Research Guidelines:
A web-based decision-guide for physicians
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Executive Summary

To assist physician-researchers assess the validity, value, reliability and merit of proposed research, to understand his or her role and responsibilities and ethical obligations as physician-researcher, The Office of Ethics, Professionalism and International Affairs at the Canadian Medical Association (CMA) has developed a web-based decision-making tool for clinical research.

The Research Guidelines (Guidelines)¹ are intended to help Canadian physician-researchers ensure that their research is scientifically rigorous, valuable and valid and meets ethical and legal standards. The Guidelines have been reviewed by the Canadian Medical Association’s Committee on Ethics and external stakeholders.

The Guidelines are not intended to be viewed from start to finish. The intent is to use the guidelines in a non-linear way; one clicks to a section or sub-section from the Table of Contents. Internal links between inter-related topics and external hyper-links to reference materials and resources are embedded.

The Guidelines are not intended to instruct physicians on how to conduct research or develop a research protocol. This tool should assist physician-researchers in independent practice who wish to conduct research assess a research protocol; they are a decision-making guide.

The Guidelines do not purport to be prescriptive; they are not a “how to” but a “be aware of” decision-guide. Because physician-researchers are responsible for disclosing the risks associated with a trial’s interventions, the physician should be a competent researcher and only participate in trials that relate to his or her area of expertise. Physician-researchers should be aware of the legal and regulatory requirements regarding privacy, confidentiality and document retention.

¹ The Clinical Trial Guidelines are intended to assist the physician in deciding whether he or she should participate in a proposed study and whether his or her patients should be enrolled as research participants. The Guidelines are not fixed protocols. The Canadian Medical Association considers adherence to the Guidelines to be voluntary with the ultimate determination regarding its application to be made by the physician-researcher with full consideration of the individual’s patient’s clinical history and needs.

The Guidelines are not entirely inclusive or exclusive of all methods and must be applied based on individual circumstances using professional judgment. While the Guidelines identify and describe generally methodologies, strategies and ethical and legal concepts, they do not constitute nor substitute the advice of a physician, lawyer, ethicist or other professional or provider.

The CMA makes no warranties, express or implied, including warranties of merchantability and fitness of the Guidelines for a particular purpose or non-infringement. The CMA does not assume any legal liability or responsibility for the accuracy, completeness, or use of the Guidelines, of any material referenced in the Guidelines or in material at other sites linked to the Guidelines. Any statement or opinion expressed in any material referenced in the Guidelines or in material at other sites linked to the Guidelines do not necessarily reflect the views or opinions of the CMA.

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Legal and regulatory environments differ but what constitutes ethical research is generalizable, e.g., if risks are high, then conscious, competent, potential participants must grant prior, expressed informed consent prior to implementing any experimental intervention. Therefore, while the Guidelines were developed to assist Canadian physicians, biomedical researchers everywhere may find the Guidelines useful.

The Guidelines are divided into six major sections: Introduction, Scientific Methodology, Research Ethics and Legal/Regulatory Requirements, Conclusion and Bibliography. The Methodology, Ethics and Legal sections are further divided into sub-sections. The sub-sections include a general introduction to the topic, e.g., experimental methodologies, and a Questions to Ask section, which lists questions the physician-researcher should consider when reviewing the study protocol. The bibliography constitutes additional resources for interested readers.

The Guidelines are not meant to be exhaustive, merely comprehensive. The Guidelines are not the definitive source to help develop a research protocol; they should be considered a decision guide. The Guidelines should be used in conjunction with other available resources, e.g., The Canadian Institutes of Health, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. Tri-Council Policy Statement, The Collège des médecins du Québec, Le Médecin et la Recherche Clinique, the World Medical Association, World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects and the Canadian Medical Association’s Code of Ethics and Guidelines for Physicians in Interactions with Industry.
Introduction

The purpose of the Guidelines is to provide clinician-researchers an in-depth toolkit to assist with reviewing study protocols. Sections include a general introduction and background information and end with a set of questions a researcher should consider when deciding whether to enrol his or her patients in a clinical trial. Links are provided to additional resources so the reader can learn more about specific topics if desired. Additional sources for material and information include local research ethics boards (REB), the Tri-Council Policy Statement and the Collège des médecins du Québec, Le Médecin et la Recherche Clinique.

Conducting research with human persons or on human biologic material is a privilege. There is no moral or legal obligation for participants to place themselves at risk for the benefit of others; no one is obligated to be a research subject or participant. Research participants (citizens) and society (governments) allow, participate in and fund research involving human subjects for anticipated benefits. Benefits may accrue to the research participant, to others similarly situated, to researchers, to sponsors or to the public. Researchers must not exploit participants for personal or private gain. Any personal gains (financial, fame or career advancement) researchers or sponsors realize are secondary. Exploitation of participants is tantamount to harm – this is contrary to the legal, ethical and moral guiding principles of research. If research participants are exploited, public trust is threatened or lost and people may no longer be willing to participate in or fund research.

However, because physicians have ethical obligations to advance medical knowledge, ethical dilemmas arise since the goals of treatment and care differ from the goals of research – discovery, generating and disseminating information and knowledge. Ethical dilemmas occur when equally valuable but competing goals, purposes or roles are sought but only one can be realized; choices must sometimes be made. Although physicians’ professional obligations as caregiver must take precedence, these obligations are not absolute - how these conflicting obligations are balanced is both context and content sensitive. See P. B. Miller and C. Weijer, Trust based obligations of the state and physician researchers to patient-subjects. Journal of Medical Ethics, September 1 2006, v. 32, Issue 9, p. 542-547.

When a physician enrols his/her patient in clinical research, the physician-researcher should recognize that his/her professional obligations as physician and care provider take precedence. When the goals, values and obligations of a physician conflict with researcher/scientist’s goals, values and obligations, those of the physician should be pursued and honoured first. The foremost role and associated obligations and duties are those of physician/caregiver.

Two primary tenets of medical ethics are “Do no harm” and “Consider first the well-being of your patients.” All medical interventions have the potential to harm. When recommending treatment, caregivers disclose the probable risks and benefits of the proposed treatment, risks and benefits of the alternatives and the consequences of no treatment. Patients, when considering whether to consent to the recommended treatment, weigh the potential risks and benefits and put these into the context of their life and goals. Uncertainty underlies the scientific endeavour; volunteering as a research subject may enhance the patient’s well-being or it may not, but a
study’s interventions should not be considered therapy. Although the risks associated with the interventions may be foreseen, the risks cannot be precisely predicted. Participants are exposed to risks, sometimes while the benefits — potential or actual — accrue primarily to society.

Epidemiologic studies have revealed causal sequences and risk factors and have contributed to prevention and treatment strategies. Individuals and society have benefited from this information. However, although individuals and the collectives to which they belong usually share common goods, values or goals, one cannot simply assume that the collective’s good and interests are identical to and correspond with the individual’s private and personal good and interests. When differences arise, the public good or interests must be balanced against the individual’s good or interests. When balancing the competing values, the World Medical Association’s Declaration of Helsinki states: “In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.”

People choose to participate in research for various and varying reasons; e.g., he/she may participate because his/her community (society or others similarly situated) may benefit from the information and knowledge gained. Patients trust physician-scientists and, partly because of this trust, they volunteer to expose themselves to additional or elevated risks from which they may not directly benefit. However, patients probably believe that the generalizable knowledge resulting from the research will benefit others — in terms of a cure, a treatment or better quality of life.

Physicians recruiting patients as research participants should be sensitive to the power asymmetries and the “therapeutic misconception” phenomenon. A patient’s decisions to participate can be unduly influenced if their doctor recruits them for research; they may not want to anger or disappoint their physician. The patient’s decision can also be unduly influenced by various misconceptions. The basic therapeutic misconception stems from physicians’ obligations of beneficence and non-maleficence. Patients assume that caregivers continue to base clinical decisions and recommendations for treatment on the patient’s best interest and, therefore, believe they will directly benefit from the intervention. Depending on the protocol the physician-researcher’s clinical autonomy, his or her decision-making authority can be restricted, reduced or eliminated. During the experiment, the physician cannot make or implement treatment decisions based on a participant’s best interest. If the physician wants to initiate treatment based on the participant’s best interest, they would have to withdraw their patient from the study.

One challenge for the physician-researcher is to balance society’s potential benefits while protecting and/or promoting his or her patient’s interests and limiting the risk of harm. Ultimately, ethical research depends on the professional and personal integrity of the physician-investigator and research team members.

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2 World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects

For pedagogical purposes, the scientific endeavour can be divided into 3 basic elements: 1) scientific method, 2) research ethics and 3) legal or regulatory requirements. These elements are not mutually exclusive but are interrelated and interdependent and each element has ethical components. If the research protocol is unsound, the trial is unethical. If the contract or the eligibility requirements for funding necessitate contravening ethical duties or sound, reliable and valid scientific methods, they are unethical. One cannot justify exposing research participants to anticipated or unknown and elevated risks if the participants, the members of their community and/or society do not stand to benefit.

**Scientific Methodology**

**Introduction**

Research is permitted because the goal it seeks is recognized as an intrinsic good. The goal is producing generalizable knowledge, information. Clinical equipoise, genuine uncertainty whether one treatment is more efficacious or preferred over others, makes enrolling subjects into a randomized clinical trial ethical.

To justify exposing research participants to elevated risks, a trial must be scientifically valuable and methodologically valid, sound and reliable. Trials that do not answer or contribute to answering relevant clinical questions (value) or are flawed (unsound, invalid or unreliable) place research participants at risk for inappropriate reasons and should not be conducted. It is unethical to expose participants to any degree of risk if the production of new, generalizable, valuable and valid data is not expected. Paragraph 11 of the Canadian Medical Association’s *Guidelines for Physicians in Interactions with Industry* states: “Practising physicians should not participate in clinical trials unless the study will be registered prior to its commencement in a publicly accessible research registry.”

**Questions to Ask about Value**

- Does the trial address an important clinical or patient-centered issue — how severe is the investigated problem and how common is it?
- Will it improve the health or well-being of the research participant?
- Will it improve the health or well-being of other patients?
- Will care, treatment, diagnosis, the delivery of services and/or the health care system be improved?

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4 Canadian Medical Association, *Guidelines for Physicians in Interactions with Industry*. 
• Will new knowledge accrue? To determine whether new knowledge will accrue, researchers need to know whether the same question(s) has already been asked and answered. Conduct a systematic review, e.g., literature search or meta-analysis of prior studies ensures that the research participants are not being exposed to risk unnecessarily. See David Moher, Deborah J. Cook, et al. *Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement* for a meta-analysis checklist and Jonathan A. C. Sterne, *Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis*, *British Medical Journal*, 14 July 2001, v. 323, p. 101-05.

• How will the new knowledge be used?

• Will the new knowledge be relevant?

**Questions to Ask about Validity**

• Will the study generate new facts or knowledge?
• Has the study been peer reviewed?
• How sound is the protocol and will the results be reliable?
• Is the study design consistent with the paradigm of treatments? (See discussion of model validity as it applies to research in *Complementary Therapies in Medicine*.)
• Which method will best test the hypothesis when correlated with acceptable levels of risks and benefits?
• Is the study design based on the “honest null hypothesis?” Is the study designed so that the hypothesis not believed to be true is just as likely to be confirmed as the hypothesis believed to be true?
• Is the surrogate endpoint (e.g., laboratory measures) an effective substitute for clinical outcomes? Studies suggest trials using surrogate endpoints bias results in favour of the new treatment. See Paul M. Ridker and Jose Torres, *Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations: 2000-2005*. *Journal of the American Medical Association*, v. 295, May 17, 2006.
• Is the surrogate endpoint related to clinically significant outcomes (e.g., measured tumour response, but morbidity or mortality rates unaffected)? See Thomas R. Fleming, et al., *Surrogate End Points in Clinical Trials: Are We Being Misled?* and The Cochrane Collaboration. Glossary of Terms, s.v. *Surrogate End Points*.
• Is the number of participants recruited sufficient to provide valid and reliable results? If too few are recruited, the test will not be sufficiently powered and results will not be reliable. If too many are recruited, then more people than necessary are placed at risk; this is unethical.
• Should research subjects be randomly assigned to various subgroups to test the hypothesis adequately and, if so, has this been done?
• Is this a randomized double-blind study? This may be a novel situation, as the physician-researcher remains ignorant of which treatment (if any) his or her patient receives.
• Are participants representative of the population that will benefit from the new diagnostic technology or treatment?
• Are the inclusion (eligibility) criteria too narrow?
• Will the exclusion criteria make generalizability (external validity) difficult or impossible (e.g., are people who have comorbidities and multiple medications excluded, but will be the targeted end users)? See Martin Roland and David Torgerson, *Understanding controlled trials: What outcomes should be measured?* British Medical Journal, v. 317, 17 October 1998, p. 1075.
• Has the hypothesis (outcome) been amended? If the endpoints or outcomes being measured or assessed or the process or procedures altered, the research ethics board must be informed.
• Will clear and accurate records of the procedures be kept?
• Will accurate records of the interim results, as well as the final research outcomes, be kept?
• Has the study been registered in registry of clinical trials with public, open access? See ClinicalTrials.gov

Study Types

Is the study’s genre appropriate to answer the questions? Traditionally research was divided into two, quantative and qualitative research. As research has become more interdisciplinary, the distinction between the two has become more arbitrary as many studies include both elements of both types of research.

Quantative Research

Quantative research is generally associated with measuring things, e.g., statistics. It answers the questions ‘what and how many’ and correlates the ‘whys’ (causal sequences). Quantative research supplies numerical data and, typically, should be reproducible. It is not context dependent, although some environmental variables may need to be controlled (experimental) or accounted for (descriptive or observational). Quantative research usually involves large numbers of participants (150 or more). It is used to determine relations between variables, an association or a causal sequence. Descriptive or observational research designs determine associations. Experimental research designs determine causal relations or sequences, e.g., health status before and after an intervention.

Although trial results may demonstrate statistical significance (suggesting that the hypothesis is true or false), it is important to remember context; what physicians and patients are interested in is clinical significance. Statistics tend to draw “artificial” lines, i.e., results above a certain value are “significant.” Demonstrating that something is “true” is not necessarily useful or sufficient to influence or guide individual behaviours.
Although the likelihood of contracting a condition may be statistically “insignificant,” e.g., if “only” 4 of 100 have or will develop a condition. However, for the 4 participants who have or will develop the condition, it is “significant” as his or her quality of life may has been or may be reduced. Results may be quite “significant” to a participant if his or her health, quality and quantity of life might be adversely affected or benefited. For example, although results from a study on weight loss in obesity may show a treatment to have statistically significant benefits, the amount of weight lost in the study participants may not be clinically significant to justify using as therapy for obese persons. See Ian Chalmers, What do I want from health research and researchers when I am a patient? British Medical Journal, v. 310, 20 May 1995, p. 1315-18.

Questions to Ask about Quantative Methodologies

- Has the appropriate method (e.g., survey, case study, cohort) been chosen for the hypothesis being tested (are safety, efficacy, comparisons of efficacious treatments or surveillance studies being proposed)?
- Are you testing to see how many people in a sample believe or think something, are affected, influenced or respond to something one way or another? One method is a survey. It is important to ensure that you have a representative sample; the model for surveys is opinion polls.
- Are you reporting an interesting or unusual occurrence? Choose descriptive case analysis.
- Are you trying to determine the efficacy of a prognostic test? Multiple regression analysis is generally used.
- Are you reporting a group of related cases? This is serial case analysis.
- Are you trying to establish negative correlations between variables (e.g., exercise and strokes)? Use prospective or concurrent longitudinal cohort studies (enrolling patients and following them forward with either passive or active follow-up studies).
- Are you are trying to establish positive correlations between variables (e.g., cancer and smoking)? Retrospective non-concurrent case control studies may be best (review cases to find the cohort and then identify outcomes).
- Is the sample size sufficient to generate reliable results or for comparisons to be made (statistical power)? See Scott D. Halpern, et al. The Continuing Unethical Conduct of Underpowered Clinical Trials. For contrary view, see Kenneth F. Schulz and David A. Grimes, Sample size calculations in randomised trials: mandatory and mystical.
- If using cohort studies, randomized or not, do the comparisons make clinical sense?
- Are the variables dichotomous? You may use chi-squared tests to determine significance \( \chi^2 \) tests.
- Are the variables continuous? Use \( t \) test.
- Will you review and assess the validity of previous studies? These are systematic reviews. See Greenhalgh, Trisha. How to read a paper: Papers that summarise other papers (systematic reviews and meta-analyses). British Medical Journal, v. 315, no. 7109, 13 September 1997, p. 672-75.
- Are you reviewing and summarizing the result of previous systematic studies? A systematic review (qualitative or narrative analysis) can be used.

Resources

For more information on systematic reviews, see The Cochrane Manual.

Experimental Methodologies

Experimental methods differ from descriptive methods in that they try to control, eliminate or add variables. Therefore, research participants must usually meet rigid inclusion or exclusion criteria. Randomization is another control mechanism. The intervention studied should, however, be based on clinical equipoise. Clinical equipoise exists when there is doubt whether 1 intervention is “better” than another, i.e., there is a genuine question of therapeutic merit. Requiring clinical equipoise as a prerequisite for randomization exposes the conflict among values, goals and roles (treatment versus knowledge acquisition) and the moral dilemma (which good to pursue) requires balancing the competing values, goals and roles. See Target Article and accompanying commentaries on clinical equipoise in the American Journal of Bioethics, v. 6, no. 4, July-August 2006 and Placebos and Deception and Therapeutic Misconceptions.

Epidemiologic investigations, usually longitudinal cohort studies that use existing personal health information or “reuse” stored biologic materials, e.g., DNA samples or “banked” tissue samples raise specific concerns. These specific concerns are discussed in the sections Informed Consent Informed Refusal and Databanks, Bio-banks and Population-based Research.

When used appropriately, marketing strategies are ethical. However, marketing strategies that masquerade as research or research used to expand market share exploits research participants and is unethical. Research should answer scientifically valid questions (safety and efficacy), not expand market share or profits (although this may be an anticipated secondary benefit). Some jurisdictions, e.g., United States, have sued sponsors and researchers under anti-kickback legislation because a trial was not: a) scientifically rigorous, b) was of questionable scientific value, c) was funded by a commercial entity, d) was used to promote or induce purchasing the sponsor’s products or services and e) the product or services were paid for by the public purse. Author conflict of interest statements or declarations of funding can help identify possible unethical research for marketing purposes.

Questions to Ask about Experimental Methodologies

• Is the efficacy of a novel treatment being tested? If yes, then use longitudinal time-series methods in which measurements are taken before and either during and/or after the intervention. Variations on this method include cross-over, cross-over with a control group randomized controlled and randomized (single- or double-blinded) controlled. The control can be standard treatment plus intervention or intervention and placebo.

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5 Although not limited to qualitative research, descriptive methods appear in the qualitative section.
• Is the trial testing a novel or alternative use (off-label)?
• Is this a trial of a new investigational drug or device or an off-label use? If yes, has the sponsor or institution received a Health Canada Notice of Compliance, a Drug Identification Number or Medical Device Licence?
• Is it reasonable to assume the novel or alternative off-label use will be efficacious?
• Is a certain control group or co-morbidities excluded for reasons other than valid scientific ones? For example, excluding common co-morbidities, such as suicidality.
• Is this a drug trial and, if yes, is the design best suited to test the hypothesis?
• Will the trial determine toxicity or safety? If so, this is a phase 1 trial and usually employs a few healthy participants to determine the maximum dose patients can tolerate. Exceptions to this are oncology studies that recruit patients with refractory cancer. See Adi E. Shamoo and David B. Resnik, *Strategies to Minimize Risks and Exploitation in Phase one Trials on Healthy Subjects*.
• Will the trial determine drug metabolism, absorption, elimination or the best mode of delivery? This is a phase 1 trial.
• If this is a phase 1 trial, have potential participants been screened appropriately? See, for example, Health Canada. “Requirements”.
• Will the trial determine whether the new intervention is biologically active or what dose is effective? This is a phase 2 trial.
• Is the purpose of the trial to determine clinical benefits and side effects (risks and harm)? This is a phase 3 trial and participants should represent the target end users.
• Will the trial determine the consequences of long-term use among or the general population who may have multiple co-morbidities and may be taking multiple medications? This is a valid phase 4 post-marketing surveillance safety study.
• Is the study structured as a post-marketing surveillance safety study but is used to introduce a new product to a physician with the hope that physician will begin using the new tool instead of the one he or she previously relied on? This is as a marketing tool and as is unethical.
• Are you being paid to switch patients from one drug, usually from a lower cost drug to another, typically newer and costlier, and fill in a form “reporting” having done so? These may be called “drug use studies,” although the practice is known as “switching.” As no scientifically appropriate hypothesis is being tested, this is not research and recruiting participants by identifying it as such is unethical. Some phase 4 (post-marketing) trials are thinly disguised marketing tools.
• Is one inclusion criterion genetic? See *Genetic Research*.

**Placebos and Deception**

Under what circumstances placebo-controlled trials or trials using deception are ethical is debatable. Proponents of placebo-controlled trials or trials using deception argue that obtaining scientifically valid and reliable results may require using a placebo or deception. Others argue that placebo-controlled trials or using deception in clinical trials that expose participants to more than minimal risk are ethical only when uncertainty exists about whether the standard treatment is more efficacious than a placebo. According to one argument, enrolling patients in experiments in which they may not receive standard treatment contravenes the physician-researcher’s fiduciary duties or therapeutic obligations. See Kenneth J. Rothman and Karin B. Michels, *The Continuing Unethical Use of Placebo Controls*. 
Article 29 of the World Medical Associations Declaration of Helsinki\textsuperscript{6} states:

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

Article 7.4 of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans stipulates, “The use of placebo controls in clinical trials is generally unacceptable when standard therapies or interventions are available for a particular patient population.”\textsuperscript{7}

If placebos are used in place of standard treatment or are being compared with standard treatment, participants must be informed. Participants must be informed that a trial uses deception and then consent to participate in a trial that involves deception, must consent to receive either the standard treatment or a placebo and grant an informed refusal of the standard treatment. See Ana Smith Itlis, Placebo Controlled Trials: Restrictions, not Prohibitions, Cambridge Quarterly of Healthcare Ethics, v. 38, 2004 p. 308-393.

Deception has been used in sham surgeries (e.g., sham implants of fetal cells in patients with Parkinsonism) and, in other situations, placebos are described as possible therapeutic agents. There is consensus that, when deception is part of the method, participants must be informed; however, whether it is essential to inform participants exactly what the deception entails is controversial. Disclosing deception prospectively is necessary because, to grant valid informed consent, participants must understand to what they are consenting and the risks involved. Disclosure allows participants to authorize the use of deception. Physician-researchers conducting placebo-controlled trials or trials using deception must pay particular attention to try to dispel any therapeutic misconceptions whenever possible. See Therapeutic Misconceptions.

Questions to Ask about Placebos and Deception

- Has the use of placebos or deception been disclosed to participants? What the deceptive part of the trial is may not have to be disclosed, just that the trial involves some form of deception.
- Is the new intervention for a condition for which no current treatment exists? If so, then using a placebo or deception is acceptable.
- Is the placebo used in place of standard treatment? If the condition studied has demonstrated high rates of placebo response, then it may be permissible to use placebo controls.
- Is the standard treatment being validated? Is the trial a form of evidence-based medicine? If no alternative exists, using placebos or deception is acceptable if participants grant informed refusal and consent.


\textsuperscript{7} Canadian Institutes of Health, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. Tri-council policy statement: ethical conduct for research involving humans.
Is the standard treatment burdensome and are refusals routine, is the alternative less burdensome and are both being compared to a placebo? The use of placebos or deception in these situations is questionable. That deception is part of the protocol must be disclosed and participants must refuse standard treatment, refuse the alternative and consent to being deceived and to participating in research.

Are proven standard treatment, an alternative and a placebo being compared? Will this trial have scientific merit? Although active control trials (standard treatment versus an alternative) can produce valid results, the legitimacy of using a placebo under these conditions is questionable.

Is deception used to compare a variation on or alternative to the standard of care with a placebo, e.g., a “me-too drug” compared with a placebo? If proven therapy exists, it may be unprofessional for a physician to enrol his or her patient in this type of placebo-controlled trial, as the standard of care is not met. It may be necessary to obtain informed refusal of standard care, disclose the use of deception and obtain consent to be deceived and to participate in the research.

If a placebo is used, has the similarity of placebo to the active treatment been discussed (is it matched for smell, taste, participant’s experience)? In these cases, will the participant’s perceptions be monitored throughout the study?

Are your therapeutic obligations as care provider in conflict with your obligations as researcher? Therapeutic obligations take precedence. Some hold that researchers have therapeutic obligations to participants, e.g., informing participants when original risk–benefit assessment is incorrect.

Will participants be fully debriefed? See Di Blasi, et al., Reactions to treatment debriefing among the participants of a placebo controlled trial.

Qualitative and Interpretive Research

Qualitative and interpretive research is associated with questions that cannot be quantified. It usually addresses why (motivation) and tends to be descriptive. It may not present a testable hypothesis due to the explorative or iterative nature of inquiry. Qualitative research is usually context specific and environmental variables are not necessarily controlled or controllable. Qualitative methods will not necessarily provide numerical data sets and are, usually, non-reproducible. Qualitative research usually involves fewer participants (≤ 100). The explorative character of qualitative research complicates consent processes. Research participants should be informed of the type of information and knowledge the study aims to produce.

A usual criticism of qualitative research is that it is not as “rigorous” as quantative research. Although qualitative results may not be reproducible (because controlling variables is more difficult), one should not assume qualitative research does not produce valid results. See Nicholas Mays and Catherine Pope, Qualitative Research: Rigour and qualitative research. British Medical Journal, v. 311, 8 July 1995, p. 109-12.
Because physician-researchers tend to conduct quantitative research, a short list of types of qualitative research with links to brief definitions of the more common qualitative methods is provided. See Catherine Pope and Nick Mays, *Qualitative Research: Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research*. British Medical Journal, v. 311, 1 July 1995, p. 42-45. For a brief introduction to and overview of qualitative research, see University of South Alabama. *Johnson Lectures* and Colorado State University. *Glossary of Key Terms*.

For ways to assess qualitative research, see Nicholas Mays and Catherine Pope, *Qualitative research in health care: Assessing quality in qualitative research*. British Medical Journal, v. 320, 1 January 2000, p. 50-52.

**Types of Qualitative Research**

- Phenomenological: “Here is the foundational question in phenomenology: What is the meaning, structure, and essence of the lived experience of this phenomenon by an individual or by many individuals.” University of South Alabama. *Johnson Lectures*
- Discourse analysis: “Discourse analysis is the examination of language use by members of a speech community. It involves looking at both language form and language function and includes the study of both spoken interaction and written texts. It identifies linguistic features that characterize different genres as well as social and cultural factors that aid in our interpretation and understanding of different texts and types of talk.” From Douglas A. Demo, *Discourse Analysis for Language Teachers*.
- Ethnographic and anthropologic: “Ethnographic analysis is an observational technique that uses a naturalistic perspective relying upon material drawn from the first-hand experience of a fieldworker in a setting, rather than in artificial or experimental conditions. It seeks to understand work environments and activities as they naturally occur, from the point of view of the people who inhabit those settings, and usually involves quite lengthy periods of time at the study site.” European MultiMedia Usability Services. See also Jan Savage, *Ethnography and health care*. British Medical Journal, v. 321, 2 December 2000, p. 1400-1402.
- Visual ethnographic research uses visual methods and media to study human behaviour.
- Grounded theory, an inductive methodology: “Grounded theory is an approach that develops the theory from the data collected. Rather than applying a theory to the data. This can be a popular approach for people exploring a new area of research.” See Online QDA: Grounded theory.
- Action research: “The term is now identified with research in which the researchers work explicitly with and for people rather than undertake research on them.” Julienne Meyer, *Qualitative research in health care: Using Qualitative methods in health related action research*. British Medical Journal, v. 320, 15 January 2000, p. 178-181.
Methods of Qualitative Research

- chain or “snowball” sampling (subjects identify others who could or should be interviewed)
- open-ended questions or questionnaires.
- document review.

Questions to Ask about Qualitative Studies

- Is the research study relevant, important and most appropriately investigated through a qualitative design?
- Are there aspects of the research that appear misleading in terms of the purpose of the study?
- Will participants be protected from physical or emotional harm in the conduct of this study?
- Is there any personal gain on the part of the researcher?
- What are the benefits to the participants or to society as a result of this research?
- Has there been an extensive review of literature on this topic prior to design of the study?
- How will the confidentiality of participants protected?
- What mechanisms will the researcher employ to ensure authenticity and trustworthiness of data (audit trails, reflexive journaling)
- How will data analysis be conducted?

Quality Assurance/Improvement Studies, Audits or Performance Evaluations

Quality assurance/improvement studies (QA and QI), audits or performance evaluations are usually distinguished from research for bureaucratic reasons, not because different scientific, ethical or legal standards apply. These studies are retrospective not prospective and, like research, the benefits accrue not to past or present but to future patients or society. “The standards expected of audit in terms of design, data collection and analysis should be at least as high as for research, if only because audit potentially leads to change in practice more often than research does and often much greater change.”8

Two issues associated with QA/QI studies, audits and performance evaluations are whether these studies require review by a research ethics board (REB) and whether expressed consent to access private health information can be waived.

The *Tri-Council Policy Statement* states: “quality assurance studies, performance reviews or testing within normal educational requirements should also not be subject to REB review.... Article 1.1(d) indicates that studies related directly to assessing the performance of an organization or its employees or students, within the mandate of the organization or according to the terms and conditions of employment or training, should also not be subject to REB review. However, performance reviews or studies that contain an element of research in addition to assessment may need ethics review.”9 See TCPS: Research Requiring Ethics Review.

The question then is which QA/QI studies contain elements of research? Two general means to determine this are proposed. One is to identify the functions of QA/QI audits and performance evaluations, the other, to identify the primary purpose of the study.

A good definition may be helpful. The National Health & Medical Research Council of Australia defines QA as:

An activity where the primary purpose is to monitor, evaluate or improve the quality of health care delivered by a health care provider (an individual, a service or an organisation) is a quality assurance study.10

QA studies and chart audits assess performance, e.g., they determine whether the standards of care are followed. To do this, access to private health information is necessary; data are obtained but not used to treat or directly benefit the data owner (patients). This constitutes a secondary purpose. Accessing private health information for secondary purposes usually requires consent from the data owner. REBs have the authority to waive consent requirements for research if the risks are minimal. If QA studies, chart reviews and performance evaluations are not research, then REB review and approval is not required.

Some try to solve this conundrum by arguing that the function of QA studies is to ensure the integrity of the institutional system of care. If the study establishes that what should be done (standard of care) is done and this check may improve patient care or safety, patients’ consent for the secondary use of their health information is assumed. If, for example, the QA study uses surveys, completion of the survey implies consent. If one may assume or infer consent, then explicit, prior consent may not be required. However, because individual health outcomes are not measured and data owners do not directly benefit, others question the legitimacy of assuming or inferring consent. See discussion on “blanket” or “advance” consent in Databanks, Bio-banks and Population-based Research.

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10 The National Health & Medical Research Council of Australia. *When does quality assurance in health care require independent ethical review?* Canberra: Legislative Services, GPO, 2003, p. 3.
If publication is planned, then an inferred goal of the study is to produce generalizable knowledge; thus, some contend the QA/QI study becomes research. SQUIRE Guidelines (Standards for Quality Improvement Reporting Excellence) are available to assist QA/QI authors. As most journals require proof of prior REB approval of research, then prospective REB review to grant a waiver for the need for prior, expressed informed consent is recommended; getting retrospective REB approval may not be possible. Although QA studies do not usually require REB approval consulting with an REB, requesting a waiver of explicit prior consent or requesting an expedited review could be beneficial.

Questions to Ask About Quality Assurance Studies

- Is the intent of the study to produce generalizable knowledge? This is research and requires REB review.
- Is the study designed to determine what should be done? This is research.
- Is the study designed to determine if what should be done is being done? This is a QA study.
- Are patients randomly assigned to different treatment groups? This is research.
- Does the study involve a new mode of treatment delivery? If the treatment involves risks or burdens beyond routine care, then an REB should review the study.
- Will an investigator, who is not a member of the care team or staff, access personal health information? Because patients expect that only clinical staff will have access to their health information on a need-to-know basis (and the need is to provide care or a direct benefit to the data owner), then REB review to is required.
- Is there any risk, burden, intervention, inconvenience or are extra assessments or information gathered above that required for normal clinical care? If yes, this may constitute research and require REB approval.

Recruitment Strategies

See Justice and Conflicts of Interest

If inappropriate subjects are recruited, results may not be valid, reliable or reproducible. The study will not have scientific merit and the benefits will no longer outweigh the risks, i.e., the study is unethical.

Physician-researchers who recruit patients who have exhausted all standard, acceptable or available treatments must insure that desperation does not unduly influencing their decision to recruit or the patient’s decision to participate in the study. Because the benefits are projected and because patients are unlikely to benefit directly from the trial intervention or participation, it is essential that participants do not base their decision to participate on a therapeutic misconception. When a physician recruits his or her patients as research participants, his or her therapeutic obligations and fiduciary duties to his or her patients take precedence. See Therapeutic Misconceptions and Forms of Justice.

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11 G. Ogrinc, SE Mooney, et.al., The SQUIRE (Standards for Quality Improvement Reporting Excellence) Guidelines for Quality Improvement Reporting: Explanation and Elaboration, Quality and Safety in Health Care 2008; 17 (suppl 1) i13-i32.
Questions to Ask about Recruitment Strategies

- Are there financial incentives for researchers to recruit participants? Finders’ fees and referral fees should not be accepted; they are unethical.
- Are there rewards for meeting quotas? This may unduly influence recruitment.
- Are the participants chosen simply because they are vulnerable, e.g., do they lack or have compromised capacity or are they from a disadvantaged social group?
- Are participants paid to cover their “out of pocket” expenses? Reimbursements, which should be revenue neutral, are acceptable.
- Are participants paid for their “time and inconvenience?” These payments are classed as compensation and should reflect the actual time and efforts of participants.
- Are payments disbursed after the trial is completed? These may be appreciation payments or bonuses. Appreciation payments or bonuses are sometimes not disclosed during recruitment so as not to unduly influence participant’s decision. Traditionally, only children and teenagers receive appreciation payments for their participation.
- Will participants be reimbursed above their out of pocket expenses, their time and inconvenience? If so, this may constitute incentive payments and unduly influence the decision to participate.
- Could any financial incentive unduly influence potential participants or recruiting practices?
- Have the advertising and recruitment materials been reviewed by an REB?
- Does the recruitment literature portray reimbursements as a benefit of participation; is it used as a recruitment incentive? Participant’s remuneration should not be considered a recruitment incentive.
- Are participants likely involved in other research studies due to a rare or unique characteristic?
- Are they under undue pressure to participate in research as a result?

Data Analysis and Tools

As data analysis can be quite complex, the assistance of a biostatistician may be warranted. Consulting with statisticians to assist with trial design and to review and analyze the results is advised.

Those conducting research should remember “significance” is an equivocal term. Assessing what is “significant” is subjective. Findings, which may not be statically significant, can be very meaningful for (have significance for) a particular participant. For example, for the one in ten who suffers from a side effect, this is “significant” for him or her.

Questions to Ask about Data Analysis and Tools

- Are the outcomes measured events (death, admission to hospital)? Survival analysis techniques are appropriate. See Statsoft.com
Are you trying to estimate how confounders relate to the outcome or estimate the effect of the intervention? Regression analysis may be appropriate, e.g., linear, (GraphPad Software, Inc.), logistic (G. David Garson), proportional hazards or multiple regression. (Statsoft.com) Are quality of life assessments (functional status, pain) or subjective patient-centered outcomes measured? Mixed regression techniques can be used. See Donald Hedeker, Generalized Linear Mixed Models. From the Encyclopedia of Statistics in Behavioral Science. John Wiley & Sons, Ltd.

Is this a multi-centre trial? Hierarchical modeling techniques can be used. See Jason W. Osborne, Advantages of hierarchical linear modeling.

Are subgroups part of the analysis? A priori defined stratification processes are appropriate See Stephen W. Lagakos, The Challenge of Subgroup Analyses — Reporting without Distorting.

Are relative or absolute risks being measured and reported? Relative risks can be statistically significant but may not be clinically relevant.

Resources


For topics in multivariate analysis, see G. David Garson. Statnotes: Topics in Multivariate Analysis.


For guidance on analyzing qualitative data, see Catherine Pope, Sue Ziebland and Nicholas Mays. Qualitative research in health care: Analysing qualitative data. British Medical Journal, v. 320, 8 January 2000, p. 114-16.

Reporting

If the purpose of research is to generate new knowledge (from which profits may be realized) and participants are motivated to volunteer to benefit themselves, others who are similarly situated, society or their community, then researchers and sponsors are obligated to report and disseminate results.

Paragraph 17 of the Canadian Medical Association’s Guidelines for Physicians in Interactions with Industry states: “Physicians should not enter into agreements that limit their right to publish or disclose results of the study or report adverse events which occur during the course of the study. Reasonable limitations which do not endanger patient health or safety may be permissible.”

See also CMAJ. Look, no strings: publishing industry-funded research. [Editorial]

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Publication in peer-reviewed journals is the optimum means of reporting and disseminating results. A number of concerns have arisen related to publication and bias.

- Are published reports biased toward positive results? Three sources of publication bias are editorial bias, publication or submission bias and undue influence of sponsors. See C. David Naylor, et al., *Early Toronto experience with new standards for industry-sponsored clinical research: a progress report*.
- Selective reporting of favourable results. See Mohit Bhandari, Jason W. Busse, et al., *Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials*. For a sponsor’s perspective see Laurence Hirsch, *Randomized clinical trials: What gets published, and when?*
- Suppression of results. See David Hailey, *Scientific harassment by pharmaceutical companies: time to stop*.
- Nondisclosure or gag clauses. See Robert Steinbrook, *Gag Clauses in Clinical-Trial Agreements*.
- Multiple submissions and reports of a trial. See Rennie Drummond, *Fair Reporting and Fair Conduct of Clinical Trials*.

Clinical trial registries exist to reduce, mitigate or eliminate these concerns. See David Moher and Alan Bernstein, *Registering CIHR-funded randomized controlled trials: a global public good*.

A controversial issue is whether, how and in what form the “data,” the research results (individual or aggregate) should be offered to participants. In some areas of research, e.g., genetic epidemiology, it is argued that certain results should not be offered. “Research activity and debate around the issue of treatment debriefing are increasing, although there are as yet no signs of an emerging consensus on best practice.”


See sections on Therapeutic Misconceptions, Disclosure and Legal and Regulatory Requirements.

**Questions to Ask about Reporting**

- Will the results be disclosed?
- To whom will the results be reported?
- Will the results be offered to participants?
- In what form will the results be disclosed to participants (raw or primary data or summary)?
- Will the results be peer reviewed? Peer review is essential as it allows for independent audit of value, validity and veracity.

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• Will the results be published?
• Is the trial registered on a publicly accessible registry? See WHO. International Clinical Trials Registry Platform.
• Have the relative and absolute risks been disclosed?
• Is there an independent agency to which adverse events are reportable?
• Will new information, which could influence participant’s decision to continue participating, be reported so participants can re-consent or withdraw?
• Does the report include a clear definition of study groups and justification of inclusion criteria?
• Does the report describe the populations being compared?
• Does the report include a discussion of the clinical context of the comparisons?
• Does the report provide justification for the comparisons?
• Has the distribution of confounders (and potential confounders) in both groups been reported?
• Are the analytical strategies clearly described?

Resources

• For a checklist of elements for reporting a randomized clinical trial, see CONSORT.
• For an revised version of the CONSORT guidelines in trials on herbs see Joel J. Gagnier et. al. Reporting Randomized, Controlled Trials of Herbal Interventions: An Elaborated CONSORT Statement.
• For a checklist of elements for reporting meta-analysis and systematic reviews of randomized trials, see QUOROM Guidelines and David Moher, Deborah J. Cook, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement.

Authorship

The results of research should be reported in a publicly available format, and the attribution of authorship is an important component of the report. There are currently concerns about who is an author. These concerns are partly caused by an expansion of multicentre clinical trials with a large number of co-investigators. Paragraph 16 of CMA's Guidelines for Physicians in Interactions with Industry stipulates that: "Physicians should only be included as an author of a published article reporting the results of an industry sponsored trial if they have contributed substantively to the study or the composition of the article." This policy should be applied when determining authorship, regardless of who sponsors the research.

Questions to ask about Authorship

• Did you contribute substantively to the study?
• Did you contribute substantively to the composition of the article?
• Did you make a substantive intellectual contribution to the hypothesis being tested or the methodology used?
• Would attribution be classed as “honorary” or “gifted” authorship?
• If the integrity of the study is questioned are you willing to take responsibility?
• Can you attest to the value and validity of the study?
• Are you able to affirm ethical norms were followed and that regulatory requirements were met?

**Misconduct**

When physician-researchers or scientists engage in misconduct, they jeopardize their career and reputation. Public disclosure of misconduct casts aspersions on the integrity, veracity and repute of medicine and science. Two general types of misconduct are research misconduct and scientific misconduct. “In our opinion, scientific misconduct — or rather, conduct inconsistent with accepted scientific standards — is a continuum ranging from honest errors to outright fraud. ... A survey of US scientists showed that a third of respondents admitted to have engaged in unethical research behaviour within the previous 3 years.”

According to the United States Department of Health and Human Services:

Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.
(a) Fabrication is making up data or results and recording or reporting them.
(b) Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
(c) Plagiarism is the appropriation of another person’s ideas, processes, results, or words without giving appropriate credit.
(d) Research misconduct does not include honest error or differences of opinion.

See the Tri-Council Policy Statement, *Integrity in Research and Scholarship*.

Some jurisdictions divide research misconduct into fraud and abuse. “The term *fraud* refers to intentional acts of deception, whereas *abuse* is generally understood to mean a significant or repeated deviation from acceptable practice.” According to De Vries and colleagues, misconduct can be divided into 4 categories: “the meaning of data, the rules of science, life with colleagues, and the pressures of production in science.” Some consider the intentional, unauthorised use and/or damage to research-related property of another, including but not limited to, apparatus, materials, writings, data, hardware or software or any other substances or devices or any disclosure or removal of such used in or produced by the conduct of research misconduct.

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17 De Vries, et al., *Normal Misbehavior: Scientists Talk About the Ethics of Research*. 

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Some jurisdictions have begun to expand the legal theory that “knowing non-compliance with a condition of payment renders claims for payment false”\(^{18}\) to non-compliance with statutory regulations. Charges have been laid alleging false claims because of inadequate consent forms, failure to obtain informed consent properly, failure to disclose conflicts of interest and false or fabricated data — although these cases are still rare. See Paul E. Kalb and Kristin Graham Koehler. *Legal Issues in Scientific Research.* *Journal of the American Medical Association*, January 2 2002, v. 287, no. 1, p. 85-91

**Questions to Ask about Research Misconduct**

- Are data created to support results? This is fabrication, a form of lying, and is misconduct.
- Are the data being changed to support results? This is falsification, another form of lying, and is misconduct.
- Are the results or data being misrepresented?
- Does the trial try to control biases, both personal and systematic?
- Are you claiming another’s work or ideas as your own or failing to give the originator or creator due credit? This is plagiarism, a form of theft, and is misconduct.
- Who will be listed as an “author?” To be named author, the person must have made a substantial scholarly contribution to the publication and be able to take responsibility for its content. See A. Newman and R. Jones, *Authorship of research papers: ethical and professional issues for short-term researchers.* *Journal of Medical Ethics*, v. 32, Issue 7, July 1 2006, p. 420-23.
- Is your or another’s name being affixed to a report that you or they did not contribute to? If you contributed to the concept or design, the analysis or interpretation of the data or drafting, composing or revising the article you may legitimately claim authorship. If the report or article is presented to you as a “finished product” and you merely “sign on,” this is plagiarism and constitutes misconduct. “Ghostwritten” reports are unethical.
- Have you identified, declared and are trying to manage your conflicts of interest?

**Questions to Ask about Scientific Misconduct**

- Is the research being conducted appropriately? Deliberate, dangerous or negligent deviations from accepted practices (including a failure to follow established protocols) in carrying out research are considered misconduct.
- Are research participants being “wantonly” endangered?
- Has the proposal been reviewed by an REB?
- Does the trial answer a “legitimate” question? If not, the research is unnecessary, exposes participants to unnecessary risks and wrongs them.
- Have the endpoints, outcomes, processes or procedures changed and have the changes been submitted to and passed by the REB? If not, this constitutes scientific misconduct.

• Has a meta-analysis, a systematic or literature review been conducted? If not, the research may duplicate previous studies and expose participants to unnecessary risks.
• Did you infringe copyright or use another’s concept without due authorization? These are forms of piracy or theft and are misconduct.
• Are research monies being used for other than their stated purpose? This is fraud, misuse of funds, and is misconduct. See Timothy F. Murphy, On being downstream from faked scientific reports. [Reviews] British Medical Journal, v. 332, 18 March 2006, p. 33.
• Have you identified and disclosed all (real, potential and perceived) conflicts of interest? See Conflicts of Interest and Disclosure.
• Have you received authorization for secondary uses of research-related property? Unauthorized use of, including but not limited to, apparatus, materials, writings, data, hardware, software or any other substances or devices or any disclosure or removal of research generated data is considered misconduct.
• Are regulatory requirements met and maintained?

Resources

See B.C. Martinson, M.S. Anderson and R.G. De Vries, Scientists behaving badly for a list of troubling behaviours.

Ethics

Introduction

Two moral precepts are of paramount importance for ethical research: liberty and justice. The ethical principles governing research on or with human participants that derive from liberty are respect for persons, autonomy and non-maleficence. The informed consent process is a means to promote, protect and honour autonomy and demonstrates respect for persons. Assessing and disclosing the risk–benefit ratio is a means to limit harm and promotes “rational” decision-making. The principles that derive from justice are equity, distributive and procedural justice. An equitable recruitment strategy fulfills one dictate of justice.

In 1974 in response to reported abuses of subjects of research, the United States Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. The Commission’s report, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, identified three basic ethical principles, respect for persons, beneficence and justice.20

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19 Some commentators have beneficence in place of non-maleficence. In the context of research ethics, we prefer non-maleficence since promoting beneficence may contribute to conflating research and clinical care, i.e., therapeutic misconceptions.
Above all, physicians and researchers must recognize human participant’s intrinsic value and protect their well-being, inherent dignity, integrity, autonomy and privacy. To do so, participants’ interests must take precedence over the physician’s, the researcher’s, the scientist’s, the institution’s, the sponsor’s and, unless the research participant places others at imminent risk of serious harm, society’s interests.

When may the responsible physician offer trial enrolment to her or his patient? Clinical equipoise provides the most widely accepted answer to this question. According to this concept, there must exist at the start of the trial a state of honest, professional disagreement in the community of expert clinicians as to the preferred treatment. Under these circumstances a state of clinical equipoise is said to exist, and the physician may offer trial enrolment to his or her patients legitimately.\(^{21}\)

Therapy provides benefits. Research is, by definition, non-therapeutic, as the benefits are unknown, unproven or potential. Research places research participants at risk of harm without compensatory personal benefit; others, however, could benefit. Hence, research is usually justified by utilitarian or consequentialist arguments (the good of the many outweighs the good of the few; a beneficial outcome for society). However, research participants must not be treated solely as means to another’s end (a precept of deontology). Thus, the scientific endeavour is constrained by rights and duties (deontology). When physicians participate in research, the fiduciary duties and obligations they owe to their patients constrict placing the good of the many over the good or rights of the individual. Requiring voluntary informed consent or voluntary refusal of standard treatment ensure that research participants are not treated solely as means to others’ ends, participants are respected as persons with intrinsic and inherent value. Participants should understand that they are participating in a study and that the intervention is not designed to treat them and probably will not result in any direct personal, therapeutic benefit (although there may be a chance of this).

Physician-researchers should remember that the goals of clinical care and therapy differ from scientific goals. When the values and goals of clinical care and scientific research conflict, physician-researchers’ primary obligation is to protect and promote the interests of their patient. The role and obligations of a physician are paramount; the role and obligations of a researcher are secondary. If the responsibilities or obligations of a researcher unduly influence or take precedence over the fiduciary duties of the physician, the physician-researcher is in a conflict of interest. Conflicts of interests should always be resolved in the patient’s favour.

Regulation and oversight may reduce unethical research, but cannot eliminate it. Ethical research is premised and reliant on the personal and professional integrity of participants — all participants — and the physician’s clinical judgement. See Franklin G. Miller, et al., *Professional Integrity in Clinical Research.*

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Sponsors use research to further health goals and sometimes as marketing strategies or tools. Two marketing techniques to be aware of are “seeding trials” and “switching campaigns.” Seeding trials are large, multicentre and usually with a combination of the following characteristics: they a) enrol few participants at each site; they b) involve a common condition; c) investigators may not be distinguished researchers, knowledgeable or experts in the field; they, d) have an open-label design; there is, e) no control group or they are not blinded; they, f) are sponsored by the marketing department; they, g) collect data with little or no clinical import; they, h) have minimal reporting requirements; and i) pay enrolment fees.

Switching campaigns that warrant careful scrutiny are efforts to switch patients to a different dose of the same product or to another (usually new, more expensive “me too”) drug in the same therapeutic class. Not all switching campaigns are unethical; if done appropriately, these campaigns can be cost effective without compromising quality of care. See David A. Kessler, et al., Therapeutic-Class Wars – Drug Promotion in a Competitive Marketplace. The New England Journal of Medicine. November 17 1994, v. 331, no. 20, p. 1350-53

If the trial or the institution at which the trial is conducted receives funding from a Canadian funding agency (Canadian Institutes of Health Research, Social Sciences and Humanities Research Council or the Natural Sciences and Engineering Research Council), then it must meet or exceed the requirements outlined in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

**Forms of Justice: Distributive, Equity, Procedural**

**Distributive Justice**

Issues regarding resource allocation involve distributive justice; what criterion determines the distribution of goods, i.e., who and what qualify someone to receive or obtain certain goods? Because resources are finite, a macro-allocation concern is what portion of a budget (government or personal) should be allocated to each competing need, e.g., health care or education? Given that health care competes with other needs, whether societal or intrapersonal needs, human and financial health care resources should not be allocated to unethical research.

Individual access to and quality of care are micro-allocation issues. Adjunct benefits, such as queue jumping and increased health monitoring, are concerns in terms of the just distribution of health care resources. Physician-researchers should be aware and evaluate whether engaging in research could adversely affect their patients’ access to their care, e.g., is clinical time diverted to research? Physician-researchers’ competing obligations, providing care to patients and contributing to the development of medicine, requires balancing and appropriate time management.
Equity

Equity ensures that participant selection is “fair.” Fair subject selection is based on the aims of the research and equality: like cases are to be treated alike, different cases treated differently. The purpose of the research and the correlations sought determines the characteristics participants should share. Thus, fair participant selection is partly an empirical question: are participants alike? Ideally, unless justified by the hypothesis (e.g., an ethnographic, ethnomedical or ethno-pharmacologic study), participant selection should reflect local demographics or the clinical population that will use or benefit from the intervention.

Although the study’s inclusion and exclusion criteria help ensure its validity, they can also ensure that the study is equitable. Equity dictates that no segment, group or class bears the risks and burdens of research while another segment, group or class gains the benefits. It is important to ensure that the population enrolled is the population most likely to be prescribed the intervention and have access to the drug, the device or the procedure if it is licensed and adopted into clinical practice.

Consider whether participants are members of a community or group that could be adversely affected by the results. Consulting an advocacy group or community leaders can be beneficial. For example, The Royal Commission on Aboriginal Peoples developed Ethical Guidelines for Research with Aboriginal Participants. See Charles Weijer, Protecting Communities in Research: Philosophical and Pragmatic Challenges. Cambridge Quarterly of Healthcare Ethics. October 1999, v. 8, Issue 4, p. 501-13.

Procedural Justice

Procedural justice is concerned with whether the rules of a system or a process are fair. Procedural justice is similar to “game theory.” If the rules of a game are such that the home team has an unfair advantage and will always win, the game (or process) is “rigged” and, thus, unfair. Procedural justice dictates assessing the methods and means of recruitment — the inducements offered to ensure that the process does not put any group at an advantage or disadvantage. For example, the reading level of recruitment posters or advertisements may unintentionally screen out a segment of the population. Processes should not be overridden for expediency. Inclusion and exclusion criteria must be based on valid scientific (methodological) reasons, elevated susceptibility or severity of harm, not simply on who is available. See W. A. Rogers, Evidence based medicine and justice: a framework for looking at the impact of EBM upon vulnerable or disadvantaged groups. Journal of Medical Ethics, v. 30, 2004, p. 141-145.

Procedural justice demands a clear separation of roles. A role, e.g., caregiver, recruiter, researcher, is identified and determined by its function. Roles and functions dictate and conscribe legitimate activities, associated rights, duties and privileges; they establish the “ground rules” and set expectations. When roles are blurred, it is no longer clear which function or what rights, duties and privileges and expectations are in play.
Research Ethics Boards

All research on humans requires prior independent review (if the research uses animals, then an Animal Care Committee provides oversight). Physician-researchers associated with academic centers have access to the center’s research ethics board (REB). Independent practitioners may not have access to institution’s research ethics committee. In these instances the trial’s sponsor may hire an independent REB. If the independent practitioner is concerned about the objectivity of the for-hire REB, he or she could approach an institutional REB and ask it to review the protocol.

Questions to Ask about REB Review

- Has the protocol been submitted for REB approval? Will it be?
- Has the protocol been disallowed, conditionally passed or passed without amendments by a REB?
- Have the amendments requested by the REB been made?
- Does the REB reviewing the protocol meet the standards outlined in the Tri-Council Policy Statement?
- Does the REB have a conflict of interest policy and procedures for its members?
- Has the REB been accredited (assuming there is a system of accreditation)?
- If the REB is affiliated with an institution, does the REB function independently?
- Is it a private REB, i.e., no formal or informal ties other than a contract with the sponsor or institution?
- If it is a private REB, is it a for-profit or not-for-profit entity?
- Does the private REB or the REB affiliated with an institution that does not receive government funding have guidelines for approval?
- Are the REB guidelines and processes published?
- Is the process for REB approval transparent?
- Is the REB accountable to anyone?
- How transparent and rigorous is the review process?
- If the research is being conducted by a contract research organization (CRO), is the REB an affiliate or subsidiary of the CRO or hired by the CRO? The working relationship between the CRO and the REB can place REB members in a conflict of interest situation.
- Will the REB monitor (audit) the trial?
- If the protocol has been amended, have the amendments been reported to and reviewed by the REB?

Informed Consent and Informed Refusal

Researchers must obtain informed consent from participants. Participant’s consent and signature on the consent form or other consent document is not the end of the dialogue — just a good start. Consider the signature a “signpost”; consent is a dynamic process, continuously reaffirmed by participant’s behaviour, their willingness and compliance with the limitations and demands placed on them by the protocol. Participants may revoke their consent at any time. Revocation of consent terminates their involvement in the trial, unless they volunteer to participate in “follow-up” processes. Informed consent is not a waiver of participants’ rights.
If a prospective research participant lacks decisional capacity to consent or refuse treatment in the clinical setting, he or she is incapable of granting informed consent to participate in research. The quality of participant’s consent is proportional to the quality of information provided (the informed portion of informed consent). Disclosure requirements vary with the type of research. A basic rule of thumb is that if the information might influence participants’ decision to participate, disclose it.

Decisional capacity is content and context specific; patients and research participants may have compromised capacity. They may be capable of consenting to some interventions but not to others because of such variables as the probability and severity of harm. “Reasonable” choice is associated with, but is different from, reasonable chance. Reasonable chance is based on available evidence, but the “reasonableness” of the choice is idiosyncratic — the participant weighs the evidence, the nature, magnitude and probability of risks and benefits, synthesizes this with his or her goals and value system and then makes a choice.

Whether surrogates may volunteer an incapacitated or incompetent person as a research participant is controversial. Some argue that it is unethical to volunteer another person for research as there is no direct benefit to the participant. Others argue that if there is potential for direct benefit, then a proxy may enrol his or her “ward,” for example, in cases where no standard treatment exists or an oncology drug study in which the new compound offers the “last best hope.” Some focus on risks and enrolling incapacitated people in studies that pose only minimal risk. Others argue that if the person was never competent, surrogates may enrol their ward only if it is in the participant’s best medical interests to do so (World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects articles 19 and 24). If participants have diminished or lack decision-making capacity, participants assent to participant should still be solicited.

Physicians who recruit their patients as research subjects must be aware that power asymmetries may unduly influence a patient’s decision to participate. Physician-researchers and their patients must clearly delineate when the physician is acting as a care provider and when he or she is acting as a scientist. Physicians must draw clear distinctions between clinical goals and research goals.

**Questions to Ask about Informed Consent or Informed Refusal**

- Is the right to and capacity for granting informed consent or refusal the standard?
- Is the nature, purpose and duration of the research disclosed?
- Is the standard of disclosure sufficient to meet the “reasonable person” standard?
- Who will recruit, inform and obtain consent from participants? Physician-researchers must be aware that patients may feel obligated to participate if their physician recruits them or participates in the informed consent process. Ideally, third parties recruit and obtain consent. Physician-researchers may recruit their patients; however, someone with no clinical (or pre-existing) relationship with the research subject should obtain the initial informed consent.
- Is the nature and source of information sought disclosed, (e.g., blood pressure readings extracted from the medical record, and/or whether researchers will access the medical record more than once)?
• Are the experimental elements (e.g., procedures, tests) identified?
• Are participants informed of the foreseeable risks, discomforts and benefits? See Risk Benefit Assessment
• Is randomization explained in terms that allow the participant to understand this concept, its meaning, determine the significance to them and their participation?
• Are participants informed that they might not receive the standard of care or any care whatsoever? This is important in blinded studies, whether with placebo or alternatives to the standard of care.
• If a placebo is used, has the placebo effect been explained to participants and thus they understand why “sham” or “dummy” pills will be used?
• Has the extent to which confidentiality can or will be protected been disclosed?
• Do participants know who will have access to what information?
• Are alternatives to participation discussed?
• How will assent be obtained from incapacitated or non-competent participants?
• Are participants told that they may withdraw at any time without penalty or loss of accrued benefits?
• If there are procedures to follow for exiting the study, are participants informed of them?
• If a participant withdraws (a revocation of consent) can they request that their data be removed (if not irretrievably delinked and anonymous) and are they informed of this?
• Are participants informed whether they will be treated or compensated for injury, who will provide treatment and who is responsible for compensation?
• Are participants offered research results? See Reporting.
• Will participants receive copies of the information sheet and their signed consent form?
• Is contact between the principle investigator, the sponsor, the site, you (the investigator) and if reviewed by a for-hire REB, the REB that reviewed the protocol provided to potential participants? See Disclosure
• If participants are audio- or video-taped, may participants review the recordings?
• What is the readability level of recruitment advertisements, posters, information documents and consent or refusal forms? A grade 8 reading level is recommended. If people whose eyesight may be compromised (e.g., the elderly) are to be participants, the size of type should be enlarged. The language should be respectful (e.g., “participants are asked”). Information documents should be written in the second person (you/your), consent/refusal forms in the first (I, me, my). Acronyms should be avoided, especially ones that may raise expectations (e.g., B.E.T.T.E.R. H.E.A.L.T.H. study).
• Are participants members of an identifiable community (e.g., racial group) that could be adversely affected by the findings? Genetic tests are paradigmatic.
• If the study involves genetic tests, are participants informed that results could have implications for other family members? See Genetic Research.
• If this is a genetic study involving a gene known to be pleiotropic, have the associated conditions and implications been disclosed to participants?

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22 MSWord may be set to display readability level after checking spelling and grammar.
• If participants are members of a “vulnerable” group or identifiable community, have the group’s or the community’s leaders been consulted and assisted with the review of the protocol (for example during the REB approval process)? See Charles Weijer, Gary Goldsand and Ezekiel J. Emanuel. Protecting communities in research: current guidelines and limits of extrapolation

• Will people with diminished or compromised decisional capacity be recruited? Whether proxies (surrogates) may volunteer wards as research subjects is controversial. Surrogates may have the legal right to volunteer wards as research participants but ethicists disagree over whether enrolling incapacitated, incompetent or non-competent persons in research is ethical.

• Is there a process to ensure the continued assent of the decisionally impaired participant and is this process disclosed to the surrogate decision-maker?

Disclosure

Sponsors, funders and Contract Research Organizations (CROs) are obligated to disclose pertinent information to investigators. Sponsors, funders, CROs and investigators are obligated to disclose pertinent information to the REB. Investigators are obligated to disclose pertinent information to participants. What qualifies as “pertinent” varies depending on the role and functions of the individual or organization.

Paragraph 22 of the World Medical Association’s Declaration of Helsinki states:

[I]n any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject’s freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

Does the consent form identify and disclose specific risks and direct benefits or probable risks and benefits and the likelihood of them occurring, does it identify adjunct or societal benefits as direct or potential benefits or some combination of all? If types, magnitude and likelihood of risks and benefits are not identified or disclosed, the potential for confusing the goals of clinical care and research is heightened (see Therapeutic Misconceptions).

It should not be forgotten that this is research, a situation where disclosure obligations are always considered to be higher, not lower, than in the clinical situation.25

**Questions to Ask about Disclosure**

- Have participants been informed that this is research and that their clinical goals or interests may not be furthered or that they will not directly benefit?
- Have participants been told about the trial type and purpose (the hypothesis being tested) e.g., that it is a clinical trial and what phase of trial: safety, efficacy, comparison, surveillance?
- Have participants been told whether randomization is part of the protocol, and when appropriate, been asked to grant informed refusal (if placebo is being used)?
- Have participants been told what procedures they will be subjected to, e.g., needle sticks, radiograph? Physicians must disclose to participants the nature of the proposed intervention, its gravity and material risks, including special or unusual risks.
- Have the risks been disclosed? If the risk is a mere possibility or if serious consequences are possible, all require disclosure. See [Risk-Benefit Assessments](#).
- Have the risk matrix, benefit matrix and inconveniences associated with the particular intervention been disclosed?
- Have participants been told which portions of the protocol are experimental?
- When appropriate, have alternative procedures or courses of treatment been discussed (including doing nothing), their attendant risks and the probable consequences if no treatment is undertaken? Disclosing alternatives may imply that the experimental procedures will further the participant’s clinical goals. See [Therapeutic Misconceptions](#).
- Are potential participants informed whether the interventions have caused an adverse reaction and how serious the harm suffered was?
- Have participants been informed what treatments or compensation available to them if they are injured, and who will cover the costs? Whether the sponsor or publicly funded insurance (taxpayers) should cover medical expenses incurred due to injuries sustained as a research participant is controversial.
- Have participants been told what costs they may incur and whether they will be reimbursed?
- Have participants been told what the length of their commitment is: the duration of the study and follow-up period?
- Have participants been told what their responsibilities are, e.g., how often they have an appointment to have blood drawn, how many and how frequent are the tests, etc.?
- Are participants informed of the inclusion and exclusion criteria and why they qualify?
- Are participants informed of their right to withdraw without penalty and that they may request removal of their data? If limitations are placed on these rights participants must be informed.
- Are the reasons and circumstances precipitating dismissal from or termination of the study outlined?

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• Does the study use deception is this disclosed to participants (general terms are acceptable)?
• Will participants know ho the sponsor is (funder of the study)?
• Will participants know who is the principal investigator?
• Will participants know who the chair of the REB that reviewed the protocol is and is their contact information provided?
• Will participants know how many participants you will enrol?
• Will participants know how many participants in total?
• Will participants know how many and the location of the other sites involved?
• Will participants know whether the study is national or international?
• Do you or your employer have financial interests in the sponsoring company and are these interests disclosed to participants? See Conflicts of Interest.
• Do you or your employer stand to gain financially from participating (e.g., a patent)? This should be disclosed to the research participants.
• Are you being paid for services (e.g., finders fees) or reimbursed for time away from practice? If you receive payment, this should be disclosed to participants.
• Have payments for speaking engagements, consulting relationships or personal investments in or from the sponsor been disclosed?
• Do participants know who has access to, monitors and stores the data?
• Do participants know how confidentiality will be ensured?
• Can data and personal health information be released to a third party? If data or personal information could be released to a third party, disclose why and what information would be released, the circumstances under which it will be disclosed and to whom.
• Do participants know who is accountable for breaches of privacy or breaking confidentiality?
• Do participants know how long the data will be kept and how data will be destroyed?
• Do participants know whether the trial is registered and whether the registry is publicly accessible?
• Do participants know whether results will be reported or submitted for publication?
• Do participants know to whom the results will be reported?
• Are participants informed whether there is a confidentiality clause that places limits your freedom to publish results?
• Will participants be “debriefed,” provided the results if they request them or both?
• Who owns and controls the data? See Conflicts of Interest. If a limiting or gag clause related to proprietary information is included in the contract these limitations must be disclosed to research participants. Gag clauses are unethical. See The “file drawer” phenomenon. Suppressing clinical evidence. Canadian Medical Association Journal.
• Do participants know whether there is a data or safety monitoring board and how to contact them?
Privacy, Confidentiality and Anonymity

Autonomy underpins privacy rights. There are various definitions and forms of privacy. In health care and biomedical research, one important definition or form of privacy is control over personal information/data. People want to control dissemination of private information because of their belief and/or value system, their relationships (intimate and otherwise) or because certain facts are associated with their self-concept, self-identity, their private and public persona and social stigma. What information and with whom one is willing to share it with is usually a matter of discretion and social context. People share personal information to receive certain services (primary purpose of data collection), health care being one such service. Disclosing personal information to obtain the services of a professional underlies health care professionals’ pledge of confidentiality and physicians’ fiduciary duties.

Usually, gathering, obtaining and access to health information are on a “need-to-know” basis, according to the patient’s needs. Health care providers gain access to information they need to know in order to provide the required services (treatment). When volunteering as a research participant, one usually agrees to share some personal information. As with information collected for health care purposes, information for research purposes should be on the “need-to-know” basis; the difference is the information gathered depends on what is needed to test the hypothesis.

Extracting information from health records or other databanks for research is a secondary purpose (a purpose other than that for which the data was originally collected) and the information is or may be linked to an identifiable individual. Whether the data owner, not just the data steward, must always grant explicit prior consent to access recorded information is debated. Only the opt-in process of informed consent guarantees that confidentiality has not breached, e.g., the data steward contacts the prospective research participant and provides the researcher’s contact information or the data steward asks the data owner for permission to give his or her name and contact information to the researcher.

Article 3.3 of the TCPS states:

If identifying information is involved, REB approval shall be sought for secondary uses of data. Researchers may gain access to identifying information if they have demonstrated to the satisfaction of the REB that:

a. Identifying information is essential to the research;
b. They will take appropriate measures to protect the privacy of the individuals, to ensure the confidentiality of the data, and to minimize harms to subjects; and
c. Individuals to whom the data refer have not objected to secondary use.26

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Some research, e.g., health systems research that relies on aggregate data may not require direct contact with data owners. These studies may use anonymous information previously compiled from medical records or other databanks. Use of aggregate data that are delinked and non-identifiable does not require expressed prior consent. All other processes entail unauthorized disclosure. See the four articles and Editorial in the British Medical Journal beginning with Dipak Kalra, et al., Confidentiality of personal health information used for research. British Medical Journal, v. 333, 22 July 2006 p. 196-98. Ross Upshur, et al., The privacy paradox: laying Orwell’s ghost to rest. Gregory E. Simon, Jürgen Unützer, et al., Large Medical Databases, Population-Based Research, and Patient Confidentiality.

See Databanks, Bio-banks and Population based Research.

Questions to Ask about Confidentiality and Anonymity

- Will private, personal, identifiable health information previously collected to meet the needs of the patient (primary purpose) be extracted from the health record? If so, then the patient/participant must grant explicit prior consent for the secondary use of their information.
- Has who will collect and who has access to personal health data been disclosed to participants? Has a “map” or classification of data sensitivity been prepared to determine which member of the research team has access to which classification? Access is based on “need to know;” what information the team member needs to fulfill his or her research function.
- Could the data or personal health information be released to a third party, e.g., regulatory authority or trial monitor? If so, disclose what information could or will be released to the third party, disclose under what circumstances it could be released and to whom (person, agency).
- Have those with access to the medical record, personal information and the data promised to keep the information confidential?
- Will the data be stored in a secure location? What measures are used to secure the data?
- How will information be anonymised? Rearranging initials is not sufficient to ensure anonymity, especially if the initials could be linked to other identifiable information. The more discreet pieces of information that can be linked, the easier it is to identify someone.
- Will the encryption code be stored separately from the data?
- Has the term of retention been determined (different jurisdictions may have differing terms) and has this been disclosed to participants?
- Have conditions under which re-identification may be necessary been identified (e.g., verifying data) and disclosed to participants?
- If re-identification becomes necessary, is there a formal procedure for this?
- Was permission granted to take and use images or photographs?
- Will the audio, video or other identifiable data be used for educational purposes? Have participants been informed of and granted consent for this use?
• How will the data be destroyed? Different media require different methods of destruction, e.g., audio and videotapes should be cut, computer drives (hard, floppy, flash) erased and paper shredded.
• Will the data be matched or linked from various databases? Matching and linking are considered secondary uses of data.
• Are participants members of a small, isolated or rural population or community? If a participants’ pre-existing relationship with the physician-researcher is known and the researcher publishes an article, if authorship and location is linked to anonymised data or minimally identifiable information, then participants’ anonymity may be compromised.

Risk–benefit Assessments

Components of the study should be separately assessed to determine risks and benefits. The potential benefits must be proportional to identified risks. If the risks outweigh the potential health benefits and knowledge gained, the research is unjustifiable and unethical as it exploits participants. Research is not treatment because treatment optimizes the interests of the patient and research does not. Since research participants volunteer to be placed at risk of physical injury or harm for the benefit of others, risk assessments must be broader than assessments of potential benefits. The spectrum of risks must be identified and participants must understand that the purpose of the intervention is research and not to provide any direct therapy. For most biomedical research, only probable or potential health-related benefits should be assessed and disclosed; adjunct benefits should not be included in risk-benefit disclosures (see discussion on benefits below). See Therapeutic Misconceptions.

Although it is impossible to know and account for every unintended consequence (whether harm or benefit) in advance — and thus cannot be included in the risk–benefit calculation or disclosed — competent physician-researchers should be capable of identifying probable consequences. If new risks or risk assessments are identified during the study, they must be disclosed to participants. Since risk assessment is subjective, a participant may decide that he or she does not want to expose him or herself to the new risk or level of risk. This disclosure ensures informed consent for exposure to the new risk and participation in the study or participants may choose to withdraw. Because physician-researchers are responsible for disclosing the risks associated with the trial’s interventions, a physician should only participate in trials that relate to his or her area of expertise.

Risks lie on a continuum: varying from minimum/minimal, to low, medium and high, risk assessments are subjective. In assessing the risk–benefit ratio, various “thresholds” can be employed, the community’s, a professions and a personal threshold. Variables that determine one’s risk-benefit threshold are her knowledge and personal experiences. Because the participant determines whether the risk–benefit ratio is conducive to his or her participation, physician-researchers may choose to base the initial risk–benefit calculation on the community’s threshold. However, because a particular participant’s or the physician-researcher’s risk–benefit “threshold” is based on knowledge and personal experiences, assessments can vary from that of the general community’s.
Different types of benefits must be clearly distinguished to allow participants to make reasonable risk–benefit assessments and informed decisions and choices. Direct or potential benefits further the participant’s health/clinical goals. Adjunct benefits are a “perk” for participating, e.g., closer monitoring of their health condition. Participants who will not benefit from the intervention (e.g., phase one clinical trials) need to demonstrate his or her understanding that he or she will not directly benefit. A participant must comprehend furthering her clinical/health goals/interests are not the intervention’s purpose and that her health or interests may not be furthered.

Three types of research benefits are proposed: direct benefits, collateral (unintended, i.e., adjunct) benefits and aspirational (potential) benefits. Direct benefits arise “from receiving the intervention being studied; collateral benefits [arise] from being a subject, even if one does not receive the experimental intervention (for example, a free physical exam...); aspirational benefit, or benefit to society and to future patients … arises from the results of the study.”27 The research protocol should identify the ultimate goal, the projected benefits, i.e., the results and implications for clinical application. The various types of benefits should not be combined or confused and must be clearly delineated for participants. The chance of a cure or the chance of realizing a direct benefit should be considered aspirational. Ross claims that: “[t]o classify research as offering the prospect of direct benefit suggests a certain probability of success, and not the mere possibility of benefit.”28

Claiming that participants will, simply by participating in the study, directly benefit may be based on “the fallacy of the package deal.” The “package” may include direct, collateral or aspirational benefits, but since the central components are experimental and unproven, the benefits are potential, not actual at the time of recruitment. “[T]he fallacy of the package deal … label[s] an entire study “therapeutic” despite the clearly experimental character and unproven benefit of its central component, e.g., the drug being studied.”29 Collateral or adjunct benefits, such as queue jumping for diagnostic services or payment for participation, should not be considered in the risk–benefit assessment and disclosure.

**Questions to Ask about Risks**

- Who is placed at risk and who will benefit?
- Do the risks outweigh the (potential) benefits?
- Has study staff been adequately trained to perform their research functions? How has this been ensured?
- What type of physical risks will participants be exposed to? There are various types of physical risks: death, irreversible damage/harm/disability, temporary disability and various levels of pain and discomfort (from minimal to severe).
- What is the magnitude of the risk: minimum, moderate, high? If this is unknown, then this uncertainty must be disclosed.
- What is the probability of a particular risk occurring?

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• What is the risk matrix, e.g., low probability of severe harm, high probability of temporary discomfort?
• Which definition of minimum does the study employ: minor increase over minimal, statistical norm, normal daily exposure or life exposure?
• Is there a clear definition of what constitutes an adverse event?
• If harm or an adverse event occurs, will it be reported? To whom will it be reported? Contracts with the sponsor must not prohibit reporting.
• Is there a safety monitoring board to which adverse events are reportable?
• How invasive are the procedures?
• How intrusive is the research?
• Is there a “washout” period during which the research participant may suffer from withdrawal or symptoms associated with the condition the intervention may treat or control?
• Have the social, psychological, cultural and emotional risks been considered and identified?
• What are the psychological and emotional risks?
• What are the social risks? Examples of social risks are risk to social standing, privacy, values or beliefs, adverse effects from sharing sexual mores, proclivities or habits, familial or community relations and links.
• If this is genetic research, have the risks of associated health conditions been identified? See Genetic Research.
• Has the correlation between the genes being studied and other health conditions been disclosed?
• Are there any financial risks? Examples of financial risks are risk to employment or occupation.
• Will participants be compensated if they are injured? Some argue participants should be compensated if injury occurs; others claim that because participants knew the risks and volunteered to participate, no compensation is necessary. See CIOMS. International Ethical Guidelines for Biomedical Research Involving Human Subjects and Robert Steinbrook, Compensation for Injured Research Subjects, New England Journal of Medicine, v. 354, no. 18, May 4, 2006, pp. 1871-1873.
• If harm occurs, who will pay for subsequent treatments?
• If new risks are identified, how will participants be informed? If new risks are discovered or the risk matrix is modified, participants must be informed, as they may not be willing to expose themselves to the new type, level or risk matrix, and may wish to revoke their consent to participate and withdraw.

Questions to Ask about Benefits
See also Therapeutic Misconception.

• Will your patient benefit directly?
• What form of benefit could be gained: medical, social, psychological, psychosocial, educational or financial?
• Is there a reasonable chance (based on available evidence) that participants could realize a direct benefit from the intervention being studied or tested?
- Are the benefits potential? If so, what is the probability that any particular participant will benefit (is this a placebo-controlled trial that randomly assigns half the participants to the control arm or to varying doses or sham treatments)?
- Will participants realize collateral or adjunct benefits? These benefits stem from being involved in the study, not necessarily from the intervention studied. Adjunct benefits, such as queue jumping, increased monitoring or other “system” benefits, should not be identified as primary or potential benefits.
- Will the benefits accrue to future patients or to society (e.g., generalizable knowledge)?
- Is the level of benefits minimal, moderate or high?
- What are the probability, onset and duration of the benefit?
- Are participants paid for participation?
- What combination of payments do participants receive?
- Are participants reimbursed for their direct research-related expenses?
- Are participants compensated for the time and inconvenience of research participation?
- Are participants given appreciation payments: bonuses, cash or non-cash gifts given when the study is terminated? Are participants informed before enrolling that they will receive post-trial bonuses or payments? Depending on the amount, appreciation payments may constitute undue influence or be coercive. The level of remuneration that amounts to undue influence is subjective: a $1000 payment to recruit a participant who earns over $50000 a year may not amount to undue influence, but offering the same amount to someone with no regular source of income may unduly influence choice.
- Do participants receive incentive payments that may unduly influence decision-making, e.g., reimbursements above actual costs, or continued participation (back-loaded payment scheme, i.e., payments increase the longer participants remain in the study, length of “service” awards, or with the number of procedures undertaken)?
- Are there other inducements or compensation for participation?

Therapeutic Misconceptions

Some participants volunteer for altruistic reasons, some for the chance of therapeutic benefit, some for financial compensation and some for a combination of reasons. Researchers should not pass judgement on the volunteer’s motives, but should ensure that the motives or goals are aligned with research goals. A function of research is to generate new knowledge (usually with an expectation that this knowledge will be generalizable). If the volunteer’s goals are not aligned with the goals of research, a participant’s decision to participate may be based on a form of therapeutic misconception.

Three misconceptions impede participants’ understanding, a necessary characteristic of informed consent. The first, identified by Applebaum and colleagues30 as the therapeutic misconception, occurs when participants do not clearly distinguish their clinical goals (i.e., cure or treatment) from the goals of research, i.e., producing generalizable knowledge. The participant continues to believe that the intervention is chosen because it will be therapeutic. The participant continues to assume that the physician-researcher is basing his or her decisions (e.g., subgroup assignment) on the participant’s best interests. The participant does not fully comprehend that the intervention he or she is assigned to is not intended to be therapeutic but is determined by the research.

protocol. If the participant fails to understand that research is by definition, nature and intent not therapy, and that the proposed intervention is not intended to benefit (treat) him, then he is unable to grant valid, adequately informed consent and should not participate. The closer the intervention is to treatment or care, the less worrisome therapeutic misconceptions are.

The other misconceptions, identified by Sam Horng and Christine Grady, are therapeutic misestimation and therapeutic optimism. Misestimation means, a participant “underestimates risk, overestimates benefit, or both.” Therapeutic misestimation compromises risk-benefit assessments and thus compromises valid informed consent. The higher the probability and severity of the risks, the less tolerable the therapeutic misestimation will be. Therapeutic optimism means the “subject hopes for the best personal outcome.” If the participant understands and adequately assesses what the risk–benefit ratio means for them and continues to hope for the best personal outcome, e.g., hopes he or she will be 1 of the 10% who benefits, then his or her consent is valid and adequately informed (in terms of understanding this element; capacity may still be compromised for other reasons).

Therapeutic misconception is more likely with some research methods and types of trials than others are. In phase 1 drug trials, it is unlikely that healthy volunteers will believe that they will realize some clinical benefit; exploitation is of more concern than therapeutic misconception. Participants in another phase of a drug trial may be more likely to believe that they will directly benefit from participation. See Questions to Ask about Benefits.

A key to ethical research is recognizing the role that hope and expectations play in participants’ decision-making and distinguishing hope from expectations and associated therapeutic misconceptions. Participants may hope or expect that they will realize some therapeutic benefit, but the investigator should ensure participants understand what the chance is of this occurring. “The chance of therapeutic benefit for patient volunteers is part of the context but not the purpose of clinical research.”

Therapeutic misconceptions can complicate the reporting of trial results to participants. Most participants will want to know and will need help interpreting whether they benefited from the intervention (especially if surrogate endpoints are used). See Trialists should tell participants results, but how? The Lancet, Volume 367, Issue 9516 [Editorial].

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31 Sam Horng and Christine Grady, Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, & Therapeutic Optimism. IRB: Ethics & Human Research. v. 25, no. 1, 2003, p. 11-16.
32 Sam Horng and Christine Grady, Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, & Therapeutic Optimism. IRB: Ethics & Human Research. v. 25, no. 1, 2003, pp. 11-16.
33 Sam Horng and Christine Grady, Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, & Therapeutic Optimism. IRB: Ethics & Human Research. v. 25, no. 1, 2003, pp. 11-16.
Questions to Ask about Misconceptions

- Do participants understand the nature and intent of research?
- Have the divergent features of research and clinical care been disclosed and explained?
- Do participants understand which features of the protocol diverge from routine clinical care?
- Does the participant understand the goals of the trial?
- Does the participant understand the procedures?
- Does participant understand that your clinical duties of care will be suspended while they participate in the research protocol?
- Do the participants you recruited understand that your relationship with them will change for the duration of the trial?
- Have you asked participants to reiterate what will determine which, if any, intervention they will be assigned (e.g., do they understand randomization)?
- Do participants understand that you are unable to direct or alter their assignment, role or initiate treatment unless they withdraw from the study?
- Do participants understand probability; do they interpret probability as odds instead of frequency?
- Have you asked participants to identify the probability of their benefiting directly?
- Have you asked participants to identify what could harm them, the likelihood of being harmed and how this harm could affect their quality of life?

Withdrawal from the Study

Research participants are volunteers who grant permission to be used by others for research purposes. Participants are under no obligation to submit to any intervention or examination for their own benefit or for the benefit of others. Participants may retract their permission at any time and withdraw from the study. Research participants do not give up their rights when they agree to participate in research. Consent documents may request follow-up or a post-study appointment or evaluations, but if a participant withdraws from the study, he or she is not obligated to keep these appointments.

Questions to Ask About Withdrawal

- Are participants informed that they can withdraw at any time without penalty?
- Are participants offered interim results so they can assess their participation?
- Are participants informed of any adverse events that have occurred so they can reassess the risk-benefit ratio and reconsider their willingness to participate?
- Are there obstacles to withdrawing?
- Are the collateral, adjunct benefits (e.g., queue jumping) such that they constitute undue inducements to remain in the trial? Payment and timing of disbursements may constitute undue influence. For example, are payments back-loaded, i.e., the payments increase the longer participants remain in the study, e.g., “length of service awards” or with the number of procedures undertaken? These may unduly influence the decision to withdraw.
Conflict of Interests

Research involves multiple stakeholders: sponsors, researchers, institutions, research participants, possibly CROs and independent REBs. Each stakeholder engages in the scientific endeavour for particular and sometimes idiosyncratic reasons. Participants have multiple and varied interests, interests that may conflict. Individuals and the organization they work with or for have mutual, competing and, sometimes, conflicting interests. Identifying and disclosing conflicting interests is a mechanism to recognize and mitigate risks, benefits and other consequences. Conflicts of interest that unduly influence decisions can skew risk–benefit assessments and place participants or other patients at greater risk of harm. Conflicts of interest that unduly influence the design, conduct and reporting of results threaten the integrity of the medical profession, the health care system and the legitimacy of research and science. See Patricia Baird, *Getting it right: Industry sponsorship and medical research*. Canadian Medical Association Journal.

A conflict of interest is a set of conditions in which [professional] judgment concerning a primary interest (such as a patient’s welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain or reputation). Conflict-of-interest rules, informal and formal, regulate the disclosure and avoidance of these conflicts.35

Conflicts of interests are not ethical dilemmas. In an ethical dilemma, the conflicting or competing goods, values or obligations (interests) are equal (symmetrical) and one must choose which to honour, which to sacrifice. Some goods, like knowledge, have inherent value, i.e., it is valued in and of itself, intrinsically valuable. Some goods, like money, have instrumental value; money is valued for its use, in other words, what it can buy. There is no consensus on the lexical ordering of inherently, intrinsically valued goods, however, most people agree that intrinsically valued goods take precedence over instrumentally valued goods. In conflict of interests, there is asymmetry between the goods or values (interests) sought. For example, an inherently valued good (research as a means to discover generalizable knowledge) conflicts with an instrumentally valued good (research as a source of income). Some competing interests are esoteric knowledge, supplemental income, career advancement (promotion or tenure), market share, equity interests and profit.

Competing multiple, inter- and intrapersonal interests are not inherently unethical. A conflict of interest becomes unethical when the secondary value or goal unduly influences one’s decisions. Secondary interests are usually legitimate goals and it is not necessary to eliminate them. The goal is to ensure the secondary interest does not take precedence over a primary interest (or duty) or unduly influence one’s decision-making.

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Two general types of conflicts are conflict of interests and conflicts of commitment (involving time). Conflict of interests are subdivided into financial and non-financial interests (examples of non-financial interests are the research imperative of academic medicine and professional prestige). Conflict of commitments happen when research tasks are performed during times routinely dedicated to patient care. Most guidelines focus on financial conflict of interests because they are more objective and easier to identify and regulate. See Dennis F. Thompson. *Understanding Financial Conflicts of Interest*.

Conflicts of interests can be actual, apparent or potential. These vary in seriousness and may be either direct (e.g., stock in sponsoring company) or indirect (e.g., status or prestige). When combined, these characteristics result in two types and various levels of seriousness, thus a matrix (similar to the risk–benefit matrix) emerges.

Currently, there is disagreement over whether disclosing or reporting a conflict of interest is sufficient to maintain public trust in science, scientists and researchers. Some argue that disclosure is not sufficient. “Disclosure does not necessarily eliminate the influence of industry funding on research or doctors’ behaviour.”36 Although disclosure may not eliminate undue influences or affect investigators’ behaviour, informing potential research participants of the conflicts of interest may affect their decision to participate.

**Questions to Ask about Conflict of Interests**

- Why do you want to conduct research? Once you identify your varied interests, a conflict of interest will be easier to prevent, mitigate and manage.
- Do you have sufficient knowledge of the disease, condition or process studied (does the trial fall within your area of medical expertise)?
- Are you being paid to identify, refer or recruit participants (finder’s fees)? Finder’s fees can unduly influence your decision to participate or the methods and means of recruitment and they are unethical.
- Does the payment influence your judgement as to which patients meet the inclusion criteria?
- Are you, your practice, employer or institution being paid to recruit a certain number of participants within a specified time?
- Are you, your practice, employer or institution being paid a recruitment incentive based on a per capita basis?
- Are you, your practice, institution or employer receiving bonuses, e.g., completion or “milestone” payments?
- Are you, your practice, institution or employer receiving a donation or equipment as inducement for participating in the trial?
- Are you paid for the services you perform? This is acceptable provided there is no double billing.
- Is the level of compensation for your services comparable to the income you will lose by dedicating time to the trial and not to your patients?
- Are the payments comparable to the normal fee structure?

• Are the payments elevated or are time estimates inflated?
• Are the payments you will receive disclosed to participants during enrolment and consent processes? Whether the amount paid must be disclosed is debated.
• Do you, a family member or a research staff member own stocks or stock options, or have any financial interest or equity vested in the sponsoring company, drug, device or technology being tested? If yes, this places you, your practice or both in a conflict of interest situation that must be disclosed to participants. See Jammi N. Rao and L. J. Sant Cassia, *Ethics of undisclosed payments to doctors recruiting patients in clinical trials*. [Education and Debate] *British Medical Journal*, v. 325, 6 July 2002, p. 36-7 and *Declaration of Helsinki* Paragraph 22.
• Do you have stock or stock options whose value could be negatively affected by results of the study? If so and you trade these before releasing the results, this may be considered insider trading and be illegal.
• Do you act as an advisor, employee, officer, director, consultant or decision-maker for or have any fiduciary role with the sponsor, for the sponsor’s competitors or for any organization that could benefit from the research? This should be disclosed to participants.
• Will you or have you received a salary, gift, loan, honorarium or any other benefit from the sponsor?
• Do you or will you receive royalty income or have a right to receive royalties under a patent or copyright related to the drug, device, innovation, method or treatment studied?
• Will participating in research help advance your career, status or prestige?
• Are sponsors able to suppress or censor research results? Disclose this.
• Does the investigator retain the right to publish a report or disclose safety concerns or injuries?
• Does the sponsor require you to get prior approval before publication to protect their intellectual property rights? Disclose this. Protecting proprietary information is permissible, but if used as a tactic to delay or deny publication, disclosure or dissemination, it is unethical.
• Who is responsible for interpreting the study results? (See controversy over rofecoxib and interpretations of APPROVE trial results).

**Databanks, Bio-banks and Population-based Research**

A concern with large-scale population health research is that individual interests will be sacrificed for the good of the collective. Some contend that the pursuit of knowledge, the scientific endeavour and “health” are so valuable that individuals are obligated to sacrifice some of their interests or rights. Others argue that there is no moral obligation of beneficence, unless one is a member of a profession that has adopted beneficence as an ethical precept.

An issue generating controversy is “advanced” or “blanket” consent for subsequent (secondary) use of data or biological material. Personal health information and biological samples are collected for a specific purpose (primary purpose) and the patient or research participant consents to the collection for this specific use. The question is whether “prospective advanced or blanket” consent is sufficient for subsequent or secondary uses or must the data owner be re-contacted and asked to grant explicit consent for the subsequent or secondary use. The dilemma is that because re-contacting the data owner may be impossible or too burdensome that some
research may not be undertaken; do you “sacrifice” autonomy for the pursuit of knowledge? See *Tri-council policy statement: ethical conduct for research involving humans*. Section 3. Privacy and Confidentiality.

**Questions to Ask about Consent, Databanks, Bio-banks and Population-based Research**

- Are you collecting data or biological samples that will be stored in a databank or bio-bank?
- Who has access to the data or bio-bank?
- What personal identifiers will be connected to the specimens?
- If a combination of data forms and types will be collected, has the reason for collection of each form and type been disclosed? Has the way in which each data form and type will be used been disclosed?
- Are participants informed whether their information, data or biologic material will be stored or destroyed?
- Did participants grant consent for the retention and storage of their material, information or data?
- If data is stored, how long will it be kept and is this disclosed to participants?
- Do participants retain the right to request their information, data or samples be removed from the data or bio-bank and be destroyed? If not, have participants been informed of this?
- Have you disclosed any associated commercial interests to participants? For example, the *Moore* case where Dr. Golde did not disclose to Mr. Moore his commercial interest in developing a cell line from Mr. Moore’s T-lymphocytes.37
- Have you disclosed the involvement of any entity that may have a commercial interest in the information or biologic material?
- Will personal identifiers be stripped from the information, data or samples?
- Are participants asked to grant prospective blanket consent for subsequent use?
- Will a participant be contacted and asked to grant explicit consent for each subsequent use?
- Is there an exclusion or inclusion clause granting “advanced” or “blanket consent” for subsequent research on a specific disease or condition?
- Would the secondary or subsequent use be sufficiently similar to the primary purpose that one could reasonably infer that the initial consent applies to the secondary use? It should be the participant’s perspective that determines whether the secondary use is sufficiently similar.
- If prospective, advance or blanket consent is given, can, will and how would data owners be informed of the results.
- If this is a subsequent study, has the new research protocol been reviewed by an REB?
- If participants are members of a community that could be adversely affected by the results, has the community and or its leaders been consulted and granted community assent?

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• If researchers are approaching potential participants to get consent for secondary use of personal information, has the contact information been checked to ensure that it is accurate? For example, has it been determined whether the person you are trying to contact is still alive?
• Are there any special circumstances that necessitate avoiding re-contact (e.g., recent death in the family)?

**Resources**


See also *CMA Health Information Privacy Code*

**Paediatric Research**

Children constitute a particular vulnerable community and additional safeguards are required to protect them. Children lack decisional capacity since they lack understanding and insight. Therefore, parental consent is necessary (a guardian or adults’ entitled to grant consent on the child’s behalf) but parental consent is not sufficient. Parental consent is a means to protect children and it respects the parents’ interests in making decisions regarding their children and families. However, while a parent grants consent, the assent of the child should also be obtained. If a child dissents, the reasons for the dissent should be discussed. If the child will not directly benefit, the risk is above minimal and the child has valid reasons for dissenting, he or she should not be enrolled. If there is the potential for the child to benefit directly, the risk is minimal and the parent(s) insist that participation is in the child’s long-term best interests, the dissent is sometimes overridden. There is no consensus in the ethics literature on whether a child’s dissent should be overridden. See Lainie Ross, *Informed Consent in Paediatric Research*. Cambridge Quarterly of Healthcare Ethics. October 2004, v. 13, Issue 4, p. 346-58.

Some children, when their age is combined with their illness experiences, have insight and wisdom “beyond their years.” As children approach the age of consent, they are considered mature minors. By allowing children as much autonomous decision-making authority as they are capable of or want, we treat them as individuals worthy of dignity and respect. Some jurisdictions allow mature minors to consent to research, if the risks do not exceed minimal
levels. If mature minors have the capacity to consent, their refusal must also be honoured. However, depending on the area of research, when dealing with mature minors, it is advisable to obtain parental assent. Researchers should be aware of the autonomy and decisional capacity ascribed to mature minors in their particular jurisdiction.

Research with children and mature minors may involve further restrictions or waivers of parental consent. An example of a further restriction is the risk-benefit matrix. If the research involves mature minors, the potential of direct benefits should be higher. Some contend that it is unethical to do paediatric research if children are exposed to greater than minimal risk of harm, if the child will not benefit directly or if the benefits are speculative and accrue only to others. Others claim only if the research is in the child’s best interests should that child participate. Some jurisdictions grant waivers of parental consent or assent if the research involves mature minors and is relates to sexually transmitted diseases. See, Royal College of Paediatrics. Child Health: Ethics Advisory Committee, *Guidelines for the ethical conduct of medical research involving children*. Archives of Disease in Childhood. v. 82, no. 2, 2002, p. 177-82.

Physician-researchers should be aware of regulations regarding how many parents are required to grant consent or assent and the circumstances under which they may consent to paediatric research. For example, if the research offers the prospect of direct benefit, 1 parent’s consent may be sufficient.

**Questions to Ask about Paediatric Research**

- Is it necessary to use children or is research with adults feasible?
- Has the appropriate age group been selected?
- Has the parent granted informed consent? See Questions to Ask about Informed Consent and Informed Refusal.
- Have the process and procedures been explained to the child in language or by other means so the child understands what will be done to or with him or her?
- Has the child granted assent? How is ongoing assent monitored?
- Does the research pose greater than a minimal risk of harm?
- Who will benefit from the research?
- Is the research in the best interests of the child?
- Will the child benefit directly?
- Will children similarly situated benefit?
- Are the benefits speculative?
- If you are not the child’s paediatrician or general practitioner, have they been informed the child is enrolled in research?
Genetic Research

With better knowledge and understanding of the role genes play in disease susceptibility and development (in combination with environmental factors), prevention, management and cures may increasingly include genetic components. Determining someone’s genetic risk or therapies based on genetics require testing for a gene or, if a polymorphic condition, genes. In addition to the normal requirements for valid and ethical research, the following questions should be considered if the research has a genetic component.

**Questions to Ask about Genetic Research**

- What type of genetic material will be collected? See [Databanks, Bio-banks and Population-based Research](#).
- How will it be used?
- Do potential participants understand the basic biologic functions of genes?
- Is the specific gene or genetic pathway identified?
- To avoid therapeutic misconceptions, do participants clearly understand what genomic research does not involve, e.g., cloning?
- Is this a hypothesis-testing study with no direct medical relevance for participants?
- Will results of genetic tests be disclosed to participants?
- Will individual genetic test results be reported to participants?
- Do participants have access to a genetic counsellor?
- What methods will ensure the confidentiality of genetic tests and counselling records?
- Will specimens or data be made anonymous or remain linked to the source?
- What personal identifiers will be connected to the specimens?
- Have participants consented to continued linkage?
- Have the risks, benefits, short-term objectives and potential long-term applications of the study been clearly explained?
- Are there any potential risks of genetic discrimination, e.g., denial of insurance coverage based on a “pre-existing condition”?
- Have the procedures for collecting, handling and storing genetic samples or data been clearly outlined?
- Is withdrawal of genetic samples (or data) after a certain trial stage impossible and has this been disclosed?
- Is destruction of genetic samples or data possible?
- Will the genetic samples, specimens or data be destroyed?
- If genetic specimens or data will be destroyed, what methods will be used to destroy them?
- If they will not be immediately destroyed, how long will genetic specimens and samples be retained?
- Have participants been informed of and consented to retention of their biologic material?
- Have participants been informed their biologic material will be “banked”?
- If participants withdraw from the study, what will happen to the data and specimens?
- Who has control of or access to the stored genetic specimens?
- Will the biologic material become part of a commercial enterprise?
• Will genetic samples be replicated, e.g., in cell lines, and has this been disclosed to participants?
• Has “ownership” of the genetic specimens and data been determined and disclosed to participants?
• Have the endpoints been disclosed in lay terms?
• Have participants been informed that determining one’s genetic make-up can have implications for other family members?
• Has disclosure of test results to family members been discussed?
• Will inadvertent genetic “discoveries” and their social or medical implications be reported to participants?
• Will trial results be reported to participants?
• If participants are members of a “vulnerable” group or identifiable community that could be adversely affected by the findings, have the group’s or community’s leaders been consulted and assisted with review of the protocol (for example during the REB approval process)? See Charles Weijer, Gary Goldsand and Ezekiel J. Emanuel. *Protecting communities in research: current guidelines and limits of extrapolation*. Nature Genetics. November 1999, v. 23, p. 275-80
• If the study involves a gene known to be pleiotropic, have the associated conditions and implications been disclosed to participants?
• Is this a genetic linkage and association study? If yes, an evaluation of the variations in copy number in the study population to determine whether an individual variation in copy number rather than a single-nucleotide polymorphism might be responsible should be done.
• Is there potential for further study of associated conditions? Has this been disclosed?
• Have all the intended uses of the results been disclosed?
• Has the potential for secondary uses been disclosed?
• Have participants granted consent for secondary, subsequent use of their biologic, genetic material or data? See Databanks, Bio-banks and Population-based Research regarding the validity of “blanket consent.”
• Will genetic specimens be used for commercial purposes and has this been disclosed to participants?
• Has the sponsor been disclosed? See Disclosure.

**Resources**


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Legal or Regulatory Requirements

Introduction

The primary means for regulating the ethical conduct of clinical research trials in Canada and internationally are through review by a research ethics board (REB). At the federal legislative level, REB review is mandated by the Food and Drugs Act. It is also mandated by policy documents, notably Health Canada’s Good Clinical Practice Consolidated Guidelines and by the Tri-Council Policy Statement, considered to be the gold standard for formal evaluations of research protocols in Canadian academic research institutions. It is of particular interest that the Tri-Council, a major source of research money, will only fund studies that comply with its policy statement.

The Good Clinical Practice Consolidated Guidelines and the Tri-Council Policy Statement incorporate principles for the protection of human subjects found in the World Medical Association’s Declaration of Helsinki and the Council of International Organization of Medical Sciences’ International Guidelines for Biomedical Research Involving Human Subjects, which are firmly accepted worldwide. Although these documents are only guidelines and, therefore, not legally binding, the Superior Court of Quebec has suggested that the Declaration of Helsinki could informally create a standard of practice to which investigators may be bound. Unfortunately, the court did not clarify the role of Canadian guidelines in establishing such a standard.

Regulating Conflicts of Interest in Clinical Research

Informed consent

A key concern in research ethics is the propensity for financial conflicts of interest inherent in the link between public and private research institutions, as they may affect the objectivity and integrity of the research enterprise. The mere existence of a conflict of interest is not necessarily ethically or legally condemning per se. Rather it is how one acts in the context of a conflict of interest that may be suspicious. In order to safeguard against ethically untoward actions, physician-researchers must ensure that participants are properly informed of potential conflicts

40 R.S.C. 1985, c. F-27
of interest and other risks involved in clinical trial participation. It is well established in Canadian health law and ethical discourse that a physician must obtain the consent of the patient prior to any medical intervention.\textsuperscript{47} The purpose of informed consent is to enable the patient to have the information necessary to make an informed choice about treatment.\textsuperscript{48} The same principle extends to physician-researchers and participants. If the process of obtaining informed consent is not properly discharged and a subject is harmed, the physician may be found liable according to the principles of the common law tort regime.

In general, tort law “provides a legal means whereby compensation, usually in the form of damages, may be paid for injuries suffered by a party as a result of the wrongful conduct of others.”\textsuperscript{49} A physician’s failure to provide all material information necessary to obtain informed consent is grounds for liability for the tort of negligence. Material information has been defined broadly by the courts and may include both medical considerations (e.g., risk of side-effects) and non-medical considerations (e.g., the potential social ramifications of a treatment choice). The standard by which a physician must abide in fulfilling the requirement for disclosure (i.e., the standard of care) is that which “could reasonably be expected of a normal, prudent practitioner.”\textsuperscript{50} In order to fully establish liability for negligence, a plaintiff must demonstrate the following:

- that the defendant owed a duty of care to the plaintiff (i.e., the duty to disclose all material information);
- that the defendant breached the standard of care (i.e., the requirement to obtain informed consent);
- that the plaintiff suffered an injury or loss; and
- that on a balance of probabilities, the defendant’s conduct was the actual and legal cause of the plaintiff’s injury or loss.

These principles are extracted from case law and are codified in provincial and territorial legislation pertaining to health care consent.

**Informed consent in the research context**

The Supreme Court of Canada has established that that the duty owed by researchers to participants is higher than that owed by medical practitioners to their patients.\textsuperscript{51} In particular, the court has noted that where there is no intended therapeutic benefit to participants, the duty of researchers to inform is the most exacting of all. Thus, all risks, even remote ones, must be disclosed, especially if the consequences are severe. For clinical trials where there is intended therapeutic benefit, the courts have not applied this disclosure standard. In either case, it is up to the researcher to ensure that participants can understand the disclosure information presented.\textsuperscript{52}

\textsuperscript{47} See for example, E. Picard and G. Robertson, *The Legal Liability of Doctors and Hospitals in Canada* (Toronto: Carswell, 1996).
\textsuperscript{51} Halushka v. University of Saskatchewan et al. (1965), 53 D.L.R. (2d) 436 (Sask C.A.).
Disclosure of conflict of interest as a requirement for informed consent

Tort law is clear that disclosure of material information is a precondition for informed consent. The requirement to disclose conflicts of interest as a material consideration, however, is not as explicitly evident. The test that has been applied by the Ontario Divisional Court is whether or not a reasonable person could conclude that the personal interests of the researcher could influence professional conduct.53

Fiduciary duty as grounds for requiring disclosure of conflicts of interest

Informed consent has its roots in fiduciary principles. In medicine, fiduciary duty balances the inequities in the physician–patient relationship. Because fiduciaries should subordinate their personal interests to those of the other, disclosure of conflicts is central to physician’s duty to act in their patients’ best interests.54 It follows that disclosure of conflicts of interest is inherent in the physician’s fiduciary duty; therefore, failure to disclose may result in a breach of the duty. Although there are no Canadian cases on point, a frequently cited case from American law supports this principle.55

Although a fiduciary duty exists for physicians in a therapeutic context, it may not necessarily mean that it exists in a research context.

Questions to Ask about Rights

- Does any oral or written information, including the consent form, require participants or their surrogate to waive any rights? Research participants should not lose, abandon, transfer or abdicate their moral, legal or human rights when they volunteer to participate in or are subjects of research.
- Does any oral or written information or consent form release or appear to release investigators, the practice, the institution, the sponsor or agents from liability for negligence or malpractice?

Regulating Research Contracts

Increased interdependency of public and private institutions has increased the importance of economic interests in biomedical research. “Gag clauses” in research contracts are a by-product of this. Gag clauses, which may be imposed on physician-researchers by private sponsors, may prohibit the disclosure of the source of funding and the risks involved in a clinical trial — information that is necessary to enable participants to make a fully informed decision about whether to participate in the research. Canadian case law and literature contains little about gag

54 See M.V. Ellis, Fiduciary Duties in Canada, (Scarborough, Ont.: Carswell, 2000) at 1-6 and 10-12 (discussing the duty of disclosure as a general fiduciary duty and one of physicians in particular). Also see M.A. Rodwin, Medicine, Money, and Morals: Physicians’ Conflicts of Interest. (New York: Oxford University Press, 1993).
clauses, particularly in the research setting. However, they are increasingly common in the United States, primarily in the health maintenance organization context. A leading American case found that, in light of the changing nature of health care, a fiduciary duty is imposed on physicians to disclose any financial interests that may be incompatible with patient interests.56

The principles of informed consent and fiduciary duty suggest that gag clauses should be illegal. The effect of a gag clause on informed consent is two-fold: it may expose participants to actual risk and it may prevent them from withdrawing from a trial based on either the actual risk or the perception of risk stemming from the physician-researcher’s conflict of interest. If it can be shown that the gag clause led directly to harm, a participant may be able to make a claim of negligence against a physician-researcher who submits to the clause. This could be done in concert with an argument for breach of fiduciary duty, based on the notion that gag clauses force physician-researchers to displace participants’ interests with those of the sponsor, which erodes trust in the fiduciary relationship. The fact that gag clauses impose a contractual obligation on physician-researchers to shield certain information does not release them from their legal responsibilities toward participants.

If physician-researchers are pressured to breach their fiduciary duty, there is an obligation to mitigate damages toward those to whom they owe the duty.57 This can be done by communicating material information to participants. All researchers should be aware of the legal and regulatory requirements surrounding their work. Physicians-researchers may want to consult the CMPA for advice 1-800-267-6522 or read more about medico-legal concerns in General Information on Clinical Research Contracts.

Resources

See Health Canada.

- Therapeutic Products Directorate
- Drugs and health products: legislation and guidelines, Health Canada
- Biologics and Genetic Therapies Directorate, Health Canada.

Questions to Ask about the Contract

- Will a lawyer protecting the institution’s, the practice’s or your interests review the contract?
- Are there pre-existing policies, procedures or tools available to assist with contract negotiations with the sponsor or CRO?
- Are the terms of the agreement confidential? Confidential agreements need to be balanced with public accountability. See Template Confidentiality Agreement for Pharmaceutical Studies
- Are the confidentiality obligations related to intellectual property and control of proprietary information outlined?

• Is there a predetermined mechanism for resolving disputes (mediation, arbitration, adjudication, litigation)?
• May investigators alter the study design?
• May the sponsor alter the study design?
• Are there restrictions on reporting adverse events?
• Does the contract allow or mandate an independent data and safety monitoring board?
• Are finders fees or referral fees paid or “buried” in the contract? Legislation and regulation may consider these fees a form of “kickback” and subject to prosecution.
• Are acceptable conditions for early termination outlined?
• Is the schedule of payments set?
• Are eligible expenses identified?
• Are investigators prohibited from discussing results with “outsiders” during the trial? Investment firms have hired physician-researchers as consultants and gained competitive advantages when, inadvertently or otherwise, preliminary results were disclosed; some have been charged with insider trading.
• Are data collection and monitoring addressed?
• Is data ownership addressed?
• Is data storage addressed?
• Does any clause place limits on researchers’ access to data? Researchers should have access to all raw or primary data; this is especially important for multicentre trials.
• Does the contract limit or restrict interpretation or analysis of the data? For example, must the sponsor review and sanction reports before publication or disclosure?
• Does the sponsor have the authority to include its own statistical analysis in the manuscript?
• Are there provisions allowing the sponsor to review the manuscript for a predetermined time before publication? This is acceptable if the period is not unreasonably long (e.g., 60–90 days).
• Are the rights of, and what qualifies for, authorship addressed?
• Is the sponsor responsible for writing the report or manuscript and the investigator(s) limited to reviewing and recommending changes? If the researcher(s) is subsequently identified as the author(s), this is ghost writing and is unethical.
• If a multicentre trial, is independent reporting or publication by individual sites permitted?
• Is there a provision that permits the sponsor to demand revisions to the manuscript not related to proprietary information? This breaches research ethics and academic freedom and should not be accepted.
• Is there a provision that grants the sponsor the right to determine if or which results may be published? This should not be accepted as it breaches research ethics and academic freedom.
• Are there restrictions on the journals to which the manuscripts can be submitted?
• Are there restrictions on subsequent or secondary uses of the data?
• Are researchers or the institution they work for or at prohibited from obtaining funding in the same field of research or from competitors of the sponsor?
• Is disclosure of results to participants or third parties prohibited or restricted (mandates what form disclosure must be)?
• Does the contract allow the sponsor access to participants’ health information or record?

Resources

For a model of contractual language, see Duke Clinical Research Institute. Contract Language for Clinical Research Agreements Between Academic Medical Centers and Industry Sponsors.

Template Confidentiality Agreement for Pharmaceutical Studies.

Questions to Ask about the Budget

• If durable goods, e.g., computers or software, are purchased from research funds, who owns the goods and retains possession after the trial?
• Are the durable goods another form of compensation or an incentive to conduct the trial?
• Are all costs covered, e.g., funds for reporting results to participants?
• Are funds available to compensate participants if they are harmed?
• Are incentives for recruitment embedded in the fees-for-service or administrative fees?

Questions to ask about Publication Clauses and Trial Registry

• Are restrictions that are intended to protect intellectual property, but necessarily limit researchers’ rights and obligation to publish or disseminate results, reasonable and able to achieve the desired purpose? Sponsors want to protect their investments and requiring a reasonable delay in order to register a patent is not unethical. Total bans on publication because the findings may affect market share or stock prices are unethical.

Conclusion

The Guidelines were not meant to be a comprehensive “how to” develop and implement a research protocol, however, it enables users to assess research projects. While the Guidelines were not designed to be read from start to finish, if one did so, they would have an excellent introduction to research ethics; i.e., understand how value, validity, informed consent, regulatory requirements and recognizing and controlling conflict of interests coalesce to insure biomedical research remains a social good.

58 See also Reporting.
Readers will also be aware of outstanding controversies, e.g., how and in what form the “data,” the research results (individual or aggregate) should be offered to participants. If a reader wants more information on a particular topic, the bibliography cites articles that contributed to the composition of the Guidelines but were not necessarily referenced in the text; thus the bibliography provides additional resources.

If a question arises that the Guidelines do not address or is a matter left to the researcher’s discretion and the researcher is unsure how to proceed, e.g., disclosing research results, it is advisable to consult with the Chair of the local, regional or provincial REB or a learned colleague.
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