BEST PRACTICES FOR HEALTH RESEARCH INVOLVING CHILDREN AND ADOLESCENTS

Genetic, Pharmaceutical, Longitudinal Studies and Palliative Care Research

Prepared by

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March 30 2011
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>Apo E 4</td>
<td>Apolipoprotein allele 4</td>
</tr>
<tr>
<td>BRC1</td>
<td>Caenorhabditis elegans BRCA1 orthologue</td>
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<tr>
<td>BRCA1</td>
<td>Breast Cancer 1</td>
</tr>
<tr>
<td>CCNE</td>
<td>National Consultative Ethics Committee for Health and Life Sciences</td>
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<tr>
<td>CE</td>
<td>Council of Europe</td>
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<tr>
<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
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<tr>
<td>CIOMS</td>
<td>Council of International Organizations of Medical Sciences</td>
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<tr>
<td>CRDP</td>
<td>Centre de recherche en droit public</td>
</tr>
<tr>
<td>CREB</td>
<td>Clinical Research Ethics Board of University of British Columbia</td>
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<tr>
<td>DMD</td>
<td>Duchenne muscular dystrophy</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
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<tr>
<td>FAP</td>
<td>Familial Adenomatous Polyposis</td>
</tr>
<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>
<td>National Council on Ethics in Human Research</td>
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<td>N/M</td>
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These Best Practices provide an overview of international and Canadian ethical norms, reflecting the current situation in Canada regarding research involving children. 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).

These Best Practices do not provide an analysis of applicable Canadian and provincial law. Nevertheless, in Guideline II – Consent to Research – the particularities of Quebec law on research were included as individuals under 18 years of age cannot by law provide an informed consent. In addition, the Comparison Tables in Appendix 1 provide detailed information on Canadian and international ethical norms that apply to paediatric research.

These Best Practices do not provide specific guidance for research involving the First Nations, Inuit and Métis peoples of Canada. For research involving these populations, readers should refer to 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-eptc2/chapter9-chapitre9/).
# HOW TO NAVIGATE THE BEST PRACTICES: AREAS OF SPECIAL INTEREST

<table>
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<th>Guideline #</th>
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<td>Juvenile pregnancy</td>
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## Parental authorization

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<td>Parental understanding</td>
<td>2.3.4</td>
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| Confidentiality | Guideline VII |
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| Payment | Guideline IX |
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| Return of results | Guideline VIII |
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For additional information on these topics in the Canadian and international policy context, please see Appendix I, Comparison Tables.
INTRODUCTION
INTRODUCTION

BACKGROUND
Today’s advances in paediatric health research improve the way we understand child health and development and how they are influenced by various factors such as environment and education. Unfortunately, the lack of specific ethical guidelines for health research involving children and adolescents can hamper important research. A major challenge is to ensure advances are achieved in a way that maximizes the benefits, offers special protection for children 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,¹ which influenced the drafting of the 1998 Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS).² TCPS outlines the guiding principles and procedures for research involving humans in Canada as well as additional protections for research subjects who are not legally competent. However, the recently adopted TCPS2 (2010) is limited in the depth and scope that it can devote to any single topic. 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. 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.

Considering the lack of clear and consistent norms on research involving children and the issues that have emerged since the 1993 report, the National Council on Ethics in Human Research (NCEHR) proposed to undertake a two-year project to study the ethical and legal issues of such research and to develop a guidance document for researchers, research ethics boards (REB), and institutions. This project was orchestrated through NCEHR’s Emerging Issues Analysis Committee, and in collaboration with the Canadian Institutes of Health Research’s (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 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.
GOALS OF THE BEST PRACTICES

The Best Practices are intended to update the 1993 Report on Research Involving Children. They also provide approaches to face 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 in the Best Practices that are not settled in 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 research, as it is becoming more common in health-related research. The primary ethical issues raised by qualitative research are more fully addressed in Chapter 10 of 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 research with children, this document would be incomplete without commenting on its use with children and adolescents. Specific issues will be addressed in Guideline I – Inclusion of Children in Research, Guideline II – Consent to Research, Guideline VII – Privacy and Confidentiality, and Guideline VIII – Return of Research Results.

STATEMENT OF VALUES

The Best Practices reflect the values 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, CIOMS’ International Ethical Guidelines for Biomedical Research Involving Human Subjects, and the United Nations Educational, Scientific and Cultural Organization’s (UNESCO) Universal Declaration on Bioethics and Human Rights.
SCOPE OF APPLICATION

Voluntary Guidance in the Canadian Context
The Best Practices are intended as voluntary guidance for the Canadian health research community working with children and adolescents. They are consistent with TCPS2, and are designed to assist in the interpretation and application of TCPS2.

Applicable Legislation and Policy
The Best Practices do not replace existing laws, policies and professional codes of conduct that apply to 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-centered research crossing provincial, territorial or even national borders, differing health and privacy laws and policies may apply.
GUIDING ETHICAL PRINCIPLES
By Lee Black and Glenn Griener
Please note that the Guiding Ethical Principles are currently being revised and will be included in the Best Practices as soon as they are completed.
BEST PRACTICES
10 GUIDELINES IN SUMMARY FORM

I. INCLUSION OF CHILDREN IN RESEARCH

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

II. CONSENT TO RESEARCH

Researchers should obtain the free and informed consent of the competent child or, if incompetent, of his/her parents.

III. ASSENT OF THE CHILD

To the extent possible, researchers should obtain the assent of the child according to his/her level of development and capacities. When the child develops the legal capacity to provide a fully informed consent or attains the legal age of majority, researchers should obtain an informed consent.

IV. DISSENT OF THE CHILD

The dissent of the child, who is capable of understanding, must 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 child or the parents.

VI. EVALUATION OF RISKS AND BENEFITS

The participation of a child 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 children who are the same age or have the same disease, condition or disability, and the child 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 safeguards, subject to applicable law.

VIII. RETURN OF RESEARCH RESULTS

Researchers should broadly disseminate general research results. Individual results should be communicated if they have significant implications for the health of the child. If incidental findings have significant implications for the child, they should also be communicated to the competent child or, if incompetent, to the parents. If feasible, the incompetent child should be informed.

The child and parents should be informed whether data or samples obtained from the child will be anonymized and what impact this will have on the return of results.
Researchers should respect the wish of the child and/or parents regarding the return of research results. However, when the health of the child may directly benefit from the communication of results, researchers may, with REB approval, override a refusal to receive results.

IX. **PAYMENT IN RESEARCH**

It may be appropriate to compensate children 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 and, if appropriate, during the assent 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. At least one member should have 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 guidelines to be considered both by researchers when designing research involving children and/or adolescents and by REBs in the specific areas of genetic research, pharmaceutical research, longitudinal studies and palliative care research. The guidelines 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” also includes legal representative(s) and legal guardian(s). In addition, the use of the term “children” includes adolescents. The specific term “adolescents” is used to indicate minors above the age of 13 or 14 years.

Each guideline chapter is divided into sections. The first section presents an analysis of the guideline topic and discusses the relevant guidance presented by Canadian and international norms. The second section distills this guidance and suggests an approach (in textboxes). The third section of each guideline discusses some of the specific issues that arise in the context of paediatric research. 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 guideline in Appendix 1. These tables compare those documents whose 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 existing federal or provincial laws. Researchers and REBs should always ensure that they respect applicable laws when designing or reviewing research projects involving children and/or adolescents.
GUIDELINE I

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

The Nuremberg Code of Ethics of 1947 did not address the issue of the inclusion of children in research. Indeed, the twentieth century was marked by unfortunate scandals in research involving children, 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 children, it was clear that deliberately harming children for the sake of research ran contrary to existing international and national ethics. In response, several guidelines were established to ensure observance of the rights of children participating in research. However, in an attempt to protect them, children were effectively excluded from research and became “therapeutic orphans”.

The unintended consequence of this exclusion was a lack of data and appropriate medical treatments for children 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 the need to include them in research. Though the need to conduct research involving children and provide guidance with regards to their inclusion is evident, it was not until the 1964 Declaration of Helsinki that the inclusion criteria for children were clearly laid out.

Today, there is consensus in international and Canadian ethical norms regarding the need to include children in research while offering appropriate protection. Guidelines from CIOMS and TCPS2 make research within the paediatric population an explicit obligation based on the notion that it would be “unjust to exclude [children] from the benefits that can be expected from research.” This reflects an important shift in norms related to research involving children.

The inclusion of children in research is subject to specific conditions to ensure their protection. Unanimity exists among international and national norms on the following conditions: children should only be involved when the research cannot be carried out on adults; consent of the parents as well as the assent of the child, when feasible, are required; research should involve no more than minimal risk if there is no prospect of direct benefit to the child; and research must be approved by an REB and satisfy 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 children, or its legality. With respect to the criterion of minimal risk, 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, without providing additional guidance. TCPS2 also allows the inclusion of children in research that involves more than minimal risk (defined in Chapter 2, section B of TCPS2) if it has “the prospect of direct benefits for them.” Thus, it would be possible for children suffering from life-threatening diseases to participate in research that involves more than minimal risk if they can benefit from it (see Guideline VI – Evaluation of Risks and Benefits).

Only a few ethical norms have taken a position on research involving very vulnerable children (e.g. impaired or institutionalized children). Even then, 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.” As for healthy children, their inclusion in research is limited to studies on prevention, vaccine trials or palatability testing (e.g. flavour of medicines).

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

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

Children 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 children 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

- participation of children in research is justifiable when the research cannot be carried out with adults;
- when the participation of children in research is necessary, least vulnerable children (e.g. older or more developed children) should be included first in the project, if possible and scientifically appropriate;
- children should derive a direct or indirect benefit from their participation in research;
- children should not be exposed to more than minimal risk when research does not hold the prospect of direct benefit.

### Healthy Children

- some research might require the participation of healthy children in order to determine, for example, the effect of diet or environmental factors on a genetic predisposition, or the efficacy of a paediatric vaccine;
- least vulnerable children should be considered first;
- the research should not expose the child to more than minimal risk.
GUIDELINE I
INCLUSION of Children in Research

Very Vulnerable Children

- impaired and institutionalized children should not be involved in research unless the research relates directly to their disease or condition;
- least vulnerable children should be considered first;
- abused or institutionalized children should not be included in research unless: 1) the research cannot be carried out with adults or less vulnerable children; 2) the research offers hope of potential benefit to the children concerned; and 3) the research involves no more than minimal risk;
- a child with a life-threatening disease may be included in research only if:
  1. participation offers hope of direct benefit to him/her;
  2. the risks of participation are commensurate with the benefits; and
  3. there is no equivalent alternative.
- a child 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 children with the same life-threatening disease.
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 children in research.

1.3.1 Inclusion of Healthy Children in Research

The inclusion of healthy children may be necessary in research to determine, for example, the normal range in healthy children in order to identify the protein causing celiac disease or to test a new vaccine.\textsuperscript{12} Their participation may also be needed to establish age-appropriate normative values.\textsuperscript{13} However, their inclusion in research raises ethical issues since these children are being exposed to physical and emotional risks or discomforts even though they usually do not benefit directly from the research.\textsuperscript{14}

In 1966, two unethical research studies involving healthy children were denounced.\textsuperscript{15} 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 research was conducted on 26 healthy newborns to determine if ureteral reflux can occur in normal bladder. These children were catheterized and radiographed to examine their bladder.

These two examples of research involving healthy children 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?”\textsuperscript{16} This question is still debated, but a few international and Canadian norms permit inclusion of healthy children if the risks are minimal and if the least vulnerable children (e.g. older children) are considered first.\textsuperscript{17}

1.3.2 Inclusion of Children in Genetic Research

Considering the nature of genetic information and the vulnerability of children, their inclusion in genetic research may be questioned. Genetic research may reveal information that will affect the child throughout life since DNA remains the same as one becomes an adult. Thus, the decision made
by the parents on behalf of the child 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 children in genetic research using experimental therapies, such as gene therapy, also raises important issues (see section 1.3.3). By contrast, the inclusion of children in genetic research may be useful to identify early onset diseases or conditions, such as polycystic kidney cancer. By identifying diseases or conditions for which prevention or treatment is possible, the child’s health and well-being will be improved.

1.3.3 Inclusion of Children in Novel Medical Experimental Therapies

The inclusion of children 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)\(^\text{18}\), gene therapy is still considered experimental, entailing serious health risks for the persons participating in gene therapy trials.\(^\text{19}\) The inclusion of children in such trials raises many ethical and legal issues.\(^\text{20}\) Because of their lack of competence and the potential risks of gene therapy, children 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 children would have increased chances of success.\(^\text{21}\) For example, research on Leber’s congenital amaurosis (a retinal dystrophy responsible for infantile blindness)\(^\text{22}\) conducted with persons aged 17 to 23 has demonstrated that gene therapy would have had more chances of success if conducted on younger children because of the progression of the disease.\(^\text{23}\) This finding raised the question of whether REBs should take into consideration the physiopathological mechanisms of action of gene therapy when deciding if children should be included in such trials. Moreover, would it be ethical to exclude children from gene therapy trials if they stand to benefit the most therefrom?

1.3.4 Lack of Pharmaceutical Data

There is currently a lack of pharmaceutical data on the paediatric population.\(^\text{24}\) Most paediatric drugs are prescribed off-label due to the fact that they have never been formally tested on children.
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Physicians may also extrapolate paediatric dosage from adult data\(^{25}\) even though “children are not small adults.”\(^{26}\) Moreover, there may be variations in maturation within the same age group of children. The absence of age-appropriate formulation of drugs and the lack of data on the efficacy and toxicity of these drugs may expose children to serious harm. CIOMS underscores that, in the past, drugs that had not been tested on children were nevertheless administered,\(^{27}\) exposing them to serious harm in the absence of sufficient knowledge on the safety and efficacy of such drugs. Moreover, developmental stages may influence the efficacy or toxicity of the drug\(^{28}\) because the prescribed drugs are metabolized, extracted or absorbed differently.\(^{29}\) 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.\(^{30}\) Over-the-counter cough and cold medicines have a long history of use in children; however, there is limited evidence supporting 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 children.\(^{31}\) For example, the United States adopted legislative provisions to increase the numbers of drug trials involving children by both offering incentives to manufacturers and by publishing requests for proposals to third parties in case of lack of interest by manufacturers.\(^{32}\) The European Commission also adopted legislative provisions to facilitate and harmonize the conduct of paediatric clinical trials.\(^{33}\) In Canada, two important initiatives were taken 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.\(^{34}\) Second, the *Food and 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.\(^{35}\)
However, the inclusion of children might not be appropriate at all stages of clinical trials. There is a significant difference in the risks undertaken in a Phase I trial, when little is known about the effects of a drug on humans, versus Phase III or IV. As noted above, much of the advocated involvement of children 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 children.

This does not mean, though, that children should never participate in Phase I or II clinical trials. In fact, there are circumstances when it would be appropriate to include children, such as trials for diseases that affect only paediatric populations and the use of adults would yield little or no useful information. Yet, even in these circumstances it is desirable to obtain initial safety and tolerability data from adult studies. Certainly, the risks from participation are still an essential factor to consider, but, as noted above, children should not be automatically excluded from all early phase trials.

1.3.5 Inclusion of Children in Longitudinal Studies

The inclusion of children in longitudinal studies raises “unique ethical issues due to the potentially lengthy period of involvement as research subject” as the data and samples collected during the study will be kept for a long period of time. During this period, the child will grow up, mature and develop the capacity to make informed decisions. Therefore, the involvement of children in the 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 child (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 Children in Palliative Care Research

The inclusion of children in palliative care research raises many ethical questions because of their double vulnerability: 1) they are children; and 2) they are dying. However, there is a lack of pharmaceutical data for children in palliative care and the use of the drugs prescribed for adults in the same situation is not recommended. Thus, physicians are forced to use drugs that have not been tested on children before. In addition, the definition of palliation and palliative care is unclear in the norms. This situation is problematic since it may exclude children from research if they are not
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“classified” as being in palliative care. These examples illustrate the need to include children in palliative care research and to better define what palliative care means. Otherwise, these children may be unjustly excluded from research that may benefit them or the group to which they belong (principle of justice).

As mentioned in Section 1.1, the need to include children in research is widely recognized. There are not always specifications with regard to the categories of children who should be included in research (e.g. healthy children or children with life-threatening illnesses). Each research project involving children should thus be evaluated on a case-by-case basis. However, some organisations have adopted specific guidelines on the participation of children in palliative care research. Thus, they seem to create a special category for children 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 children can participate in palliative care 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 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 children in palliative care research is the potential burden of participation in research. Some authors assert that these children might be asked to take on a bigger burden than other children 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 arising from their participation does not support this finding. Therefore, it would be unjust to exclude them from research on this basis. There may be a need to conduct research to determine the perceptions of the child and parents regarding their participation in palliative care research.

1.3.7 Inclusion of Children in Qualitative Research

Including children 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 a
voice and to help understand, from a child’s viewpoint, their cognitive, emotional, behavioural and health issues.

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

1.3.8 The Uncertainties of Including Children in Research

The discussion in this guideline implies that inclusion of children 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 children are tempered by the recognition that children are still in need of special protection and that inclusion in all types of research is not always appropriate (see Guideline VI – Evaluation of Risks and Benefits). A critical analysis of the inclusion of children advances the Guiding Ethical Principles of concern for welfare and justice. If the exploitation of children in research studies as recent as the mid-20th century gives reason to researchers, REBs and families to revisit the current role of children 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 children in research is presented in Table 1 of Appendix 1.
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CONSENT to Research
2.1 Consent to Research: International and Canadian Contexts

This guideline should be read together with Guideline III, Assent of the Child, and Guideline IV, Dissent of the Child, 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 guideline is divided into four sections. The first section will cover the situation where the child 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 child is impossible. The third section will address the requirements needed to obtain free and informed consent. 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 Child

In Canada, provincial laws differ as to when a child is presumed to be legally competent to provide fully informed consent and this may differ between consent to care and consent to research. Thus, persons under the age of majority may be deemed legally competent 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, which does not depend on a legislatively mandated age for consent. This principle is influenced by the mature minor doctrine used in medical care, which emphasizes the capacity of the child to make informed decisions rather than considering only the age of the child. Such minors are legally considered to have the same competency as competent adults and can provide a free and informed consent to research. Researchers should, therefore, be aware of legal or other guidance in their jurisdiction which determines when children are competent to consent to research participation.

In Quebec, the doctrine of mature minors does not apply. The age of consent for research is fixed at 18 years old. Thus, parental consent is always required prior to the inclusion of a child in research in Quebec. The assent of the child is also needed, when feasible. Nevertheless, a minor who is fully emancipated (e.g. by marriage) is able “to exercise his civil rights as if he were of full age” and so...
can consent to research even if under the age of 18. Note, however, that the age of consent for medical care is 14 years in Quebec. 

**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, the Best Practices will use the term “consent” in accordance with TCPS2.

Parental consent is required when the child is not deemed competent to provide a fully informed consent. In Quebec, parental consent is always required before including a child in research except in the case of emancipated minors. In addition to parental consent, the assent of the child must be obtained when feasible (Guideline III – Assent of the Child).

**2.1.3 Free and Informed Consent Requirements**

The informed consent of the competent child or, if incompetent, the parents’ is subject to a number of requirements according to international and Canadian norms on ethical research involving human subjects. These requirements 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 child or the parents before inclusion in research. They are also in agreement on its characteristics. Indeed, 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).

There is agreement on a list of core elements to be discussed and included in the consent process, which ensures 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 to the participant and family. As for 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 mentioned in the consent form. In the context of longitudinal studies using biobanks, the future research uses, storage and destruction of data and/or samples, and ownership of the samples should also be mentioned. Moreover, 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. Finally, and most importantly, the best interests of the child should be taken into consideration. Usually, it is held that parents are the best persons to determine what is in the best interest of their child.

International norms as well as Canadian norms state that information should be given in understandable language. Researchers must 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, or if a written consent is contrary to local custom. If this situation occurs, verbal consent is possible but must be documented and witnessed. 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 how it is documented. 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.

Researchers should also ensure that the competent child or the parents 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 subjects. 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
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“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 needs to 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 children and/or their parents. Consent should be renewed when: 1) significant changes arise in the research; 2) new information is available and may affect the willingness of the participant to stay in the research; or 3) participants are involved in a long-term research project.

In the case of research in emergency health situations, research may be carried out 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.”

When the competent child regains capacity or when the parents are found in the case of an incompetent child, their informed consent to continue the participation in research should be promptly obtained. Note that there is no similar provision for research in emergency health situations in Quebec.

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

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

In the context of databases and biobanks, some organizations are in favour of optimizing the use of the data and samples to ensure progress in research. For example, the European Society of Human Genetics specifies that “[t]he 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.”¹⁷ 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 of secondary use research. Though a number of these norms specifically permit use of tissue or data beyond the original purpose if previously consented to¹⁸—and even with no consent if tissue or data are anonymized or de-identified¹⁹—others are not as clear. For example, WMA states that “data […] must be used only for the purposes for which authorization has been given.”²⁰ This does not speak directly to secondary use, but implies that if consent was provided for additional uses of data, such use is permissible. Even less clear is UNESCO, which prohibits uses that are incompatible with the original consent.²¹ A contrario, this means that a secondary use studying the same condition would be permissible.²² It would also be possible for public health purposes without consent since UNESCO explicitly recognizes public health needs as an exception.²³

TCPS2 discusses secondary use of data and tissues separately. REB approval is required if secondary use of data involves identifying information (i.e. information that can be linked to the research participant).²⁴ In this situation, an REB may require researchers to obtain the consent of the participant concerned or his/her parents.²⁵ It should be noted that these requirements do not apply to personal information that is anonymous, anonymized or coded when the research team does not have access to the code.²⁶ Thus, researchers using coded data without access to the key would not need to seek REB approval for secondary uses. As for previously collected tissue, the consent of the participant or the parents should also be obtained when identification is possible and when secondary use for future unspecified research was unforeseen at the time of the original consent.²⁷ When tissues are anonymized or anonymous and there are no potential harms for the participants, TCPS2 stresses that consent is not needed.²⁸ 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.²⁹ In the case of deceased children, parental consent should be obtained when required.³⁰

To avoid the need to continually seek new consent, some norms suggest using broad consent.³¹ Such consent contrasts with traditional notions of informed consent – a consent for each study that the participant is involved in – in that it permits the continued use of samples and data for new research.
projects without requiring repeated consents from the parents or the child.\textsuperscript{32} Although the possibility of using broad consent in longitudinal studies is currently emerging,\textsuperscript{33} it is not yet recognized as the norm for other types of research.\textsuperscript{34} 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 child or, if incompetent, of his/her parents.

Researchers should obtain the consent of the competent child or parents. 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 child in research, or whether both are required to provide consent. When providing consent on behalf of their child, 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 must 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;
- take into consideration cultural background.

Legally Emancipated and Mature or Capable Minors

Subject to applicable law, such minors can provide a free and informed consent, even where the law does not normally recognize the capacity of a child to consent to research.
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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 child 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 findings with a potential of leading to interventions;
- reasons to terminate the participation;
- possibility of commercialization;
- existence of any actual, potential or perceived conflicts of interest involving the researcher(s) participating in the research;
- source(s) of funding;
- name and general contact information of the researcher(s);
- 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. treatment will be provided free of charge);
- professional background of the researcher(s);
- name of the REB that reviewed and approved the protocol;
- number of participants involved in research;
- disclosure of experimental procedures, if any.
### Secondary Use of Personal Information and Tissues

- when using identifiable information or tissue: REB approval is required;
- REBs may require the consent of the participant or parents;
- if the tissue is anonymized or anonymous and there are no potential harms for the participant, consent is not needed.

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### Process of Consent

- competent child or parents 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 the 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 child or the parents understand the information disclosed in the consent form;
- consent is a continuing process that should be maintained throughout the research project. If there are significant changes in the research, new information that changes the risk of participation becomes available, or the legal status of the participant changes, consent should be renewed.

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### 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.\(^{35}\)
- consent of the competent child or of the parents in the case of incompetent child should be sought promptly to continue the participation in research.
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 results.36 These results may identify conditions for which prevention or treatment may or may not be possible. Results may also have important consequences for the child’s well-being beyond immediate physical health, through possible stigmatization, impaired self-esteem and anxiety.37 Considering the uncertainty of the results, the possibility to prevent or treat the condition identified and the consequences for the child’s life, do parents have the authority to consent to such testing on behalf of their child?38

In the clinical care context, there is a consensus against the use of predictive testing for adult-onset conditions and carrier status testing in children.39 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 child reaches the age of majority or has developed mature decision-making capacities.40 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 child from future harms.41

Although there is concern with genetic testing in the clinical context, testing in research might not raise the same issues because the goal of genetic testing is not primarily 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 child is of the appropriate age. Questions surrounding the disclosure of genetic testing results in research are discussed in more detail in Guideline IX – Return of 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 child may attain capacity to consent while the study is ongoing. Moreover, there may be 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.\(^\text{42}\) 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. It is unclear whether broad consent could fulfill this function as the purpose and methods of future research would not be known. In addition, biobanks accompanying such studies serve as an infrastructure for future biomedical research of an unspecified nature. This is the very function of such infrastructures and thus a broad consent is necessary and honest.

By contrast to longitudinal studies or biobanks, broad consent is not an acceptable approach for other disease-specific studies or clinical trials, as the informed nature of the consent is distorted: “the more general the consent is, the less informed it becomes.”\(^\text{43}\) In this situation, broad consent does not allow the parents to provide a fully informed consent. Yet, one study revealed that even in clinical studies, parents of children 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.\(^\text{44}\)

Another question raised by parental broad consent is whether the growing child will ever have the opportunity to exercise autonomous choice regarding the use of data and/or samples.\(^\text{45}\) At first glance, the use of parental broad consent would seem to deprive the child of the opportunity to exercise autonomy by not allowing his or her ratification of the parental consent at a later date. As noted earlier, children 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 child can be informed throughout the research and the consent of the competent minor should be obtained in order to continue participation or the use of data and samples.\(^\text{46}\)
Finally, it is well recognized in international norms that participants have the right to withdraw from research at any time.\textsuperscript{47} In the context of parental broad consent, will the child be able to exercise this right to withdraw? 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 child to withdraw may not be executable if the child is not informed of the existence of the new study.\textsuperscript{48} A way to overcome this issue would be for researchers to maintain contact with the child. Therefore, the data and/or samples should be coded (i.e. not anonymized or anonymous) in order to re-contact the child. 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” since the donor (i.e. the child) did not consent to the use and storage of data and/or samples.\textsuperscript{49} Accordingly parental broad consent currently may not be permissible for genetic research involving children. 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 and paediatric genetic research is the only avenue to understanding the disease and developing treatment.

### 2.3.3 Parental Consent for a Phase I and II Clinical Trial

Pharmaceutical research also raises the question of whether parents can consent to the participation of their child in a Phase I clinical trial.\textsuperscript{50} 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...”\textsuperscript{51} Thus, there is a low chance that children participating in a Phase I or II 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 children to more than minimal risk. For these reasons, it is unlikely that healthy children will be permitted to participate in the early phases of clinical trials due to the increase in risk. Nonetheless, the inclusion of terminally ill children may be considered for Phase I or II studies since “it can be comparable to the chance of benefit from palliative care or continuation of past therapies that have failed.”\textsuperscript{52} This, however, is not specifically addressed in TCPS2. Children may benefit from the research even if the probability of success is low. Children may also get an indirect benefit through altruism for others. 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.

2.3.5 Informational Entanglement

An issue that has arisen in longitudinal studies is information entanglement, which means that the information collected concerns both the parent and the child (e.g. birth cohort studies). In such a situation, what happens if the parent wants to withdraw and the child wants to continue participation or vice versa? Parental consent is only valid as long as the child does not have the capacity to make independent decisions concerning participation in research. Once an incompetent child becomes a competent minor, any decision should be respected. 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, Secondary Use 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 include all babies. 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. However, their continued storage and use for research raises important ethical questions because parents are not asked for their consent for storage or research. There is currently no unanimity on the question of the need to obtain consent for storage and newborn screening research or other types of research. Some authors state that the explicit
GUIDELINE II
CONSENT to Research

consent of the parents should be required, while others suggest the use of broad consent or a waiver of consent. Due to increasing public debate over this issue, there is an urgent need to elaborate clear guidelines regarding the secondary use of bloodspots and the parental consent.

2.3.7 Parental Consent and Palliative Care Research

It has been demonstrated that children are a vulnerable group because of their lack of capacity. In palliative care research involving children, 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 feel grief and, thus, may not be able to make an objective decision. Moreover, the fact that the researcher is often the child’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 and part of the 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 Palliative Care Research and Therapeutic Misconception

Children and parents involved in palliative care research 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 1 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 child 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."77

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 TCPS2.

A unique ethical challenge in qualitative research using open-ended interviews, in-depth discussions, focus groups, and observation78 is the unpredictable and often unstructured nature of the data collection process. This raises concerns about consent, since to give informed consent participants must be provided with relevant risk information.

Acknowledging the unpredictable nature of these qualitative research methods, researchers using them should build safeguards to warn participants about the risks of overdisclosure and their 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.79

Considering that the researcher in qualitative research aims to gain acceptance, build trust, and foster positive relationships with children, it is important to recognize the ethical issues associated with developing such a relationship between the researcher and the child participant. Moreover, when participating in longitudinal studies for a prolonged period of time, a dependent relationship can develop. In addition, during interviews children may feel that the researcher is the expert, the authority or the counsellor, because of the inequality in power and status between adults and children creates such an atmosphere.80

This imbalance is greatly felt in qualitative research. It is critical that researchers be aware of the amount of influence and power they have over children. For example, researchers need to consider the possible threat to voluntary withdrawal.81 One study has revealed that children believed that investigators would react negatively and be unhappy if they withdrew after the study began.82
GUIDELINE II
CONSENT to Research

When considering the issue of imbalance a number of suggestions have been proposed to minimize power differentials including: using methods that allow children to feel part of the research process; being responsive to children’s agenda; involving children as part of the research team; using group interviews; checking the child's willingness to participate throughout the interview; being aware of non-verbal cues such as body language; rehearsing with children how to decline answering questions or participation; reassuring children that withdrawing is permitted; and during interview situations giving children control over the tape recorder.83

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

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

This guideline should be read together with Guideline II, Consent to Research, and Guideline IV, Dissent of the Child, along with the discussion in TCPS2, sections 3.9 and 3.10. Combined, these 3 guidelines represent the process of recruiting individual children and adolescents into research and ensuring their informed participation.

Subject to provincial law, children are not necessarily presumed to have the required competency to consent to their participation in research. Quebec is the only province that differs from the other Canadian provinces in that a child cannot legally provide informed consent for research until the age of 18 years. For children who are not considered to be legally competent or are not legally emancipated, assent, rather than consent, should be sought. In such situations, most international and Canadian ethical norms acknowledge the importance of including children in the decision-making process and of obtaining their assent. Assent may be defined as the child’s willingness to participate in the proposed research.

The 1989 United Nations’ Convention on the Rights of the Child states that, when children are able to express their own views, they have the right to express those views freely. Furthermore, “the views of the child [must be] given due weight in accordance with the age and maturity of the child.” International and Canadian ethical norms require that researchers obtain the assent of children 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, clinical state of the child or complex research). However, when children regain capacity, 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 children who are developmentally and cognitively challenged and, obviously, to newborns and the very young.

The child’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 consent, neither international nor Canadian ethical norms detail the elements to include in obtaining assent. 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 child. No further guidance is provided for researchers. Therefore, it may
be useful to refer to the elements needed for an informed consent as guidance 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 are important, the assent process should not be as legalistic as the consent process, considering that children have a limited comprehension of the research. In most Canadian jurisdictions, when the child has a level of comprehension similar to a competent adult, consent should be sought. In the case of Quebec, where consent of minors is not possible, the assent process should then become more formal to ensure respect for the growing autonomy of the minor. In such a situation, researchers may use the parental consent form to seek the assent of the child.

When seeking assent, researchers need to take into consideration the child’s age, degree of maturity, developmental stage and intellectual capacities (e.g. children with special needs or learning difficulties). Most paediatric norms regard obtaining assent from 7 year olds for research (as opposed to treatment) to be meaningful. Children 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, entangling the last two age groups. According to the literature, adolescence starts at 14 years of age, although there is not complete agreement on this. Therefore, it can be presumed that the second group would refer to children from 3 years of age to 13 and the last group would be adolescents from 14 years of age to 18.

Information provided in the assent process should be disclosed to the extent allowed by the child’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 concerned. The terms used must be understandable and honest but not deemed to be frightening.

International and national norms do not necessarily require that assent be written. According to the ICH and the European Commission, assent should preferably be written if the child can read and write.
GUIDELINE III
ASSENT of the Child

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

Should the assent form be distinct from the consent form when in writing? Most ethical norms are silent regarding this issue. 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 child. Thus, researchers can explain the research to the child, verbally and in appropriate language, and document the assent on the consent form. When the child has provided a written assent, either on the same form as the consent or on a separate form, a copy of the assent form should be given to him/her as well as to the parents.

Finally, like consent, assent is a continuing process that should be renewed throughout the research project as the child’s capacities or the nature of the research changes. In the context of longitudinal studies, there is a need to continually reassess and renew assent throughout the duration of the research project as the child’s capacities or the nature of the research changes. Also, when children 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, their informed consent should be sought as a condition to their continued participation in the research project.
3.2 General Statement on the Assent of the Child

To the extent possible, researchers should obtain the assent of the child according to his/her level of development and capacities. When the child develops the legal capacity to provide a fully informed consent or attains the legal age of majority, researchers should obtain an informed consent.

Seeking assent in research is justified by 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 child’s maturity, development and capacity. This process allows children 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 child is unable to provide consent, researchers should obtain the assent of the child before involving him/her in research;
- assent is impossible to obtain in some very specific situations, such as:
  - newborns and very young children;
  - developmentally and cognitively challenged children; or
  - clinical state of the child (e.g. coma, unconsciousness).

Elements to Consider When Seeking Assent

Researchers should take into consideration the child’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 who have experience with illness may be more mature than other children).

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);
- compensation; and
- return of research results.
GUIDELINE III
ASSENT of the Child

Information Disclosure

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

Assent Process

- assent should be obtained after the consent of the parents;
- assent should be provided freely (e.g. without parental pressure);
- 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 child can read and write. If impossible, it should be documented and witnessed;
- when provided in writing, a copy of the assent form should be given to the child and the parents;
- if the child 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;
- separate information sheets and consent and assent forms should be used to facilitate comprehension by the child;
- the child should be given:
  - time to provide assent;
  - opportunity to ask questions; and
  - opportunity to discuss participation with others (e.g. parents, relatives, friends, teachers).
- when seeking the assent of a school-aged child, i.e. 6-13, the process should ensure the child’s assent is not unduly influenced by his or her parents;
- 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 significant changes or if the research comes to a point of significant potential burden to the child.

Assent and Majority

- In the course of the research, when the child reaches the legal age of majority or acquires capacity to consent, researchers should, in general, obtain confirmation of the child’s initial decision through fully informed consent. Thus, Guideline II – Consent to Research applies.
Age Groups

Guidelines rarely state explicitly how to adapt the information to the age or capacity of the child. 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 child. Assent should be viewed differently depending on the age group, such as newborns and preschoolers, school-age children, adolescents, and mature minors and legally emancipated minors.

Newborns and Preschoolers
- it is impossible to obtain a meaningful assent (newborns);
- preschoolers (3-5 years) may have some ability to understand some expression of altruism and may be informed to some extent of the research in language adapted to their age, their degree of understanding and their stage of development.

School-age Children (around 7 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 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.
GUIDELINE III
ASSENT of the Child

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 child 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 children to understand. For example, children may not be able to understand terms such as “calories”, “blood sample”, “randomization” or “deoxyribonucleic acid (DNA)”. Moreover, children may not comprehend abstract concepts such as confidentiality or voluntariness. Thus, simplified language that the child 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.” It is also recommended to use an active voice in the assent form to ease the comprehension of the children. 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].”

Some 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 children should have a basic understanding of the elements disclosed during the assent process since they cannot make a fully informed decision. However, according to age, some children (e.g. adolescents, mature minors) may have the capacity to make such a fully informed decision.

3.3.2 Assent of the Child in Longitudinal Studies

Many longitudinal studies begin at the time of a child’s birth or during infancy, 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 child has the capability to assent and, later, consent to ongoing research they should communicate with the child using age-appropriate language, preferably obtaining assent or consent at pre-specified intervals or when additional samples or data are necessary. Such communication may occur several times, as the research follows the child into adolescence and adulthood. At each instance, and where feasible and the child remains identifiable, the assent of the child or the consent of the competent minor could determine continued participation in research or the use of data and/or samples collected.

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

This guideline should be read together with Guideline II, Consent to Research, and Guideline III, Assent of the Child, along with the discussion in TCPS2, sections 3.9 and 3.10. Combined, these 3 guidelines represent the process of recruiting individuals into research and ensuring their informed participation.

4.1.1 Respect for Dissent

Just as refusal is the opposite of consent, dissent is the opposite of assent and may be defined as the opposition of the child to participate in the proposed research. It may be expressed verbally or physically (e.g. crying, resistance). The European Commission recommends documenting the dissent of the child.

Most international and Canadian ethical norms do not provide detailed guidance on the dissent of children, 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 child and his/her parents or legal representative.”¹ But if the child expresses strong and definitive objections, the dissent should then prevail. In Canada, the TCPS2 states that children’s “expression of dissent or signs suggesting they do not wish to participate must be respected”² with no provisions for overriding considerations.

4.1.2 Overriding Dissent

Elsewhere, some norms maintain that overriding dissent is possible in some rare circumstances, although there is no unanimity regarding this question. Indeed, both CIOMS and ICH specify that the dissent of the child may be overridden when: 1) the child 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 child is suffering from a serious or life-threatening disease and dissent would jeopardize his/her welfare.
GUIDELINE IV
DISSENT of the Child

Where 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 child 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 child in research.

Researchers should be aware of differences between Canadian and international ethical guidance—as well as their legal responsibilities—with regards to dissent and whether it can be overridden.
4.2 General Statement on the Dissent of the Child

The dissent of the child, who is capable of understanding, must be respected.

Dissent may be verbal or behavioural (e.g. body movements) and may be expressed at any time during the research. It must be respected even if the parents consented to their child’s participation in the research project.

Dissent During the Research

Objections raised by the child 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.

Overriding Dissent

In Canada, TCPS2 does not contemplate overriding dissent.

In jurisdictions where overriding dissent is possible, it would be on the following grounds:

- the child is too young, too immature, or incapable of understanding; or
- the involvement in research constitutes the only possible intervention and offers hope of benefit for the child according to health care practitioners; or
- if the child is suffering from a serious life-threatening disease, the research shows promise of preserving or prolonging life of acceptable quality and there is no alternative treatment.

Research with Indirect Benefit

The child’s dissent should always be respected with regards to research with indirect benefit.

Mature Minors and Legally Emancipated Minors

Since these minors are competent to provide an informed consent, their decision to not participate in the research should always be respected.

REB Approval

REB approval is needed to override dissent if the dissenting child is:

- capable of making mature decisions; or
- suffering from a serious life-threatening disease that is the focus of the research, and the parents refuse to withdraw their consent.
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 child.

4.3.1 Dissent of the Child in Longitudinal Studies

In longitudinal studies, children may be recruited at an age when they cannot effectively dissent. When a child 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 will compromise the quality of research. However, this is not a sufficient reason to override dissent. Thus, the dissent or withdrawal of the child should be respected, as discussed in this section, in consideration of the child’s increasing autonomy.

4.3.2 Nature of the Dissent of the Child

The majority of the norms analyzed do not provide guidance on the nature of the dissent of the child. Does dissent entail any expression of disapproval on the part of the child? 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 children should be included when possible because it is easier to evaluate their objection. Further research is needed on the concept of dissent to provide clear guidance.

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

Consent of the competent child or parents is a fundamental requirement for participation of research. However, some ethical norms acknowledge that this obligation may be abrogated under very specific and limited conditions.

International and Canadian norms provide examples of research that may justify the absence of consent. 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 child at risk or may compromise the research. In these instances, the child should be informed of the research in the same manner as with assent, while in the case of a competent child, consent should be obtained. In some epidemiological and psycho-social research, such as observational research or studies involving a degree of deception, where explicit consent could create bias in the selection of participants, a departure from the requirement of consent may also be justified. Departures from consent 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, an exception from consent may be possible if the information has been anonymized or if the data is publicly available.

However, to ensure appropriate protection of the population included in the proposed research, a departure from consent is subject to REB approval. When evaluating such a request from researchers, REBs should take into consideration ethical and legal standards, public international law as well as international human rights law. As to the latter, the 1989 United Nations Convention on the Rights of the Child states that the “best interest of the child should 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.” Moreover, according to the Organisation for Economic Co-operation and Development (OECD), the risks to the participants and the respect of the rights and welfare of the participants should be taken into consideration. When parental consent would normally be required, researchers and REBs should consider whether parental knowledge of the research could actually put the child at risk (for intimidation or other type of abuse, for instance).
In Canada, 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 the access to the information in time, 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 child or the parents.

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.

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Exceptional Circumstances Allowing Departure From Consent

Exceptional circumstances that may allow a departure from consent include:

- child is the victim of abuse or neglect;
- child is not living with the parents (e.g. “street kids”);
- research on sexual behaviour, use of recreational drugs or domestic violence;
- psycho-social research (e.g. deception, observational studies), where bias would be possible;
- some epidemiological research (e.g. longitudinal studies, registries, quality assurance);
- research with publicly available data;
- research with anonymized data and/or samples.

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REB Approval

- the following requirements must be met for a departure from consent:
  - research involves not more than minimal risk;
  - the departure is unlikely to adversely affect the rights and welfare of the subjects;
  - 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
  - research does not involve a therapeutic intervention.
- such a departure should be subject to continuing oversight by an REB.

A comparison of international and Canadian ethical norms on the departure from consent is presented in Table 5 of Appendix 1.
GUIDELINE 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 by the overarching principle of ‘concern for welfare’. These principles impose the following ethical obligations: 1) to do no harm; and 2) to maximize possible benefits while minimizing possible harms. Benefit may be defined as “something of positive value related to health or welfare.” 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. Examples of direct and indirect benefits would be, respectively, the improvement of the child’s health, or a 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.” It may affect the child, the family, or even the community. It may also be physical, psychological, legal, social or financial. Risk may vary according to the different age groups. In the calculation of risk, examples of harms to be considered include: the invasiveness of the procedure, the adverse side effects of the drug tested, and the identification of an unwanted gene or condition in a specific community (e.g. Tay-Sachs disease, prevalence of alcoholism).

International and Canadian ethical norms agree on the importance of balancing the risks and benefits before involving human subjects in research. Risks and benefits should be evaluated on the basis of their probability and magnitude. TCPS2 recommends taking into consideration the interests of the persons concerned and the magnitude or seriousness of the risk. The European Commission adds other criteria, such as the duration and the severity of the condition or disease under study.

When research holds out the prospect of direct benefit to the child, there is unanimity on the justification for a child’s participation. However, risks should be justified in light of the anticipated benefits. As mentioned in the Canadian Paediatric Society’s Ethical Issues in Health Research in Children: “[a]llowable risk in therapeutic procedures is commensurate with the prospect of direct benefit.”
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When research does not offer hope of direct benefit to the child, specific requirements apply. First, the proposed research must have a strong chance of contributing to the health of other children in the same age category or with the same disease or condition.\textsuperscript{11} Second, the risk should be “reasonable in relation to the importance of the knowledge to be gained.”\textsuperscript{12} Third, the research should entail no more than minimal risk and burden for the child concerned, and should be no greater than the risk attached to routine medical or psychological examination of the child concerned. 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.\textsuperscript{13}

6.1.2 Minimal Risk

The requirement of minimal risk raises many questions. Minimal risk has been defined 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.”\textsuperscript{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.”\textsuperscript{15} So, while there is an international consensus on the use of ‘minimal risk’, 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 compare to risks faced in research?\textsuperscript{16} Are these the risks related to the practice of a sport, to crossing a street to go to school or to body piercing? Do their 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.\textsuperscript{17}

As well, the risk comparable to that of a routine medical exam is subjective and seems to require an individual analysis for each child. For example, a routine medical exam for a sick child will involve procedures, such as blood drawing, injections or even chemotherapy. In contrast, healthy children may never have been subject to any invasive procedures. This situation raises an important question regarding the participation of healthy children in medical research: does the minimal risk criterion exclude these children from nearly all research that does not offer direct benefit?
Finally, neither international nor Canadian ethical norms mention whether the evaluation of risks and benefits should be evaluated from a child’s perspective. This way of approaching the assessment of risks in research involving children is relevant. Indeed, it may be inappropriate to extrapolate the adult experience to children. For example, a venipuncture is considered to be minimal risk for adults. However, this procedure may cause substantial psychological stress or risk of anxiety for children. Therefore, researchers should think about how a child may perceive the interventions and procedures proposed in order to conduct an appropriate evaluation of the risks. 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.

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. CIOMS provides a few examples to guide researchers, such as additional lumbar punctures and bone-marrow aspirations. 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.

CIOMS provides 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 provided its approval. 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 that 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.” 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.”
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Canada takes a more restrictive – although succinct – approach as to when research with more than minimal risk may take place. TCPS2 permits this research if it has the prospect of direct benefits for participants.27 Unlike CIOMS, overriding scientific or medical rationales are not sufficient to allow the additional risk to children. 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 child 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 children of the same age or with the same disease, condition or disability, and the child should not be exposed to more than minimal risk.

Consideration of Potential Harms

- consideration of potential harms must include harms that are physical, psychological, social or financial; and 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 a child’s perspective.

Justifying Risk

- participation of a child in research should offer hope of direct benefit for the child.
- when the research holds out the prospect of direct benefits, risks should be justified in the light of these anticipated benefits.
- if the child will not benefit directly from the research, he or she should not be exposed to more than minimal risk, which means a risk comparable to that which the child is exposed to in everyday life that relate to the research, or during medical care. “Minimal risk” will vary according to the life experience and medical condition/treatment of the child.

Understanding ‘Minimal Risk’

- 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 child.
- any increased risk(s) should be subject to REB approval.
- in jurisdictions that permits a slight or minor increase above minimal risk, REBs should ensure: “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 that 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”
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 and Benefits in Genetic Research

The evaluation of risks and benefits in the field of genetic research may be influenced by the fact that the information collected is considered especially sensitive. Genetic research may involve not only physical and psychological risks but also psychosocial and economic ones for both children and their families. Researchers, parents and the child 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 children (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.

In addition, 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 ethic committees need to consider the interests of these communities or groups when evaluating the risks and benefits of the proposed research.

6.3.2 Evaluation of Risks and Benefits in Secondary Use of Data/Samples and Longitudinal Studies

If secondary use of data or 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
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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.

6.3.3 Evaluation of Risks and Benefits in Clinical Trials

The inclusion of children in clinical trials is now a broadly accepted necessity in order to meet their health needs. However, this acceptance also acknowledges the varying levels of risk inherent in different phases of clinical trial research. Participation of children in late phase trials (III or IV) is perhaps the most justifiable from a risk perspective. Generally, by these phases the toxicity and efficacy of the drug will be known, at least in adults. Participants in these trials would also include ill children, for whom a higher than minimal risk is appropriate if direct benefit can be expected.

However, addressing the challenge of risk in early phase trials (I or II) is more difficult. These trials will generally, by their nature, have higher than minimal risks. Under TCPS2, these risks preclude the participation of healthy children, although other guidance such as CIOMS suggests that there might be circumstances when their inclusion is possible. TCPS2 does provide for the inclusion of disease-affected children in early phase trials, as they are the only ones who could potentially directly benefit. Left unanswered in the ethical norms, though, is how to balance the risks represented by Phase I or II trials against the potential benefits, of which few can be expected (especially in Phase I).

A potential benefit of participation in clinical trials is access to new drugs. 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.

6.3.4 Evaluation of Risks and Benefits in Palliative Care Research

In palliative care research involving children, particular attention should be paid to the evaluation of risks and benefits since these children are very vulnerable. TCPS2 underscores that “their inclusion in research should not exacerbate their vulnerability.” In addition, to the extent that poor health status could compromise the voluntariness of consent, REBs should carefully consider the ethical obligations toward potential participants in palliative research.
Some authors suggest taking into consideration the quality of life of the child involved in palliative care research.\textsuperscript{36} In its 2002 \textit{Opinion no. 73 on Phase 1 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{37} In addition, the European Parliament’s \textit{Directive 2001/20/EC} specifies that trials involving children should minimize pain, discomfort, fear and any other potential risks related to the disease and the developmental stage of the child concerned.\textsuperscript{38} These two European documents provide additional guidance on the special considerations to look at when the research involves children in palliative care. However, they also demonstrate a need to adapt the international and Canadian criteria to evaluate the risks and benefits related to the participation of children in palliative care research because of their double vulnerability.

6.3.5 \hspace{1ex} \textbf{Evaluation of Risks and Benefits in Novel Medical Experimental Therapies}

As seen in Guideline I – Inclusion of Children in Research, the participation of children in novel medical experimental therapies is controversial.\textsuperscript{39} 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 children suffering from X-SCID\textsuperscript{40} but were also linked to the development of leukemia as well as to the death of an 18 year old boy.\textsuperscript{41} Gene therapy trials have been since considered as experiments involving serious risks. REBs are now reluctant to allow the inclusion of children in such trials because of those risks.

This situation raises the following question: are the current criteria on 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 is no evidence that the child will receive any direct benefits from participation precisely because of the experimental nature of the trial. Thus, it would be evaluated from the prospect of indirect benefits and the minimal risk principle would apply. 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. Children suffering from this disease face imminent death and are generally terminally ill by the age of 17 years.\textsuperscript{42} The
participation of these children in gene therapy trials may be their last hope. It may improve their quality of life by increasing their mobility or improve the quality of life of other children suffering from the same fatal disease.43 However, the application of the minimal risk principle would preclude the participation of these children 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?44 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.45

6.3.6 A Continually Evolving Perception of Allowable Risk

The previous discussion highlights the difficulty of determining appropriate levels of risk for children 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 children is likely to change over time, as it has up to now. For example, the use of children in research such as the Willowbrook study demonstrated a willingness to expose children to a level of risk that is no longer acceptable. Currently, changes in guidelines illustrate further the evolving notions of acceptable risk levels. In both the first and second editions of the Tri-Council Policy Statement, increases over ‘minimal risk’ are permitted only if the child 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 static even if the basic definitions are.

A comparison of international and Canadian ethical norms on the evaluation of risks and benefits is presented in Table 6 in Appendix 1.
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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 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 TCPS2 recognizes that researchers have a duty to identify and minimize privacy risks.5 In Quebec, the Professional Code maintains that “[e]very professional must preserve the secrecy of all confidential information that becomes known to him in the practice of his profession.”6

Important issues of privacy and confidentiality are raised in the specific context of health research. Researchers generally 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. A breach of confidentiality may have important consequences for participants and their families, such as implications for employment or an increase in premiums or denial of insurance. Thus, international and Canadian ethical norms set out mechanisms to ensure the privacy and confidentiality of personal data.

These norms provide guidance on the issue of access to personal information collected by researchers. UNESCO, the Council of Europe and the European Commission state that the 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 concerned. UNESCO adds that disclosure may also 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 (e.g. incompetent child). Furthermore, CIOMS and TCPS2 provide guidance on results of genetic testing by stating that they should be protected from access by third parties (although 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 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 child (e.g. parents, siblings etc.), especially when it relates to inheritable disorders. Although 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 will be 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 to emphasize 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
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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.”

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.

Of all these safeguards for personal information, one of the most important is the coding of data and samples. In its 2007 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories E15, ICH provides guidance to harmonize and facilitate the coding of data and samples. It underscores the four general categories of coding: 1) identified; 2) coded (e.g. single or double coded); 3) anonymized; and 4) anonymous.

1) Identified Data and Samples
Identified data and samples are usually labelled with personal identifiers (e.g. name, social security number). The information collected is directly traceable back to participants. As in the situation of medical care, it is possible for participants to withdraw from the study or to receive individual results.
This category is generally appropriate for individualised diagnostic testing, drug or device testing or for samples within a patient registry.\textsuperscript{11}

2) Coded Data and Samples
These data and samples are provided with at least one specific code and do not carry any personal identifiers. Single coded data and samples are labelled with a single specific code, while double coded data and samples are also labelled with a single specific code, but then relabelled with a second code, which is linked to the first code by a key. In both cases, the principal researcher is responsible for maintaining the coding keys. Coded data and samples are traceable to participants. In the case of double coding, both keys are needed to trace back participants. This category of coding protects personal data and allows participants to receive individual results or to withdraw as they wish.

3) Anonymized Data and Samples
Anonymized data and samples are data and samples that have been initially coded but subsequently deprived permanently of their initial link to participants’ personal identifiers or code. Thus, it is impossible to trace back participants and participants cannot withdraw from the research study or receive individual results.

4) Anonymous Data and Samples
Anonymous data and samples were never labelled with personal identifiers or code when initially collected. These data and samples also cannot be traced back to individuals.
7.2 General Statement on Privacy and Confidentiality

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

### Confidentiality

- the principal investigator and staff authorized to access a child’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 child or, if incompetent, the parents. If feasible, the assent of the incompetent child 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.

### 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. children 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 child may still occur, and the child 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 child or the incompetent child’s parents consented to such disclosure in writing. If feasible, the assent of the incompetent child should be obtained;
- In exceptional circumstances, and subject to the applicable law, researchers may have an obligation to disclose genetic information to the child’s family, despite opposition of the incompetent child or the refusal of the competent child or, if incompetent, of the 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;
- Where there is no legal obligation to disclose, the decision to disclose or not is one of professional ethical judgment;
- The competent child or, if incompetent, the parents should be informed of the consequences that could result from the disclosure of genetic information. The incompetent child should also be informed, if feasible.
- If non-consensual disclosure is necessary, collaboration with the treating physician is recommended to encourage discussion with the child and parents about the family follow-up and the consequences of refusing to communicate the information in question;
- Other than in the exceptions foreseen by law, no genetic information can be transmitted to insurers, employers, educational institutions, or other public institutions, without the consent of the competent child or, if incompetent, the parents. If feasible, the assent of the incompetent child 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 and/or aggregated data.

### Organizational Safeguards

- “There should be ongoing commitment to privacy and continued emphasis of its importance by all involved in the research and the institution/organizational management.
- All involved in the research project should be subject to a pledge of confidentiality.
- Access to personal information should be strictly limited in terms of numbers of persons, for legitimate purposes, and strictly on a realistic need-to-know basis.
- Data-sharing agreements between the researcher/institution and all involved should be signed prior to providing any access to data.
- Consequences for breach of confidentiality, including dismissal and/or loss of institutional privileges, should be clearly stipulated.
- Institutions and organizations housing research projects and archived data should, with ongoing commitment of adequate resources:
  - 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.”
- Access to the information should be limited to authorized researchers and to those responsible for the operation and maintenance of the information;
- Access should be limited to the information needed to conduct the proposed research efficiently.
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**Technological Measures**

- “Encryption, scrambling of data and other methods of reducing the identifiability of data should be used to eliminate unique profiles of potentially identifying information.
- Direct identifiers should be removed or destroyed at the earliest possible opportunity.
- If direct identifiers must be retained, they should be isolated on a separate dedicated server/network without external access.
- Camouflage sampling [...] or other techniques should be used, when appropriate, to prevent researchers from viewing health-related information of eligible individuals prior to gaining their consent.
- Authentication measures (such as computer password protection, unique log-on identification, etc.) should be implemented to ensure only authorized personnel can access data.
- Special protection for remote electronic access to data should be installed.
- Virus-checking programs and disaster recovery safeguards such as regular back-ups should be implemented.
- Where possible, a detailed audit trail monitoring system should be instituted to document the person, time, and nature of data access, with flags for aberrant use and “abort” algorithms to end questionable or inappropriate access.”\(^{13}\)
- Unique identifiers should be assigned to each participant (e.g. coded);
- The principal researcher should be the person in charge of maintaining the link between the code and the information collected;
- Standard Operating Procedures (SOPs) should be implemented.

**Physical Measures**

- “Computers and files that hold personal information should be housed in secure settings in rooms protected by such methods as combination lock doors or smart card door entry, with paper files stored in locked storage cabinets.
- The number of locations in which personal information is stored should be minimized.
- Architectural space should be designed to preclude public access to areas where sensitive data are held.
- Routine surveillance should be conducted.
- Physical security measures should be in place to protect data from hazards such as floods or fire.”\(^{14}\)
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. The fear is that insurers and employers may discriminate against individuals based on their genetic information regardless of phenotypic expression. Children are not excluded from this risk since their research results may potentially follow them for their entire life. Indeed, the DNA of children will stay the same as they become adults. Insurers and employers eventually could use genetic information to decide whether to cover or hire research participants, their parents or siblings. Moreover, educational institutions may also discriminate based on a child’s genetic information. Although this issue remains the topic of international debate, UNESCO acknowledges the importance of protecting individuals from discrimination based on their genetic information.

7.3.2 Confidentiality in Longitudinal Studies

In longitudinal 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. Thus, longitudinal studies raise important issues of privacy and confidentiality, and increased security and governance are the norm. 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. 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 child. In such a situation, who should be told about the pregnancy of the child?

As seen under Guideline II – Consent to Research, a competent child can provide a fully informed consent. When the child is deemed competent, 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 children may be participating at the same time. Thus, the parents would likely be aware of their child’s participation, subject to the child’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 child is deemed incompetent or has not reached the age of majority required to consent to participation (e.g. in Quebec), the question of who should be told about the pregnancy of the child is the subject of debate. Some REBs will choose to disclose the information directly to the parents since the child is incompetent, while others will inform the child 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 sometime 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.”

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GUIDELINE VII
PRIVACY and Confidentiality

With the emergence of 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 E15. As mentioned in Section 7.1, ICH proposes four categories of coding: 1) identified; 2) coded; 3) anonymized; and 4) anonymous. The TCPS2 expands this to 5 categories, essentially creating two separate categories of identifiable information coding for: 1) directly identifiable; 2) indirectly identifiable; 3) coded; 4) anonymized; and 5) anonymous. Thus it may still prove challenging to harmonize the terminology used to describe confidentiality mechanisms.

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 considerable controversy as to 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 children in some circumstances have a right to control the information that will be revealed during the research, it is important to clarify to the child participant and 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.”

A comparison of international and Canadian ethical norms on privacy and confidentiality is presented in Table 7 in Appendix 1.
GUIDELINE VIII
RETURN of Research Results
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 there is an obligation to disclose general research results to participants, whether results are positive or negative. Researchers must provide this information by using language that is clear and understandable to the parents and, if appropriate, the children. 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.5

The majority of the norms analyzed are silent on the disclosure of individual results, as research is the search for generalizable results. Moreover, among those documents that do provide 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 refers to incidental findings, which can be defined as “unexpected findings discovered in the course of research but ‘beyond the aims of the study’.” TCPS2 adds that these findings may have “significant welfare implications for the 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 TCPS2 and UNESCO provide guidance on the disclosure of incidental findings. TCPS2 considers the communication of material incidental findings to be part of the disclosure obligations to participants. Thus, it requires that researchers develop a plan for handling such findings and notes also that incidental findings may trigger legal reporting obligations. UNESCO specifies that non-paternity is an incidental finding, which should be disclosed only to the mother.

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 is the only one to specify that the respect of this right is impossible when the data and samples have been anonymized or when the research did not generate individual results concerning the participants. In addition, participants often have the right to decide not to be informed of their results. UNESCO, the Human Genome Organisation (HUGO) and WHO provide that this right to not know should be extended to the relatives of the participant who may be affected by the results of the research.

This 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 Guideline 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
GUIDELINE VIII
RETURN of Research Results

results should be returned by a trained professional. TCPS2 implies that the researcher should be the one returning the results.\textsuperscript{14} It also adds that s/he may be assisted by a research geneticist in the context of genetic research.\textsuperscript{15} Given the 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, results should be communicated to the competent child or, if incompetent, to the parents. 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{16} There is no guidance on how and when children should be made aware of their results. Therefore, it is left to the researchers to determine when it is appropriate to inform children about their results according to their age and level of maturity. Thus, each case must be evaluated on an individual basis. In this evaluation, researchers must take into consideration the right of the child not to know the results and the uncertain nature of research results.\textsuperscript{17} When research results have not been communicated to the child (e.g. because of age, parents’ refusal to know the results), researchers should offer the disclosure of the research results to the child when s/he reaches maturity or majority.

The return of research results should be discussed during the consent process. During this process, competent children or their parents should be informed about the disclosure of the results of the research (general, individual and/or incidental), their right not to know their results and the situations where it is impossible to return the results (e.g. anonymization) or where their refusal may be overridden. It should also be discussed when the results will be communicated (e.g. during the research, at the completion of the research) and how (e.g. website, letter, personal visit, etc.). Incompetent children 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. Individual results should be communicated if they have significant implications for the health of the child. Incidental findings should also be communicated to the competent child or, if incompetent, to the parents if the findings have significant implications for the child. If feasible, the incompetent child should be informed.

The child and parents should be informed whether data or samples obtained from the child will be anonymized and what impact this will have on the return of results.

Researchers should respect the wish of the child and/or parents regarding the return of research results. However, when the health of the child may directly benefit from the communication of results, researchers may, with REB approval, override a refusal to receive results.

The duty to return the results of research is justified by the principle of respect for persons. The communication of the results also allows transparency of the research by enhancing the dissemination of the research findings.

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

- Individual results should be communicated when they are clinically valid and reliable and where there are significant implications for the health of the participant and either prevention or treatment is available;
- When parents refuse to know the results, researchers should offer the results to the child when s/he reaches maturity or majority;
- When the research involves young children, the information should be disclosed to the parents;
- When the research involves school-age children and adolescents, the information should also be delivered to them in a manner appropriate to their development, level of understanding and degree of maturity;
- When returning such results, counselling should be offered to the parents and, if appropriate, to the child;
- 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;
- There can be no return of results when the data and/or samples are anonymized.

### Communication of Incidental Findings

- Researchers should discuss with potential participants and/or parents the likelihood of incidental findings being discovered in the course of research during the informed consent process;
- The method of disclosure of these findings should be detailed in the consent form;
- If appropriate and possible, incidental findings should be discussed with the incompetent child during the assent process as well as described in the assent form;
- Incidental findings without clear and proximate clinical importance should be discussed with the REB and, if appropriate, offered to the child and/or parents;
- Incidental findings with clear and proximate clinical importance should be disclosed to the child and/or parents;
- In some circumstances, it may be appropriate to disclose sensitive information to the adolescent first (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;
- Non-paternity should be disclosed to the mother only;
- When communicating such findings, counselling should be offered to the child and/or parents.

### Right Not To Know

- Researchers should take into account the right of the child and/or parents not to know the results of the study when they have expressly indicated their wish to not receive individual results;
- Researchers may override the right not to know when there is a need to protect another person’s life or when in the best interests of the child; parents cannot refuse the return of results or incidental findings on behalf of the child when there are significant health implications for the child;
- REB approval is needed to override this right;
- The right not to know can be extended to the relatives of the participants that may be affected by the research results (e.g. genetic research results).
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

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 child’s family have access to the child’s results?18 The answer to this question is unclear in the Canadian context.19 The difficulty lies in the fact that physicians have a duty to maintain confidentiality as well as a duty to prevent harm to other patients and to provide them all with necessary information to make informed decisions about their health.20

Different approaches are suggested in the literature and law to resolve this question: 1) strict confidentiality, where physicians will not disclose any results without the consent of the person concerned; 2) duty to warn, according to which the patient is the family and, therefore, physicians have a duty to warn the relatives of the risk revealed by the results; 3) informed consent, in which physicians 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).21 Thus, physicians should inform patients about the importance that the disclosure of genetic results might have for their relatives and encourage them 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.”22

8.3.2 Disclosure of Incidental Findings in Paediatric Research

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.23 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 if the information should be disclosed to the child and/or the parents. 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 child/adolescent concerned and the parents. They also propose that sensitive information (e.g. pregnancy) should be disclosed first to the child, and serious information (e.g. cancer) first to the parents. Researchers should also take into consideration the will of the parents or the child to limit the information disclosed to one of them. Before disclosing any results to the child and/or parents, researchers should develop a plan for handling clear and proximate information that may be clinically important to the child. Following this step, researchers should communicate their plan to the child and parents. The authors also underscore the importance of researchers having a private discussion with the child to make sure that s/he understands and agrees with the plan proposed.

8.3.3 Disclosure of Research Results in Longitudinal Studies

As seen in Guideline III – Assent of the Child, children 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. As mentioned in Section 8.1, the appropriateness of the disclosure of research results depends on the level of maturity. When deciding to whom research results should be disclosed, researchers should consider the growing maturity of the child concerned. Thus, during the course of the research the information may be offered to different people. When the child attains the capacity to provide informed consent, the research results should be disclosed directly. Moreover, when research results have not been disclosed to the child because of the exercise of the parental right not to know, researchers should offer to disclose these results to the competent minor.

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. There is little guidance on this question. TCPS2 specifies only that the disclosure of incidental findings is included in the obligation of ongoing disclosure of information to participants.
GUIDELINE VIII
RETURN of Research Results

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.”

8.3.5 Return of Research Results in Qualitative Research

Researchers must 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 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.
9.1 Payment in Research: International and Canadian Contexts

There are four types of payments for participation in research. The first is reimbursement. It compensates the parents and the child 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 child for their time and inconvenience. The third is appreciation payment. Researchers may decide to offer a bonus to the child once the research is completed to thank him or her. The fourth type of payment is incentive payment, which encourages the child to participate in research (e.g. enrolment).

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

It should be noted that researchers and participants may view compensation payments as incentives as well, depending on the circumstances of the study and amount of compensation. In addition, the mere availability of research, especially for terminally ill children, might also be viewed as an incentive for participation. This could be due to therapeutic misconception, discussed in greater detail in Guideline 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.

Payments should be discussed during the informed consent process and be stipulated in the consent form. Researchers should explain to the competent child or, if incompetent, to the parents the plan of payment, which includes the methods, amounts, and schedule of payments. None of the norms studied specify if this information should also be communicated to the incompetent child during the
assent process. For the sake of transparency, when the incompetent child is able to assent, payment should be discussed in the assent process as well as in the assent process.

The majority of international and Canadian ethical norms on research involving human subjects provide that expenses related to participation in the research should be reimbursed (e.g. travel costs, subsistence costs). In addition, parents and children may be compensated for lost earnings, inconvenience and time. As for lost earnings, the norms do not provide any 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.

If the child withdraws from the research, CIOMS as well as ICH state that the parents and the child may still be compensated. To that end, CIOMS illustrate three situations: 1) if the competent child or the parents 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 compensation proposed. 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 children should not be punished for the non-compliance of their parents and should receive the payment to which they are entitled.

CIOMS, ICH and TCPS2 state that an REB should 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 persuade the participants to “take undue risks […] against their better judgment” or that would “encourage reckless disregard of risks.”
9.2 General Statement on Payments in Research

It may be appropriate to compensate children 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 and, if appropriate, during the assent process. An REB should review the payment plan proposed.

Types of Payments

- **reimbursement** payments to compensate parents and/or children for their direct expenses related to participation (e.g. transportation, meals, accommodation, babysitters, etc.);
- **compensation** payments to compensate parents and/or children for their time and inconvenience caused to them and their family by participation;
- **appreciation** payments, which are bonuses given to children after their participation to thank them;
- **incentive** payments to encourage the participation of children in research.

Payment Process

- the type of payments offered should be discussed during the informed consent process;
- the payment process should be clearly stipulated in the consent form;
- if incompetent children are able to assent, it should be discussed in the assent process as well as in the assent form;
- when the payment proposed to the incompetent child 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 for time and expenses.

Withdrawal from the Research

- the child should still be entitled to receive the appreciation payment for his/her participation;
- if withdrawing for health reasons, the parents and the child should be paid as if full participation had taken place;
- the parents and the child 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 child should not be punished for the noncompliance of his/her parents and should receive the payment to which s/he is otherwise entitled.
### Elements To Consider When Determining Payment

- what is being paid for (e.g. time, lost earnings, pain, inconvenience, discomfort, expenses related to the research, etc.)?
- who will receive the payment: the child, 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 child 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 payment, the REB should consider the:

- effect of the payments on the scientific or social value of the research proposed;
- possibility that the payments may affect the scientific validity of the research;
- persons to whom the payment is offered to avoid targeting, or under or over recruiting, specific populations;
- possibility that the payment may be considered as a benefit of participation or may minimize the potential risks;
- possibility that the payment may alter the risk perception of the children 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 children.

9.3.1 Disclosure of Appreciation Payment to the Child

There is currently a debate as to when appreciation payments should be disclosed to the child. 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 child. 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 as well as during the assent process. However, it should not prevent researchers from offering non-monetary payment to children 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 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 child or the parents 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 children in research is also 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 fear that such a payment may “distort parent’s or children’s decision making.” However, 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 child and/or the parents subject to an REB approval. The REB must ensure that the incentive payment is justified and ethically acceptable. This should be done on a case-by-case 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 do not provide any guidance on how parental lost earnings should be compensated. 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. However, compensation cannot be based on individual parental wage. 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*. 
GUIDELINE 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 professionals of differing expertise within medicine and research as well as non-medical members. They should also be independent. According to 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. 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 children should have a paediatric expertise. If members do not have such expertise, CIOMS and TCPS2 suggest nominating ad hoc members with an expertise in paediatrics (e.g. experience in paediatric care or in paediatric clinical trials).

Finally, CIOMS and the European Commission recommend the inclusion of a child 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. At least one member should have 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 that 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.5

- 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 an expert in the field, on an ad hoc basis;
- if possible, a children’s representative should sit as a member if the REB frequently reviews protocols involving children and adolescents.

A comparison of international and Canadian ethical norms on payments in research is presented in Table 10 of Appendix 1.
APPENDIX 1: COMPARISON TABLES

Legend:
Rows: Positions on major themes of paediatric research

Columns: international institutions/bodies (exception being TCPS2)
- 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 of the normative documents can be found following Table 10.
Table 1 presents a comparison of international and Canadian ethical norms on the inclusion of children in research.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WMA</td>
<td>UNESCO</td>
</tr>
<tr>
<td>Children should be included in research</td>
<td>2008, s. 27</td>
<td>2005, s. 7; 2003, ss. 8(b)-(d); 1997, s. 5(e)</td>
</tr>
<tr>
<td>Necessary to promote the health of the paediatric population</td>
<td>2008, s. 27</td>
<td>2005, s. 7(b); 2002, gl. 12</td>
</tr>
<tr>
<td>Type of research cannot be performed on legally competent adults</td>
<td>2008, s. 27</td>
<td>2005, s. 7(b); 2002, gl. 19(c)(i)</td>
</tr>
<tr>
<td>Child’s consent or parents/legal representative’s permission obtained</td>
<td>2008, s. 27</td>
<td>2005, s. 7(a); 2002, gl. 19(c)(ii)</td>
</tr>
<tr>
<td>Assent obtained from child to the extent of her capabilities</td>
<td>2008, s. 28</td>
<td>2005, s. 7(a); 2002, gl. 19(c)(ii)</td>
</tr>
<tr>
<td>Older children to be included first</td>
<td>2002, gl. 14; 2008, gl. 14</td>
<td>REB approval; Expert advocate opinion may be required [2002, gl. 14; 2008, gl. 14]</td>
</tr>
<tr>
<td>Research may involve very vulnerable children</td>
<td>2008, s. 18</td>
<td>Palatability testing; Prevention trials; Vaccine trials [2008, s. 15]</td>
</tr>
<tr>
<td>Research can involve healthy children</td>
<td>2008, s. 18</td>
<td>Not prohibited by law; REB approval for non-therapeutic research; Direct benefit for the group of children represented; Essential to validate adult data; Relates directly to a clinical paediatric condition [s. 6.1]</td>
</tr>
<tr>
<td>Additional elements</td>
<td>Benefit to the community; benefit to category of persons from which the subject is drawn [2002, gl. 12]</td>
<td>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)]</td>
</tr>
</tbody>
</table>
Table 2 presents a comparison of international and Canadian ethical norms on consent to research.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent must be free and informed</td>
<td>WMA: 2008, ss. 24, 27; UNESCO: 2003, ss. 8(a), (b); CIOMS: 2002, gl. 11, 12, 19(b), (c)(i); ICH: 2002, gl. 4, 5, 14; 2008, gl. 4, 5, 14; HUGO: 1996, ss. 4.8, 4.8.3, 4.8.10(m); 2000, ss. 2.6.2, 2.6.3</td>
<td>TCPS2: 2008, ss. 5.6, 6.1; ICH E11 Addendum: 3.1(a), 3.2; CCMG/CAGS: s. 7</td>
</tr>
<tr>
<td>Aims, goals, methods and/or procedures</td>
<td>2008, s. 24; 2002, g. 5(9)-11; 2008, g. 5(9)-11</td>
<td>2008, ss. 6.1, 27(1), 27(6)</td>
</tr>
<tr>
<td>Duration of the participation</td>
<td>2002, g. 5(5); 2008, g. 5(5)</td>
<td>2008, s. 27</td>
</tr>
<tr>
<td>Understandability</td>
<td>2005, s. 6(2)</td>
<td>2005, s. 13(2)(i)</td>
</tr>
<tr>
<td>Potential risks and benefits</td>
<td>2002, g. 5(9); 2002, g. 5(9)-11</td>
<td>2008, ss. 5.6, 6.1, 27(9)-10, 27(13)</td>
</tr>
<tr>
<td>Right to withdraw</td>
<td>2003, ss. 6(d), 7; 2005, s. 6(2)</td>
<td>2008, s. 6.5</td>
</tr>
<tr>
<td>Protection of privacy &amp; confidentiality</td>
<td>2002, g. 5(2); 2002, g. 5(2)</td>
<td>2008, s. 27(16)</td>
</tr>
<tr>
<td>Participant access to info. &amp; results</td>
<td>2002, g. 5(7); 2008, g. 5(7)</td>
<td>2008, s. 27(22), 24</td>
</tr>
<tr>
<td>Third-party access to info.</td>
<td>2002, g. 6.1</td>
<td>2005, s. 13(2)(vi)</td>
</tr>
<tr>
<td>Possibility of commercialization</td>
<td>2002, g. 5(20); 2008, g. 5(20)</td>
<td>2005, s. 13(2)(vii)</td>
</tr>
<tr>
<td>Source(s) of funding</td>
<td>2002, g. 5(17); 2008, g. 5(17)</td>
<td>2008, s. 27(23)</td>
</tr>
<tr>
<td>Compensation (for participation or in case of)</td>
<td>2002, g. 5(6), 23, 24, 7; 2008, g. 5(6), 23, 24, 7</td>
<td>2005, s. 13(2)(vi)</td>
</tr>
</tbody>
</table>

Consent must be free and informed:
- 2008, ss. 24, 27
- 2005, ss. 6, 7(a); 2002, gl. 11, 12, 19(b), (c)(i)
- 2002, gl. 4, 5, 14; 2008, gl. 4, 5, 14
- 1996, ss. 4.8, 4.8.3, 4.8.10(m); 2000, ss. 2.6.2, 2.6.3
- 1995
- Annotations at para. 31

Aims, goals, methods and/or procedures:
- 2008, s. 24
- 2002, g. 5(3); 2008, g. 5(3)
- 1996, ss. 4.8.10(b), 4.8.10(d)
- 1995
- 1997, s. 5, 2005, ss. 13(2)(i), 16
- 2008, ss. 6.1, 27(1), 27(6)
- 3.2(b)
- s. 7(i)

Duration of the participation:
- 2002, g. 5(5); 2008, g. 5(5)
- 1996, s. 4.8.6; 2000, s. 2.6.3
- 1995
- ss. 4.3
- 2005, s. 13(1)
- 2008, s. 27
- 3.2(b)
- s. 7

Understandability:
- 2005, s. 6(2)
- 2002, g. 5(5); 2008, g. 5(5)
- 1996, s. 4.8.6; 2000, s. 2.6.3
- 1995
- ss. 4.3
- 2005, s. 13(1)
- 2008, s. 27
- 3.2(b)
- s. 7

Potential risks and benefits:
- 2002, g. 5(9)-11; 2008, g. 5(9)-11
- 1996, ss. 4.8.10(g)-(h)
- 1995
- ss. 4.1, 4.13, annotations at para. 35
- 2002, s. 4(a)
- 2008, s. 27(9)-(10), 27(13)
- 3.2(c)
- s. 6.2
- s. 7(ii)

Right to withdraw:
- 2003, ss. 6(d), 7; 2005, s. 6(2)
- 2002, g. 5(2); 2008, g. 5(2)
- 1996, ss. 4.8.10(m); 2000, s. 2.6.3
- 2002, s. 4(a)
- 2008, s. 27(9)-(10), 27(13)
- 3.2(d)
- s. 7(iv)

Protection of privacy & confidentiality:
- 2002, g. 14
- 2002, g. 5(14)-(15); 2008, g. 5(14)-(15)
- 1996, s. 4.8.10(o)
- 2002, s. 4(c)
- 2008, s. 27(16)
- 3.2(i)
- s. 7(v)

Participant access to info. & results:
- 2002, g. 5(7); 2008, g. 5(7)
- 1996, s. 4.8.10(n)
- 2005, s. 13(2)(vi)
- 2008, s. 27(22), 24
- 3.2(i)

Third-party access to info.:
- 1996, s. 4.8.10(n)
- s. 7.F, annotations at para. 69
- 3.2(i)

Possibility of commercialization:
- 2002, g. 5(20); 2008, g. 5(20)
- 2008, g. 5(20)
- s. 4. H, 9.D, annotations at para. 35, 45
- 2005, s. 13(2)(vi)
- 3.2(e)
- s. 7(x)

Source(s) of funding:
- 2002, g. 5(17); 2008, g. 5(17)
- 2002, g. 5(20); 2008, g. 5(20)
- 2005, s. 13(2)(vii)
- 2008, s. 27(23)
- 3.2(b)
- s. 7(vi)

Compensation (for participation or in case of):
- 2002, g. 5(6), 23, 24, 7; 2008, g. 5(6), 23, 24, 7
- 1996, ss. 4.8.10(j), (k)
- 2005, s. 13(2)(vi)
- 2008, s. 27(5)
- 3.2(j), (k)
<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WMA</td>
<td>UNESCO</td>
</tr>
<tr>
<td>adverse events)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject’s responsibilities</td>
<td>1996, s. 4.8.10(c)</td>
<td></td>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Reasons to terminate the participation</td>
<td>1996, s. 4.8.10(r)</td>
<td></td>
</tr>
<tr>
<td>Contact info. for questions and/or complaints</td>
<td>1996, s. 4.8.10(q)</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>Consent should be written</td>
<td>2002, s. 3(3); If not possible, oral consent must be documented and witnessed [2008, s. 24]</td>
<td>Except if there are cultural reasons [2002, gl. 11(b)]</td>
</tr>
<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>
</tr>
<tr>
<td>Positions</td>
<td>International</td>
<td>Canadian</td>
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</tr>
<tr>
<td>WMA</td>
<td>UNESCO</td>
<td>CIOMS</td>
</tr>
<tr>
<td>Consent not required for secondary use of non-identifiable data and/or tissue</td>
<td>[2002, gl. 4, 6; 2008, gl. 4, 6]</td>
<td></td>
</tr>
<tr>
<td>Secondary use of data and/or tissue must be limited to purposes compatible with original consent, otherwise new consent is required</td>
<td>2008, ss. 24, 25</td>
<td>2002, gl. 18; 2003, s. 16(b)</td>
</tr>
<tr>
<td>Secondary uses should not inhibit patients from confiding information for their own health care needs, exploit vulnerability or inappropriately borrow on</td>
<td>If consent is impossible, impracticable or would threaten the validity of the research, REB approval is required [2008, s. 25]; Unless the use corresponds to an important public interest reason [2003, s. 16(a)]</td>
<td>Participants have right to decide about future use [2008, gl. 5(19)] Unless: minimal risk; rights or interests of the patients violated; research is designed to answer an important question; consent is impracticable [2008, g1s. 4, 5(18), 24]</td>
</tr>
<tr>
<td>Other issues to be raised regarding secondary use of data and/or tissue</td>
<td>“secondary uses should not inhibit patients from confiding information for their own health care needs, exploit vulnerability or inappropriately borrow on</td>
<td>Informed consent required when collecting for future epidemiological research, including foreseeable uses whether known or undefined [2008, gl. 24]</td>
</tr>
<tr>
<td></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>UNESCO</td>
<td>CIOMS</td>
</tr>
<tr>
<td>trust&quot; [2002, s. 6]</td>
<td>annotations at para. 41</td>
<td>Biobank could consider a consent that permits specimens/data to be used to address unforeseen research [s. 4.6, annotations at para. 27]</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Cultural background should be considered</td>
<td>2002, intro, gls. 2, 4; 2008, intro, gls. 2,4</td>
<td>1995; 1998</td>
</tr>
<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 investigator's</td>
</tr>
<tr>
<td>Positions</td>
<td>WMA</td>
<td>UNESCO</td>
</tr>
<tr>
<td>-----------</td>
<td>-----</td>
<td>--------</td>
</tr>
<tr>
<td>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]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.8.10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfer; Disposal techniques [4.D, annotations at para. 36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disclosure of information that may affect the willingness of the participant [3.2(d), 3.3, 11.8]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental findings [3.4, 12.2(g)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linkage of tissue with participant info [12.2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Table 3** presents a comparison of international and Canadian ethical norms on the assent of the child.

<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>Assent required</td>
<td>2008, s. 28</td>
<td>2002, gl. (c)(ii); 2003, s. 8(c); 2005, s. 7(a)</td>
</tr>
<tr>
<td>Assent alone is insufficient to permit participation</td>
<td>2008, s. 28</td>
<td>2003, s. 8</td>
</tr>
<tr>
<td>Elements to include in assent information sheet and/or form</td>
<td>Nature of the research; Risks and consequences [2002, gl. 19(b)]</td>
<td>Study information; Right to decline to participate; Right to withdraw at any time [2000, s. 2.6.3]</td>
</tr>
<tr>
<td>Elements to consider in the assent process</td>
<td>Age appropriate information [2002, gl. 19(a)]</td>
<td>Child’s maturity</td>
</tr>
<tr>
<td>How should the information be disclosed?</td>
<td>Age appropriate information [2002, gl. 19(a)]</td>
<td>To the extent of the child’s maturity and intelligence [2002, gl. 14; 2008, gl. 14]</td>
</tr>
<tr>
<td>Should assent and consent forms be separate?</td>
<td>Not necessarily [2000, s. 2.6.3]</td>
<td>YES [2008, s. 7]</td>
</tr>
<tr>
<td>Assent must be renewed</td>
<td>When child becomes capable of independent informed consent [2002, gl. 14; 2008, gl. 14]</td>
<td>2008, s. 7</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>TCPS2</td>
</tr>
<tr>
<td>CIOMS</td>
<td>ICH</td>
<td>EC</td>
</tr>
<tr>
<td>CE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Age groups**

**Age of assent may vary in provinces or states:**
- Children can understand the implications of informed consent and go through the process;
- Children over the age of 12 or 13 years can understand what is necessary to give their assent;
- Emancipated or mature minors can provide a free and informed consent [2002, gl. 14; 2008, gl. 14]

**Age of assent is to be determined by REBs or be consistent with applicable law:**
- Emancipated or mature minors can provide a free and informed consent [2000, 2.6.3]

**Age of assent is to be determined by REBs or be consistent with applicable law:**
- Children of 3-4 years can understand some expression of altruism;
- Children of 6-7 years can provide a meaningful assent;
- Children of 9 years may understand risks and benefits;
- Adolescents have the capacity to make adult decisions in many other areas of life and have an emerging capacity for independent decision-making [2008, s. 7.1]

**Emancipated minors can provide a free & informed consent [2008, s. 6.1]**
Table 4 presents a comparison of international and Canadian ethical norms on the dissent of the child.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissent should be respected</td>
<td>WMA: 2008, s. 28; UNESCO: 2002, gl. 19(c)(iii); CIOMS: 2002, gl. 14; ICH: 2000, ss. 2.6.3, 2.6.5; EC: 2008, ss. 7, 7.1.3, 7.2</td>
<td>ICH E11 Addendum: 3.10</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>NO Prospective participant’s dissent will preclude his/her participation; The prospective participant’s expression of dissent must be respected [3.10]</td>
</tr>
<tr>
<td>Is REB approval needed to override child’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>YES Strong and definitive objection from the child should be respected [2008, s. 7.2]</td>
<td></td>
</tr>
<tr>
<td>Must dissent be written?</td>
<td>Not necessarily; The response of the child should be documented [2008, s. 7]</td>
<td>NO Dissent may be expressed verbally or physically [3.10]</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>Departure from consent is possible</td>
<td>WMA 2002, s. 18; 2008, s. 25, UNESCO 1997, s. 9, CIOMS 2002, gl. 14; 2008, gl. 14, HUGO 1995, OECD s. 4.5, TCPS2 3.7</td>
<td></td>
</tr>
<tr>
<td>Departure is subject to REB approval</td>
<td>WMA 2002, ss. 17, 18; 2008, s. 25, UNESCO 2003, ss. 6(b), 16(b), CIOMS 2002, gl. 14; 2008, gl. 14</td>
<td>if possible and appropriate, children and parents/legal representative will be provided with additional pertinent information after participation</td>
</tr>
<tr>
<td>Elements to consider to approve a departure</td>
<td>National legal requirements [2002, s. 18], Respect of: 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)], If parental knowledge may place the child at some risk of questioning or intimidation by his/her parents [2002, gl. 14; 2008, gl. 14], If research with identifiable material: Minimal risk; Use of publicly available data; Consent would be impracticable [2008, gl. 4], REBs should consider: 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>
<td>Applicable laws or ethical principles in the jurisdiction [annotations at para. 27], No more than minimal risk, Unlikely to adversely affect the welfare of children, Research could not practicably be carried out without the departure from consent, Does not involve a therapeutic intervention [3.7(e)]</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>2008, ss. 18, 20</td>
<td>2008, ss. 11.1, 12.1</td>
</tr>
<tr>
<td>Nature of the risks and/or benefits</td>
<td>1997, s. 5(e); 2005, s. 20</td>
<td>2005, s. 7(b)</td>
</tr>
<tr>
<td>WMA</td>
<td>2002, gls. 8-9; 2008, gls. 8-9</td>
<td>1997, ss. 17(1)(ii), 17(2); 2005, ss. 6(1), 15(1)(i)</td>
</tr>
<tr>
<td>UNESCO</td>
<td>1996, s. 2.2; 2000, s. 2.6.4</td>
<td>2008, ss. 11.1, 12.1</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Direct</td>
<td>Direct; Research has no potential to produce results of direct benefit to the health of the person concerned [1997, s. 17(2)(ii); 2005, s. 15(2)]</td>
</tr>
<tr>
<td>ICH</td>
<td>Intervention/procedures that hold out the prospect of direct [...] benefit</td>
<td>Physical Psychological Social Immediate Delayed [2008, s. 11.1]</td>
</tr>
<tr>
<td>HUGO</td>
<td>Intervention/procedures that do not hold out the prospect of direct [...] benefit</td>
<td>Direct benefit for the individual Direct benefit for the group The term &quot;indirect benefit&quot; is not used [2008, s. 11.1]</td>
</tr>
<tr>
<td>CE</td>
<td>Beneficial interventions</td>
<td>Societal/general [ch. 2B at 22]</td>
</tr>
<tr>
<td>EC</td>
<td>Non-beneficial interventions [2002, gls. 8-9; 2008, gls. 8-9]</td>
<td></td>
</tr>
<tr>
<td>TCPS2</td>
<td></td>
<td>2.9</td>
</tr>
<tr>
<td>ICH E11 Addendum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WMA</td>
<td>UNESCO</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(c); 2005, s. 7(b)</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>Minimal risk and minimal burden</td>
<td>Benefit to children in the same age category or afflicted with the same</td>
</tr>
<tr>
<td></td>
<td>Research is intended to contribute to the health benefit of other persons in</td>
<td>disease, disorder or condition;</td>
</tr>
<tr>
<td></td>
<td>the same age category or with the same genetic condition</td>
<td>Minimal risk and minimal burden;</td>
</tr>
<tr>
<td></td>
<td>Subject to the conditions prescribed by law</td>
<td>Importance of the knowledge to be gained;</td>
</tr>
<tr>
<td></td>
<td>Such research is compatible with the protection of the individual’s human</td>
<td>Severity of the disease or condition;</td>
</tr>
<tr>
<td></td>
<td>rights [1997, s. 5(e); 2005, 7(b)]</td>
<td>Commonality of the disease or condition under study;</td>
</tr>
<tr>
<td></td>
<td>No more likely and not greater than the risk attached to routine medical or</td>
<td>Likelihood of obtaining results from the research;</td>
</tr>
<tr>
<td></td>
<td>psychological examination of the children concerned</td>
<td>Usefulness of benefits obtained [2008, ss. 12-12.1]</td>
</tr>
<tr>
<td></td>
<td>Risk is justified in relation to the expected benefits to society</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk is reasonable in relation to the importance of the knowledge to be</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gained [2002, gls. 8-9; 2008, gls. 8-9]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1996, s. 4.8.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If significant improvement in the scientific understanding of the condition,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>disease or disorder;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benefit to other persons in the same age category or afflicted with the</td>
<td></td>
</tr>
<tr>
<td></td>
<td>same disease, disorder or condition;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimal risk and minimal burden [1997, s. 17(2); 2005, ss. 6(2), 15(2)]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimal risk [4.6(b),(c)]</td>
<td></td>
</tr>
</tbody>
</table>

**Can children participate in research that offers indirect benefits?**

2008, ss. 17, 18

1996, s. 4.8.14
<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>Elements to consider to approve an increase above minimal risk</td>
<td>Existence of an overriding scientific or medical rationale</td>
<td>Approval of an REB</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>Must privacy/confidentiality be protected?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMA</td>
<td>UNESCO</td>
<td>CIOMS</td>
</tr>
<tr>
<td>Access to the information collected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unauthorized or inappropriate use of health information should be avoided [2002, s. 14]</td>
<td>Participants should have access to their data unless: Drug regulation authorities (e.g. Health Canada)</td>
<td>Access for trial related monitoring, audits, REB review, and regulatory inspection. [1996, ss. 5.15, 6.10]</td>
</tr>
<tr>
<td>Patients should have access to the audit record of their own information [2002, s. 15]</td>
<td>Limited access by law (e.g. interest of public health) [2003, s. 13]</td>
<td>Sponsors for audit [2002, gl. 8; 2008, gl. 8]</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>2000, para. 52</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>UNESCO</td>
<td>Important public interest reason [2000, para. 64; 2003, s. 13]</td>
<td>When there are legal or ethical obligations (e.g. children in need of protection)</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Public health purposes [2000, para. 64]</td>
<td>To protect the health, life or safety of the participants or third parties [5.1]</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>Communicable diseases; Child abuse or neglect [2002, gl. 18; 2008, gl. 18]</td>
<td></td>
</tr>
<tr>
<td>OECD</td>
<td>Authorized by law; With the consent of the participant [1998]</td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>If required by law [s. 7.F]</td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>Participant provided an informed consent [2000, paras. 39, 63; 2003, s. 14(b)]</td>
<td></td>
</tr>
<tr>
<td>TCPS2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIHR</td>
<td>Data is anonymized[2000, paras. 63, 64]</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 the consent of the participant [1998]
- Authorized by law; With the consent of the participant [1998]
- If required by law [s. 7.F]
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Safeguard measures</td>
<td>Keep a record on who has accessed the information and when [2002, s. 15]</td>
<td>Arrangements to ensure secured transmission of the information [2002, s. 14]</td>
<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>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” “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” “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)-1(e)]</td>
<td>Omit information that might lead to the identification of the participants</td>
<td>Restrict access to the information</td>
<td>Anonymized data</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>
<td>For electronic trial data: Standard Operating procedures (SOPs) Security system</td>
</tr>
<tr>
<td>Categories of coding for data and tissue</td>
<td>International</td>
<td>Canadian</td>
<td></td>
<td></td>
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<tr>
<td>Positions</td>
<td>WMA</td>
<td>UNESCO</td>
<td>CIOMS</td>
<td>ICH</td>
<td>HUGO</td>
<td>OECD</td>
<td>CE</td>
<td>EC</td>
<td>TCPS2</td>
<td>CIHR</td>
</tr>
<tr>
<td>Identified: labelled with personal identifiers such as name or identification</td>
<td>Identified samples</td>
<td>Identified data</td>
<td>Identified: labelled with personal identifiers such as name or identification</td>
<td>Identified: labelled with personal identifiers such as name or identification</td>
<td>Identified: labelled with personal identifiers such as name or identification</td>
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<td>Identified: labelled with personal identifiers such as name or identification</td>
<td>Identified: labelled with personal identifiers such as name or identification</td>
</tr>
<tr>
<td>Coded: labelled with at least one specific code &amp; do not carry any personal identifiers</td>
<td>Coded samples</td>
<td>Unlinked/anonymized data</td>
<td>Coded: labelled with at least one specific code &amp; do not carry any personal identifiers</td>
<td>Coded: labelled with at least one specific code &amp; do not carry any personal identifiers</td>
<td>Coded: labelled with at least one specific code &amp; do not carry any personal identifiers</td>
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<td>Coded: labelled with at least one specific code &amp; do not carry any personal identifiers</td>
</tr>
<tr>
<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>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>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>
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<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>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
<td>Anonymized (or not identifiable) samples</td>
<td>Anonymizable data</td>
<td>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
<td>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
<td>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
<td>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
<td>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
<td>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
<td>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
<td>Anonymized: initially single or double coded but link between identifiers and code(s) is subsequently deleted</td>
</tr>
</tbody>
</table>

Coded: labelled with at least one specific code & do not carry any personal identifiers

**Directly identifying:** can be immediately linked to a specific individual (e.g. tag or patient number)

**Indirectly identifying:** can reasonably be expected to identify participants through a combination of indirect identifiers (e.g. date of birth, place of residence, unique personal characteristic)

**De-identified/coded:** where identifiers are removed and replaced by a code

**Anonymized:** where identifiers are irrevocably stripped and a code is not kept

**Anonymous:** where identifiers had never been associated to the information or tissue

[2002, ss. 3, 24]
[2002, gl. 14]
[2002, gl. 18; 2008, gl. 18]
[1998]
[ch. 5A at 56, ch. 12A at 170]
<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>
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<tr>
<td></td>
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</tbody>
</table>

with personal identifiers and no coding key generated [2008, s. 2.5]
Table 8 presents a comparison of international and Canadian ethical norms on the return of research results.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO</td>
<td>WMA</td>
</tr>
<tr>
<td>General results should be communicated</td>
<td>Authors have a duty to make results publicly available</td>
<td></td>
</tr>
<tr>
<td>Individual results should be communicated</td>
<td>2003, s. 10 “there should be communication to individual participants which emerges which is relevant to their health” [2002, gl. 16]</td>
<td>2002, gl. 5(7); 2008, gl. 5(7)</td>
</tr>
<tr>
<td>Incidental findings should be communicated</td>
<td>“there should be communication to individual participants which emerges which is relevant to their health” [2002, gl. 16] “incidental findings of non-paternity by a medical geneticist may be disclosed, only to the mother” [2000, gl. at para. 75]</td>
<td>May be communicated [1995]</td>
</tr>
<tr>
<td>Participants have a right to decide whether or not to be informed of the results</td>
<td>2003 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>
</tbody>
</table>

127
<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right not to know should be extended to relatives</td>
<td>2003, s. 10</td>
<td></td>
</tr>
<tr>
<td></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>The right not to know can be overridden</td>
<td></td>
<td></td>
</tr>
<tr>
<td></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>Results can be communicated to the relatives</td>
<td>“Where there is a high risk of having or transmitting a serious disorder and prevention or treatment is available, immediate relatives should have access to stored DNA for the purpose of learning their own status” [1998]</td>
<td>In the context of genetic research, by the genetic researcher. He may be helped by a genetic counsellor [13.3, 13.4]</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></td>
</tr>
<tr>
<td></td>
<td>Trained professionals [para. 46]</td>
<td></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 [13.2(c)]</td>
</tr>
<tr>
<td></td>
<td>When obtaining consent [2002, gl. 5(7); 2008, gl. 5(7)]</td>
<td>When obtaining consent [2008, s. 27(22)]</td>
</tr>
<tr>
<td></td>
<td>When obtaining consent [para. 35]</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></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></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>POSSIBLY [para. 46] 2005, s. 27 In the context of human genetic research [13.3, 13.4] 2008</td>
</tr>
</tbody>
</table>
Table 9 presents a comparison of international and Canadian ethical norms on payments in research.

<table>
<thead>
<tr>
<th>Positions</th>
<th>International</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td>When should payments be discussed?</td>
<td>During the informed consent process [2002, gl. 5(6); 2008, gl. 5(6)]</td>
<td>During the informed consent process [2008, s. 27(5)]</td>
</tr>
<tr>
<td>Expenses can be reimbursed</td>
<td>Travel costs &lt;br&gt; Lost earnings &lt;br&gt; Inconvenience &lt;br&gt; Time &lt;br&gt; Free medical services &lt;br&gt; Other expenses incurred in taking part in the research [2002, gl. 7; 2008, gl. 7]</td>
<td>Reimbursement &lt;br&gt; Subsistence costs [2000, s. 2.6.2]</td>
</tr>
<tr>
<td>Parents cannot be paid for the participation of their child</td>
<td>2002 gl. 7; 2008, gl. 7</td>
<td></td>
</tr>
<tr>
<td>Parents/ participants can still be compensated if they withdraw</td>
<td>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>“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>Payment must be approved by an REB</td>
<td>2002, gl. 7; 2008, gl. 7</td>
<td>1996, s. 3.1.8; 2000, s. 2.6.2</td>
</tr>
<tr>
<td>What constitutes an unacceptable payment?</td>
<td>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>Payment of “a magnitude so as to provide inducement to participate” [s. 4.2, annotations, para. 37]</td>
</tr>
</tbody>
</table>
Table 10 presents a comparison of international and Canadian ethical norms on the composition of REBs.

<table>
<thead>
<tr>
<th>Positions</th>
<th>WMA</th>
<th>UNESCO</th>
<th>CIOMS</th>
<th>ICH</th>
<th>CE</th>
<th>EC</th>
<th>TCPS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>REBs must be</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>multidisciplinary</td>
<td>1997, s. 16; 2003, s. 6(b); 2005, s. 19</td>
<td>2002, gl. 2; 2008, gl. 2</td>
<td>1996, s. 1.31</td>
<td>1997, s. 16(iii); 2005, s. 9(2)</td>
<td></td>
<td></td>
<td>6.4</td>
</tr>
<tr>
<td>REBs must be</td>
<td>2008, s. 15</td>
<td>1997, s. 16; 2003, s. 6(b); 2005, s. 19</td>
<td>2002, gl. 2; 2008, gl. 2</td>
<td>1996, ss. 1.31, 3.2.1</td>
<td>1997, s. 16(iii); 2005, ss. 9(1), 10</td>
<td>2008, s. 8</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Composition of the REB

Professionals such as: Physicians; Scientists; Nurses; Lawyers; Clergy; Representatives of the culture and moral values of the community concerned [2002, gl. 2; 2008, gl. 2]

At least one member whose primary area of interest is in nonscientific area;

At least one member who is independent of the institution/trial site [1996, s. 3.2.1(a)-(c)]

Medical, scientific and non-scientific members [1996, s. 1.31]

Paediatric experts, such as: Physicians with paediatric qualification; Paediatric ethicists; Paediatric pharmacologist; Qualified paediatric nurses; Psychologists [2008, s. 8.1]

Parents [2008, s. 8]

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]
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]

TCPS2

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

HC
CCMG/CAGC

CPS
INTRODUCTION

6 World Medical Association (WMA), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, (Seoul: 2008).

GUIDELINE I

5 World Medical Association (WMA), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, (Finland: 1964).
7 CIHR, Tri-Council Policy Statement, ibid. at Ch. 2B, p. 23.
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].
11 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. 15 [EMEA, Ethical Considerations for Clinical Trials].
14 Ibid.
15 Ibid.
29 Ibid.
33 EMEA, Ethical Considerations for Clinical Trials, supra note 11.
34 ICH, Clinical Investigation E11, supra note 10.
35 Regulations Amending the Food and Drug Regulations (Data Protection), C. Gaz. 1996. I.
36 ICH, Clinical Investigation E11, supra note 10, s. 2.3.
37 Ibid.
41 Ibid.


Ibid.


Tomlinson, “Challenges,” supra note 45.


GUIDELINE II


Civil Code of Quebec, ss. 21, 153.

Ibid. ss. 175–76.

Ibid. s. 14.


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


Ibid.

Ibid.

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].

CIHR, Tri-Council Policy Statement, supra note 8, s. 3.2.

Ibid., s. 3.8.

Ibid.


20 World Medical Association (WMA), Declaration on Ethical Considerations Regarding Health Databases, (Washington: 2002), s. 22, online: <http://www.wma.net/e/policy/d1.htm>.

21 UNESCO, Declaration on Human Genetic Data 2003, supra note 19, s. 16(a).


23 UNESCO, Declaration on Human Genetic Data 2003, supra note 19, s. 16(b).

24 CIHR, Tri-Council Policy Statement, supra note 8, art. 5.5.

25 Ibid.

26 Ibid., Ch. 5 at 56.

27 Ibid., s. 12.3.

28 Ibid., s. 12.3.

29 Ibid., s. 5.6, 12.4.

30 Ibid., art. 12.1(c).


35 CIHR, Tri-Council Policy Statement, supra note 8, s. 3.8.


21 C.F.R. § 312.21.


Ibid.


Ibid.


GUIDELINE III

1 It is important to note that in Quebec the doctrine of the mature minor does not apply and the age of consent is fixed at 18 years old (Civil Code of Quebec, arts. 21, 153).
2 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), s. 5.7, online: <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/ethical_considerations.pdf> [EMEA, *Ethical Considerations for Clinical Trials*].


4 EMEA, *Ethical Considerations for Clinical Trials*, ss. 7, 27.

5 It should be noted that usually consent form should be written at a Grade 6 or Secondary 1 reading level. When this common rule is respected, the consent form can be used to seek the assent of adolescents who have a level of comprehension similar to a competent adult. See T.M. Burke, R Abramovitch & S Zlotkin, “Children’s Understanding of the Risks and Benefits Associated with Research,” (2005) 31 J. Med. Ethics 715.


7 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).

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. 4.8.12 [ICH, *Guidelines E6*]; EMEA, *Ethical Considerations for Clinical Trials*, supra note 2, s. 7.1.2.


11 CIHR, *Tri-Council Policy Statement*, supra note 9, art. 3.9(e).


16 Canadian Pharmacogenomic Network for Drug Safety, “Participants 7-13 Years of Age Informed Assent, Genotype Specific Approaches To Therapy in Childhood (GATC),” (February 2009).


18 Ibid.


GUIDELINE IV

1 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. 7.2 [EMEA, Ethical Considerations for Clinical Trials].
4 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.

GUIDELINE V

3 Ibid., s. 24.
4 CIHR, Tri-Council Policy Statement, supra note 1, art. 3.7.

GUIDELINE VI

GUIDELINE VII

2 Ibid. at 56
3 Ibid.
5 CIHR, Tri-Council Policy Statement, supra note 1, Ch. 5 at 55.
6 Professional Code, R.S.Q. c. C-26, s. 60.4.
7 CIHR, Tri-Council Policy Statement, supra note 1, Ch. 11A.
8 CIHR, Tri-Council Policy Statement, supra note 1, Art. 5.1.
9 Ibid., art. 13.3.
10 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 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Guidance for Industry: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories E15, (2007), s. 2.3.1 [ICH, Definitions E15].
12 CIHR, Best Practices, supra note 10, s. 7.2.1.
13 Ibid. s. 7.2.2.
14 Ibid. s. 7.2.3.
GUIDELINE VIII


1. Ibid.


9. Ibid.

10. Ibid.
GUIDELINE IX

2 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.


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>.


GUIDELINE X


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

3 CIHR, Tri-Council Policy Statement, supra note 1, art. 6.4.

4 Ibid., art. 6.5

5 Ibid., art. 6.4.