REBs), whose members are expected to represent local communities and their values. The research is structured in a way that not only respects the participants directly involved, but is also socially beneficial to the populations that fundamentally support it.



4. PUBLIC TRUST AND EXEMPLARY CONDUCT IN RESEARCH

Public trust is a central element of medical practice. It is especially important when physicians are conducting or collaborating on clinical research, as the participants rarely derive personal benefits from participating and most often do so altruistically. Even in clinical trials, the benefits expected by sick participants (and researchers) are often quite far from the benefits achieved (e.g. placebo, discouraging overall outcomes, etc.).

The REBs and profuse standards that govern medical research were established in response to the numerous past violations that tarnished public trust in research and researchers. One need only recall the scandals-the thalidomide scandal, those revealed in 1966 at Harvard by Dr. Henry K. Beecher,¹⁸ more recently the cases of Allan Memorial¹⁹ and Poisson²⁰ in Quebec, or the case of Raniit Chandra²¹ in Newfoundland and Labrador-to observe that many of them were caused by physicians. Public trust in research is gained through exemplary conduct by all research stakeholders, and in particular researchers, including physicians conducting or collaborating on research, their institutions, and the research staff. Additionally, specific provisions related to conducting research have been included in the Code of ethics of physicians since its revision in 2002.22

Various national and international normative texts have recently highlighted the fundamental concepts of scientific integrity and responsible conduct in research.²³ These texts respond to a need: Recalling the importance of flawless conduct in maintaining research excellence and promoting public trust.

Fraud is a serious, intentional violation in conducting research and in disseminating outcomes, excluding errors in good faith or honest differences of opinion.²⁴ There are three main types of fraud: fabrication, falsification, and plagiarism. In addition to these major offences, minor fraud and negligence²⁵—which happen more often, are less circumscribed²⁶ and more difficult to detect—are also a matter of scientific misconduct.

26 Bouter L.M. et al. (2016).

¹⁸ Beecher, H. K. (1966). A reported 22 experiments were considered unethical (lack of participant consent, poor risk assessment, etc.).

Risk-inducing experiments with no scientific basis were conducted on patients at the Allan Memorial Psychiatric Institute at McGill University (1957-1963). See Doucet H (2002), p. 54.

²⁰ In 1996, Dr. Poisson falsified numerous clinical trial data as part of breast cancer research conducted in North America and funded by the National Institutes of Health (NIH). 21 The physician, who conducted several studies on infant formula and multivitamin products, was convicted of fraud in 2016. Memorial University buried the case for over a decade.

 ²² Code of ethics of physicians, sections 28 to 31, 44, 48, 61, 78, 84, 87.
 23 FRQ (2014); ALLEAL (2017); Singapore Statement on Research Integrity (2010); Montreal Statement on Research Integrity in Cross-Boundary Research Collaborations (2013); Amsterdam Agenda (2017); CCA (2010) Chapter 5, Roles and Responsibilities: An Integrated Approach to Research Integrity; Social Sciences and Humanities Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, Canadian Institutes of Health Research (2016).

²⁴ Letellier L. (2011).25 Martinson B.C. et al. (2005).

Several studies suggest an increase in the occurrence of such incidents of misconduct: Analysis of cases of retracted scientific papers shows a tenfold increase from 1977 to 2013, from 1 retraction per 100 000 to 50 per 100 000 during the period; 67.4% of the retraction requests were related to suspected fraud.²⁷ In 2016, 972 erroneous or fraudulent articles were retracted after publication.²⁸ As the philosopher Anne Fagot-Largeault said: [Translation] "As successful fraud is undetected. it is misleading to assess the frequency of fraud through counting officially confirmed cases (...) or the number of papers removed from the PubMed database for containing errors."²⁹ Additionally, a survey of about 2 000 researchers funded by the National Institutes of Health (NIH) revealed that, at the time of its publication in 2005, 33% of these researchers had conducted unethical practices in the last three years, namely: change in methodology or modification of study outcomes due to pressure from the source of funding (15%);

falsification, fabrication, and plagiarism (1.7%); nondisclosure of conflict of interest (0.3%); non-compliance with ethical rules with patients (0.3%); use of another person's ideas without permission or recognition, or use of confidential information (3.1%).³⁰

More recently, various news articles have highlighted this situation in Quebec.³¹ The political and social impacts of scientific fraud can be extensive,³² as evidenced by British doctor Andrew Wakefield's study on immunization coverage and the increase in measles cases in some countries. In 1998, based on manufactured data, his findings suggested a link between the measles, mumps, and rubella (MMR) vaccine and autism, coupled with an intestinal issue.³³ Beyond trust in research and researchers, these infractions, however minimal, jeopardize the health and safety of patients whose treatments are directly based on the state of scientific knowledge.

Societal expectations and the current context of clinical research demand that any physician conducting or collaborating on research assess their own integrity and exercise caution in their actions.

When problematic behaviour in research is observed, it brings up the highly delicate issue of reporting misconduct, which seldom occurs if previously published statistics are to be trusted. While exemplary research is a virtue that all researchers adhere to in theory, it is more complex to apply in practice. When a researcher witnesses a potentially reportable situation, they are likely to feel conflicted (not wanting to cause harm to colleagues, not wanting to rock the boat, fear of reprisals, fear of causing harm to the research centre's reputation and, consequently, fear of indirectly damaging their own reputation, etc.). Researchers may be tempted to stay quiet, procrastinate, or even hope someone else reports the situation.

 Fagot-Largeault A. (2011).
 Martinson B.C. et al. (2005). Also see Fanelli D. (2009). 31 Malboeuf M-C. (2017).

²⁷ Ferric C. et al. (2012).

²⁸ Malboeuf M-C. (2017)

³² Deer B. (2011).

³³ Wakefield A.J. et al. (1998) [Retraction (2010)] and the editors of The Lancet (2010).

Maintaining public trust and exemplary conduct in research requires courage. Mechanisms have been implemented in public institutions to report and manage such situations. Thus, the regulatory framework for research at each institution must contain provisions for managing cases of scientific and ethical misconduct.34 The Fonds de recherche du Québec (FRQ) indicate that it is the institution's responsibility to produce a policy on responsible conduct in research and investigate any allegations of breaches of conduct among their researchers, students, research staff, and fund managers.³⁵ The three federal research agencies and the FRQ have established guidelines and processes to deal with breaches in research integrity.³⁶

In addition to these local mechanisms, section 119 of the *Code of ethics of physicians*³⁷ stipulates that a physician must report to the Collège any physician, medical student, resident, medical fellow, or any person authorized to practise medicine whom they believe dishonest. Adequately reporting specific details allows the syndic of the Collège to investigate. The *Act to amend various legislation mainly with respect to admission to professions and the governance of the professional system*, adopted in June 2017, goes further and allows, under certain circumstances, to grant immunity from any complaint before the disciplinary council to a professional that was a party to the offence.³⁸ Additionally, it is forbidden to take or threaten to take reprisals against a person on the ground that the person has sent information to a syndic to the effect that a professional has committed an offence or on the ground that the person has cooperated in an inquiry conducted by a syndic.³⁹

Physicians involved in research activities should take notice of these reporting mechanisms and, when required, take action to preserve research excellence and public trust in research and researchers.

It is essential to act with diligence and discretion in response to a report of misconduct and during the investigation. The investigation must be conducted by people who are independent, and any personal and institutional conflicts of interest in the processing of these files must be meticulously assessed beforehand.

³⁴ MSSS (2020), standard 9.

³⁵ FRQ (2014), sections 5.2.2 and 5.2.4.

³⁶ SSHRC, NSERC, CIHR (2016), and FRQ (2014).

³⁷ Code of ethics of physicians, section 119: "A physician must report to the Collège any physician, medical student, resident, medical fellow or any person authorized to practise medicine whom he believes to be unfit to practise, incompetent or dishonest, or who has performed acts in contravention of the Professional Code (chapter C-26), Medical Act (chapter M-9) or regulations ensuing therefrom. The physician must, furthermore, try to assist a colleague who presents a health problem likely to affect the quality of his practice."

³⁸ Act to amend various legislation mainly with respect to admission to professional and the governance of the professional system, section 70: [...] "123.9. Where the person who has sent information to the syndic to the effect that a professional has committed an offence is a professional who is himself a party to the offence, a syndic may, if the syndic considers it warranted by the circumstances, grant that person immunity from any complaint lodged with the disciplinary council in connection with the facts related to the commission of the offence. A syndic must, before granting immunity, consider such factors as the protection of the public, the importance of maintaining public trust in the members of the order, the nature and seriousness of the offence, the importance of the alleged facts for the conduct of the inquiry and their reliability, the professional's collaboration during the inquiry and the extent of the professional's participation in the offence."

³⁹ Act to amend various legislation mainly with respect to admission to professions and the governance of the professional system, section 67: "It is forbidden to take or threaten to take reprisals against a person on the ground that the person has sent information to a syndic to the effect that a professional has committed an offence referred to in section 116 or on the ground that the person has cooperated in an inquiry conducted by a syndic."

5. THE DOUBLE ROLE OF THE PHYSICIAN CONDUCTING OR COLLABORATING ON RESEARCH: A SENSITIVE ISSUE

An individual that simultaneously conducts physician activities and researcher activities is putting themselves in a position that, in addition to being demanding, puts them at risk of conflict.

5.1. CONFLICTING ROLES

Responsibility

Conflicting roles are inherent to clinical research. Physicians conducting or collaborating on research have an obligation to protect the health, well-being, and rights of participants at all times. When collaborating on or leading clinical research, physicians are responsible, both legally and ethically, for the research participants. Even when a participant decides to withdraw or is removed from the research, for any reason whatsoever, the physician must continue providing care or ensure the participant has access to necessary care.

Benefits for the patient-participant

Physicians conducting or collaborating on research should also address the following question for each patient they are considering as a participant in a research project: "Is the research that I am working on as a principal investigator or collaborator the most appropriate for this patient? In other words, "Is the potential benefit for this patient greater in this research project than in others, or a project led by one of my colleagues?"

Clinical research does not lessen any of the obligations that physicians are bound to with regard to a patient, and the role of treating physician takes precedence over that of researcher.

This questioning becomes all the more useful when a physician is not practising in university or hospital centres and not familiar with the various ongoing research on the patient's disease.⁴⁰

⁴⁰ Consultation of public sites such as clinicaltrial.gov allows for researching public and ongoing private clinical trials throughout the world.

Clinical research and medical practice

We cannot overstate how important it is for physicians conducting or collaborating on research to make the distinction with the participant-who is also a patient-between clinical research and common medical practice, whose objective is to contribute directly to health. There is potential for prospective patient-participants to become confused when clinical research and medical practice are conducted simultaneously. This is why physicians requesting a patient's participation in a research project, regardless of whether they are the treating physician, must explicitly state that the purpose of research is not, a priori, the same as that which motivated the consultation and, to the extent possible, direct them to a person who has no connections to the original clinical relationship to inform their consent. As such, the physician must not knowingly or unknowingly withhold any information, nor intimidate or improperly influence the prospective research participant. The latter must be aware and understand that the methodological requirements of the protocol limit the physician's therapeutic intervention. In addition, like any researcher, the physician must be fully objective and transparent with the prospective participant at all times when addressing the details about the clinical research being proposed.



5.2. CONFLICTS OF INTEREST

There are several definitions attempting to describe a conflict of interest. According to the definition in the TCPS 2, "A conflict of interest may arise when activities or situations place an individual or institution in a real, potential or perceived conflict between the duties or responsibilities related to research, and personal, institutional or other interests. These interests include, but are not limited to, business, commercial or financial interests pertaining to the institution and/or the individual, their family members, friends, or their former, current or prospective professional associates."⁴¹ Other definitions take a step further and also consider political and ideological interests.⁴²

The Code of ethics of physicians requires transparency in the profession: The physician must disclose any real, apparent, or potential conflicts of interest.⁴³ The physician must inform the REB and each participant that they will acquire benefits from their participation or retention in the research project,⁴⁴ so that the prospective participant can make an informed decision on whether or not to participate.

Having multiple loyalties raises a question of risk, that of neglecting concern for the well-being of participants.

The physician's professional independence must be safeguarded at all times and centred on the patient's interest. The same applies to research participants, whether or not they are patients under the physician's care.

The physician must refuse to collaborate or participate in any act contrary to the participant's interest and must refuse any benefit that would call their professional independence into question or jeopardize public trust.45

As indicated by the TCPS 2,⁴⁶ conflicts of interest of researchers can originate from:

- Interpersonal relationships;
- Financial partnerships;
- Other economic interests (e.g. spin-off companies in which researchers have stakes or private contract research outside of the academic community);
- Academic interests;
- Any other incentives that may compromise research integrity or respect of the core ethics principles.

⁴¹ TCPS 2 (2022), Chapter 7

⁴² Université de Montréal (2015), Translated excerpt from disclosure of interest form: "A conflict of interest can arise when activities or situations expose an individual or an organization to commercial, financial, or non-monetary interest (e.g. religious beliefs, values) which conflict with the interests inherent to the duties and responsibilities related to their status or function. These interests may relate to the organization and/or the individual, family members, friends, or professional associates - present, past, or future.'

⁴³ Code of ethics of physicians, sections 63 and 78.

⁴⁴ Ibid., section 30.

⁴⁵ *Ibid.*, sections 60 and 78.
46 TCPS 2 (2022), Chapter 7.

Financial conflicts of interest

The most common conflicts of interest in research are financial. In this regard, the TCPS 2 stipulates that, when submitting a research project to the REB, researchers must disclose all kinds and amounts of payments (financial or in kind) that they received or will receive from their sponsor, their commercial interests, consultative or other relationships, and any other information that may affect the project (e.g. donation to an institution by a research sponsor). Researchers must also provide all additional relevant documentation and identify strategies to prevent, disclose, minimize, or otherwise manage conflicts. According to the TCPS 2, researchers should pay particular attention to contracts binding them to sponsors in regard to payment arrangements to ensure that they do not result in any immediate recruitment incentives, which are ethically unacceptable, at the expense of a careful study of the characteristics sought in potential participants. Unreasonable payments or undue inducements may place the researcher, and sometimes the institution, in a conflict between maximizing financial remuneration, on the one hand, and protecting participants and meeting the scientific requirements of the project on the other. In this regard, it is important to remind physicians conducting or collaborating on research of the official prohibition of double payment for acts performed as part of a clinical research activity.

Detection, disclosure, and intervention

According to the documentation, a conflict of interest calls for three types of successive actions: detection, disclosure, and intervention.

With regard to detection, researchers are too often asked to detect their own potential conflicts of interest. One issue arising from this is the likelihood that researchers are not always aware of all of their own conflicts of interest, or are fully convinced that these dual loyalties have no influence on their professional judgment.

This is compounded by the fact that the topic of conflicts of interest has become a drastically more sensitive issue in recent years, and thus what was once accepted, is no longer permitted. As a result, researchers have an obligation to educate themselves on the reality and extent of conflicts of interest, and to inform their teams in this regard. However, the sole accountability of researchers in this respect seems insufficient. An integrated approach is recommended for organizations (both public and private) in which researchers carry out research activities so that research directorates, REBs, and quality care and service managers can work together to foster the detection of conflicts of interest in research. As with breaches of integrity, detecting conflicts of interest requires a proactive, collaborative attitude not only within the organization, but also between organizations (e.g. universities, research centres in health care institutions, etc.).

With regard to reporting misconduct, as we have just seen, it is essentially up to the good faith of the researchers, since there is no equivalent in Quebec or in Canada to the American Sunshine Act (2010), which requires industries (in particular pharmaceutical companies) involved with federal public health care programs to disclose their financial connections with physicians and their university hospitals.⁴⁷ Beyond financial connections, researchers should produce an objective and up-to-date description of all their commercial, financial, and non-financial relationships for the research directorates and the REB at least once a year (e.g. anti-vaccination beliefs, conscientious objection to abortion), related to their professional expertise, as well as those of close relatives (e.g. a spouse who is also a shareholder or an employee of a company whose product is under study), regardless of their perceived degree of conflict.

The measures to be taken in the case of a conflict of interest by a physician conducting or collaborating on research are to be determined on a case-by-case basis, equitably, and taking into account the best practices in the field. Thus, simply disclosing a conflict of interest to research participants in the information and consent form (ICF) is a necessary, but often insufficient measure.

With these various contextual elements established, it is now possible to implement them by way of a procedure intended for physicians interested in committing to clinical research.

⁴⁷ Physician Payments Sunshine Act of 2009: S.301 - 111th Congress (2009-2010).

PART II

PROCEDURE TO BE FOLLOWED

THE PHYSICIAN AND CLINICAL RESEARCH / 22

6. THE COMPETENCE OF PHYSICIANS CONDUCTING OR COLLABORATING ON RESEARCH

Physicians conducting or collaborating on research projects must be experienced, duly qualified, and competent to conduct the specific research. The credibility of research would be seriously compromised should the public not be able to rely on competent professionals who are aware of their limitations and follow a rigorous clinical and experimental approach in line with scientific standards. Note:

The designation of physician does not necessarily mean that the physician can conduct or collaborate on any type of clinical research.

An oncologist, for example, would hardly be considered competent to lead research in cardiac surgery, or to even collaborate on it.

For example, a family physician in a private practice who is asked to collaborate on or recruit patients for clinical research must have sufficient expertise in the field under study to make an informed decision, assess the project relevance with regard to patients, and propose it appropriately and judiciously.

The Collège does not grant any special researcher status to its members. In contrast, institutions in the health system have a responsibility to grant research privileges.⁴⁸ The physician's recognition as a researcher is based primarily on demonstrating their competence in the field in which their research activities take place. This competence may be demonstrated through conducted studies, acquired diplomas, accreditation or certification by reputable bodies, publications as author, experience in the field, and peer recognition, among others.

48 Sections 214 and 242 of the ARHSSS provide that an institution's board of directors can grant research privileges to physicians on the recommendations of the council of physicians, dentists, and pharmacists.

Competence is not limited only to the scientific aspect, it is also essential in research ethics.⁴⁹ Research granting agencies generally make it an obligation for funding recipients. Standards for research ethics are changing rapidly, and like all researchers, physicians conducting or collaborating on research must not only be trained in research ethics, but also regularly update their knowledge.⁵⁰ They are encouraged to participate in the discussion for the development and application of these ethical standards.

The physician must also ensure that the members of their research team are not only competent and qualified by virtue of their training and experience to conduct the research, but also familiar with research ethics.

Learners and supervisors must assume their respective responsibilities in this regard.⁵¹

Finally, the physician must ensure that the locations where research activities take place are designed to ensure the safety of research participants at all times. In addition, the physician must ensure the cleanliness and hygiene of the premises. For example, during vaccination the physician must be able to administer adrenaline in the event of anaphylaxis; likewise, a cardiologist performing exercise electrocardiograms must have access to the appropriate resuscitation equipment.

⁴⁹ WMA (2013), article 12: Medical research involving humans must only be conducted by persons who have acquired appropriate education, training, and qualifications in ethics and science.

⁵⁰ See the *Règlement sur la formation continue obligatoire des médecins* and the Collège des médecins du Québec (2019).

⁵¹ See the guide entitled Role and Responsibilities of the Learner and the Supervisor published by the Collège des médecins du Québec in 2016.

7. THE SCIENTIFIC VALIDITY OF THE RESEARCH PROJECT

Firstly, it should be recalled that the physician must not use insufficiently tested examinations, investigations, or treatments, except in the context of an official research project in a recognized scientific environment.

In the same vein, a physician conducting or collaborating on research involving human subjects must comply with the scientific principles and ethical standards generally recognized, accepted, and justified by the nature and purpose of their research. In order for a physician to collaborate on a research project, the project must be scientifically valid, relevant, well founded in terms of both methodology and objectives, and be based on proper knowledge of the relevant scientific literature. In addition, it must contribute to advancing knowledge.

In short, a research project that is not scientifically valid, relevant, and well founded is unacceptable from an ethical point of view.

Scientific evaluation of projects must be conducted by a recognized peer committee, such as:

- Scientific committee established by another institution of the health and social services network (HSSN);
- Scientific committee of one of the granting agencies, provincial or federal, or of an organization (national or international) recognized by either, whether or not the project receives a grant;
- Scientific committee of a university or college in Quebec or another province of Canada, or a scientific committee recognized by such an institution (e.g. program committee, thesis committee, departmental authority).⁵²

In the absence of a scientific evaluation committee, external and independent reviewers can be called on to conduct a scientific evaluation of the project. A full scholarly review by the REB is another option, provided that the REB has the necessary scientific expertise.⁵³ It should be noted that the more the project is deemed high-risk, the more in-depth the scholarly review must be.

A point of contention between researchers and REBs is that of scholarly reviews conducted by these same committees. It must be noted that, as part of the ethical review of research, the REB must examine the ethical, methodological, and research implications.⁵⁴ For clinical trials, Health Canada's *Good Clinical Practices* (GCP) provides that the REB "should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial."⁵⁵ (Our emphasis.) As a result, there is a high number of clarification requests on a research project's scientific aspects, and an REB can request changes or outright reject a project it considers scientifically flawed.

These situations rarely occur when projects are funded by recognized granting agencies, but can occasionally still happen. As an example, an international clinical trial funded by a U.S. granting agency and planning to compare experimental drug X to a placebo, given the lack of a standardized drug authorized by the Food and Drug Administration (FDA), could be denied by an REB in Quebec if an approved standard treatment exists in Canada for the indication in question. On the other end of the spectrum, "in-house" research, pilot projects, and student projects should not suffer from a less structured scientific approach, under the pretext of their limited scope. Physicians supervising student research have a duty to ensure the scientific quality of these projects.

- 53 TCPS 2 (2022), article 2.7. 54 *Ibid*.
- 55 Health Canada (2017), section 3.2.1.

8. HEALTH CANADA'S EVALUATION OF CLINICAL TRIALS: THE NO OBJECTION LETTER

Clinical trials governed by Health Canada must undergo an additional level of review. All clinical trial applications (CTAs) and clinical trial application - amendments (CTA-As) must obtain a No Objection Letter (NOL) prior to conducting or modifying the clinical trial. A preliminary assessment is conducted before the application is sent for review of the clinical information (safety and efficacy) and/or review of the quality information (chemistry and manufacturing). If major deficiencies are identified during the application review or the research sponsor does not immediately respond to a clarification request, a Not Satisfactory Notice (NSN) will be sent to the sponsor. However, if there are no deficiencies identified and the request is deemed acceptable, a NOL will be issued. All CTA and CTA-As are subject to a 30-day review period.⁵⁶

⁵⁶ Health Canada (2006); MSSS (2020).

9. LEGAL REVIEW OF RESEARCH CONTRACTS AND AGREEMENTS

The legal review of research contracts and agreements, particularly those of the industry, must be systematically organized prior to their signing, whether the project is conducted in a public or a private institution. The protection of researchers, organizations, and participants is at stake. This step is crucial to ensuring compliance with the standards, rights, and ethical principles established in Quebec and in Canada.⁵⁷

For example, clauses such as those relating to compensation, freedom of publication, applicable law or jurisdiction of courts should be carefully studied by a qualified legal advisor, bearing in mind that a contract is an inseparable whole.

The consequences for a researcher who has not adequately negotiated a research contract are sorely evident in conflict situations. For example, as indicated by the Canadian Medical Protective Association (CMPA), when sponsors are located outside Canada, "What is of greater concern is when the governing law and jurisdiction are stipulated to be that of another country such as the United States. This could expose the physician to significant damage awards, serious disruption of his or her practice and the possibility that the CMPA may not be in a position to provide assistance in that foreign country."⁵⁸ This single clause on the applicable law and jurisdiction has serious impacts for researchers. The initial savings from not performing a legal review could result in disproportionate financial, human, and psychological costs in the event of a conflict.

It is essential that physicians conducting or collaborating on research do not blindly trust the fairness of the contract being offered to them, but rather err on the side of caution.

10. ETHICAL REVIEW OF THE RESEARCH PROJECT

Once a clinical research project has received a favourable scientific assessment, it must obtain approval from an REB that adheres to existing standards, notably regarding its composition and modus operandi.⁵⁹ The project must be submitted to the REB before undertaking research on humans, whether it is a simple desk study or research conducted entirely in the physician's private office. Too often, researchers seek REB approval when they are ready to publish their findings, as renowned scientific journals ask them to confirm that their project has been ethically reviewed.⁶⁰

59 Code of ethics of physicians, section 31. 60 ICMJE (2019).

10.1. RESEARCH ETHICS COMMITTEES: MANDATE, JURISDICTION, POWERS, AND COMPOSITION

REBs are mandated to ensure the protection of research participants and maintain their rights, safety, well-being, and dignity. As such, they evaluate research projects submitted to them to ensure ethical compliance before authorizing their implementation. They therefore have the capacity to examine a project's scientific aspects as well as any other element that could undermine its integrity (e.g. performance bonuses, conflicts of interest, dissemination of results).

The scope of REBs covers any research activity with participants, including the creation or use of a database or biobank. Research with living human participants encompasses research that includes personal information or human biological material: embryos, fetuses, fetal tissues, reproductive material, and stem cells. This applies to materials derived from living and deceased individuals and any information produced therefrom, regardless of whether this information allows for the identification of these individuals.⁶¹ Access to patient data in clinical records for research purposes must therefore be authorized by an REB even for patients treated by the investigating physician. However, some research projects can be exempted from ethical review if they meet the criteria stated in the TCPS 2, specifically when the information is public.62

While the principle of filing a clinical research project with the REB is not generally difficult per se, the same cannot be said when it comes to quality assurance studies, assessments, and monitoring activities that include a research component. These hybrid projects must also be submitted to REBs before they begin. When in doubt, researchers must contact the REB,⁶³ which can issue a letter, if needed, confirming that no ethical review is required. This letter can be presented to scientific journals to have research results published.

REBs are composed of a minimum of five members who have both the training and expertise needed to fully and effectively assess the scientific and ethical character of research projects.⁶⁴ Of these five members, two must have broad knowledge of the research methods or areas within the competence of the committee, one must be specialized in ethics, one in law, and one represents the public. The REB can also consult ad hoc experts: for example, the proliferation of biobanks would justify calling on experts in computer security. Similarly, REBs will likely utilize artificial intelligence (AI) expertise, when required.⁶⁵

- 62 Ibid., Section 2.2.
- 63 MSSS (2020). 64 Quebec (2018).

⁶¹ TCPS 2 (2018), Section 2.1; MSSS (2020).

⁶⁵ See Chapter 21: Open Science, Big Data, and Artificial Intelligence.

REBs have the authority to approve or require amendments, and to reject all or part of any research activity submitted for their review. They can also suspend their initial approval or order the termination of an ongoing activity they had previously authorized. They also manage the continuous monitoring of approved research projects, and any changes to a research project must have their approval prior to implementation.

Public trust in research requires that the blodgu the decisions researcher and commitments they have made to an REB. As such, a clear sanctions mechanism must be implemented for violation of the requirements imposed by the REB.⁶⁶ These sanctions can potentially result in termination of the project, destruction of the data and samples collected, and notification of granting agencies and research sponsors. It should be noted that maintaining or granting research privileges must be closely linked to the researcher's compliance with their ethical commitments.

When an ethical review is carried out by an REB in another province, the physician conducting or collaborating on the research must ensure that the project complies with the applicable standards in Quebec,⁶⁷ most notably the provisions of the *Code of ethics of physicians*.

In this sense, physicians that are members of the order and conducting research in Quebec, or elsewhere from Quebec, must submit the project to an REB in Quebec⁶⁸ in order to comply with section 31 of the *Code of ethics of physicians*. Determination of the competent Quebec REB is based on the researcher's affiliation or lack of affiliation with an institution, the proposed recruitment sites, and the competence of the local REB to evaluate the project.

⁶⁶ See Chapter 4: Public Trust and Exemplary Conduct in Research.

⁶⁷ TCPS 2 (2018), Chapter 8; MSSS (2020).

⁶⁸ The Répertoire des ressources du réseau de la santé et des services sociaux en éthique et autorisation des recherches is available at <u>http://www.msss.gouv.gc.ca/professionnels/ethique/ethique-en-sante-et-services-sociaux/repertoires/</u>

10.2. QUEBEC'S VARIOUS RESEARCH ETHICS BOARDS

Depending on the researcher's affiliation, the proposed recruitment locations, the vulnerability of the participants, and the existing agreements (including the ethical review of multi-centre research projects), research projects must be submitted either to REBs in the health and social services network, to the Comité central d'éthique de la recherche (central ethics committee) of the Ministère de la Santé et des Services sociaux, or to private REBs.

10.2.1. Research ethics boards of health institutions

The boards of directors of health and social services network institutions are accountable for the research activities carried out in their institutions. Given the REBs' responsibilities in the approval process for research projects, it is imperative that the institutions in which the research projects are conducted have a credible and efficient ethics board that reports directly to the board of directors⁶⁹ and has sufficient resources to carry out their mandate within a reasonable timeframe. The ethical review of multi-centre research projects⁷⁰ (conducted in more than one network institution) does not, however, exempt the institution from liability regarding the ethical acceptability of the project it is authorizing on its premises. Researchers at each participating institution must contribute to the vigilance effort with regard to the consideration of the local ethical characteristics of the project, in particular with regard to the vulnerability of the client base served.

In Quebec, research projects involving minors, persons of full age who are incapable of giving consent, or persons of full age who recently became incapable of giving consent (in emergency medical situations) are subject to a specific legislative framework (section 21 of the C.C.Q) to provide these individuals, described as "vulnerable," with increased protection when asked to participate in a research project.⁷¹ Therefore, a researcher who wants to conduct research with the participation of such vulnerable persons must submit their research project to an REB designated by the Minister of Health and Social Services.

REBs in health care institutions are required to produce an annual report on their activities. All REBs are subject to the board of directors of the institution that created them and they report to them.⁷² Additionally, annual reporting to the Ministère de la Santé et des Services sociaux (MSSS) is mandatory for the designated REB under section 21 of the C.C.Q. Reporting is also mandatory for REBs of the network that can act as reviewers under the mechanism of ethical review for multi-centre research projects, whether they have been designated or not.⁷³ For other REBs, reporting to the MSSS is optional.

72 MSSS (2020), standard 4.

⁶⁹ Concerning the responsibility of the institution's board of directors with regard to the REB, see MSSS (2020), standard 4.

 ⁷⁰ MSSS (2016).
 71 See Chapter 16 which addresses the special considerations for research involving minors or persons of full age who are incapable of giving consent.

⁷³ MSSS (2019).

10.2.2. The Comité central d'éthique de la recherche of the Minister of Health and Social Services

When a research project has to be conducted in a location with no designated REB and involves minors or persons of full age who are incapable of giving consent, the researcher must submit their research project to the Comité central d'éthique de la recherche (CCER) of the Minister of Health and Social Services.⁷⁴ Under a mandate expanded by the MSSS to all categories of research participants, a researcher whose institution does not have an REB may submit their project to the CCER, even if it involves only capable persons. In addition, the CCER acts as a forum for appealing decisions made by REBs of institutions that do not have an appeals board.

Since fall 2015, under the Act to enact the Act to promote access to family medicine and specialized medicine services and to amend various legislative provisions relating to assisted procreation, the CCER is the only REB in Quebec with the authority to approve research projects involving assisted human reproduction activities or using embryos that are derived from them, but which have not been used for this purpose.

10.2.3. Private research ethics boards

In the same manner as REBs of institutions within Quebec's health and social services network and the CCER of the Minister of Health and Social Services, private REBs must comply with the standards in force, which includes their composition and operating procedures.

The scope of these boards is limited to research projects involving persons of full age capable of giving consent and that are conducted outside the institutions of Quebec's health and social services network.

An ethical review conducted by a private REB from another Canadian province or a foreign country cannot guarantee compliance with Quebec's standards, as discussed earlier. In this regard, the Collège reiterates that evaluation by a Quebec REB is required, even when the project is not conducted within the health and social services network.

The independence and competence of these private boards are essential and should be regularly audited (every three to five years) by an external body (e.g. Accreditation Canada).

⁷⁴ For more information, See MSSS (2019b).

11. AUTHORIZATION FROM THE INSTITUTION IN WHICH THE RESEARCH IS CONDUCTED

Researchers planning to recruit in institutions from the health and social services network must ensure they obtain authorization⁷⁵ following a review of their project's institutional suitability.⁷⁶ As part of the ethical review mechanism for multicentre research projects implemented by the MSSS, medical researchers must ensure to obtain an authorization letter for their research from the individual officially mandated by each participating institution.⁷⁷

Once the regulatory framework has been recalled, it is important to review the various practical aspects of clinical research. Although it would be impossible to address all issues, this guide aims to raise awareness among physicians who conduct or collaborate on research.

⁷⁵ MSSS (2020), standard 3.

⁷⁶ Ibid., standard 2.

⁷⁷ For more details on the ethical review mechanism for research projects conducted in more than one institution, see MSSS (2016).

ELEMENTS FOR REFLECTION AND PRACTICAL CONSIDERATIONS

12. THE PARTICIPANT RECRUITMENT PROCESS

12.1. IDENTIFICATION OF POTENTIAL PARTICIPANTS

Identifying potential participants calls for reflection on the practical application of the principle of justice in research. "The principle of Justice holds that particular individuals, groups or communities should neither bear an unfair share of the direct burdens of participating in research, nor should they be unfairly excluded from the potential benefits of research participation."⁷⁸ Identifying potential participants and recruiting them must, in addition, allow for avoiding selection bias. Specifically, researchers must avoid two pitfalls: Under-recruiting and over-recruiting certain persons or groups of persons.

Under-recruitment

It should be ensured that persons or groups of persons are not inappropriately excluded on the basis of their culture, language, sex, gender, race, ethnicity, age, or disability.⁷⁹ By way of example, for a long time clinical research excluded women and children from the outset, meaning the efficacy and safety of the treatments they received were not confirmed. While today there are efforts made in this regard, at least in the case of gender, some areas of clinical research still appear discriminatory and deserve acknowledgement and attention. For example, children and adolescents remain largely excluded from clinical trials on mental health drugs, yet

their use is widespread among these populations. While this exclusion could be explained, a priori, by a protective trend, other less formal arguments can also be put forth, such as the risk management calculations performed by the pharmaceutical companies funding these research projects.

Excluding categories of participants is obviously an option when supported by scientific justification that is relevant to the research topic, and not solely based on reasons of convenience. Researchers must submit justification to the REB for the proposed inclusions/ exclusions for the research projects they are conducting.

⁷⁸ TCPS 2 (2018), Chapter 4. 79 *Ibid*.
Over-recruitment

As previously explained, the principle of justice must lead not only to a fair distribution of risk, but also of research benefits. Some individuals are recruited more than others, occasionally to the point of becoming "expert participants." This may be the case of individuals registered in participant banks with small and/or very specific pools, who agree to be contacted regularly to participate in research projects. This reality has an impact: From an ethical point of view, by thus facilitating the identification of potential participants, there is a risk of undermining the equal opportunities for access to clinical research; from a methodological point of view, the learning effect (which means that by performing a task or test repeatedly, the person becomes faster and more experienced) has an impact on how the results are interpreted. Researchers must pay close attention to this reality and its potential consequences.

Sollicitation: Use of personal information

Consultation of clinical data is often required in order to identify and solicit potential participants. The Act to modernize legislative provisions as regards the protection of personal information⁸⁰ explicitly provides for the possibility for researchers to obtain identifying information from public or private organizations without the consent of individuals, under certain conditions (see Chapter 14: Privacy, Professional Secrecy, and Confidentiality).

12.2. RECRUITING PROSPECTIVE PARTICIPANTS AND CONSENT TO RESEARCH

Recruiting participants and seeking their consent to participate in research are among the most complex and challenging areas to be addressed in clinical research, especially when the researcher is also the treating physician of a prospective participant.

As with consent to care, for consent to research to be valid, it must be free, informed, and continuous throughout the participation.⁸¹ Particular attention should be paid to consent in the context of clinical research as the requirements for obtaining consent from the participant or their legal representative, if the participant is incapable of giving consent, are stricter than in a solely clinical context, especially as the person will retain little (or no) benefit from their participation in the research.

⁸⁰ The Act to modernize legislative provisions as regards the protection of personal information amends, with respect to research, the Act respecting Access to documents held by public bodies and the Protection of personal information, s. 67.2.1 – 67.2.2 – 67.2.3, the Act respecting the protection of personal information in the private sector, s. 21 – 21.0.1 – 21.0.2, and the Act respecting health services and social services, s. 19.2.

⁸¹ Code of ethics of physicians, section 30. 2.

12.2.1. Right to participate in research

Undue influence, coercion, or any use of incentives can undermine the voluntary nature of participation in research. There may be undue manipulation or influence if the recruitment of potential participants is carried out by persons in a position of authority. According to the TCPS 2,82 participants may feel constrained to follow the wishes of those who have some form of control over them. This control may be physical, psychological, financial, or professional, and may involve offering some form of inducement or threatening some form of deprivation.

Patient-physician relationship

Physicians conducting or collaborating on research must pay close attention to elements related to the relationship of trust and dependency they have with the patients they intend to recruit. These relationships can cause undue influence on patients in a position of dependence.⁸³ This influence can be exercised consciously by the physician, but more often it will be subtle in nature without the physician necessarily realizing it. For example, a patient might fear offending the physician or potentially receiving care of a lesser quality if they refuse to participate in clinical research. This example highlights the importance of considering constraints that may potentially be perceived by the patient. Article 27 of the *Declaration of Helsinki* states the following:

"When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship."84

The GCP extends this requirement by providing that "Neither the investigator, nor the trial staff, should, in any way, coerce or influence a subject to participate or to continue to participate in a trial."⁸⁵ In addition, it is recommended that physicians who provide health care to the patient be minimally involved in the recruitment and consent process for the research.⁸⁶

This separation of roles gives patients more freedom to accept or refuse to participate. However, in no way should this be considered an absolute guarantee: as such, the person outside the physician-patient relationship who is providing information and obtaining consent must be careful in this regard and question the patient if in any doubt.

- 85 Health Canada (2017), section 4.8.3.
- 86 TCPS 2 (2022), art.11.5 and application.

⁸² TCPS 2 (2022), Chapter 3.

⁸³ Ibid. 84 WMA (2013).

Competitive recruitment

Even including this precaution, there are still other aspects worth mentioning. Some multi-centre clinical trials include competitive recruitment between participating centres, meaning centres have to recruit participants quickly or they may end up devoting time and energy to obtaining administrative and ethical approvals in vain. Moreover, in institutions where research is highly integrated, competition can be observed between projects on the same site. Thus, research nurses strive to be the first to identify potential participants and recruit them for the research project they are managing, as participation in a clinical research project generally excludes the ability to participate in other projects. What impact do these competitive practices have on how patients are approached and how the research is proposed to them? Can the aforementioned objectivity and independence, which ensure freedom of participation, be realistically maintained under these circumstances? Physicians conducting or collaborating on research should pay close attention to these issues.

Right to withdraw

The right to participate in research goes hand in hand with the participant's right to withdraw from it at any time, with no requirement to give any reason. A participant's withdrawal usually raises the question of whether their collected data and samples should be preserved or destroyed. Although it makes sense to store and analyze this information in a clinical trial context for security reasons, or if the data was collected anonymously from the outset or is to be anonymized at some point in the project, the same cannot necessarily be said of all situations. Beyond researchers' obvious interest in retaining and analyzing data that required human and financial resources to collect, there is the issue of the effectiveness of the participant's withdrawal.

This issue takes even more meaning when the withdrawal occurs after the study procedures have been completed, but before the outcomes are published or disseminated. What does participant withdrawal mean when all of the collected data and samples are used for analyzing the research project? This right to withdraw then becomes theoretical. Destroying the data and samples, if technically possible and not putting a participant's security at risk, must be systematically proposed to the individual intending to withdraw, and respected if requested. If not, the participant must be clearly notified.

12.2.2. Informed consent: An ideal (im)possible to achieve?

In research, informed consent is the explicit expression of a person's willingness to participate in a project after receiving all of the necessary information. The requirement to obtain informed consent is twofold and includes, on the one hand, the obligation to provide information that allows the person whose consent is sought to exercise their autonomy, and on the other hand, the obligation to convey the information in a manner that the person can understand.

Information to be conveyed

With regard to the first aspect, the information conveyed to the prospective participant must be as complete as possible. This obligation is stronger than in a care context due to the experimental nature of what is being proposed to the participant, and there is no place in research to invoke therapeutic privilege or the possibility for the patient to renounce being informed.⁸⁷ While the Code of ethics of *physicians* specifies the main topics that must be discussed,⁸⁸ other texts such as the TCPS 2⁸⁹ and GCP⁹⁰ provide a much more detailed list. The information must include descriptions of the research project's nature, goals, and objectives, as well as comprehensive information on the conduct of the research, the benefits, risks (this will be discussed later), disadvantages, other methods and, if relevant, other possible treatment regimens including their risks and benefits, confidentiality, compensation for damages, compensation, right to participate and withdraw, etc.

Conveying information

Arising from the importance of the content of the information conveyed is another obligation, which is to convey this information in a manner that the person can adequately understand. This is truly a challenge.

Consent must generally be obtained in writing, but in 2013, the Quebec legislature opened the possibility of giving consent using alternative means if justified in the circumstances according to an REB. In such a case, the board shall establish the procedures that determine the proper manner, for evidential purposes, of obtaining consent.⁹¹ Note, however, that the GCP specifically requires written consent for clinical trials.92

Obviously, the more complex the research project, the greater the risk of the prospective participant misunderstanding the commitment being made. More complex projects entail more numerous and varied procedures or testing, and risk increases with each procedure, therefore requiring longer information and consent forms (ICFs). Along with the informative elements are more legal provisions that aim as much, if not more, to protect the interests and responsibility of research partners, particularly private sponsors. For example, it is not uncommon for ICFs in clinical trials to be more than 20 pages long.

⁸⁷ Philips-Nootens S. et al. (2016), p. 234.

⁸⁸ Code of ethics of physicians, sections 28 to 30.

⁸⁹ TCPS 2 (2022), article 3.2. 90 GCP (2017), section 4.8.10.

⁹¹ C.C.Q, section 24.

⁹² GCP (2010), section 4.8.8.

In Quebec, according to the Institut de la statistique du Québec, 53% of people aged 16 to 65 are "functionally illiterate," meaning they can read but have difficulty understanding all information in more complex texts.⁹³ There are also additional elements to be considered, such as recent immigration, cultural dimensions, language, etc., which could hinder comprehension of the information conveyed.

As a result,⁹⁴ physicians conducting or collaborating on research must acknowledge two things:

- Firstly, that significant efforts must be made to draft ICFs that facilitate reading;
- Secondly, that:

The traditional ICF is an essential tool, but cannot alone guarantee informed consent. It is necessary, but insufficient.

In spite of the above, out of respect for participants, the medical researcher must make sure to draft the ICF in plain language, with as little technical wording as possible, and in good French and/or English. Various types of support are available to researchers for this purpose.⁹⁵ That being said, creativity and exploring appropriate complementary strategies should be part of the equation to make complex projects easier to understand (e.g. preparation of brochures, videos, etc.). Tablets and apps (such as ResearchKit or ResearchStack) are beginning to be used to convey information, consent, and research data. When these tools are designed by third parties and not by the researcher and their team, verification of the online interface is required, as simply accepting "screenshot" information transmitted by the third party is inadequate. The researcher must also provide the REB with the technical possibility to verify the content. Several elements must be considered when using remote contact to inform and obtain consent, namely: security of the collected data, respect for the participant's privacy and vulnerability (e.g. the risky nature of a videoconference in a context of domestic violence), their support, and follow-up. In research as elsewhere, the benefits of using mobile applications must be weighed against the risks and disadvantages.

While these complementary arrangements are relevant, in-person or face-to-face communication nonetheless remains crucial in the process of obtaining consent.

⁹³ Desrosiers H. (2015).

⁹⁴ The exact figures for functional illiteracy in Quebec are subject to challenge. See for example Fortin P. (2017).

It should be noted, however, that this reality has to be taken into account in research.

⁹⁵ Lemieux V. (2013); Richard C. et al. (2016).

Participation in a research project is part of a relationship of trust between a researcher and a participant, and current technical arrangements cannot exempt professionals from such personto-person exchanges. Accordingly, researchers should take practical measures to ensure the quality and content of this verbal communication. This precaution is all the more relevant as, by signing the ICFs, researchers certify that explanations were given and all questions from participants were appropriately answered. Some would like to remove this clause alleging a lack of control over these aspects, but they remain responsible for ensuring (by means of their choice) that sufficient understandable and explanations have been given to the prospective participant for their consent to be informed. The specific responsibilities of the learner and their supervisor in this area must, where appropriate, be known and respected.⁹⁶

When the person whose consent is sought does not understand English or French, research teams usually ask a family member or relative to translate; this consent is then considered valid. This solution, while practical, raises obvious issues, as it is impossible for the team to verify the content of the information conveyed, and consequently, the validity of the consent. In addition, family members have their own feelings toward the research project, hopes for what it may or may not produce, and may try to sway the potential participant in either direction. While this practice is quite common in care, it should be the exception in clinical research. Moreover, the higher the participant's implied risk in the project, the more essential it is to confirm their understanding of what they are committing to. As a result, researchers should propose this approach only as a last resort, having taken and documented the necessary steps to obtain a professional translator within a reasonable timeframe.

Verification of understanding

Once the information has been provided, strategies for verifying the participants' understanding should also be implemented and developed when the research is complex, participants are fragile, or their risk-benefit profile is disadvantageous. For example, a guide intended for staff tasked with seeking participant consent that would outline key elements (through a checklist) to verify participants' understanding could be useful.⁹⁷

⁹⁶ See the guide entitled *Role and Responsibilities of the Learner and the Supervisor* published by the Collège des médecins du Québec (2016).
97 See for example: Jeste D.V. et al. (2007) and Hugonot-Diener L. (2008).

Continuous process

Recall that consent is an ongoing process that begins from initial contact and continues throughout and until the end of the research project. Any information likely to affect participants' willingness to continue participating in the research must be communicated to them, with the same precautions as previously mentioned.

As just explained, obtaining free and informed consent in research is a demanding process for researchers. Nevertheless, it remains a principle fundamental to the trust that citizens grant to researchers and research.

12.2.3. Recruitment bonuses

Recruitment bonuses are a sensitive issue, and a distinction is made between:

- Finders fees and recruitment bonuses (amount paid or any other benefit granted by the sponsor or researcher to a person in return for recruiting a research participant⁹⁸);
- Head hunter bonuses (substantial amount of money paid by the sponsor to the researcher, based on the number of participants to the research project);
- Competitive enrolment bonuses (bonuses paid by the sponsor to the institution, researcher, or person in charge of recruiting participants when occurring within the time limits established by the sponsor).

These bonuses can be paid for simply identifying participants, or they may be subject to a competitive timeframe. Incidentally, the TCPS 2 warns institutions and researchers, and encourages institutions to "look for issues such as inappropriate payments or other unexplained expenses that may raise questions about conflict of interest. Payment provisions should be scrutinized to ensure they do not create ethically inappropriate incentives to recruit quickly, at the expense of a careful review of the suitability of prospective participants. Unreasonable payments or undue inducements may place the researcher, and sometimes the institution, in a conflict between maximizing financial remuneration, on the one hand, and protecting participants and meeting the scientific requirements of the project on the other. Disclosure of the kinds and amounts of payments and other budgetary details encourages the researchers to identify and appropriately manage potential conflicts of interest and helps the institution to assess them. Management by institutions may include prohibiting certain forms of payment."⁹⁹

 ⁹⁸ FRSQ (2008), section 13.
 99 TCPS 2 (2022), Chapter 7, Section D.

The Code of ethics of physicians stipulates that "A physician must refrain from accepting, in his capacity as a physician or by using his title of physician, any commission, rebate or material benefit with the exception of customary presents and gifts of modest value."¹⁰⁰

Due to the risk of a conflict of interest and the potential adverse impact on the protection of participants, the scientific value of research, and the quality of medical practice, finders fees, headhunter bonuses, and competitive recruitment bonuses are unacceptable, whether the research is conducted in Quebec's public or private sector.

These bonuses differ from fair and reasonable fees covering expertise and the time required to accurately assess a patient's potential participation in a research project. The *Code of ethics of physicians* provides that "Remuneration or compensation of a physician for the time and professional expertise he devotes to research must be reasonable and known to the ethics committee."¹⁰¹ To assess whether fees are reasonable, physicians conducting or collaborating on research must carefully analyze:

- the time and work required for meticulously identifying and recruiting participants;
- the amount of money or benefits proposed for this work;
- the balance of proportions between these two elements; and
- the impact of this remuneration/ compensation on their will to participate in recruiting for the research project.

The kinds and amounts of payment and other budgetary details must be disclosed to an REB for evaluation and management of potential conflicts of interest.¹⁰² They should also be disclosed to the research branch of the institution or organization, as appropriate.

¹⁰⁰ Code of ethics of physicians, section 73. 3.

¹⁰¹ *Ibid.*, section 78, paragraph 3.102 TCPS 2 (2022), Chapter 7, Section D.

13. MANAGEMENT OF THE BENEFITS, RISKS, AND DISADVANTAGES OF RESEARCH

Management of benefits, risks, and disadvantages is a central aspect of clinical research that calls for careful professional medical judgment.

13.1 RESEARCH BENEFITS

Although a distinction is often made between personal benefits from research and benefits for the advancement of scientific knowledge, they are actually part of a whole (benefits for relatives, for the group represented, for the community, etc.).

Advancement of scientific knowledge

This category of benefits is, a priori, a given and spurs discussion on the relevance of the proposed research: Does it result in new knowledge? Although this may seem a trivial reminder, sometimes research projects are authorized despite not adding much to the current state of scientific knowledge. In such cases, the ethical and scientific bodies of health institutions tend to examine the project in terms of the risks incurred by participants and to consider the project acceptable if the risk is low. For physicians leading, supervising, or collaborating on this type of research, consideration must be given to mobilizing the resources required to carry out these projects, both for staff and participants. The expected impact on the advancement of knowledge must always be presented to participants in detail and with caution.

Personal benefits

There is an observed tendency for participants to be optimistic, sometimes overly so, about the potential personal benefits that clinical research will yield to them.¹⁰³ This potentially refers to "therapeutic misconception," which means that participants are misinformed about the purpose, benefits, or risks associated with the research, particularly in clinical trials. Often, participants are not aware that research is primarily aimed at producing knowledge, and that as a result, it may not provide them with therapeutic benefits. There is also a therapeutic misconception when participants engage in a clinical trial without understanding how research-specific elements could interfere with their own objectives regarding the health care they receive. Physicians conducting or collaborating on research should, like all researchers, be attentive to participants' unreasonable beliefs about the personal benefits they may derive from the research. This misunderstanding can be reinforced by the researcher's own enthusiasm.

This reality must be taken into account and participants must be cautiously informed about the individual benefits they may expect. It must be highlighted that clinical research, particularly clinical trials, aims to understand not only the effects and benefits, but also the potential risks of a molecule, treatment, etc.

Additionally, researchers must ensure that, after the end of a clinical trial, appropriate provisions for post-trial access to the intervention or drug tested are provided for and discussed in the protocol.¹⁰⁴ This should be addressed in discussions with the study's sponsors where appropriate, and even with the government, under article 34 of the *Declaration of Helsinki*. It can be very frustrating for a physician conducting or collaborating on research and for a participant to observe benefits from an experimental treatment, only to be unable to continue the treatment after the study comes to an end. This information must be disclosed to participants when seeking their consent.¹⁰⁵

¹⁰³ For example, see Halpern J. et al. (2018).

¹⁰⁴ WMA (2013), article 22.

¹⁰⁵ Ibid., article 34.

13.2. RISKS OF RESEARCH

"Research is a step into the unknown. Because it seeks to understand something not yet revealed, research often entails risks to participants and others. These risks can be trivial or profound, physical or psychological, individual or social. History offers unfortunate examples where research participants have been needlessly, and at times profoundly, harmed by research, sometimes even dying as a result."¹⁰⁶ There are many risks (or harm), which may be psychological, physical, social, professional, economical, related to cultural identity, etc. They may concern an individual or a family (e.g. risk to fetal development, impact on family life), or associated with the community (e.g. risk of stigmatization).

Foreseeable risks, clinical equipoise

A researcher must objectively assess any potential harm related to a research project, regardless of its nature, and reduce it to a minimum.¹⁰⁷ The magnitude and likelihood of harm are part of the "foreseeable risks" concept. In accordance with the principle of respect for persons, it is therefore the responsibility of the researcher to clearly and accurately outline to potential participants all foreseeable risks related to the research,¹⁰⁸ including the cumulative risks. Note that providing this information is particularly challenging in the context of a research project, as the researcher has a duty to disclose all known risks, even if rarely occurring or marginal, and all the more so when these risks could result in serious consequences.

Although participants generally have a good understanding of the study's objective and methodology and of their right to withdraw, several studies suggest that participants of full age who are capable of giving consent lack proper understanding of the risks associated with participating in research.¹⁰⁹ Their enthusiasm regarding potential health benefits, combined with poor numeracy skills (56% of Quebecers aged 16 to 65)¹¹⁰ and trust that their physician would never ask them to participate in research that could potentially cause them harm, are factors that contribute to their difficulty in understanding and their underestimation of the risks related to the research.

Based on this evidence, the responsibility of making a fair assessment of the personal risks they are willing to accept should not solely rest on the participant, in the name of the principle of autonomy of will and in the interest of science.¹¹¹

107 WMA (2013), articles 16 to 18.

¹⁰⁶ TCPS 2 (2022), Chapter 1, section A.

¹⁰⁸ Health Canada (2017), section 4.8.10.

¹⁰⁹ Mandava A. et al. (2012). 110 Desrosiers H. (2015).

¹¹⁰ Desrosiers H. (2015).

I WMA (2013), article 9: "It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent."

Recall that the concept of consent to receive care or participate in research is the result of an ongoing, joint decision-making process, and that clinical judgment must be exercised prior to offering any care or participation in research.

As research is a step into the unknown, benevolence is required within this context.

Due diligence must be exercised in the preliminary assessment of the foreseeable risks associated with the research. This diligence shall be exercised at two levels:

- At the macro level, physicians as well as researchers shall assess the foreseeable general risks associated with the research they are conducting or collaborating on, and they must be able to justify these risks in relation to the expected benefits while reducing the former to a minimum.
- At the micro level, they shall perform the same exercise based on the specifics of each person they wish to recruit in the project, including regarding possible consequences on their health, quality of life, family support, and community environment, if applicable. In this regard, the physician conducting or collaborating on research must keep in mind that they are still bound by their ethical obligations. They must ensure that the research will not deny the patient access to established effective therapies that would be in their best interest.

Clinical equipoise is the recommended criterion for this purpose. This criterion requires that, in order for a trial to begin, "a genuine uncertainty exists on the part of the relevant expert community about what interventions are most effective for a given condition. This uncertainty necessitates the conduct of research to determine the comparative therapeutic merits of different interventions (not all of which may be represented in a given clinical trial). Clinical equipoise provides a link between the duty of care of a clinician and the need to do research to ensure that the therapies or interventions offered are demonstrably safe and effective."112 Clinical equipoise is generally considered as the moral foundation of randomized controlled trials.

Monitoring mechanisms

Diligence implies a duty to monitor. Risk management obviously involves adopting means and strategies to ensure that, for the entire duration of the research, risks to participants are mitigated and that participant safety is monitored. Unforeseen circumstances, such as unexpected reactions (e.g. side effects of a medication), protocol deviations or violations, etc., must be duly analyzed and reported to the relevant authorities.

For clinical trials, researchers are required to submit a safety monitoring plan, which must provide a mechanism by which participants can be removed from a study and by which trials can be stopped or amended due to evidence of being dangerous, futile (e.g. if it is determined that the trial is unlikely to yield valid outcomes), or conclusive.¹¹³ Should an independent Data and Safety Monitoring Board (DSMB)¹¹⁴ be established, the researcher will rely on its analysis while maintaining responsibility for the participants they have recruited in the study. For example, if following data analysis, the DSMB decides to move forward with the project despite the occurrence of a serious side effect, the physician conducting or collaborating on the research maintains their clinical judgment and is entitled to consider that the specific balance between the risks and benefits for one or several of their participants is unfavourable, and thus, that they should still be removed from the study.

In multi-centre clinical trials, this duty to monitor extends beyond having the sponsors shut down the site. The researcher must be assured that they will regularly receive updated safety data on the trial and have access to the general outcomes of the research, even when unfavourable or non-significant, and even if compiled five to ten years down the line. If this data could potentially result in significant consequences now or in the future on the physical health, mental health, or well-being of the participants recruited by the researcher, they must be informed of this outcome. In this regard, it is concerning to note that shutdown of a clinical trial site¹¹⁵ by the sponsor generally results in discontinuation of the ethical follow-up by the REBs of public institutions, regardless of the magnitude and duration of the risks incurred by the participants. Doing so effectively removes part of the protection granted to research participants by circumscribing it to their active participation, as following discontinuation of the treatments, tests, and procedures related to the study, ethical follow-up of complications on the medium-to-long term is not ensured.

The Collège recommends that physicians conducting a research project discuss with the REB the possibility of adopting a scaled-down follow-up mechanism after the shutdown of the site when deemed appropriate (e.g. trials on new assisted reproduction procedures). In any case, the general outcomes of the research must be communicated to the REB that assessed the project, even when ethical follow-up has been discontinued.¹¹⁶

¹¹³ TCPS 2 (2022), Chapter 11, section C.

¹¹⁴ Health Canada (2017), section 1.25: "Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee). An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial."

<sup>Health Canada (2013), section 2.8.3.
Health Canada (2017), section 4.13: "Final Report(s) by Investigator. Upon completion of the trial, the investigator, where applicable, should inform the institution;
Health Canada (2017), section 4.13: "Final Report(s) by Investigator. Upon completion of the trial, the investigator, where applicable, should inform the institution;</sup> the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

13.3. LIMITATION OR EXCLUSION OF LIABILITY FOR HARM

No clause of limitation or exclusion of liability contained in an ICF shall be deemed valid or acceptable, whether from a legal or ethical point of view.

This proscription of limitation or exclusion of liability shall apply to the researcher, the research project sponsor, as well as the institution where the research is being conducted.

Like any researcher, the physician undertaking a research project shall not accept that the research agreement, ICF, or any other document with legal value contain any provision stating that the physician, sponsor, or institution shall be limited or excluded from liability, and shall also refuse any clause drafted in obtuse or unclear language.

Regarding clinical trials, in the document Standard legal clauses for information and consent forms for clinical trials, the MSSS and the Fonds de recherche du Québec – Santé (FRQS) recommend using the following formulation for addressing participants: [Translation] "Should you suffer harm of any kind following administration of the study drug or any other procedure related to this research study, you will receive appropriate care and services as required by your health status. By agreeing to participate in this research study, you are in no way waiving any of your legal rights nor relieving the physician leading the study, the sponsor, or the institution of their civil and professional responsibilities."¹¹⁷

It is indeed unacceptable that the remedies or rights to receive care for a participant in Quebec be limited as a result of their participation in a research project.

The Collège states that physicians conducting research must adapt this specific clause and other similar clauses in ICFs for clinical research conducted in Quebec, in both the public and private sectors.

13.4. BURDENS OF RESEARCH

Burdens are generally mild or minor (travel requirements, loss of time, absence from work, school, etc.). Although research teams generally highlight research risks to participants, they place less emphasis on burdens. Yet, burdens may have a decisive impact not only on a person's consent or refusal to participate in a research project, but also on their willingness to continue their participation throughout the project, especially if the project spans a long period of time. The perception of burdens is subjective according to each person's lifestyle. Thus, research which poses minimal risks but requires travelling during working hours will not have the same impact on workers as on retirees, for example, especially if there is little personal benefit. Likewise, moving a participant with a severe cognitive impairment to a hospital is more challenging and demanding for caregivers.

These constraints must be given due consideration by researchers to not only foster recruitment and attrition rates, but also prevent methodological biases.

13.5. COMPENSATION FOR PARTICIPATION

The principle of absence of gain and of no commercial use of the human body is explicitly emphasized in the *Civil Code of Québec*.

More specifically, in the field of research, the second paragraph of section 25 provides that: "A person's participation in research that could interfere with the integrity of his person may not give rise to any financial reward other than the payment of an indemnity as compensation for the loss and inconvenience suffered."¹¹⁸

There is no specific standard establishing a reasonable scale regarding the amounts paid to a participant to compensate for losses and constraints experienced as a result of their participation in a research project. Compensation is often based on the funds available to the researcher. Thus, under equal conditions, there are often great discrepancies in participant compensation.

Researchers and REBs are responsible for ensuring that the compensation paid for participating in a research project is exclusively intended to compensate for the losses and constraints that participants may experience as a result of their participation in the project. This compensation shall in no way exercise any influence over the participant that may unduly cause them to participate. In this regard, special consideration must be given to the vulnerable position of prospective participants (e.g. persons living in institutions, in a position of dependency, or in a situation of financial precariousness) for whom simple compensation might constitute a sufficient incentive to take risks they would not have taken otherwise.¹¹⁹

In addition to compensation, the terms of payment must also be examined. Indeed, deposits made by the sponsor on prepaid credit cards could be problematic as they could constitute a breach of privacy should the sponsor gain access to privileged information about the participants outside the scope of research.

Moreover, should a participant be removed from the study, the amount paid should be in proportion to their effective participation and not conditional upon the completion of all procedures included in the study. It is a matter of respect for their freedom to participate.

In the case of research involving a minor or a person of full age incapable of giving consent, the balance between the constraints suffered by the participant and those suffered by the relative(s) to enable them to participate in the research (e.g. travel, babysitting for other children, etc.) is not as clear-cut. The Civil Code does not draw any such distinction. Researchers should take into consideration all of the constraints suffered and also remember to plan compensation for the participants.

Moreover, participants must be informed when the total compensation they receive for their participation in one or several clinical trials over one year exceeds \$1500, as the surplus amount is subject to taxation.¹²⁰

118 C.C.Q., section 25.
119 TCPS 2 (2022), article 3.1 and application; article 4.7.
120 Revenu Québec (2018), 17. Other Deductions (line 250).

13.6. COMMUNICATION OF OUTCOMES AND FINDINGS TO PARTICIPANTS

General outcomes of the research

As soon as the initial consent is obtained, researchers must systematically offer participants the opportunity to access the general outcomes of the research after they have been translated into plain language,¹²¹ in such a manner that does not place the burden of seeking information on the participants. Therefore, indications often proposed in ICFs such as "the results of this research will be communicated upon request" or "the results will be accessible on the clinicaltrial.gov website" do not do justice to their altruistic participation and are not necessarily effective ways to communicate with the average layman. Current technology, such as e-mail communication or publication on the website of a research lab, are simple and inexpensive ways available to researchers for disclosing information to participants in plain, meaningful, and useful language.¹²²

Individual outcomes and incidental findings

Individual outcomes of tests, procedures, and examinations carried out as part of the research are not systematically communicated to participants, except for incidental findings. The TCPS 2 provides for the requirement of disclosing to a participant significant incidental findings if they "are reasonably determined to have significant welfare implications for the participant."¹²³

"An incidental finding is a discovery about research participants or prospective participants that occurs in the course of research, but is outside the objectives of the research study."¹²⁴

Three points deserve particular attention:

- (1) The Collège considers that the obligation to disclose also extends to significant findings that are non-incidental, i.e. when a test, procedure, or questionnaire used in research could realistically result in the detection of an issue or reveal a specific pathology. For instance, a urinalysis to measure blood sugar levels within the context of research on the prevalence of diabetes has a high likelihood of revealing glucosuria in some participants. Likewise, it is reasonable to assume that MRIs performed within the context of research have the potential to reveal brain tumours.
- (2) The obligation to report significant findings, whether they are incidental or not, also prevails when the findings arise from scientifically and clinically valid examinations or tests and bear clinical utility, i.e. when there are ways of prevention or treatment and the benefits of disclosure outweigh the risks incurred.
- (3) If in practice significant findings related to physical health are for the most part reported to the participant, the same cannot be said for disclosing and taking action regarding clinically significant outcomes to tests related to mental health performed within the context of research on physical health. This type of outcome is not yet subject to a systematic disclosure plan, even for suicidal risk, although the law has provisions regarding the lifting of professional secrecy in such situations. Concerns are often raised over the resulting divide between the roles of researcher and physician, the delay for analyzing individual data, and the burden that disclosure imposes on researchers. The use of such a differentiating approach is questionable in terms of ethics and professional conduct.

¹²³ TCPS 2 (2022), article 3.4. See also, Interagency Advisory Panel on Research Ethics (2019). 124 *Ibid.*, Chapter 3.

Physicians conducting research should give due consideration to establishing a plan for the systematic disclosure of significant findings, whether incidental or not, and submitting it to the REB when clinically valid and relevant tests are conducted for the purpose of physical and mental health research. Regarding the outcomes of tests used in research that have not been clinically validated, the need for verification through clinically validated tests should at the very least be examined.

In addition, such action plans must be well known and understood by the research staff and explained to participants when obtaining their consent to participate in research. When disclosure is under consideration, consent should in principle be confirmed once again as part of this ongoing process.¹²⁵

However, the physician involved in the research should not systematically be required to alone bear the heavy responsibility of monitoring and treating all participants that are impacted by findings related to physical or mental health. Such responsibility extends beyond their researcher role and may have adverse effects on a great deal of research. The physician's role is rather to ensure that:

- (1) the medical information is of significant concern to the participant's health;
- (2) the information is communicated to the most appropriate persons, with the consent of the participants or their representatives.

Depending on the circumstances, reporting information to participants and health professionals, and establishing a service corridor constitute appropriate measures that must be decided upon while focusing on proportionality and the participant's interest.

¹²⁵ On the topic of consent to participate in research, see Chapter 12, section 2.3 of this document.

14. PRIVACY, PROFESSIONAL SECRECY, AND CONFIDENTIALITY

Physicians involved in a research project are subject to the same confidentiality rules as in a clinical setting. The physician is bound by professional secrecy when carrying out their professional activities, whether working within an institution or private practice.

Research records must remain confidential both in private practice and institutional settings within the health and social services network.

Access to medical records

Special attention must be given to medical records and their access. Recall that a medical record is filed by the physician on every person to whom they provide professional services. However, to use the information contained in this record for purposes other than their original clinical intent, the physician must first obtain consent from the person involved, unless access is permitted by a specific legal provision to that effect. In other words, research is no justification for violation of professional secrecy.

Whether in a private practice or an institution, access to medical records for research purposes may be granted with the patient's consent. This consent must, however, meet certain criteria: It must be clear, free and informed, and obtained in writing for specific purposes and a set duration. Additionally, access to medical records for research purposes may be granted without patient consent, but subject to even more stringent conditions.¹²⁶

126 The Act to modernize legislative provisions as regards the protection of personal information amends, with respect to research, the Act respecting Access to documents held by public bodies and the Protection of personal information, s. 67.2.1 – 67.2.3, the Act respecting the protection of personal information in the private sector, s. 21 – 21.0.1 – 21.0.2, and the Act respecting health services and social services, s. 19.2.

Disclosure of identifying information may be made without consent if a privacy impact assessment concludes that:

- the research objective can only be achieved if the information is provided in a way that identifies the persons concerned;
- it is unreasonable to require the researcher to obtain the consent of the individuals concerned;
- the objective of the research in the public's interest outweighs the impact of the disclosure and use of the information on the privacy of the individuals concerned;
- the personal information will be used in a manner that ensures its confidentiality;
- only the necessary information is provided.

The researcher must then, in collaboration with the public or private organization:

- submit a request in writing;
- detail the research activities;
- justify that the above-listed conditions are met;
- list any persons and organizations to whom a similar request has been made for research purposes;
- if applicable, describe the different technologies to be used to process the information;
- send research approval by an REB.

The researcher and the public or private organization from which the personal information comes from must establish an agreement prior to disclosing the information that provides:

- the usual confidentiality measures relating to the use of data;
- the information to be given to prospective participants in order to reach them to participate in the research;
- the obligation to notify the organization of the destruction of the information transmitted;
- the obligation to notify the organization and the Commission d'accès à l'information (CAI) of any breach of a condition of the agreement, any breach of the agreement, or any event likely to affect the confidentiality of this information.

Once the agreement is reached, it must be forwarded to the CAI and it enters into force 30 days following its reception by the CAI.

Thus, in the case of medical records kept by a health institution, the institution's director of professional services (DPS) or, if there is no such director, the executive director may authorize a professional to examine a user's record, under the same abovementioned conditions.¹²⁷

Outside Quebec and Canada

In closing, it should be noted that a researcher disclosing personal information held by private or public organizations for research purposes outside of Quebec must first take all the reasonable means to ensure that the information disclosed will only be used for purposes relevant to the study and in a secure manner.¹²⁸

In early September 2023, a written agreement will have to be produced between the parties to transfer this information.¹²⁹ It will take into account the assessment of the sensitivity of the information, the purpose of intended use, the measures to protect confidentiality, including contractual measures, and the legal framework applicable in the jurisdiction in which the information will be disclosed. This assessment must conclude that the information disclosed is appropriately protected in terms of commonly recognized protection principles. The agreement must establish, as applicable, the terms and conditions for mitigating the risks identified in this assessment.

In addition, when such information is communicated between provinces or outside of Canada, the federal *Personal Information Protection and Electronic Documents Act* (PIPEDA) also applies. In doing so, the law requires that the fiduciary—the person who has the information in Canada—make sure that the person receiving the information outside of Canada will provide a level of protection comparable to that granted by the federal legislation.

The enactment in May 2018 of the *General Data Protection Regulation* (GDPR) in all countries of Europe has strengthened provisions on data protection (including health data), namely with regard to international data transfers and the processing of personal information for scientific research purposes.¹³⁰ Certain rights that are now guaranteed in Europe are not provided for in Quebec and in the rest of Canada, therefore having consequences on clinical research conducted in Canada by sponsors headquartered in Europe (e.g. the right to restrict data processing during a request for correction, right to transfer data from a study to a third party in a commonly used and legible format, etc.).

In light of these changes, a review is needed on the current equivalence of data protection legislation in Quebec and Canada.

Act respecting Access to documents held by public bodies and the Protection of personal information, section 70.1; Act respecting the protection of personal information in the private sector, section 17.
 Act to modernize legislative provisions as regards the protection of personal information.

¹³⁰ Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). In particular, see Chapter V.

15. REQUIREMENTS INHERENT TO THE CREATION OF A MEDICAL RESEARCH RECORD

The requirements inherent to the creation and maintenance of a medical research record are set out in the *Règlement sur les dossiers, les lieux d'exercice et la cessation d'exercice d'un médecin.*¹³¹

As a general rule, the physician must create, keep, own, and maintain a medical research record on any person who participates in a research project.

In addition to the general information required, a medical research record created on any person who participates in a research project must contain the following information:

- the title of the research project, identification of the research protocol (including the protocol number), identification of the principal investigator and their associates, as well as the REB authorization form attesting that the applicable standards are met, namely with regard to the REB's composition and operational procedures;
- the ICF duly signed by the research participant, or in the case of a minor or a person of full age incapable of giving consent, the ICF duly signed by a legally authorized person;

- a copy of the document given to the participant, or in the case of a minor or a person of full age incapable of giving consent, to the legally authorized person, attesting to their participation in a research project and containing the information required to ensure followup with their treating physician or in an institution, as applicable;
- information proving that the person was administered the doses of the test product as specified in the protocol, along with any observations regarding side effects reported during the study and the measures taken in that regard;
- a final note stating completion of the project or, if applicable, the reasons for its discontinuation.

The physician must keep the medical research record created on any person who participates in a research project for a sufficient period following the end of the study to allow for the necessary verifications to be made, within reason in comparison to the duration of the project itself. Furthermore, the obligation to keep records on clinical trials is set at a minimum of 15 years.¹³²

In addition, the physician is required, in every private practice or office in which they carry out their professional activities, to create, keep, own, and maintain a list of every person they examine or treat, or whose treatment they oversee within the context of a research project.

131 *Medical Act* (CQLR c M-9, section 3) and *Professional Code* (CQLR c C-26, section 91). 132 Health Canada (2019), section C.05.012(4).

16. RESEARCH INVOLVING A MINOR OR A PERSON OF FULL AGE INCAPABLE OF GIVING CONSENT

The standard slightly differs when the project involves a minor or a person of full age incapable of giving consent.

A minor (person under 18 years of age) or a person of full age incapable of giving consent is considered as vulnerable by the Quebec legislature. The legislature therefore introduced a series of measures to provide greater protection to these persons when they are asked to participate in a research project.

Benefits in proportion with risks

Section 21 of the C.C.Q. provides that a minor or a person of full age who is incapable of giving consent may participate in research that could interfere with their integrity only if the risk incurred, taking into account his state of health and personal condition, is not disproportionate to the benefit that may reasonably be anticipated. Therefore there must be a balance in proportions, where the higher the risks, the higher the expected benefits should be.

The legislature also makes a distinction between research involving a single minor or person of full age incapable of giving consent, versus research involving a group of minors or persons of full age incapable of giving consent.

Research involving a single minor or person of full age incapable of giving consent must have the potential to produce benefits for their health.

Research involving a group of minors or persons of full age incapable of giving consent is permitted if it has the potential to produce results capable of "conferring benefit to other persons in the same age category or having the same disease or handicap."¹³³ This requirement therefore excludes minors or persons of full age incapable of giving consent when the research project is focused on characteristics or diseases that are not relevant to their group.

133 C.C.Q, section 21.

Consent

In all cases, a minor or a person of full age incapable of giving consent shall not participate in such research if they understand the nature and consequences of the research and object to participating.

Minor under 18 years of age

For a minor under 18 years of age, consent to research may be given by the tutor or person with parental authority. Although a minor of 14 years of age and over may give consent alone to care required by their state of health, the rule is nonetheless different in a research context, and researchers have the obligation, in principle, to obtain consent from the guardian or person with parental authority.

- A child's parents are *de facto* considered as having parental authority. Moreover, this parental authority is jointly exercised by both parents. However, it is not always necessary to obtain consent from both parents. Where one parent performs alone any act of authority concerning their child, they are, with regard to third persons in good faith, presumed to be acting with the consent of the other parent.
- Even after divorce or separation, each parent continues to have parental authority over their child, even when one parent has sole custody of the child.

While in most cases consent from only one parent is sufficient, in cases where researchers are aware of difficult family situations, a precautionary approach should be adopted to ensure that both parents give consent for their child to participate in the research, in particular when there are risks involved for the child. Before 2013, the principle of parental consent for children's participation in research, which was a requirement in any and all circumstances, resulted in complex and even unreasonable situations. For example, a 15-year-old girl could choose to have an abortion on her own, but could not decide to participate in a research project on the physiological impact of this abortion. In 2013, the legislature eased the principle of parental consent for projects with minimal risk, i.e. projects that do not expose minors to greater risks than their daily activities.

Consequently, a minor 14 years of age and over may give consent alone if, in the opinion of the REB, the research involves only minimal risk and the circumstances justify it.¹³⁴ This is in no way a blank cheque, and requests are examined by the REB on a case-by-case basis. A researcher seeking to obtain an exemption for parental consent for the participation of a minor aged 14 and over in a project with minimal risk must document the situation to demonstrate the necessity of such an exemption to the REB.

Person of full age incapable of giving consent

Consent to research that could interfere with the integrity of a person of full age incapable of giving consent may be given by the mandatary, tutor or curator. However, where such a person of full age is not so represented and the research involves only minimal risk, consent may be given by the person qualified to consent to any care required by the state of health of the person of full age, i.e. by his or her married, civil union or de facto spouse or, if the person has no spouse or his or her spouse is prevented from giving consent, it is given by a close relative or a person who shows a special interest in the person of full age.¹³⁵ It is incumbent upon the competent REB to determine, when evaluating the research project, whether it meets the prescribed requirements.¹³⁶

The key point to remember is that for persons of full age incapable of giving consent, only those under protective supervision, i.e. under tutorship, curatorship, or a protection mandate duly endorsed by the court may participate in a research project that involves more than minimal risk.

Assent

Among the specific measures for protecting minors and persons of full age incapable of giving consent is the concept of assent.

Assent allows a minor or a person of full age incapable of giving consent to express that they do not object to participating in a research project, under the condition that they understand its nature and consequences. It must be acknowledged that the Quebec legislature provides no formal requirement for assent. As such, a minor or a person of full age incapable of giving consent is not required to sign an ICF to express that they do not object to participating in a project. However, should they express objection, they shall not participate in the research project.

Regarding clinical trials, the GCP provides that a minor or a person of full age incapable of giving consent should be provided with information about the trial within the limits of their understanding and that, if capable of doing so, they must personally sign and date the ICF.¹³⁷

When a minor reaches the age of 18 during an ongoing research project, the researchers are required to contact them to obtain their personal consent to participate in the research. The same applies to a person who was incapable of giving consent that regained their ability to give consent.

Incidental and non-incidental findings

Another point to consider is the communication of incidental or non-incidental findings involving minors or persons of full age incapable of giving consent.

When the aforementioned criteria for scientific validity, clinical validity, and clinical utility have been met,¹³⁸ researchers should provide a provision in their information disclosure plan to readily communicate these results without requiring prior consent from the parents or legal representatives. This information must be explicitly provided for when seeking consent to participate in research.

Even so, in the event that a parent or legal representative objects to disclosure during the course of the research, the researcher must promptly notify the REB to jointly devise a strategy. The strategy must take into account not only the severity and urgency of the information to be communicated, but also the family's current human context; it may simply be the wrong timing as the family is experiencing a crisis, in which case it would be medically and ethically acceptable to temporarily postpone disclosure. Calling on authorities to judicially force such disclosure should only be considered as a last resort.

¹³⁵ C.C.Q, section 15.

¹³⁶ C.C.Q, section 21.

¹³⁷ Health Canada (2017), section 4.8.12.

¹³⁸ See Chapter 13, section 13.6.

17. RESEARCH IN EMERGENCY HEALTH SITUATIONS

In 1998, the Quebec legislature amended the C.C.Q., to specifically include the concept of research in emergency health situations. Minor amendments were also made in 2013.

Thus, consent may be given by the person qualified to consent to any care required by the state of health of a person of full age under the following conditions:

- a person of full age suddenly becomes incapable of giving consent; and
- the research, insofar as it must be undertaken promptly after the appearance of the condition giving rise to it, does not permit, for lack of time, the designation of a legal representative for the person of full age.

In both cases, it is incumbent upon the competent REB to determine, when evaluating the research project, whether it meets the prescribed requirements.¹³⁹

Thus, when the REB is of the opinion that the research project meets all of the prescribed requirements and in the absence of a mandatary, tutor, or curator, the persons qualified to give consent are firstly the spouse, whether through marriage, civil union, or by *de facto*. If the person has no spouse or their spouse is unable to give consent, it is given by a close relative or a person who shows a special interest in the person of full age.¹⁴⁰

The C.C.Q. does not provide for research that must begin without obtaining consent from a representative or relative in a timely manner. This is the case of some research conducted in the emergency departments and intensive care units of hospitals. After experiencing great difficulty in recruiting due to the complexity of reaching out to representatives or relatives in these situations, several research teams have asked REBs to allow for deferred consent, which is obtaining consent from the representative or relatives after the research has begun. It should be noted that the TCPS 2 contains provisions for amending requirements pertaining to consent under certain conditions.¹⁴¹

139 C.C.Q, section 21. 140 C.C.Q, section 15. 141 TCPS 2 (2022), art. 3.7A.

18. USE OF PLACEBOS IN CLINICAL TRIALS

The use of placebos in clinical research has been the subject of much debate from both an ethical and scientific standpoint.

In the presence of an established effective therapy or intervention, the experimental therapy should generally be tested against this "standard" treatment. Use of a placebo in a clinical trial is therefore an exception, as it deprives participants of needed therapy.

Conditions

A placebo control is ethically acceptable in a randomized controlled clinical trial only if all the following conditions are met:

- Its use is scientifically and methodologically sound in establishing the efficacy or safety of the test therapy or intervention;
- It does not compromise the safety or health of participants;
- The researcher articulates to the REB a compelling scientific justification for the use of the placebo control;
- The general principles of consent are respected and participants or their authorized third parties are specifically informed about any intervention or therapy that will be withdrawn or withheld for purposes of the research, as well as about the anticipated consequences of withdrawing or withholding the intervention or therapy.¹⁴²

Regarding compelling scientific justification, the use of placebo comparators is acceptable in any of the following situations:

- There are no established effective therapies for the population or for the indication under study;
- Existing evidence raises substantial doubt within the relevant expert community regarding the net therapeutic benefit of available therapies;
- Available therapies are known to be ineffective for patients by virtue of their past treatment history or known medical history;
- The trial involves adding a new experimental therapy to established effective therapies, i.e. the established effective therapy plus new therapy is compared to the established effective therapy plus placebo;
- Patients with decision-making capacity have provided an informed refusal of established effective therapy, and withholding such therapy will not cause them serious or irreversible harm.¹⁴³

¹⁴² TCPS 2 (2022), article 11.4. 143 *Ibid.*, application of article 11.4.

Briefing participants

When conducting a clinical trial that includes administration of a placebo based on one of the exceptions listed above, the researcher and REB bear the responsibility of providing participants with all of the required information, namely through the ICF, and making sure they understand it. This information must explain the treatments that will be withdrawn or withheld and the risks associated with such withdrawing or withholding, as well as the risks associated with administration of the placebo. Participants must also be informed of the anticipated consequences of withdrawing or withholding the therapy over the entire duration of the study. In addition, researchers must justify their decision to use a placebo control instead of other possible options.

Geographical characteristics

Unusual situations may occur; for example, use of a placebo may be deemed acceptable in the United States in the absence of a commercially available treatment for the medical condition under study, but unacceptable in Canada if Health Canada has authorized the sale of a treatment whose effectiveness for this condition is not in question. Researchers should thus be particularly vigilant regarding the use of placebos suggested in research protocols developed abroad.

Researchers shall also refrain from engaging in geographical tourism that would enable them to design or participate in clinical trials that use placebos, thus taking advantage of the vulnerability of underprivileged populations in countries without access to treatments considered as standard in Canada.

Any physician who is a member in good standing with the professional order of Quebec physicians is liable for their actions, regardless of where they practise.

19. GENETIC RESEARCH

Genetic research or research with a genetic component is becoming widespread in clinical research. Although a distinction should be made between genetics researchers focusing specifically on certain genes vs. genomics researchers studying the functioning of an organism, organ, cancer, etc. at the genome-wide scale,¹⁴⁴ we will use the term "genetic research" in a broad sense that includes genomics in a manner similar to that of the TCPS 2: "Human genetic research involves the study of genetic factors responsible for human traits and the interaction of those factors with each other, and with the environment. Research in this area includes the identification of genes that comprise: the human genome; functions of genes; the characterization of normal and disease conditions in individuals, biological relatives, families, communities and groups; and studies involving gene therapy."145 Genetic research thus produces vast amounts of data to be processed by powerful computing tools designed to provide a greater understanding of or improved treatments for diseases.¹⁴⁶

Such research makes it possible to obtain information that is important not only for the health of those participating, but also for that of biological relatives as well as others who share the same genetic ancestry, or come from the same community or population.

Genetic research comes with its own set of specific issues which must be addressed.

144 Génome Québec. 145 TCPS 2 (2022), Chapter 13. 146 On the topic of big data and artificial intelligence, see Chapter 21 of this document.

Recruitment of participants

Regarding recruitment for genetic research, there may be advantages to recruiting several members from a single family or community. In such situations, particular vigilance should be exercised with regard to the suggested recruitment process. Contact mav be established directly by research teams, by family members, or by third parties suggested by the family. Researchers must ensure they have a strategy to foster freedom of choice and limit to the extent possible any undue influence when seeking consent. For example, it would be unacceptable for a researcher to task a participant with recruiting one of their relatives, providing them the information, explaining the ICF, and obtaining their consent under the pretext that this is the simplest solution.

In the case of genetic research on a community, the researchers may start by contacting the community's leaders or representatives. Once again, it would be important to ensure that consent from community leaders does not put pressure on individuals to participate.

Whether on the family or community level, compliance with this duty to ensure free and informed consent¹⁴⁷ in genetic research is not so straightforward and must be adapted to the extent possible on a case-by-case basis.

Participants who are minors or persons of full age incapable of giving consent

Great caution must be exercised regarding the participation of minors to genetic research. As we have mentioned, section 21 of the C.C.Q. states that a minor may participate in such research only if, where the minor is the only subject of the research, it has the potential to produce benefit to their health or only if, in the case of research on a group, it has the potential to produce results capable of conferring benefit to other persons in the same age category or having the same disease or handicap. Therefore, the participation of minors in genetic research is acceptable only if the research cannot be conducted on persons of full age and there are benefits expected for the minor or children in the same age category or situation.

When research must be conducted on minors, it is preferable to recruit the eldest, as they are the most likely to understand the research and its implications and can thus give informed consent.

The same precautions apply to persons of full age incapable of giving consent who cannot afford to miss out on the potential benefits of the genetic research (e.g. neurodegenerative disorders). Naturally, as in any type of research, their consent (assent) should be obtained in addition to that of the parental authority or person who is legally authorized to give consent on their behalf. In addition, as with any research involving persons of full age capable of giving consent, the researchers are required to contact a minor who reaches the age of 18 or a person incapable of giving consent who regains their ability during the course of a research project in order to obtain their personal consent.¹⁴⁸

¹⁴⁷ On the topic of free and informed consent to participate in research, see Chapter 12, section 12.2 of this document. 148 RMGA (2016).

Management plan on outcomes and findings

Researchers planning to conduct genetic research should establish a plan to manage the outcomes and findings that may result from the project and have it approved by the REB.

Clinical relevance as well as the potential benefits and risks for participants and their relatives must be taken into account when drafting this plan.

The plan must address the possibility of reporting individual outcomes (incidental or not) to biological relatives and others with whom the participants have a family, community, or group relationship.

This plan shall provide participants with an opportunity to express their preferences for transmitting results to themselves or to their loved ones. The plan must also include provisions regarding the use of genetic counselling services to explain the meaning and implications of this information.¹⁴⁹

Given that minors are involved, the principle discussed in Chapter 16 regarding the disclosure of outcomes shall be adapted. In genetic research, certain tests that are scientifically and clinically valid may only be relevant to the future health of the child once they have become of full age. If no preventative measures can be taken during childhood, reporting of such outcomes is unwarranted. However, the researcher is required to discuss the matter with the REB in order to assess the relevance, feasibility, and terms with regard to contacting the child once they are of full age to give them this information. The factors to be taken into consideration are as follows:

- severity of the health issue;
- likelihood of its occurrence;
- availability of ways of prevention or proper treatment once they are of full age;
- feasibility of the research team re-establishing contact with the participant.

Moreover, in exceptional cases, the RMGA provides for the possibility to disclose such outcomes where they may have immediate implications for the health of a relative, based on the following factors:

- the risk presents a high likelihood of occurrence;
- the risk poses a threat to the life of the relative; and
- methods for prevention or treatment are available.¹⁵⁰

The risk of stigmatization or disadvantageous treatment of persons, communities, or groups based on genetic characteristics has been decried for many years.¹⁵¹ To account for this, researchers should exercise caution when designing their research and fully inform participants about these risks.

¹⁴⁹ TCPS 2 (2022), art. 13.2, 13.3, and 13.4.

¹⁵⁰ RMGA (2016).

¹⁵¹ See for example: ECOSOC (2004), section 3: "Urges States to ensure that no one shall be subjected to discrimination based on genetic information." UNESCO (1997), article 6: "No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity."

Risk of genetic discrimination

Collectively, special consideration must be given to avoid stigmatization of a community or population following publication of the general outcomes of genetic research. Such is the case, for instance, with research linking predisposing genes that are particularly prevalent within certain communities to a social phenomenon such as alcoholism or obesity.

Individually, the risks of discrimination most often mentioned in ICFs relate to the possible impact on the insurability and employability of participants. For example, if a person has undergone genetic testing to screen for a disease as part of a study, even in the case of predisposition testing, they would normally be required to disclose such information to their insurance provider and prospective employers to sign an agreement in good faith. Moreover, should these research outcomes be deemed clinically valid and relevant and thus documented in the participant's clinical record, they become potentially accessible to any of their authorized third parties. Of course, insurance providers and employers may request such access to clinical records.

The Genetic Non-Discrimination Act, enacted on April 4, 2017, prohibits any person from requiring an individual to undergo a genetic test or to disclose the results of a genetic test as a prerequisite for the provision of a service or to enter an agreement. It also prohibits an employer from penalizing an employee on the grounds of their refusal to undergo a genetic test or disclose its outcomes. The act was the subject of a reference to the Court of Appeal of Quebec to challenge its constitutionality.¹⁵² On July 10, 2020, the Superior Court ruled that the act oversteps the bounds of authority of the Parliament of Canada regarding criminal law as laid out in subsection 91(27) of the Constitutional Act. 1867.153

With regard to the individual insurance, insofar as family history is always taken into account, the scope of the legislation is undermined, as insurance providers reserve the right to deny coverage to clients deemed too high-risk, whether backed by genetic testing or not. Actuarial calculations did not wait to rely on genetics to assess client risk, and participation in genetic research on specific diseases has an overall low impact on insurability, given that patients and participants are generally aware of their diagnosis or risk of contracting the disease, and are already required to disclose it.

However, when there are truly incidental findings over the course of a study, they can be life changing, particularly in cases of predisposition to unsuspected and asymptomatic diseases. This is particularly true for control groups in genetic studies and research targeting a specific population or community. As a result of the reference to the Court of Appeal, it is recommended that researchers clearly explain these risks when asking participants to give consent to participate in research, as well as before disclosing findings.

¹⁵² Court of Appeal of Quebec (2017). 153 Reference re *Genetic Non-Discrimination Act,* 2020 SCC 17.

20. RESEARCH BANKS AND SECONDARY USE OF RESEARCH DATASETS

Definition

"Traditional" clinical research requires huge investments in terms of time and financial and human resources in order to design and carry out a research project and disseminate its findings. This is in addition to the generous contribution of participants for the advancement of knowledge. The possibility to deposit the participants' data or biological specimens (e.g. blood, urine, DNA, etc.) in research banks is an interesting option for researchers as it makes it possible to leverage the research by using the data or stored specimens in future studies at a low cost and without having to systematically obtain renewed consent from participants insofar as they have authorized the proposed use, while limiting the constraints and risks to which the participants are exposed.

There are various types of research banks, namely research datasets, biobanks (which contain biological materials, including of a genetic nature, and the associated data), banks of participants (which facilitate recruitment), population banks, etc. These research banks, primarily compiled for the purpose of advancing scientific knowledge, are different from clinicaladministrative banks (e.g. RAMQ, MedEcho, etc.) whose main purpose is not research, but whose data may be used in the context of research projects or to compile research banks, under certain conditions.¹⁵⁴ In the TCPS 2, "secondary use" refers to the use in research of information originally collected for a purpose other than the current research. Although there are some largescale research banks, such as those compiled by pharmaceutical companies sponsoring clinical trials, others are small-scale and managed by a researcher based on the data collected from participants in their own research.

154 Regarding secondary use of this data in research, see chapters 5 and 12 of the TCPS 2 (2022).

A delicate issue thus arises regarding what specifically differentiates a research bank from a databank, a record, secondary use, etc. It is not simply a question of semantics given the aforementioned regulatory framework, insofar as it concerns research banks. In Quebec, the prevailing definition is that put forward by the FRQS in 2006, according to which a bank is constituted from the systematic collection of data or biological materials which may be used to support health research. The TCPS 2 does not provide any explicit definition recognizing the wide range of different types of banks, and provides that a research bank can be used only

for the purposes of a single project.¹⁵⁵ These definitions have the merit of being inclusive, but at the cost of effectively having little operational value. Thus, a researcher who decides to preserve data from a research project after it has been collected and organized for a single secondary use (e.g. a student project under their supervision), should state that they are compiling a research bank. The constraints imposed on compiling and managing research banks may deter the researcher from such secondary use.

According to the Collège, various other elements must be included for collected data to be defined as a research bank.

A research bank must include the three following elements:

- Its content must be collected, stored, and disseminated (i.e. the data must be available for use by researchers who are not part of the original research team);
- 2) Its content must be used for several subsequent research projects;
- 3) Its content must be stored using a long-term approach.¹⁵⁶

This definition makes it possible to differentiate a research bank from a simple digital dataset, commonly referred to as a "database."

It also differs from the reuse of data or biological materials collected for the original research project without necessarily resorting to compiling a research bank. Thus, reuse of research data or material for a limited number of subsequent projects (two to three) on the same subject, by the same research team, before their planned date of destruction, and without further data matching may be authorized by the participants (with their explicit consent for such reuse of their research data or biological materials) and by an REB (preferably the same) without requiring systematic compilation of a research bank. Reuse of research data is possible under these conditions, regardless of the original source of the data (administrative, clinical records, etc.). The option of leveraging this data or biological material for reuse under such conditions is clearly beneficial to the researcher and to research at large; moreover, it does not cause any additional disadvantages to participants who have given explicit consent.

¹⁵⁵ TCPS 2 (2022), Chapter 12, section D.

¹⁵⁶ Based on the definition proposed in the Rapport du Comité interministériel sur l'encadrement éthique de la recherche et la protection des sujets de recherche (2007).

Researchers are encouraged to plan and provide for these secondary uses from the outset in the original research project design and its associated protocol in order to obtain informed consent that explicitly permits reuse of the research data or biological materials for a limited period of time and for a predetermined set of uses for authorized researchers.

This proposed definition of a research bank may also include certain registries (e.g. regarding a specific disease), provided that they are produced to advance knowledge and not only the quality of care.

Management

Participants who agree to deposit their data or biological materials in research banks are demonstrating full confidence in the sound management of the bank, its long-term preservation, and the full and diligent use of its content. This implies that researchers must be committed to managing the research bank with utmost rigour and excellence.

There are several considerations in this regard: In order for a research bank to be used to its full extent, adequate financial resources must be allocated to its management both on a daily basis and in the long term. A discussion must be systematically held between the physicians advocating for research banks and the institutions where they will be hosted at the upstream stage of their creation to clarify the expectations of all parties.

Some researchers who recognize the benefits of research banks establish unstructured banks, often encompassing all of the data or biological materials collected through any means and from all the research projects they are conducting (or most of them). Such "catch-all" banks should be avoided, as the quality of a bank is based on the coherence and quality of its content. A lack of standards regarding the storage of variables results in a "Swiss cheese" effect that is detrimental to their use. Researchers are encouraged to create banks whose content is structured to adequately leverage their potential.

The ethical and legal framework surrounding research banks is different from that of simple research projects, as it takes into account the technical possibility of data matching, which exacerbates the already existing risks of jeopardizing the privacy and autonomy of participants.¹⁵⁷ The creation of a research bank notably entails drafting a strict management framework covering aspects such as:

- the description of the bank;
- the administrative management structure;
- the collection of data and biological materials;
- the management of data and biological materials;
- the protection of privacy and confidentiality;
- the commercialization of intellectual property;
- the conditions for accessing the banked data or biological materials;¹⁵⁸
- the REB that will perform the ethical review when creating the bank and thereafter.¹⁵⁹

It should be noted that the management framework should also include specific provisions for re-establishing contact with participants when necessary, for instance when they become of full age, in cases where the banked data or biological materials concern minors and the original consent was given by the parents or tutors. The bank management framework and any other document intended for prospective participants or the general public (e.g. recruitment letter, ICF, brochure) must be submitted to the REB for preapproval by the researcher sponsoring the bank, whether it will be managed in an institutional or a private setting. Where applicable, the REB must also review any agreement regarding funding of the bank by a private party and ensure ethical oversight of the bank while it is operational.

Moreover, any request to use a research bank shall be subject to scientific and ethical review, and participants' consent shall not be regarded as a substitute for this requirement. When a research project proposes concomitant inclusion of data in a research bank, a separate ICF must be drafted to allow banking of the data. It is unfortunate that in some instances an ICF drafted for a research project with minimal risk can be relatively long, but only contain a few lines regarding banking, despite the inherent risks for data matching and re-identification, as well as the various potential long-term implications. Such an approach compromises the validity of consent, particularly in terms of being informed.

The standard approach should be to obtain explicit consent from the participants to deposit their personal data or biological materials in a research bank.¹⁶⁰ In exceptional circumstances, researchers can submit a request to deposit data in a research bank without re-establishing contact with the participants to obtain their explicit consent. Various justifications may be invoked: many years have passed since the data or biological materials in question were collected and stored for research purposes; the data was collected for a retrospective review of records authorized by the director of professional services of a health care institution; the data or biological materials already used in research were anonymous or have been anonymized, etc.
(1) the identifying biological material is essential

(2) the use of the identifying biological material without the participants' consent is unlikely to adversely affect the welfare of the individuals to whom the information relates;

162 *Ibid.*, Chapter 12, section C. 163 Based on TCPS 2 (2022), article 12.3A. 164 TCPS 2 (2022), article 12.3B.

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Although section 22 of the C.C.Q. states from the outset that a part of the body, whether an organ, tissue or other substance, removed from a person as part of the care they receive may, with their consent or that of the person qualified to give consent on their behalf, be used for purposes of research, it does not include specific provisions on special cases regarding the banking of data or biological materials that are already preserved by researchers. The principle of participant consent still applies, and the use of personal data and identifiable materials without consent constitutes an exception.

For these special cases, researchers who have not specifically obtained consent from participants for secondary use¹⁶¹ (or inclusion in research banks) of previously collected identifying information kept for research purposes shall use such information for these purposes under the same terms and conditions set out in Chapter 14: Privacy, Professional Secrecy, and Confidentiality.

For biological material per se, which is only covered in Quebec by section 22 of the C.C.Q. the researcher must also rely on the mechanism provided for by the TCPS.

Researchers who have not obtained consent from participants for secondary use¹⁶² (or inclusion in research banks) of previously collected identifying biological material kept for research purposes shall not use such information for these purposes unless they have satisfied

the REB that:

to the research;

161 TCPS 2 (2022), Chapter 5, section D.

- (3) the researchers will take the appropriate measures to protect the privacy of the individuals and to safeguard the identifying biological material;
- (4) the researchers will comply with any known preferences previously expressed by the individuals about any use of their biological material:
- (5) it is impossible or almost impossible to seek consent from individuals to whom the information relates:
- (6) the researchers have obtained any other necessary permission for secondary use of the biological material for research purposes.

If a researcher satisfies all of these conditions. the REB may approve the research without requiring consent from the individuals to whom the identifying biological material relates.¹⁶³

Under the TCPS 2, if the biological material does not allow for any identification, consent from these individuals is not required for secondary use.¹⁶⁴

21. OPEN SCIENCE, BIG DATA, **AND ARTIFICIAL INTELLIGENCE**

21.1. OPEN SCIENCE AND OPEN DATA

Open science aims for unrestricted access to scientific papers and data stemming from public and collaborative research, which is made possible through the use of new information and communication technologies. Broadening access to scientific data and papers is conducive to the appropriation of research findings on a large scale and a greater dissemination of the potential benefits.165

Facilitating access to research data is part of the concept known as open data, or data sharing, which has been gaining a lot of momentum in research¹⁶⁶ with the advent of information technologies such as cloud computing that have streamlined data storage and sharing.

Research data can take many forms: experimental, observational, operational, third party, public sector, surveillance, processed, repurposed, etc.¹⁶⁷

Open data is part of a movement that considers information as collective property whose dissemination benefits the public interest.¹⁶⁸ In research, data transparency is also one of the essential principles for the advancement of knowledge. Many concerns have been expressed regarding how accessing research data is difficult for peer reviewers of scientific journals.¹⁶⁹ Several journals (e.g. PLOS, Psychological Science) now require that researchers seeking to publish papers deposit their research data in a registry that is made publicly accessible to other researchers.

Since July 2018, editors who are members of the International Committee of Medical Journal Editors (ICMJE)¹⁷⁰ require that manuscripts reporting on the findings of clinical trials that are submitted for publication in relevant journals include specific provisions on sharing research data. Since January 1, 2019, these provisions must be specified when registering a clinical trial.¹⁷¹ Although sharing research data is not yet a mandatory requirement, editors have made clear statements indicating that data sharing is one of the aspects taken into account when reviewing applications for publication.

165 Based on OECD.

166 Gewin V. (2016).

167 CASRAI (2015). 168 Malarmey A. (2017), p. 3.

169 Hrynaszkiewicz I. (2010); Naik G. (2017).

170 The journal members of the ICMJE are: Annals of Internal Medicine, British Medical Journal, Bulletin of the World Health Organization, Deutsches Ärzteblatt (German Medical Journal), Ethiopian Journal of Health Sciences, Iranian Journal of Medical Sciences, JAMA (Journal of the American Medical Association), Journal of Korean Medical Science, New England Journal of Medicine, New Zealand Medical Journal, The Lancet, Revista Médica de Chile (Medical Journal of Chile), Ugeskrift for Laeger (Danish Medical Journal), the U.S. National Library of Medicine, and the World Association of Medical Editors,

171 Darren B. Taichman et al. (2017).

In Canada, following the *Tri-Agency Statement* of *Principles* on *Digital Data Management* (2016),¹⁷² the draft of the *Tri-Agency Research Data Management Policy*¹⁷³ requires that researchers receiving funding submit a data management plan.¹⁷⁴

As for institutions, they should be required to create an institutional research data management strategy outlining how the institution will provide its researchers with an environment that supports the use of the best practices recognized for managing research data.

Data sharing unquestionably presents admirable virtues, as it makes it possible to avoid duplication of research efforts, check the reproducibility of studies, and report fraud or error, all of which are conducive to scientific integrity and guality. Most of all, it has a significant multiplier effect on the advancement of knowledge, namely by providing access to a large amount of data collected from complex ad hoc or longitudinal studies at a lower cost and within shorter timeframes.¹⁷⁵ Researchers also benefit from an individual point of view as the studies generated from data sharing are also published in renowned journals and receive just as many citations¹⁷⁶, which constitutes a non-negligible advantage considering the current competitive environment in the field of research.177

Two points deserve special mention. Currently, the regulations in force in Quebec require explicit consent from participants to use their data for research purposes, unless otherwise permitted by law (DPS, CAI). As a result, researchers must submit their data sharing plan to an REB for approval, in particular when a journal makes it a prerequisite for publication. Researchers should, however, use caution when drafting such plans given the pernicious effects that are unfortunately associated with data sharing in certain research fields. Indeed, researchers working on climate change, the impact of tobacco use, or vaccines may sometimes be the target of intimidation campaigns, falsification of findings, or have complaints filed against their university.¹⁷⁸ These risks should therefore be given due consideration when creating data sharing plans, and it is advisable to remain vigilant once data is shared.

Therefore, whether conducting a clinical or other type of trial, researchers developing a research protocol should weigh the various options from the outset regarding the use of a data sharing plan, in compliance with the current legislation in force that is applicable to the proposed project, and submit them to the REB for approval.

177 See Chapter 2 of the document.

¹⁷² CIHR, NSERC, and SSHRC (2016).

¹⁷³ CIHR, NSERC, and SSHRC (2017).

¹⁷⁴ According to this document, the content and length of data management plans (DMPs) depend on the research project, but all DMPs should describe the following: (1) how data will be collected, documented, formatted, protected and preserved; (2) how existing datasets will be used and what new data will be created over the course of the research project; (3) whether and how data will be shared; (4) where data will be deposited. DMPs also indicate who is responsible for managing the project's data, describe the succession plans in place should that person leave the research team, and identify the data-related roles and responsibilities of other team members where appropriate. CIHR, NSERC, and SSHRC (2017).

¹⁷⁵ Data sharing and the future of science, Nat Commun. 2018; 9: 2817.

¹⁷⁶ Example in neuroimaging: see Milham, M. P. et al. (2018).

¹⁷⁸ Lewandowsky S. and Bishop D. (2016).

21.2. BIG DATA AND ARTIFICIAL **INTELLIGENCE**

The current trend of big data¹⁷⁹ makes the idea of open data in research all the more interesting. Big data refers to datasets that have grown so large that they extend beyond human intuition and analytical capability, and even beyond conventional computer database and information management solutions.¹⁸⁰

Their complex analyses are distinguished through the rule referred to as the "three Vs" (volume, variety, velocity).

The expansion in volume of available digital data is linked to the use of terminals (computers, tablets, cellphones) combined with the simultaneous growth in data storage capacity.

Variety among the type of data stored is also a characteristic of big data. These are not traditional relational databases: the data is raw, semistructured, and even unstructured (will require structuring). This data may be in various formats, such as images, texts, dates, locations, and videos.

Velocity essentially measures how fast data comes in, i.e. the frequency at which data is generated, captured, shared, and updated.

Other "Vs" may come into the equation, in particular veracity in the context of research. If the data is not reliable (i.e. of poor quality) or is rife with irregularities, its use and interpretation will be impacted.

Artificial intelligence (AI) is defined as encompassing all of the theories and techniques "dealing with the simulation of intelligent behaviour in computers."¹⁸¹ Big data constitutes the building blocks of machine learning, an ever-more efficient AI method that is becoming increasingly popular. The learning algorithms (such as deep neural networks) processing this data are of such unfathomable complexity that they make it difficult to understand and justify their decisions.¹⁸²

Big data and AI are already being used in many fields, such as scientific programs, business tools, open-source software, etc. As a matter of fact, while they are a product of research, they also have the potential to stimulate and produce research.¹⁸³ Research ending in "-omics," such as genomics, leverages the full potential of big data and AI. Their widespread use in the field of health is destined for a promising future and is sometimes even referred to as the El Dorado of researchers. This big data is essentially comprised of personal data, including health data. The enormous potential for this health data therefore calls for a certain degree of caution.

183 Big data, Wikipedia, other source.

^{179 &}quot;Big data means the availability either of a large amount of data or of data of large size that can only be treated effectively by digital tools combining algorithms with great computing power. The change in scale is such that only machines, and no longer humans, are able to collect, store, and analyze data, these data are characterized mainly by three properties: their permanence (they can be copied and reused indefinitely); their dissemination in time and space, which enables their rapid and borderless sharing: the generation of secondary data, ie, new information obtained by the processing and cross-referencing the initial data with other sources, which makes these data usable well beyond the purposes of the initial collection," CCNE (2019).

¹⁸⁰ Big data, Wikipedia, Gandomi A., Haider M. (2015). 181 Definition from *Merriam-Webster*.

¹⁸² Cyr H. et al. (2018).

Generating knowledge based on big data requires careful consideration: Without delving too deep in detail, we foresee the possibility of big data leading to the replacement of the hypothetico-deductive method with an empirico-inductive approach, in which intellectual exploration would be driven by data rather than hypothesis or theory. Knowledge in the field of health would then develop from an aggregation of heterogeneous big data which is supposedly neutral. However, data, especially health data, is not neutral. It is always extracted by a specific data collection mechanism whose presetting and calibration are based on scientific or clinical hypotheses and intentions. Data aggregation in itself, which is the basis for exploiting big data, is not neutral and has its own inherent limitations.¹⁸⁴ The underlying feelings, emotions, and societal contextual factors of health data cannot be digitized. Generating knowledge based on big data could thus potentially produce improper deductions, but also misinterpretation of certain data related to otherness.¹⁸⁵ Findings stemming from learning algorithms that reproduce bias contained in data could result in discrimination against certain segments of the population. For example, in the area of abuse, an American study has demonstrated how some analyses based on data regarding the use of public social services may to a certain degree have caused low-income families to be discriminated against by child protection services.¹⁸⁶

There are also considerable risks to privacy and fundamental rights. A greater level of protection is required when it comes to health data when compared to other types of data, in particular with regard to consent from the holder regarding its use and dissemination. The current Canadian and Quebec laws in force are drafted accordingly.¹⁸⁷ Advocates for adopting the open data model regarding the use of health data for research purposes have criticized these laws, arguing that they are overly cautious, and have requested relaxation of the regulations on consent (general consent, implicit consent, etc.), if not complete elimination of the requirement to obtain consent for using identifiable health data for research purposes, invoking a moral duty to participate in such research.¹⁸⁸

One of the arguments often used to support this request is the fact that anonymization of health data, which will subsequently be aggregated, itself constitutes a sufficient counter to the potential misuses of this data, such as invasion of privacy, stigmatization, or discrimination. This underlying premise for anonymization is, however, undermined by the reality of cross-referencing between databases and the increasing amount of data available on a single individual.¹⁸⁹ In fact, researchers specializing in big data have themselves confirmed that they are able to re-identify individuals based on such cross-referenced¹⁹⁰ and aggregated data. Therefore, how can a proper balance be ensured between the expected benefits of health research and respect of individual rights? Who should be responsible for giving consent to using personal data and through what process? How can appropriate safety processes be implemented? Who should be in control and held accountable, in particular when data is being used by thirdparty or foreign researchers over whom very little control can be exercised? This creates a certain incongruence between the possibility (to access big data) and duty (not to re-identify data), which should be taken into consideration.

185 Ibid.

188 For example: Ballantyne A., Schaefer G.O. (2018). 189 Devillier N. (2017).

¹⁸⁴ Coutellec L. and Weil-Dubuc P.-L. (2017).

¹⁸⁶ Eubanks V. (2018).

¹⁸⁷ Personal Information Protection and Electronic Documents Act, S.C. 2000, ch. 5, Act respecting Access to documents held by public

¹⁹⁰ In genetics: Homer N. et al. (2008).

One of the current pitfalls is the fragmented opinions regarding the issue of big data and AI in Quebec. In some major hospital centres of Quebec, data repositories are being developed to support research based on health big data and AI, without having conducted any prior societal decision-making process regarding the provisions for their design and use.

Moreover, social media and digital platforms for sharing health data intended for patients can be used to target patients and recruit them for research purposes. These platforms essentially constitute valuable "real-life" data for advancing health-related knowledge, and numerous researchers are eager to make broader use of this information made public by social media users. However, broad and unrestrained use of this data poses ethical risks on various levels, ranging from prejudice to their autonomy (limiting the scope of their consent for secondary uses of their data) to stigmatization (based on social particularities inferred from their behaviour on social media).¹⁹¹

Facilitation of access to health data in Quebec must imperatively go hand in hand with a culture of transparency, both in terms of the data collected from individuals and the operation of the learning algorithms using this data,¹⁹² to ensure that the resulting research and findings guiding the development of policies and health care are in line with the rights and freedoms of individuals and the values upheld by Quebec society. A democratic debate on big data and AI must be quickly initiated among all stakeholders (policy makers, researchers, citizens, professional orders, etc.) in order to produce an integrated solution that is representative of Quebec values.¹⁹³

¹⁹¹ CCNE (2019).

Cyr H. et al. (2018).
See for example the reflection and resulting measures taken in Europe: de Lecuona I., Villalobos-Quesada M. (2018);
At the intermeticate leurch Université de Martréel (2019).

at the international level: Université de Montréal (2018).

CONCLUSION

Regardless of their involvement in research, any physician would benefit from gaining a proper understanding of the issues surrounding clinical research, for both themselves as potential collaborators and the patients who are likely to participate.

In addition to the challenging aspects of its funding and increasingly complex organization, current research subjects researchers to a dense regulatory framework that they are required to master. Moreover, a physician conducting or collaborating on research is always bound by their obligations as a physician.

The practice guide outlines the main challenges to be aware of so that a physician can mitigate them to the extent possible when undertaking or collaborating on a clinical research project. It also guides researchers through the process of scientific, financial, and ethical assessment of research projects as required in Quebec. It invites readers to join the current discussion on new technological and technical avenues which, although capable of increasing research capacities tenfold, strain the boundaries established by society to protect participants and foster research integrity, thus leaving no other option but to evolve. Throughout its chapters, the document encourages physicians to reflect on their own responsibilities when, in collaboration with patient-participants, they contribute to research and thus the advancement of medicine.

[Translation] "What drives a physician to pursue training in and devote their career to research? Arguably, curiosity, a desire to understand, and the feeling of doing their part to overcome disease, however small their contribution may be. Another aspect is enjoying working in close collaboration with fellow scientists and sharing hope and disappointments in finding a scientific solution to a medical issue, as accounted by Brown and Goldstein, two medical researchers with a Nobel Prize in Medicine."¹⁹⁴

The challenge is to ensure this curiosity is cultivated harmoniously in respect of everyone and their best interests.

194 Corvol, P. (2015).

LIST OF QUESTIONS A PHYSICIAN SHOULD ASK THEMSELVES WHEN OFFERED TO CONDUCT OR COLLABORATE ON A RESEARCH PROJECT

- Why have I been asked to participate?
- What are my personal motivations for taking part in this project?
- Does the knowledge that could be gained from this research justify recruiting patients under my care?
- Do I have access to the necessary infrastructure and human resources to accommodate this project?
- Is my knowledge of the field of research and research ethics up to date?
- Does my staff have adequate training in research and research ethics, or can my staff receive such training?
- If the project is conducted in a foreign country, is the methodology used adapted to the Canadian and Quebec reality?
- Has the project been evaluated by a recognized scientific committee, or will it in the future?
- Has the project been evaluated by a Quebec research ethics committee, or will it in the future?
- Has Health Canada issued an official document to authorize the project (e.g. No Objection Letter, Letter of Authorization)?
- What controls have been established to ensure patient-participant safety and the reliability of outcomes?

- Will I be notified of the general outcomes of the research, even if they are negative? How?
- Once the recruitment period in my clinic or institution comes to an end, will I be notified of any information that could significantly impact the health of the patient-participants recruited on-site?
- Will I be able to publish the outcomes of this research? What is my margin of discretion?
- Will the patient-participants be able to benefit from the experimental treatment once their participation comes to an end? Who is funding this treatment?
- Is there a genetics or genomics component of this research project?
- Will the data or biological materials of patient-participants be deposited in a research bank? Is this research bank located in a foreign country? Do I have knowledge of the regulations and procedures that govern this research bank? Do these regulations comply with Canadian and Quebec standards in this regard? Is explicit consent required from participants to deposit their data in the research bank?

LIST OF QUESTIONS A PERSON ASKED TO PARTICIPATE IN A RESEARCH PROJECT MAY DISCUSS WITH THE PHYSICIAN

The research project

- What is its objective?
- What is the current scientific knowledge on the intervention or medicine under investigation in this study?
 - Is the intervention or medicine already approved and accessible in Canada for any other use than that being investigated in this research project?
 - Has the intervention or medicine already been tested on human subjects? What were the outcomes? How does the intervention or medicine compare with those that have already been approved?
- What is the expected duration of the project?
- How many participants are the researchers seeking to recruit, in Canada and elsewhere around the world?
- Who are the researchers? With what host organization are they associated?
- Is the project financed by public funds or by private interests? What are they?
- Has any possible conflict of interest been disclosed by the researchers, the host organization, or the project sponsors?
- Has the project been evaluated by a Quebec research ethics committee?

My participation

- Why is the physician asking me to participate in this research project?
- Can I refuse to participate? If I refuse, will I still be under my physician's care?
- If I cannot participate or do not want to participate, are there any other options available to me?
- If I participate, what are the personal benefits and risks?
- If I accept to participate in the project, but decide to withdraw over the course of the project, will I suffer any penalties or be required to waive some of my rights?
- Will I be notified in a timely manner of any new information that may influence my decision to continue participating?
- How is my disease most likely to progress, with or without the intervention or medicine under study? Will my participation in the project improve the outcome of my disease?
- What types of tests, interventions, and medical treatments will I undergo over the course of my participation? How often, and for how long?
- Does the project require me to be hospitalized? How often, and for how long?
- What is the total expected duration of my participation?

My participation (continued)

- Will I experience side effects from the intervention or medicine under study? What are they? Can they be prevented or treated?
- Will I be required to stop my current medications or refrain from certain activities to participate in the project?
- Where will I receive medical care during my participation? Who will be responsible for providing me with medical care?
- Am I expected to pay for the intervention or medicine under study?
- Who will assume financial consequences in the event that I suffer an injury, illness, or deterioration of my health condition during my participation?
- How will my daily activities be hindered?
- Will I be reimbursed for travel expenses related to the project? How?
- Can I receive compensation for the time and effort I will invest through my participation? How much, how, and how often?
- When will I be informed of whether the intervention or medicine is effective? What happens if it is not?
- Once my participation is finished, what type of follow-up is planned? How often, and for how long?

- Once the project has been completed, will I receive a report on the outcomes of the research? If not, how will I be able to access it? Will I be informed of my individual outcomes?
- If the intervention or medicine under study proves to be beneficial, will I have access to it once the project has been completed? Under what conditions?
- Who will be notified of my participation in this research? Should my family physician be notified?
- Are the participants in the research project allowed to meet and discuss among themselves?
- How will the participants' data be preserved? How long will it be preserved, and in what country? Will the data be destroyed at the end of the project?
- Will my data or biological materials be deposited in a research bank? Is this research bank public or private? Who will have access to my information?
- Do the researchers plan to publish the outcomes of this research? If so, will it be possible to identify me?
- Whom can I contact if I have any questions about the research project? Whom can I contact if I have any questions about my rights as a participant?

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