BEST PRACTICES FOR HEALTH RESEARCH INVOLVING CHILDREN AND ADOLESCENTS

Genetic, Pharmaceutical, and Longitudinal Studies

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Institute for Human Development, Child and Youth Health (CIHR); and
Ethics Office (CIHR)

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<td>BRC1</td>
<td>Caenorhabditis elegans BRCA1 orthologue</td>
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<td>BRCA1</td>
<td>Breast Cancer 1</td>
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<td>CCNE</td>
<td>National Consultative Ethics Committee for Health and Life Sciences</td>
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<td>CE</td>
<td>Council of Europe</td>
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<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
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<td>CIOMS</td>
<td>Council of International Organizations of Medical Sciences</td>
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<td>CPS</td>
<td>Canadian Paediatric Society</td>
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<tr>
<td>CRDP</td>
<td>Centre de recherche en droit public</td>
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<tr>
<td>CREB</td>
<td>Clinical Research Ethics Board of University of British Columbia</td>
</tr>
<tr>
<td>DMD</td>
<td>Duchenne muscular dystrophy</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>EC</td>
<td>European Commission</td>
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<tr>
<td>FAP</td>
<td>Familial Adenomatous Polyposis</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>IHDCYH</td>
<td>Institute of Human Development, Child and Youth Health</td>
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<tr>
<td>HUGO</td>
<td>Human Genome Organisation</td>
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<tr>
<td>MICYRN</td>
<td>Maternal, Infant, Child, Youth, Research Network</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>NCBHR</td>
<td>National Council on Bioethics in Human Research</td>
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<td>NCEHR</td>
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<td>N/M</td>
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<td>Acronym</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<td>REB</td>
<td>Research Ethics Board</td>
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<tr>
<td>SOPs</td>
<td>Standard Operating Procedures</td>
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<tr>
<td>TriA</td>
<td>Triacetyloleandomycin</td>
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<tr>
<td>UNESCO</td>
<td>United Nations Educational, Scientific and Cultural Organization (for the approval level of UNESCO documents in the text, see their website at <a href="http://www.unesco.org">www.unesco.org</a>)</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WMA</td>
<td>World Medical Association</td>
</tr>
<tr>
<td>X-SCID</td>
<td>Severe combined immunodeficiency x-linked</td>
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</table>
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### Parental authorization

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<td>Parental understanding</td>
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### Data/samples collection

| Blood spots | 2.3.6 |
| Confidentiality | Chapter VII |
| Coding terminology | 7.3.4 |
| Genetic information | 1.3.2/7.3.1/8.3.1 |
| Secondary use | 2.1.4/2.3.6/6.3.2 |

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| Inclusion | Chapter I |
| Incidental findings | 8.3.2 |
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| Risks and benefits | Chapter VI |
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For additional information on these topics in the Canadian and international policy context, please see Appendix I, Comparison Tables.
SCOPE OF APPLICATION

The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS2) is and will remain the chief policy governing the ethics of all research involving human subjects taking place in Canadian institutions. These *Best Practices* are designed to assist in the application of the TCPS2 in the paediatric population. They are complementary to, and do not supersede, the TCPS2, and are intended as voluntary guidance for the Canadian health research community working with children and adolescents.

These *Best Practices* provide an overview of international and Canadian ethical norms, reflecting the current situation in Canada regarding health research involving children and adolescents. For a more critical analysis of these norms, please refer to *Pediatric Research in Canada* (D. Avard, J. Samuël and B.M. Knoppers (eds), Les Éditions Thémis, 2009) and *La recherche clinique avec les enfants: à la croisée de l’éthique et du droit -Belgique, France, Québec* (ML Delfosse, MH Parizeau et JP Amann (éd.) PUL & Anthémis, 2009).

These *Best Practices* also do not provide specific guidance for research involving the First Nations, Inuit and Métis peoples of Canada. For research involving Aboriginal children and youth, the *Best Practices* should be used in conjunction with the Tri-Council Policy Statement, Chapter 9, “Research Involving the First Nations, Inuit and Métis Peoples of Canada” ([http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-epet2/chapter9-chapitre9/](http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-epet2/chapter9-chapitre9/)).

APPLICABLE LEGISLATION AND POLICY

The *Best Practices* do not replace existing laws, policies and professional codes of conduct that apply to health research involving children and adolescents. Researchers, REBs and institutions should be aware of, and continue to comply with, relevant laws, policies and codes that govern research activities in their respective local jurisdictions. In the case of multi-centre research crossing provincial, territorial or even national borders, differing health and privacy laws and policies may apply.
INTRODUCTION
INTRODUCTION

The 1989 United Nations Convention on the Rights of the Child states that the “best interests of the child shall be a primary consideration” in all actions concerning children. It also recognizes the “right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health.”

THE DEVELOPMENT OF THE BEST PRACTICES

Advances in paediatric health research improve the way we understand child and adolescent health and development and how they are influenced by various factors such as the environment and education. Unfortunately, the lack of specific ethical guidelines for health research involving minors may unnecessarily complicate the ethical evaluation of important research. A major challenge is to ensure advances are achieved in a way that maximizes the benefits, offers special protection for children and adolescents and respects both parental authority and the developing autonomy of minors.

In 1991, the National Council on Bioethics in Human Research (NCBHR), with the support of the Canadian Paediatric Society, launched a project to review the ethical issues surrounding research involving children. After wide consultation, a task force prepared the Report on Research Involving Children, which influenced the drafting of the 1998 Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS). The TCPS was revised in 2010 to reflect changes in the research environment since the adoption of the original TCPS in 1998. However, as a broad document involving all human subject research, TCPS2 cannot provide an in-depth discussion of every ethical issue arising in research. In addition, since the publication of the Report on Research Involving Children in 1993, detailed provisions guiding the participation of children and adolescents in research have not been systematically addressed in Canada. Consequently, these Best Practices seek to augment the guidance of the TCPS2 by focusing strictly on both common and emerging issues in paediatric health research.

Considering the need for more explicit discussion of paediatric health research, the National Council on Ethics in Human Research (NCEHR) proposed in 2008 to undertake a two-year project to develop a guidance document for paediatric health researchers, research ethics boards (REB), and institutions. This project was initiated and orchestrated through NCEHR’s Emerging Issues Analysis Committee, and in collaboration with the Canadian Institutes of Health Research (CIHR) Institute of Human Development, Child and Youth Health (IHDCYH), the CIHR Ethics Office, Health Canada, and other key organizations such as the Maternal, Infant, Child, Youth, Research Network (MICYRN). The Centre of Genomics and
INTRODUCTION

Policy at McGill University, formerly part of the Centre de recherche en droit public (CRDP) at the University of Montreal, conducted the research and prepared the Best Practices.

Over a period of two years, the Steering Committee and the National Advisory Board (made up of experts from different disciplines, clinical perspectives and geographic locations) generated recommendations, developed in light of international and Canadian norms, which were then circulated for comment. An editorial group carried out a comparative review of international paediatric guidelines, which was supplemented by a literature review. Finally, the tables in Appendix 1 were developed to compare positions in national and international guidelines regarding the ten areas of special interest. Together, this work constituted the initial draft of the Best Practices.

Three drafts of the Best Practices were circulated previous to this final version. In early 2010, the first draft was circulated via relevant mailing lists, and was presented during a number of key conferences (NCEHR, CBS, CPS). In addition, governmental agencies (Health Canada, CIHR) and individuals submitted comments that assisted in the revision of the draft.

In December 2010, publication of the TCPS2 provided further opportunity to revise the Best Practices draft and ensure that it harmonized with the new edition of the TCPS. Following this revision a series of consultations were held on the second draft at regional health sciences centres across the country and at key academic conferences. Those attending the consultations were asked to review and evaluate the recommendations of the Best Practices, note any missing information, and assess the relevance of the recommendations in the Canadian context. In addition, thorough feedback on the second draft was provided by Health Canada (Bioethics and Policy Integration Division, and Health Research Involving Children Working Group), the CIHR Standing Committee on Ethics and the Drug Safety and Effectiveness Network.

In January 2012, a third draft of the Best Practices was put online with a call for commentaries. Commentators were asked to address particularly the addition of a chapter on guiding principles and certain modifications made to integrate suggestions from the last consultation. Various government (Health Canada and the Interagency Advisory Panel on Research Ethics and non-government organizations submitted commentaries that have allowed the finalization of the Best Practices.

A list of consultations that took place and organizations that submitted comments for the three drafts of the Best Practices appears in Appendix 2.
This final version of the *Best Practices* represents the culmination of these earlier efforts. The comments and concerns received through the consultation process surrounding the previous drafts assisted greatly in the preparation of this final version, and highlighted the practical issues that should be a consideration of any document that hopes to demonstrate best practices.

**GOALS OF THE BEST PRACTICES**

The *Best Practices* are intended to update the 1993 *Report on Research Involving Children*. They also suggest approaches for facing the new challenges raised by health research involving children and adolescents. In particular, the *Best Practices* are meant to:

- identify the issues that have emerged since the publication of the 1993 report as well as the policies that have been implemented;
- highlight the different approaches to ethics in various Canadian and international sources;
- provide guidance to researchers when designing their research projects involving children and adolescents;
- be a resource for REBs and institutions when reviewing research projects that involve children and adolescents; and
- harmonize and contribute to the current ethical norms on research involving children and adolescents.

In addition, there are some issues discussed in the *Best Practices* that are not settled in current Canadian or international guidelines. In these instances, the intent of the *Best Practices* is to illuminate and contribute to the discussion rather than provide concrete guidance.

The *Best Practices* also address qualitative health research, as it is becoming more common in paediatric health-related research. The primary ethical issues raised by qualitative research are more fully addressed in Chapter 10 of the TCPS2 and elsewhere in the literature. While it is not our intention to provide a detailed account of the range of ethical issues that arise when conducting qualitative health research with minors, this document would be incomplete without commenting on its use with children and adolescents. Specific issues will be addressed in Chapter I – Inclusion of Minors in Research, Chapter II – Consent to Research, Chapter VII – Privacy and Confidentiality, and Chapter VIII – Return of Research Results.
GUIDING PRINCIPLES

The Best Practices reflect the guiding principles stated in the TPCS2: ‘respect for persons’; ‘concern for welfare’; and ‘justice’. In addition, the Best Practices respect the ethical principles recognized by international instruments, such as the World Medical Association’s (WMA) Declaration of Helsinki,\textsuperscript{8} CIOMS’ International Ethical Guidelines for Biomedical Research Involving Human Subjects,\textsuperscript{9} and the United Nations Educational, Scientific and Cultural Organization’s (UNESCO) Universal Declaration on Bioethics and Human Rights.\textsuperscript{10}
GUIDING ETHICAL PRINCIPLES
GUIDING ETHICAL PRINCIPLES

Medical ethics in research are guided by underlying principles. Early development of these principles is represented by the Nuremberg Code\(^1\) and the Declaration of Helsinki\(^1,2\), where the autonomy and informed consent of research participants were first promoted. Later developments, such as the Belmont Report in the United States,\(^3\) set forth clearly delineated principles that are still accepted today.\(^4\) For its part, the second edition of Canada’s Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS), utilizes these same basic principles,\(^5\) which will be analyzed below in the specific context of paediatric research.

1. Evolution of Research Ethics

The practice of medicine has long had a singular ethical guidepost: “do no harm.”\(^6\) However, until the 20\(^{th}\) century there was no equivalent basic principle in medical research. To the contrary, the development of research ethics has often been driven by scandals in the field. History’s mark on the evolution of biomedical research ethics is exemplified by two events: the adoption of the Nuremberg Code following World War II, and the development of the ethical principles of the Belmont Report, the result of a concerted effort to address continuing deficiencies in the treatment of human research participants.

The Nuremberg Code was drafted in response to horrendous experiments which shared two salient features: they were conducted by physicians, and on subjects who had no choice about participation. Thus the attention of the drafters was drawn to the clear violations of the doctors’ obligation to promote the well-being of all those who fall under their care, and to the absence of choice by the research participants.

The hallmark of the Nuremberg Code is its endorsement of the need to obtain the informed consent of the research participant. The Code’s first principle – “The voluntary consent of the human subject is absolutely essential” – is followed by an explanatory paragraph setting out the basic elements of informed consent. The individual must have capacity to make decisions, must be provided with information about the experiment, and must remain free in his or her decision making. This requirement for informed consent taken at face value clearly precludes any experimentation involving those who lack the capacity to consent.\(^7\) Whether intentionally or not, the Nuremberg Code simply makes impossible any experimentation involving minors before they attain the legal capacity to make decisions. However, the Declaration of Helsinki, adopted nearly two decades later, remedied this deficiency by stating that when the potential participant lacked legal capacity “consent should be procured from the legal guardian.”\(^8\)
GUIDING ETHICAL PRINCIPLES

In the mid-1970s, following widespread public criticism of a number of research projects such as the Tuskegee Syphilis Study and the hepatitis studies conducted using disabled children in the Willowbrook State School, the United States Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This Commission published The Belmont Report: Ethical Principles for Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report recommended that three ethical principles be applied to human subject research: respect for persons, beneficence and justice. These principles are particularly important for Canadian researchers because they have been adopted, with some modification, as the core principles of the recent revision of the TCPS.

The principles of biomedical ethics, as they exist today, stem from the moral consciousness that, although the patient’s best interest still guides medical and research decision-making, patients and participants—or, in the case of children and adolescents not competent to consent, their parents or guardians—should have more control over decisions that affect their well-being. In the context of paediatric research, the formulation of ethical principles has served to enable research involving children and adolescents, albeit with limitations. This is all the more important considering that many paediatric conditions have no adult counterpart.

Given the sometimes sordid history of human subject research, ethical principles serve as both a poignant reminder and crucial protective measure. History teaches us that minors risk being used in research for which their inclusion is entirely inappropriate particularly as they are essentially a voiceless population. It is important to note, however, that ethical principles do not in themselves provide absolute protection: “the rights of the individual can be violated, even where codified ethical standards exist to protect those rights.” However, the evolution of ethical principles in human subject research provides us with a baseline that was not previously available for judging the acceptability of research.

2. Guiding Principles

The Best Practices use the three ethical principles introduced in the TCPS2 – respect for persons, concern for welfare and justice – as Guiding Principles because of their importance within the discourse of biomedical ethics. These are essentially the same principles adopted in The Belmont Report, and similar to the principles used by Beauchamp and Childress in their widely cited Principles of Biomedical Ethics. This does not mean that all ethical norms incorporate the definitions or terms used by the TCPS2, or that all commentators accept these principles, but the foundation of each principle is incorporated into the Best Practices to guide research decisions.
Respect for Persons

Respect for persons as envisioned in the TCPS2 includes the “dual moral obligations to respect autonomy and to protect those with developing, impaired or diminished autonomy.” This follows closely the principle as laid out in *The Belmont Report*, which is divided into “two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.” Another common framing of this principle, and the one seen in Beauchamp and Childress, suggests respect for autonomy alone. This more limited view of respect for persons is likely due to its origins focusing solely on adults. However, as discussed below, the broader perspective of ‘respect for persons’ used by the TCPS2 is a more appropriate statement of the principle where research with minors is concerned.

The application of this principle requires, as a first step, a determination of whether the potential research participant possesses autonomy. On the common understanding, to have autonomy means that a person can act intentionally, with understanding, and without any controlling influences determining actions. This definition distinguishes the simple act of doing what one wants to do from the specific exercise of autonomy, “which may also be doing what one wants to do but on the basis of thought or reasoning.” Thus, autonomy includes “the ability to deliberate about a decision and to act based on that deliberation.” However, it does not require the complete absence of others’ influences.

Assessing the capacity to make decisions about research participation is crucial to respect for persons, but it is neither a simple task nor reducible to any straightforward test. Capacity involves an ability to understand the information relevant to the decision at hand. Understanding is not just a matter of being able to repeat information. What is needed is an ability to use that information in a reasoned decision that is consistent with one’s settled values and goals. This account recognises that not every decision made will be made with complete understanding, and social, cultural and economic contexts of interpretation will differ.

The typical means of demonstrating respect for autonomy is the practice of informed consent. If the individual is deemed capable of self-determination, researchers have positive obligations both to provide adequate information about the research project and to solicit the individual’s consent to participation. Providing the information which reasonable people would consider relevant and answering the individual’s questions demonstrate respect for human reason. In addition researchers have an obligation to avoid any actions which may interfere with the freedom to decide. It may be difficult for many potential research participants to truly understand complex research questions, but “[r]esearch participants cannot
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make an autonomous choice about whether to participate in a study if they do not have information that is relevant to their making that choice.\textsuperscript{18}

There is a temptation to interpret the principle of respect for persons in a simplistic manner. The assessment of capacity is sometimes seen as an all-or-nothing judgment,\textsuperscript{19} with entirely distinct courses of action following from that determination. Thus if the individual is deemed to have the capacity to decide, then his or her informed consent must be obtained and maintained. Conversely, if the individual lacks capacity then a surrogate decision-maker, independent of the research team, must be identified and the interests of the individual must determine whether he or she can participate.

A closer reading of ethical guidance documents, particularly the TCPS2, suggests that this temptation to simplicity should be resisted. We cannot expect that participants will have a complete and full understanding of everything they are told. This may stem from the complexity of the information provided, but also from “an information substrate that is grossly distorted”;\textsuperscript{20} in other words, a misunderstanding of research and the goals of the particular project. As well, and as discussed below, as children and adolescents grow older their capability for understanding increases and therefore even if legally prohibited from providing consent, they can still participate more fully in the informed consent process. The burden, therefore, is placed on researchers to determine what information is needed and to provide the information in a way that most respects the minor.

\textit{Respect for Persons in the Paediatric Research Context}

It is clear that the morally important capacity to make decisions and determine the course of one’s own life does not instantaneously spring, fully formed, into existence. Rather it develops over time and through exercise. Moreover, it may also be diminished or impaired to varying degrees by illness or other conditions. One must carefully consider how to demonstrate respect for the person with diminished capacity, which includes minors. Moreover, legal restrictions often exist that limit the decision-making capacities of minors. Most provinces promote an individual determination of capacity, but not all.

In those instances where the capacity is developing, but not yet sufficiently developed, one must respect the nascent autonomy and foster its further development, while at the same time protecting the interests of the individual. Ethically robust respect for the developing autonomy of a child or adolescent is shown by the procedures of informing the minor about the proposed research; doing so in a manner tailored to the child’s ability to understand; soliciting his or her assent for participation; and respecting dissent. In some instances respecting the child’s potential for the development of autonomy may provide a very strong
reason to delay recruitment until that autonomy blossoms and the mature child can decide whether to participate.

When initial recruitment cannot be delayed and the individual’s participation continues over a long period, the requirement that informed consent be maintained generates a need to revisit assent and, subsequently, consent as autonomy advances. As the capacity of a child or adolescent to understand information matures, the sophistication of the information provided to him or to her should increase and the ethical importance of assent increases. And at the point the individual achieves autonomy (e.g. legal capacity) continued participation will require his or her informed consent.

An additional and important consideration in paediatric research is that minors are rarely, if ever, in a position to make decisions free from outside influence. Even as children and adolescents gain greater capability to understand, they still rely on their parents or guardians for most decisions in their lives. Moreover, physicians (or researchers) are likely to be in a position of trust and, even without overt action on their part, minors may do what is wanted of them merely because it is suggested by a trusted person. This represents an additional difficulty when determining whether an adolescent has developed autonomy to an extent permitting independent decision-making.

In sum, the use in the TCPS2 of ‘respect for persons’—and the adoption of this principle in the Best Practices—goes beyond the traditional concept of autonomy to include protection of those with diminished or no autonomy. In paediatric research, this extension serves to improve the ethical standing of minors. This principle is further strengthened by the second Guiding Principle of ‘concern for welfare.’

**Concern for Welfare**

The *Belmont Report* articulates a principle of beneficence, which it describes as a set of strict obligations to avoid doing harm, to maximize possible benefits and to minimize possible harms. The TCPS2 names its second core principle ‘concern for welfare’ and describes it in essentially the same way; it is a principle encompassing the traditional ethical principles of nonmaleficence and beneficence.

Concern for welfare takes into consideration “the impact on individuals of factors such as their physical, mental and spiritual health, as well as their physical, economic and social circumstances.” This phrase is more appropriate for use in research because the separate principle of nonmaleficence (used by Beauchamp and Childress) is not easily transposed to the research context. Nonmaleficence requires that physicians and researchers not inflict harm on others, and also prevent harm. However, in the research context some level of harm or discomfort is often unavoidable. Today, research projects are designed to
minimize the risk of harm, and institutional bodies have been created (such as Research Ethics Boards) to oversee these projects and ensure that participants are protected to the extent possible.

One effect of concern for welfare is the potential limitation on the autonomy of research participants. For example, a healthy person volunteering to participate in research to test an artificial heart might be prohibited from participating even if his or her decision is free and informed. Outside the research setting autonomous individuals often choose to put themselves in harm’s way for the sake of others, and without any expectation of any personal benefit. And there is no obvious reason to think they should be prevented from acting altruistically in the research setting. Nevertheless, the ethics approval process does place limits on such action.

Research ethics review manages the risks to such participants through a number of measures. Some of these clearly aim to ensure that participants are acting autonomously. Research ethics boards may exhibit heightened concern that information about risks and benefits is clearly presented: ensuring that the individual understands the potential risks involved; heightened sensitivity to the presence of controlling influences; and measures to assess the individuals’ capability to make decisions. In addition to such measures, research ethics boards typically set an upper limit to the risk that even an autonomous individual may be allowed to assume. One such limit is established considering the following principle of the Nuremberg Code: “The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.”

Concern for welfare also implores researchers to promote well-being. Such ‘beneficence’ is the moral obligation to act for the benefit of others. This demands much from researchers “because agents must take positive steps to help others, not merely refrain from harmful acts.”

In addition to the beneficence incorporated in the principle of concern for welfare, another important aspect of the principle is that researchers be cognizant of the harms which could be caused by their research. If the existing evidence base in the field is insufficient, researchers may need to conduct initial studies to elucidate what the actual risks are. It is not enough simply to understand the risks. Researchers are also responsible for designing appropriate measures to protect research participants from harm to the extent possible. These would encompass both procedures aimed at reducing the probability of harm occurring as well as those for detecting and then ameliorating harmful effects of research procedures.

The balancing of potential benefits and harms envisioned by a concern for welfare is a difficult task. It is understood that research involves risks that might not be accompanied by direct benefit; true beneficence in research would greatly limit how research is performed. Historically, when considering risks the
focus of attention remained firmly fixed on the risks to research participants. But the consideration of benefits has always taken a much wider view. “Research involving humans may produce benefits that positively affect the welfare of society as a whole through the advancement of knowledge for future generations, for participants themselves or for other individuals. However, much research offers little or no direct benefit to participants.”

**Concern for Welfare in the Paediatric Context**

Application of the principle of concern for welfare to the context of paediatric research is similar to research involving adults: researchers still have an obligation to minimize harms and to promote the benefit of the participant. Research involving minors does, however, have different standards for when participation is permissible, illustrating the practical difference between adult and paediatric research. For instance, there must be sufficient justification for the research to be performed on minors instead of on adults. Additionally, the risk generally should be minimal. (The difficulties in defining minimal risk will be discussed in greater detail in Chapter VI.) When the minor lacks the capacity to consent, the TCPS2 requires either that the research pose no more than minimal risk or that participation is in the minor’s best interests – that is, research participation is the best option available to the minor. Notably, this requirement is somewhat more restrictive than that in the earlier version of the TCPS, and it is also more restrictive than regulations in the United States.

The concept of ‘best interest’ deserves additional discussion in the context of children. A competent adult can be expected to judge his or her own best interests – so long as the risk is within accepted bounds. A child or adolescent, though, trusts others to make this judgment. Children and adolescents “are particularly vulnerable to conflicting interests and values. The historical record demonstrates that those who make decisions on their behalf do not always serve the children’s best interest. At times, even their parents’ interests conflict with theirs.” Researchers, parents, guardians and research ethics boards should be careful that other considerations do not impact a determination of what is in the best interest of a child or adolescent.

**Justice**

The principle of justice was first explicitly stated as a principle of research ethics in the *Belmont Report*. Its authors’ concern focused on problems posed by the particular historical context of the questionable research methods it considered. The burdens of being a research participant seemed to fall disproportionately on the members of certain segments of the population, namely those who, for reasons of poverty or their position in society, were vulnerable to exploitation by researchers.
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A second and related concern was that the same socioeconomic conditions that led individuals to subject themselves to research often prevented them from having access to the products created by the research. The general question of justice posed by the Belmont Report was the following: “[w]ho ought to receive the benefits of research and bear its burdens?” The practical measures proposed by the Report were aimed at ensuring the burdens of research were justly distributed.

In Canada, justice, as defined by the TCPS2, refers to “the obligation to treat people fairly and equitably” and a freedom from domination. In terms of research, this means that in the distribution of burdens and benefits, a just system of research does not place the burden solely on one population for the benefit of another. There are circumstances, though, when research will benefit only one population; therefore, it might be appropriate to use only that group as a pool of participants. Although an equal distribution of participants across age, gender and race may be desirable in terms of absolute justice, it is not always feasible or necessary.

The TCPS2 clearly recognizes the existence of a broader social justice issue, and it also recognizes that research ethics governance can exacerbate the problem. On the one hand, it notes that researchers should avoid inappropriate exclusion from research based on such considerations as race, gender, disability, age or the capacity to provide informed consent. On the other hand, it follows the general approach of the Belmont Report in setting out additional conditions which must be met in order to justify the inclusion in research of those who lack the capacity to consent.

Justice in the Paediatric Context

Applying the principle of justice creates unavoidable tension in the context of research with children and adolescents. At the broadest level of social policy, justice calls for research aimed at issues affecting children. Such research will inevitably need to recruit minors as participants, and in a great many instances minors who are unable to make decisions for themselves. The vulnerability of certain participants who can’t decide for themselves, such as children and adolescents, is an important difference that must be taken into account so that they may enjoy equitable treatment in research. Consequently, additional measures are required to protect those who are not in a position to protect themselves.

Justice also requires researchers not to deliberately avoid including children and adolescents in an effort to reduce the perceived difficulty involved in conducting research ethically. It also requires those who perform ethics review to carefully consider the necessity of such inclusion and to work with researchers to avoid exploitation.
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The TCPS2 recognizes that it would be unfair to exclude minors from research that might benefit them, especially as there are diseases that are unique to children and adolescents, or that are expressed differently in children. This could particularly concern specific cancers that affect the pediatric population. Furthermore, inclusion of minors in areas such as pharmaceutical research could provide essential information of efficacy and dosage of medication when physicians are otherwise left without guidance. However, particular care must be taken to ensure that minors in research are not shouldered with disproportionate or unreasonable risk, especially in light of their vulnerability and general inability to consent to research on their own behalf.

3. Application of the Guiding Principles to the Best Practices

These Guiding Principles serve as the backdrop to the Best Practices. However, as they are generally applied in the context of adult research, their applicability to paediatric research is imperfect. Yet, perfection is not necessary. Indeed, “principles are neither the start nor the end of the process of ethical reflection.” No single principle has primacy when considering potential outcomes for research participants. The principles are interdependent and complementary. They represent questions that should be asked and considerations that should be taken into account, and perhaps will lead to a deeper discussion of the ethical issues facing researchers, REBs and families working with the paediatric population.

The following ten chapters place paediatric research within the framework of the three Guiding Principles. They provide a notion of how to proceed ethically with health research involving children and adolescents.
I. **Inclusion of Minors in Research**

The inclusion of minors in research promotes their safety and well-being.

II. **Consent to Research**

Researchers should obtain the free and informed consent of the competent adolescent, or that of the parents if the minor is not competent to consent.

III. **Assent of the Minor**

Researchers should seek the assent of the minor according to his/her level of development and capacities. However, when the adolescent develops the legal capacity to provide a fully informed consent or attains the legal age of majority during the research, researchers should seek an informed consent.

IV. **Dissent of the Minor**

The dissent of the minor, who is capable of understanding, should be respected.

V. **Departures from Consent**

Exceptionally, researchers may seek the approval of an REB to depart from the obligation to obtain the consent of the competent adolescent, or that of the parents if the minor is not competent to consent.

VI. **Evaluation of Risks and Benefits**

The participation of a minor in research should offer the possibility of a direct benefit to his/her health. Where no direct benefit is likely, the results should benefit other minors of the same age or with the same disease, exposure, condition or disability, and the minor should not be exposed to more than minimal risk.

VII. **Privacy and Confidentiality**

In order to ensure that privacy and confidentiality are maintained, researchers should adopt appropriate and reasonable safeguards, subject to applicable law.

VIII. **Return of Research Results**

Researchers should broadly disseminate general research results. Generally, researchers should respect the wishes of the competent adolescent, or those of the parents, if the minor is not competent to consent, regarding the return of research results. However, individual results and incidental findings should be communicated 1) if they are scientifically valid,
2) if they have significant implications for the health of the child or adolescent, and 3) if there is a means of prevention or treatment available during childhood or adolescence.

The competent adolescent, or the parents if the minor is not competent to consent, should be informed whether data or samples obtained from the child will be anonymized and, if so, that it will be impossible to return individual results or incidental findings.

IX. PAYMENT IN RESEARCH

It may be appropriate to compensate minors and parents participating in research. Parents should not receive any payment other than the reimbursement of their expenses related to the participation of their child and their time. Payment should be discussed during the consent process. An REB should review the payment plan proposed.

X. COMPOSITION OF RESEARCH ETHICS BOARDS

Research Ethics Boards reviewing research protocols involving children and adolescents should be multidisciplinary and independent. REB membership should include those with expertise in conducting paediatric research. Where none of the members has such expertise, the REB should seek the advice of an ad hoc expert.
The *Best Practices* are composed of ten chapters to be considered as much by researchers when designing research involving children and/or adolescents, as by REBs in the specific areas of genetic research, pharmaceutical research, longitudinal studies and research involving children and adolescents at the end of life. The chapters should be read in conjunction with each other, since many of them are interdependent.

To facilitate the reading of the *Best Practices*, it should be noted that the term “parents” is used to denote parents or the custodial parent of a minor (where applicable); legal representative(s); and legal guardian(s). In addition, the use of the term “minor” includes children and adolescents. The word “minor” can apply both to adolescents competent to consent (e.g. “mature minors” or emancipated minors) and to those not competent to consent. The specific term “children” is generally used to designate minors in the first period of life, i.e. between birth and adolescence. It can also be used, however, in particular circumstances to refer to both children and adolescents. This would be the case, for instance, when it is used in a citation to refer to concepts such as “the best interests of the child” and “the development of the child”, or to refer to sons and daughters of parents. The specific term “adolescents” is used to designate minors above the age of 13 or 14 years.

Each chapter is divided into sections. The first section (e.g. 1.1) presents an analysis of the chapter topic and discusses the relevant guidance presented by Canadian and international norms. The second section (e.g. 1.2) distills this guidance and suggests an approach (in textboxes). The third section (e.g. 1.3) discusses some of the specific issues that arise in the context of paediatric research that may be emerging or unsettled under current guidance. The intent of this section is to raise questions for consideration, but not necessarily to offer definitive answers. In many instances, this section points to knowledge gaps that require further research.

Readers will find comparison tables associated with each chapter in Appendix 1. These tables compare those documents of which the ethical norms were used in the analysis of the international and Canadian contexts. Often documents did not take a position or provide guidance on a particular subject matter, and therefore do not appear in the corresponding table.
It is important to emphasize that the *Best Practices* do not replace the TCPS2 or existing federal or provincial laws. Researchers and REBs should always ensure that they respect applicable laws and the ethical guidance of the TCPS2 when designing or reviewing research projects involving children and/or adolescents.
CHAPTER I

INCLUSION of Minors in Research
1.1 Inclusion of Minors in Research: International and Canadian Contexts

The Nuremberg Code of Ethics of 1947 did not address the inclusion of minors in research. This is unfortunate, as some research that took place during the Nazi period in Germany used children. Following the Nuremberg Code, the twentieth century was further marked by a number of scandals involving paediatric research, for example the Willowbrook case in the 1950s. While conducting a hepatitis study on healthy institutionalized children, researchers intentionally infected them with hepatitis in order to understand the disease and to develop a vaccine. Even without guidance that directly addressed research involving minors, it was clear that deliberately harming them for the sake of paediatric research ran contrary to existing international and national ethics. In response, several guidelines were established to ensure observance specifically of the rights of minors participating in research. However, in an attempt to protect them, minors were effectively excluded from research and became “therapeutic orphans.”

The unintended consequence of this exclusion was a lack of knowledge of paediatric development and of appropriate medical treatments for minors in general, thereby jeopardizing their health and well-being in the long term. It then became necessary for the international community to re-evaluate their normative guidance documents in order to promote a balance between the duty to protect vulnerable persons, such as children and adolescents, and the need to include them in research. Though the need to conduct research involving children and provide guidance for their inclusion is evident, it was not until the 1964 Declaration of Helsinki that inclusion criteria for minors were clearly laid out.

Today, there is consensus in international and Canadian ethical norms regarding the need to include children and adolescents in research while offering appropriate protection. Guidelines from the Council of International Organizations of Medical Sciences (CIOMS) mention that the participation of minors is indispensable for research concerning diseases affecting infants and the TCPS2 states that inequity is created “when particular groups fail to receive fair benefits of research or when groups, or their data or their biological materials, are excluded from research arbitrarily or for reasons unrelated to the research question.” This reflects an important shift in norms related to research involving minors.
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The inclusion of minors in research is subject to specific conditions to ensure their protection. Unanimity exists among international and national norms on the following conditions: minors should only be involved when the research cannot be carried out on adults; consent of the parents as well as the assent of the minor, when feasible, are required; research should involve no more than minimal risk if there is no prospect of direct benefit to the minor; and research should be approved by an REB and satisfy the legal requirements of the jurisdiction. Additional elements may also be considered, such as the importance of the research in validating adult data, its direct relation to a condition occurring in minors, or its legality.

With respect to the criterion of minimal risk, the TCPS2 specifies that “REBs have special ethical obligations to individuals or groups whose circumstances make them vulnerable” (e.g. children) and that their inclusion should not exacerbate their vulnerability. The TCPS2 also allows the inclusion of minors in research that involves more than minimal risk (defined in Chapter 2, section B of the TCPS2) if it has “the prospect of direct benefits for them.” Thus, it would be possible for minors suffering from life-threatening diseases to participate in research that involves more than minimal risk if they can benefit from it (for additional discussion of minimal risk, see Chapter VI – Evaluation of Risks and Benefits).

Only a few ethical norms have addressed research involving very vulnerable minors (e.g. impaired or institutionalized minors). However, such inclusion is limited to specific projects. For example, the International Conference on Harmonization (ICH) Clinical Investigation of Medicinal Products in the Pediatric Population E11 provides that such research should be limited to “diseases or conditions found principally or exclusively in these groups.” In addition, impaired or institutionalized minors may be otherwise healthy, which creates additional complexity when considering their participation in research: should protections for these populations be even greater than for healthy minors who are not impaired or institutionalised? The inclusion of healthy minors in research is generally limited to studies on prevention or vaccine trials.

Finally, international and Canadian ethical norms do not generally provide an order of preference in the selection of different groups of children or adolescents for inclusion. However, CIOMS, ICH and the European Commission address the issue of involving older minors first in research, if possible. The rationale for this age-based stratification of child participants is based on the decreasing vulnerability of minors as they mature.
1.2 General Statement on the Inclusion of Minors in Research

The inclusion of minors in research promotes their safety and well-being.

Children and adolescents differ significantly from adults, physiologically and psychologically, as well as developmentally. Their developmental stages influence the limitations and potential benefits of research. Some diseases are found only in the paediatric population. However, given that minors are a vulnerable population, research should be subject to a rigorous governance framework complying with national ethical and professional norms and legislation, and informed by international ones. This framework respects the fundamental principles of research involving human subjects.

Conditions for Inclusion of Minors in Research

- the rights, safety and well-being of minors are of paramount consideration;
- participation of minors in research is justifiable when the research cannot be carried out with adults;
- when research requires the participation of minors, least vulnerable minors (e.g. older or more developed children or adolescents) should be included first in the project, if possible and scientifically appropriate;
- minors should derive a direct or indirect benefit from their participation in research;
- minors should not be exposed to more than minimal risk when research does not hold the prospect of direct benefit;
- a minor with a life-threatening disease may be included in research with hope of direct benefit only if:
  1. the risks of participation are commensurate with the benefits; and
  2. there is no treatment from which the minor can hope to benefit;
- a minor with a life-threatening disease may be included in research which does not offer hope of direct benefit to her/him only if:
  1. the research does not expose him/her to more than minimal risk; and
  2. the research may benefit minors with the same life-threatening disease.
- impaired, abused or institutionalized minors should only be included in research if:
  1. the research relates directly to their disease or condition; and
  2. the research offers hope of potential benefit to the minor concerned or the research represents no more than minimal risk;
- some research might require the participation of healthy minors in order to determine, for example, the effect of diet or environmental factors on a genetic predisposition, or the efficacy of a paediatric vaccine, but the research should not expose healthy minors to more than minimal risk.
1.3 Specific Issues

This section provides a brief analysis of specific emerging issues identified in the relevant literature and related to the inclusion of minors in research.

1.3.1 Inclusion of Healthy Minors in Research

The inclusion of healthy minors may be necessary in both observational and interventional research. Intervention-based research might investigate, for example, the normal range in healthy minors in order to identify the protein causing celiac disease or to test a new vaccine. Their participation may also be needed to establish age-appropriate normative values. Research on the exposure of minors to various risk factors is another example of research requiring the inclusion of healthy minors. However, inclusion of minors in research that exposes them to physical and emotional risks or discomforts raises ethical issues as these minors usually do not benefit directly from the research.

In 1966, two unethical research studies involving healthy minors took place. The first study tested a drug called Triacetyloleandomycin (TriA), which was used to treat acne. After performing liver biopsies, researchers found that TriA was causing liver abnormalities and dysfunction in the participants. The second study was conducted on 26 healthy newborns to determine if ureteral reflux can occur in a normal bladder. These children were catheterized and radiographed to examine their bladders.

These two examples of research involving healthy minors raise the following question: “to how much risk, if any, may healthy children be exposed in research that does not offer them the prospect of therapeutic benefit?” This question is still debated, but a few international and Canadian norms permit inclusion of healthy minors if the risks are minimal and if the least vulnerable minors (e.g. older minors) are considered first, where this is possible and scientifically appropriate.

1.3.2 Inclusion of Minors in Genetic Research

Considering the nature of genetic information and the vulnerability of minors, their inclusion in genetic research may be questioned. Genetic research may reveal information that will affect the minor throughout life since DNA remains constant into adulthood. Thus, the decision made by the
parents on behalf of the child or adolescent may have an important impact on his/her future. For example, the use of predictive testing for adult-onset conditions and carrier status in children raises many questions with regard to the scope of parental consent (see section 2.3.1). The inclusion of minors in genetic research using experimental therapies, such as gene therapy, also raises important issues (see section 1.3.3). By contrast, the inclusion of minors in genetic research may be useful to identify the sources of paediatric conditions or early onset diseases, such as polycystic kidney disease and kidney cancer. Genetic research that seeks to identify diseases or conditions for which prevention or treatment becomes possible during childhood or adolescence will improve the health and well-being of minors.

1.3.3 Inclusion of Minors in Novel Medical Experimental Therapies

The inclusion of minors in novel medical experimental therapies is controversial. The example of gene therapy trials illustrates this situation. Despite its success in treating some important childhood diseases such as X-linked severe combined immunodeficiency (X-SCID), gene therapy is still considered experimental, entailing health risks for the persons participating in gene therapy trials. The inclusion of minors in such trials raises many ethical and legal issues. Because of their lack of competence and the potentially high risks of gene therapy, minors are mostly excluded from gene therapy trials. Thus, paradoxically, adults are recruited to participate in trials that aim to treat degenerative childhood diseases, such as Duchenne muscular dystrophy.

Some gene therapy trials have shown that the inclusion of minors would have increased chances of success. For example, research on Leber’s congenital amaurosis (a retinal dystrophy responsible for infantile blindness) conducted with persons aged 17 to 23 has demonstrated that gene therapy would have had more chances of success if conducted on younger minors because of the progression of the disease. This finding raised the question of whether REBs should take into consideration the physiopathological mechanisms of action of gene therapy when deciding if minors should be included in such trials. Moreover, would ethical principles be respected by the exclusion of minors from gene therapy trials if they stand to benefit the most therefrom?
There is currently a lack of pharmaceutical data on the paediatric population. Most paediatric drugs are prescribed off-label due to the fact that they either have never been formally tested on children or adolescents, or data from paediatric clinical trials in other countries has not yet been submitted in Canada. Physicians may also extrapolate paediatric dosage from adult data even though “children are not small adults.” Moreover, there may be variations in maturation within the same age group of minors. The absence of age-appropriate formulation of drugs and the lack of data on the efficacy and toxicity of these drugs may expose minors to serious harm. CIOMS underscores that, in the past, drugs that had not been tested on children were nevertheless administered, exposing them to serious harm in the absence of sufficient knowledge on the safety and efficacy of such drugs. Even today, although drug labels may clearly state that the drug has not been approved for use in children and adolescents, clinicians might still prescribe the drug because there is nothing else available. This is problematic because developmental stages may influence the efficacy or toxicity of the drug—prescribed drugs are metabolized, extracted or absorbed differently. For example, Health Canada decided in 2008 that some over-the-counter cough and cold medicines (e.g. antitussives and expectorants) should not be labelled for use in children under 6 years old. Over-the-counter cough and cold medicines have a long history of use in children; however, there is limited evidence available to support the efficacy of these products in this population. In addition, reports of misuse, overdose and rare side-effects have raised concerns about the use of these medicines in children under six.

Some countries and organizations have begun initiatives to encourage clinical research involving the paediatric population. For example, the United States adopted legislative provisions to increase the numbers of drug trials involving minors by both offering incentives to manufacturers and by publishing requests for proposals to third parties in case of lack of interest by manufacturers. The European Commission also adopted legislative provisions to facilitate and harmonize the conduct of paediatric clinical trials. In Canada, two important initiatives were undertaken to encourage paediatric research. First, Health Canada adopted a guidance document called Guidance for Industry: Clinical Investigation of Medicinal Products in the Pediatric Population, ICH Topic E11 and prepared a document called Health Canada Addendum to ICH Guidance Document E11: Clinical Investigation of Medicinal Products in the Pediatric Population to assist the industry and the researchers conducting research on medicinal products for paediatric use. Second, the Food and...
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Drug Regulations were amended in 2006 to extend the data protection period by six months for certain paediatric drugs. To obtain this extension, manufacturers must, within the first five years of the protection period, submit the results of paediatric clinical trials, designed and conducted for the purpose of increasing knowledge of the use of the drug in paediatric populations. Extending the term of data protection in this manner is intended to encourage the submission of paediatric research results to provide health benefits to children and adolescents.37

However, the inclusion of minors may not always be appropriate at all stages of clinical trials. This rule includes exceptions. Trials carried out on healthy minors to develop vaccines and other preventative treatments are considered legitimate.38 There is, however, a significant difference between the risks of a Phase I trial, when little is known about the effects of a drug on humans, and the risks of a Phase III or IV trial. As will be seen below (Section 6.3.3 Evaluation of Risks and Benefits in Clinical Trials), much of the advocated involvement of minors is targeted at inclusion in later phases, such as after a drug has been approved for use in adults and the goal is to understand its effects and benefits for minors.

This does not mean, however, that minors should never participate in Phase I or II clinical trials. There are circumstances when it would be appropriate to include minors in the initial phases, such as trials for diseases that affect only paediatric populations or trials in which the use of adults would yield little or no useful information (e.g. trials concerning the use of surfactant with premature babies).39 In the absence of adult samples, the benefits for the paediatric population of certain clinical trials on therapeutic products destined uniquely for minors could be justified (e.g. for the treatment of certain metabolic problems). Yet, even in these circumstances, it is desirable to obtain initial safety and tolerability data from adult studies.40 Certainly, the risks from participation are still an essential factor to consider, but, as noted above, minors should not be automatically excluded from all early phase trials. (See also Section 2.3.3, Parental Consent for an Early Phase Clinical Trial.)

1.3.5 Inclusion of Minors in Longitudinal Studies

The inclusion of minors in longitudinal studies raises “unique ethical issues due to the potentially lengthy period of involvement as research subjects”41 as the data and samples collected during the study will be kept for a long period of time. During this period, the minor will grow up, mature and develop the capacity to make informed decisions. Therefore, the involvement of minors in the
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decision-making process will grow and their opinion will have more weight. This situation raises issues with regard to the scope of parental consent (see section 2.3.2), the assent of the minor (see section 3.3.2), the return of research results (see section 8.3.3), and the confidentiality of the information collected (see section 7.3.2).

1.3.6 Inclusion of Minors in Research at the End of Life

The inclusion in research of minors who are dying and are receiving palliative care raises many ethical questions because of their double vulnerability: 1) they are minors; and 2) they are dying. As mentioned in Section 1.1, the need to include minors in research is widely recognized. There are not always specifications with regard to the categories of children or adolescents who should be included in research (e.g. healthy minors or minors with life-threatening illnesses). Each research project involving minors should thus be evaluated on a case-by-case basis. However, some organisations have adopted specific guidelines on the participation of dying minors in research. Thus, they seem to create a special category for children and adolescents who present with a life-limiting illness and for whom there is no scientifically proven curative therapy available. For example, the American Academy of Pediatrics recognized specifically that minors at the end of life can participate in research when they suffer from “a life-threatening condition that does not respond to all standard therapies, and the [child’s] illness is such that death is imminent.”

The following conditions apply to such research:

1. The question being addressed is extremely important.
2. The therapy [experimental treatment] being proposed is well founded in animal and clinical research and/or there is a good expectation that the therapy may be beneficial.
3. Physicians who are not involved in the research must document that the clinical condition of the patient is such that death appears inevitable and standard therapy has not improved the patient’s prognosis.
4. The potential benefits outweigh the potential risks.

An ethical argument often raised against the inclusion of dying minors in research is the potential burden of participation in research. Some authors assert that these children or adolescents might be asked to take on a bigger burden than other minors because of their “compromised health status and limited remaining time.” Moreover, they may prefer to spend their remaining time in other ways than participating in research. However, the data collected to date on the potential burden on children and adolescents arising from their participation does not support this finding. Therefore, it would be unjust to exclude them from research on this basis. There may however be a need to
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conduct research to determine the perceptions of the minors and parents regarding their participation in research.

For a discussion of therapeutic misconception and research at the end of life, see Sections 2.3.7 and 2.3.8.

1.3.7 Inclusion of Minors in Qualitative Research

Including minors in qualitative research allows them to describe their experiences from their own perspectives. Qualitative research is an excellent method to permit researchers to give children and adolescents a voice and to help understand, from a child’s viewpoint, their cognitive, emotional, behavioural and health issues.

If minors are to benefit from qualitative research, greater effort is needed to involve minors as key stakeholders in all stages of the research, from planning, to interviewing, to analysis. This will demand sensitivity, creativity and awareness of the special nature of the relationship between the researcher and the child or adolescent.

1.3.8 The Uncertainties of Including Minors in Research

The discussion in this chapter implies that inclusion of minors in research is generally accepted which, by measures of Canadian and international guidelines and the literature, it is. However, general acceptance does not equate with a lack of debate over this issue. Indeed, many of the statements advocating inclusion of minors are tempered by the recognition that minors are still in need of special protection and that inclusion in all types of research is not always appropriate (see Chapter VI – Evaluation of Risks and Benefits). A critical analysis of the inclusion of minors advances the Guiding Ethical Principles of concern for welfare and justice. If the exploitation of children and adolescents in research studies as recently as the mid-20th century gives reason to researchers, REBs and families to revisit the current role of minors in health research, so much the better for the ethical integrity of their continued participation.

A comparison of international and Canadian ethical norms on the inclusion of minors in research is presented in Table 1 of Appendix 1.
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2.1 Consent to Research: International and Canadian Contexts

This chapter should be read together with Chapter III, Assent of the Minor, and Chapter IV, Dissent of the Minor, along with the discussion in TCPS2, sections 3.9 and 3.10. Combined, this guidance represents the process of recruiting individuals into research and ensuring their informed participation.

This chapter is divided into four sections. The first section will cover the situation where the adolescent has the legal capacity to provide fully informed consent. The second section will focus on parental consent in the context where obtaining the consent of the minor is impossible. The third section will address the standards of consent, to be free and informed. The fourth section will analyze the norms related to the secondary use of personal information and previously collected tissue.

2.1.1 Consent of the Competent Adolescent

In Canada, provincial laws differ regarding when an adolescent is presumed to be legally competent to provide fully informed consent, and may also distinguish between consent to care and consent to research. Thus, persons under the legal age of majority may be deemed legally incompetent in some provinces to provide informed consent to their participation in research. In contrast, other provinces use a competence-based system to evaluate the capacity of the research participant to consent to research regardless of their age, and so do not depend on a legislatively mandated age for consent to research. This principle is influenced by the mature minor doctrine used in the context of medical care, which emphasizes the capacity of the adolescent to make informed decisions rather than considering only the age of the child. Such “mature” minors are legally considered to have the same competency as competent adults and can thus provide a free and informed consent to research. Researchers should, therefore, be aware of legal or other guidance in their jurisdiction that determines when adolescents are competent to consent to research participation, and what is required to obtain consent.
2.1.2 Parental Consent

It is interesting to note that different terms are used to denote informed consent, such as “permission” or “authorization.” This situation may be influenced by the fact that the term “consent” should be reserved for competent individuals. However, in accordance with convention, the Best Practices will use the term “consent” to include parental authorization on behalf of minors. This is also consistent with the TCPS2.

Parental consent is required when the minor is deemed not competent to provide an informed consent. Where an adolescent’s competency to consent for participation in research is set at a certain age by law, parental consent is always required before including a minor in research (with limited exception such as in the case of emancipated minors). In addition to parental consent, the assent of the minor should be obtained when feasible (Chapter III – Assent of the Minor).

Importantly, any parental decision to consent to the participation of their child or adolescent must consider the best interests of the child. Usually, the parents are considered the most appropriate persons to determine this.

2.1.3 Free and Informed Consent Requirements

The informed consent of the competent adolescent, or that of the parents if the minor is not competent to consent, is subject to a number of requirements according to international and Canadian norms on ethical research involving human participants. These requirements—which are generally applicable to all research participants and not just minors—mainly focus on the quality of the consent (e.g. free and informed), the elements to include in the consent form, the capacity to understand the information provided and the actual process of obtaining informed consent. It should be noted that these Best Practices do not provide guidance on how to assess competency.

International and Canadian ethical norms agree on the need to obtain the consent of the competent adolescent, or that of the parents if the minor is not competent to consent, before inclusion in research. They are also in agreement on the characteristics of that consent. Indeed, all of the norms analyzed provide that consent must be free (e.g. obtained without manipulation or undue influence) and informed (e.g. researchers must provide all pertinent information).
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There is agreement on a list of core elements to be discussed and included in the consent process, which attempts to ensure that all pertinent information is provided. These core elements include: the aims of the research, research procedures, potential risks and benefits, participant or third party access to the information collected, compensation of the participant and/or family, right of withdrawal and a description of alternative treatments. However, this list is not exhaustive. Depending on the type of research conducted, additional elements may need to be included in the consent form. For example, in genetic research, it may be necessary to state the policy on the disclosure of results of genetic tests and their familial implications to the participant and family. In pharmaceutical research, the availability of the drug after the completion of a trial or the lack of information on the drug being studied should be included in the consent form. In the context of longitudinal studies using biobanks, the future research uses (and the requirement for REB approval for those studies), storage and destruction of data and/or samples, who can access the biobank, and who has governance and control over the biobank should also be stated.

International norms as well as Canadian norms state that information should be given in understandable language. Researchers should therefore adapt the language used to the abilities of the person consenting. Consent should also be written except when the person consenting cannot read or write, if a written consent is contrary to local custom, or when another reason is judged acceptable by a REB. If this situation occurs, verbal consent is possible but should be documented. CIOMS and TCPS2 address the possibility of an implied consent, meaning a consent implied by voluntary actions (e.g. return of a questionnaire by mail). It is worth mentioning that TCPS2 suggests greater focus on the quality of the consent rather than the form of its documentation. While not requiring a written consent, it advises researchers to leave “a written statement of the information conveyed” and requires that the procedures used to seek consent be documented.

Similarly, international and Canadian ethical norms strongly recommend that cultural background be considered (for additional information, refer to TCPS2, Chapter 9, “Research Involving the First Nations, Inuit and Métis Peoples of Canada”). For example, in some communities, a handshake may constitute evidence of trust sufficient to express consent, while in other communities the giving and receiving of gifts constitutes consent.
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Researchers should also ensure that competent adolescents, or parents for minors not competent to consent, understand the information disclosed. In a *Joint Statement on the Process of Informed Consent for Genetic Research*, the Canadian College of Medical Geneticists and the Canadian Association of Genetic Counsellors insist on the importance of dialogue between researchers and participants/parents. Although this Statement focuses on genetic research, its principles may be applied in other types of research involving human participants.

Parents or participants also should be given sufficient time to provide their consent. TCPS2 specifies that the time for decision-making will depend on different factors, such as “the magnitude and probability of harms, the complexity of the information conveyed, and the setting where the information is given.”

The norms stress that consent is a continuing process that should be maintained throughout the course of research. This is especially true in longitudinal studies where changing circumstances or the need for additional information or samples necessitate additional contact with minors and/or their parents. Researchers have a continuous obligation to inform participants of modifications to a research protocol that could affect them. Consent should be renewed when: 1) changes to the research protocol germane to the participant’s decision to participate are required; 2) new information is available and may affect the willingness of the participant to stay in the research (e.g. incidental findings or new risks); or 3) participants are involved in a long-term research project.

In the case of research in emergency health situations, the TCPS2 allows for research without the informed consent of the participant (or parents) if all of the following conditions are respected:

“(a) a serious threat to the prospective participant requires immediate intervention;
(b) either no standard efficacious care exists or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care;
(c) either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant;
(d) the prospective participant is unconscious or lacks capacity to understand the risks, methods and purposes of the research project;
(e) third party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so; and
(f) no relevant prior directive by the participant is known to exist.”
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When the adolescent able to consent regains capacity or, in the case of an minor incompetent to consent, when the parents become available, informed consent to continue the participation in research should be promptly sought.14

Departures from the general process of consent will be analyzed in Chapter V.

2.1.4 Consent and Secondary Use of Personal Information and Previously Collected Tissue

In the context of databases and biobanks, some organizations promote the optimal use of the data and samples to ensure progress in research. For example, the European Society of Human Genetics specifies that “[the] full benefits for which the subjects gave their samples will be realized through maximizing collaborative high quality research. Therefore, there is an ethical imperative to promote access and exchange information.”15 In the absence of consent to secondary use in the initial consent process, this imperative raises the question of whether or not a new consent is needed for the secondary use of the data and/or samples.

International and Canadian norms generally recognize limited applications for the secondary use of data, though a number of these norms specifically permit use of tissue or data beyond the original purpose, if previously consented to16—and even with no consent if tissue or data are anonymized or de-identified17. UNESCO prohibits uses that are incompatible with the original consent.18 This means that secondary use to study the same condition would be permissible.19 But the question of whether such subsequent research should only be performed by those who sought the original consent is left unclear. In UNESCO’s view, secondary use would also be possible for public health purposes without consent since the organization explicitly recognizes public health needs as an exception to the basic requirement of consent.20

TCPS2 discusses secondary use of data and tissues separately. First, participants may have expressed, at the moment of consent, their preferences concerning the eventual use of their samples and tissue. These previously expressed preferences by adolescents competent to consent or the parents of minors not competent to consent must be respected by researchers.21 If secondary use of data involves identifying information (i.e. it is reasonable to believe that they would allow identification of a person, whether they would be used alone or in combination with other available information), an
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REB may approve the project without requiring researchers to obtain the consent of the participant concerned or his/her parents if certain conditions are met. It should be noted that this requirement does not apply to personal information that is not identifiable. Thus, researchers using non-identifiable data would not need to seek consent of the participants or their parents for secondary uses. For previously collected, identifiable tissue, again, the consent of the participant or the parents should also be obtained, as least to demonstrate to an REB that certain conditions are met. When tissues are non-identifiable, the TCPS2 stresses that consent is not needed, although ethical approval is always required. In the eyes of Health Canada, the anonymization of tissues does not diminish the importance of informed consent, which must still be respected. In consequence, it would be unacceptable to anonymize tissues in order to avoid the withdrawal requests of participants. Finally, when researchers want to re-contact the participants to collect additional information or samples they need to obtain an REB approval, unless such re-contact was foreseen in the original consent. In the case of deceased minors, parental consent should be obtained when required.

To avoid the need to continually seek new consent, some norms suggest using broad consent. Such consent contrasts with traditional notions of specific informed consent (i.e., a consent specific for each study in which the participant is involved) in that following REB approval, it permits the continued use of samples and data for future, unspecified research projects without requiring repeated consents from parents or adolescents competent to consent. Even if broad consent is given without all the details of future research uses, several modalities are already determined and mentioned in the consent. For example, the type of consent can be linked to a determined theme (e.g. child development) or a precise disease (e.g. a cancer). The latitude provided to researchers by broad consent is traditionally framed by additional protections assuring the respect of participant autonomy and their consent of by certain governance mechanisms. For example, an independent oversight committee could evaluate the future uses in order to determine if they correspond with the spirit of the broad consent obtained. Updates could also be offered to participants on the progress of research. Although the possibility of using broad consent in longitudinal studies is currently emerging, it is only gradually being recognized for other types of research and so may include statements such as “[…] for cancer or related conditions.” This issue is examined in the Specific Issues Section 2.3.
2.2 General Statement on Consent To Research

Researchers should obtain the free and informed consent of the competent adolescent or that of the parents if the minor is not competent to consent.

Researchers should obtain the consent of the competent adolescent or that of the parents if the minor is not competent to consent. When parental consent is needed and the parents are separated or divorced, researchers should refer to the applicable law or policy to determine which parent has the authority to consent to the inclusion of the minor in research, or whether both are required to provide consent. When providing consent on behalf of their child or adolescent, the parents should base their decision on the child’s best interests.

Character of the Consent

- consent should be free: obtained without manipulation, coercion or undue influence;
- consent should be informed: all relevant information should be communicated prior to obtaining consent;
- researchers should ensure that the individual has the capacity to understand the information and its consequences;
- consent should consider cultural differences, meaning that community consent may, in some circumstances, be obtained in addition to individual consent.

Disclosure of the Information

The information should:

- be stated in clear, easy to understand language and be adapted to the abilities of the person consenting; and
- take into consideration cultural background.

Legally Emancipated and Mature Minors

Subject to applicable law, emancipated, mature, or otherwise competent minors to consent can provide a free and informed consent.
Consent Form – Essential Elements to Include

- nature and goals of the research, research methods, feature of the research design, expected results of the research and their impacts (e.g. the impact of health care decisions on participants and/or family members), and the length of the participation;
- potential risks and benefits (both immediate and long-term);
- right to withdraw from the research at any time, without the minor suffering any harm, as well as the situations where withdrawal is impossible (e.g. anonymized data and samples);
- mechanisms for protection of and limitations to privacy and confidentiality;
- access to the information collected by the participant and third parties;
- access to the findings and/or results of the research (general or individual research results);
- plan for handling incidental findings;
- compensation for participation and adverse consequences;
- possibility of alternative treatments;
- disclosure of research findings that might lead to medical interventions;
- voluntariness of participation;
- reasons to terminate the participation;
- possibility of commercialization;
- number of participants involved in research;
- existence of any actual, potential or perceived conflicts of interest involving the researcher(s) participating in the research;
- source(s) of funding;
- name, affiliation, and general contact information of the researcher(s);
- name of the REB that reviewed and approved the protocol; contact information for complaints.

Additional elements that should be included, if applicable:
- availability of the drug/device after the research;
- possibility of future uses (secondary uses) of data or samples collected;
- storage and destruction of data and samples collected;
- responsibility of the researcher(s) to provide medical services;
- duality of the role of the researcher(s), if applicable;
- role of the participant’s physician;
- disclosure of new information that may affect the willingness of the participant to participate in the research;
- arrangements in case of adverse events or research-related injury (e.g. who will pay for medical care); disclosure of experimental procedures, if any.
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Process of Consent

- the competent adolescent or the parents if the minor is not competent to consent, should:
  - be given sufficient time to provide consent;
  - have the opportunity to ask questions;
  - have the opportunity to discuss participation in the research with friends, family, or other professionals;
- consent should be obtained in writing before enrolment. However, in some exceptional circumstances, verbal consent is acceptable. In such cases, consent should be documented and witnessed;
- researchers should verify that the competent adolescent, or the parents if the minor is not competent to consent, understand the information disclosed in the consent form;
- consent is a continuing process that should be maintained throughout the research project. If there are changes that could be germane to the participant to the research protocol, new information that changes the risk of participation becomes available, or the legal status of the participant changes, consent should be renewed, if feasible.

Research in Emergency Health Situations

- should only address the emergency needs of participants involved;
- criteria should be established in advance and approved by an REB;
- all of the following conditions should be met:
  "(a) a serious threat to the prospective participant requires immediate intervention;
  (b) either no standard efficacious care exists or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care;
  (c) either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant;
  (d) the prospective participant is unconscious or lacks capacity to understand the risks, methods and purposes of the research project;
  (e) third party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so; and
  (f) no relevant prior directive by the participant is known to exist."37
- consent of the competent adolescent or that of the parents if the minor is not competent to consent, should be sought promptly to continue participation in research.

Secondary Use of Personal Information and Tissues

- secondary use should be anticipated prior to obtaining consent of the research participant and the consent form should be worded accordingly;
- when accessing anonymous information or tissue for a secondary use, REB approval is not required on the condition that coupling, storage, and diffusion procedures do not create identifiable information.
- If the information or tissues are identifiable, REBs may approve the project without requiring the consent of the participant or parents if certain conditions are met.
- if the information or tissue is not identifiable, consent is not necessary, but ethical approval is required.
2.3 Specific Issues

This section provides a brief analysis of specific emerging issues identified in the relevant literature and related to consent to research.

2.3.1 Parental Consent and Genetic Testing in Research

Genetic testing may be used in paediatric research to identify pre-symptomatic risks for conditions (e.g. Huntington’s disease), susceptibility to a specific condition (e.g. breast cancer), or carrier status (e.g. sickle cell anemia). Contrary to clinical genetic information, genetic research results are more likely to be uncertain and ambiguous since the goal of research is to produce generalizable knowledge and not necessarily validated individual results. These results may identify conditions for which prevention or treatment may or may not be possible. Results may also have important consequences for the minor’s well-being beyond immediate physical health, through possible stigmatization, impaired self-esteem and anxiety. Considering the uncertainty of the results, the possibility to prevent or treat the condition identified and the consequences for the life of the child or adolescent, do parents have the authority to consent to such testing on behalf of their child?

In the clinical care context, there is a consensus against the use of predictive testing for adult-onset conditions and carrier status testing in minors. International and national norms addressing genetic testing provide that the use of genetic testing to detect adult-onset conditions or carrier status should be deferred until the minor reaches the age of majority or has developed mature decision-making capacities. However, some authors contend that this approach needs to be reconsidered since genetic testing could provide awareness of risks for potential conditions and thereby protect the minor from future harms.

Although there is concern with genetic testing in the clinical context, testing in research might not raise the same issues because, as with all research, the primary goal is not to provide clinically relevant feedback. Thus, for research that can detect genetic variations related to adult-onset disorders, researchers should be clear in the consent process with parents that clinically relevant results will either not be collected or, if collected, will not be shared until the minor is of the appropriate age unless such results can benefit the minor during childhood or adolescence. Questions
surrounding the disclosure of genetic testing results in research are discussed in more detail in Chapter VIII – Return of Research Results.

2.3.2 Parental Broad Consent in Longitudinal Studies and Biobanks

Longitudinal studies raise special issues of consent because of their extended duration. In the context of paediatric longitudinal studies, parents must consent on behalf of their child for continued access to data and/or samples. The minor may attain capacity to consent while the study is ongoing. Moreover, there may be some secondary uses of the data and/or samples that require a new consent. The use of broad consent has been suggested to address these issues. However, is it ethical for parents to give a broad consent on behalf of their child?

One purpose of informed consent is to provide an understanding of the research project for which the parents are consenting on behalf of their child. As seen in the analysis of the international and Canadian norms, informing the parents of the purposes or aims of the research is a core element of informed consent. In the case of biobanks, however, these elements are not always clear at the moment of consent because the exact goals and precise methodologies of the eventual research have yet to be defined. It is unclear therefore whether broad consent could fulfill this function as the purpose and methods of future research would not be known. However, the case of biobanks is slightly different. By their very nature, biobanks imply future, unspecified research. As explained in section 2.1.4, broad consent is normally accompanied by particular methods of governance that limit the latitude given to researchers. These mechanisms aim to protect the autonomy and consent of participants. In consequence, broad consent appears to be an appropriate means of obtaining consent in the context of biobanks.

In contrast to longitudinal studies or biobanks, broad consent may not be an acceptable approach for other disease-specific studies or clinical trials, as the informed nature of the consent could become distorted: “the more general the consent is, the less informed it becomes.” However, when researchers require repeated access to information or samples, anecdotal evidence and at least one study suggest that even in clinical studies, parents of children or adolescents with cancer would be in favour of providing broad consent on behalf of their child instead of being contacted to provide a new consent for each new research project using their child’s data and/or samples. Indeed, broadly
consenting to research on a particular disease together with “related conditions” may well serve the interests of the child in a family at-risk for a common condition such as cancer.

Another question raised by parental broad consent is whether the growing minor will ever have the opportunity to exercise autonomous choice regarding the use of data and/or samples. At first glance, the use of parental broad consent would seem to deprive the minor of the opportunity to exercise autonomy by not allowing his or her ratification of the parental consent at a later date. As noted earlier, minors are maturing throughout the period of research. Some of them may acquire the legal capacity to consent to their participation during the life of the project. In such a situation, the minor can be informed throughout the research and ideally, the consent of the competent minor would be obtained in order to continue participation or the use of data and samples. This may however be infeasible and unrealistic in research that is not specifically longitudinal in nature where re-contact with participants over time is not foreseen.

Finally, international norms recognize that participants have the right to withdraw from research at any time. In the context of parental broad consent however, there may be practical limitations preventing the minor from exercising this right to withdraw. For instance, one purpose of broad consent is to avoid the continual re-contact of participants for each new study using their information. Thus, the right of the minor to withdraw may not be executable if the minor is not informed of the existence of the new study. A way to overcome this issue would be for researchers to maintain contact with the minor. Therefore, the data and/or samples should be coded (i.e. not anonymized or anonymous) in order to re-contact the minor. Such re-contact is inherent in paediatric longitudinal studies.

In the case of genetic research, some authors suggest limiting parental consent “only to specific research protocols or research on certain genes or diseases” where the donor (i.e. the minor) did not consent to the use and storage of data and/or samples. According to this opinion, parental broad consent currently may not be permissible for genetic research involving minors. Assuming that this situation limits or prevents such research taking place at all, it raises issues of equity, as many genetic diseases first manifest during childhood or adolescence and paediatric genetic research is the only avenue to understanding the disease and developing treatment.
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2.3.3 Parental Consent for an Early Phase Clinical Trial

Pharmaceutical research also raises the question of whether parents can consent to the participation of their child in an early phase clinical trial. Usually, Phase I examines the “metabolism and pharmacologic actions of the drug in humans” while Phase II examines the “effectiveness of the drug for a particular indication [...] in patients with the disease or condition under study [...]” Thus, there is a low chance that anyone participating in a Phase I trial would directly benefit since the aim is not to test the efficacy of the new drug but rather its toxicity. Furthermore, Phase I or II studies generally expose minors to more than minimal risk. For these reasons, it is unlikely that healthy minors would be permitted to participate in the early phases of clinical trials due to the increase in risk. Evidently, the development of vaccines and other preventative treatments with healthy minors is legitimate prima facie. Nonetheless, the inclusion of terminally ill minors may be considered for early phase studies. REBs should consider that minors may benefit from the research even if the probability of success is low. In any case, the best interest of the child should prevail.

2.3.4 Research Concepts and Parental Understanding

Some tools of clinical trials, such as randomization, blinding or placebo grouping may be unfamiliar to parents. An American survey showed that 50% of parents did not understand the concept of randomization even if researchers provided explanations before seeking consent. The survey recommended providing clarifications on randomization and assessing parental understanding of this concept. This example illustrates the need for researchers to make sure that the parents understand the elements disclosed in the consent form and that it is important for the information to be presented in an understandable way.

2.3.5 Informational Entanglement

An issue that has arisen in familial or longitudinal studies is information entanglement, which means that the information collected concerns both the parent and the minor (e.g. birth cohort studies, where there may be shared biological fluids or tissues). In such a situation, what happens if the parent wants to withdraw and the minor wants to continue participation or vice versa? Parental consent is only valid as long as the minor does not have the capacity to make independent decisions concerning participation in research. Once an minor incompetent to consent becomes capable of
understanding the research, any decision should be respected, including dissent. However, if there is a dispute regarding the use of the information concerned, the decision of the person who wishes to withdraw should be respected.

2.3.6 Consent and Secondary Use: The Case of Bloodspots Collected in Newborn Screening

In many provinces, newborn screening programs are in place to systematically detect severe physical and mental abnormalities in newborns. For example, Ontario’s newborn screening program may identify up to 27 conditions. Some states in the United States detect as many as 50 conditions. Traditional newborn screening programs for treatable conditions are considered part of routine paediatric care and necessarily include all babies. But, the bloodspots collected at the time of the screening test can be stored for varying periods of time, and are seen as a valuable resource for genetic, epidemiological, and environmental research. Such continued storage and/or use for research raises ethical questions because on the whole, parents generally are not asked for their consent for these purposes. There is currently no unanimity on the question of the need to obtain consent for storage of surplus spots or for newborn screening research or other types of research. Some authors state that the explicit consent of the parents should be required, while others suggest the use of broad consent or a waiver of consent. It goes without saying that newborn bloodspots may need to be stored for confirmation of those children found to be affected or for quality assurance purposes. Nevertheless, due to increasing public debate over this issue, there is an urgent need to elaborate clear guidelines regarding the storage and secondary use of bloodspots for research and parental consent.

2.3.7 Parental Consent and Research at the End of Life

It has been demonstrated that minors may be vulnerable due to their lack of capacity to consent to research. In research involving minors at the end of life, when they may be receiving palliative care, the parents are also in a situation of vulnerability. Parents facing the death of their child may want to try any procedure or intervention that may have a chance to save their child. These parents may suffer and, thus, may not be able to make an objective decision. Moreover, the fact that the researcher is often the minor’s physician may add pressure on the parents. Thus, the vulnerability of the parents raises questions about their capacity to provide free and informed consent. It is
appropriate to take into consideration the vulnerability of the parents when seeking their consent. Researchers should be aware that parents may feel guilty or be very distressed by the situation. There is a need to improve reliable parental outreach information to better inform them about the differences between research and therapy as a tool for recruitment as part of informed consent. In Europe, the National Consultative Ethics Committee for Health and Life Sciences (CCNE) recommends that “no effort must be spared to ensure that parents are never made to feel guilty about any decision they may have taken.” However, the norms as well as the relevant literature do not provide additional guidance on how researchers should deal with the vulnerability of the parents.

2.3.8 Research at the End of Life and Therapeutic Misconception

Therapeutic misconception refers to “the notion that unless otherwise informed, research participants will assume (especially, but not exclusively, in experimental therapy) that decisions about their care are being made solely with their benefit in mind.” Because the goal of research is the attainment of generalizable knowledge and not necessarily the benefit of the participant, this confusion is problematic.

Minors and parents involved in research at the end of the child’s life when he or she may be receiving palliative care may think that such research will be therapeutic. They may see their participation as “their best chance of survival.” This situation probably derives from the fact that research is the only option available when there is no possible treatment. In its Opinion no 73 on Phase I Studies in Cancerology, CCNE recommends avoiding the use of the word “treatment” in the consent form. It also suggests that researchers should focus on the objective of the trial, which is to study the toxicity of the new drug tested. Researchers should explain to the minor and the parents the difference between research and therapy. This way of proceeding should reduce the risk of therapeutic misconception, although it might be impossible to eliminate the risk entirely. In addition, some authors argue that researchers should ensure that the participant and/or parents understand: “(1) the risks and benefits inherent in the research, (2) the fact that the trial does not properly constitute treatment and (3) the fact that participation is unlikely to extend survival.”
2.3.9 Consent and Qualitative Research

Informed consent is a key issue in qualitative research. Its principles are discussed in greater detail in Chapter 10 of the TCPS2.

A unique ethical challenge in qualitative research using open-ended interviews, in depth discussions, focus groups, and observation is the unpredictable and often unstructured nature of the data collection process. This raises concerns about consent, since to give informed consent, participants should be provided with relevant risk information.

Acknowledging the unpredictable nature of these qualitative research methods, researchers using them should build in safeguards to alert participants to the risks of over-disclosure and to the researchers’ duty to report (according to laws of the jurisdiction). However, in the case of children this is complicated and difficult to address because children have different reference points when describing discomfort or harm.

Considering that the researcher in qualitative research aims to gain acceptance, build trust, and foster positive relationships with minors, it is important to recognize the ethical issues associated with developing such a relationship between the researcher and the minors. Moreover, when participating in longitudinal studies for a prolonged period of time, a close and potentially dependent relationship can develop. In addition, during interviews minors may feel that the researcher is the expert, the authority or the counselor, because the inequality in power and status between adults and minors creates such an atmosphere.

This imbalance is greatly felt in qualitative research. It is critical that researchers be aware of the amount of influence and power they have with respect to minors. For example, researchers need to consider the possible threat to voluntary withdrawal. One study has revealed that minors believed that investigators would react negatively and be unhappy if they withdrew after a study had begun.

When considering the issue of imbalance, a number of suggestions have been proposed to minimize power differentials including: using methods that allow minors to feel part of the research process; being responsive to minors’ agenda; involving minors as part of the research team; using group interviews; verifying willingness to participate throughout the interview; being aware of non-verbal
cues such as body language; rehearsing with minors how to decline answering questions or participation; reassuring minors that withdrawal is permitted; and during interview situations giving minors control over the tape recorder. 87

A comparison of international and Canadian ethical norms on consent to research is presented in Table 2 of Appendix 1.
CHAPTER III

ASSENT of the Minor
3.1 Assent of the Minor: International and Canadian Contexts

This chapter should be read together with Chapter II, Consent to Research, and Chapter IV, Dissent of the Minor, along with the discussion in TCPS2, sections 3.9 and 3.10. Combined, these texts represent the process of recruiting individual children and adolescents into research and ensuring their informed participation.

Minors are not presumed, as adults are, to have the required competency to provide a free and informed consent to their participation in research. For minor who are not considered to be legally competent or are not legally emancipated, assent, rather than consent, should be sought, together with parental consent. Most international and Canadian ethical norms acknowledge the importance of including children and adolescents, who are capable of understanding, in the decision-making process and of obtaining their assent. Assent may be defined as the minor’s willingness to participate in the proposed research.1

The 1989 United Nations’ Convention on the Rights of the Child states that, when minors are able to express their own views, they have the right to express those views freely. Furthermore, “the views of the child [should be] given due weight in accordance with the age and maturity of the child.”2 International and Canadian ethical norms require that researchers obtain the assent of minors before involving them in research. However, assent might be impossible or impracticable to obtain in some circumstances. Only a few policy documents address this matter by stating that not all age groups can provide an assent (e.g. when the child is too immature) and not all situations or types of research can foster this requirement (e.g. emergency research, serious illness). However, when minors regain capacity (e.g. following an emergency), assent should be sought to continue their participation in research. Even if ethical norms do not frame such contexts, exceptions to obtaining assent should also be extended to minors who cannot assent because of developmental and cognitive disability and, obviously, to newborns and the very young; that is, to all children who do not have the capacity to understand. In most Canadian jurisdictions, when the adolescent has a level of comprehension of research similar to a competent adult, consent should be sought.

The minor’s assent alone is insufficient to be included in research. It should be obtained in addition to the consent given by the parents, and should include important information about the proposed research project. Yet, unlike with consent, neither international nor Canadian ethical norms detail the elements to include in obtaining assent, nor do they advise on who should discuss assent with the minor (e.g. the
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researcher or someone else on the research team). Some norms specify that information about the project (e.g. nature and purpose of the research), the right to decline, the right to withdraw and information on potential risks and benefits should be provided to the minor. No further guidance is provided for researchers. Therefore, it may be useful to refer to the elements needed for an informed consent, and to adapt these to the particular context of assent. This was suggested by the European Commission in its 2008 Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population. Although these elements of consent should be considered, the assent process should not be as legalistic as the consent process, considering that minors have a limited comprehension of the research. However, since comprehension will evolve with age, an adolescent should receive more information than a 7-year old, for instance.

Indeed, when seeking assent from a child or adolescent not competent to consent, researchers need to take into consideration age, degree of maturity, developmental stage and intellectual capacities (e.g. special needs or learning difficulties). Yet, minors of the same age do not necessarily have the same degree of maturity and may not be at the same developmental stage. Thus, competency for assent should be determined on a case-by-case basis. The European Commission suggests that assent be obtained in a manner appropriate to one of three different age groups: 1) children from birth to 3 years of age (where assent is impossible); 2) children from 3 years of age and up (where children between ages 3-5 can understand some expression of altruism; children from ages 6-7 who have an emerging capacity to agree and understand; and children from age 9 who can understand the risks and benefits); and 3) adolescents (with an emerging capacity for independent decision-making and the capacity to make adult decisions in many areas of their life). The European Commission does not draw a line as to when adolescence begins. According to much of the literature, adolescence starts at 14 years of age, although there is not complete agreement on this.

Information provided in the assent process should be disclosed to the extent allowed by the minor’s maturity and intelligence. Researchers should use a level of language and wording that is appropriate to the age and psychological and intellectual maturity of the child or adolescent concerned, and should also take into consideration any developmental or cognitive challenges. The terms used should be understandable and honest.

International and national norms do not necessarily require that assent be written. According to the ICH and the European Commission, it is preferable that assent be written if the minor can read and write.
CHAPTER III
ASSENT of the Minor

However, TCPS2 acknowledges that assent may be expressed verbally or physically. Since not all minors can read and/or write, the assent process should be documented to ensure that the rights of the minors concerned have been respected.

When assent is written, should the assent form be distinct from the consent form? Most ethical norms are silent regarding this question. ICH states that the assent form may be separate from the consent form, but does not clearly insist on this point. In contrast, the European Commission requires that the two documents be separate in order to ensure the use of age appropriate information. However, a common practice is to allow a space on the parental consent form for the assent of the minor. Thus, researchers can explain the research to the minor, verbally and in appropriate language, and document the assent on the consent form. When the minor has provided a written assent, either on the same form as the consent or on a separate form, a copy of the assent form can be given to him/her where appropriate (primarily taking into account age).

Finally, like consent, assent is a continuing process that should be renewed throughout the research project as the minor’s capacities or the nature of the research changes. For instance, in the context of longitudinal studies, there is a need to continually reassess and renew assent throughout the duration of the research project. Also, when adolescents develop the legal capacity to provide a fully informed consent for themselves or reach the legal age of majority and are capable of making independent decisions during the research, their informed consent should be sought when feasible – as a condition to their continued participation in the research project.
3.2 General Statement on the Assent of the Minor

Researchers should seek the assent of the minor according to his/her level of development and capacities. However, when the adolescent develops the legal capacity to provide a fully informed consent or attains the legal age of majority during the research, researchers should seek an informed consent.

Seeking assent in research satisfies the principle of respect for persons. Assent is distinct from consent in that it is based on the assumption of a limited comprehension of the nature and implications of the research according to the minor’s maturity, development and capacity. This process allows minors to exercise their right to participate in the decision-making process within the limits of their capacity to do so. Therefore, assent is subject to a number of requirements.

Obligation to Obtain Assent

- If the minor is not competent to provide consent, researchers should seek the assent of the minor before involving him/her in research;
- Assent is impossible to obtain in some very specific situations, such as:
  - newborns and young children;
  - some minors are not capable of assent because of developmental and cognitive challenges; or
  - clinical state of the minor does not permit assent (e.g. coma, unconsciousness).

Elements to Consider When Seeking Assent

Researchers should take into consideration the minor’s:
- age;
- intellectual capacities;
- complexity of the research protocol;
- risks and benefits of the research to the participants;
- cultural context; and
- life/disease experience (e.g. children and adolescents who have experience with illness may be more mature than others).

Elements to disclose

- nature of the research;
- research methods and procedures;
- risks and benefits of participation;
- right of withdrawal and how to withdraw;
- situations where withdrawal may be impossible (e.g. anonymized data/samples); and
- return of research results.
CHAPTER III
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Information Disclosure

Information should be provided in language (spoken and/or written) that is appropriate to:
- the age of the minor;
- his/her level of understanding and developmental stage; and
- his/her culture.

Assent Process

- assent should be provided freely (e.g. without parental pressure);
- if possible, someone on the research team other than the researcher should seek assent;
- explicit procedures for obtaining assent should be included in the protocol;
- Information provided as part of the assent process should be age appropriate;
- assent should preferably be obtained in writing if the minor can read and write. If impossible, the assent should be documented;
- when provided in writing, a copy of the assent form can be given to the minor where appropriate;
- separate information sheets and consent and assent forms should be used to facilitate comprehension by the minor, and if the minor has a level of comprehension similar to a competent adult (e.g. adolescent) but is still legally incompetent to provide consent, the consent form may be used to seek assent;
- the minor should be given:
  - appropriate time to provide assent;
  - opportunity to ask questions; and
  - opportunity to discuss participation with others (e.g. parents, relatives, friends, teachers).
- when seeking assent, the process should ensure the child’s assent is not unduly influenced by his or her parents or others in a position of power in relation to the child;
- assent is a continuing process that requires confirmation over the course of the research project;
- assent should be re-obtained when the research project undergoes changes germane to the participant's decision to participate, when new information becomes available that changes the risk of participation, if the research comes to a point of significant potential burden to the minor, and at intervals appropriate to the increasing maturity of the minor.

Assent and Majority

- In the course of the research, when the adolescent reaches the legal age of majority or acquires capacity to consent, researchers should seek his or her fully informed consent. Thus, Chapter II – Consent to Research applies.
Age Groups

Guidelines rarely state explicitly how to adapt the information to the age or capacity of the minor. Thus, the parameters for assent should be determined for each individual and based on an evaluation of the cognitive and developmental skills that emerge over time in the minor. Assent should be viewed differently depending on the age group, such as school-age children, adolescents, and mature minors and legally emancipated minors.

**School-age Children (around 6 to 13 years old)**
- ability to make and understand decisions is emerging;
- children of 6-7 years may be able to provide a meaningful assent and may be able to read and sign the assent form since they have some understanding of the research;
- children of 9 years may be able understand the risks and benefits of research, but might have difficulty understanding conflicting or abstract information or long-term implications and consequences;
- assent forms should be phrased in clear and easy to understand language adapted to the child’s age, level of understanding and stage of development;
- preferably, children should sign the assent form when they are able to understand, read and write.

**Adolescents (14 to 18 years old)**
- have generally acquired an ability to make decisions akin to that of adults;
- their right to self-determination should be respected as much as possible;
- researchers should provide adolescents incompetent to consent with the same information as that provided to the parents during the consent process, and the assent form should contain essentially the same information as the consent form but presented in an appropriate manner and language;
- the adolescent’s signature should be obtained in addition to that of the parents.
CHAPTER III
ASSENT of the Minor

3.3 Specific Issues

This section provides a brief analysis of specific emerging issues identified in the relevant literature and related to the assent of the minor in research.

3.3.1 Understanding the Elements Disclosed During Assent Process

The terms used in research are often sophisticated and may be difficult for minors to understand. For example, minors may not be able to understand terms such as “calories”, “blood sample”, “anonymization”, “randomization” or “deoxyribonucleic acid (DNA).” Moreover, minors may not comprehend abstract concepts such as confidentiality or voluntariness. Thus, simplified language that the minor may be familiar with should be used to describe the nature of the research, the methods and procedures, and the risks and benefits. For example, a biobank may be described as “a place where a little bit of your blood in a tube is kept for study over many years.” Or a blood sample may be explained as “we will take little bit of your blood from a vein in your arm.” An active voice should also be used in the assent form to enhance the comprehension of the minors. Ford et al. provide the following example to illustrate the use of active voice: instead of saying “an adult has read this Information Sheet with me” they suggest to say “I have read the information letter with Karen [name of the researcher].”

A few authors argue that, when the information is adapted for the level of comprehension and stage of development, children of 5 years of age can understand the purpose of the research and express their willingness to participate. It is important to note that minors should be given a basic understanding of the elements disclosed during the assent process since they cannot make a fully informed decision. However, according to age, some minors (e.g. adolescents, mature minors) may have the capacity to make such a fully informed decision.

3.3.2 Assent of the Minor in Longitudinal Studies

Many longitudinal studies begin at the time of a child’s birth or during infancy, and even less when the child is incapable of providing assent or consent. Since the purpose of these studies is long-term evaluation, children often reach an age where they are capable of comprehending the research in which they are participating, before the research is complete. In the course of the research, once
researchers determine that a minor has the capability to assent and, later, to consent to ongoing research, they should communicate with the minor using age-appropriate language, preferably obtaining assent or consent at pre-specified intervals or when additional samples or data are necessary.\(^\text{19}\) Such communication may occur several times, as the research follows the child into adolescence and adulthood. At each instance, and where feasible and the minor remains identifiable, the assent of the minor or the consent of the competent adolescent could determine continued participation in research or the use of data and/or samples collected.\(^\text{20}\)

A comparison of international and Canadian ethical norms on the assent of the minor is presented in Table 3 of Appendix 1.
CHAPTER IV
DISSENT of the Minor
4.1 Dissent of the Minor: International and Canadian Contexts

This chapter should be read together with Chapter II, Consent to Research, and Chapter III, Assent of the Minor, along with the discussion in TCPS2, sections 3.9 and 3.10. Combined, these texts represent the process of recruiting individuals into research and ensuring their informed participation.

4.1.1 Respecting Dissent

Just as refusal is the opposite of consent, dissent is the opposite of assent and may be defined as the opposition of the minor incompetent to consent to participate in the proposed research. Dissent requires of the minor the same level of capacity to understand as does assent. It may be expressed verbally or physically (e.g. crying, resistance). The European Commission recommends documenting the dissent of the minor.

Most international and Canadian ethical norms do not provide detailed guidance on the dissent of minors, except to state that it should be respected. The European Commission states that an “effort should be made to understand and respect differences of opinion between the minor and his/her parents or legal representative.” But if the minor expresses strong and definitive objections, the dissent should then prevail. In Canada, the TCPS2 states that minor’s “expression of dissent or signs suggesting they do not wish to participate must be respected” with no provisions for overriding considerations except when the minor does not have the ability to understand the significance of the research. This inability to understand could be caused by age or lack or maturity (e.g. newborns or very young children), or cognitive or mental disorders.

4.1.2 Overriding Dissent

It is worth noting that ethical norms used in some jurisdictions suggest that overriding dissent is possible in particular circumstances, although there is no unanimity regarding this question. For example, both CIOMS and ICH specify that the dissent of the minor may be overridden when: 1) the minor is too immature or too young; 2) there is no reasonable alternative other than what is available in research, and there are reasonable grounds to believe that it will offer benefit; or 3) the minor is suffering from a serious or life-threatening disease and dissent would jeopardize his/her welfare.
When overriding dissent is possible, it is not clear whether researchers need REB approval to do so. While CIOMS provides that such an approval is necessary to override the dissent of a minor who is “older and more nearly capable of independent informed consent,” ICH states that continued parental consent should be sufficient to maintain the participation of the minor in research.
4.2 General Statement on the Dissent of the Minor

*The dissent of the minor, who is capable of understanding, should be respected.*

Dissent may be verbal or behavioural (e.g. body movements) and may be expressed at any time during the research. It should be respected if the minor is capable of understanding, even if the parents consented to their minor’s participation in the research project.

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<th>Dissent During the Research</th>
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<tr>
<td>Objections raised by the minor, capable of understanding, during the course of the research project should also be considered and his/her wishes should be respected if the choice is not harmful to his/her health.</td>
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<tr>
<th>Mature Minors and Legally Emancipated Minors</th>
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<tr>
<td>Since these minors are competent to provide an informed consent, their decision to not participate in research should always be respected.</td>
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</table>
CHAPTER IV
DISSENT of the Minor

4.3 Specific Issues

This section provides a brief analysis of specific emerging issues identified in the relevant literature and related to the dissent of the minor.

4.3.1 Dissent of the Minor in Longitudinal Studies

In longitudinal studies, children may be recruited at an age when they cannot effectively dissent. When a minor has been involved in a study for a number of years and subsequently exercises the right to dissent or to withdraw, this may create dilemmas for researchers in some circumstances. Indeed, researchers may be afraid that dissent or withdrawal of the minor will compromise the quality of research. However, this is not a sufficient reason to override the dissent of the minor who is capable of understanding. Thus, the dissent or withdrawal of the minor should be respected, as discussed in this section, in consideration of the minor’s increasing autonomy.

4.3.2 Nature of the Dissent of the Minor

The majority of the norms analyzed do not provide guidance on the nature of the dissent of the minor. Does dissent entail any expression of disapproval on the part of the minor? Does a single “no” on a single day constitute dissent or would it require repetitive objections? Should dissent be proportional to the burden of the intervention (e.g. the greater the burden, the lesser the need for a strong expression of dissent)? Only CIOMS underscores that a distinction should be made between the “deliberate objection of an older child” and the “behaviour of an infant.” However, CIOMS does not provide much guidance on this issue. It simply adds that older minors should be included when possible because it is easier to evaluate their objection.

A comparison of international and Canadian ethical norms on the dissent of the minor is presented in Table 4 of Appendix 1.
CHAPTER V
DEPARTURES from Consent
5.1 *Departures from Consent: International and Canadian Contexts*

Consent of the competent adolescent, or that of the parents if the minor is not competent to consent, is a fundamental requirement for participation in research. However, this obligation may be abrogated under very specific and limited conditions.

An international norm and a Canadian norm provide examples of research that may justify the absence of consent by the parents.¹ Such a departure may be justified according to the nature of the proposed research. For example, research on sexual behavior, use of recreational drugs, domestic violence or child abuse may be such that obtaining consent from the parents may place the minor at risk or may compromise the research. In these instances, researchers should seek assent of the minor or the consent of the competent adolescent. Often, it is the most vulnerable minors, such as those suffering from abuse or neglect, who are not generally asked for their permission. When research involves such minors, it is especially important to ensure that their assent or consent is sought.

In some epidemiological and psycho-social research, such as observational research or studies involving a degree of deception, where explicit consent of competent adolescents or assent of non-competent minors could create bias in the selection of participants, a departure from the requirement of consent of the competent adolescent and assent of the non-competent minor may also be justified.²

In situations where re-consent is sought, departures from the procedure might also be granted due to the impossibility or impracticability of obtaining re-consent of the participants (e.g. participants moved and cannot be reached). In the context of research using data or samples stored in a bank for purposes other than the one described in the initial consent, a departure from consent or assent may be approved by the REB if the information and tissues are non-identifiable and certain conditions are fulfilled.³

In all cases, to ensure appropriate protection of the population included in the proposed research a departure from consent is subject to REB approval at the very least. In Canada, with the exception of secondary uses, the TCPS2 goes further by requiring that all of the 5 following elements be satisfied before any departure from the general process of consent may be approved:

“(a) the research involves no more than minimal risk to the participants;
(b) the lack of the participant’s consent is unlikely to adversely affect the welfare of the participant;
(c) it is impossible or impracticable to carry out the research and to answer the research question properly, given the research design, if the prior consent of the participant is required;
(d) whenever possible and appropriate, after participation, or at a later time during the study, participants will be debriefed and provided with additional pertinent information in accordance with Articles 3.2 and 3.4, at which point they will have the opportunity to refuse consent in accordance with Article 3.1; and
(e) the research does not involve a therapeutic intervention, or other clinical or diagnostic interventions.  

In addition, CIOMS suggests that REBs limit access to the information in time, and ensure that there is no known objection from the participant to the use proposed and examine if mitigation of the potential harms imposed by the departure from consent is possible (e.g. anonymization).
5.2 General Statement on Departures From Consent

Exceptionally, researchers may seek the approval of an REB to depart from the obligation to obtain the consent of the competent adolescent, or that of the parents if the minor is not competent to consent.

A departure from the general requirement to obtain consent is an exceptional situation. It should always be explicitly approved by an REB and be in accordance with applicable law.

Exceptional Circumstances Allowing Departure from Consent

Exceptional circumstances that may allow a departure from parental or competent adolescent consent include:

- minor is the victim of abuse or neglect;
- minor is not living with the parents (e.g. "street kids");
- research on sexual behaviour, use of recreational drugs or domestic violence where seeking parental consent could place the minor at risk;
- psycho-social research (e.g. deception, observational studies), where bias would be possible;
- some epidemiological research (e.g. longitudinal studies, where re-contact is impossible or impracticable, registries, quality assurance);
- secondary uses of identifiable samples or data when certain conditions are met in the eyes of an REB.

REB Approval

- a departure from consent should be approved by an REB.
- Outside of situations of secondary use, REBs should ensure that:
  - the research in question involves not more than minimal risk;
  - the departure is unlikely to adversely affect the rights and welfare of the participants;
  - the research could not practicably be carried out without the departure;
  - whenever possible and appropriate, the participants will be provided with additional pertinent information after participation;
  - there is no prior directive from the participants for the use proposed; and
  - the research does not involve a therapeutic intervention.

A comparison of international and Canadian ethical norms on the departure from consent is presented in Table 5 of Appendix 1.
CHAPTER VI

EVALUATION of Risks and Benefits
6.1 Evaluation of Risks and Benefits: International and Canadian Contexts

6.1.1 Risks and Benefits

The obligation for researchers to balance the risks and benefits of the research is directed by the classical principles of nonmaleficence and beneficence, which are subsumed here and the TCPS2 by the overarching principle of ‘concern for welfare’. These principles impose the following ethical obligations: 1) to prevent harm; and 2) to maximize possible benefits while minimizing possible harms.\(^1\) Benefit may be defined as “something of positive value related to health or welfare.”\(^2\) Research may have a direct benefit for the individual concerned or a benefit for the group to which the individual belongs by virtue of age and medical condition. An example of a direct benefit would be the improvement of the individual minor’s health, while an indirect benefit would be better understanding of the cause of a childhood disease or condition.

Risk may be defined as “a function of the magnitude or seriousness of the harm, and the probability that it will occur.”\(^3\) Risk may affect the minor, the family, or even the community. The harms can be physical, psychological, legal, social or financial.\(^4\) Risk may vary according to the different age groups.\(^5\) In the calculation of risk, examples of harms to be considered might include: the invasiveness of the procedure, the adverse side effects of what is being tested, or the identification of an unwanted gene or condition in a specific community that could lead to discrimination (e.g. Tay-Sachs disease, prevalence of alcoholism).\(^6\) Research methodology and protocols should be designed to expose participants to the least amount of risk necessary to achieve the goals of the study.

International and Canadian ethical norms agree on the importance of balancing the risks and benefits before involving human participants in research.\(^7\) Risks and benefits should be evaluated on the basis of their probability and the magnitude of their associated impact. In this respect, for example, a low probability of a great harm will be examined differently than a low probability of a minor harm. The TCPS2 recommends taking into consideration the interests of the persons concerned and the magnitude or seriousness of potential harm.\(^8\) The European Commission adds other criteria, such as the duration and the severity of the condition or disease under study.\(^9\)
CHAPTER VI
EVALUATION of Risks and Benefits

When research holds out the prospect of direct benefit to the minor, there is unanimity among the various ethical norms on the justification for a minor’s participation. However, risks should be weighed against the anticipated benefits.\(^\text{10}\)

When research does not offer hope of direct benefit to the minor, specific requirements apply. First, the proposed research should have a strong chance of contributing to the health of other children or adolescents in the same age category or with the same disease, exposure or condition.\(^\text{11}\) Second, the risk should be “reasonable in relation to the importance of the knowledge to be gained.”\(^\text{12}\) Third, the research should impose no more than minimal risk and burden on the minor concerned – the risk should be no greater than the risk associated with routine medical or psychological examination or treatment. In addition to these requirements, the European Commission suggests considering the severity of the disease or condition, its commonality, the likelihood of obtaining results from the research, and the usefulness of the benefits obtained.\(^\text{13}\)

6.1.2 Minimal Risk

The requirement of minimal risk raises many questions, including what, exactly, it means. A number of definitions of minimal risk exist. First, minimal risk is defined in the TCPS2 from an individual perspective, as risks that are “no greater than those encountered by participants in those aspects of their everyday life that relate to the research.”\(^\text{14}\) It has also been defined in a more objective manner as “no more likely and not greater than the risk attached to routine medical or psychological examination of [the] persons.”\(^\text{15}\) Elsewhere, it has been defined in a way that combines these two perspectives: “Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”\(^\text{16}\)

So, while there is an international consensus on the use of ‘minimal risk’ as a criterion of participation, its practical application lacks precision. Indeed, the criteria of risk comparable to that of “everyday life” and “during a routine medical exam” are not clear. For example, how do risks ordinarily encountered in the daily life of a child or adolescent compare to risks faced in research?\(^\text{17}\) Are these the risks related to the practice of a sport, to crossing a street to go to school or to body piercing? Do participants’ life experiences or health status impact their perception of risk? Although
the answer to these questions is unclear, some procedures have been recognized as being minimal risk, such as a questionnaire, observation, and the collection of urine and blood samples.18

As well, the risk comparable to that of a routine medical exam is subjective and seems to require analysis on a case by case basis. For example, a routine medical exam for a sick minor will involve procedures, such as blood draws, injections or even chemotherapy. In contrast, healthy minors may never have been subject to any invasive procedures other than vaccinations. This situation raises an important question regarding the participation of healthy minors in medical research. In what types of research, if any, may a healthy minor participate given that 1) they may not be exposed to more than minimal risk because 2) they would not expect to draw any benefit from the research by virtue of their already healthy status? For additional discussion on the inclusion of healthy minors in research, see Section 1.3.1.

Finally, neither international nor Canadian ethical norms mention whether the evaluation of risks and benefits should be conducted from a minor’s perspective.19 This way of approaching the assessment of risks in research involving minors is relevant. Indeed, it may be inappropriate to extrapolate the adult experience to minors. For example, a venipuncture is generally considered to be minimal risk for adults. However, this procedure may cause substantial psychological stress or anxiety for children.20 Therefore, researchers should think about how a child or adolescent may perceive the interventions and procedures proposed in order to conduct an appropriate evaluation of the risks.21 They should also think about the cumulative burden of research risks. For example, a single venipuncture might constitute a minimal risk, while many pokes may constitute a significant burden on the child. Finally, they should consider the developmental stage of the child. For young children, even a single venipuncture might be stressful.

6.1.3 A Slight Increase Above Minimal Risk

The lack of precision surrounding the concept of minimal risk impacts the notion of slightly increased risk. Slightly increased risk is not defined in any international or national norms and CIOMS acknowledges that no definition currently exists.22 CIOMS provides a few examples to guide researchers, such as additional lumbar punctures and supplementary bone-marrow aspirations for minors regularly prescribed these exams in clinical practice.23 The European Commission also provides examples of minor increase over minimal risk, such as arterial puncture, placement of an
umbilical catheter, skin punch biopsy and magnetic resonance imaging (MRI) scan. However, CIOMS and the European Commission guidelines are not specifically intended for the paediatric population, and the perception of risk from the procedures may be higher in the paediatric than in the adult context.

CIOMS states that slight or minor increases above minimal risk are acceptable when: 1) there is an overriding scientific or medical rationale for such an increase and 2) an REB has approved the increase. Before giving its approval, the REB must conclude: “1) that the research is designed to be responsive to the disease affecting the prospective subjects or to conditions to which they are particularly susceptible; 2) that the risks of the research interventions are only slightly greater than those associated with routine medical or psychological examination of such persons for the condition or set of clinical circumstances under investigation; 3) that the objective of the research is sufficiently important to justify exposure of the subjects to the increased risk; and 4) that the interventions are reasonably commensurate with clinical interventions that the subjects have experienced or may be expected to experience in relation to the condition under investigation.” Similarly, under the Common Rule in the United States, a minor increase above minimal risk is possible in part if the increase is commensurate with “their actual or expected medical, dental, psychological, social, or educational situations,” thus taking into consideration the minor’s subjective experiences. In contrast, the Council of Europe imposes a limit to such increase in risk by specifying that “any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk.”

Canada takes a more restrictive – although succinct – approach as to when research with more than minimal risk may take place. The TCPS2 permits such research if it has the prospect of direct benefits for participants. Unlike CIOMS, overarching scientific or medical rationales are not sufficient to allow the additional risk to minors. The TCPS2 also does not differentiate between “more than minimal risk” and “slight increase above minimal risk”: anything above minimal risk without direct benefit to the participant is proscribed.
6.2 General Statement on the Evaluation of Risks and Benefits

The participation of a minor in research should offer the possibility of a direct benefit to his/her health. Where no direct benefit is likely, the results should benefit other minors of the same age or with the same disease, exposure, condition or disability, and the minor should not be exposed to more than minimal risk.

Consideration of Potential Harms

- consideration of potential harms should include harms that are physical, psychological, social or financial, as well as harms that may affect individuals or communities.
- cumulative harms should be considered in assessing the individual harms that occur from research participation.
- potential harms should be evaluated from the perspective of the child or adolescent.

Justifying Risk

- participation of a minor in research should offer hope of direct benefit for the minor.
- when the research holds out the prospect of direct benefits, risks should be measured against these anticipated benefits.
- if the minor will not benefit directly from the research, he or she should not be exposed to more than minimal risk.

Understanding ‘Minimal Risk’

- under the TCPS2, minimal risk means risks that are “no greater than those encountered by participants in those aspects of their everyday life that relate to the research.” It has also been defined in a more objective manner as “no more likely and not greater than the risk attached to routine medical or psychological examination of [the] persons.”
- minimal risk will vary according to the perception and life experience of the minor.
6.3 Specific Issues

This section provides a brief analysis of specific emerging issues identified in the relevant literature and related to the evaluation of risks and benefits in the context of paediatric research.

6.3.1 Evaluation of Risks in Genetic Research

The evaluation of risks in the field of genetic research may be influenced by the fact that the information collected is considered sensitive. Genetic research may involve not only physical and psychological risks but also psychosocial and economic risks both for minors and their families. Researchers, parents and the minor should understand the implications of genetic information for all those who might be affected by knowledge of genetic risks. An example of psychosocial risk would be that minors (as well as their parents) might perceive themselves differently after the return of their research results, which could affect life choices as they age. Furthermore, knowledge of one child’s genetic risks could impact parents’ decisions regarding future pregnancies.

As for economic risks, these could result from access by insurers or employers to the information collected during the research. These risks could have important consequences for the education, employment or insurance prospects of participants and their family members. Yet, when research reveals genetic conditions where prevention or treatment is possible during childhood or adolescence, such information offers health benefits for the minor.

Genetic research may involve risks for a specific community or for a particular ethnic group. For example, the publication of research findings revealing the susceptibility of a defined ethnic group to a genetic disorder may stigmatize this group or expose it to discrimination. Thus, researchers and research ethics committees need to consider the interests of these communities or groups when evaluating the risks and benefits of the proposed research.

An additional risk is that of informational entanglement. This issue is discussed in Section 2.3.5, “Informational Entanglement”. 
6.3.2 Evaluation of Risks and Benefits in Secondary Use of Data/Samples

If secondary use of data or tissue samples for research projects is not contemplated or specifically consented to at the time of the original informed consent, an informational gap for participants exists. If a broad or general consent was obtained—thus eliminating the need to re-consent—the participant may have consented based upon representations that future research would be of low risk. Yet, how can researchers “know and predict low risk of future research projects”? REBs may have the authority to approve secondary uses of data or samples without re-consent, but some risks to participants of inadvertent or inappropriate use of data or samples and the risks to privacy remain and should be considered by the REB.

See also Section 2.3.6, “Consent and Secondary Use: The Case of Bloodspots Collected in Newborn Screening”.

6.3.3 Evaluation of Risks and Benefits in Clinical Trials

The inclusion of minors in clinical trials is now a broadly accepted necessity in order to meet the health needs of this demographic group. However, this acceptance also acknowledges the varying levels of risk inherent in different phases of clinical trial research. Participation of minors in late phase trials (III or IV) is perhaps the most easily acceptable from a risk perspective. Generally, by the time a drug has reached these phases of testing, there will be significant data about its toxicity and efficacy in adults to help evaluate the potential risks in minors. Participants in these trials should include only ill children or adolescents, for whom a higher than minimal risk is appropriate if direct benefit can be anticipated. Exceptionally, the participation of healthy minors in the development of vaccines and other preventative treatments may be legitimate.

Addressing the challenge of risk is more difficult for phase I trials than for subsequent phases. These trials will generally, by their nature, have higher than minimal risks and no large likelihood of benefit for the minor. Since the goal of the earliest trials (phase I) is generally to establish the safety of the drug, there might be little knowledge of the potential harms, nor the likelihood of their occurring. Under the TCPS2, such risks would preclude the participation of healthy minors, although other guidance such as CIOMS suggests that there might be circumstances when their inclusion is possible. The TCPS2 implies that disease-affected minors can be included in clinical trials and be exposed to
greater than minimal risk if there is the prospect of direct benefit.\textsuperscript{36} In certain cases, however, the expectation of potential benefit in a Phase I trial may be so tenuous that the inclusion of even disease-affected children cannot be ethically justified. It remains true that certain phase I trials with minors can be considered to meet ethical norms. Phase I trials in paediatric oncology, in some circumstances, are unavoidable.\textsuperscript{37} In this domain, a record is made of the occurrence of therapeutic benefits.\textsuperscript{38} Left unanswered in the ethical norms, then, is how to balance the risks represented by certain Phase I trials against the potential benefits, when they are difficult to predict.

A potential benefit of participation in clinical trials, which may be weighed against the risks, is access to new drugs, though this will likely only be a factor in later-phase trials. According to the Declaration of Helsinki, researchers conducting clinical trials should address in the informed consent information regarding the continued access to treatment following the research phase. It is unclear whether such an ongoing obligation applies in fundamental research where there is no treatment, drugs or other interventions.

\textbf{6.3.4 Evaluation of Risks and Benefits in Research at the End of Life}

In research involving minors at the end of life, particular attention should be paid to the evaluation of risks and benefits since these minors are very vulnerable. The TCPS2 underscores that “their inclusion in research should not exacerbate their vulnerability.”\textsuperscript{39} In addition, to the extent that poor health status could compromise the voluntariness of consent, REBs should carefully consider the ethical obligations toward these potential research participants.\textsuperscript{40}

Some authors suggest taking into consideration the quality of life of the minor at the end of life.\textsuperscript{41} In its 2002 Opinion no. 73 on Phase I Studies in Cancerology, CCNE states that “[t]he patient’s quality of life must always enter into the equation, and should never in any circumstances be compromised by depriving him of any palliative care he is entitled to receive.”\textsuperscript{42} In addition, the European Parliament’s Directive 2001/20/EC specifies that trials involving minors should minimize pain, discomfort, fear and any other potential risks related to the disease and the developmental stage of the minor concerned.\textsuperscript{43} These two European documents provide additional guidance on the special considerations to look at when the research involves terminally ill minors. They also point to the need for REBs to adopt a highly nuanced approach to the appraisal of risks and benefits that includes a
range of paediatric circumstances, which may not be adequately addressed in the existing normative guidelines.

6.3.5 Evaluation of Risks and Benefits in Novel Medical Experimental Therapies

As discussed in Chapter I – Inclusion of Minors in Research, the participation of minors in novel medical experimental therapies is controversial.\textsuperscript{44} One reason for this reluctance is the evaluation of risks and benefits. To illustrate, the example of gene therapy trials will again be used. In the past, gene therapy trials successfully treated minors suffering from X-SCID\textsuperscript{45} but were also linked to the development of leukemia as well as to the death of an 18 year old boy.\textsuperscript{46} Gene therapy trials have since been considered as experiments involving serious risks. REBs are now reluctant to allow the inclusion of minors in such trials because of those risks.

This situation raises the following question: are the current criteria regarding the evaluation of risks and benefits appropriate in the context of novel medical experimental therapies aiming to study fatal degenerative childhood diseases? The example of a gene therapy trial for Duchenne Muscular Dystrophy (DMD) illustrates this issue. In such a trial, there would be no evidence that the minor will receive any direct benefits from participation precisely because of the experimental nature of the trial. Thus, it would be evaluated on the basis of indirect benefits, meaning that the minimal risk criterion would be applied. The risks associated with gene therapy trials cannot be qualified as minimal and do not constitute a minor increase above minimal risk (e.g. potential immune system reaction, risk of cancer, or death). These risks are serious and may outweigh the potential benefits of the experiment. On the other hand, DMD is a life-threatening disease for which no treatment exists. Minors suffering from this disease face imminent death and are generally terminally ill by the age of 17 years.\textsuperscript{47} DMD gene therapy trials may improve their quality of life by increasing their mobility or improve the quality of life of other minors suffering from the same fatal disease.\textsuperscript{48} However, the application of the minimal risk criterion would preclude the participation of these minors in gene therapy trials directed at their very condition.

Considering these elements, would a criterion of proportionality be more appropriate to evaluate the risks and benefits in such a context?\textsuperscript{49} This criterion was applied in a court decision in England, where two persons aged 16 and 18 years were suffering from a variant of the Creutzfeldt-Jacob disease. Considering the absence of treatment and the imminent death of those persons, the judge
considered the risks of not receiving the experimental treatment to be outweighed by the potential benefits and allowed it. The proportionate approach forms part of the TCPS2.

### 6.3.6 A Continually Evolving Perception of Allowable Risk

The previous discussion highlights the difficulty of determining appropriate levels of risk for minors in research. Although the definition of minimal risk has remained relatively static in recent years, however imperfect it may be, the amount of risk to which we are willing to expose minors is likely to change over time, as it has already. For example, the use of minors in research such as the Willowbrook study demonstrated a willingness to expose minors to a level of risk that is no longer acceptable. Changes over time and differences across guidelines illustrate further the evolving notions of acceptable risk levels for minors. In both the first and second editions of the *Tri-Council Policy Statement*, increases over ‘minimal risk’ are permitted only if the minor directly benefits from the research. Other guidelines, such as CIOMS, utilize a less strict standard, demonstrating that notions of *appropriate* levels of risk are not uniform even if the basic definitions of risk are.

A comparison of international and Canadian ethical norms on the evaluation of risks and benefits is presented in Table 6 in Appendix 1.
7.1 Privacy and Confidentiality: International and Canadian Contexts

Privacy and confidentiality are two well-established concepts in international and Canadian ethical norms. According to the TCPS2, “[p]rivacy refers to an individual’s right to be free from intrusion or interference by others.”¹ Thus, the right of privacy is respected when the participant “has an opportunity to exercise control over personal information by consenting to, or withholding consent for, the collection, use and/or disclosure of information.”² Confidentiality is a duty that refers to “the obligation of an individual or organization to safeguard entrusted information.”³ Privacy and confidentiality include professional secrecy. The Canadian Medical Association’s Code of Ethics acknowledges that physicians should ensure the confidentiality of the personal health information of their patients.⁴ The TCPS2 recognizes that researchers have a duty to identify and minimize privacy risks.⁵

Important issues of privacy and confidentiality are raised in the specific context of paediatric health research. Depending on their research, researchers may collect data on age, medical history, lifestyle, demographics, and genetic/family history. Because of its individualized nature, this information needs to be protected from unauthorized access or use, including from both third parties and potentially the family of the child or adolescent. A breach of confidentiality may have important consequences for participants and their families, such as implications for employment or an increase in insurance premiums. Thus, international and Canadian ethical norms set out mechanisms to ensure the privacy and confidentiality of personal data.

These norms also provide guidance on access to personal information collected by researchers. UNESCO, the Council of Europe and the European Commission state that participants are entitled to know any information collected about them and should be able to access it, unless the data is anonymized or the applicable law limits access (e.g. public health interest). CIOMS and ICH add that access to personal information may be allowed for monitoring, auditing, review or regulatory inspection conducted by REBs, drug regulatory authorities (e.g. Health Canada) or sponsors. WMA states that participants should have access to the audit record of their own information. The 2005 CIHR Best Practices for Protecting Privacy in Health Research specifies clearly that access to personal information should be strictly limited to avoid unauthorized disclosure.
Can the personal information collected on participants be disclosed to third parties? International and Canadian ethical norms agree that, in general, personal information should not be disclosed to third parties without the informed consent of the participant. UNESCO suggests that disclosure may be possible when the data is anonymized. UNESCO, OECD and TCPS2 specify that genetic information should not be disclosed to insurance companies, employers, educational institutions, or family without the consent of the participant or the parents. Furthermore, CIOMS and TCPS2 provide guidance on results of genetic testing by stating that they should be protected from access by third parties (although the TCPS2 permits disclosure to a participant’s physician when there is information relevant to the participant’s health) and should not be disclosed to relatives without the informed consent of the participant. However, the duty of confidentiality is not absolute. As the TCPS2 underscores: “in exceptional and compelling circumstances, researchers may be subject to obligations to report information to authorities to protect the health, life or safety of a participant or third party.”

CIOMS and TCPS2 provide examples of exceptional or compelling circumstances, such as in the case of child abuse or neglect, communicable diseases and sexually transmitted diseases. To that list of exceptions, UNESCO adds important public health reasons and public health purposes.

There might also be compelling reasons to disclose information to biological relatives of the minor (e.g. parents, siblings etc.), especially when it relates to inheritable disorders. Although the TCPS2 generally permits participants to determine whether family should receive the results, it recognizes that these decisions “are subject to overriding considerations that may warrant disclosure of information to relatives in exceptional circumstances” such as a serious, life-threatening disease that can be treated or prevented.

International and Canadian ethical norms suggest a range of safeguards that researchers should implement to ensure the protection of personal information collected during the course of their research. These measures are divided into three categories according to the 2005 CIHR Best Practices for Protecting Privacy in Health Research.

The first category is organizational safeguards. The ethical norms analyzed strongly suggest implementing organizational safeguards within the institution or organization, emphasizing the importance of protecting the privacy and confidentiality of research participants. Examples of such safeguards include requiring the signature of a pledge of confidentiality from persons accessing the information, preparing data-sharing agreements between the researcher/institution and persons
seeking access to the data, preparing transfer agreements, making a list of persons authorized to make data changes, identifying a person responsible for ensuring the protection of privacy, and limiting the number of persons who may access the information. Moreover, when the organizations are housing research projects, CIHR suggests that they “develop, monitor, and enforce privacy and security policies and procedures; appoint privacy officers and create data stewardship committees as needed; and implement internal and external privacy reviews and audits.”9

The second category concerns technological measures, which include: assigning a unique identifier to each participant; implementing Standard Operating Procedures (SOPs); implementing authentication measures (e.g. password, username); securing the coding of data (e.g. encryption, scrambling of data); implementing virus-checking programs; implementing disaster recovery safeguards; using camouflage sampling; installing protection for remote electronic access; backing up data; isolating on a separate server or network without external access the direct identifiers that must be retained; and implementing a detailed audit trail monitoring system (e.g. person, time, and nature of data access).

The third category concerns physical measures. International and Canadian ethical norms suggest adopting physical safeguards to protect the information collected. Examples of actions that can be taken to achieve that goal would be protecting data from hazards (e.g. flood, earthquake, and hurricane), minimizing the number of locations where data is kept, keeping the computers in a secure setting, designing the architectural space in a way that precludes public access to sensitive data, and conducting routine surveillance.

It is important to note that the safeguards and measures necessary to protect the privacy and confidentiality of research participants may change over time with the introduction of new technologies and research methodologies. The safeguards and measures listed above and in Section 7.2 should not be considered a comprehensive list.

Of all these safeguards for personal information, one of the most important is the coding of data and samples. In 2010, the TCPS2 adopted distinct categories permitting the evaluation of information or human biological materials serving to identify a person.
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This classification contains five categories concerning information:

1) Directly identifying information
   The information identifies a specific individual through direct identifiers (e.g., name, social insurance number, personal health number).

2) Indirectly identifying information
   The information can reasonably be expected to identify an individual through a combination of indirect identifiers (e.g., date of birth, place of residence or unique personal characteristic).

3) Coded information
   Direct identifiers are removed from the information and replaced with a code. Depending on access to the code, it may be possible to re-identify specific participants (e.g., the principal investigator retains a list that links the participants’ code names with their actual name so data can be re-linked if necessary).

4) Anonymized information
   The information is irrevocably stripped of direct identifiers, a code is not kept to allow future re-linkage, and risk of re-identification of individuals from remaining indirect identifiers is low or very low.

5) Anonymous information
   The information never had identifiers associated with it (e.g., anonymous surveys) and risk of identification of individuals is low or very low.

The classification also includes four categories on biological material:

1) Identified human biological materials
   The materials are labelled with a direct identifier (e.g. name, personal health number). Materials and any associated information are directly traceable back to a specific individual.
2) Coded human biological materials
Direct identifiers are removed from the materials and replaced with a code. Depending on access to
the code, it may be possible to re-identify specific individuals (e.g. a principal investigator retains a
key that links the coded material with a specific individual if re-linkage is necessary).

3) Anonymized human biological materials
The materials are irrevocably stripped of direct identifiers, a code is not kept to allow future re-
linkage, and risk of re-identification of individuals from remaining indirect identifiers is low or very
low.

4) Anonymous human biological materials
The materials never had identifiers attached to them and risk of identification of individuals is low or
very low.
7.2 General Statement on Privacy and Confidentiality

In order to ensure that privacy and confidentiality are maintained, researchers should adopt appropriate and reasonable safeguards, subject to applicable law.

Confidentiality

- the principal investigator and staff authorized to access a minor's medical, familial, and research files should be identified;
- the principal investigator and all members of his/her team are subject to confidentiality both inside and outside research laboratories and in the management and communication of data;
- confidentiality also includes persons involved in research who do not have professional status, such as technicians, graduate students and research fellows.

Access to the Information Collected

- subject to applicable law, access to the information collected in research is dependent on the consent of the competent adolescent, or that of the parents if the minor is not competent to consent. If feasible, the assent of the incompetent minor should be obtained;
- the principal researcher is responsible for controlling access to the information collected;
- control of this access is similar to the control exercised over delegated medical acts;
- those authorized to access such information are under the supervision of the principal researcher;
- participants should have access to their information, if feasible (e.g. data is not anonymized);
- access may be allowed for monitoring, auditing, review or regulatory inspections;
- researchers should also consider the impact that disclosure of sensitive information to the parents might have on the minor (e.g. pregnancy, reports of abuse, substance use) if the parents request access.

Limits to Confidentiality

The duty of confidentiality is not absolute. Personal information may be disclosed without the consent of the participant or parents in some exceptional circumstances, such as child abuse or neglect or communicable and sexually transmitted disease (when notification is required by law).

Moreover, absolute confidentiality may be difficult to ensure in some very special circumstances (e.g. minors suffering from a very rare condition or disease). In this case, even if researchers comply with all the safeguard measures, the disclosure of confidential information of the minor may still occur, and the minor may be identifiable just by virtue of the rarity of the condition. Therefore, researchers should inform the participant and/or parents about this possibility during the informed consent process.
**Disclosure to Third Parties**

- Researchers and members of the research team should never disclose personal information about a participant to a third party unless the competent adolescent or the incompetent minor’s parents consented to such disclosure in writing. If feasible, the assent of the incompetent minor should be obtained;
- In exceptional circumstances, and subject to the applicable law, researchers may have an obligation to disclose genetic information to the minor’s family, despite opposition of the minor (whether competent to consent or not), or the minor’s parents. Three conditions should be met before considering the possibility of disclosure in such circumstances:
  1) non-disclosure could lead to serious and foreseeable harm for members of the biological family;
  2) members of the biological family are identifiable; and
  3) the risk of harm could be avoided by prevention or treatment. In this evaluation, the risk of harm resulting from disclosure should not be greater than the risk of harm to family members from non-disclosure;
- The competent adolescent or the parents if the minor is not competent to consent, should be informed of the consequences that could result from the disclosure of genetic information. The incompetent adolescent should also be informed, if feasible.
- If non-consensual disclosure is necessary, collaboration with the treating physician is recommended, where applicable, to encourage discussion with the minor and his or her parents about the family follow-up and the consequences of refusing to communicate the information in question;
- Other than in the exceptions by law, no genetic information can be transmitted to insurers, employers, educational institutions, or other public institutions, without the consent of the competent adolescent or that of the parents if the minor is not competent to consent. If feasible, the assent of the incompetent adolescent should be obtained;
- In cases where non-paternity is discovered during research, unless it can be shown to be in the immediate and best interest of the health of the child, it should not be disclosed;
- Unless participants consent to the publication of identifiable data and there is a reason to do so, researchers should only publish non-identifying data.
7.3 Specific Issues

This section provides a brief analysis of specific emerging issues identified in the relevant literature and related to privacy and confidentiality.

7.3.1 Confidentiality of Genetic Information

An important issue raised by the confidentiality of genetic information is its risk of disclosure to insurers or employers.\textsuperscript{10} The fear is that insurers and (potential) employers may discriminate against individuals based on their genetic information regardless of phenotypic expression.\textsuperscript{11} Minors are not excluded from this risk since their research results may potentially follow them for their entire life,\textsuperscript{12} as the DNA of minors will not change as they age.\textsuperscript{13} Insurers and employers eventually could use genetic information to decide whether or not to cover or hire research participants, their parents or siblings. Moreover, educational institutions may also discriminate based on a minor’s genetic information.\textsuperscript{14} This issue remains the topic of international debate, and UNESCO acknowledges the importance of protecting individuals from discrimination based on their genetic information.\textsuperscript{15}

7.3.2 Confidentiality in Longitudinal and Biobank Studies

In longitudinal and biobank studies, the information collected is usually stored and used for many years (e.g. 25 or 50 years). The duration of these studies creates additional risk of unauthorized access—a breach of confidentiality may impact insurance coverage, employability, and even family relationships. As well, the duration means that the volume of the information grows, providing more and more detailed information about the participant as the study progresses. Thus, longitudinal studies raise important issues of privacy and confidentiality, and increased security and governance are the norm.\textsuperscript{16} To limit the risk of unauthorized access, researchers should put in place appropriate security measures and keep pace with the new technologies that may allow the re-identification of the participants.\textsuperscript{17} They may also need to update or replace their security measures over time to ensure the highest degree of privacy and confidentiality.

7.3.3 Confidentiality and Juvenile Reproductive Issues

Research projects may require a pregnancy test prior to recruitment. If the test is positive, it may lead to the exclusion of the adolescent. In such a situation, who should be told about the pregnancy?
As seen in Chapter II – Consent to Research, a competent adolescent can provide a fully informed consent. When the adolescent is deemed competent to consent, the discovery of the pregnancy should be revealed to her in confidence. She will then decide if she wants to share this information with her parents and/or the baby’s father. In some research projects, parents and their children may be participating at the same time. Thus, the parents would likely be aware of their child’s participation, subject to the adolescent’s consent, if competent, as well as of the requirements of participation (e.g. pregnancy testing). In such a situation, researchers should be careful to not disclose confidential information (e.g. pregnancy) to the parents. Otherwise, it may constitute a breach of confidentiality.

To avoid this situation, researchers should plan a private interview with the child concerned to allow him/her to refuse to participate in the research if she is or may be pregnant. When parents are participating, their consent form should specify that in the case of their child’s exclusion from the research the reason justifying this decision will not be disclosed. Finally, researchers should develop a plan to manage the discovery of pregnancy so as to ensure a relevant clinical follow-up.

When the adolescent is deemed incompetent or, pursuant to legislation, has not reached the age of majority required to consent to participation, the question of who should be told about the pregnancy of the child is the subject of debate. In certain provinces, incompetent adolescents may be considered competent to make decisions alone about certain medical care. In such a situation, where permissible by law, the pregnancy can be discussed confidentially with the adolescent. In other cases, REBs may choose to disclose the information directly to the parents since the adolescent is incompetent to consent, while others will inform the adolescent first and then discuss with the parents. There is currently no clear guidance on this issue.

Any discussions between researchers and participants regarding the use of contraception should be kept confidential. This issue might arise, for example, if birth control medications are an exclusion criterion for the study.

7.3.4 Coding Terminology

In the last decade, terms used to define the confidentiality mechanisms have multiplied and overlapped, thereby creating confusion within the research community. For example, the terms “anonymized” and “de-linked” are both used to refer to double-coded data as well as to irretrievably
unlinked data. The term “coded” is sometimes replaced by the terms “identifiable”, “linked”, “pseudomized” or “proportional anonymity”, while the term “anonymized” is replaced by “absolute anonymity”, “de-identified”, “unlinked” or “irretrievably unlinked.” These examples clearly demonstrate that the terminology used became “so ‘babelesque’ as to ultimately impede the sharing of research data.”

With the emergence of paediatric biobanks, the sharing of research data and samples at international and national levels is becoming an important concern. If the terminology used is different and does not mean the same thing, such sharing may be jeopardized. For the sake of providing a clear terminology of the confidentiality mechanisms, ICH adopted its 2007 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. The ICH proposes four categories of coding: 1) identified; 2) coded; 3) anonymized; and 4) anonymous. For its part, the TCPS2 divides information relating to human biological materials into five categories: 1) directly identifiable; 2) indirectly identifiable; 3) coded; 4) anonymized; and 5) anonymous. Biological materials are divided into four categories: 1) identified; 2) coded; 3) anonymized; and 4) anonymous human biological materials. Researchers working internationally should be aware of these differences in terminology and ensure that they match their practices to the jurisdiction’s requirements.

7.3.5 Privacy and Confidentiality in Qualitative Research

In qualitative research, the boundaries of confidentiality are a contentious issue because of the open-ended nature of qualitative research methods and because qualitative studies collect a large amount of detailed personal information. As one probes to understand sensitive topics such as sexual behaviour, bullying, drug abuse, or neglect for instance, it is not unusual to obtain spontaneous, unexpected and intimate disclosures. This raises questions about whether the researcher has the duty to breach confidentiality by reporting to parents or authorities.

Moreover, although in the majority of research parental consent must be obtained, parents sometimes request information about their child obtained during the course of research. Since minors in some circumstances have a right to control the information that will be revealed during the research, it is important to clarify to the minor participant and to the parents how the researcher plans to manage the disclosure of sensitive information. There may be a need for researchers to explain “their intentions
with respect to sharing any information with a parent, and the process they will follow with the child and the parent to ensure both the child and the parent understand the process in advance.\textsuperscript{26}

A comparison of international and Canadian ethical norms on privacy and confidentiality is presented in Table 7 in Appendix 1.
8.1 Return of Research Results: International and Canadian Contexts

The offer to return research results to participants is an ethical duty, founded on the principle of respect for the person. Nevertheless, how, to whom and when the results should be communicated remain subject to debate. International and Canadian ethical norms do not provide much guidance on these questions.

Most of the norms agree that general research results can be disclosed to participants, whether results are positive or negative. Researchers should provide this information by using language that is clear and understandable to the parents and, if appropriate, to the minors. The communication of such results may be provided by a personal letter, a news bulletin, a newspaper article or a website. The mode of communication should consider the potential harms to the participant, with more personal methods used for more sensitive results.

The majority of the norms analyzed are not specific to paediatric research and are silent on the disclosure of individual results, treating research as the search for generalizable results. Moreover, among those documents that do provide some guidance, there is little consensus. OECD specifies that individual results should only be disclosed when permitted by law or by other appropriate authorities without providing more guidance. CIOMS, UNESCO and the Council of Europe explicitly state that participants should be informed of any findings relevant to their health or quality of life. In the context of genetic research, the World Health Organization (WHO) requires the following before disclosing individual results to participants: “a) the data have been instrumental in identifying a clear clinical benefit to identifiable individuals; b) the disclosure of the data to the relevant individuals will avert or minimize significant harm to those individuals; c) there is no indication that the individuals in question would prefer not to know.” This is important, as research results by their very nature are neither individual nor significant for health care because they are not validated in the clinic. However, clinical research may provide extremely significant results for the health of the participants (e.g. identification of the BRCA1 gene mutation conferring high risk for breast or ovarian cancer).

Another category of information that may be communicated to participants is incidental findings, which can be defined as “unexpected findings discovered in the course of research but ‘beyond the aims of the study’.” The TCPS2 adds that these findings may have “significant welfare implications for the individual participant, whether health-related, psychological or social.” Examples of such
findings would be the discovery of BRCA1 carrier status, a sexually transmitted disease, or non-paternity. Of the documents analysed, only the TCPS2 and UNESCO provide guidance on the disclosure of incidental findings. The TCPS2 considers the communication of material incidental findings to be part of the disclosure obligations to participants. Thus, it suggests that researchers develop a plan for handling such findings and notes also that incidental findings may trigger legal reporting obligations.

Most of the norms analyzed recognize the right of the participants to decide whether or not to be informed about the results of the research, whether individual or general. UNESCO, the Human Genome Organisation (HUGO) and WHO provide that this right to not know, when information is available, should be extended to the relatives of the participant who may be affected by the results of the research. UNESCO is the only one to specify that the respect of this right to decide is impossible when the data and samples have been anonymized or when the research did not generate individual results concerning the participants.

The right not to know, however, is not absolute and may be overridden in specific situations. UNESCO limits this right only to the information that is relevant for the health of the family members. HUGO adds that relatives should be informed when the risk of transmitting a serious disorder is high and a treatment exists (see also Chapter VII – Privacy and Confidentiality). Thus, it may be the case in genetic research identifying an inherited condition, such as Familial Adenomatous Polyposis (FAP), that relatives should be informed. In its 1981 Declaration on the Rights of the Patient, the World Medical Association states that the right not to know may be overridden if “required for the protection of another person’s life.” In the field of genetic research, WHO’s 1997 Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services provides that this right may be overridden in the context of clinical results when it is a question of the “testing of newborns or children for treatable conditions.” However, UNESCO underlines that the participant may insist on not receiving the information since the Universal Declaration on the Human Genome and Human Rights does not provide any derogation of the right to not know.

While recognizing the obligation to disclose the results of the research, international and Canadian ethical norms do not mention who should communicate such results. In the case of non-paternity, UNESCO states that it should be disclosed by a medical geneticist. OECD only specifies that the results should be returned by a trained professional. The TCPS2 indicates that the researcher can
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return the results,\textsuperscript{16} but it also adds that s/he may be assisted by a genetic counsellor in the context of genetic research.\textsuperscript{17} Given the potential medical and psychological consequences, it may not always be appropriate for the principal researcher to disclose genetic results; these may be better provided by a health care provider familiar with the context of the participant. The majority of the norms studied recommend that counselling be offered to the participants when returning research results.

In the context of paediatric research, if the individual research results or incidental findings should be communicated (according to the criteria outlined below), they should be communicated to the competent adolescent or to the parents if the minor is incompetent to consent.

Research results and incidental findings should be communicated 1) if scientifically valid, 2) if they have significant health implications for the child, and 3) if a means of prevention or treatment is available during childhood or adolescence. When these criteria are met, parents should not refuse to receive results because this would be analogous to refusing care. It is interesting to note that none of the norms analyzed impose an ethical duty to the parents to disclose research results to their child, even after the child attains competency. However, in the case of genetic research, UNESCO specifies that “parents remain the guardians, on behalf of their child, of information about them. It is their duty, if necessary in agreement with genetic counsellors and pediatricians, to decide to what extent, when and in what form the child be informed about his/her genetic data.”\textsuperscript{18} There is no guidance on how and when children or adolescents should be made aware of results. Therefore, it is left to the parents to determine when it is appropriate to inform minors about their results according to their age and level of maturity. Thus, each case should be evaluated on an individual basis. In this evaluation, researchers should take into consideration the right of the minor not to know the results when they are of an uncertain nature.\textsuperscript{19}

The return of research results should be discussed during the consent process.\textsuperscript{20} During this process, competent adolescents or the parents if the minors are incompetent to consent should be informed about the disclosure of the results of the research (general, individual and/or incidental), their right not to know their results (except when it is in the best interests of the child for the parents to know), and the situations where it is impossible to return the results (e.g. anonymization) or where their refusal may be overridden. The timing of return of results (e.g. during the research, at the completion of the research) and the process (e.g. website, letter, personal visit, etc.) should also be discussed.
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Minors incompetent to consent should also be informed about the return of results during the assent process, to the extent of their capacities.


8.2 General Statement on the Return of Research Results

Researchers should broadly disseminate general research results. Generally, researchers should respect the wishes of the competent adolescent, or those of the parents if the minor is not competent to consent, regarding the return of research results. However, individual research results and incidental findings should be communicated 1) if they are scientifically valid, 2) if they have significant implications for the health of the child or adolescent, and 3) if a treatment or method of prevention is available during childhood or adolescence.

The competent adolescent or the parents of a minor not competent to consent should be informed whether data or samples obtained from the child will be anonymized and, if so, that it will be impossible to return individual research results or incidental findings.

The duty to return the results of research is justified by respect for persons and their well-being. The communication of the results also furthers the transparency of research by enhancing the dissemination of the research findings.

Communication of General Results

- where appropriate and possible, the principal investigator should publish in a language accessible to the minor and/or parents the information relating to the general results of the research, whether they be positive or negative, with the shortest delay;
- this information should be as comprehensive as possible and should conform to current scientific principles;
- the team should ensure a high level of precision in the information, clinical knowledge, and, if appropriate, genetic advice;
- researchers should also offer the adolescent and/or parents the possibility to obtain a copy of published papers related to the research in which they participated; and
- researchers should provide guidance and clear explanations about the interpretation of the results to the adolescent and/or parents to limit the potential distress that the results may cause them.
Communication of Individual Research Results and Incidental Findings

- during the informed consent process, researchers should discuss with the competent adolescent, or the parents of a minor not competent to consent, the potential for research results and incidental findings being disclosed to them in the course of the research;
- the method of disclosure of the individual research results or incidental findings should be disclosed during the consent process;
- if appropriate and possible, the potential for returning individual research results and incidental findings should be discussed with an incompetent adolescent during the assent process as well as described in the assent form;
- individual research results and incidental findings should be communicated 1) if they are scientifically valid, 2) if they have significant implications for the health of the child or adolescent, and 3) if a treatment or method of prevention is available during childhood or adolescence. When these conditions are met, parents should not refuse to receive the results;
- individual research results and incidental findings that do not meet these criteria may be communicated when 1) the advantages associated with their communication exceed the disadvantages 2) with REB approval, and 3) the competent adolescent or the parents of an incompetent minor accept to receive them;
- when the research involves school-age minors capable of assent, the information should also be delivered to them with the agreement of their parents, and in a manner appropriate to their development, level of understanding and degree of maturity;
- when returning individual research results or incidental findings, counselling should be offered to the parents and, if appropriate, to the minor;
- researchers should also discuss the following considerations: the choices available, the limitations of available clinical services, the accessibility of counselling services, and the familial implications of the information;
- in some circumstances, it may be appropriate to disclose sensitive information to the incompetent adolescent first, or even uniquely to the incompetent adolescent where permitted by law (e.g., pregnancy). This may also be the case when there is a risk that the disclosure of the incidental findings may expose the child/adolescent to abuses or harms from the parents;
- there can be no return of individual results or incidental findings when the data and/or samples are anonymized.

Right Not To Know

- parents should not be permitted to refuse the return of results or incidental findings on behalf of the child 1) if they are scientifically valid, 2) if they have significant implications for the health of the child or adolescent, and 3) if a treatment or method of prevention is available during childhood or adolescence.
- researchers should take into the account the right of the competent adolescent or the right of the parents of the incompetent minor not to know the results that do not respond to the criteria enumerated above, when they have explicitly expressed their desire not to receive the individual results.
- REB approval should be obtained to override this right;
8.3 Specific Issues

This section provides a brief analysis of specific emerging issues identified in the relevant literature and related to the return of research results in the context of paediatric research.

8.3.1 Return of Research Results in Genetic Research

The TCPS2 requires researchers doing genetic research to develop a plan to manage information, to submit it to their REB, and to advise prospective participants and their parents of the plan. This plan is required because of the types of the information that can emerge from genetic research, and the implications of this information for participants. During the consent process, researchers using human biological materials should inform their participants or their parents of the means whereby they plan to treat results and conclusion, including pertinent clinical information and incidental findings.

When researchers communicate individual results issuing from genetic research, they should give participants or their parents the choice to be aware of them and the possibility to express preferences about whether information will be shared with biological family members, or others linked to the participant by a family, community, or group relationship.

In effect, genetic results reveal important information not only about the participants themselves, but also about their families. The disclosure of genetic results to participants and their family members is a heavily debated issue. Because of the nature of genetic information, should the minor’s family have access to the child’s or adolescent’s results? The answer to this question is unclear in the Canadian context. The difficulty lies in the fact that researchers have a duty to maintain confidentiality as well as a duty to prevent harm to other individuals.

Different approaches are suggested in the literature and law to resolve this question: 1) strict confidentiality, where researchers will not disclose any results without the consent of the person concerned; 2) duty to warn, according to which the participant is the family and, therefore, researchers have a duty to warn the relatives of the risk revealed by the results; 3) informed consent, in which researchers will specify the particular situations where they may disclose the genetic results to the relatives without the consent of the person concerned; and 4) an intermediate position, which suggests that the confidentiality should be respected but non-consensual disclosure may be allowed in exceptional circumstances (seriousness of the harm, its preventability and the necessity of the disclosure). Thus, researchers should inform participants about the importance that the disclosure of
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genetic results might have for their relatives and encourage participants to discuss it with them. However, if there is a “serious, imminent genetic condition that is preventable or treatable, the benefits of the disclosure may be so great as to justify it on ethical grounds.”

8.3.2 Disclosure of Incidental Findings in Paediatric Research

The literature provides some guidance on the disclosure of incidental findings in the specific context of paediatric research. Wilfond and Carpenter separate incidental findings into two categories. The first category includes incidental findings without clear proximate clinical importance, such as the finding that Apolipoprotein allele 4 (ApoE4) may increase the risk later in life for Alzheimer disease. In such a situation, researchers should discuss with the REB whether it is appropriate to disclose the information to the minor and/or the parents, as there is no way to treat or prevent the disease during childhood or adolescence. The second category includes incidental findings with clear proximate clinical importance, such as pregnancy or psychiatric issues. The authors suggest disclosing the information to both the minor concerned and the parents. They also propose that sensitive information (e.g., pregnancy) should be disclosed first to the adolescent, and serious information (e.g., cancer) first to the parents. Researchers should also take into consideration the will of the parents or the adolescent to limit the information disclosed to one of them. However, when scientifically validated incidental findings reveal a condition with significant health implications, that is preventable or treatable in childhood, the information should be communicated to the parents.

Before disclosing any results to the minor and/or parents, researchers should develop a plan, as part of the research protocol, for handling clear and proximate information that may be clinically important to the minor that takes into consideration the minor’s age, maturity and familial context. Following this step, researchers should communicate their plan to the competent adolescent or the parents of the minor not competent to consent, preferably at the time of consent.

8.3.3 Disclosure of Research Results in Longitudinal Studies

As discussed in Chapter III – Assent of the Minor, minors participating in longitudinal studies may gain the necessary capacity to provide assent or consent during the research project. Therefore, researchers should take this fact into consideration when offering to return research results. The appropriateness of the disclosure of research results depends on the capacity of the adolescent to
consent, on the law, and on his or her level of maturity. When deciding to whom research results should be disclosed, researchers should consider the growing maturity of the minor concerned. Thus, during the course of the research the information may be offered to different people. When the adolescent attains the capacity to provide informed consent, the research results should be disclosed directly.

### 8.3.4 Length of the Duty to Return Research Results

Many longitudinal studies are using biological materials such as blood and DNA, to conduct research on human genetics. These samples can be stored and used for a long period of time, such as 25 or 50 years. Thus, it raises the question of the duration of the researchers’ duty to return research results to participants, especially as minor participants may not reach the age of majority until long after enrolled in a study.

There is little guidance on this question. The TCPS2 specifies only that the disclosure of incidental findings is included in the obligation of ongoing disclosure of information to participants. It does not analyze the duration of the obligation to return results. The Pharmacogenetics Working Group states that “some pragmatic limitations on the research endeavour should be put in place so that responsibilities of investigators [...] are not left open ended.” The American National, Heart, Lung, and Blood Institute Working Group on Reporting Genetic Results in Research Studies takes a clear position: the “responsibilities of the investigators cannot extend beyond the period of funding.” The general lack of specific guidance on the duration of the responsibility to return results can be problematic from both practical and funding perspectives.

### 8.3.5 Return of Research Results in Qualitative Research

Researchers should give careful consideration to the return of qualitative research results. It is considered good practice to develop child-friendly tools for the communication of general results where appropriate. Typically, in qualitative research, researchers use face-to-face meetings or written reports. In the process of developing follow-up information, it will be important to use creative and child-friendly tools like plays, comics or the internet. Developing methods in partnership with children and adolescents will ensure that the results are better understood by them.
A comparison of international and Canadian ethical norms on the return of research results is presented in Table 8 in Appendix 1.
CHAPTER IX
PAYMENT in Research
9.1 Payment in Research: International and Canadian Contexts

There are four types of payments to participants for their participation in research.¹ The first is reimbursement. It compensates the parents and the minor for expenses incurred by their participation, such as transportation, meals and lodging. The second type of payment is compensation, which compensates the parents and the minor for their time and inconvenience. The third is appreciation payment. Researchers may decide to offer a bonus to the minor once the research is completed to thank him or her. The fourth type of payment is incentive payment, which encourages the minor to participate in research (e.g. enrolment incentive).

<table>
<thead>
<tr>
<th>Types of Payment</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reimbursement</td>
<td>Transportation, parking, meals, lodging, babysitting</td>
</tr>
<tr>
<td>Compensation</td>
<td>Time, inconvenience</td>
</tr>
<tr>
<td>Appreciation</td>
<td>Toys, gift certificates, movie coupons, books, computer games, hockey tickets</td>
</tr>
<tr>
<td>Incentive</td>
<td>Draw, lottery, community service credit</td>
</tr>
</tbody>
</table>

Although reimbursement, compensation and appreciation payments are generally accepted because they don’t generally rise to the level of undue inducement, incentive payments should be used rarely due to the possibility that they might induce participation without careful consideration of risks. It should be noted that researchers and participants may view compensation or reimbursement (e.g. covering a flight and hotel stay) payments as incentives as well, depending on the circumstances of the study and amount/nature of the payment. Offering community service credit² in return for research participation could be considered an incentive as well, especially if the adolescent is capable of providing his or her own consent. In addition, the possibility of research participation, especially for terminally ill minors, might be viewed as an incentive, which could stem from therapeutic misconception, discussed in greater detail in Chapter II – Consent to Research. However, none of the guidelines examined took this position. Indeed, even if the offer of research was considered an incentive it is unlikely that it would reach the level of undue inducement. To best address this
concern, it is crucial that researchers clearly explain the goals of the research during the informed consent process.

Any payments should be discussed during the informed consent process and be stipulated in the consent form. Researchers should explain to the consenting adolescent, or the parents of the incompetent minor to consent, the plan of payment, which includes the methods, amounts, and schedule of payments.

The majority of international and Canadian ethical norms analyzed permit the reimbursement of expenses related to participation in the research (e.g. travel costs, subsistence costs). In addition, parents and minors may be compensated for lost earnings, inconvenience and time. As for lost earnings, the norms provide little guidance on how parental wages should be compensated. CIOMS and the European Commission simply underscore that parents cannot be paid for their child’s participation in research. The TCPS2 indicates that unpaid leave constitutes losses linked to participation and evokes the possibility of reimbursement.

If the minor withdraws from the research, CIOMS as well as ICH state that the parents and the minor may still be compensated. To that end, CIOMS illustrates three situations: 1) if the competent adolescent or the parents of the incompetent minor withdraw for health reasons (e.g. side effect of the drug tested), they should be paid as if they had fully participated; 2) if they withdraw for other reasons, they should be paid pro rata; and 3) if they are excluded from the research for noncompliance, the researcher may withhold part or all of the proposed payment. ICH only states that “payments […] should be prorated and not wholly contingent to the completion of the trial by the subject.” Regarding the third situation, incompetent minors to consent should not be denied payment to which they are entitled due to the non-compliance of their parents.

CIOMS, ICH and TCPS2 state that an REB must approve the payments proposed to ensure that there is no undue inducement. CIOMS and TCPS2 provide guidance to decide whether or not the payment constitutes an inappropriate inducement. For example, an undue inducement would be one that would “encourage reckless disregard of risks” or persuade the participants to “take undue risks […] against their better judgment.”
9.2 General Statement on Payments in Research

It may be appropriate to compensate minors and parents participating in research. Parents should not receive any payment other than the reimbursement of their expenses related to the participation of their child, and compensation for their time. Payment should be discussed during the consent process. An REB should review the payment plan proposed.

Types of Payments

- **reimbursement** payments to compensate parents and/or minors for expenses directly or indirectly related to participation (e.g. transportation, meals, accommodation, babysitters, unpaid leave, etc.);
- **compensation** payments to compensate parents and/or minors for their time and inconvenience caused to them and their family by participation;
- **appreciation** payments, which are bonuses given to minors after their participation to thank them;
- **incentive** payments to encourage the participation of minors in research (e.g. lottery, draw, community service credit).

Payment Process

- the type of payment offered should be discussed during the informed consent process;
- the payment process should be clearly stipulated in the consent form;
- if incompetent minors to consent are able to assent, it can be discussed in the assent process as well as in the assent form, when this does not risk exercising undue influence;
- when the payment proposed to the incompetent minor to consent is an appreciation payment, it may be appropriate to give it as a surprise at the end of the research to thank the child for participation;
- parents should never be paid for the participation of their child in research, other than reimbursement of their expenses and compensation for their time.

Withdrawal from the Research

- the minor should still be entitled to receive the appreciation payment for his/her participation;
- if withdrawing for health reasons, the parents and the minor should be paid as if full participation had taken place;
- the parents and the minor should be paid in proportion to their participation if they withdraw for other reasons;
- researchers may withhold part or all of the payment if participants are excluded from the research for noncompliance. However, the minor should not be denied payment to which they are entitled, due to the non-compliance of the parents.
### Elements To Consider When Determining Payment

- what is being paid for (e.g. time, lost earnings, inconvenience, discomfort, expenses related to the research, etc.)?
- who will receive the payment: the minor, the parents or both?
- will participants be paid equally?
- how and when will information on payment be disclosed? Will it be disclosed in the consent and, if appropriate, assent process? Or at the end of the research as a surprise? Or after the parents and/or the minor have agreed to participate?
- what form will it take (e.g. money, card, gift, toys)?
- what is the payment schedule and the process (e.g. for the reimbursement of expenses)?

### Elements To Consider When Reviewing Payment

The payment proposed by researchers should be reviewed and approved by a competent REB to ensure that it does not constitute an undue inducement. When reviewing payments, the REB should consider the:

- effect of the payments on the scientific or social value of the research proposed;
- persons to whom the payment is offered to avoid targeting, or under or over recruiting, specific populations;
- possibility that the payment, taken cumulatively (e.g. a compensation payment), could rise to the level of an incentive or may minimize the potential risks;
- possibility that the payment may alter the risk perception of the minors or parents;
- impact of the payment offered on the ability to give a free and informed consent or, if appropriate, assent.
9.3 Specific Issues

This section provides a brief analysis of specific emerging issues identified in the relevant literature and related to incentives in research involving minors.

9.3.1 Disclosure of Appreciation Payment to the Minor

There is currently debate as to when appreciation payments should be disclosed to the minor. The American Academy of Pediatrics recommends disclosing the appreciation payment at the completion of the research to ensure that the payment is not the main reason justifying the participation of the minor. Some authors disagree with this guideline and suggest that all types of payment be disclosed during the consent and assent processes for the sake of transparency. In Canada, there is currently no norm governing this issue.

Since all the relevant information should be disclosed to the participants and/or parents, all types of payment should be mentioned during the consent process. However, it should not prevent researchers from offering non-monetary payment to minors at the end of the research as a surprise to thank them. For example, researchers may give a certificate of excellence to the child or adolescent, or an age-appropriate gift, such as a book, video, or movie pass. REBs should evaluate on a case-by-case basis if such a non-disclosure may prevent the competent adolescent or the parents of the incompetent minor to consent from providing an informed consent.

9.3.2 Legitimacy of Incentive Payment in Paediatric Research

The question as to whether researchers may offer incentive payments to encourage the enrollment of minors in research is well-debated. The European Union and the European Commission expressly prohibit all incentives or financial inducements for paediatric research. This guideline is justified by the concern that such a payment may “distort parents’ or children’s decision making.” According to the TCPS2, the age and aptitude to consent of participants are aspects to consider in the evaluation of the possibility that a payment inciting participation amounts to undue influence. Some authors underscore that compensation and appreciation payments may not be sufficient to encourage families to participate in paediatric research. Therefore, they suggest that an incentive payment may be offered to the minor and/or the parents subject to an REB approval. The REB should ensure that the incentive payment is justified and ethically acceptable and not contrary to the best interests of the
child. This should be done on a project-by-project basis considering the specificities of each research project.

To that end, REBs should prepare a policy regarding the diverse payments offered to the participants and/or parents. For example, the University of British Columbia’s Clinical Research Ethics Board (CREB) elaborated a Guidance Notes for New Applications for Clinical Ethical Review, in which guidelines on payments are provided. CREB considers that incentives, such as draws, are acceptable in research if “the draw is not contingent on participation in the research and any subjects who withdraw must also have the opportunity to have their names included in such draws.”

### 9.3.3 Compensating Parental Lost Earnings

The international and Canadian norms under study provide little guidance on how parental lost earnings should be compensated. The TCPS2 considers unpaid leave an indirect expense corresponding to losses from participation that could be reimbursed. It does not mention whether there is a limit to such reimbursement, or how to address differences in revenue loss between parents. The same research study may involve parents with highly paid professions as well as those who are unemployed. It may be argued that the first category does not need to be compensated since these parents are earning a good salary, while the research may constitute a significant burden for the second category. What should be kept in mind is that reimbursement “is intended to ensure that participants are not put at a direct or indirect financial disadvantage for the time and inconvenience of participation in research.” Therefore, researchers need to establish how compensation will be determined. Some authors propose to compensate the parents based on “the minimum wage of unskilled, essential jobs.” More research should be conducted on this issue.

A comparison of international and Canadian ethical norms on payments in research is presented in Table 9 in Appendix 1.
CHAPTER X

COMPOSITION of Research Ethics Boards
10.1 Composition of Research Ethics Boards: International and Canadian Contexts

International and Canadian ethical norms all agree that REBs should be multidisciplinary, which means that they should include individuals of differing expertise, including medical and research professionals as well as non-medical members, such as lawyers, ethicists and community members. They should also be independent. According to the TCPS2, “[t]he membership of the REB is designed to ensure competent independent research ethics review.” CIOMS, TCPS2 and the Canadian Food and Drug Regulations specify that there should be a minimum of five members on an REB. Most of the norms analyzed also require that members come from medical, scientific and non-scientific fields. CIOMS provides examples of professionals to include in the membership of an REB, such as physicians, scientists, nurses, lawyers, clergy and representatives of the culture and moral values of the community concerned. The European Commission also provides examples, such as physicians with paediatric qualification, paediatric ethicists, paediatric pharmacologists and qualified paediatric nurses or psychologists. The TCPS2 is more general in its requirements by stating that “(a) at least two members have expertise in relevant research disciplines, fields and methodologies covered by the REB; (b) at least one member is knowledgeable in ethics; (c) at least one member is knowledgeable in the relevant law [...]; and (d) at least one community member who has no affiliation with the institution.”

ICH and the European Commission specify that REBs reviewing research protocols involving minors should include paediatric expertise. If members do not have such expertise, CIOMS and TCPS2 suggest nominating ad hoc members or special consultants with expertise in paediatrics (e.g. experience in paediatric care or in paediatric clinical trials). The inclusion of members with expertise in paediatric research or medicine is important, as these individuals would be better placed to detect issues in the protocol or consent form that could affect the well-being of children and adolescents differently than adults.

Finally, CIOMS recommends the inclusion of a minor representative (e.g. parent) to sit as a member of the REB to ensure that their views are expressed.
10.2 General Statement on the Composition of Research Ethics Boards

Research Ethics Boards reviewing research protocols involving children and adolescents should be multidisciplinary and independent. REB membership should include those with expertise in conducting paediatric research. Where none of the members has such expertise, the REB should seek the advice of an ad hoc expert.

Composition of the REBs

- REBs should be composed of at least five members who should include:
  - (a) at least two members who have expertise in relevant research disciplines, fields and methodologies covered by the REB;
  - (b) at least one member is knowledgeable in ethics;
  - (c) at least one member is knowledgeable in the relevant law (but that member should not be the institution's legal counsel or risk manager). This is mandatory for biomedical research and is advisable, but not mandatory, for other areas of research; and
  - (d) at least one community member who has no affiliation with the institution.8
- REBs should be multidisciplinary;
- REBs should be independent;
- REBs should include members with expertise in research conducted with children and adolescents;
- if none of the members can provide such expertise, REBs should seek the advice of expert special consultant;
- if possible, a minor’s representative (e.g. a parent) should sit as a member if the REB frequently reviews protocols involving children and adolescents.

A comparison of international and Canadian ethical norms on the composition of REBs is presented in Table 10 of Appendix 1.
## APPENDIX 1:

### COMPARISON TABLES

#### Legend:

**Rows:** Positions on major themes of paediatric research

**Columns:** International and Canadian ethical norms

- If the institution mentions the theme in one of its documents, the precise section number (e.g. s. 23, or ss. 23, 25), guideline number (e.g. gl. 3, or gls. 3, 4) or, for the TCPS2, article number (e.g. 3.2, 3.5) is provided.
- The year of adoption is provided to distinguish documents from the same institution (e.g. 2008, s. 3; 2009, s. 4).
- Not all documents are divided into sections, in which case only the year is provided (1998).
- Blank cells indicate the absence of any mention of the position.

Full citations for each normative document can be found following Table 10.
Table 1 presents a comparison of international and Canadian ethical norms on the inclusion of minors in research.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
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<tr>
<td><strong>Minors should be included in research</strong></td>
<td></td>
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</tr>
<tr>
<td>WMA</td>
<td>2008, s. 27; 2003, ss. 8(b)-(d); 1997, s. 5(e)</td>
<td>2008, s. 27</td>
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<td>2002, gl. 14; 2008, gl. 14</td>
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<td>1997, s. 4.8.14; 2000, s. 2.6.3</td>
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<td>1997, s. 4.8.14; 2000, s. 2.6.3</td>
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<td>TCPS2</td>
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<td>ICH E11 Addendum</td>
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</table>

**Necessary to promote the health of the paediatric population**

| WMA | 2008, s. 27 | 2002, gl. 14; 2008, gl. 14 | | | |
| UNESCO | 2005, s.7; 2003, ss. 8(b)-(d); 1997, s. 5(e) | 2002, gl. 14; 2008, gl. 14 | | | |
| CIOMS | 2002, gl. 14; 2008, gl. 14 | 1997, s. 4.8.14; 2000, s. 2.1 | 1997, s. 17(1)(i); 2005, s. 15(1)(ii) | | |
| ICH | 1997, s. 4.8.14; 2000, s. 2.1 | | | | |
| CE | | | | | |
| EC | | | | | |
| TCPS2 | | | | | |
| ICH E11 Addendum | | | | | |

**Type of research cannot be performed on legally competent adults**

| WMA | 2008, s. 27 | 2005, s. 7(b); 2002, gl. 12 | | | |
| UNESCO | 2005, s.7; 2003, ss. 8(b)-(d); 1997, s. 5(e) | 2002, gl. 14; 2008, gl. 14 | | | |
| CIOMS | 2002, gl. 14; 2008, gl. 14 | 1997, s. 4.8.14; 2000, s. 2.6.3 | 1997, s. 17(1)(ii); 2005, s. 15(1)(i)-(ii) | | |
| ICH | 1997, s. 4.8.14; 2000, s. 2.6.3 | | | | |
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| TCPS2 | | | | | |
| ICH E11 Addendum | | | | | |

**Consent of competent adolescent or parents/legal representative of incompetent minor obtained**

| WMA | 2008, s. 27 | 2005, s. 7(b); 2002, gl. 19(c)(i) | | | |
| UNESCO | 2005, s.7; 2003, ss. 8(b)-(d); 1997, s. 5(e) | 2002, gl. 14; 2008, gl. 14 | | | |
| CIOMS | 2002, gl. 14; 2008, gl. 14 | 1997, s. 4.8.14; 2000, s. 2.6.3 | 1997, ss. 6.2, 17(1)(iv); 2005, s. 15(1)(iv) | | |
| ICH | 1997, s. 4.8.14; 2000, s. 2.6.3 | | | | |
| CE | | | | | |
| EC | | | | | |
| TCPS2 | | | | | |
| ICH E11 Addendum | | | | | |

**Assent obtained from minor to the extent of her capabilities**

| WMA | 2008, s. 27 | 2005, s. 7(a); 2002, gl. 19(c)(ii) | | | |
| UNESCO | 2005, s.7; 2003, ss. 8(b)-(d); 1997, s. 5(e) | 2002, gl. 14; 2008, gl. 14 | | | |
| CIOMS | 2002, gl. 14; 2008, gl. 14 | 1997, s. 4.8.12; 2000, s. 2.6.3 | 1997, ss. 6.2, 17(1)(v); 2005, s. 15(1)(v) | | |
| ICH | 1997, s. 4.8.12; 2000, s. 2.6.3 | | | | |
| CE | | | | | |
| EC | | | | | |
| TCPS2 | | | | | |
| ICH E11 Addendum | | | | | |

**Older minors to be included first**

| WMA | 2002, gl. 14; 2008, gl. 14 | 2000, s. 2.6.3 | | | |
| UNESCO | 2005, s.7; 2003, ss. 8(b)-(d); 1997, s. 5(e) | | | | |
| CIOMS | 2002, gl. 14; 2008, gl. 14 | | | | |
| ICH | | | | | |
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| EC | | | | | |
| TCPS2 | | | | | |
| ICH E11 Addendum | | | | | |

**Research may involve very vulnerable minors**

| WMA | REB approval; Expert advocate opinion may be required [2002, gl. 14; 2008, gl. 14] | Limited to: Diseases or conditions found principally or exclusively in these groups; where the disease or condition in these groups is expected to alter the disposition or pharmaco-dynamic effects of a medicinal product [2000, s. 2.6.3] | | | |
| UNESCO | 2005, s.7; 2003, ss. 8(b)-(d); 1997, s. 5(e) | | | | |
| CIOMS | 2002, gl. 14; 2008, gl. 14 | | | | |
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| TCPS2 | | | | | |
| ICH E11 Addendum | | | | | |

**Research can involve healthy minors**

| WMA | 2008, s. 18 | Palatability testing; Prevention trials; Vaccine trials [2008, s. 15] | | | |
| UNESCO | 2005, s.7; 2003, ss. 8(b)-(d); 1997, s. 5(e) | | | | |
| CIOMS | 2002, gl. 14; 2008, gl. 14 | | | | |
| ICH | | | | | |
| CE | | | | | |
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| TCPS2 | | | | | |
| ICH E11 Addendum | | | | | |

**Additional elements**

| WMA | Benefit to the community; benefit to category of persons from which the subject is drawn [2002, gl. 12] | No alternative of comparable effectiveness to research on humans; Risks are not disproportionate to the potential benefits; REB approval; Participants have been informed of their rights [1997, ss. 16(i)-(iv), 17(1)(i)] | | | |
| UNESCO | 2005, s.7; 2003, ss. 8(b)-(d); 1997, s. 5(e) | | | | |
| CIOMS | 2002, gl. 14; 2008, gl. 14 | | | | |
| ICH | | | | | |
| CE | | | | | |
| EC | | | | | |
| TCPS2 | | | | | |
| ICH E11 Addendum | | | | | |

**Norms for protection of children's rights and welfare**

| WMA | 2008, s. 27 | 2005, s. 7(b); 2002, gl. 12 | | | |
| UNESCO | 2005, s.7; 2003, ss. 8(b)-(d); 1997, s. 5(e) | 2002, gl. 14; 2008, gl. 14 | | | |
| CIOMS | 2002, gl. 14; 2008, gl. 14 | 1997, s. 4.8.14; 2000, s. 2.1 | 1997, s. 17(1)(i); 2005, s. 15(1)(ii) | | |
| ICH | 1997, s. 4.8.14; 2000, s. 2.1 | | | | |
| CE | | | | | |
| EC | | | | | |
| TCPS2 | | | | | |
| ICH E11 Addendum | | | | | |
Table 2 presents a comparison of international and Canadian ethical norms on consent to research.

<table>
<thead>
<tr>
<th>Positions</th>
<th>WMA</th>
<th>UNESCO</th>
<th>CIOMS</th>
<th>ICH</th>
<th>HUGO</th>
<th>OECD</th>
<th>CE</th>
<th>EC</th>
<th>TCPS2</th>
<th>ICH E11 Addendum</th>
<th>CCMG/ CAGS</th>
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</thead>
<tbody>
<tr>
<td>Consent must be free and informed</td>
<td>2008, ss. 24, 27</td>
<td>1997, ss. 5(b),(c); 2003, s. 8(a),(b); 2005, ss. 6, 7(a); 2002, gl. 11, 12, 19(b),(c)(i)</td>
<td>2002, gl. 4, 5, 14; 2008, gl. 4, 5, 14</td>
<td>1996, ss. 4.8, 4.8.3, 4.8.10(m); 2000, ss. 2.6.2, 2.6.3</td>
<td>1995</td>
<td>s. 4.B, annotations at para. 31</td>
<td>1997, ss. 5, 6(2),(4); 2005, ss. 14(1), 15(1)(iv)</td>
<td>2008, ss. 5.6, 6.1</td>
<td>3.1(a), 3.2</td>
<td>s. 6.2</td>
<td>s. 7</td>
</tr>
<tr>
<td>Aims, goals, methods and/or procedures</td>
<td>2008, s. 24</td>
<td>2002, gls. 11(a), 19(b)</td>
<td>2002, gl. 5(3); 2008, gl. 5(3)</td>
<td>1996, ss. 4.8.10(b), 4.8.10(d)</td>
<td>1995</td>
<td>s. 5, 2005, ss. 5.2(2)(i), 16</td>
<td>2008, ss. 6.1, 27(1), 27(6)</td>
<td>3.2(b)</td>
<td>s. 7(i)</td>
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<tr>
<td>Duration of the participation</td>
<td>2008, s. 24</td>
<td>2002, gl. 5(9)-(11); 2008, gl. 5(9)-(11)</td>
<td>1996, ss. 4.8.10(g)(b)</td>
<td>1995</td>
<td>s. 4.1, annotations at para. 35</td>
<td>1997, s. 5, 2005, ss. 13(2)(i), 16</td>
<td>2008, ss. 5.6, 6.1, 27(9)-(10), 27(13)</td>
<td>3.2(c)</td>
<td>s. 6.2</td>
<td>s. 7(ii)</td>
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<tr>
<td>Understandability</td>
<td>2008, s. 24</td>
<td>2002, gl. 5(9)-(11); 2008, gl. 5(9)-(11)</td>
<td>1996, ss. 4.8.10(g)(b)</td>
<td>1995</td>
<td>s. 4.1, annotations at para. 35</td>
<td>1997, s. 5, 2005, ss. 13(2)(i), 16</td>
<td>2008, ss. 5.6, 6.1, 27(9)-(10), 27(13)</td>
<td>3.2(c)</td>
<td>s. 6.2</td>
<td>s. 7(ii)</td>
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<tr>
<td>Right to withdraw</td>
<td>2008, s. 24</td>
<td>2003, ss. 6(d), 9; 2005, ss. 6(2)</td>
<td>2002, gl. 5(2); 2008, gl. 5(2)</td>
<td>2002, s. 4(a)</td>
<td>ss. 4.13, annotations at para. 35</td>
<td>1997, s. 5, 2005, ss. 13(2), 16</td>
<td>2008, ss. 6.5</td>
<td>3.2(d)</td>
<td>s. 7(iv)</td>
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<tr>
<td>Protection of privacy &amp; confidentiality</td>
<td>2002, gl. 14</td>
<td>2002, gl. 5(14)-(15); 2008, gl. 5(14)-(15)</td>
<td>1996, s. 4.8.10(o)</td>
<td>2002, s. 4(c)</td>
<td>s. 6.C, annotations at para. 35</td>
<td>2005, s. 13(2)(iv)</td>
<td>2008, s. 27(16)</td>
<td>3.2(i)</td>
<td>s. 7(v)</td>
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<tr>
<td>Participant access to info. &amp; results</td>
<td>2002, gl. 16</td>
<td>2002, gl. 5(7); 2008, gl. 5(7)</td>
<td>1996, s. 4.8.10(n)</td>
<td>1996, s. 4.8.10(n)</td>
<td>s. 7.F, annotations at para. 69</td>
<td>2005, s. 13(2)(v)</td>
<td>2008, s. 27(22),(24)</td>
<td>3.2(i)</td>
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<tr>
<td>Third-party access to info.</td>
<td>2002, gl. 16</td>
<td>2002, gl. 5(7); 2008, gl. 5(7)</td>
<td>1996, s. 4.8.10(n)</td>
<td>1996, s. 4.8.10(n)</td>
<td>s. 7.F, annotations at para. 69</td>
<td>2005, s. 13(2)(v)</td>
<td>2008, s. 27(22),(24)</td>
<td>3.2(i)</td>
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<tr>
<td>Possibility of commercialization</td>
<td>2002, gl. 5(20); 2008, gl. 5(20)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>s. 7(x)</td>
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<tr>
<td>Source(s) of funding</td>
<td>2008, s. 24</td>
<td>2002, gls. 5(17); 2008, gl. 5(17)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>1996, ss. 4.8.10(j)(k)</td>
<td>s. 7(x)</td>
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<td>Compensation (for participation or in case of)</td>
<td>2002, gl. 11(a)</td>
<td>2002, gls. 5(6),(23),(24), 7; 2008, gls. 5(6),(23),(24), 7</td>
<td>1996, s. 4.8.10(j)(k)</td>
<td>1996, s. 4.8.10(j)(k)</td>
<td>1996, s. 4.8.10(j)(k)</td>
<td>1996, s. 4.8.10(j)(k)</td>
<td>1996, s. 4.8.10(j)(k)</td>
<td>1996, s. 4.8.10(j)(k)</td>
<td>s. 7(x)</td>
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<td>Features of research design (ex. randomization, blinding)</td>
<td>2002, gls. 4, 5; 2008, gls. 4,5</td>
<td>1996, s. 4.8.10</td>
<td>2005, s. 13(2)(ii)</td>
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<td>3.2(b)</td>
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<td>Possibility of alternative treatments, if any</td>
<td>2002, gls. 4, 5; 2008, gls. 4,5</td>
<td>1996, s. 4.8.10(i)</td>
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<td>Reasons to terminate the participation</td>
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<td>Contact info. for questions and/or complaints</td>
<td>1996, s. 4.8.10(q)</td>
<td>s. 4.12, annotations at para. 35</td>
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<td>3.2(l)</td>
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<tr>
<td>Ability for participant/parents to withdraw</td>
<td>2002, s. 3(3); 2008, s. 24</td>
<td>2002, gl. 13; 2003, s.9; 2005, ss. 6,7</td>
<td>1996, ss. 4.6, 4.13, annotations at paras. 35, 42, 43</td>
<td>1997, ss. 5, 6(5); 2005, s. 14(2)</td>
<td>2008, ss. 6.1, 6.5</td>
<td>3.2(d)</td>
<td>s. 17(iv)</td>
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<tr>
<td>Consent should be written</td>
<td>2002, s. 3(3); Except if there are cultural reasons [2002, gl. 11(b)]</td>
<td>May be implied by voluntary actions or expressed orally; documented [2002, gl. 4; 2008, gl. 4]</td>
<td>1996, ss. 4.8.8-9 If impossible, oral consent must be documented [2000, s. 2.6.3]</td>
<td>Consent material should be written [s. 4.3]</td>
<td>1997, s. 17(1)(iv); 2005, s. 15(1)(iv)</td>
<td>If impossible, oral consent must be documented[2008, s. 5.6]</td>
<td>NO. Researchers may use a range of consent procedures, including oral consent, field notes and other strategies [3.12]</td>
<td>But the dialogue between the researcher and the participant cannot be replaced by a written consent form [s. 7]</td>
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<tr>
<td>Should consent be renewed?</td>
<td>2002, s. 21</td>
<td>Not necessarily; Blanket consent may be preferable in some circumstances [2002, gl. 11]</td>
<td>In long-term studies at predetermined intervals; If significant changes; If new information that may affect the willingness to participate [2002, gl. 4, 6;</td>
<td>For new use of data/samples [ss. 4.5]</td>
<td>2005, s. 24(2)(iii)</td>
<td>2008, s. 6.4</td>
<td>Consent is an ongoing process [3.3, 11.8]</td>
<td>For secondary use, consent must be obtained in accordance with applicable law, with limited</td>
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<td>Positions</td>
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<tr>
<td>Consent not required for secondary use of non-identifying data and/or tissue</td>
<td>2008, gl. 4, 6]</td>
<td>exception [12.3]</td>
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| Secondary use of data and/or tissue must be limited to purposes compatible with original consent, otherwise new consent is required | 2008, ss. 24, 25  
2002, gl. 18; 2003, s. 16(b)  
2008, gls. 4, 5(18), 24  
1998 | 5.5, 12.3 | 5.5, 12.3 |
| Other issues to be raised regarding secondary use of data and/or tissue | “secondary uses should not inhibit patients from confiding information for their own health care needs, exploit vulnerability or inappropriate ly borrow on trust” [2002,  
Informed consent required when collecting for future epidemiological research, including foreseeable uses whether known or undefined [2008, gl. 24]  
Choices made with regard to storage or other uses should be respected [1995] | At time of consent participants should be provided information on re-contacting, such as when research that is significantly different from the original is contemplated [s. 4.D, annotations at |
<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
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<tr>
<td>WMA</td>
<td>UNESCO</td>
<td>CIOMS</td>
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<td>s. 6]</td>
<td>para. 41]</td>
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<tr>
<td>Broad consent allowed?</td>
<td>NO, It underscores that broad consent is highly debatable and unacceptable in several countries [2008, gl. 24]</td>
<td>YES [2002]</td>
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<tr>
<td>Best interest of the child should be considered</td>
<td>1997, s. 5(b); 2003, s. 8(b); 2005, s. 7(a)</td>
<td>2002, gl. 14; 2008, gl. 14</td>
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<tr>
<td>Cultural background should be considered</td>
<td>2002, intro, gls. 2, 4; 2008, intro, gls. 2,4</td>
<td>1995; 1998</td>
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<tr>
<td>Procedures for use and future use of information and samples</td>
<td>Health information [2002, s. 16]</td>
<td>Sample collection and use [2002, gl. 11(a)]</td>
</tr>
<tr>
<td>Additional elements</td>
<td>[2003, s. 6(d)]</td>
<td>Availability of the drug after the research; Policy on the use and disclosure of results of genetic tests and familial genetic information; Duality of the role of the investigator; Extent of the Experimental procedures or aspects; Anticipated expenses; Disclosure of new information that may affect the participant’s willingness to participate; Number of subjects involved in the Alternatives to the research [1995]</td>
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<td>Positions</td>
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- Investigator's responsibility to provide medical services to the participant; Treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research; REB approval [2002, gl. 5; 2008, gl. 5]
- Intended uses; Transfer; Disposal techniques [4.D, annotations at para. 36]
- Disclosure of information that may affect the willingness of the participant [3.2(d), 3.3, 11.8]
- Incidental findings [3.4, 12.2(g)]
- Linkage of tissue with participant info [12.2]
- Coding of data and samples; Location and duration of storage; Custodianship of data and samples; Access to data and samples (e.g. how, who); Destruction of data and samples [s. 7(iv)]
Table 3 presents a comparison of international and Canadian ethical norms on the assent of the minor.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
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<tr>
<td>Assent required</td>
<td>WMA: 2008, s. 28; UNESCO: 2002, gl. 19(c)(ii); 2003, s. 8(c); 2005, s. 7(a); CIOMS: Except when the child is too immature [2002, gl. 14; 2008, gl. 14]; ICH: 1996, s. 4.8.12; 2000, s. 2.6.3; CE: 1997, s. 6(2); 2005, s. 15(1)(iv)-(v); EC: May not be possible in all age groups or in all research conditions (e.g. emergency research) [2008, s. 7]; TCPS2: May not be possible in all research conditions (e.g. emergency research) [3.9, 3.10]; ICH E11 Addendum: s. 6.2</td>
<td>Assent required: 2008, s. 28; 2002, gl. 19(c)(ii); 2003, s. 8(c); 2005, s. 7(a)</td>
</tr>
<tr>
<td>Elements to include in assent information sheet and/or form</td>
<td>WMA: Nature of the research; Risks and consequences [2002, gl. 19(b)]; UNESCO: 2002, gl. 14; 2008, gl. 14; CIOMS: Study information; Right to decline to participate; Right to withdraw at any time [2000, s. 2.6.3]; ICH: Same elements as for consent, such as: Purpose of the trial; Potential risks and benefits [2008, ss. 7, 27]; CE: Significance of the research [3.10]; EC:</td>
<td>Elements to include in assent information sheet and/or form: 2002, gl. 14; 2008, gl. 14</td>
</tr>
<tr>
<td>Elements to consider in the assent process</td>
<td>WMA: Age appropriate information [2002, gl. 19(a)]; UNESCO: Child’s maturity; Child’s intelligence [2002, gl. 14; 2008, gl. 14]; CIOMS: Age; Degree of maturity [1997, s. 6(2); 2005, s. 15(1)(iv)]; ICH: Age; Developmental stage; Intellectual capacities (e.g. learning difficulties); Life/disease experience [2008, s. 7]; CE:</td>
<td>Elements to consider in the assent process: Age appropriate information [2002, gl. 19(a)]; Study information; Right to decline to participate; Right to withdraw at any time [2000, s. 2.6.3];</td>
</tr>
<tr>
<td>How should the information be disclosed?</td>
<td>WMA: Age appropriate information [2002, gl. 19(a)]; UNESCO: To the extent of the child’s maturity and intelligence [2002, gl. 14; 2008, gl. 14]; CIOMS: In language and terms they are able to understand [2000, s. 2.6.3]; ICH: In language and wording appropriate to age, psychological and intellectual maturity; Use of terms that are honest, but not frightening [2008, s. 7]; CE:</td>
<td>How should the information be disclosed: Age appropriate information [2002, gl. 19(a)]; Study information; Right to decline to participate; Right to withdraw at any time [2000, s. 2.6.3];</td>
</tr>
<tr>
<td>Should assent and consent forms be separate?</td>
<td>WMA: Not necessarily [2000, s. 2.6.3]; UNESCO:</td>
<td>Should assent and consent forms be separate: YES [2008, s. 7];</td>
</tr>
<tr>
<td>Assent must be renewed</td>
<td>WMA: When child becomes capable of independent informed consent [2002, gl. 14; 2008, gl. 14]; UNESCO:</td>
<td>Assent must be renewed: 2008, s. 7</td>
</tr>
<tr>
<td>Age groups</td>
<td>Positions</td>
<td>International</td>
</tr>
<tr>
<td>------------</td>
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<td>---------------</td>
</tr>
<tr>
<td></td>
<td>WMA</td>
<td>UNESCO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From birth to 3 years:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children of 3-4 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>can understand some expression of altruism;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children of 6-7 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>can provide a meaningful assent;</td>
<td></td>
<td></td>
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<tr>
<td>Children of 9 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>may understand risks and benefits;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents have the capacity to make adult decisions in many other areas of life and have an emerging capacity for independent decision-making</td>
<td></td>
<td></td>
</tr>
<tr>
<td>from REBs or be consistent with applicable law;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emancipated or mature minors can provide a free and informed consent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008, s. 7.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emancipated minors can provide a free &amp; informed consent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Table 4** presents a comparison of international and Canadian ethical norms on the dissent of the minor.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>WMA</strong></td>
<td><strong>UNESCO</strong></td>
</tr>
<tr>
<td>Dissent should be respected</td>
<td>2008, s. 28</td>
<td>2002, gl. 19(0)(ii); 2005, s. 6(2)</td>
</tr>
<tr>
<td>Can dissent be overridden?</td>
<td>YES, if child is too young or immature; Child needs treatment that is not available outside the context of research; Investigational intervention shows promise of therapeutic benefit; AND No acceptable alternative therapy. For children with a fatal illness, when intervention shows promise of preserving or prolonging life; AND No acceptable alternative treatment [2002, gl. 14; 2008, gl. 14]</td>
<td>YES If the child’s welfare would be jeopardized by his/her dissent [2000, s. 2.6.3]</td>
</tr>
<tr>
<td>Is REB approval needed to override minor’s dissent?</td>
<td>YES, if child is more nearly capable of independent informed consent, or suffering from a fatal illness [2002, gl. 14; 2008, gl. 14]</td>
<td>NO, continued parental consent should be sufficient [2000, s. 2.6.3]</td>
</tr>
<tr>
<td>In case of disagreement, does child’s dissent prevail over parental consent?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Must dissent be written?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5 presents a comparison of international and Canadian ethical norms on the departure from consent.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Departure from consent is possible</strong></td>
<td>WMA</td>
<td>2002, s. 18; 2008, s. 25</td>
</tr>
<tr>
<td></td>
<td>UNESCO</td>
<td>1997, s. 9</td>
</tr>
<tr>
<td></td>
<td>CIOMS</td>
<td>2002, gl. 14; 2008, gl. 14</td>
</tr>
<tr>
<td></td>
<td>HUGO</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>OECD TCPS2</td>
<td></td>
</tr>
<tr>
<td><strong>Departure is subject to REB approval</strong></td>
<td>WMA</td>
<td>2002, ss. 17, 18; 2008, s. 25</td>
</tr>
<tr>
<td></td>
<td>UNESCO</td>
<td>2003, ss. 6(b), 16(b)</td>
</tr>
<tr>
<td></td>
<td>CIOMS</td>
<td>2002, gl. 14; 2008, gl. 14</td>
</tr>
<tr>
<td></td>
<td>HUGO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OECD TCPS2</td>
<td></td>
</tr>
<tr>
<td><strong>Elements to consider to approve a departure</strong></td>
<td>WMA</td>
<td>National legal requirements [2002, s. 18]</td>
</tr>
<tr>
<td></td>
<td>UNESCO</td>
<td>Respect of:</td>
</tr>
<tr>
<td></td>
<td>CIOMS</td>
<td>Ethical and legal standards adopted by States; UNESCO Declaration’s principles; Public international law; International human rights law [1997, s. 9; 2003, s. 8(a); 2005, s. 6(2)]</td>
</tr>
<tr>
<td></td>
<td>HUGO</td>
<td>If parental knowledge may place the child at some risk of questioning or intimidation by his/her parents [2002, gl. 14; 2008, gl. 14]</td>
</tr>
<tr>
<td></td>
<td>OECD TCPS2</td>
<td>If research with identifiable material: Minimal risk; Use of publicly available data; Consent would be impracticable [2008, gl. 4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>REBs should consider:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Access is strictly limited in time; Interests of the persons concerned will not be compromised; Risks will be minimized; Respect of applicable law; No known objection of the individual to such use; If mitigation can be undertaken (e.g. anonymization) [2008, gl. 4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Applicable laws or ethical principles in the jurisdiction [annotations at para. 27]</td>
</tr>
<tr>
<td></td>
<td>OECD TCPS2</td>
<td>No more than minimal risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unlikely to adversely affect the welfare of children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Research could not practicably be carried out without the departure from consent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If possible and appropriate, children and parents/legal representative will be provided with additional pertinent information after participation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not involve a therapeutic intervention [3.7(c)]</td>
</tr>
</tbody>
</table>
Table 6 presents a comparison of international and Canadian ethical norms on the evaluation of risks and benefits.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research must be preceded by an evaluation of risks &amp; benefits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMA</td>
<td>UNESCO</td>
<td>CIOMS</td>
</tr>
<tr>
<td>2008, ss. 18,20</td>
<td>1997, s. 5(e); 2005, s. 20</td>
<td>2002, gls. 8-9; 2008, gls. 8-9</td>
</tr>
<tr>
<td>Nature of the risks and/or benefits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>Research which does not have an expected direct health benefit [1997, s. 5(e); 2005, s. 7(b)]</td>
<td>Intervention/procedures that hold out the prospect of direct [...] benefit</td>
</tr>
<tr>
<td>Positions</td>
<td>International</td>
<td>Canadian</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>WMA</td>
<td>UNESCO</td>
<td>CIOMS</td>
</tr>
<tr>
<td>Elements to consider when evaluating risks and benefits</td>
<td>Potential benefits should justify the risks [2008, s.21]</td>
<td>Reasonable balance between potential benefits and risks; Risks must be justified in the light of the potential benefits [2002, gls. 8-9; 2008, gls. 8-9]</td>
</tr>
<tr>
<td>Can participate in research that offers direct benefits</td>
<td>2008, s. 17</td>
<td>1997, s. 5(e); 2005, s. 7(b)</td>
</tr>
</tbody>
</table>

- Potential benefits should justify the risks [2008, s.21]
- Reasonable balance between potential benefits and risks; Risks must be justified in the light of the potential benefits [2002, gls. 8-9; 2008, gls. 8-9]
- Potential benefits should justify the risks [1996, s. 2.2]
- Probability; Magnitude; Duration; Age groups [2008, s. 11.1]
- Assumption; Severity of the condition or disease; Benefits of alternative treatments [2008, s. 12.1]
- Nature of the harm; Magnitude or seriousness of the harm; Probability of occurrence of the harm [ch. 2B at 22]
- Potential benefits should justify the risks [s. 5]
<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMA</td>
<td>Minimal risk and minimal burden</td>
<td>Benefit to children in the same age category or afflicted with the same disease, disorder or condition; Minimal risk and minimal burden; Importance of the knowledge to be gained; Severity of the disease or condition; Commonality of the disease or condition under study; Likelihood of obtaining results from the research; Usefulness of benefits obtained [2008, ss. 12-12.1]</td>
</tr>
<tr>
<td>UNESCO</td>
<td>Research is intended to contribute to the health benefit of other persons in the same age category or with the same genetic condition</td>
<td></td>
</tr>
<tr>
<td>CIOMS</td>
<td>No more likely and not greater than the risk attached to routine medical or psychological examination of the children concerned</td>
<td>Risk is justified in relation to the expected benefits to society</td>
</tr>
<tr>
<td>ICH</td>
<td>Risk is reasonable in relation to the importance of the knowledge to be gained [2002, gls. 8-9; 2008, gls. 8-9]</td>
<td>Benefit to other persons in the same age category or afflicted with the same disease, disorder or condition; Minimal risk and minimal burden [1997, s. 17(2); 2005, ss. 6(2), 15(2)]</td>
</tr>
<tr>
<td>HUGO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCPS2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH E11 Addendum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Can minors participate in research that offers indirect benefits?

2008, ss. 17, 18

1996, s. 4.8.14

[1997, s. 5(e); 2005, 7(b)]

[1997, s. 17(2); 2005, ss. 6(2), 15(2)]

[2002, gls. 8-9; 2008, gls. 8-9]
<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMA</td>
<td>UNESCO</td>
<td>CIOMS</td>
</tr>
<tr>
<td><strong>Elements to consider to approve an increase above minimal risk</strong></td>
<td>Existence of an overriding scientific or medical rationale</td>
<td></td>
</tr>
<tr>
<td>Approval of an REB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elements that REBs need to consider: Whether research responds to disease affecting the subjects or conditions to which they are particularly susceptible; level of risk compared to routine medical or psychol. examination for the subject; objective of research sufficiently important to justify exposure to the increased risk; AND</td>
<td>“any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden” [2005, s. 15(2)(ii)]</td>
<td></td>
</tr>
<tr>
<td>“interventions are reasonably commensurate with the clinical interventions that the subjects have experienced or may be expected to experience in relation to the condition under investigation.” [2002, gl. 9; 2008, gl. 9]</td>
<td>“benefit to individual or benefit to the group, and with the benefit to risk balance being at least as favourable as that of available alternative approaches” [2008, s. 12.1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Research should have “the prospect of direct benefits for them [4.6(b),(c)]</td>
<td></td>
</tr>
</tbody>
</table>
Table 7 presents a comparison of international and Canadian ethical norms on privacy and confidentiality.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Must privacy/confidentiality be protected?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMA</td>
<td>2002, s. 12; 2008, ss. 11,23</td>
<td>1997, ss. 7, 9; 2002, gl. 14; 2003, s. 14; 2005, s. 9</td>
</tr>
<tr>
<td>UNESCO</td>
<td>2002, gl. 18; 2008, gl. 18</td>
<td>1995; 1998</td>
</tr>
<tr>
<td>CIOMS</td>
<td>1996, s. 2.11</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td></td>
<td></td>
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<tr>
<td>HUGO</td>
<td></td>
<td></td>
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<tr>
<td>OECD</td>
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<tr>
<td>CE</td>
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</tr>
<tr>
<td>EC</td>
<td></td>
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<tr>
<td>TCPS2</td>
<td></td>
<td></td>
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<tr>
<td>CIHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Access to the information collected</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMA</td>
<td>Unauthorized or inappropriate use of health information should be avoided [2002, s. 14]</td>
<td></td>
</tr>
<tr>
<td>UNESCO</td>
<td>Participants should have access to their data unless: Drug regulation authorities (e.g. Health Canada) Limited access by law (e.g. interest of public health) Sponsors for audit [2002, gl. 8, 2008, gl. 8]</td>
<td></td>
</tr>
<tr>
<td>CIOMS</td>
<td>Access for trial related monitoring, audits, REB review, and regulatory inspection. [1996, ss. 5.15, 6.10]</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>Access for trial related monitoring, audits, REB review, and regulatory inspection. [1996, ss. 5.15, 6.10]</td>
<td></td>
</tr>
<tr>
<td>HUGO</td>
<td>Only with authorization International standardization of ethical requirements for control and access to samples and information is essential [1998]</td>
<td></td>
</tr>
<tr>
<td>OECD</td>
<td>Access requests should include a scientifically sound and ethically appropriate research plan [s. 7.B]</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCPS2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>Children &quot;are entitled to know any information collected about their health. Other personal information collected for a research project will need to be made accessible to them in conformity with national laws on the protection of individual data&quot; [2008, s. 18]</td>
<td></td>
</tr>
<tr>
<td><strong>Access to personal data should be strictly limited</strong> [element 8]</td>
<td></td>
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<tr>
<td>Positions</td>
<td>International</td>
<td>Canadian</td>
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</tr>
<tr>
<td>WMA</td>
<td>2000, para. 52</td>
<td></td>
</tr>
<tr>
<td>UNESCO</td>
<td>Important public interest reason [2000, para. 64; 2003, s. 13]</td>
<td></td>
</tr>
<tr>
<td>CIOMS</td>
<td>Public health purposes [2000, para. 64]</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>Restrictively provided for by domestic law [2003, s. 14(b)]</td>
<td></td>
</tr>
<tr>
<td>HUGO</td>
<td>Consistent with the international law of human rights [2003, s. 14(b)]</td>
<td></td>
</tr>
<tr>
<td>OECD</td>
<td>Participant provided an informed consent [2000, paras. 39, 63; 2003, s. 14(b)]</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td>Information should not be disclosed for purposes other than those for which it was collected or consented [2005, s. 9]</td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>Data is anonymized [2000, paras. 63,64]</td>
<td></td>
</tr>
<tr>
<td>TCPS2</td>
<td>Communicable diseases; Child abuse or neglect [2002, gl. 18; 2008, gl. 18]</td>
<td></td>
</tr>
<tr>
<td>CIHR</td>
<td>Authorized by law; With the consent of the participant [1998]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If required by law [s. 7.F]</td>
<td>“The law shall protect against inappropriate disclosure of any other information related to a research project that has been submitted to an ethics committee […]” [2005, s. 25(2)]</td>
</tr>
<tr>
<td></td>
<td>With the consent of the participant [s. 8.3]</td>
<td></td>
</tr>
</tbody>
</table>

**Disclosure to third parties permitted in certain instances**

- With authorization from the guardian of the database [2002, s. 20]
- With consent of the participant [2002, gl. 18; 2008, gl. 18]
- Authorized by law; With the consent of the participant [1998]
- If required by law [s. 7.F]
- “The law shall protect against inappropriate disclosure of any other information related to a research project that has been submitted to an ethics committee […]” [2005, s. 25(2)]
- With the consent of the participant [s. 8.3]
<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMA</td>
<td>UNESCO</td>
<td>CIOMS</td>
</tr>
<tr>
<td>Keep a record on who has accessed the information and when [2002, s. 15]</td>
<td>coding of samples [2002, s. 29]</td>
<td>Recipients of data/samples must have adequate safeguards for privacy/confidentiality [s. 7.C]</td>
</tr>
<tr>
<td>Arrangements to ensure secured transmission of the information [2002, s. 14]</td>
<td>human genetic data, human proteomic data and biological samples: “collected for the purposes of scientific research should not normally be linked to an identifiable person”</td>
<td>May have stratified access or fee policies [s. 7.4]</td>
</tr>
<tr>
<td>People who collect use, disclose or access information “must be subjected to an enforceable duty to keep the information secure” [2002, s. 23]</td>
<td>“collected for medical and scientific research purposes can remain linked to an identifiable person, only if necessary to carry out the research and provided that the privacy of the individual and the confidentiality [...] are protected”</td>
<td>Confidentiality or access agreement [s. 7.5]</td>
</tr>
<tr>
<td>Safeguard measures</td>
<td>“should not be kept in a form which allows the data subject to be identified for any longer than is necessary for achieving the purposes for which they were collected or subsequently processed” [2003, ss. 14(c)-e]</td>
<td>Terms of access should be set out in MTAs [s. 7.A]</td>
</tr>
<tr>
<td></td>
<td>Omit information that might lead to the identification of the participants</td>
<td>Coding</td>
</tr>
<tr>
<td></td>
<td>Restrict access to the information</td>
<td>Procedures for controlled access</td>
</tr>
<tr>
<td></td>
<td>Anonymized data</td>
<td>Policies for the transfer and conservation of samples [1998]</td>
</tr>
<tr>
<td></td>
<td>Secured coding of the samples (e.g. encryption) [2002, gl. 18; 2008, gl. 18]</td>
<td>Unique identifier [1996, ss. 1.58, 5.5.5]</td>
</tr>
<tr>
<td></td>
<td>Backup of the data [1996, ss. 1.58, 5.5.3]</td>
<td>For electronic trial data: Standard Operating procedures (SOPs)</td>
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<tr>
<td></td>
<td>Security system</td>
<td>Security system</td>
</tr>
<tr>
<td></td>
<td>Security system</td>
<td>List of persons authorized to make data changes</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Categories of coding for data and tissue</td>
<td>International</td>
<td>Canadian</td>
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<tr>
<td>----------------------------------------</td>
<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td>Coded samples</td>
<td>Coded</td>
<td>Identified information – Information that may reasonably be expected to identify an individual, alone or in combination with other available information.</td>
</tr>
<tr>
<td>De-identified</td>
<td></td>
<td>Non-identifiable information [Glossary at 193]</td>
</tr>
<tr>
<td>Identified samples</td>
<td>Identified: labelled with personal identifiers such as name or identification</td>
<td></td>
</tr>
<tr>
<td>Coded samples</td>
<td>Coded: labelled with at least one specific code &amp; do not carry any personal identifiers</td>
<td></td>
</tr>
<tr>
<td>Anonymized (or not identifiable) samples</td>
<td>Single-coded: labelled with a single specific code &amp; don’t carry any personal identifiers</td>
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</tr>
<tr>
<td>[2002, ss. 3,24]</td>
<td>Double-coded: initially labelled with a single specific code &amp; do not carry any personal identifiers, then relabelled with a second code, which is linked to the first code via a second coding key</td>
<td></td>
</tr>
<tr>
<td>[2002, gl. 18; 2008, gl. 18]</td>
<td>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
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</tr>
<tr>
<td></td>
<td>Anonymous: never labelled</td>
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</tr>
<tr>
<td>Identified data</td>
<td>Identify the person</td>
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<td>Unlinked/anonymized data</td>
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<table>
<thead>
<tr>
<th>Positions</th>
<th>WMA</th>
<th>UNESCO</th>
<th>CIOMS</th>
<th>ICH</th>
<th>HUGO</th>
<th>OECD</th>
<th>CE</th>
<th>EC</th>
<th>TCPS2</th>
<th>CIHR</th>
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139
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<th>Positions</th>
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</table>
Table 8 presents a comparison of international and Canadian ethical norms on the return of research results.

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<tr>
<th>Positions</th>
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<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General results should be communicated</strong></td>
<td>Authors have a duty to make results publicly available [2008, s. 30]</td>
<td>2008, s. 30</td>
</tr>
<tr>
<td>WHO</td>
<td>May be communicated [2002, gl. 16]</td>
<td>2002, gl. 5(7); 2008, gl. 5(7)</td>
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<td>WMA</td>
<td>2002, gl. 5(7); 2008, gl. 5(7)</td>
<td>May be communicated [1995]</td>
</tr>
<tr>
<td>UNESCO</td>
<td>May be communicated [1995]</td>
<td>2005, ss. 28(2),3(3)</td>
</tr>
<tr>
<td>CIOMS</td>
<td>2002, gl. 5(7); 2008, gl. 5(7)</td>
<td>2008, s. 19.1</td>
</tr>
<tr>
<td>HUGO</td>
<td>May be communicated [1995]</td>
<td>3.2f, 11.12 (clinical trials)</td>
</tr>
<tr>
<td>OECD</td>
<td>May be communicated [s. 1.II, 9.4]</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td>Must be a policy with regards to dealing with aggregate and generalised research findings, [annotations at para. 13]</td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>2002, gl. 5(7); 2008, gl. 5(7)</td>
<td></td>
</tr>
<tr>
<td>TCPS2</td>
<td>May be communicated [1995]</td>
<td></td>
</tr>
<tr>
<td>CPS</td>
<td>2003, s. 10</td>
<td></td>
</tr>
<tr>
<td><strong>Individual results should be communicated</strong></td>
<td>“there should be communication to individual participants which emerges which is relevant to their health” [2002, gl. 16]</td>
<td>Where permitted by law and the appropriate authorities. [s. 4.14]</td>
</tr>
<tr>
<td></td>
<td>2002, gl. 5(7); 2008, gl. 5(7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be communicated [1995]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2003, s. 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“there should be communication to individual participants which emerges which is relevant to their health” [2002, gl. 16]</td>
<td></td>
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<tr>
<td></td>
<td>“incidental findings of non-paternity by a medical geneticist may be disclosed, only to the mother” [2000, gl. at para. 75]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be communicated [1995]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2005, s. 26(1)</td>
<td></td>
</tr>
<tr>
<td><strong>Incidental findings should be communicated</strong></td>
<td>“there should be communication to individual participants which emerges which is relevant to their health” [2002, gl. 16]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“incidental findings of non-paternity by a medical geneticist may be disclosed, only to the mother” [2000, gl. at para. 75]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be communicated [1995]</td>
<td></td>
</tr>
<tr>
<td><strong>Participants have a right to decide whether or not to be informed of the results</strong></td>
<td>Does not apply to: Data irretrievably unlinked; Data that do not lead to individual findings concerning the participant [1997, s. 5(c); 2003, s. 10]</td>
<td>“Choices to be informed or not with regard to results or incidental findings should also be respected” [1995]</td>
</tr>
<tr>
<td></td>
<td>2003, s. 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Choices to be informed or not with regard to results or incidental findings should also be respected” [1995]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1997, s. 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In the context of human genetic research [13.3(a)]</td>
<td></td>
</tr>
<tr>
<td>Positions</td>
<td>International</td>
<td>Canadian</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Right not to know should be extended to relatives</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>The right not to know can be overridden</td>
<td>“In the absence of a provision allowing a derogation […] the person tested could insist on the information not being given to him/her” [2000, para. 42]</td>
<td></td>
</tr>
<tr>
<td>Results can be communicated to the relatives</td>
<td>With consent; For reasons of public health and protection of rights and freedoms of others; Family members “could be informed of as much of that data is relevant to them” [2000, para. 47]</td>
<td>Participants may express their preferences; preferences subject to overriding considerations that may warrant disclosure of information to relatives in exceptional circumstances (e.g., revelation of a serious or life-threatening, preventable or treatable condition) [13.3]</td>
</tr>
<tr>
<td>Who should disclose research results?</td>
<td>Non-paternity should be disclosed by a medical geneticist [2000, para. 75]</td>
<td>Trained professionals [para. 46]</td>
</tr>
<tr>
<td>When should the return of results be discussed?</td>
<td>When obtaining consent [2002, gl. 16; 2003, s. 10]</td>
<td>When obtaining consent [2002, gl. 5(7); 2008, gl. 5(7)]</td>
</tr>
<tr>
<td></td>
<td>When obtaining consent [2005, s. 13(2)(v)]</td>
<td>When obtaining consent [2005, s. 13(2)(v)]</td>
</tr>
<tr>
<td></td>
<td>When obtaining consent [2008, s. 27(22)]</td>
<td>When obtaining consent [13.2(c)]</td>
</tr>
<tr>
<td></td>
<td>Prior to testing 2008</td>
<td></td>
</tr>
<tr>
<td>Positions</td>
<td>International</td>
<td>Canadian</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>When should results be communicated?</td>
<td>It may be ethical to disclose the result only once the research has ended, subject to an REB approval [2002, gl. 4; 2008, gl. 4]</td>
<td>TCPS2</td>
</tr>
<tr>
<td>Must parents disclose results to their child?</td>
<td>Parents are guardians of child’s information; Duty to decide to what extent, when and in what form the child be informed about his/her genetic data [2000, para. 51]</td>
<td>CPS</td>
</tr>
<tr>
<td>Should counselling be offered when returning research results?</td>
<td>2000, paras. 84-86; 2002 gl. 7; 2003, s. 11</td>
<td>2005, s. 27</td>
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</table>

POSSIBLY [para. 46]
Table 9 presents a comparison of international and Canadian ethical norms on payments in research.

<table>
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<tr>
<th>Positions</th>
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<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When should payments be discussed?</strong></td>
<td>CIOMS During the informed consent process [2002, gl. 5(6); 2008, gl. 5(6)]</td>
<td>ICH During the informed consent process and in other written information provided to the participants [1996, ss. 3.1.9, 4.8.10(k)]</td>
</tr>
<tr>
<td><strong>Expenses can be reimbursed</strong></td>
<td>CIOMS Travel costs; Lost earnings; Inconvenience; Time</td>
<td>ICH Subsistence costs [2000, s. 2.6.2]</td>
</tr>
<tr>
<td><strong>Parents cannot be paid for the participation of their child</strong></td>
<td>2002 gl. 7; 2008, gl. 7</td>
<td></td>
</tr>
<tr>
<td><strong>Parents/ participants can still be compensated if they withdraw</strong></td>
<td>CIOMS If they withdraw for health purposes, they should be paid as if full participation had taken place; If they withdraw for other reasons, they should be paid in proportion to the amount of participation; If they are excluded for noncompliance, researcher may withhold part or all of the payment [2002, gl. 7; 2008, gl. 7]</td>
<td>ICH “Payments […] should be prorated and not wholly contingent to the completion of the trial by the subject” [1996, s. 3.1.8]</td>
</tr>
<tr>
<td><strong>Payment must be approved by an REB</strong></td>
<td>2002, gl. 7; 2008, gl. 7</td>
<td>1996, s. 3.1.8; 2000, s. 2.6.2</td>
</tr>
<tr>
<td><strong>What constitutes an unacceptable payment?</strong></td>
<td>CIOMS Payments that would persuade the participants to take undue risks or volunteer against their better judgment; Payments that would undermine a person’s capacity to exercise free decision [2002, gl. 7; 2008, gl. 7]</td>
<td>ICH</td>
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</tbody>
</table>
Table 10 presents a comparison of international and Canadian ethical norms on the composition of REBs.

<table>
<thead>
<tr>
<th>Positions</th>
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<td>REBs must be multidisciplinary</td>
<td>WMA 1997, s. 16; 2003, s. 6(b); 2005, s. 19 2002, gl. 2; 2008, gl. 2 1996, s. 1.31 1997, s. 16(iii); 2005, s. 9(2)</td>
<td>6.4</td>
</tr>
<tr>
<td>REBs must be independent</td>
<td>UNESCO 1997, s. 16; 2003, s. 6(b); 2005, s. 19 2002, gl. 2; 2008, gl. 2 1996, ss. 1.31, 3.2.1 1997, s. 16(iii); 2005, ss. 9(1), 10 2008, s. 8</td>
<td>6.2</td>
</tr>
<tr>
<td>Composition of the REB</td>
<td>CIOMS 2002, gl. 2; 2008, gl. 2 1996, ss. 1.31, 3.2.1 1997, s. 16(iii); 2005, ss. 9(1), 10 2008, s. 8</td>
<td>at least five members that should include: “(a) at least two members have expertise in relevant research disciplines, fields and methodologies covered by the REB; (b) at least one member is knowledgeable in ethics; (c) at least one member is knowledgeable in the relevant law (but that member should not be the institution’s legal counsel or risk manager). This is mandatory for biomedical research and is advisable, but not mandatory, for other areas of research; and (d) at least one community member who has no affiliation with the institution.” [6.4]</td>
</tr>
<tr>
<td></td>
<td>ICH 1996, s. 1.31 1997, s. 16(iii); 2005, s. 9(2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CE 1997, s. 16(iii); 2005, s. 9(2)</td>
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<tr>
<td></td>
<td>EC 2008, s. 8</td>
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<tr>
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<td>TCPS2 6.4</td>
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</table>
TABLE REFERENCES:

WHO

WMA
2002: World Medical Association (WMA), Declaration on Ethical Considerations Regarding Health Databases (Washington: 2002) [WMA, Declaration on Ethical Considerations]
2008: World Medical Association (WMA), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (Seoul: 2008) [WMA, Declaration of Helsinki, 2008]

UNESCO

CIOMS

ICH
1996: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice: Consolidated Guidelines E6(R1) (10th June 1996) [ICH, Guidelines E6]
HUGO


OECD

Council of Europe


2005: Council of Europe, Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research (Strasbourg: 2005), [Council of Europe, Additional Protocol on Biomedical Research]

EMEA
2008: European Medicines Agency (EMEA), Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population (Recommendations of the Ad Hoc Group for the Development of Implementing Guidelines for Directive 2001/20/EC Relating To Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use) (2008) [EMEA, Ethical Considerations for Clinical Trials]

TCPS


CIHR
2005: Canadian Institutes of Health Research (CIHR), Best Practices for Protecting Privacy in Health Research (2005), [CIHR, Best Practices].

HC
CCMG/CAGC
2009: Canadian College of Medical Geneticists and Canadian Association of Genetic Counsellors, Joint Statement on the Process of Informed Consent for Genetic Research (2009), [forthcoming] [Canadian College of Medical Geneticists, Joint Statement]

CPS
### APPENDIX 2:

CONSULTATIONS AND COMMENTATORS

**Best Practices for Health Research Involving Children and Adolescents**

**Consultations and Presentations**

2009-2012

<table>
<thead>
<tr>
<th>Location or Organisation</th>
<th>Date</th>
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<tr>
<td><strong>FIRST CONSULTATION</strong></td>
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<tr>
<td>National Council on Ethics in Human Research</td>
<td>February 20, 2010</td>
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<tr>
<td>National Conference</td>
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<tr>
<td>Ottawa, ON</td>
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<tr>
<td>Canadian Bioethics Society</td>
<td>June 9-12, 2010</td>
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<tr>
<td>Kelowna, BC</td>
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<tr>
<td>C17 Meeting</td>
<td>June 10, 2010</td>
</tr>
<tr>
<td>Quebec, QC</td>
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<tr>
<td>Canadian Paediatric Society Annual</td>
<td>June 22, 2010</td>
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<tr>
<td>Meeting (UBC/BC Children’s Hospital)</td>
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<tr>
<td>Vancouver, BC</td>
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<tr>
<td>Meeting of the Canadian Network for the Governance of Ethical Health Research</td>
<td>July 17, 2010</td>
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<td>Involving Humans</td>
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<td>Whistler, BC</td>
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<td>StaR Child Health Summit</td>
<td>September 12, 2010</td>
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<tr>
<td>Vancouver, BC</td>
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<td><strong>SECOND CONSULTATION</strong></td>
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<tr>
<td>Mother, Infant, Child, Youth Research Network (MICYRN) Harmonization Workshop</td>
<td>February 17-18, 2011</td>
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<td>Vancouver, BC</td>
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<td>Alberta Children’s Hospital Conference site: Edmonton</td>
<td>April 11, 2011</td>
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<td>Calgary, AB</td>
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<td>IWK Hospital</td>
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<tr>
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<td>Date</td>
</tr>
<tr>
<td>--------------------------</td>
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<tr>
<td>John Buhler Research Centre University of Manitoba Winnipeg, MB</td>
<td>May 18, 2011</td>
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<tr>
<td>Developing an Integrated Strategy to Support Pediatric and Perinatal Clinical Trials across Canada Eastern Townships, QC</td>
<td>May 29, 2011</td>
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<tr>
<td>SickKids Conference site: McMaster University Toronto, ON</td>
<td>June 2, 2011</td>
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<tr>
<td>Hôpital Ste-Justine Conference sites: Laval University, Sherbrooke University Montreal Children’s Hospital Montreal, QC</td>
<td>August 22, 2011</td>
</tr>
<tr>
<td>Children’s Hospital of Eastern Ontario Conference sites: Laurentian University, Queen’s University Ottawa, ON</td>
<td>August 29, 2011</td>
</tr>
<tr>
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<tr>
<td>CIHR Standing Committee on Ethics</td>
<td>Comments by Teleconference September 2011</td>
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<td>Le Comité universitaire d’éthique de la recherche de l’Université de Montréal (CUÉR) et le Comité de liaison en éthique de la recherche de l’Université de Montréal (CLÉRUM)</td>
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<td>Association pour la recherche au collégial</td>
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<td>Written comments for 3rd Draft (February 2012)</td>
</tr>
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<td><strong>Comité de liaison en éthique de la recherche de l'Université de Montréal (CLÉRUM)</strong></td>
<td>Written comments for 3rd Draft (February 2012)</td>
</tr>
<tr>
<td><strong>Health Canada</strong></td>
<td>Written comments for 3rd Draft (February 2012)</td>
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<tr>
<td><strong>Interagency Advisory Panel on Research Ethics</strong></td>
<td>Written comments for 3rd Draft (February 2012)</td>
</tr>
</tbody>
</table>
INTRODUCTION

2 Ibid., s. 24.
8 World Medical Association (WMA), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, (Seoul: 2008).

GUIDING ETHICAL PRINCIPLES

7 The Nuremberg Code takes this to be a matter for legal determination: “… the person involved should have legal capacity to give consent.”
8 World Medical Association, Declaration of Helsinki, supra note 2.
11 Beauchamp, Biomedical Ethics, supra note 9.
12 CIHR, Tri-Council Policy Statement, supra note 5 Art. 1.1.
13 Belmont Report at 5.
14 Beauchamp, Biomedical Ethics, supra note 9 at 101.
CHAPTER I


8 Ibid. at s. 4.6(b).

9 Ibid.

10 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *Clinical Investigation of Medicinal Products in the Pediatric Population E11* (20th July 2000), s. 2.6.3 [ICH, *Clinical Investigation E11*].


13 Ibid.

14 Ibid.


24 Ibid.


CHAPTER II

3 Council of Europe, ETS, Convention for the Protection of Human Rights and Dignity of the Human Being With Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, no. 164, (Oviedo: 1997) s. 6 [Council of Europe, Convention on Human Rights and Biomedicine]; Council of Europe,
Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research, (Strasbourg: 2005) s. 15 [Council of Europe, Additional Protocol on Biomedical Research].

4 BM Knoppers et al., “Children and Incompetent Adults in Genetic Research: Consent and Safeguards” (2002) 3 Nature Genetics 221.


6 To ease the reading of this document, the term “parents” also refers to legal representative or legal guardian of the child.

7 CIHR, Tri-Council Policy Statement, supra note 5, art. 3.12.

8 Ibid.

9 Ibid.

10 Canadian College of Medical Geneticists and Canadian Association of Genetic Counsellors, Joint Statement on the Process of Informed Consent for Genetic Research (2009), ss. 2, 7 [forthcoming] [Canadian College of Medical Geneticists, Joint Statement].

11 CIHR, Tri-Council Policy Statement, supra note 5, s. 3.2.

12 Ibid. at 33.

13 Ibid., s. 3.8.

14 Ibid.


18 UNESCO, Declaration on Human Genetic Data 2003, supra note 17, s. 16(a).


20 UNESCO, Declaration on Human Genetic Data 2003, supra note 17, s. 16(b).


22 Ibid., art. 5.5.

23 Ibid., Ch. 5 at 56.

24 Ibid., s. 12.3.

25 Ibid., s. 12.3.

26 Health Canada, Draft Guidance for Health Canada – Biobanking of Human Biological Material, Ottawa (2011), art. 2.5.3.2.

27 Ibid.

28 Ibid., art. 5.6, 12.4.

29 Ibid., art. 12.1(c).

32 Health Canada, Draft Guidance for Health Canada – Biobanking of Human Biological Material, supra, note 27 art. 2.5.3.2.
34 Ibid.
37 CIHR, Tri-Council Policy Statement, supra note 5, s. 3.8.
53 21 C.F.R. § 312.21.
56 Ibid.
58 Ibid.
CHAPTER III

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3 EMEA, Ethical Considerations for Clinical Trials, ss. 7, 27.


6 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice: Consolidated Guidelines E6(R1), (10th June 1996), s. 4.8.12 [ICH, Guidelines E6]; EMEA, Ethical Considerations for Clinical Trials, supra note 1, s. 7.1.2.

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5 ICH, Clinical Investigation E11, supra note 3.


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3 Ibid. arts. 5.5, 12.3.
4 Ibid., art. 3.7.

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6 Ibid.
8 CIHR, Tri-Council Policy Statement, supra note 3, Ch. 2B at 23-24.
9 EMEA, Ethical Considerations for Clinical Trials, supra note 3, ss. 11.1, 12.1.
17 EMEA, Ethical Considerations for Clinical Trials, supra note 3, s. 28.
19 Council of Europe, Additional Protocol on Biomedical Research, supra note 11 s. 15(2) (ii).
20 CIHR, Tri-Council Policy Statement, supra note 3, Ch. 2B at 23.
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25 CIHR, Tri-Council Policy Statement, supra note 3, art. 4.6.
27 National Consultative Ethics Committee for Health and Life Sciences (CCNE), Opinion no 73 on Phase 1 Studies in Cancerology, (2002) at 3 [CCNE, Opinion].
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29 Ibid., art. 4.7.
30 T St-Laurent-Gagnon, “Research Involving Children in Palliative Care: Norms and Ethical Dilemma” (Communication presented at the 19th Canadian Bioethics Society Annual Conference, St. John’s, 18 June 2008).
31 CCNE, Opinion, supra note 37, at 12.
32 Ibid., art. 4.7.
34 See s. 1.3.3 at 39, above, for further discussion of this topic.
36 Ibid.
37 G Camirand, Développement d’un protocole d’induction de tolérance immunologique applicable à la transplantation de myoblastes comme traitement de la dystrophie musculaire de Duchenne (PhD Thesis, University of Laval, Faculty of Medicine, 2004) at 5.
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2 Ibid. at 56
3 Ibid.
5 CIHR, Tri-Council Policy Statement, supra note 1, Ch. 5 at 55.
6 CIHR, Tri-Council Policy Statement, supra note 1, Ch. 11A.
7 CIHR, Tri-Council Policy Statement, supra note 1, Art. 5.1.
8 Ibid., art. 13.3.
9 Canadian Institutes of Health Research (CIHR), Best Practices for Protecting Privacy in Health Research (2005) at 75, s. 7.2.1 [CIHR, Best Practices].
11 Ibid. at 25-27; Privacy Commissioner of Canada, Genetic Testing and Privacy, (Ottawa: Minister of Supply and Services Canada, 1995), online: <http://www.privcom.gc.ca/information/02_05_11_e.pdf>.
12 D Avard, T Silverstein, G Sillon & Y Joly, “Researchers’ Perception of the Ethical Implications of Pharmacogenomics Research with Children” (2009) 12 PHG 191 at 199 [Avard, “Ethical Implications”].
19 Ibid.
21 Ibid.
22 Ibid.
23 CIHR, Tri-Council Policy Statement, supra note 1, Chapter 5.
24 Ibid at 169.
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2 Knoppers, “Ethical Duty to Disclose,” supra note 1.


5 Knoppers, “Ethical Duty to Disclose,” supra note 1 at 1173.


7 Council of Europe, Additional Protocol on Biomedical Research, supra note 3, s. 4.14.


10 World Medical Association (WMA), Declaration on the Rights of the Patient, (Lisbon: 1981, revised in 1995 and 2005), s. 7(d) online: <http://www.wma.net/e/policy/l4.htm>.


12 CIHR, Tri-Council Policy Statement, supra note 3, art. 3.4.

13 Ibid.

14 Ibid.


17 CIHR, Tri-Council Policy Statement, supra note 3, art 3.2(f).

18 Ibid., art 13.2.

19 Ibid., art 12.2.
CHAPTER IX


2 Many school districts in Canada now require students to undertake community volunteer activities as part of their academic curriculum.

3 Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2010), art. 3.2(j) [CIHR, Tri-Council Policy Statement].

4 Ibid. at 33.

5 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice: Consolidated Guidelines E6 (R1), (10th June 1996), s. 3.1.8.

6 CIHR, Tri-Council Policy Statement, supra note 3, art. 3.1.


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6 University of British Columbia, Clinical Research Ethics Board (CREB), *Guidance Notes for New Applications for Clinical Ethical Review*, s. 25.2.1, online: <http://rise.ubc.ca/helpCenter/GN/CREB_Guidance_Notes.html#top>.


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2 Regulations Amending the Food and Drug Regulations (1024 – Clinical Trials), R.S.C. 2001, Division 5, C.05.001(b) of research ethics board definition.


4 European Medicines Agency (EMEA), *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population (Recommendations of the Ad Hoc Group for the Development of Implementing Guidelines for Directive 2001/20/EC Relating To Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use)*, (2008), online: <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/ethical_considerations.pdf>, s. 8; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice: Consolidated Guidelines E6(R1) (10th June 1996), s. 3.2.6.


