I. Overview:

The purpose of this pamphlet is to aid Research Ethics Boards (REBs) in identifying and addressing the ethical and policy issues raised by the practice of donating cord blood and its subsequent use in biomedical research.

This document

☑ Introduces Canadian Blood Services’ (CBS) National Public Cord Blood Bank (NPCBB) and illustrates how the NPCBB system addresses ethical concerns;

☑ Highlights some of the more common issues faced by REBs when reviewing protocols for cord blood donation for biomedical research use;

☑ Identifies Canadian normative documents that are relevant to the ethical review of cord blood research protocols.

What is cord blood?

Umbilical cord blood (cord blood) is a source of blood stem cells that can help save lives. Cord blood is increasingly valued as a resource for transplantation and cell therapy. Since 1988, hematopoietic (blood-forming) stem cells from cord blood transplants have been used for the treatment of various malignant and non-malignant disorders including lymphoid and myeloid leukemias, Fanconi’s and aplastic anemias, β-thalassemia, sickle cell disease and others.

In addition to their uses in the treatment of blood-borne disorders, stem cells in cord blood are an important tool in biomedical research. A greater understanding of how these blood stem cells work will hopefully provide safer and more effective medical therapies. Recent studies demonstrate that cells from cord blood can also be used to generate non-hematopoietic cells for non blood-related diseases. Specifically, cord blood can be used to generate induced pluripotent stem cells (iPSCs) which, like embryonic stem cells, are capable of forming any cell type in the body, holding much promise for medical care in the future. Other biomedical research, which does not relate to stem cells, may also be undertaken with cord blood and lead to new discoveries that may improve medical care in the future.

How is cord blood obtained?

Cord blood is obtained in one of two ways. Cord blood can be collected after the baby is delivered, but before the placenta is delivered, by a hospital physician or a licensed midwife (in-utero collection). Alternatively, cord blood can be collected by designated health care professionals after the baby and the placenta are delivered (ex-utero collection). Cord blood is collected in a purposely made collection bag which contains anticoagulants. The process of cord blood collection does not interfere with the delivery of the baby or the care of the mother and baby. The current standard medical care protocol is to discard cord blood.
Until recently, if an expectant mother wanted her child’s cord blood to be stored for later use, her primary option was to store it in a privately run cord blood bank. These banks store cord blood solely for use by the child (autologous use) or a family member, if needed. Thus, if cord blood was needed by a patient in the health care system, typically it would be purchased from an international bank. If researchers needed cord blood, they were required to collaborate with hospitals and contact mothers directly.

Prior to the establishment of the NPCBB, there were three public blood banks in Canada – the Héma-Québec Cord Blood Bank (Montreal, Québec), the Alberta Cord Blood Bank (Edmonton, Alberta), and the Victoria Angel Public Cord Blood Bank (Toronto, Ontario). While supporting the national and international cord blood stem cell transplantation needs, these banks collect from a limited geographical area and provide limited access to cord blood for researchers.

2013 saw the introduction of Canada’s National Public Cord Blood Bank (NPCBB) – described in detail in section II. It will allow donation of a child’s cord blood to a National bank to be used to treat patients in need across the country and around the world. It will also allow cord blood samples that are unsuitable for medical use to be accessible to the Canadian and global biomedical research community.

Storing cord blood in Canada
II. National Public Cord Blood Bank (NPCBB)

Approximately 50 percent of patients who need an unrelated blood stem cell transplant are unable to find a suitable match. This is particularly true for Canadian patients who have unique stem cell matching needs reflecting Canada’s extensive ethnic diversity. Public cord blood banks can provide additional opportunities for finding a match. As such, in response to the growing need, Canadian Blood Services has established and operates a National Public Cord Blood Bank (NPCBB) accessible to Canadian and international patients.

Via four hospital collection sites across the country, the NPCBB will prepare ethnically diverse, quality controlled and ethically sourced cord blood stem cell units for use by transplant physicians. Any healthy pregnant woman, 18 years of age or older who is 34 weeks pregnant, can consent to donate cord blood at any NPCBB collection site across Canada.

Furthermore, cord blood donated to the NPCBB will be made available for biomedical research. Such research can increase our knowledge about current blood stem cell transplantation practices (including processes for collecting, manufacturing and storing cord blood) and other areas of medical innovation. Canadian Blood Services has developed a Cord Blood for Research Program (the “Program”) to distribute cord blood that does not meet criteria for storage (for transplantation) to researchers with approved research projects. In order to ensure cord blood donation for research purposes follows the highest legal, ethical and scientific standards, a custom-designed consent (Figure 1) and distribution (Figure 2) process has been developed and will be optimized for local needs as implementation proceeds.

The NPCBB will:

- collect, process, test and store cord blood units donated for use by any Canadian or international patient in need of a stem cell transplant;
- provide information about stored cord blood units to the OneMatch Stem Cell and Marrow Network stem cell registry so that potential matches can be identified for patients in need;
- coordinate the delivery of a cord blood stem cell unit when a match is found;
- promote efforts that contribute to research and improved clinical care by facilitating access to non-bankable units available for research.
Consent forms can be found on the Canadian Blood Services website at [http://www.blood.ca/cordblood](http://www.blood.ca/cordblood).
III. Ethical Considerations

There are several core ethical issues that REBs should focus on when reviewing applications for research projects that use cord blood. Many of these issues are addressed in existing guidance (Section IV). Here we will highlight the key elements and illustrate how they are addressed in the current Canadian Blood Services Program.

1. Research Consent

As described in Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), for agreement to participation in a research project to be valid, consent must be “free, informed and ongoing”11. There are key issues within each of these elements to consent that need to be considered in the context of cord blood donation for research purposes (discussed below).

In addition, cord blood collection raises questions such as whether consent from the father is required, when informed consent should be obtained, and what the potential options and outcomes of donation are12. Institutions collecting, storing and distributing cord blood should have policies addressing such questions. In particular, each institution must decide how and when it is going to obtain consent. If a cord blood sample will be used for research, and the research application is considered “secondary use” of an unidentifiable sample, consent may not be required. If consent is contained for cord blood donation and use, there are two general models for doing so. Under the first model, there is a one-stage consent process. Consent is obtained before delivery and covers the entire process of collection, storage, distribution and use. Under the second model, there is a two-stage consent process in which consent for collection of cord blood is obtained prior to delivery, while consent for storage, distribution and use is obtained after.

In following current bioethical norms and understanding of donor preferences for the management of biological samples13, Canadian Blood Services has designed a research consent “opt-in” to obtain consent for the research use of cord blood samples it collects as part of its Program. It is part of a customized two stages model in which consent for the research use of samples is obtained at the time of consent for collection (stage 1). Consent for storage, distribution and use for transplantation is obtained in stage 2.

If consent for research use is obtained, forms are stored by Canadian Blood Services in a central location along with all related research study documents.

Free – or voluntary – consent requires that donors should not be influenced or coerced into participation. This may occur when individuals in a position of authority have reason to affect a donor’s decision to participate, or when incentives are put in place that may impact a donor’s decision. In the context of cord blood donation for biomedical research, care must be taken to ensure those involved in obtaining consent are not motivated to influence donors. Donors must be aware that there are no direct financial or medical benefits for the mother or child.

Canadian Blood Services Research Program ensures consent is free from inducement. • Researchers are not directly involved in the consent and collection process. • Costs and benefits from participation in the program are described in the consent form and supporting information provided to mothers. • The altruistic nature of the program is clearly explained, and mothers are told participation is voluntary and that there are neither personal direct benefits to her nor for the newborn – financial or medical.

Full disclosure of any information that may impact a donor’s decision to participate should be provided. There are many aspects and elements that may be relevant, and the institutions involved must decide what should be included for any particular research project. Moreover, information provided should be in plain language that a prospective donor can understand. Donors should be given sufficient time to consider this information before a decision is made. When obtaining consent for cord blood collection and use, the donor must be aware of the details, including the purpose(s), risks and benefits of the entire process. This includes awareness of how samples and personal information are collected and managed in the hospital, and how samples and data are going to be used and managed by the researcher. In particular, donors should be aware of the commercial potential of their donation14. It may impact a donor’s perception to know that while their donation is altruistic, there is the potential for researchers or companies to generate profits from samples used.

Canadian Blood Services Research Program ensures consent is informed by providing a “Maternal Information Kit” that explains the various elements of the NPCBB system, such as the donation process, privacy policies, and information on biomedical research. • The Information Kit is provided by their health care providers or from the CBS website. • Information can be read at leisure. • There is ample opportunity to ask questions of their health care providers or by phoning the CBS National Contact Centre for research-related questions. • In signing the “Permission to Collect Consent” and ticking the “Research Opt-in”, mothers acknowledge they have read and understood the information provided. • Hospital staff confirms knowledge and consent to collection at the time of delivery. • The specifics of research projects are not necessarily known in advance, so general information regarding the possible nature of research is provided in the Maternal Information Kit and lay summaries of approved research projects are available on the CBS website. • While participants will not be contacted regarding research results, an annual summary of results will be provided by researchers and posted on the CBS website. • Donor are notified that potential patents or commercialization rights are transferred to the researcher or his/her institution, as appropriate.
The consent process does not end once the consent forms are signed. Researchers have a duty to inform donors of any new information that may influence their decision to participate. Awareness of the option to withdraw consent is important. Withdrawal should come without disadvantage or reprisal, and conditions under which samples or data cannot be withdrawn should be clearly outlined. It should be noted that the window of opportunity to withdraw from a research project after collection of the cord blood sample may be small, particularly if the sample is distributed to researchers fresh (i.e. not frozen).

Canadian Blood Services Research Program ensures the mothers know of their right to withdraw without penalty. ♦ The withdrawal process is outlined in the signed Permission to Collect Form and supporting information provided in the Maternal Information Kit. ♦ They are also notified that most research samples will be shipped within 48 hours of collection, and once used in research the samples and data cannot be withdrawn. ♦ To withdraw, mothers are required to call the CBS National Call Centre to indicate their intention and obtain a withdrawal form. If the sample has not been distributed or has not been used in research, it will be destroyed.

2. Privacy

TCP2 states privacy refers to “an individual’s right to be free from intrusion or interference” with respect to their “bodies, personal information, expressed thoughts and opinions, personal communications with others, and spaces they occupy”15. It calls for individual and institutional requirements for confidentiality (the duty to safeguard information) and security (measures to protect information)14.

In the context of cord blood donation and research, privacy applies to the donation itself and the management of subsequent information and data – for the mother and her baby. Institutions collecting and managing cord blood need to ensure their staff and collaborators are familiar with their privacy and confidentiality obligations. Decisions must also be made regarding the donor information that will be required and used in research and how to securely safeguard this information. For most research applications, linkage or traceability of the sample to the donor is typically removed by de-identifying the sample in order to protect donor privacy.

Canadian Blood Services Research Program provides mothers with a copy of the CBS Privacy Policy and explains how it applies to cord blood donation for research before consent is signed. ♦ CBS ensures privacy is maintained by coding samples before shipment to the researcher. ♦ Researchers receive no or minimal donor information (date and time of delivery, gender and criteria used to determine suitability for research). ♦ MTAs will include provisions to prohibit re-identification of donors, including a requirement to notify CBS if identification has occurred, as well as requirements regarding security measures to protect information. ♦ CBS is a health information custodian and is subject to provincial privacy legislation across Canada.

3. Governance

Governance is generally conceived as the “efficient management” of organizations and activities. It requires that stem cell banks implement “structures, processes and bodies” that are “independent, accountable, and transparent” in order to ensure “scientific and ethical integrity”17. In application, it works at two levels: at the internal level through mechanisms governing the day-to-day activities of the bank, and at the external level, by independently assessing the overall bank performance and making the bank accountable to all its stakeholders18.

In biomedical research, REBs play a key role in ensuring governance mechanisms are in place and systems are transparent. In research using cord blood, it is important that each of the relevant stakeholders (involved in collection, processing, storage and research) are represented in governing processes and structures. REBs and other governance bodies which fulfill review and oversight duties must be separate and independent from bodies responsible for management and funding of the bank and research programs19. These efforts, along with the open publication of research results and clinical trials, help sustain public support and public benefits of research endeavors.

Canadian Blood Services Research Program ensures governance of research via the implementation of scientific and ethics review processes as well as via conditions stipulated in the Material Transfer Agreements (MTAs) signed between CBS and research institutions. ♦ CBS also encourages researchers to share the results of their research at meetings and in scientific publications. ♦ There are a number of governance structures in place to manage the Programs and processes. ♦ One key element is the arm’s length CBS Research Ethics Board which provides research ethics review and oversight to the Program, including approval of all research projects. ♦ Additional groups provide oversight to the NPCBB and the Program, and include representation from all key stakeholders.
A number of government agencies and professional organizations have published regulations, policy statements and guidelines providing legal and ethical guidance on donated cord blood which address their use for therapeutic and biomedical research.

These bodies are described in Table 1 (see their websites for more information). REBs should be aware of the norms presented in these documents, how they apply to research, and when necessary use them as resources to aid in decision-making. Highlights of key documents are provided in Table 2.
Health Canada (HC)

HC is tasked with ensuring medical products available in Canada meet appropriate quality and safety standards. As such, under the Canadian Food and Drug Act (FDA)\(^2\), HC develops and applies the regulations intended to govern human blood and blood components intended for transfusion, transplantation or for further manufacturing into pharmaceuticals. Cord blood which has undergone standard processing for use in transplantation would be regulated under the Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations)\(^2\). The purpose of the CTO Regulations is to minimize the potential health risks by outlining the responsibilities establishments that distribute or import cells and tissues must follow to ensure product safety.

Cord blood used in products classified as biologic drugs – cells that have been more than minimally manipulated and intended for non-homologous use – would be regulated under the Food and Drug Regulations (FDR)\(^2\). Part C of the FDR outlines the requirements for drug products to obtain authorization for sale and use in Canada. Among other things, it covers provisions for manufacturing (Division 2) and clinical trials (Division 5).

Table 1. Key Canadian organizations and their documents.

**Public Health Agency of Canada (PHAC)**

PHAC is responsible for public health at the national level, including protecting Canadians from infectious diseases. It is responsible for governing implementation of the Human Pathogens and Toxins Act (HPTA)\(^2\). The purpose of the HPTA is to establish a safety system to protect the public from risks posed by substances that may contain a pathogen, such as blood products. In the research context, it is the HPTA that applies to the handling of cord blood not intended for medical use. The Framework for implementation of the HPTA is provided by the Canadian Biosafety Standards and Guidelines (CBSG)\(^2\). The CBSG applies to researchers conducting activities with material, such as cord blood, that may contain a pathogen or toxin. It outlines the requirements for facilities where infectious material or toxins are handled or stored, and provides guidance on how those requirements are to be achieved.

**Canadian Institutes of Health Research (CIHR)**

In addition to being the primary funding agency for health research in Canada, CIHR also monitors research involving human pluripotent stem cells. This includes the creation and update of the Guidelines for Human Pluripotent Stem Cell Research\(^2\) (the Guidelines), the maintenance of a registry of human embryonic stem cell lines created in Canada, and the creation of a Stem Cell Oversight Committee (SCOC)\(^2\). While initially focused on research involving stem cells generated from human embryos, the Guidelines now also apply to the study of stem cell lines from other sources, including umbilical cords and placenta. Since the Guidelines are based on provisions from TCPS2 and follow the same guiding principles, CIHR along with the other research Agencies have proposed the integration of the two documents (seeking comments in 2014).

**Society of Obstetricians and Gynaecologists of Canada (SOGC)**

In March of 2005, the SOGC evaluated the risks and benefits associated with cord blood banking and issued Clinical Practice Guidelines\(^2\) for prenatal care providers regarding the counselling, procedural, and ethical implications of cord blood banking. Prenatal care providers as well as obstetric facilities should be informed about the clinical potential of cord blood and the current practices regarding its collection, storage and usage. While the clinical practice guidelines do not address cord blood donation for research purposes directly, they do make recommendations regarding ethical practices for donor recruitment and cord blood collection that are relevant to the donation process.

**Stem Cell Network (SCN)**

The SCN has as its stated mission to act as a “catalyst for Canadian research that translates stem cell research into new therapies, commercial products and public policy”\(^9\). Moreover, the SCN facilitates collaboration between industry, university research institutions, governments and non-governmental organizations by forming new partnerships. The SCN “believes that Canadian researchers must work within an ethical and legal framework that reflects the values of the majority of Canadians”\(^9\). To facilitate this, the SCN has developed a Public Policy & Ethical, Legal and Social Issues research program, generated policy papers\(^3\), and funded academic research on a range of topics, including the use of cord blood for research.
Research consent must be obtained prior to the collection of the cord blood (Articles 3.12 & 12.1). The use of human biological materials requires REB review as well as the consent of the participant, which for the purposes of cord blood donation would mean the mother (Article 12.1). Specific information should be given in order to make a voluntary and informed decision with regards to donating biological materials, including: information regarding cord blood donation procedure, notification of potential commercialization, the right of withdrawal, and safeguards with regards to the privacy and confidentiality of the participant, and plans for handling clinically relevant findings (Article 12.2).

Consent need not be obtained for secondary use of un-identifiable human biological material for further research (Articles 5.5, 12.3).

- The storage of cord blood in biobanks requires appropriate facilities, equipment, policies, procedures and safeguards (Article 12.5). In addition, provisions related to research involving materials related to human reproduction apply. This means:
- Any research involving foetal tissue, which includes “membranes, placenta, umbilical cord, amniotic fluid, and other tissue that contains genetic information about the fetus”, should not interfere or compromise with the woman’s ability to decide whether to continue her pregnancy (Article 12.9).
- Educational material on the medical and research use of cord blood should be made available to doctors, the public and prospective patients.
- Donation should be altruistic and aim to increase the ethnic diversity of banked cord blood samples, so as to ensure benefits to all Canadians.
- National cord blood collection organized by a non-for-profit entity with independent ethics review and scientific oversight should be supported. National and international registries should be linkable to public cord blood banks.
- Any collection of cord blood by researchers without parental consent undermines respect for donor autonomy and should be discouraged.
- Hospital admission consents should provide information for routine collection aimed for clinical or research use. Cord blood samples that do not meet criteria for clinical use should, subject to the donor’s consent, be available for research approved by an appropriate ethics committee REB.
- Public banks should consider broad written consent for the use of cord blood samples for research. This includes general information concerning the possible range for future research uses and the possibility for international collaboration.
- In accordance with the Helsinki Declaration, researchers should publish research results on the outcomes of clinical trials.

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**Table 2. Ethics recommendations from key Canadian normative documents.**

**Highlights from...**

**“TCPS2”**
- Research consent must be obtained prior to the collection of the cord blood (Articles 3.12 & 12.1).
- The use of human biological materials requires REB review as well as the consent of the participant, which for the purposes of cord blood donation would mean the mother (Article 12.1).
- Specific information should be given in order to make a voluntary and informed decision with regards to donating biological materials, including: information regarding cord blood donation procedure, notification of potential commercialization, the right of withdrawal, and safeguards with regards to the privacy and confidentiality of the participant, and plans for handling clinically relevant findings (Article 12.2).
- Consent need not be obtained for secondary use of un-identifiable human biological material for further research (Articles 5.5, 12.3).
- The storage of cord blood in biobanks requires appropriate facilities, equipment, policies, procedures and safeguards (Article 12.5).

**“SOGC Clinical Practice Guidelines”**
- Altruistic donation of cord blood for public banking and subsequent allogeneic transplantation (for a recipient other than the donor) should be considered, but the long term storage of cord blood for autologous (self) donation was not recommended. There are unresolved issues regarding the rise of for-profit cord blood banks.
- The safe management of obstetric delivery should never be compromised to facilitate cord blood collection.
- Donors should be recruited in a manner that is both fair and non-coercive.
- Informed consent for collection and banking should be obtained during prenatal care, before the onset of labour, and then a confirmation of consent should be obtained after delivery.
- Policies should be developed with regards to the disclosure of any abnormal test results.
- Ensure donor privacy and confidentiality is respected.

**“Updated Guidelines for Human Pluripotent Stem Cell Research” (CIHR)**
- SCOC review is required for research proposals involving human embryonic stem cells and/or the grafting of human pluripotent stem cells into human of non-human animals. Approval is still also required from local REBs and Animal Care Committees.
- Research to derive or study stem cells from cord blood is allowed provided that there was consent from the mother or both parents if there are “two people committed to parenting”. Cord blood cannot be used for research if there is a disagreement between parents.
- Additional information must be explained to obtain informed consent, including: anonymization practices, right to withdraw before a cell line is created, temporal & global nature of research, and no direct benefit to participants.
- Cell lines must be anonymized.
- Commercial interests must be disclosed to SCOC, REB and prospective research participants.

**“SCN” funded research (Bordet et al.32)**
- Educational material on the medical and research use of cord blood should be made available to doctors, the public and prospective patients.
- Donation should be altruistic and aim to increase the ethnic diversity of banked cord blood samples, so as to ensure benefits to all Canadians.
- National cord blood collection organized by a non-for-profit entity with independent ethics review and scientific oversight should be supported. National and international registries should be linkable to public cord blood banks.
- Any collection of cord blood by researchers without parental consent undermines respect for donor autonomy and should be discouraged.
- Hospital admission consents should provide information for routine collection aimed for clinical or research use. Cord blood samples that do not meet criteria for clinical use should, subject to the donor’s consent, be available for research approved by an appropriate ethics committee REB.
- Public banks should consider broad written consent for the use of cord blood samples for research. This includes general information concerning the possible range for future research uses and the possibility for international collaboration.
- In accordance with the Helsinki Declaration, researchers should publish research results on the outcomes of clinical trials.
V. Conclusion

Cord blood will play a growing role in both basic research and medical use in the future. The recently established NPCBB will facilitate this by providing biomedical researchers and patients greater access to cord blood. CBS has ensured that its processes and procedures meet the legal and ethical requirements for donation, banking, research and distribution.

In Canada, government bodies and professional organizations have adopted normative documents with guidance and recommendations to guide the research use of cord blood. These documents highlight the importance of informed consent and address a number of relevant ethical issues, including: withdrawal, privacy, confidentiality, disclosure of results, and the publication and commercialization of research.

REBs are recognized as playing a vital role in ensuring that the biomedical research process meets ethical norms. While core ethical and legal issues have been identified and addressed by the available guidelines, inevitably REBs will find themselves with the challenge of judging, interpreting and applying these norms.

This Primer is intended to be a first step in understanding the current Canadian context for cord blood donation, the role the NPCBB plays in the procurement of samples for research, and the key organizations involved in policy setting. Further work is required to ensure that these policies are interpreted and applied in a harmonized manner across the country.

We would like to solicit feedback from the REB and scientific community on the Primer; as well as on ethical, legal and social issues which will need to be further addressed in REB reviews. Please send comments to rosario.isasi@mcgill.ca.
References


15TCP2 (reference 11), page 55

16TCP2 (reference 11), page 56


18Ibid

19Ibid


25TCP2 (reference 11)

26Updated Guidelines for Human Pluripotent Stem Cell Research, June 30, 2010 http://www.cihr-ircsc.gc.ca/e/42071.html

27CIHR Stem cell research http://www.cihr-ircsc.gc.ca/e/15255.html


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