Proposed Revision of
Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans

- Chapter 11 -

Interventional Research

Introduction

The scope of this chapter encompasses all research involving human participants that involves (1) the prospective assignment of participants to one or more interventions and that also (2) presents more than minimal risk to participants. For the purposes of this Policy, research that meets both of these criteria is referred to as "interventional research." For example, a study of student learning success that prospectively assigns children to groups that will receive either the standard curriculum or an experimental curriculum uses prospective assignment and may present more than minimal risks to participants. A study that prospectively assigns participants to view words in different colours is a minimal risk study and would therefore not fall within this chapter. Similarly, a study that compares the effects of three different cancer treatments by tracking the outcomes of patients in a cancer treatment registry does not involve prospective assignment to the intervention and would, therefore, also not fall within this chapter. Relevant guidance in other chapters of this Policy should be sufficient to address any ethical issues raised by these types of studies.

This chapter provides guidance for issues that are frequently encountered in more-than-minimal risk interventional research such as intervention equipoise, justification of control groups and use of placebos, requirements for data and safety monitoring plans, reporting of new information, determining when an independent data and safety monitoring body (DSMB) may be necessary, and the registration of interventional research. Ethics issues specific to different phases and types of clinical trial designs are addressed at the end of the chapter.

In addition to the specific guidance provided in this chapter, the guidance provided elsewhere in TCPS 2 with respect to general ethics issues (e.g., consent), applies equally to interventional research. As is the case throughout this Policy, the welfare of participants takes precedence over the interests of researchers, institutions and sponsors.

Section A: Key Concepts

Interventional Research / Interventional Studies

For the purposes of this Policy, an interventional study is any study that prospectively assigns individuals or groups, to receive, or not receive, one or more interventions and that may involve more than minimal risk to participants. This definition includes pilot studies/trials, all phases of clinical trials and studies that may affect health or other aspects of participant welfare (e.g., educational opportunities, socio-economic status, access to services). Research that is focused on observing the effects of different conditions experienced by people due to circumstances other than researcher-directed prospective assignment (e.g., clinician prescription, provincial legislation, employer direction, natural occurrence), does not meet this definition of interventional research.

Intervention

An intervention is the planned imposition of a set of conditions on participants for the purposes of research. The conditions may be such things as a task, an activity, a treatment, exposure to stimuli, or a change to environment. The purpose of the research may be to describe, measure, evaluate, explain, or observe participants' reactions or responses to one or more of the imposed conditions.

Health-Related Intervention

A health-related intervention (e.g., involving drugs, surgical procedures, devices, behavioral treatments, psychological therapies, dietary interventions, environmental changes, process-of-care changes) is intended to affect participants' health. Although most health-related research is intended to confer direct or indirect benefits on participants or to groups to which participants belong, some research (e.g., phase I clinical trials) is focused on testing for the presence or absence of any harmful effects of an intervention.

Outcome

An outcome in the context of this Policy is a change (or absence of change) in a measure affected by an intervention in the context of research. That measure may be the variable or attribute of interest and/or related variables or attributes.

Health-Related Outcome

A health-related outcome is any outcome that concerns the health status of an individual, group or population.

Interventions may, or may not be, health-related and may, or may not, have a health-related outcome. For example, a comparison of the efficacy/effectiveness of two different hearing aids may have health-related outcomes (i.e., better hearing) as well as outcomes related to other aspects of welfare (e.g., increased confidence, better relationships). Similarly, a campaign that promotes prevention of bullying in selected schools may result in better peer relationships but also fewer incidences of physical assault than schools that have not yet implemented the campaign.

Clinical Trials

For the purposes of this Policy, a clinical trial is any interventional study in which both the intervention(s) and the outcome(s) are health-related.

Prospective Assignment of Participants

When a study involves one or more interventions and the study design or the principal investigator determines which intervention each participant will experience, this is known as prospective assignment. Prospective assignment may be randomized or based on specific criteria relevant to the study conditions. This assignment normally takes place before data collection, though it may be preceded by a screening process to help researchers determine whether prospective participants meet the inclusion criteria for the study. This screening process requires participant consent.

Prospective assignment may also take place at different points during a study. For example, a study may begin with all participants in the same group (or assigned to multiple groups), and after a period of observation or testing, the participants may be re-assigned to different groups.

Prospective assignment may be conducted at the level of individuals, groups or populations. For example, prospective assignment for a comparison of the effects of vitamin D on the general health and mood of seniors could be carried out by:

- randomizing individual participants to receive either vitamin D supplements or placebo pills; or

- running a cluster randomized trial in which health professionals in some clinics are assigned to give high dose vitamin D injections to their senior patients and health professionals in other clinics are asked to give low dose vitamin D injections.

Alterations to consent requirements that may be necessary for studies conducted at the group and population level are discussed in Article 3.7A.

Intervention Equipoise

Equipoise means a genuine uncertainty exists on the part of the relevant expert community about what interventions are most effective. This uncertainty necessitates the conduct of research to determine the comparative merits of existing interventions (not all of which may be represented in a given study). It is the starting point for interventional study design and review. In the context of clinical trials, this is referred to as "clinical equipoise." For interventional studies, this Policy refers to this as "intervention equipoise."

In studies where participants are prospectively assigned to different interventions (e.g., intervention A or intervention B or control group), ethical issues relevant to the principle of Justice arise when one group may fare better or worse than another. Intervention equipoise provides a link between the duty of care of the researcher with the need to do research to ensure that the interventions offered are demonstrably safe and effective.

Duty of Care

The concept of duty of care can be found in such contexts as teaching, social work, coaching, the manufacture of products, the provision of services, and the building of infrastructure. In a health care setting a health professional treating or managing a patient's conditions has a duty of care towards their patient. That is, the health professional is responsible for the patient's welfare and is obligated to:

- ensure patients are receiving an accepted standard of care;

- identify and manage any foreseeable risks to patients that may be associated with their care; and

- ensure patients are provided with enough information to make an informed choice about their care.

In a research setting, the researcher is responsible for participants' welfare (see Article 1.1) and is obligated to:

- identify and manage any foreseeable risks to participants that may be associated with the research (Chapter 2, Section B);

- provide participants with enough information to make an informed choice about whether to participate in the research (see Articles 3.1 to 3.3); and

- communicate any new information that may affect participants' welfare or consent decision (see Articles 3.4 and 11.8).

Researchers' responsibilities for the welfare of their participants are directly related to the level and types of risk and potential benefits posed by the research (see Article 2.10 research-attributable risk). A researcher has greater responsibilities towards participants than those of a health professional to a patient because, unlike clinical care, research is not premised on providing participants a direct benefit.

Risk and Proportionate Approach

Interventional studies, like other research covered by this Policy, are subject to a proportionate approach to research ethics review. Studies that pose greater foreseeable risk to participants should receive proportionately higher levels of scrutiny (see Article 2.9). Not all interventional studies are high risk and care should be taken to avoid automatically classifying them as such (see Article 2.10 re: Research-Attributable Risk). However, because some interventional studies may include people who are in circumstances of vulnerability, the risk of serious harm or death must be considered. Interventional studies, including pilot studies that are classified as more than minimal risk shall be reviewed accordingly (see Articles 6.11 and 6.12).

It is the responsibility of researchers to clearly describe all foreseeable risks and potential benefits of their research to prospective participants in the consent process (see Article 3.2). It is the responsibility of the REB to weigh the foreseeable risks to participants against the potential benefits of the research in the context of a proportionate approach to research ethics review, and to discuss with the researcher ways to eliminate or minimize risks where possible.

Principal Investigator

In studies involving more than one researcher, particularly multi-site studies, the researcher who has overall responsibility for the ethical conduct of the study, and for the actions of any member of the research team, is known as the principal investigator (PI). The PI is responsible for communicating any changes to the study, material incidental findings, new information, and/or unanticipated events to their own REB as well as to local site researchers, who must then inform their local REBs.

Stopping Rules

In the context of balancing foreseeable risks and potential benefits, researchers and REBs must consider the need for mechanisms to (a) remove individual participants from a study for their own safety, and (b) stop the study (temporarily or permanently) due to evidence of greater than expected harms or greater than expected benefits in any of the study conditions. These mechanisms are most commonly referred to as "stopping rules."

A stopping rule is a pre-determined rule that specifies the conditions under which a decision may be taken to remove individuals from a study (individually-based stopping rule) or to pause or stop a study before its planned end date (study-wide stopping rule). Stopping rules may also specify what action should be taken (e.g., referring a participant for alternative treatment, or moving to another phase of the study,). An individually-based stopping rule can also specify that participants who are not complying with the study procedure may be removed from the study. All individually-based stopping rules must be disclosed to participants during the consent procedure (see Article 3.2). Stopping rules are most commonly used in clinical trials, but there may be some circumstances under which they apply to non-clinical intervention studies. Factors to consider in determining the need for stopping rules appear in Article 11.5.

Study-wide stopping rules help researchers identify when a study should be stopped due to compelling evidence that:

- a study condition is more or less efficacious or effective than another;
- a study condition is more or less safe than another; or
- the study is futile because:
    - the data are invalid or unreliable (e.g., due to insufficient numbers of participants);
    - it is unlikely that the findings will be able to address the research question based on the collected data.

Study conditions are experimental intervention, standard of care, and control conditions.

A stopping rule consists of one or more safety and efficacy criteria (end-points) that individual or study-wide data must meet to warrant a temporary or permanent stop to:

- participant involvement in a study;
- one or more arms of a study; or
- the entire study.

For example, in a study comparing an experimental drug for leukemia with the standard treatment, one end point may be the onset of an infection due to some participants' weakened immune systems. This end point may be used to remove participants from the study for their own safety but may not warrant stopping the entire study. Another end point may be the onset of remission in a pre-set percentage of participants in any arm of the study. If the experimental intervention is achieving higher rates of remission than the standard of care, then this may trigger a decision to pause or stop the trial for reasons of superior efficacy. If the severity of side effects is greater than expected among participants receiving the experimental intervention, then the study may be stopped for reasons of inferior safety. If the study cannot attract enough participants to yield valid results or if the design of the study was compromised in some way (e.g., mistakes in procedure, non-compliance of participants) the researcher may decide to end the study for reasons of futility. To avoid real, perceived or potential conflicts of interest, researchers may have an independent DSMB assess whether the interim analyses of a study meet the criteria that might trigger a stopping rule.

Section B: Scope of the Chapter

Article 11.1

All studies (including pilot studies/trials – see Articles 2.1, 6.11 and Section F) that meet the following two criteria are required to follow applicable guidance in this chapter:

a) the methodology includes prospective assignment to one or more interventions; and

b) one or more interventions involve more than minimal risk to participants.

Application

Paragraph (a) recognizes that the methodology of prospective assignment gives the researcher the power to determine which participants will receive an experimental intervention, a standard intervention, or no intervention. In contrast to observational research, where the researcher has no role in determining the conditions of the interventions that participants do or do not experience, interventional research places greater responsibility on the researcher for the welfare of participants.

As indicated in paragraph (b), research that involves prospective assignment and poses minimal, or below minimal, risk to participants does not fall within the scope of this chapter. The use of prospective assignment is considered to be mitigated in studies that are unlikely to affect participants' welfare (e.g., perception or opinion studies in which different groups of participants are exposed to different sets of minimal risk stimuli).

The table below provides examples of studies that do and do not meet Article 11.1 criteria (a) and (b):

Prospective Assignment	More than Minimal Risk	Research Examples	Required to Follow Chapter 11 Guidance
Yes	Yes	A phase 1 clinical trial in which one group of healthy volunteers is exposed to a new treatment for depression for the purpose of assessing dosage and safety.	**Yes** This study uses prospective assignment and may present more than minimal risks to participants (e.g., effect of treatment on physical and mental health).
Yes	Yes	A comparison of the safety and efficacy of a vegan nutrition program for seniors in which participants are prospectively assigned to receive three months of meals representing one of three programs (vegan, vegetarian, or meat inclusive).	**Yes** This study uses prospective assignment and may present more than minimal risks to participants (e.g., effect of diet on physical and mental health).
Yes	Yes	A study of student learning success that prospectively assigns children in an early education program to groups that will receive either the standard curriculum or an experimental curriculum that may improve short and long-term learning outcomes.	**Yes** This study uses prospective assignment and may present more than minimal risks to participants (e.g., effect of learning outcomes due to curriculum on social or economic status, self-esteem, mental health).
Yes	No	A study of voter turnout comparing the effectiveness of two interventions: Participants are randomly selected to receive either a phone call or a letter.	**No** This study uses prospective assignment but the interventions do not present more than minimal risk to participants.

Prospective Assignment	More than Minimal Risk	Research Examples	Required to Follow Chapter 11 Guidance
Yes	No	A comparison of two types of online health survey questionnaires in order to see which one is more user-friendly in terms of structure, navigation, and readability. Participants are prospectively assigned to one of two questionnaires.	**No** This study uses prospective assignment but the interventions do not present more than minimal risk to participants.
No	No	A comparison of the efficacy of two different chemotherapy regimens currently accepted as the standard of care for children diagnosed with Hodgkin's Lymphoma. The choice of regimen is made by each patient's circle of care rather than the researcher.	**No** This is an observational study as the researchers play no role in the assignment of participants to interventions. Any risks or benefits of the interventions would occur regardless of whether the observational study was carried out.
No	No	1) An online survey of the frequency and type of internet usage reported by high school students. 2) A comparison of the frequency and type of health-care service usage by populations of urban centres and rural areas using de-identified administrative data from provincial health care systems.	**No** Neither of these studies uses prospective assignment and they do not present more than minimal risk to participants.

Section C: Assessing Safety and Minimizing Risk

Participants enrolled in interventional studies may be exposed to specific, and possibly unknown, risks. Because of the experimental nature of interventions, the potential harms can be physical, psychological social or economic. In some cases, they may cause lasting, irreparable damage. Prospectively assigning participants to receive, or not receive, an intervention carries with it a heightened responsibility for participants' welfare because the nature and extent of foreseeable risks and/or potential benefits that participants may experience is dictated by the researcher. It is the responsibility of researchers and REBs to ensure that (a) foreseeable risks to participants are minimized and appropriately evaluated alongside potential benefits, and (b) participants are clearly informed as to the nature of these foreseeable risks and potential benefits.

Article 11.2

Researchers and REBs shall:

a) identify all reasonably foreseeable risks and potential benefits;

b) indicate how identified risks will be eliminated, minimized and/or managed; and

c) demonstrate that the foreseeable risks to participants are justified by the potential benefits to be gained (see Chapter 2, Section B).

Application

Disciplinary standards applicable to the research should be considered, as well as any particular ethical issues that correspond to the study (e.g., pilot studies or trials, phase I through IV clinical trials, socio-behavioral studies, cluster randomized designs). As stated in Article 6.4, the REB must have reviewers with the appropriate expertise who can evaluate the research proposal in the context of relevant disciplinary standards and assess the likelihood and magnitude of foreseeable risks to participants.

The proportionate approach to research ethics review dictates that interventional studies determined to be a higher level of risk should be subject to a higher level of scrutiny. The researcher has a responsibility to present the proposed research in the context of a systematic review of the literature on that topic. Interventional research should not be conducted unnecessarily on questions that have already been definitively answered. The REB should carefully evaluate previous relevant research provided by the researcher (e.g., laboratory, animal and human research with a drug or other therapy in the case of clinical trials), and/or have an expert evaluation undertaken on its behalf.

Throughout the life of a study, if there is evidence that participants' welfare is unexpectedly being affected (positively or negatively) beyond anticipated risks and benefits by some element of the study, the researcher must report this as an unanticipated event to their REB, formulate a plan for disclosure of the information, and take any other steps that are necessary to promote the welfare and safety of participants (see Articles 6.14, 6.15 and 6.16).

Control Group Studies

Assessing Risks for Control Groups

It is important to avoid the error of equating the absence of a potential benefit to participants who are assigned to a control group as a risk. For example, in a study comparing the addition of a new treatment for heroin addiction to the standard treatment, some participants will be prospectively assigned to receive this intervention and some will not. Those who are assigned to the control group are no better or worse off than if no research were taking place. It is the intervention group that is exposed to any harms or benefits of the intervention, e.g., the intervention may or may not work, or it may have unforeseen side effects.

The role of the researcher is to address the research question – to discover if a particular intervention is beneficial or less harmful than the status quo. It is the role of advocates, policy makers and service providers to use the findings of research to ensure the equitable distribution of potential benefits.

Justification of Control Group

In the design of interventional studies, the choice of control group or comparison group raises specific ethical issues. The balance of foreseeable risks and potential benefits to participants must be carefully

considered – regardless of whether the design requires comparison of the experimental intervention group with a standard condition group, a placebo group, a no-condition group, or a staggered application of an intervention group (e.g., wait-list group). Article 11.3 addresses the considerations required of researchers and REB members to assess whether a particular control group design is ethically acceptable. Article 11.4 deals specifically with the ethical issues pertaining to the use of placebos.

Article 11.3

Researchers must justify their choice of control group(s) to the REB by demonstrating that the choice is:

a) relevant to the research question;

b) appropriate for the population of interest; and

c) consistent with the criteria for intervention equipoise.

Application

The use of prospective assignment of participants to different groups may result in one group of participants experiencing greater benefits or greater harms than another. Prospective assignment must be justified by the research question. It is important that the researcher take into account relevant characteristics of the participant population when choosing the type of control group. For example, a wait-list control group may not be appropriate for investigation of a behavioural approach to anxiety due to the increased anxiety participants in the wait-list condition may experience.

In the context of studies that involve interventions intended to have a beneficial effect upon participants, there must exist a genuine uncertainty (i.e., intervention equipoise) on the part of the relevant expert community about what interventions are most effective.

Use of Placebos

The term “placebo” traditionally refers to an inactive substance or treatment (e.g., a pill, an injection, exposure to light) given to participants to simulate an active substance or treatment. The purpose of using a placebo as a comparator is to control for the reaction participants may have to any kind of intervention and their beliefs about its possible effects in order to focus on any real effects of the experimental intervention.

The use of placebos raises specific ethical issues such as whether the foreseeable risks and potential benefits of the study justify some participants receiving the experimental intervention and others receiving an inactive imitation.

It is the responsibility of the researcher or sponsor to provide justification to the REB for the choice of a placebo control group, as opposed to the other possible choices (e.g., active control, wait-list control, dose-response and combination therapies).

Article 11.4

A new therapy or intervention should generally be tested against an established effective therapy. Use of placebos may be justified when all of the following conditions apply:

a) The use of placebos does not compromise the safety, health, or welfare of participants;

b) It is not possible or practicable for the control group to receive an established effective intervention as a comparator. There are several circumstances in which this situation might arise, including, but not limited to instances where:

- there are no established effective interventions for the population or for the indication (e.g., disorder, illness, behaviour) under study;
- existing evidence raises substantial doubt within the relevant expert community regarding the net benefit of available interventions;
- prospective participants are resistant to the available interventions; and/or
- prospective participants have provided an informed refusal of established effective interventions.

c) The researcher provides to the REB a compelling justification for the use of placebos, as opposed to other possible choices, to establish the safety and efficacy of the experimental intervention or therapy;

d) The researcher and the REB ensure that the general principles of consent are respected and that participants or their authorized third parties will be specifically informed about (see Article 3.2):

- any intervention or therapy that will be withdrawn or withheld for purposes of the research; and
- the anticipated consequences of withdrawing or withholding the intervention or therapy.

Application

Researchers should always first consider an available, proven, effective intervention or therapy for use as a comparator. If this is not possible, however, then using placebos can be an ethically acceptable choice as long as the criteria in Article 11.4 are met.

With respect to paragraph (a), some studies involving use of placebos may pose only minimal risk to participants while others may pose greater than minimal risk. Chapter 2, Section B, should be considered when assessing the risks to participants. Risks must be assessed for all participants regardless of the group to which they are assigned. For example, consider the following two designs:

- a group receiving a placebo is compared to a group receiving an experimental therapy;
- a group receiving an established effective therapy supplemented with an experimental therapy is compared to a group receiving an established effective therapy plus a placebo.

Paragraph (b) indicates that use of placebos may be justified only when it is not possible or practicable for the control group to receive an established, effective intervention and provides a list of some circumstances where this might be the case. For example, when prospective participants are resistant to available interventions, they would derive no benefit from receiving them, and are therefore not disadvantaged by being assigned to a placebo control group. The determination of resistance (i.e., the established intervention is not, or is no longer, effective) must take place outside the context of recruitment and prior to offering study participation to the prospective participant. The determination must be documented. The same holds true for situations in which the potential participant has provided an informed refusal of the established, effective intervention.[1]

Paragraph (c) requires the researcher to justify the decision to use placebo control instead of other possible options. The design must be methodologically sound to be ethically acceptable research. The use of placebos must be necessary to address the research question. For example, in a study comparing a combination of two therapies against two therapies normally administered singly, the research design would call for an intervention group to receive the combined therapy. One control group would receive one therapy plus a placebo. A second control group would receive the other therapy plus a placebo. This design preserves the integrity of blinding and protects the scientific validity of the study without posing unnecessary additional risks to participants.

According to paragraph (d), participants must be told that they may be assigned to a placebo group as part of the informed consent process (see Article 3.2).

Use of Placebos in Superiority and Non-Inferiority Studies

A superiority study is one in which the researchers empirically test whether an experimental intervention is more effective or beneficial than a control intervention. A superiority study may be placebo-controlled when the control intervention is a placebo or sham intervention, or it may be actively controlled when the control intervention is an established effective intervention. The use of an active control comparator in a study of an experimental intervention is an ethically appropriate study design when an established effective intervention exists for the population included in the study.

A non-inferiority trial is one in which the researchers empirically test that an experimental intervention that offers some advantage, is not unacceptably less effective or beneficial than a control intervention. From an ethical perspective, a critical component in such trials is defining, in advance of the trial, the maximal lowering of effectiveness that would be acceptable in order to justify use of the experimental treatment. An advantage of a non-inferiority trial is that placebos are not used and both groups receive an active intervention.

For example, consider a trial of an experimental medication for lung cancer. The experimental medication offers one or more advantages over the established treatment such as fewer side effects, lower cost, or easier administration. Physicians and patients would like to capitalize on these advantages and use the experimental medication, but only if this does not come at the cost of significantly lowering survival. In such an instance, one would conduct a non-inferiority trial to show that the experimental medication is not unacceptably less effective than the established treatment with respect to survival.

To properly assess the ethics of placebo-controlled superiority design vs. active controlled non-inferiority design, an appreciation of the interplay of ethics and science is required (see Article 2.7). There may also be regulatory considerations. Conditions that work against carrying out a non-inferiority trial successfully include low and/or variable response to the existing treatment. The researcher must provide adequate justification for the use of a non-inferiority design.

Section D: Safety Monitoring and Reporting New Information

In accordance with the core principle of Concern for Welfare, it is a key responsibility of researchers and REBs to ensure that, as interventional studies proceed, any evidence of positive or negative effects is recorded, any risks to participants remain in the acceptable range, and the safety of participants is monitored. This is part of the responsibilities of researchers towards participants that are sometimes referred to as a duty of care.

Article 11.5

Researchers shall provide the REB with an acceptable plan for monitoring safety, efficacy/effectiveness (where feasible) and validity. This plan shall describe:

a) how participant safety will be monitored and what actions will be taken in the event of a threat to participant safety;

b) how intervention efficacy will be monitored (where feasible) and what actions will be taken if efficacy is found to be greater than expected;

c) the individually-based stopping rules by which participants may be removed from a study for safety reasons;

d) the study-wide stopping rules (if any), by which studies may be stopped or amended due to evidence of inferior safety, superior efficacy or futility; and

e) the reporting procedure that will be followed to ensure any information relevant to participant welfare or consent is reported clearly and in a timely fashion to the REB.

A data and safety monitoring plan may (but need not) include the establishment of an independent DSMB.

Application

Researchers and REBs must ensure that every interventional research proposal includes a plan to monitor the ongoing safety of participants, the efficacy of interventions (where feasible) and the validity of the study itself. The responsibility for establishing a data and safety monitoring plan lies with the researcher or the research sponsor. The REB must assess whether the plan sufficiently addresses the foreseeable risks and potential benefits for study participants.

Paragraphs (c) and (d) require that the data and safety monitoring plan describe any mechanisms for removing participants for safety reasons and/or for stopping a study for reasons of safety, efficacy or futility. Stopping rules are the most common mechanism for making these decisions. All interventional research that poses more than minimal risk to participants should have individually-based stopping rules by which participants who are experiencing harm can be removed from the study. See Article 11.6 for factors to consider when deciding whether a study should have study-wide stopping rules and/or an independent DSMB.

Paragraph (e) requires the data and safety monitoring plan to describe the reporting procedure that will be followed. In order to fulfill their mandate to safeguard the interests of participants, REBs require sufficient information about the study design, stopping rules, monitoring mechanisms at the point of initial review, as well as reports of unanticipated events and any proposed changes to approved study design (Article 6.14 to 6.16 and 11.8).

Researchers are responsible for ensuring that the results of any interim analyses that affect participant welfare or consent are provided to REBs. This summary report should be provided promptly and should include information about the context and significance of reported data to permit a fair interpretation and meaningful review by the REB. When the REB requires additional information, the researcher shall provide it. If necessary, the REB may require that this evaluation be conducted by a qualified source. This source should be independent of any sponsor – such as an independent DSMB (if a DSMB does not already exist). The source should not be in conflict of interest (see Chapter 7).

Additional Considerations for Clinical Trials

In the case of clinical trials, there are provincial, national and international guidelines or legal requirements that govern data and safety monitoring and reporting of new information. It is the responsibility of researchers to be aware of any additional guidelines that apply to their research and to adhere to them for the safety and benefit of participants.

Independent Data and Safety Monitoring Bodies (DSMBs)

DSMBs are known by a variety of names including "data monitoring committees," "data safety committees," and "data and safety monitoring boards." They are comprised of people with the relevant scientific, ethical and/or community expertise to oversee the data and procedures of one or more ongoing studies with respect to participant safety, intervention effects and data validity. The duties of independent monitoring bodies are typically described in a charter based on a study design approved by an REB. These duties may include applying stopping rules and recommending changes to the study design.

An independent DSMB normally conducts regular monitoring of the data from all sites (in the case of multi-site studies) at pre-set intervals. In the case of blinded studies, independent DSMBs can unblind data for the purpose of making recommendations based on the results of interim analyses. Information pertaining to the welfare and/or consent of participants must be reported to any REBs that have approved the study (see Articles 6.14, 6.15 and 11.7). Not every study is required to have an independent DSMB. Factors to consider when making this decision appear in Article 11.6.

The appointment of an independent DSMB does not alter the responsibilities of researchers and REBs to monitor safety, efficacy and validity throughout the conduct of the study. In the context of multi-site research, when new information or material incidental findings at one site could be relevant to participant welfare and consent at other sites, principal investigators must ensure that this information is shared with researchers at each site and with REBs (Article 3.4 and 11.7). The REB must be prepared to act upon these reports, especially where urgent action is required (see Article 11.8).

Article 11.6

The following factors should be considered to determine whether a study, with or without stopping rules, should have an independent DSMB:

a) the magnitude of foreseeable research-attributable harms to participants;

b) whether the circumstances of the participants make them vulnerable in the context of research;

c) the feasibility of interim data analysis;

d) the complexity of the study; and

e) conflicts of interest.

Application

Not all interventional studies require an independent DSMB but it is important to consider the factors listed in this article before making this decision. As participants in an interventional study may be prospectively assigned to an intervention that poses more than minimal risk, the magnitude of foreseeable harm is a primary consideration even if the probability is low. If the possible outcomes for participants in an interventional study are severe (irreversible harm or death), the study is more likely to need an

independent DSMB and stopping rules than a study in which the possible outcomes are moderate (temporary, non-life-threatening conditions). For example, a study assessing the effectiveness of a non-toxic remedy for the relief of cold symptoms may be less likely to need stopping rules than a study assessing the effect of a highly toxic drug on rates of lung cancer mortality. Researchers and REBs should also consider the invasiveness of the intervention involved and whether there is prior evidence of high risk to participant safety.

Interventional studies in which the intended participant population is already at risk due to their existing circumstances (e.g., weakened mental state, weakened immunity, lack of access to support) may need stopping rules to ensure that researchers and/or independent DSMBs can recognize when incidents of harm to participants require a reconsideration of the study design. It is important to distinguish between idiosyncratic incidents of harms that are limited to a small number of participants from incidents of harm that indicate a general problem with the study design and/or procedures.

For a stopping rule to be effective there must be sufficient data available for analysis prior to the conclusion of the study. Studies of short-term interventions or studies of small participant groups may not generate enough data to permit the use of a study-wide stopping rule. However, in short-term studies in which participants are at high risk of severe outcomes, researchers and REBs should consider whether a staged enrollment design with pauses to permit interim analyses and application of stopping rules is warranted. In studies of interventions that may not reveal their effects on participants until long after the intervention has ended (e.g., the effect of elementary school abstinence education on rates of teen pregnancy), interim analyses are not practicable. If the study design does not permit timely interim data analyses that could have an impact on participant safety or well-being, there may be no purpose to establishing study-wide stopping rules.

Studies that involve multiple data collection sites, blinded data, long-term data collection and/or large numbers of participants may need an independent DSMB regardless of whether study-wide stopping rules are indicated. The interim analysis of all available data is necessary to determine whether measures of harm or benefit to participants meet the criteria for individually-based or study-wide stopping rules. Individual site researchers without the same level of access to data and the expertise to conduct the necessary analyses may not be able to make informed decisions in the best interests of participants. Conversely, a single site study with unblinded data collection and clear stopping rules may not require an independent DSMB.

The use of independent DSMBs is one way to manage studies in which conflicts of interest within the research team or among research partners are a concern. Safety can be maximized and futility minimized by having an independent DSMB conduct interim analyses of data. The DSMB can also make recommendations about the study design and real, potential or perceived conflicts of interest that could affect decisions about the validity of data or evidence for efficacy/effectiveness. The membership of the DSMB should also be as free of real, potential and/or perceived conflicts of interest as possible (see Chapter 7).

Reporting New Information: Considerations for Interventional Research

Article 11.7

Researchers shall promptly report new information revealed during the conduct of the study that might affect the welfare or consent of participants, to the REB, to a publicly accessible registry (where relevant – see Article 11.9) and to other appropriate regulatory or advisory bodies. When new information is relevant to participants' welfare, researchers shall promptly inform all participants to whom the

information applies (including former participants). Researchers shall work with their REB to determine which participants must be informed, and how the information should be conveyed.

Application

In the course of any type of interventional study, new information may arise that is relevant to participants' welfare or their ongoing consent to participate (see Articles 2.8, 3.3, 3.4, 6.15 and 6.16) This new information might arise from unanticipated issues (e.g., adverse reactions to interventions) or from routine evaluations of participant health or welfare that occur in the context of the study. It might pertain to all participants, to those in one arm of an intervention, or only to one participant with a particular issue. It might be information that arises from other related research that has repercussions for ongoing studies. To understand the particular relevance of new information, it should be considered from the perspective of the participant. Article 11.7 outlines the continuing duty of researchers to share new and relevant information regarding interventional studies with the REB, the publicly accessible registry (if applicable – see Article 11.9) and other appropriate bodies. This information may also need to be shared with participants and, possibly, other relevant third parties (e.g., family members, circle of care), as indicated by the nature of the information. The more relevant, serious and urgent the information, the more promptly it should be disclosed.

New information that arises outside the study (e.g., new findings in related research) must also be disclosed when that information is relevant to the participants' ongoing consent to participation. Researchers should also promptly share new information about an intervention with other researchers or health professionals administering it to participants or patients, and with the scientific community – to the extent that it may be relevant to the general public's welfare. New information thus covers a range of matters that includes, but is not limited to, the following:

- changes to the research design;
- evidence of any new risks;
- unanticipated issues that have possible health or safety consequences for participants;
- new information discovered in the course of the study before the end of study date that decisively shows that the benefits of one intervention exceed those of another;
- new research findings, including relevant non-study findings discovered before the end of study date;
- unanticipated problems involving lack of efficacy/effectiveness, recruitment issues or other matters determined to be serious enough to warrant disclosure; or
- closure of studies at other sites for reasons that may be relevant to the welfare or consent of participants in the ongoing study.

The duty to report new information to the REB, along with the necessary analysis and evaluation to make the new information interpretable, lies with the researcher. It is incumbent upon the researcher to keep abreast of reports of findings from studies investigating similar interventions (e.g., through professional journals, online reports, conferences, contact with colleagues). New findings that are reported during the conduct of a study may affect the assumption of equipoise between the interventions/control groups made

during the design phase of that study. For example, if a study reported that intervention A was conclusively safer or more effective than intervention B, any other studies testing either of these two interventions would need to report this finding to their REBs (and/or DSMBs where in use) and consider the impact of this finding on equipoise, participant welfare and participants' ongoing consent.

In the case of newly discovered risks or unanticipated issues, the report shall also include a plan to eliminate or mitigate any increased risks to participants. The REB should encourage researchers to raise potentially relevant developments with the REB at an early stage to better determine the appropriate scope and timing of information sharing with participants and regulatory authorities.

When new information is relevant to the welfare of all participants, researchers and REBs have a duty to ensure that all participants are informed. Where new information affects only participants currently in the study, the REB may decide that former participants need not be informed. However, researchers may decide to voluntarily share this information with all participants if they choose.

In multi-site studies, when new information arises at one site that may affect participant welfare or consent at other sites, the researcher in charge of that site shall promptly inform the principal investigator of the study. The principal investigator shall inform researchers at all other sites of the study. It is the responsibility of the researcher in charge of each site to ensure that their REB receives this information in a timely fashion.

The welfare of participants must also be considered when a study is unexpectedly discontinued. When a researcher, a sponsor or other body stops or unblinds all or part of an interventional study, the principal investigator has an ethical and, in the case of clinical trials, a regulatory responsibility to inform both study participants and the REB of the discontinuance or unblinding and the reasons for it. For studies that are registered with a publicly accessible registry (see Article 11.9), this information must be added to the appropriate fields (see Article 11.10). Any risks to participants that may arise from the unexpected closing of the study must be communicated in writing to the REB and the participants. The researcher shall indicate any measures that will be taken to mitigate these risks.

The obligation to report new information ends with the completion of the study. The formal end of the study must be defined in the application for REB review. Any change to the end of study definition would require a submission of a request for change to the study design (see Article 6.16) for REB review. Typically, the end of the study will be the last contact with the last participant for the purposes of collecting data or human biological materials, or for the purposes of follow-up monitoring as described in the study design. If there is concern that new information might be revealed during the analysis of data, the completion of final data analysis may be defined as the formal end of study**.**

Article 11.8

REBs shall develop procedures to review reports concerning safety, efficacy and/or validity, incidental findings and other new information arising from interventional research that may affect the welfare or consent of participants. They should be prepared to take appropriate steps in response to these reports.

Application

As noted in the preceding articles and elsewhere in the Policy (e.g., Articles 3.4, 6.15, 6.16, 11.9, 11.10), REBs can expect to receive safety reports, efficacy reports, material incidental findings and new information, including, but not limited to, unanticipated issues, changes to the research design and newly discovered benefits or risks. It is the REB's responsibility to establish procedures for reviewing these reports that will be used to determine how they will respond to evidence of increased risks or benefits to

participants, and to be ready to implement these responses as needed. Responses shall be relative to the magnitude and likelihood of the risk or benefit to the welfare of participants within their jurisdiction. REBs may advise researchers as to the steps to take to eliminate or mitigate newly reported risks, or to equitably distribute benefits, and how this information should be shared with participants (see Articles 3.4, 6.15, 6.16 and 11.8). In exceptional cases, REBs may decide to suspend recruitment, or to suspend all participant involvement in a study pending further investigation.

Section E: Transparency and Accountability

To best serve the interests of participants and the wider research community, it is essential that research be conducted responsibly – that real, perceived and potential conflicts of interest affecting the research be managed appropriately, and that research findings be accessible and verifiable. Ultimately, this best serves the general public who rely on the findings of research.

The guidance in this section addresses the responsibilities of researchers, institutions, and sponsors of research to ensure that the:

- details of interventional research (e.g., existence of studies, changes to the study, findings) are readily available through publicly accessible registries; and
- contribution of participants to the research enterprise is respected through timely and accessible dissemination of all findings.

Fulfilling these responsibilities results in improved transparency of research conduct and greater accountability on the part of researchers, institutions and sponsors. It also leads to better accessibility of findings for all members of the research community and for society at large.

Registration of Interventional Research

There are compelling ethical reasons for the registration of all interventional studies. Registration improves researchers' awareness of similar studies so that they may avoid unnecessary duplication and thereby reduce the burden on participants. Registration also improves researchers' ability to identify potential collaborators and/or gaps in research so that they may pursue new avenues of inquiry with potential benefits to participants and to society. Perhaps of most concern is the danger that some researchers or sponsors may only report studies with favourable outcomes. When all studies must be registered, it makes it easier to identify those studies where outcomes have not been reported or findings have been withheld. At present, registration is only required for clinical trials, but this practice should be encouraged wherever it is possible to register other types of interventional studies.

The registration of interventional research upholds the principles of Respect for Persons, Concern for Welfare, and Justice, by ensuring that the efforts of all participants in interventional research are acknowledged, and by reducing the potential for endangerment of others through publication bias.

Article 11.9

All clinical trials shall be registered before recruitment of the first trial participant in a publicly accessible registry that is acceptable to the World Health Organization (WHO) or the International Committee of Medical Journal Editors (ICMJE). The registration of non-clinical interventional studies is strongly encouraged where possible.

Application

This Article applies to all clinical trials, including those that are minimal risk.

Clinical trial registries are intended to increase transparency and accountability by providing a record of clinical trials at the recruitment stage that can be used to locate publication of trial results. This helps prevent publication bias, that is, the selective publication of only those trials that yield results in support of an intervention. These registries contribute to a multi-faceted approach to eliminate non-disclosure. The collective goal is to reduce publication bias, and prevent the suppression of data in clinical research. It is possible to register non-clinical interventional studies with several of the WHO/ICMJE accepted registries. When this is not possible for non-clinical interventional studies, a discipline-specific registry is acceptable.

Clinical trials shall be registered in a registry that is compliant with the criteria set by the World Health Organization (WHO) or International Committee of Medical Journal Editors (ICMJE). All fields outlined in the WHO Trial Registration Data Set (TRDS) must be completed in order for a trial to be considered fully registered. Researchers shall provide the REB with the number assigned to the trial upon registration.

Article 11.10

Following registration of their study in accordance with Article 11.9, researchers are responsible for ensuring that, the registry is updated in a timely manner with:

- new information (see Article 11.7);
- safety and, where feasible, efficacy reports (see Articles 11.5);
- reasons for stopping a trial early; and
- location of findings.

Application

Researchers shall promptly update the study registry with any new information that may affect the welfare or consent of participants. Updates to the registry are also required for any changes to the trial that require REB review and approval, safety information such as unanticipated events that occur during a trial, and decisions taken to end a trial early. In the case of a trial that has stopped early, an explanation must be provided as part of the update to the registry. Where no specific field for this information exists, updates can be added to descriptions of study design and/or intervention (or an equivalent data field).

When the trial has ended, researchers are required to update the registry with reports of findings or information about where to access findings (e.g., lists of publications, links to publications or to the trial website) as they become available. Where possible, this information can be reported earlier to the registry in descriptions of study design, intervention, or an equivalent data field.

Conflicts of Interest in Sponsored Research

Interventional research can be affected by all types of conflict of interest: personal; professional; and institutional (as described in Chapter 7). Financial conflicts of interest can be of particular concern to interventional researchers. For example, it has been empirically established that financial conflicts of

interest in sponsored interventional studies (particularly clinical trials) can undermine the ethical conduct of research.

Article 11.11

Researchers and REBs should be aware of, and consider the possibility of, financial conflicts of interest in sponsored interventional research. They shall ensure that financial considerations do not affect participant safety, scientific validity and/or the transparency of the research process.

Application

Researchers and REBs shall consider the potential for conflicts of interest when designing and reviewing interventional studies. They should ensure that interventional studies meet appropriate standards of participant safety in accordance with the core principles of this Policy. See Article 7.4 for guidance on identifying and managing financial conflicts of interest.

Section F: Ethical Issues for Clinical Trial Design and Review

This section discusses ethical issues associated with the design and review of clinical trials. Guidance for the most common types of clinical trials (pharmaceuticals, medical devices) as well as other types of trials (natural health products, psychotherapy and surgery), is provided in sub-sections of the Application of Article 11.12. Though not all possible clinical trial designs are represented in this section, the guidance provided can be applied and adapted as needed. In all clinical trials, researchers and REBs should be aware of ethical issues including, but not limited to, registration, safety, selection and recruitment of participants, undue inducement, consent, dissemination of findings, and real, potential or perceived conflicts of interest. Researchers and REBs should also consider how applicable regulations affect the design and conduct of clinical trials.

Article 11.12

In the design and review of a clinical trial, researchers and REBs shall consider the type of trial (e.g., pharmaceutical, natural health product, medical device, psychotherapy), its phase (if appropriate) and the corresponding ethical issues associated with it, in light of the core principles of this Policy.

Application

Each type of clinical trial has specific ethical issues that correspond to the risks faced by the participants. In a proposal submitted for research ethics review, the researcher shall clearly specify the type of trial proposed (and, where relevant, its phase), identify the potential benefits, the foreseeable risks and how they will be managed, and show how this information will be clearly communicated to participants in the consent process (see Article 3.2).

REBs reviewing clinical trials need to be familiar with the ethical issues raised by different phases, and by different types, of clinical trials. REBs should satisfy themselves (with the assistance of external expertise, if necessary) that the trial is appropriate and that the foreseeable risks to participants are justified by the potential benefits. This guidance applies equally to continuing research ethics review, including requests to make changes to the method, statistical procedures, inclusion/exclusion criteria, or other elements of approved research (see Articles 6.14 and 6.16).

Pilot Trials

Pilot trials, also known as feasibility or vanguard trials, are done to assess the feasibility of a clinical trial and are not expected to produce definitive results. For example, they may assess the safety of interventions, recruitment potential or coordination of multiple centres. They can be used to determine the necessary sample size needed for the main trial and are sometimes built into the research proposal for the main trial. The benefit of pilot trials is that they can prevent the investment of participant and research time and effort in trials that are unlikely to succeed in addressing the research question. As with main trials, pilot trials shall undergo ethics review. Clarity of purpose and informed consent are the primary ethical issues concerning pilot trials. While there are often no direct benefits from the findings of pilot trials, they do provide an indirect benefit to participant groups and society of informing the design of the main trial (and other similar trials). A fear that prospective participants will not be interested in joining a trial that will not yield conclusive findings about the intervention can lead to reluctance on the part of researchers to be clear about the purpose of the trial. REBs must ensure that the recruitment and consent processes for pilot trials disclose their true purpose and do not over-estimate potential benefits or underplay risks.

Pharmaceutical Trials

Clinical trials involving pharmaceutical products are commonly categorized into four phases, each of which gives rise to particular ethical issues. Detailed descriptions of the phases of clinical trials are provided in other guidance documents (see References). The ethical concerns described are most likely to arise in a specific phase of a clinical trial. Some issues may arise at any phase of a clinical trial.

Phase I Trials

Safety concerns are particularly acute in phase I research because it may be the first time participants are exposed to the new drug ("first-in-human" trials), and there may be little or no experience with the drug. Phase I trials often depend on healthy participants who are offered incentives for their participation, or they may include participants with specific diseases for whom conventional therapy has failed. The combination of clinical risk with uncertain or no likelihood of clinical benefit, and the often substantial incentives offered to participants, raises ethical concerns about safety, the selection and recruitment of participants, and the consent process. For safety, it is important to ensure that the drug is initially given to a small number of participants and that dosing is increased in clearly defined increments only after participants' responses to the initial dose is known. Recruitment and consent procedures shall ensure that participants are aware of the untested nature of the therapy and that participants do not accept, because of the incentives being offered, risks they would otherwise refuse.

Phase II Trials

Phase II, or combined phase I/II clinical trials raise particular ethical concerns, because they are often conducted with populations whose therapeutic options have been exhausted. Examples include patients with cancer that is incurable by standard therapies, or people with conditions that cause them acute or chronic pain. These circumstances may affect the perceptions of patients and their families as to the balance between the risks and potential benefits of the trial and thus may affect their decision whether to participate. Additionally, because participants in phase II trials may include patients who are unwell and frequently not working, the REB should ensure incentives for participation are not coercive, and patients do not accept risks they would otherwise refuse because of the incentives being offered. Researchers are encouraged to consult with the REB at an early stage about any recruiting, consent or safety issues that arise.

During the course of a phase II clinical trial, participants will have access to a new drug that may or may not provide clinical benefit. Researchers shall: (a) provide details on access to the new drug upon trial completion as part of the consent process; and (b) make reasonable efforts to secure continued access to the drug following the phase II trial, for those patient-participants for whom the drugs appear to be beneficial.

Phase III Trials

Phase III trials are normally conducted with participants in need of treatment and may involve clinicians in dual roles as researchers. Researchers should also provide a plan for interim analysis of data, early unblinding of clinicians and/or participants, and/or ending the trial if the drug should prove effective or harmful. The REB should evaluate such plans with due consideration for the welfare of the participants and the group which is the focus of the research (see Article 3.2).

Researchers in dual roles should explain how they will eliminate, minimize or manage their involvement with any of their patients recruited to the trial. REBs should examine the prospective assignment method to ensure that care of patient-participants will not be compromised in their assignment to any arm of the trial (including the placebo arm – see Article 11.6).

Researchers and the REB should also address the issue of continuing access to the experimental therapy after the trial closes. If the treatment benefits participants and is safe, the proposal should state whether it will continue to be provided and under what conditions. REBs should be concerned about what provisions are possible to ensure that participants continue to receive adequate treatment.

Phase IV Studies/Trials

Phase IV trials are not actually trials using prospective assignment but are included among the clinical trial phases because they are often part of the overall research plan for a clinical trial. They are normally surveillance or observational studies conducted to assess the long term safety and effectiveness of marketed drugs and devices through the identification of side effects, toxicities, drug interactions and overall tolerance that may only emerge over time. However, in some cases, phase IV trials may be designed to serve primarily as marketing initiatives to encourage the prescription and continued use of an approved drug. For example, a clinician may be paid a per capita fee by a sponsor to collect data on the side effects and acceptance by patients of a drug being marketed by that drug's sponsor. REBs should carefully consider the financial terms between sponsors and investigators associated with these trials as they may create problems such as inappropriate prescription practices, billing practices and/or inappropriate utilization of public resources (e.g., diagnostic services and medical imaging). Researchers and REBs must ensure that trials are undertaken for a bona fide scientific purpose, which includes a design and objectives that are scientifically, rather than commercially, driven. Phase IV trials designed with the primary goal of increasing sales do not constitute legitimate research.

Natural Health Product Trials

Natural health products (NHPs) may be viewed as safe simply because they are natural. Some NHPs, however, can pose serious health risks. NHPs may also be part of a multi-treatment therapeutic approach (e.g., a herbal medicine added to a conventional medicine or to a complementary alternative therapy). A research proposal for an NHP clinical trial shall clearly identify the known effects of the product under investigation and its possible contraindications. REBs should ensure that NHP clinical trial proposals are reviewed with the appropriate level of scrutiny as indicated by the foreseeable risks to the participants.

In evaluating the research design REBs should consider the history of the NHP as provided in the literature review contained in the researcher's brochure and/or in a monograph (such as those published by Health Canada setting out approved uses and cautionary information). For NHPs with an established safe history of human use, the researcher does not have to present the findings of prior testing with animals, if the proposed conditions of use in the trial do not differ from approved uses. However, if the NHP is a new product without an established safe history of human use, prior animal testing may be necessary before it can be approved for first-in-human trials.

Some natural health products do not fall under the jurisdiction of Health Canada and their effectiveness has often not been rigorously tested. Researchers and REB members should know how federal regulations affect the design and conduct of NHP clinical trials.

Medical Device Trials

Medical devices may take many forms (e.g., magnetic resonance imaging machine, cardiac pacemaker, hip implant). The term "medical device" covers a wide range of instruments used in the prevention, diagnosis, mitigation, or treatment of a disease or abnormal physical condition or the restoration, correction or modification of body function or structure.

Researchers are responsible for providing up-to-date information about the device, for example, any feasibility studies it has been subject to in Canada or in other countries, and its risk classification. If an REB does not have enough safety information about the device to consider in its review of the trial, the researcher should be advised to work with the manufacturer of the device to provide appropriate risk information in the research proposal.

Psychotherapy Trials

A psychotherapy trial tests a psychotherapeutic approach in patient populations with the same psychological diagnosis. It may compare the outcomes of those receiving the therapy to those on a wait list. Often a trial will compare a psychotherapeutic approach to a pharmaceutical approach or to some combination of both.

REBs should be aware that trials involving psychotherapy may be more focused on effectiveness in real world conditions than on efficacy under tightly controlled conditions. For example, the research question may be how participants undergoing a particular therapy are functioning in their daily lives. The duration of these trials may be longer as a function of the therapeutic approach and the characteristics of the condition to which it is applied. Researchers must clearly identify any risk of a negative impact on participants' mental health and how they intend to minimize and/or manage these risks.

Issues of participant privacy and confidentiality may receive closer scrutiny in cases where people with specific psychological profiles are being recruited from the same institution as the researchers. Researchers shall indicate how recruitment, data collection and management, and compensation procedures have been designed to protect participant confidentiality (see Chapter 5).

Surgical Trials

Some of the issues surrounding the comparison of different surgical techniques are the appropriateness of the technique to the participants, whether the technique has been validated, whether the tools required have been approved for use in Canada, how well the experimental procedures have been explained to

prospective participants, and whether it is appropriate to employ a control group that undergoes sham surgeries.

When there is a crossover from non-surgical to surgical treatment, it can be difficult to assess whether participants' health outcomes were due to the surgical intervention. The risk of subjecting participants to a potentially scientifically inconclusive trial needs to be weighed against the risk of subjecting them to a potentially harmful placebo intervention. REBs should be satisfied that the research question cannot be addressed in any other way. To ensure participants are fully aware that they may be undergoing unnecessary surgery, REBs should examine the consent process for clear explanations of the experimental procedures, rationale, risks and potential benefits in language that is appropriate for the participant group (Article 3.2).

REBs should be aware that it is possible that the principal investigators of surgical clinical trials need not, themselves, be a surgeon or technician trained in the procedure. For example, a biomechanical engineer who has developed a new type of skin graft material to aid in surgical repair may conduct a surgical clinical trial, with the assistance of a surgical team, to compare the new material with an existing material.

Cluster Randomized Trials

Cluster randomized trials (CRTs) involve the prospective assignment to one or more interventions at the level of a group or population (e.g., hospital wards, schools, communities) rather than at the level of the individual participants. They may involve outcome evaluation at the level of group or 'cluster' or the individual cluster members.

CRTs raise issues of participant autonomy depending on whether the design is based on an exception to the requirement to seek prior consent from individual participants. Researchers and REBs need to consider whether:

- the randomization of clusters will take place before it is possible to identify participants and seek consent;
- individuals who are in the cluster but who are not the primary focus of the trial may be directly or indirectly affected by any intervention applied to the cluster; and
- cluster-level trial interventions may be difficult or impossible for individuals to avoid, removing the possibility of refusing to participate.

Where individual consent is possible in CRTs, it shall be sought and the process of prospective assignment shall be explained so that individual participants are aware that they may or not be receiving an intervention. When this approach would render the trial impossible or impracticable to carry out, the researcher must be able to justify an alteration to, or a waiver of, the consent requirements to the satisfaction of the REB (see Article 3.7A).

When seeking the involvement of communities, researchers should follow the guidance in Chapter 9 regarding community engagement. Researchers must demonstrate to the REB that the people they have identified as representing the community are regarded as representatives by the community. Researchers must also clearly identify risks to individuals, to the cluster as a whole, and to any sub-groups within the cluster.

Adaptive Design Trials

Adaptive design trials are also known as multi-stage design, flexible/dynamic design, or data-driven design. They typically include a prospective adaptation of some design features according to decision points based on accrued data (e.g., analysis of trial arm outcomes after one month will determine which participants stay in their assigned arm and which will be moved to another arm). They may include re-estimation of sample size, changes to allocation ratio, stopping rules, the trial objective or hypothesis (e.g., from superiority to non-inferiority), the primary outcome, the population, and/or dropping or adding an intervention or control arm. Adaptations to trial design may affect informed consent, clinical equipoise and the fair distribution of risks and benefits throughout the trial. There should be strong justification for the criteria set for adaptation decision points regarding exposure of greater numbers of participants to possible undetected risks of an intervention. There should be a plan to manage or minimize the involvement of clinician-researchers in research decisions that may affect their patients (e.g., prospective assignment, data-driven changes to trial design).

The possible advantages of adaptive design trials are shorter trials with fewer participants and earlier identification of the most and least promising interventions, particularly for interventions that cannot be tested with a conventional approach. For example, to test the safety and efficacy of an experimental intervention for a rare disease in a conventional clinical trial, researchers would have to recruit far more participants than the number of people who actually have the disease. Using an adaptive design, it could be possible to achieve the same statistical power with fewer participants participating in a sequence of interventions, permitting quicker identification of risks and benefits to each participant.

However, adaptive designs also raise particular ethical issues. Participants joining a trial in a later phase might experience fewer risks and greater benefits than those who were involved in the earlier phases of the same trial. The re-assignment of more participants to an intervention that looks more promising could inadvertently expose more participants to side-effects that take longer to emerge. Smaller numbers of participants may also make it more difficult to balance key factors across interventions and/or control arms, reduce the ability of the researchers to do more focused analyses (e.g., sub-groups), and avoid the possibility of false negative or false positive results.

REBs must consider whether researchers have adequately addressed these and other ethical issues in their adaptive clinical trial design.

Registry-Based Trials

Registry-based trials use health registries as platforms for different aspects of trial operations such as recruitment, data collection, randomization, and/or follow-up. Health registries are collections of patient health information. In registry-based trials researchers seek access to registries in order to recruit participants and prospectively assign interventions, which may include standard of care. The intervention, measurement and/or analysis may be at the group or individual level. Different levels of intervention, measurement and analysis can present different issues of consent and privacy. Although registry-based trials are relatively recent, it appears that the ethics issues they present are not novel and are currently addressed by the principles of this Policy.

Registry-based trials are efficient because they offer researchers access to a pool of participants within an existing infrastructure for recruitment, data collection and/or follow-up. Such trials require coordination with registry administrators as aspects of their roles may overlap with the roles of the researchers, e.g., safeguarding privacy, or monitoring safety.

Endnote

[1] These conditions are drawn from the recommendations of the *Final Report of the National Placebo Working Committee on the Appropriate Use of Placebos in Clinical Trials in Canada* (July 2004), with amendments.

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