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CAN/CGSB-191.1-2013

ICS 03.120.01

WITHDRAWAL

July 2018

Research ethics oversight of biomedical clinical trials

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RETRAIT

Juillet 2018

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Research ethics oversight of biomedical clinical trials

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Introduction

Context

Every year thousands of Canadians volunteer to be research subjects in biomedical clinical trials designed to evaluate new drugs, vaccines, natural health products or medical devices (known collectively as health products). Health Canada is the federal regulatory agency with the authority to permit the conduct of biomedical clinical trials, and to evaluate the results of biomedical clinical trial research that will inform decisions concerning the marketing of health products in Canada. Biomedical clinical trials are conducted under the responsibility of licensed professionals in partnership with the pharmaceutical and biotechnology manufacturers that develop new health products to diagnose, alleviate, or prevent disease or medical conditions. Private and public sector sponsors provide the funding to conduct biomedical clinical trial research both independently and in joint relationships.

Canada's Food and Drugs Act and applicable *Regulations* incorporate internationally accepted good clinical practices that require favourable ethics review by committees known as Research Ethics Boards before a biomedical clinical trial can begin. A Research Ethics Board is responsible for determining whether a proposed biomedical clinical trial is scientifically and ethically sound, and acceptably safe. Research Ethics Boards are required to exercise fair and impartial judgment, on an ongoing basis, in assessing whether the potential benefits of participating as a subject in a clinical trial continue to outweigh the risks and to thereby protect the rights, safety and well-being of research subjects.

Objectives

This National Standard of Canada *Research Ethics Oversight of Biomedical Clinical Trials* (the Standard) was developed as a basis for establishing unambiguous Research Ethics Board policies and procedures that adhere to Canadian and international norms and presumably should serve to reduce the uneven interpretation of regulations. It is intended that consistent application of the Standard will improve the quality and reliability of the work of Research Ethics Boards overseeing research ethics in Canada, and will enhance interactions among all parties involved in the biomedical clinical trial research. Consistency will also engender credibility and support for health research among Canadians, and promote Canada as a reliable jurisdiction in which to conduct biomedical clinical trial research.

The Standard is intended to serve as a reference for those with authority to monitor the quality of the research ethics oversight of biomedical clinical trial research in Canada. The Standard describes Research Ethics Board responsibilities and presents the minimum set of processes that an organization with a Research Ethics Board must have in place to oversee biomedical clinical trial research conducted under its auspices. The intended users of this Standard are those individuals and groups responsible for ensuring that biomedical clinical trial research meets the high standard of research ethics expected by Canadians.

Language

In this Standard, "shall" states a mandatory requirement, "should" expresses a recommendation and "may" is used to express an option or that which is permissible within the limits of this Standard. Notes accompanying clauses do not include requirements or alternative requirements; the purpose of a note accompanying a clause is to separate from the text explanatory or informative material.

Research ethics oversight of biomedical clinical trials

1 Scope

This National Standard of Canada applies to Research Ethics Boards (REBs) that evaluate applications for ethical acceptability. If an REB grants ethics approval to conduct biomedical clinical trials, it will provide research ethics oversight of biomedical clinical trials that are subject to the *Food and Drugs Act* and applicable *Regulations* (see 2.1).

This Standard does not preclude or override any applicable regulatory or legal requirement.

Intended users —This Standard is intended for use primarily by

— REB chairs, members and administrative staff,

— qualified investigators and study teams conducting biomedical clinical trials,

— sponsors and funders of biomedical clinical trials,

— those with responsibility for establishing and ensuring effective REB operations,

— those with responsibility for research ethics oversight of biomedical clinical trials in organizations where they are conducted, and

— regulatory authorities that evaluate REBs with research ethics oversight of biomedical clinical trials.

An organization with an REB intending to use this Standard will take responsible measures to ensure that the roles and responsibilities of the REB are defined, resources are made available, and processes are in place for research ethics oversight of biomedical clinical trials conducted under its auspices, to ensure that the REB meets the requirements of this Standard and applicable statutory and regulatory requirements.

2 Normative references

The following documents contain provisions that, through reference in this text, constitute provisions of this National Standard of Canada. The referenced documents may be obtained from the sources noted below.

An undated reference is to the latest edition or revision of the reference or document in question, unless otherwise specified by the authority applying this standard. A dated reference is to the specified revision or edition of the reference or document in question. However, parties to agreements based on this National Standard of Canada are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below.

2.1 Health Canada

Food and Drugs Act

Food and Drug Regulations: Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects

Medical Devices Regulations

Natural Health Products Regulations.

2.1.1 Source

The above may be obtained from the Department of Justice Canada, Communications Branch, Public Affairs Division, 284 Wellington Street, Ottawa, ON K1A 0H8, Telephone 613-957-4222, Facsimile 613-954-0811, http://canada.justice.gc.ca.

2.2 International Conference on Harmonisation (ICH)

ICH GCP International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – ICH Harmonised Tripartite Guideline — Guideline for Good Clinical Practice E6(R1), http://www.ich.org/LOB/media/MEDIA482.pdf.

2.2.1 Source

The above may be obtained from ICH Secretariat, c/o IFPMA, 15 ch. Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland, Telephone +41 (22) 338 32 06, Facsimile: +41 (22) 338 32 30, http://www.ich.org.

2.3 World Medical Association

World Medical Association, Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, http://www.wma.net/en/30publications/10policies/b3/index.html.

2.3.1 Source

The above may be obtained from the World Medical Association (WMA), 13, ch. du Levant, CIB - Bâtiment A, 01210 Ferney-Voltaire, France, Telephone +33 4 50 40 75 75, Facsimile: +33 4 50 40 59 37, http://www.wma.net.

3 Terms and definitions

For the purposes of this National Standard of Canada, the following terms and definitions, and those set out in the *Food and Drugs Act* and applicable *Regulations,* apply:

3.1
applicant
individual, sponsor, institution or organization which applies to an REB for an ethics review of a biomedical clinical trial.

3.2
application
request by an applicant for the initial review by an REB of a biomedical clinical trial or requests for review of protocol amendments, changes to consent documents, advertising, or any other materials or changes related to a clinical trial reviewed by the REB of Record as part of its research ethics oversight of the biomedical clinical trial.

3.3
assent
affirmative agreement to participate in a biomedical clinical trial given by a child or other person incapable of giving informed consent.

3.4
biomedical clinical trial
investigation in which a health product (drug, medical device, or natural health product) is administered to or used by humans and that is intended to discover or verify the clinical, pharmacodynamic or pharmacokinetic effects of the product, or ascertain the safety or efficacy of the product.

3.5
community member
member of the general public with no formal affiliation with the sponsor of the biomedical clinical trial, with the organization under whose auspices the biomedical clinical trial is being conducted, or with any site where the biomedical clinical trial is being conducted.

NOTE An example of a community member is a patient or a former research subject.

3.6
conflict of interest
circumstance of a person or organization in a real, perceived or potential conflict between their duties or responsibilities related to research and their personal, institutional or other interests.

EXAMPLE Conflicts of interest may occur when individuals' judgments and actions or organizations' actions in relation to research are, or could be, affected by personal, organizational or other interests, including, but not limited to, business, commercial or financial interests, whether of individuals, their family members, their friends, or their former, current or prospective professional associations or of the organization itself.

3.7
continuing review
process of research ethics review for continuing ethical acceptability of an ongoing biomedical clinical trial conducted by the REB at an interval no greater than every twelve months and prior to the expiration of the preceding ethics approval.

3.8
delegated review
expedited review
review carried out on behalf of the REB by the Chair and/or members of the REB according to eligibility criteria and processes authorized by the REB.

3.9
ethical conduct of research
obligation to comply with applicable ethical principles, theories and guidelines, documenting their origin in the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.

3.10
informed consent
process by which an individual voluntarily confirms his or her willingness to participate in a particular biomedical clinical trial, after having been informed of all aspects of the biomedical clinical trial that are relevant to the individual's decision to participate.

NOTE Adapted from ICH-GCP.

3.11
initial review
process of research ethics review of an application for ethical acceptability of a biomedical clinical trial conducted by the REB of Record prior to the initiation of the biomedical clinical trial.

3.12
ongoing review
continuing process of research ethics review encompassing any changes to the protocol, the informed consent document, research subject-specific changes or other related material, after an REB of Record has granted ethics approval to conduct a biomedical clinical trial.

3.13
protocol
document that describes the objective(s), design, methodology, statistical and ethical considerations, and organization of a clinical trial.

NOTE 1 Some of these considerations may be provided in other documents referred to in the protocol.

NOTE 2 Adapted from ICH GCP.

3.14
protocol deviation
generic term for local non-compliance with any operation described in the research protocol.

3.15
qualified investigator
any person who meets the definition of qualified investigator under the Food and Drugs Act and applicable Regulations.

3.16
quality
measure of the ability of a product, process, or service to satisfy stated or implied needs and/or the degree to which a product, process or service fulfills stated or generally accepted requirements.

NOTE Adapted from WHO “Handbook for Good Clinical Research Practice (GCP)” and ISO 9000:2005.

3.17
quality control
part of the level of quality management focused on ensuring that applicable requirements are fulfilled, including the operational techniques and activities routinely undertaken to ensure quality.

NOTE Adapted from WHO “Handbook for Good Clinical Research Practice (GCP)” and “ICH E6: Good Clinical Practice” and ISO 9000:2005

3.18
quality improvement
part of the level of quality management focused on taking the knowledge gained through quality control and other activities and using this knowledge to make changes to systems and activities in order to increase the ability to fulfil applicable requirements now and in the future.

NOTE Adapted from WHO “Handbook for Good Clinical Practice (GCP)” and ISO 9000:2005

3.19
REB of record
Research Ethics Board that has been appointed by an institution or organization, under whose auspices the biomedical clinical trial is being conducted, to serve as the primary or sole authority for the research ethics oversight of a biomedical clinical trial.

3.20
research ethics oversight
processes for initial review, ongoing review, and continuing review by which the REB ensures compliance with the measures to protect the rights, safety, and well-being of research subjects.

NOTE This includes procedures for observing the free and informed consent process and other research processes consistent with the REB mandate.

3.21
research subject
individual who participates in research either as a recipient of the investigational product or as a control.

NOTE In other documents “research subjects” may be referred to as “participants” or “research participants.”

3.22
sponsor
individual, corporate body or organization that is accountable or responsible for the initiation, management, and/or financing of a biomedical clinical trial.

NOTE Adapted from ICH GCP.

3.23
standard operating procedures
detailed, written instructions to achieve uniformity of the performance of a specific function.

[ICH GCP]

3.24
study completion
formal completion of all activities related to the conduct of a biomedical clinical trial at a clinical trial site that is reported to the REB of Record by the qualified investigator authorized by the REB to conduct the biomedical clinical trial.

3.25
vulnerable persons
individuals whose specific circumstances may limit their ability to fully safeguard their own interests or whose willingness to volunteer in a biomedical clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation.

NOTE These may include individuals who are in dependent situations and who may fear retaliation if they refuse to participate. It also includes individuals who have diminished capacity to exercise autonomy in choosing whether to participate in a biomedical clinical trial.

4 Requirements

4.1 General

4.1.1 Requirements for assessment

4.1.1.1 The information sources required for assessment against this Standard shall include, but not be limited to

a) review of organizational policies and procedures, and agreements as they apply to biomedical clinical trials;

b) review of REB policies and procedures, agreements and records of members/staff qualifications;

c) interviews with officials of the organization, REB members, and staff; and

d) review of organizational and REB documentation relating to specific clinical trials.

4.1.1.2 The information sources required for assessment against this Standard may include interviews with applicants, qualified investigators, sponsors and research subjects.

4.1.2 Exchange of information

4.1.2.1 While recognizing the need to ensure the confidentiality of information, it is essential that there be minimal barriers to, and maximal facilitation of, the exchange of information among REBs and between REBs and regulators. The exchange of information shall be relevant to the protection of the rights, safety and well-being of research subjects.

NOTE It is recommended that regulators and REBs that meet the requirements of this Standard and have confidentiality safeguards in place to solicit, offer and exchange such information.

4.2 Governance, mandate, authority, and resources

4.2.1 General

4.2.1.1 An organization with an REB shall have a governance structure to provide the REB with the mandate, independence, autonomy, jurisdiction, authority, and sufficient resources and personnel to enable the REB to meet its responsibilities in a manner consistent with the requirements of this Standard and with applicable statutory and regulatory requirements.

NOTE Not every biomedical clinical trial supplying data that leads to market authorization in Canada of a new or existing health product falls under the authority of a Canadian REB. Determination of whether a non-Canadian ethics committee meets the requirements of this Standard is dealt with by the applicable regulatory authority. It is expected that a non-Canadian ethics committee should consider whether its governance, mandate, authority, and resources conform with the requirements of this Standard, or with an internationally accepted ethical standard deemed to provide protections equal to or greater than those provided by this Standard.

4.2.2 Governance and mandate of the REB

4.2.2.1 An REB shall have the responsibility for research ethics oversight delegated to it by the highest body of the organization that has authorized it. An REB shall have its mandate, operations, and jurisdiction established through the authority of written policies and procedures.

4.2.2.2 The highest body within the organization that establishes the REB shall define an appropriate reporting relationship with the REB. The reporting structure, policies, and procedures shall identify, manage, and eliminate or minimize any real or perceived undue influence or conflict of interest with respect to the establishment, operations, and decision making of the REB. To ensure continuing accountability and fulfilment of its mandate, the REB shall deliver a written report of its operations and the ensuing issues at least annually.

4.2.2.3 The highest body of the organization with an REB may appoint an REB of Record for the research ethics oversight of a multi-centre biomedical clinical trial under the terms of a jurisdictional or collaboration agreement.

4.2.2.4 The organization with an REB shall have formal procedures for the selection, appointment, terms of membership, and performance evaluations of the REB members, including the Chair and Vice-Chair or equivalent.

4.2.2.5 The organization with an REB and under whose auspices the biomedical clinical trial is being conducted is responsible for ensuring that the REB of Record's ethics review, deliberation, and decision making are not subject to inappropriate pressure or undue influence by any person or group from within or outside the organization. Where the REB of Record has not granted ethics approval, the organization shall not permit the conduct of the biomedical clinical trial to proceed. A biomedical clinical trial that has received ethics approval from the REB of Record may be subject to further review that might result in the biomedical clinical trial being disallowed by officials of the organization. Apart from the possibility of disallowing an approved biomedical clinical trial, no person or group shall set aside any decision of the REB of Record, except through appropriate use of the appeals process as stipulated in 4.4.8.

4.2.2.6 The organization with an REB shall have policies and procedures to declare and manage conflicts of interest situations within the REB and other conflicts of interest that could influence the REB's mandate, operations and/or jurisdiction.

4.2.3 REB authority

4.2.3.1 Where an application is submitted for a biomedical clinical trial, the REB shall require the applicant to comply with all REB decisions with respect to the ethical conduct of the research.

4.2.3.2 Where an application is submitted for a biomedical clinical trial, the REB shall have the authority to make the following decisions:

a) Grant ethics approval to conduct the proposed biomedical clinical trial

b) Require modifications to the proposed biomedical clinical trial

c) Disapprove the proposed biomedical clinical trial, and

d) Suspend or terminate ethics approval to conduct the biomedical clinical trial.

4.2.3.3 The REB that has approved a biomedical clinical trial at one or more clinical trial sites within its jurisdiction shall, subject to any collaboration agreements, serve as the REB of Record for those clinical trial sites and shall have the authority to

a) establish the ethics review processes, and promote the ethical conduct of the biomedical clinical trial by maintaining research ethics oversight of the trial;

b) seek, share, and receive any information involving the biomedical clinical trial under its research ethics oversight that it deems necessary to fulfil its mandate, while maintaining confidentiality and respecting privacy;

c) ensure that the applicant, and qualified investigator have policies and procedures in place to protect the rights, safety, and well-being of research subjects;

d) take any action it deems reasonably necessary, and consistent with its written policies and procedures, to ensure the protection of the rights, safety, and well-being of any research subjects in biomedical clinical trials under its jurisdiction.

4.2.3.4 Where action is taken regarding research under 4.2.3.3 d), or where ethics approval of a biomedical clinical trial is suspended or terminated, the REB shall notify the qualified investigator and the organization under whose auspices the biomedical clinical trial is conducted. The REB shall have the authority to notify the sponsor and/or appropriate regulatory authorities.

4.2.4 Resources

4.2.4.1 The organization with an REB shall provide the REB with the necessary material, human, infrastructure, and financial resources in order to meet the requirements of this Standard and applicable statutory and regulatory requirements.

4.2.4.2 The REB Chair and the REB administrators shall assess the educational and training needs of the REB members, REB administrators, and staff in order to

a) identify any gaps in knowledge, skills or competencies required to fulfil their respective duties;

b) act to address these gaps, and;

c) ensure that REB members, REB administrators and staff are provided with ongoing educational and training opportunities within the scope of the REB mandate.

4.3 REB composition, appointment, and administrative support

4.3.1 General

4.3.1.1 The REB shall be constituted so as to ensure that its members have the requisite expertise, experience, knowledge, and perspectives to conduct thorough ethics reviews of the application and associated documents. The REB's membership shall be diverse and shall include considerations of gender, ethnicity, cultural backgrounds, disability, and sensitivity to such issues as community perspectives. The membership collectively shall have sufficient qualifications, including the knowledge and experience required to review and evaluate the scientific, methodological, and clinical aspects of the biomedical clinical trial submissions, and to ensure that their decisions can be reconciled with the well-being of the research subjects and with broader ethical considerations.

4.3.2 REB members

4.3.2.1 The REB shall have at least five members, including both men and women, and collectively shall include

a) at least two members whose primary expertise is in a scientific discipline and who have experience in the relevant methods and research areas usually reviewed by the REB;

b) at least one member who practices medicine or dentistry and who is a member in good standing with his or her respective regulatory authority;

NOTE To practice in Canada, medical and dental practitioners are licensed by their respective provincial/territorial medical or dental regulatory authorities.

c) at least one member who is a community member;

d) at least one member whose primary experience and expertise are in a non-scientific discipline;

e) at least one member who is knowledgeable in the law relevant to biomedical clinical trials;

f) at least one member who is knowledgeable in ethics relevant to biomedical clinical trials;

g) at least one member, when possible, who is from an identifiable Aboriginal community or Native centre, where the REB reviews biomedical clinical trials that, due to the requirements of the biomedical clinical trials or the demographic make-up of the population, recruit participants from those communities. The Aboriginal member may be from the REB's vicinity or participate by electronic conferencing.

NOTE In Canada, the identifiable Aboriginal communities are First Nations, Inuit, and Métis, and Native centres include Aboriginal urban and rural community and health centres.

h) at least one member who is knowledgeable in complementary or alternative health care, where the REB provides ethics reviews of biomedical clinical trials involving natural health products. This individual may serve on the REB to participate solely in ethics reviews of biomedical clinical trials involving such products;

i) at least one member who is knowledgeable in paediatric health research, where the REB provides ethics reviews of biomedical clinical trials involving children; and

j) additional members as required by applicable legislation or regulations.

4.3.2.2 A member of the REB may not fulfil more than two representative capacities and disciplines.

4.3.2.3 The citizenship or permanent residency of REB members shall meet the requirements of the applicable regulations.

NOTE In Canada, *Food and Drug Regulations: Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects* set out the requirements for citizenship or permanent residency.

4.3.2.4 To ensure it has the ability to conduct timely and competent ethics reviews, the REB may appoint alternate members with qualifications comparable to those of the primary member(s) for whom they will serve as alternates.

4.3.2.5 In order to provide a thorough ethics review for the range of applications it is called upon to review, the REB may require additional members with expertise in scientific disciplines or methods of research or with experience working with particular populations. If the size of the REB is increased, there shall be a commensurate increase in the number of community members.

4.3.2.6 When the REB lacks the experience or expertise to conduct competent ethics review of a particular biomedical clinical trial, the REB shall seek the assistance of one or more ad hoc advisors. Ad hoc advisors shall not be voting members or participate in the decisions of the REB. An REB which regularly seeks recourse to ad hoc advisors in the same or similar disciplines should re-examine its composition.

4.3.2.7 REB members shall engage in ongoing group-based and self-directed learning to enhance their ability to fulfil their ethics review responsibilities.

4.3.2.8 REB members shall be knowledgeable about the conflicts of interest which may arise in ethics reviews and about the relevant policies and procedures (see 4.2.2.6) of the organization with an REB:

a) When clearly in a conflict of interest, the REB member shall be excluded when the REB discusses its decision, reaches a consensus or votes on the application

b) When in any doubt as to whether a conflict of interest exists, the REB member shall disclose the situation to the REB Chair and abide by the REB's decision regarding any actions required to mitigate his or her real or perceived conflict of interest.

4.3.2.9 REB members and ad hoc advisors shall maintain the confidentiality of the documents submitted for ethics review and of the REB discussions.

4.3.3 REB Chair and Vice-Chair or equivalent

4.3.3.1 The REB Chair should normally be an experienced and respected REB member with at least two years of experience on an REB, and shall have a broad and deep knowledge of research ethics literature and debates, national and international guidelines, statutes and regulations, as well as policies and their application to the biomedical clinical trials undertaken within the jurisdiction of the REB. The organization with an REB shall establish the knowledge criteria for the REB Chair as stipulated in 4.2.2.4.

4.3.3.2 The REB Chair, in collaboration with administrative staff, as appropriate, shall advise the organization on policies and procedures related to the ethical conduct of research involving human subjects. The Chair shall advise the organization on the evaluation of performance of REB members and administrative staff.

4.3.3.3 The REB Chair shall be responsible for ensuring that the REB ethics review process meets the requirements of this Standard. The role of the REB Chair shall be to provide overall leadership for the REB and facilitate the REB ethics review process, based on the requirements of this Standard, the policies and procedures of the organization with the REB, and the applicable statutes, regulations and guidelines. The Chair shall monitor the REB's decisions for consistency and ensure that these decisions are recorded accurately. The Chair shall ensure that all members of the REB are free to participate in discussions during convened meetings of the REB. When reviews are delegated, the Chair shall ensure that the reviewer(s) are selected with due regard to the experience and expertise required. The organization with the REB shall provide the necessary resources to enable the REB Chair to fulfil his or her responsibilities as stipulated in 4.2.1.1.

4.3.3.4 The REB Vice-Chair or equivalent shall

a) discharge the responsibilities of the Chair when the Chair is unable to do so,

b) discharge the responsibilities assigned by the Chair, and

c) assist in the overall operation of the REB, as requested.

4.3.4 REB administrative staff

4.3.4.1 Administrative staff with sufficient expertise and resources shall be employed in sufficient numbers to support the REB's operations and to allow the REB to meet its responsibilities effectively and efficiently.

4.3.4.2 The organization with an REB shall develop policies and procedures that define the roles and responsibilities of the REB administrative staff. This may include the appointment of REB administrative staff to serve as REB members.

4.3.4.3 REB administrative staff responsibilities may include

a) pre-review of submissions and requests to the REB,

b) quality management activities (see 4.6),

c) management of administrative issues involving REB research ethics oversight,

d) implementation of REB directives, and

e) provision of advice and information to the REB.

4.3.4.4 The appointment of REB administrative staff to serve as REB members shall be limited to REB administrative staff who have knowledge, experience, and training comparable to what is expected of REB members. The organization with an REB shall have policies and procedures in place to ensure that administrative staff can fulfil their responsibilities as REB members independently.

4.3.4.5 The REB policies and procedures established in accordance with 4.4.4.1.1 shall stipulate that where REB administrative staff have been appointed to serve as REB members in accordance with 4.4.4.4.4 and 4.4.4.4.5. The REB policies and procedures shall stipulate that REB administrative staff may attend convened meetings and participate in discussion, but they shall not be counted in determining quorum nor shall they participate in any vote.

4.3.4.6 The REB policies and procedures established in accordance with 4.4.4.1.1 shall stipulate that where REB administrative staff have been appointed to serve as REB members, they may perform delegated review in accordance with 4.4.4.5.2 through 4.4.4.5.4. The REB policies and procedures shall stipulate that such performance of delegated review by REB administrative staff appointed to serve as REB members shall meet the requirements of this Standard relating to delegated review.

4.3.4.7 REB members and REB administrative staff shall be subject to privacy and confidentiality policies of the organization and the REB.

4.4 REB operations

4.4.1 REB standard operating procedures

4.4.1.1 REBs shall have written and accessible standard operating procedures (SOPs) which ensure the transparency of REB processes for applicants and sponsors and permit appropriate REB review and research

ethics oversight of biomedical clinical trials. SOPs set out and describe REB processes at all stages, from initial application to completion of the biomedical clinical trial, including modifications and other changes, continuing reviews and other periodic reports, reported adverse events and protocol deviations.

NOTE Written SOPs promote quality and uniformity in ethics review and research ethics oversight processes; facilitate compliance with applicable ethical, regulatory and organizational requirements; and provide the framework for ensuring the protection of the rights, safety, and well-being of research subjects.

4.4.1.2 When there are discrepancies among good clinical practices, statutory or regulatory requirements or ethical considerations, the REB or the organization with an REB shall establish procedures to document the rationale for its decisions that attempt to strike a balance between the compliance with applicable regulatory and ethical requirements for ensuring the protection of the rights, safety, and well-being of research subjects.

4.4.2 Standard operating procedures for REB operations during publicly declared emergencies

4.4.2.1 Publicly declared emergencies are extraordinary events that arise suddenly or unexpectedly and require urgent or quick responses. Such emergencies may represent significant risks for research subjects in biomedical clinical trials or new biomedical clinical trials initiated as a result of the emergency. Potential research subjects who may not normally be considered vulnerable may become so by the very nature of the public emergencies. Those already vulnerable may become acutely so. Emergencies present extraordinary public risks that warrant special responses, legislation or public policies and usually require that they be officially proclaimed or declared. During a publicly declared emergency, REBs need to be particularly vigilant, enhance ethics oversight, and exercise special diligence in abiding by ethical principles, standard operating procedures, and the law.

NOTE For the purposes of this Standard, public emergencies are limited to those that are declared by an authorized public health official.

4.4.2.2 REBs shall develop emergency preparedness plans and procedures to address basic operational questions including, but not limited to

a) how emergencies may affect research ethics oversight of biomedical clinical trials,

b) how REBs conduct business or meetings during an emergency,

c) what procedures govern ethics review in emergency circumstances, and

d) what evaluation methods need to be developed for post-response evaluations so as to inform any revisions to emergency preparedness and emergency procedures.

4.4.2.3 These plans and procedures shall ensure that the REB has the capacity to undertake reviews, provide research ethics oversight of biomedical clinical trials, and respond appropriately to communications with qualified investigators, sponsors, regulators, and public health officials and should cease as soon as is feasible after the declared emergency ends.

4.4.2.4 REB plans and procedures may warrant reasonable adjustments to address the timing, the location, and the convening of REB meetings during emergency situations. When an REB is significantly compromised by the publicly declared emergency, consideration should be given to

a) deferring the ethics review of new biomedical clinical trials that are unrelated to the emergency,

b) suspending ongoing biomedical clinical trials unless it is in the best of interest of research subjects to continue their participation, or

c) referring the ethics review and research ethics oversight of new and ongoing biomedical clinical trials to another REB.

4.4.3 Application procedures

4.4.3.1 The REB shall establish and make available clear written requirements for submission of an application for initial, ongoing, and continuing review. These requirements shall include, but are not limited to

a) the name and address of the REB office where application materials are to be submitted;

b) the format for submission, including provisions for electronic submission (if any);

c) deadlines for submission in relation to review dates;

d) the means by which an application will be acknowledged, including notification when the application is incomplete;

e) the application procedure for proposed changes to the protocol, informed consent document, research subject-specific changes or other materials related to the clinical trial; and

f) documentation required to be submitted (see 4.4.3.2 through 4.4.3.4).

4.4.3.2 The documentation required for a thorough ethics review of a biomedical clinical trial shall include, but is not limited to:

a) an application, authenticated and dated;

b) the protocol of the proposed biomedical clinical trial (clearly identified and dated), together with supporting documents and appendices;

c) a summary of all safety data and either pharmacological, pharmaceutical, toxicological data or medical device data available on the investigational product(s), together with a summary of clinical experience with the investigational product(s) to date (e.g., recent investigator's brochure, published data, a summary of the product's characteristics, medical device manuals);

d) a written attestation that the qualified investigator is entitled to provide health care under the applicable laws and that he/she is a member in good standing with his or her respective regulatory authority. Additional documentation shall be provided including a curriculum vitae or a statement that the qualified investigator is qualified to perform the proposed clinical trial. Such statement may be provided by a superior from the qualified investigator's organization;

NOTE To practice in Canada, medical and dental practitioners are licensed by the respective provincial/territorial medical or dental regulatory authorities. For REBs that review multi-centre clinical trials, the review of investigator documents [these may include but not be limited to items e) through m) and p)] may take place at a time and place separate from the review of the biomedical clinical trial.

e) a description of all processes used for recruitment of research subjects;

f) copies of all material to be used for recruitment of research subjects, including all advertisements;

g) a description of all processes used to obtain informed consent and assent;

h) the process whereby research subjects may withdraw their consent, if given, and associated documentation;

i) a description of the processes used to provide research subjects with new information which may affect their willingness to participate, and to obtain their ongoing consent;

j) copies of the consent document, and documentation for other forms of information for potential research subjects in the language(s) understood by the potential research subjects who are expected to participate in the biomedical clinical trials;

k) a statement describing any compensation to be given to research subjects;

l) a disclosure of any financial interest or other potential conflict of interest that the qualified investigator has in the biomedical clinical trial;

m) the biomedical clinical trial budget in sufficient detail to ensure that conflicts of interest are identified, minimized, or otherwise managed;

n) a statement and description of any safety monitoring process provided by the sponsor or qualified investigator, such as a data and safety monitoring board (DSMB);

o) all previous decisions, if known (e.g., those leading to a negative decision or modified protocol), by other REBs or regulatory authorities for the proposed biomedical clinical trial (whether in the same location or elsewhere), an indication of modification(s) to the protocol made on that account, and the reasons for previous negative decisions;

NOTE In Canada, other REBs or regulatory authorities include non-Canadian ethics committees and regulatory authorities.

p) a statement by the qualified investigator that he/she is aware of and shall make all reasonable efforts to comply with applicable laws, guidelines, policies, and professional obligations; and

q) if the biomedical clinical trial involves optional genetic testing, a description of the separate processes used for obtaining and documenting informed consent and assent for such genetic testing.

4.4.3.3 If the biomedical clinical trial has been registered in an internationally recognized clinical trial registry, the name of the clinical trial registry, the unique identifying code assigned to the clinical trial by the registry, and information regarding where the results of the clinical trial will be made publicly available shall be provided to the REB. For applicable biomedical clinical trials, the sponsor or qualified investigators shall submit to the REB the name of the internationally recognized clinical trial registry, and the unique identifying code assigned to the clinical trial by the registry upon receipt.

4.4.3.4 The REB may require the qualified investigator to submit additional documentation when it deems this necessary for the ethics review, or for research ethics oversight of biomedical clinical trials granted ethics approval.

4.4.4 Ethics review processes

4.4.4.1 General

4.4.4.1.1 The REB shall establish and implement written procedures to evaluate applications for ethics review. The procedures shall describe the process and criteria to determine whether a biomedical clinical trial shall be reviewed at a convened meeting of the REB, or by delegated review. Delegated review may be conducted by a sub-committee of REB members, or by the Chair of the REB or an experienced REB member authorized to act on behalf of the REB. The type of review shall comply with the applicable regulations and the procedures shall describe the decision making process for each level of ethics review.

4.4.4.2 Requirements and criteria for ethics review

4.4.4.2.1 The REB shall conduct a thorough ethics review of the application and its supporting documentation. The REB shall consider but not necessarily limit its review to the following

a) the protection of the rights, safety, and well-being of research subjects;

b) the nature and safety of the research intervention;

c) the recruitment and retention of research subjects; and

d) the scientific validity of the protocol.

4.4.4.2.2 Prior to granting ethics approval, the REB shall ensure that the biomedical clinical trial being reviewed meets all of the requirements set out in 4.4.4.2.3 through 4.4.4.2.16. In making its decision, the REB should generally consider the criteria related to these requirements that it deems applicable to the biomedical clinical trial being reviewed.

4.4.4.2.3 Taking account of evidence of prior scientific reviews and of such advice as it deems applicable, the REB shall satisfy itself that the clinical trial design is appropriate. In ascertaining whether the clinical trial is appropriate, it should generally consider

a) the objectives of the clinical trial;

b) statistical considerations, including sample size calculations (when appropriate);

c) the potential for reaching sound conclusions while minimizing risk to research subjects; and

d) the proposed measures for monitoring and reporting adverse events and other information such as DSMB reports, as well as scientific information that arises which could impact the safety or free and informed consent of research subjects in the clinical trial.

4.4.4.2.4 The REB shall decide whether to grant ethics approval to conduct the biomedical clinical trial. In reaching its decision, the REB should generally consider the

a) justification for the use of control arms, including both placebo and active comparators;

b) justification for any plans to withhold or withdraw standard therapies or clinical management protocols for the purpose of the proposed clinical trial;

c) qualified investigator's qualifications and experience to conduct the proposed clinical trial in accordance with the protocol and good clinical practices;

d) suitability and feasibility of the available facilities at the research clinical trial site, and available care in the case of an emergency, all of which may be attested by a Department Head or Division Chief, responsible organizational official, or sponsor;

e) plans for reporting and publishing the results of the clinical trial and any restrictions on the researchers' use or publication of data; and

f) arrangements for the protection of confidential information that might be accessed or acquired through the conduct of the clinical trial.

4.4.4.2.5 The REB shall assure itself that the research procedures do not expose the research subjects to unnecessary risks. In its consideration of risk, the REB should generally consider the appropriateness of

a) the inclusion and exclusion criteria for research subjects;

b) the background and safety information derived from earlier human, animal, and in vitro studies;

c) the risks and benefits of any intervention to be used in the proposed clinical trial;

d) the procedures to minimize risks to the research subjects, where appropriate, by ensuring that the qualified investigator uses procedures already being performed on the research subjects for diagnostic or treatment purposes;

e) the health care to be provided to research subjects during and after the course of their participation, including procedures for seeking the research subjects' consent to inform their primary health care provider about the proposed clinical trial, if appropriate;

f) the criteria for the premature withdrawal of research subjects, and the steps to be taken if research subjects voluntarily withdraw or are withdrawn by the qualified investigator during the course of the proposed clinical trial; and

g) the criteria for unblinding the research subjects to their study intervention, if necessary, in order to ensure their safety.

4.4.4.2.6 The REB shall determine that the risks to research subjects are reasonable in comparison with the anticipated benefits. In making this determination, the REB should generally consider the anticipated benefits to

a) the research subjects;

b) other individuals with similar needs relevant to the study;

c) concerned communities; and

d) society as a whole, given the importance of the knowledge to be gained.

4.4.4.2.7 The REB shall require any study eligibility criteria identifying vulnerable persons to be justified in light of the objectives and the risk-benefit analysis of the clinical trial.

4.4.4.2.8 The REB shall ensure that informed consent will be sought from each prospective research subject or from an appropriate representative for that prospective research subject under applicable legislation.

4.4.4.2.9 The informed consent process should generally include the following elements:

a) A statement that the research subject is being invited to participate in a clinical trial

b) An explanation of the purposes of the clinical trial

c) The expected duration and nature of the research subject's participation

d) A description of the clinical trial interventions and the probability of assignment to each intervention

e) A description of the procedures to be used as part of the clinical trial, including a clear indication of which procedures are experimental

f) A description of available alternative procedures or courses of treatments outside the scope of the clinical trial

g) A description of the known risks to the research subjects and to other persons, as applicable, including pregnant mothers, nursing infants or the fetus

h) A statement that the particular treatment or procedure may involve risks to the research subject (or to the embryo or fetus, if the research subject is or may become pregnant) which are currently unforeseeable

i) A description of any possible foreseeable benefits to the research subject or to others; when there is no known clinical benefit to the research subject, the research subject shall be informed

j) A description of how the confidentiality of research records identifying the research subject will be maintained, and any limits to their confidentiality

k) A statement to the effect that monitors, auditors, the REB, and regulatory authorities will be granted direct access to the research subject's medical and research records for verification of the clinical trial data, as well as organization officials for legitimate purposes, including quality management

l) A description of the compensation, if any, that will be provided to the research subject in the event he or she is injured during the clinical trial

m) A statement that the research subject does not waive any legal rights that he or she would otherwise have but for being a research subject in the clinical trial. Any offers of compensation in the event of injury shall not limit recourse to other legal remedies

n) A description of the type of response that will be undertaken if injury occurs to the research subject during the clinical trial (for example, that treatment will be made available and covered by the clinical trial funding), or that no such response is planned

o) A statement that participation in the clinical trial is voluntary and that refusal to participate or, once agreeing to participate, a decision to withdraw from the clinical trial at any time, involves no loss of any benefit to which the research subject is otherwise entitled

p) A statement that outlines the process involved for termination of participation

q) The circumstances or reasons under which the research subject's participation in the clinical trial may be terminated by the qualified investigator and a statement identifying any other persons with the authority to modify the research subject's participation, such as the sponsor

r) A statement that new findings discovered during the clinical trial which may affect the research subject's willingness to continue participation shall be provided to the research subject in a timely fashion

s) The research subject's responsibilities

t) Any anticipated expenses associated with participation in the clinical trial

u) Any payments or incentives for participation in the clinical trial

v) The identity of the sponsors and qualified investigator(s)

w) The approximate number of research subjects in the clinical trial

x) The person to contact for further information about the clinical trial

y) The person or office to contact for further information about the rights of research subjects in clinical trials

z) The person to contact in the event of clinical trial related injuries

aa) A statement concerning any personal benefits that may accrue to the qualified investigator, if applicable and deemed necessary by the REB.

4.4.4.2.10 The REB shall require that the qualified investigator provide each research subject with a document that specifies those elements included in the informed consent process described in 4.4.4.2.9. This document shall be signed and dated and a copy provided to the research subject, or his/her appropriate representative, prior to the research subject's participation in the biomedical clinical trial.

4.4.4.2.11 If the clinical trial has been registered in an internationally recognized clinical trial registry, the name of the clinical trial registry, the unique identifying code assigned to the clinical trial by the registry, and information regarding where the results of the clinical trial will be made publicly available shall be provided to the research subject in a manner deemed suitable by the REB.

4.4.4.2.12 The REB shall determine that the methods for obtaining, maintaining, and documenting each research subject's informed consent are acceptable. If recruitment is to include research subjects who are unable to read the consent document, but are otherwise capable of giving informed consent, the REB should generally ascertain that the qualified investigator has processes for the provision of an independent translator or reader.

4.4.4.2.13 Where the applicable law permits and the nature of the research requires research subjects to be recruited into clinical trials without their personal informed consent, the REB should generally consider the following, prior to granting ethics approval to conduct a biomedical clinical trial:

a) Specific legal requirements and restrictions for such studies

b) Reasons why the research subject may be unable to provide consent

c) Competence of the qualified investigator(s) to undertake the clinical trial

d) Risks and potential benefits to research subjects

e) Importance of the proposed study to the public

f) Advisability of community or public consultation prior to commencement of non-consensual enrolment in the clinical trial

g) Invasion of personal privacy

h) Alternative means of protecting the interests and rights of those research subjects whose consent would be waived

i) Need for and possibility of surrogate consent by a legal representative, and

j) Provisions for consent to continued participation in the event that the research subject gains or regains capacity to give consent.

4.4.4.2.14 Where the study proposes the inclusion of vulnerable persons, the REB shall ensure that appropriate processes are in place to mitigate against the possibility of undue influence or coercion, and that extra measures are taken to protect the rights, safety, and well-being of those vulnerable persons. Prior to granting ethics approval to conduct a biomedical clinical trial, the REB should generally consider the following:

a) The justification for including such individuals in the biomedical clinical trial, and

b) Processes to protect the rights, safety, and well-being of those research subjects who may be likely to be vulnerable to coercion or undue influence.

4.4.4.2.15 Where the study proposes the inclusion of persons incapable of giving legally informed consent, the REB shall ensure that extra measures are taken to protect the rights, safety, and well-being of those research subjects. Prior to granting ethics approval to conduct a biomedical clinical trial, the REB should generally consider:

a) the justification for inclusion of such research subjects in the clinical trial based on scientific, clinical, and risk-benefit analysis;

b) the process to obtain informed consent or authorization from an appropriate representative for that research subject under applicable legislation;

c) the process to ensure that, should the research subject become capable of giving free and informed consent during the course of participation, his or her consent shall be obtained for continued participation;

d) the process to ensure compliance with the measures to protect the rights, safety, and well-being of those research subjects who are likely to be vulnerable to coercion or undue influence or whose legal representative may be vulnerable to coercion or undue influence;

e) the *Declaration of Helsinki*, when considering the enrolment of persons incapable of giving informed consent as research subjects in a clinical trial; and

f) the process for documenting the research subjects' wishes and respecting their assent or dissent.

4.4.4.2.16 The REB shall require that the sponsor and qualified investigator provide protection and respect for the privacy of the research subjects' personal information in the course of and subsequent to their participation in a biomedical clinical trial. The REB should generally consider:

a) the method of identifying and contacting potential research subjects

b) the measures taken to ensure the confidentiality and security of personal information concerning research subjects

c) how data or biological specimens will be obtained and the purposes for which they will be used

d) whether, when, and how information or biological specimens will be de-identified

e) where and for how long data or biological specimens will be stored and secured

f) whether the biological specimens or data may be used for secondary purposes or by people other than those of the approved investigation for secondary use, and

g) what measures are in place to ensure that secondary uses of data and biological specimens respect the privacy interests and consent provisions of the research subjects.

4.4.4.3 Initial review

4.4.4.3.1 The REB shall require that every application for initial review be reviewed at a convened meeting of the REB, unless the application for ethics review meets criteria for review via delegated procedures. Where the outcome of a delegated review would otherwise result in disapproving the application for ethical acceptability of a biomedical clinical trial, a disapproval of the application shall not be issued. Instead the application shall be referred to a convened meeting of the REB.

4.4.4.3.2 Applications for initial ethics review of the following activities that present no more than minimal risk may be reviewed through delegated review:

a) Biomedical clinical trials that are not subject to prior authorization by the applicable regulatory authority

NOTE In Canada, these include:

1) biomedical clinical trials involving drugs that are being used according to the approved labelling,

2) biomedical clinical trials involving class 1 medical devices, and

3) phase IV biomedical clinical trials or observational studies involving natural health products that are being used according to the approved labelling.

b) Biomedical clinical trials where the only difference from standard care is that research subjects are randomized among two or more existing current standards of intervention.

4.4.4.4 Review at a convened meeting of the REB

4.4.4.4.1 Normally the REB shall review applications at a regularly scheduled meeting of the REB. The REB shall publish a schedule of meeting dates, with submission deadlines, for the conduct of reviews. The schedule shall be published in such a way that it is accessible to and gives reasonable advance notice to all REB members and to the applicants.

4.4.4.4.2 The REB shall have policies and procedures in place for convening unscheduled meetings to deal with exigencies. The Chair of the REB shall ensure that all members, applicants, and the host organization are notified as quickly as possible and that reasonable justification for convening the unscheduled meeting is provided.

4.4.4.4.3 Convened meetings shall normally be conducted in person. However,

a) some members may attend via electronic conferencing, when travel or other operational factors make this necessary, and their participation shall serve to meet quorum. The Chair shall ensure that this does not diminish the quality of the board members' communication, and shall allow remote participation at his or her discretion. Prior to allowing such long-distance participation, the REB shall ensure that this is in keeping with any requirements of the funding organization and the host organization; and

b) during exigencies, meetings of the REB may be convened by electronic conferencing, at the Chair's discretion and only where permitted by the REB's policy and procedures.

4.4.4.4.4 The organization with an REB shall have a policy establishing the quorum for a convened meeting of the REB. This policy shall ensure that the quorum reflects the expertise, experience, knowledge and perspectives required in 4.3.2.1 and 4.3.2.2.

4.4.4.4.5 The standard operating procedures shall describe the decision making processes for the REB, taking into consideration the documentation requirements described in 4.5.3.3. Decisions made at a convened meeting shall require a quorum to be present and shall be taken by vote (i.e., a majority of the members participating in the discussion) or by consensus. If consensus cannot be reached, there shall be a vote and the results of the vote, including objections or abstentions, shall be noted in the minutes. Should the quorum be lost during a meeting, no further decisions that must be made at a convened meeting of the REB shall be made until quorum is restored.

4.4.4.4.6 The REB shall seek the advice of experts who are not members of the REB when it deems this necessary for considering any relevant aspect of a specific application. These ad hoc advisors may provide written comments, or speak and respond to questions at a meeting, but

a) shall not otherwise participate when the REB discusses its decision, reaches consensus or votes on the application;

b) they shall agree in writing to maintain the confidentiality of the documentation and REB proceedings;

c) if the expertise relates specifically to an ethno-cultural community, including Aboriginal communities, the REB should draw ad hoc advisors either directly from that community or from those ad hoc advisors who work closely with that community; and

NOTE In Canada, the identifiable Aboriginal communities are First Nations, Inuit, and Métis, and Native centres include Aboriginal urban and rural community and health centres.

d) shall provide a declaration of any potential conflict of interest.

4.4.4.4.7 Written comments from absent members shall be allowed to inform the consideration of an application, but only members participating in the meeting, including any members participating via electronic conferencing at which the specific application is considered, shall participate in any vote or decision.

4.4.4.4.8 The REB may allow applicants or qualified investigators to attend its meetings for the purpose of helping its members understand the application. Applicants and qualified investigators shall be excluded when the REB discusses its decision, reaches consensus or votes on the application.

4.4.4.4.9 Members who have a declared conflict of interest shall be excluded when the REB discusses its decision, reaches consensus or votes on the application.

4.4.4.4.10 The outcome of the review at a convened meeting of the REB shall be to

a) approve the application as submitted,

b) require modification to any aspect of the application or receipt of clarification or further information before considering it eligible for ethics approval,

c) disapprove the application as submitted, or

d) defer decision making on the application and continue the deliberation of the application at a future meeting.

4.4.4.4.11 When the REB requires modifications as stipulated in 4.4.4.4.10 b), the review to verify concurrence with the REB requirements for approval may be conducted by the Chair or by an REB member, or may take place at the next convened meeting, as determined by the REB at the convened meeting. The authorized reviewer then determines

a) whether the applicant has complied with all REB requirements for ethics approval the REB may grant ethics approval to conduct the biomedical clinical trial, or

b) whether the applicant has not complied with all REB requirements for ethics approval to conduct the biomedical clinical trial and the applicant's responses are referred back to the applicant for additional clarification or to the next convened meeting of the REB for discussion.

4.4.4.4.12 REBs may allow observers to attend meetings. Observers

a) shall not participate when the REB discusses its decision, reaches consensus or votes on the application;

b) shall agree in writing to maintain the confidentiality of the REB proceedings; and

c) where the REB finds that an observer otherwise qualifies as an expert in relation to the research under consideration, the observer may be allowed to contribute input if it is relevant and significant to discussion. However the observer shall not participate when the REB discusses its decision, reaches consensus or votes on the application. The minutes shall reflect the expertise and contributions of any observer.

4.4.4.5 Delegated review

4.4.4.5.1 The REB shall have policies and procedures in place to allow applications to be evaluated via delegated review procedures according to the requirements of this Standard. Delegated review may be conducted by the REB Chair, Vice-Chair or equivalent, a subcommittee, or one or more experienced REB members, designated by the Chair (see 4.4.4.3.2).

4.4.4.5.2 The delegated reviewers shall be authorized to

a) approve the application,

b) require modification to any aspect of the application or receipt of clarifications or further information before considering it for ethical acceptability, or

c) refer the application as submitted for a review at a convened meeting of the REB.

4.4.4.5.3 If the delegated reviewers cannot reach a unanimous decision concerning the application, the application as submitted shall be referred for review at a convened meeting of the REB.

4.4.4.5.4 All decisions taken through a delegated review shall be reported to the REB at the next scheduled convened meeting.

4.4.5 Notification of REB decision

4.4.5.1 The REB shall have written policies and procedures for notifying applicants of REB decisions.

4.4.5.2 All REB decisions concerning an application shall be communicated in writing to the applicant in a timely fashion, and shall contain the following information:

a) Unambiguous identification of the application reviewed

b) Whether the application was reviewed at a convened meeting of the REB and, if so, the date of that meeting

c) A statement of the decision reached by the REB, and

d) A statement that the REB meets the requirements of this Standard and is in compliance with the applicable statutes and regulations.

4.4.5.3 When the REB grants ethics approval to conduct the biomedical clinical trial, the communication to the applicant shall include

a) a list of all the documents and any items approved for use or distribution at the biomedical clinical trial site;

b) a statement of the date REB ethics approval takes effect and the ethics approval expiry date;

c) a statement of the requirements for ongoing and continuing review of the biomedical clinical trial;

d) a statement that the protocol, informed consent document, and conduct of the biomedical clinical trial must not be altered unless a request for amendment of the conditions for ethics approval has been reviewed and ethics approval has been granted by the REB, except in those situations where a modification is required to eliminate an immediate hazard to research subjects, or the changes are logistical or administrative in nature;

e) a statement that the REB meets the requirements of this Standard and is in compliance with the applicable statutes and regulations.

4.4.5.4 When the REB requires modifications to be made before it will consider approval of the application, the communication to the applicant shall include a clear statement of all required modifications, the rationale for the required changes, and the process for review once the modifications have been submitted.

4.4.5.5 When the REB disapproves the application, the communication to the applicant shall include a clear statement of the reasons for that decision.

4.4.5.6 Communications about REB decisions made at convened meetings should include, or the REB should provide at the request of the applicant

a) a copy of the REB membership roster in effect on the date of the meeting, and a statement confirming that quorum was present during the REB decision regarding the applicant's study; and

b) each member's academic qualifications, affiliation, gender, and status (regular or alternate member).

4.4.5.7 When the REB suspends or terminates the ethics approval of a biomedical clinical trial, the communication to the applicant shall include a clear statement of the reasons for that decision (See 4.2.3.2 d) and 4.2.3.4). 4.4.8 shall apply.

4.4.6 Ongoing review

4.4.6.1 The REB of Record shall, subject to jurisdictional or collaboration agreements, ensure ongoing review of the biomedical clinical trials that it has reviewed and approved in accordance with this Standard.

4.4.6.2 The REB shall require the applicant or qualified investigator to submit for prior review any proposed change to the protocol, informed consent document, research subject-specific changes or other materials related to the clinical trial, except as exempted under 4.4.5.3 d).

4.4.6.3 Any changes that affect the rights, safety, or well-being of the research subjects or the integrity of the biomedical clinical trial shall be reviewed at a convened meeting of the REB, including but not limited to

a) changes that affect the selection, monitoring or withdrawal of research subjects;

b) changes that significantly increase the risk to the health of a research subject;

c) changes that extend the duration of participation in the clinical trial;

d) changes that affect the evaluation of the clinical efficacy of the investigational product(s); and

e) changes that affect the safety evaluation of the investigational product(s).

4.4.6.4 If permitted by the policies and procedures of the organization with an REB and of the organization under whose auspices the biomedical clinical trial is being conducted and by the regulations applicable to the biomedical clinical trial, changes in the approved biomedical clinical trial which have no significant effect on the rights, safety or well-being of the research subjects, including the addition of another clinical trial site, may be reviewed by a delegated review procedure.

4.4.6.5 The REB shall permit the qualified investigator to modify the conduct of the biomedical clinical trial without prior review when this is necessary to eliminate an immediate hazard to research subjects or to implement minor logistical changes, such as changes to study personnel and contact information.

4.4.6.6 The REB shall require the qualified investigator to report the following within a time specified by the REB:

a) Discontinuation of the clinical trial at the local clinical trial site and the reasons for it

b) New information that raises questions about the safety of the biomedical clinical trial or which could influence the decision of research subjects to continue their participation in the biomedical clinical trial

c) Unanticipated problems in accordance with 4.4.6.7

d) Serious or continuing non-compliance with organizational policy or REB requirements and determinations, and

e) Local protocol deviations that jeopardize research subjects' safety or data integrity.

4.4.6.7 The REB shall have written policies and procedures concerning the review of unanticipated problems, including serious unexpected adverse events/reactions, that comply with applicable regulations, and the principles of good clinical practice.

4.4.6.8 The REB shall require active independent monitoring of the clinical trial as it is carried out, when the REB concludes that such direct monitoring is required.

4.4.6.9 The REB shall have the authority to review any study documentation for compliance with biomedical clinical trial procedures, REB requirements, and ethical standards and to observe the consent process.

4.4.7 Continuing review

4.4.7.1 Initial REB approval of a clinical trial shall expire no later than one year from the date of approval, unless an earlier expiry date is specified by the REB. Upon application for continuing review of an ongoing clinical trial the REB shall reassess the risk and the progress of the biomedical clinical trial to decide if ethics approval to continue to conduct the biomedical clinical trial shall be granted. Successive continuing reviews shall be conducted at intervals no greater than twelve months from the date of the previous REB review and ethics approval, until study termination.

4.4.7.2 The REB shall develop policies and procedures for the continuing review of biomedical clinical trials.

4.4.7.3 The REB shall ensure continuing review of ongoing biomedical clinical trials and shall require the qualified investigator and the sponsor (if appropriate) to provide progress reports at a frequency and in the detail it deems necessary relative to the risk of the biomedical clinical trial to the research subjects. Documents that should be reviewed as part of continuing review include, but are not limited to

a) the initial protocol review along with ongoing reviews (e.g., protocol amendments, DSMB reports);

b) proposed changes to the protocol or informed consent document;

c) new material provided by the sponsor (e.g., progress reports on the clinical trial, investigator's brochure, regulatory actions, changes in benefit/risk ratios);

d) the continuing review report including, but not limited to, details on

   1) recruitment of research subjects, withdrawals, and complaints;

   2) current protocol and consent document versions;

   3) summary of all local protocol deviations and unanticipated problems;

e) otherwise available information that would alter the REB's prior determination on the ethical acceptability of the biomedical clinical trial.

4.4.7.4 Applications for continuing review shall be reviewed at a convened meeting of the REB unless the policies and procedures of the organization under whose auspices the biomedical clinical trial is being conducted and regulations applicable to the biomedical clinical trial allow for a delegated review procedure. Delegated review of approved biomedical clinical trials should be permitted when one of the following conditions applies:

a) The biomedical clinical trial is permanently closed to the enrolment of new research subjects, all research subjects have completed research-related interventions, and the research remains active only for long-term follow-up of research subjects, or

b) No research subjects have been enrolled and no additional risks have been identified, or

c) The remaining research activities are limited to data analysis.

4.4.7.5 Delegated review should also normally be permitted for the continuing review of biomedical clinical trials, provided that no additional risks have been identified and that there have been no changes to the clinical trial that would materially increase the risks to research subjects, or that would substantially change the conduct of the biomedical clinical trial, its design or objectives.

4.4.8 Reconsideration and appeals

4.4.8.1 The organization with an REB shall establish and make available upon request policies and procedures for reconsideration of the REB decision and an appeal process. An applicant and/or qualified investigator shall have the right to have an unfavourable REB decision reconsidered at a convened meeting of the REB. An applicant and/or qualified investigator shall have the right to be heard at the convened meeting of the REB when the unfavourable REB decision is reconsidered.

4.4.8.2 Referral of an application for ethics review to an appeal process shall be permitted only after efforts to resolve the controverted issues through reconsideration by the REB have failed.

4.4.8.3 An applicant and/or qualified investigator shall have the right to request an appeal of an REB decision. An appeal can be launched for procedural or substantive reasons. The onus shall be on the applicant or qualified investigator to justify the grounds on which they request an appeal and to indicate any breaches to the research ethics review process or any elements of the REB decision that are not supported by this standard, and/or applicable statutes, regulations, guidelines and organizational policies and procedures governing ethical review of biomedical clinical trials.

4.4.9 Study completion and conclusion of REB oversight

4.4.9.1 A biomedical clinical trial shall be reported as completed or terminated to the REB of Record promptly following the sponsor's close-out activities at that clinical trial site. The final submission to the REB of Record shall be a study completion report provided by the qualified investigator authorized by the REB to conduct the biomedical clinical trial. REB acceptance of the study completion report shall formally conclude the ethics approval and research ethics oversight for the biomedical clinical trial at that site.

4.5 Documents and record keeping

4.5.1 General

4.5.1.1 The REB shall prepare adequate documentation of its activities, decisions and actions, and maintain these documents in secure storage.

4.5.2 Documentation of policies and procedures

4.5.2.1 The REB shall document its policies and procedures and make them available upon request. These shall include, but not be limited to the following

a) managing conflicts of interest for REB members, ad hoc advisors, and REB administrative staff;

b) composition of the REB;

c) selection, appointment terms, duties, and performance evaluations of REB members, including the Chair and Vice-Chair or equivalent;

d) training and education of REB members and REB administrative staff;

e) delegation of signing authority;

f) confidentiality of information on clinical trials submitted for review;

g) REB application/submission procedures;

h) the process for decision making at REB meetings;

i) procedures for initial review, ongoing review, and continuing review and criteria for REB ethical acceptability, including review at a convened meeting of the REB and delegated review;

j) communication with qualified investigators and qualified investigator staff, with research subjects and with other individuals or organizations;

k) guidelines on informed consent processes;

l) management of non-compliance of qualified investigators;

m) document management and retention;

n) requirements for handling unanticipated problems;

o) requirements for reporting protocol deviations;

p) emergency preparedness.

4.5.3 Documents related to ethics reviews

4.5.3.1 To ensure maximum disclosure by applicants and qualified investigators and protection of information received in confidence, all records and documentation pertaining to each application that is reviewed shall be kept confidential within the limits allowed by applicable statutes.

4.5.3.2 The REB shall maintain a record of

a) the protocol of the clinical trial and any related documents submitted for initial review, ongoing review, and continuing review over the course of the clinical trial;

b) the initial review, ongoing review, and continuing review activities related to each clinical trial;

c) all original correspondence received from the qualified investigator, and copies of all correspondence from the REB to the qualified investigator; and

d) meeting agendas and minutes.

4.5.3.3 Minutes of REB meetings shall include REB discussions of its decisions, consensus or votes on the application, actions flowing from the REB determination, and shall include the following information:

a) Attendance of REB members and others

b) Date, time, and place of meeting

c) The decision(s) made by the REB, by consensus or by majority vote, including the number of members voting for, against, and abstaining

d) The rationale for disapproving or requiring modifications

e) A summary of the discussion of controverted issues and their resolution

f) A summary of any formal claims and/or discussions of actual, potential or apparent conflicts of interest involving REB members, and the decision taken by the REB to address them, and

g) The recusal of any REB member with a potential or real conflict of interest.

4.5.4 Retention of REB documents

4.5.4.1 The REB records required by this Standard shall be retained for the maximum amount of time stipulated in any applicable regulations. The retention period shall begin on the date of the meeting when the REB accepts the study completion report or when REB approval expires. In the absence of a regulatory requirement for REB record retention, the REB records required by the Standard shall be retained in a manner consistent with good clinical practices for a period of at least three years.

4.6 Quality management

4.6.1 General

4.6.1.1 As appropriate to the nature and volume of the biomedical clinical trials that the REB reviews, the REB shall collaborate with the highest body within the organization to identify appropriate levels of quality management and shall establish policies and procedures for evaluating and assessing performance. Such policies and procedures shall include both quality control and quality improvement processes.

NOTE The scale and comprehensive nature of the quality management level may differ from one organization to another due to the size of the organization, type of activities and complexity of their processes and interactions. For example, quality management processes may be the responsibility of the REB Chair and REB administrative staff or may be the responsibility of a distinct entity within the organization.

4.6.1.2 The quality management activities for the REB should promote the quality and effectiveness of the processes and activities of the REB.

4.6.1.3 The quality management activities for the REB should consist of initiatives designed to operationalize the ethical oversight of research involving research subjects through the review, evaluation, performance measurement, control of deviations, and continuous improvement for REB activities as set out in 4.6.2 through 4.6.6.

4.6.2 Quality management review

4.6.2.1 The quality management review of the REB should consist of a review of the following at planned intervals:

a) Existence, completeness, and status of the REB's written policies and SOPs

b) Results of routine evaluations of the REB and the REB administration

c) REB performance metrics and annual reports

d) Feedback from applicants, qualified investigators, sponsors, funders, and public outreach to research subjects

e) Feedback from regulators relevant to the protection of the rights, safety and well-being of research subjects

f) Continuous improvement activities

g) New requirements (ethical, statutory or regulatory)

h) Status of any deviations as specified in 4.6.5.1

i) Status of action items from previous reviews

j) Compliance with the requirements of this Standard.

4.6.2.2 Recommendations for improvements to the REB and related processes resulting from the quality management review should consist of the following:

a) New policies and/or SOPs or modification of existing policies or SOPs

b) Additional training or educational activities or modifications to existing activities, and

c) Additional resources or modifications to existing resources.

4.6.3 Evaluation of the REB

4.6.3.1 The REB shall, in collaboration with the highest body within the organization, plan and implement a routine or directed evaluation of the REB to assure the organization that the REB is complying with the requirements of this Standard.

NOTE An organization with an REB may choose to implement a more formal audit program which is independent of the REB and reports to the highest level of the organization. The defined responsibilities and requirements for planning and conducting audits, and reporting, recording, and storing the results should be described in documented procedures.

4.6.4 Performance measurement of ongoing REB activities

4.6.4.1 The REB should, in collaboration with the highest body within the organization, identify meaningful indicators of the performance of the REB such as

a) the REB workload (e.g., volume of research reviewed, specifying any research that it considers to be high risk or involving vulnerable persons);

b) the timeline REB metrics (turnaround time from submission of an application for ethics review to REB decision);

c) the number of research subjects participating in research under the ethics oversight of the REB;

d) the nature and status of training and educational activities; and

e) the stakeholder satisfaction surveys.

4.6.5 Control of deviations

4.6.5.1 The REB shall, in collaboration with the highest body within the organization, take remedial action where a deviation from this Standard or from ethical, statutory or regulatory requirements, or from the organization's policies, where applicable, has been identified. Such actions shall include measures implemented to determine the cause of the deviation, and any corrective and preventative actions taken. The REB should assess whether re-review of the biomedical clinical trial is required. All decisions and actions shall be documented and reported in accordance with the policies of the organization.

4.6.6 Continuous improvement

4.6.6.1 Continuous improvement of the REB is achieved through an ongoing program consisting of the review of the following in order to implement corrective actions and preventative actions:

a) Routine or directed evaluations of the REB

b) Routine or directed evaluations of the research, which may include evaluation of consent processes, safety monitoring, and data integrity

c) Any feedback from investigators, sponsors, funders, and research subjects, and

d) Any feedback from regulators relevant to the protection of the rights, safety, and well-being of research subjects.

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