



Handbook for Clinical Researchers

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May 2013

*Created under the auspices of the Saskatoon Centre for Patient-Oriented Research
and the Office of the Associate Vice-President Research - Health, University of
Saskatchewan/Vice-President Research and Innovation, Saskatoon Health Region.*

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Glossary

Adverse Drug Reaction (ADR). Any noxious and unintended response associated with the use of a drug in humans. (1) Before a drug is approved for marketing (e.g., during a phase I, II, or III clinical trial), an ADR is an adverse event that occurs at any dose and where a causal relationship is at least a reasonable possibility. (2) After a drug is approved for marketing, an ADR is an adverse event that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. (ICH 1994, 1996a; Applied Clinical Trials 2009)

Adverse Event (AE). Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH 1996a)

Blinding. A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware, and double-blinding usually refers to the participant(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). (ICH 1996a) See *open-label study*.

Case Report Form (CRF). A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant (ICH 1996a). NOTE: In common usage, CRF can refer to either a CRF page, which denotes a group of one or more data items linked together for collection and display, or a casebook, which includes the entire group of CRF pages on which a set of clinical study observations and other information can be or have been collected, or the information actually collected by completion of such CRF pages for a participant in a clinical study (Applied Clinical Trials 2009).

Clinical Research. The study of human disease, including its prevention, diagnosis and treatment, using human participants, human populations or materials of human origin.

Clinical Trial. A research study involving human participants that is designed to answer specific questions about the safety and efficacy of a biomedical intervention (e.g., drug or device) (Applied Clinical Trials 2009). Clinical trials also include studies intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of a drug, or study the absorption, distribution, metabolism and excretion of a drug (HPFB 2003).

Consent Form. Document used during the informed consent process that is the basis for explaining to potential participants the risks and potential benefits of a study and the rights and responsibilities of the parties involved. The informed consent document provides a summary of a study (purpose, treatment procedures and schedule, potential risks and benefits, alternatives to participation, etc.) and explains an individual's rights as a participant. It is designed to begin the informed consent process, which consists of conversations between the participant and the research team. If the individual then decides to enter the trial, she/he gives her/his official consent by signing the document. Synonym: informed consent form. (Applied Clinical Trials 2009)

Contract Research Organization (CRO). An organization (commercial, academic, or other) contracted by the sponsor to perform one or more of the sponsor's research-related duties and functions (ICH 1996a). Synonym: clinical research organization.

Control Group. The group of participants in a controlled study that receives no treatment, a standard treatment or a placebo (U.S. 21 CFR 314.126).

Controlled Study. A study in which a test article is compared with a treatment that has known effects (i.e., control group) (Applied Clinical Trials 2009).

Data and Safety Monitoring Board (DSMB). A multidisciplinary, expert advisory group that meets regularly and is responsible for safeguarding the interests of participants by reviewing emerging data, assessing the safety and efficacy of trial procedures, and monitoring the overall conduct of a trial (TCPS2). Based on its assessment, the DSMB recommends to the sponsor whether to continue, modify or stop the trial (ICH 1996a). Synonyms: data safety monitoring board (DSMB), data and safety monitoring committee (DSMC), data safety committee (DSC), data monitoring committee (DMC), independent data monitoring committee (IDMC).

Declaration of Helsinki. A set of recommendations or basic principles that guide medical doctors in the conduct of biomedical research involving human participants (Applied Clinical Trials 2009).

Department Impact Assessment. A process used by the Saskatoon Health Region before a research study begins that allows all potentially affected SHR departments to review the research study, assess the operational impact of the study, determine how the proposed research will affect their functions, and where appropriate, prepare a budget for cost-recovery.

Efficacy. The capacity of a drug or treatment to produce beneficial effects on the course or duration of a disease at the dose tested and against the illness (and patient population) for which it is designed (Applied Clinical Trials 2009).

Good Clinical Practice (GCP). A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected (ICH 1996a).

Good Laboratory Practice (GLP). A quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported (OECD 2003).

Good Manufacturing Practices (GMP). The part of quality assurance that ensures that drugs are consistently produced and controlled in such a way to meet the quality standards appropriate to their intended use, as required by the marketing authorization (HPFB 2009).

Health Information Protection Act (HIPA). Saskatchewan provincial legislation regarding the rights of individuals and obligations of the trustees (physicians, regional health authorities, health professionals, etc.) in the health system with respect to personal health information.

Indication. A health problem or disease that is identified as likely to be benefited by a therapy being studied in clinical trials. NOTE: Where such a benefit has been established and approved by regulatory authorities, the therapy is said to be approved for such an indication. (Applied Clinical Trials 2009)

Informed Consent. The ongoing process that provides the participant with explanations that will help them make educated decisions about whether to begin or continue participating in a study. Informed consent is an ongoing, interactive process rather than a onetime information session. (Applied Clinical Trials 2009, TCPS2)

Investigator. The person responsible for the conduct of clinical research at a research site. Synonym: principal investigator. NOTE: Health Canada refers to the responsible investigator at a site as the *qualified investigator*. See *principal investigator, qualified investigator, sub-investigator*. (ICH 1996a, HPFB 2003, U.S. 21 CFR 312, U of S Policies 2002b)

Investigator's Brochure. A document containing the preclinical and clinical data on a drug as described in section C.05.005(e) of Division 5 of Canada's *Food and Drug Regulations*.

Investigator-Initiated Research. Research that is initiated and managed (i.e., sponsored), and conducted, by an investigator. See *sponsor, sponsor-investigator*.

Multi-Centre Trial. A clinical trial conducted according to a single protocol but at more than one investigative site and, therefore, carried out by more than one investigator.

Off-Label Use. Use of a drug or device for an unapproved indication or in an unapproved age group, unapproved dose or unapproved form of administration (Stafford 2008).

Open-Label Study. A trial in which participants and investigators know which product each participant is receiving; opposite of a blinded study. See *blinding*. (Applied Clinical Trials 2009)

Participant. Those individuals whose data, or responses to interventions, stimuli, or questions by the researcher, are relevant to answering the research question (TCPS2). Synonym: subject.

Personal Health Information. With respect to an individual, whether living or deceased: (1) information with respect to the physical or mental health of the individual; (2) information with respect to any health service provided to the individual; (3) information with respect to the donation by the individual of any body part or any bodily substance of the individual or information derived from the testing or examination of a body part or bodily substance of the individual; (4) information that is collected (a) in the course of providing health services to the individual, or (b) incidentally to the provision of health services to the individual; or (5) registration information (HIPA).

Pharmacodynamics. Branch of pharmacology that studies reactions between drugs and living structures, including the physiological responses to pharmacological, biochemical, physiological and therapeutic agents (Applied Clinical Trials 2009). Pharmacodynamics is often summarized as the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug (University of Auckland¹).

Pharmacokinetics. Study of the processes of bodily absorption, distribution, metabolism and excretion (ADME) of medicinal products (Applied Clinical Trials 2009). See *pharmacodynamics*.

Placebo. An inactive substance or intervention, such as an inactive tablet or sham surgery, that resembles the comparable active substance or intervention (TCPS2, ICH 2011, London and Kadane 2002, Birch 2006, Macklin 1999). See *control group*.

Placebo-Controlled Trial. A clinical trial in which the safety or efficacy of one or more interventions are compared with a placebo control group (TCPS2).

Principal Investigator. The person responsible for the conduct of clinical research at a research site. Synonym: investigator. NOTE: Health Canada refers to the responsible investigator at a site as the *qualified investigator*. See *investigator, qualified investigator, sub-investigator*. (U of S Policies 2002b, HPFB 2003)

Protocol. A document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial. The protocol usually also gives the

¹ History of Pharmacometrics.

<http://www.fmhs.auckland.ac.nz/sms/pharmacology/holford/teaching/pharmacometrics/history/default.aspx>

background and rationale for the trial, but these could be provided in other protocol referenced documents. (ICH 1996a)

Qualified Investigator. The person responsible for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is (1) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association, and (2) in any other case, a physician and a member in good standing of a professional medical association (HPFB 2003). See *principal investigator*.

Randomization. The process of assigning clinical trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias (ICH 1996a).

Research Ethics Board (REB). A body of researchers, community members, and others with specific expertise (e.g. in ethics, in relevant research disciplines) established by an institution to review the ethical acceptability of all research involving humans conducted within the institution's jurisdiction or under its auspices (TCPS2). Synonym: institutional review board (IRB).

Research Contract. A binding agreement, which usually includes financial support, for an investigator to conduct research in a particular subject area or field under specific stipulations and conditions (patent and publication rights, timing, etc.).

Research Grant. Financial support for conducting research in a particular subject area or field, without any formal detailed stipulations as to the direction of such research.

Safety. The absence of harmful side effects (i.e., adverse reactions) resulting from the use of a drug or treatment (Applied Clinical Trials 2009).

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction. Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (ICH 1994, 1996a).

Source Documents. Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH 1996a)

Sponsor. An individual, company, institution or organization that takes responsibility for the initiation and management of clinical research and compliance with applicable regulations. The sponsor may or may not be the main funding organization. (Applied Clinical Trials 2009)

Sponsor-Investigator. An investigator who not only conducts but also initiates and manages (i.e., sponsors) a clinical study. The sponsor-investigator must be a person (e.g., cannot be a corporation or agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (ICH 1996a) See *investigator-initiated research*.

Study Coordinator. A person who works at a clinical research site under the immediate direction of a principal investigator performing activities such as site preparation, patient screening and recruitment, patient enrollment, conducting study visits, maintaining and dispensing drug supplies, completing and ensuring the quality of case report forms, maintaining source documents and ensuring site quality. Synonyms: clinical research coordinator, research coordinator, clinical coordinator, research nurse. (Adapted from ACRP definition² and Applied Clinical Trials 2009.)

Sub-investigator. A member of a clinical study team designated and overseen by the principal investigator at a study site to perform critical study-related procedures or to make important study-related decisions (or both) (ICH 1996a).

Subject. An individual who participates in a clinical study. A subject may be the recipient of the drug, device, or procedure under study or may serve as a control, which may involve receiving a placebo. (Adapted from ICH 1996a.) Synonym: participant.

Tri-Agencies (or Tri-Council). The three federal agencies that provide public funding for university-based research and training in Canada: Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council (NSERC), Social Sciences and Humanities Research Council (SSHRC). (Heslegrave 2010)

Unexpected Adverse Drug Reaction. An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (ICH 1994, 1996a)

² Association of Clinical Research Professionals.

<http://www.acrpnet.org/MainMenuCategory/Certification/StandardofScopeACRPCertificationExams.aspx>

Acronyms

ADR	adverse drug reaction
AE	adverse event
C of A	Certificate of Ethics Approval
CCA	Council of Canadian Academies
CDA	confidential disclosure agreement
CFI	Canadian Foundation for Innovation
CFR	Code of (U.S.) Federal Regulations
CIHR	Canadian Institutes of Health Research
CIOMS	Council of International Organizations of Medical Sciences
CRF	case report form
CRO	contract research organization, clinical research organization
CTA	Clinical Trial Application (Health Canada)
DIN	Drug Identification Number (Health Canada)
DMC	data monitoring committee
DSC	data safety committee
DSMB	data and safety monitoring board, data safety monitoring board
DSMC	data and safety monitoring committee
FDA	U.S. Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practices
HIPA	Health Information Protection Act
HPFB	Health Products and Food Branch, Health Canada

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ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IVRS	interactive voice-response system
IWRS	interactive web response system
NDA	non-disclosure agreement
NER	Notice of Ethical Review
NIH	U.S. National Institutes of Health
NOC	Notice of Compliance (Health Canada)
NOL	No Objection Letter (Health Canada)
NSERC	Natural Sciences and Engineering Research Council
OECD	Organisation for Economic Co-operation and Development
OHRP	U.S. Office for Human Research Protections
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	principal investigator
REB	research ethics board
SAE	serious adverse event
SCA	Saskatchewan Cancer Agency
SCPOR	Saskatoon Centre for Patient-Oriented Research
SHR	Saskatoon Health Region
SHRF	Saskatchewan Health Research Foundation
SOP	standard operating procedure
SSHRC	Social Sciences and Humanities Research Council
TCPS2	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 2 nd Edition
U of S	University of Saskatchewan
WHO	World Health Organization

1. Introduction

Saskatoon is fortunate to have several prominent institutions, including the University of Saskatchewan (U of S), Saskatoon Health Region (SHR) and Saskatchewan Cancer Agency (SCA), which conduct clinical research and support clinical researchers. This handbook is designed to help clinical researchers at the U of S, SHR and SCA navigate the administrative and regulatory requirements for conducting their studies. Its purpose is to briefly describe those requirements and to list additional resources where further information can be obtained.

Also included in Saskatoon's clinical research infrastructure is the Saskatoon Centre for Patient-Oriented Research, which was created by the U of S, SHR and SCA to advance patient-oriented research in the Saskatoon area. All four of these organizations provide tools, resources and services that clinical researchers can use to help them successfully conduct their research.

2. Definition of Clinical Research

For the purposes of this handbook, *clinical research* is defined as the study of human disease, including its prevention, diagnosis and treatment, using human participants, human populations or materials of human origin.

3. Patient-Oriented Research and SCPOR

3.1. Patient-Oriented Research

The Canadian Institutes of Health Research (CIHR) has launched a national initiative based on a *Strategy for Patient-Oriented Research* (CIHR 2011). CIHR defines *patient-oriented research* as a continuum of research which includes:

- Clinical research;
- Health services research; and
- The synthesis, dissemination and integration of new knowledge into the health-care system and clinical practice.

The goal of patient-oriented research is to better ensure the translation of innovative diagnostic and therapeutic approaches to the point-of-care, as well as to help the provinces and territories meet the challenge of delivering high quality, cost-effective health care. It involves ensuring that the right patient receives the right clinical intervention at the right time, ultimately leading to better health outcomes.

3.2. Saskatoon Centre for Patient-Oriented Research (SCPOR)

The *Saskatoon Centre for Patient-Oriented Research (SCPOR)* is an organization established to advance patient-oriented research in the Saskatoon area. SCPOR (pronounced “skipper”) was created and is supported by its members: the University of Saskatchewan, Saskatoon Health Region and Saskatchewan Cancer Agency. SCPOR provides a variety of administrative, technical and clinical support services – including an eight-bed clinical research facility at Saskatoon City Hospital – to health researchers in Saskatchewan.

The creation of SCPOR brought together several clinical research resources that already existed at the U of S, SHR and SCA. Among those resources was the University’s Saskatchewan Drug Research Institute (SDRI). SCPOR continues to offer services that were provided to clinical researchers by SDRI, including:

- Confidential disclosure agreements
- Contract and budget negotiations
- Ethics submissions (applications, amendments, renewals, closures, reporting of unanticipated problems)
- Health region operational approval applications
- Health Canada submissions, including Clinical Trial Applications
- Financial services, including invoicing of research sponsors, processing of sponsor payments and payment of study-related expenses
- Clinical research nurses and clinical research coordinators

Many of the services offered by SCPOR are described in this handbook. Clinical researchers can contact SCPOR for assistance with their research at:

Saskatoon Centre for Patient-Oriented Research
Royal University Hospital, C-Wing, Room 5681
103 Hospital Drive
Saskatoon, SK S7N 0W8
(306) 978-8300
scpor@usask.ca
www.usask.ca/scpor

4. Grant-Funded Research

U of S, SHR and SCA researchers may conduct research funded by a grant from a federal agency, not-for-profit foundation or other source. A *research grant* is financial support for conducting research in a particular subject area or field, without any formal detailed stipulations as to the direction of such research.

4.1. Federal Funding

The main federal funding agencies for research in Canada are:

- Canadian Institutes for Health Research (CIHR)
- Natural Sciences and Engineering Research Council of Canada (NSERC)
- Social Sciences and Humanities Research Council (SSHRC)

Collectively, these three agencies are known as the *Tri-Agencies* (or *Tri-Council*). CIHR provides the majority of the federal funding for clinical and patient-oriented research.

4.2. Not-for-Profit Foundations

Various not-for-profit foundations are also important sources of grants for clinical research. Examples include:

- Canadian Foundation for Innovation (CFI)
- Saskatchewan Health Research Foundation (SHRF)³
- Heart and Stroke Foundation of Saskatchewan
- Kidney Foundation of Canada
- Canadian Cancer Society Research Institute
- Royal University Hospital Foundation

4.3. Other Sources

Funding from other sources may be available to U of S, SHR and SCA clinical researchers. For example, internal funding (i.e., funding provided by the University) may be available to students, medical residents and new faculty at the U of S. Students, residents and faculty should consult with their college or department about the possibilities for obtaining internal

³ SHRF oversees the Province of Saskatchewan's competitive research grant programs and research agency funding.

funding. Grants from private companies (i.e., industry) are also a source of funding for clinical research.⁴

4.4. Deadlines for Grant Submissions

Funding agencies (e.g., CIHR) and foundations (e.g., SHRF) have deadlines by which grant applications must be submitted. To be successful in obtaining grants, researchers must allow ample time to prepare high-quality applications and meet the deadlines of the funding agencies. Also, researchers must meet any internal deadlines in effect at their institution. The University of Saskatchewan requires that all research grant applications be submitted to Research Services (see *Section 4.5*) for institutional approval prior to the funding agency's deadline. Research Services requests that grants be submitted at least five working days prior to the funding agency deadline. While not mandatory, the University has initiated internal peer reviews for some grant competitions, including CIHR open operating grants and Heart and Stroke Foundation of Saskatchewan grants. The internal reviews begin as much as six months prior to the external grant deadline and are designed to provide the grantee feedback on the application prior to submission. Researchers should consult with Research Services for further details.

4.5. University of Saskatchewan Research Services

University of Saskatchewan Research Services is an administrative unit of the Office of the Vice-President Research and is responsible for institutional approval of grant applications and post-award administration of all research grants and contracts, except clinical research contracts and clinical research grants from industry. (Clinical research contracts and grants from industry are administered by the Saskatoon Centre for Patient-Oriented Research; see *Section 5*).

See the Research Services website for further details and contact information:

http://www.usask.ca/research/research_services

5. Contracted Research

Clinical researchers at the U of S, SHR and SCA often conduct research under a contractual arrangement with a sponsor, such as a pharmaceutical company or a university in another province. A *research contract* is a binding agreement, which usually includes financial support, for an investigator to conduct research in a particular subject area or field under specific stipulations and conditions (patent and publication rights, timing, etc.).

⁴ Although industry support for a clinical study may be offered as a grant, in most cases, industry-supported studies are conducted under a contractual arrangement. Contracted research is subject to specific stipulations and conditions that do not apply to grant-funded research. (See *Section 5*.)

Contracts for clinical research conducted under the auspices of the U of S are administered by the Saskatoon Centre for Patient-Oriented Research (SCPOR). Industry grants for clinical research at the U of S are also administered by SCPOR. Contact SCPOR (*Section 3.2*) for further information about administering contracts and industry grants for clinical research.

6. Investigators and Principal Investigators

Investigator or, more commonly, *principal investigator (PI)* is the term used for the person responsible for the conduct of a clinical research project at a research site. Sub-investigators are members of a clinical study team designated and overseen by the principal investigator at a study site to perform critical study-related procedures or to make important study-related decisions (or both). Health Canada refers to the responsible investigator (i.e., principal investigator) at a site as the *qualified investigator* (see *Section 9.3.3*). (ICH 1996a, U.S. 21 CFR 312, U of S Policies 2002b, HPFB 2003).

Students and medical residents cannot be principal investigators. For their research, the student's or resident's supervisor is considered the principal investigator.

7. Research Sponsorship

A *sponsor* is an individual, company, institution or organization that takes responsibility for the initiation and management of clinical research and compliance with applicable regulations. Initiating research involves activities such as designing the study, writing the protocol and obtaining funding. The sponsor may or may not be the source of funding for the research. Clinical trials that are subject to Health Canada regulations can have only one sponsor. (Applied Clinical Trials 2009, Holbein 2009, Walsh 2011)

7.1. Industry-Sponsored Research

A large share of clinical research is initiated and managed (as well as funded) by pharmaceutical, biotechnology, and medical device companies. These industry sponsors must conduct clinical trials to document the safety and effectiveness of drugs and medical devices they intend to bring to market.

Drug and medical device companies, and the research they conduct, are closely regulated. Health Canada is the federal agency responsible for regulating drugs and medical devices in Canada. In the United States, the U.S. Food and Drug Administration (FDA) has regulatory authority over these products. (See *Section 9*.)

Drug and medical device companies may choose to outsource some of their responsibilities to *contract research organizations (CROs)*. A CRO is an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of the sponsor's research-related duties and functions (ICH 1996a). CROs are also known as *clinical research organizations*.

7.2. Investigator-Initiated Research

Investigator-initiated research is research that an investigator not only conducts but also initiates and manages (i.e., sponsors). FDA regulations (U.S. 21 CFR 312) refer to the (lead) principal investigator of an investigator-initiated study as the *sponsor-investigator*, since she or he is responsible for initiating and managing, as well as conducting, the research.

Investigator-initiated research may be funded internally or by a grant from a government agency, a not-for-profit foundation or industry. There may be multiple funding sources.

The regulatory requirements for sponsor-investigators conducting investigator-initiated clinical trials (see *Section 8. Clinical Trials*) are generally the same as those applied to pharmaceutical and biotechnology companies (Sedgeworth and Derewlany 2006). Sponsor-investigators can contact the Saskatoon Centre for Patient-Oriented Research (see *Section 3.2*) for help in understanding and complying with the regulatory requirements for their research.

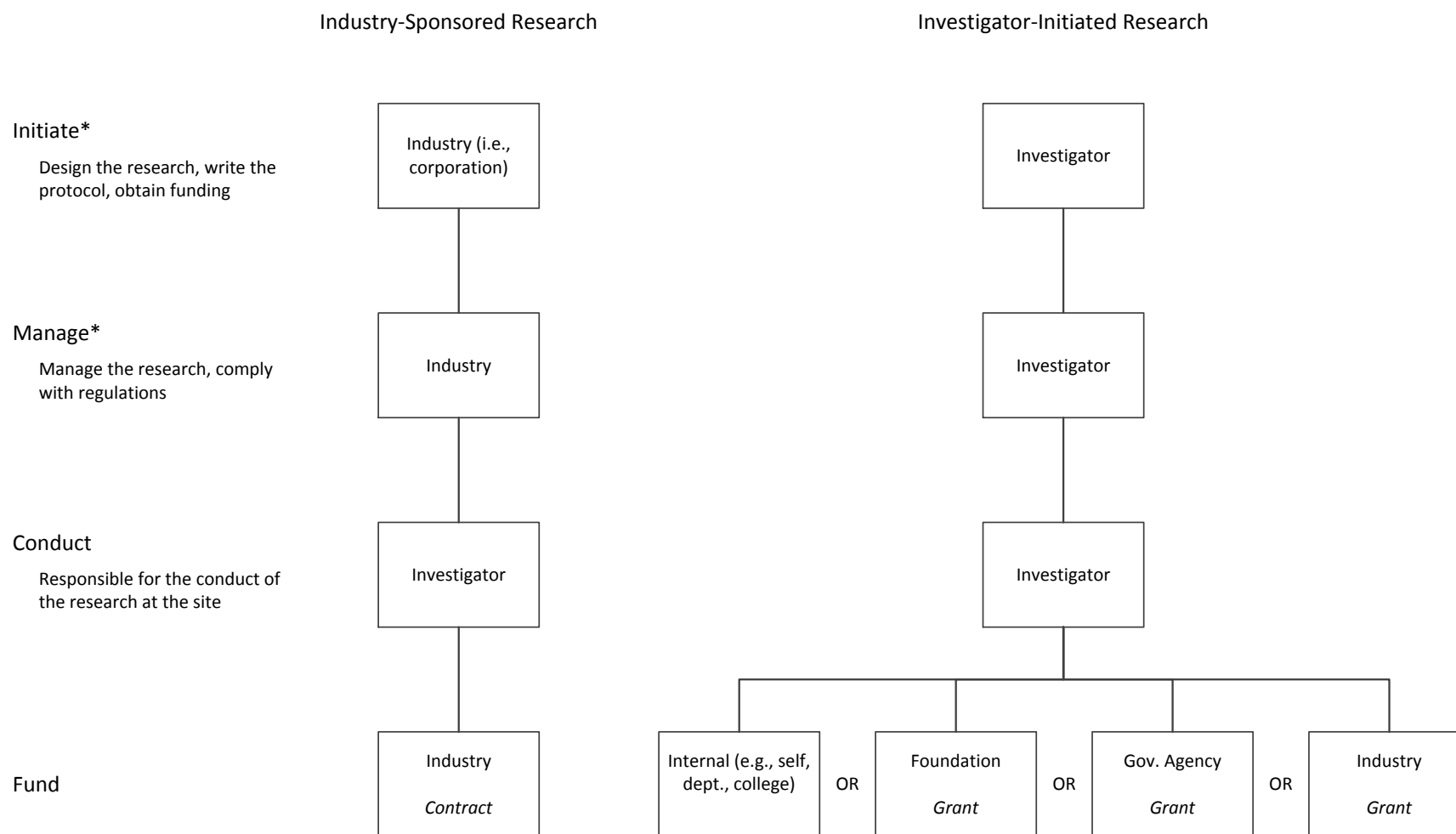
7.3. Industry-Sponsored vs. Investigator-Initiated Research

Figure 1 summarizes differences between industry-sponsored and investigator-initiated research. For both types of research, the investigator is responsible for conducting the research at a research site. For industry-sponsored research, an industry sponsor (i.e., a corporation) initiates and manages the research. For investigator-initiated research, the principal investigator (i.e., sponsor-investigator) initiates and manages (i.e., sponsors) the research. Funding for industry-sponsored research is provided by the corporate sponsor, and for these studies, a contract lays out the obligations of the sponsor and the site. Funding for investigator-initiated research may be internal or may be a grant from a foundation, a government agency or industry; there may be multiple funding sources.

7.4. Multi-Centre Studies

A study may be conducted at a single or at multiple *clinical centres*, or *sites*. U of S, SHR and SCA researchers are often contracted by commercial sponsors and CROs to participate as a site for multi-centre, industry-sponsored research. Similarly, U of S and SHR investigators are sometimes contracted by another institution (e.g., a university) to participate as one of the sites in a multi-centre, investigator-initiated study led by that institution.

Figure 1. Industry-Sponsored vs. Investigator-Initiated Research



*The sponsor is the party that initiates and manages the research. For investigator-initiated research, the investigator is the sponsor.

8. Clinical Trials

A *clinical trial* is a research study involving human participants that is designed to answer specific questions about the safety⁵ and efficacy⁶ of a biomedical intervention (e.g., drug or device) (Applied Clinical Trials 2009). Clinical trials also include studies intended to discover or verify the clinical, pharmacological, or pharmacodynamic effects of a drug, or study the absorption, distribution, metabolism, and excretion of a drug (HPFB 2003).

A clinical trial is a type of clinical research that is often (but not always) sponsored by a pharmaceutical, biotechnology or medical device company.

Before a company can obtain approval from a federal agency, such as Health Canada or the U.S. Food and Drug Administration (FDA), to put a new drug or device on the market it must conduct a series of clinical trials to prove that the intervention is both safe and effective. Even after the drug or device is approved and put on the market, the company must continue to conduct trials to confirm its safety. Post-marketing studies must also be done if the company wants to gain approval to market the intervention for new *indications*⁷.

Although clinical trials are often associated with pharmaceutical companies, many more clinical trials are initiated and run by non-industry researchers than by industry. For example, between 1986 and 2006, more than three times as many academic institutions and individuals applied to the FDA for approval to conduct new drug research than did pharmaceutical and biotechnology companies. (Arbit 2008)

8.1. Clinical Trial Phases

Drug and device testing begins with extensive laboratory research, which can involve years of experiments in animals and human cells. If this “pre-clinical” laboratory research is successful, the owner of the drug or device sends the data to Health Canada (or the FDA in the U.S.) for approval to continue research in humans. Once approved, human testing in clinical trials of the experimental drug or device can begin. (CenterWatch 2011)

The series of clinical trials that must be conducted to document the effectiveness (or “efficacy”) and safety of a drug or device consists of four phases (see Table 1).

⁵ Safety refers to the absence of harmful side effects (i.e., adverse reactions) resulting from the use of a drug or treatment (Applied Clinical Trials 2009).

⁶ Efficacy refers to the capacity of a drug or treatment to produce beneficial effects on the course or duration of a disease at the dose tested and against the illness (and patient population) for which it is designed (Applied Clinical Trials 2009).

⁷ An *indication* is a health problem or disease that is identified as likely to be benefited by a therapy being studied in clinical trials. Note: Where such a benefit has been established and approved by regulatory authorities, the therapy is said to be approved for such an indication. (Applied Clinical Trials 2009)

8.1.1. Phase I Clinical Trials

Phase I clinical trials may be called *human pharmacology* trials. They involve the initial introduction of an investigational new drug or experimental device in humans. Phase I studies are typically closely monitored and may be conducted in patients or healthy volunteer participants. For drugs, these studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. The total number of participants included in phase I studies is generally in the range of 20 to 80. (Applied Clinical Trials 2009, HPFB 2003, CIOMS 2002, ICH 1997)

8.1.2. Phase II Clinical Trials

Phase II clinical trials may be called *therapeutic exploratory* trials. They are clinical studies conducted to (1) evaluate the effectiveness of the drug or device for a particular indication or indications in patients with the disease or condition under study and (2) to determine the common short-term side effects and risks associated with the drug or device. Phase II studies are typically conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population which is closely monitored. These studies typically consist of a relatively small number of patients, usually involving no more than several hundred participants. (Applied Clinical Trials 2009, HPFB 2003, CIOMS 2002, ICH 1997)

8.1.3. Phase III Clinical Trials

Phase III clinical trials may be called *therapeutic confirmatory* trials. They are expanded trials performed after preliminary evidence suggesting effectiveness of the drug or device has been obtained. Phase III trials are intended to gather the additional information about effectiveness and safety that is needed to confirm efficacy and evaluate the overall benefit-risk relationship of the drug or device. These studies are intended to provide an adequate basis for marketing approval. Phase III studies are typically randomized, controlled, multi-centre trials on large participant groups, usually involving from several hundred to several thousand participants. (Applied Clinical Trials 2009, HPFB 2003, CIOMS 2002, ICH 1997)

8.1.4. Phase IV Clinical Trials

Phase IV clinical trials may be called *therapeutic use* trials. They are studies performed after the drug or device has been approved by the regulator for the market, and related to the approved indication. Commonly conducted studies include safety studies and studies designed to support use under the approved indication, such as mortality and morbidity studies or epidemiological studies. If a drug or device that has been approved for marketing is to be investigated for a new

indication (i.e., *off-label use*), then those clinical trials are generally considered phase II or phase III, rather than phase IV, trials. (HPFB 2003, ICH 1997)

Table 1. Objectives and Examples of Clinical Trial Phases (Adapted from ICH 1997)

Phase	Study Objectives	Study Examples
Phase I (Human Pharmacology)	<ul style="list-style-type: none"> • Assess tolerance • Define/describe PK⁸ and PD⁹ • Explore drug metabolism and drug interactions • Estimate activity 	<ul style="list-style-type: none"> • Dose-tolerance studies • Single and multiple dose PK and/or PD studies
Phase II (Therapeutic Exploratory)	<ul style="list-style-type: none"> • Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, endpoints, methodologies 	<ul style="list-style-type: none"> • Earliest trials of relatively short duration in well- defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures • Dose-response exploration studies
Phase III (Therapeutic Confirmatory)	<ul style="list-style-type: none"> • Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response relationship 	<ul style="list-style-type: none"> • Adequate, and well controlled studies to establish efficacy • Randomized parallel dose-response studies • Clinical safety studies • Studies of mortality/ morbidity outcomes • Large simple trials • Comparative studies

⁸ Pharmacokinetics: Study of the processes of bodily absorption, distribution, metabolism and excretion (ADME) of medicinal products (Applied Clinical Trials 2009).

⁹ Pharmacodynamics: Branch of pharmacology that studies reactions between drugs and living structures, including the physiological responses to pharmacological, biochemical, physiological and therapeutic agents (Applied Clinical Trials 2009). Pharmacodynamics is often summarized as the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug (University of Auckland, *History of Pharmacometrics*.

<http://www.fmhs.auckland.ac.nz/sms/pharmacology/holford/teaching/pharmacometrics/history/default.aspx>).

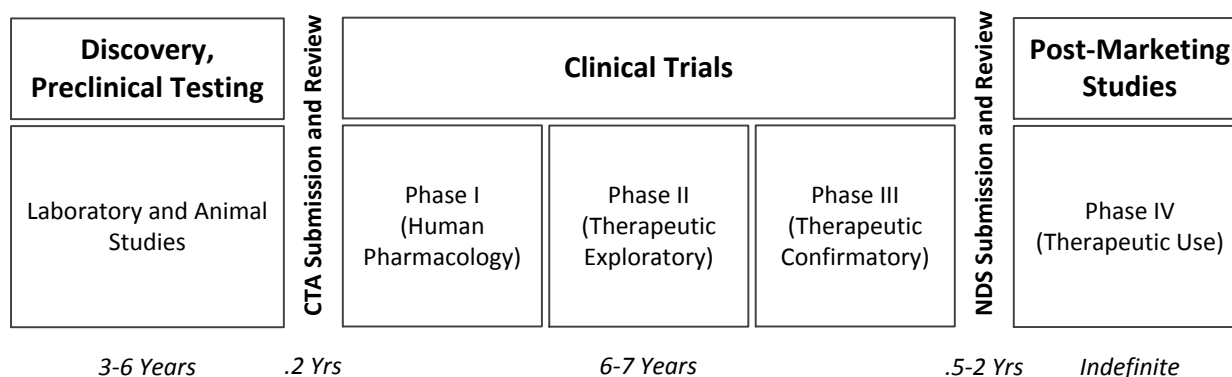
Phase	Study Objectives	Study Examples
Phase IV (Therapeutic Use)	<ul style="list-style-type: none"> • Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation 	<ul style="list-style-type: none"> • Comparative effectiveness studies • Studies of mortality/morbidity outcomes • Studies of additional endpoints • Large simple trials • Pharmacoeconomic studies

8.2. Drug Development Process

Figure 2 summarizes the stages of drug development starting with discovery of new drug prospects and preclinical (i.e., laboratory and animal) testing; followed by phase I, II and III clinical (i.e., human) trials; and ending with post-marketing (i.e., phase IV) studies.

In Canada, before a clinical trial can begin, the sponsor must submit a Clinical Trial Application (CTA) to Health Canada and receive Health Canada's approval (see *Section 9.3.4*). After sufficient evidence of safety and efficacy has been obtained through clinical testing, the sponsor completes a New Drug Submission (NDS) to apply for Health Canada's authorization to market the drug in Canada. It can take as long as 15 years to develop a new drug. (PhRMA 2012)

Figure 2. Drug Development Process (Adapted from PhRMA 2012)



8.3. Randomized Controlled Trials

8.3.1. RCTs and Randomization

A *randomized controlled trial*, or *RCT*, is a form of clinical trial in which study participants are randomly allocated to receive one or other of the alternative treatments under study (or a placebo) (Stanley 2007, Jadad 1998). The process of randomly assigning participants to treatment groups (also called *treatment arms*) is called *randomization*. RCTs are the most rigorous way to determine whether a cause-effect relationship exists between treatment and outcome (Sibbald 1998). A scientifically valid comparison between treatment groups depends on the groups being alike as much as possible, except for the specific treatments under investigation. Without such an assurance, healthier patients may be given one treatment and sicker patients another treatment, and the observed result would be biased in favour of the healthier patients (Stanley 2007). Randomly assigning participants to treatment arms (i.e., randomization) before the intervention begins minimizes allocation bias, maximizing the likelihood that the participants in one treatment arm are similar to those in the other(s).

To further eliminate conscious or unconscious bias in assigning treatment arms, it is important that the sequence of random assignments be *concealed* from the researcher. Concealment of the randomization sequence ensures that researchers cannot predict or change the allocation of participants to treatment groups. Unconcealed randomization can lead to researchers scheduling participants such that those with particular characteristics receive a certain assignment, thereby biasing the allocation. Methods for concealing the sequence of assignments include using sealed opaque envelopes, telephone-based interactive voice-response systems (IVRS) and interactive web response systems (IWRS). Concealed randomization is a prerequisite to double-blinding (see *Section 8.3.3*). (Altman and Schulz 2001, Schulz et al. 1995)

An RCT is a type of *controlled study* in that it typically compares results for participants who receive one or more test treatments against results for participants who receive a treatment (or no treatment) that has known effects, i.e., a *control group*. The control group may receive no treatment, a standard treatment or a placebo (U.S. 21 CFR 314, Applied Clinical Trials 2009).

8.3.2. Placebo-Controlled Trials

A *placebo-controlled trial* is a trial in which the participants in the control group are given a placebo. A *placebo* is an inactive substance or intervention, such as an inactive tablet or sham surgery, that resembles the comparable active substance or intervention. (TCPS2, ICH 2011, London and Kadane 2002, Birch 2006, Macklin 1999)

8.3.3. Blinding

Ideally, participants in RCTs are *blinded* as to which treatment they are receiving. In placebo-controlled trials, participants must be blinded as to whether they are receiving treatment or placebo. In *single-blind* studies, only the participants are unaware of the treatment (or placebo) they are receiving. Often, however, RCTs are *double-blinded* so that the researchers, as well as the participants, do not know which treatment, or placebo, is being given to which patients. Blinding ensures that the preconceived views of participants and (for double-blind studies) clinicians cannot systematically bias the assessment of outcomes (Sibbald 1998). Blinded studies are not always feasible or appropriate. For example, when a sham surgical procedure poses a significant risk to study participants, use of the sham surgery to maintain blinding may be considered unethical (London and Kadane 2002, Macklin 1999). Studies that are not blinded are often called *open-label studies* (Applied Clinical Trials 2009).

9. Regulatory Requirements

9.1. Introduction

Researchers must be aware of and comply with the various laws and regulations that apply to their research. Some laws, such as *The Health Information Protection Act (HIPA)*, are so broad that they effectively apply to all clinical research conducted by U of S, SHR and SCA researchers. Other laws and regulations, such as those pertaining to clinical trials or medical-device studies, are specific to certain types of research. In some cases, researchers must comply with foreign (e.g., U.S. FDA) regulations.

Various government agencies are responsible for establishing and enforcing federal laws, regulations, and policies pertaining to clinical research. The Tri-Agencies (CIHR, NSERC, SSHRC) have authority to sanction institutions and researchers who violate their policies. Health Canada is the agency that regulates drugs and medical devices in Canada. It oversees compliance with Canada's *Food and Drugs Act*, *Food and Drug Regulations*, and *Medical Devices Regulations*, including the regulations that pertain to drug and device research. The FDA has similar regulatory authority over drugs and medical devices in the U.S.

The *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*, or *ICH*, has created international standards for the research, development, and manufacturing of pharmaceuticals. Health Canada has adopted many of the ICH standards as guidelines for complying with the laws, regulations and policies that fall within Health Canada's purview (see *Section 9.3.14*).

9.2. Privacy Regulations

Privacy regulations that pertain to clinical research include the federal *Personal Information Protection and Electronic Documents Act (PIPEDA)* and *The Health Information Protection Act (HIPA)* of Saskatchewan. PIPEDA applies to the private sector, setting out privacy requirements for organizations that collect, use or disclose personal information in the course of commercial activities. HIPA governs the collection, use, and disclosure of *personal health information (PHI)*.¹⁰ HIPA is particularly relevant for the health sector and clinical researchers.

Compliance with HIPA is mandatory for all research in Saskatchewan that uses PHI. HIPA spells out the rights of individuals and the obligations of trustees in the health system (physicians, regional health authorities, health professionals, etc.) with respect to personal health information. Section 29 of HIPA pertains to use and disclosure of personal health information for research.

Researchers must make every reasonable effort to protect research participants' privacy and maintain confidentiality. Researchers must safeguard the information entrusted to them and not misuse or wrongfully disclose it. (TCPS2)

Privacy is respected if an individual has an opportunity to exercise control over personal information by consenting to, or withholding consent for, the collection, use or disclosure of information (TCPS2; see *Section 10.5. Informed Consent*).

Confidentiality refers to the obligation to safeguard entrusted information. Researchers must put in place appropriate security measures, including physical, administrative and technical safeguards, to protect information from unauthorized access, use, disclosure, modification, loss or theft. Physical safeguards include the use of locked filing cabinets and locating computers containing research data away from public areas. Administrative safeguards include the development and enforcement of organizational rules about who has access to personal information about participants. Technical safeguards include use of computer passwords, firewalls, anti-virus software, encryption and other measures that protect data from unauthorized access, loss or modification. (TCPS2)

¹⁰ *Personal health information* is, with respect to an individual, whether living or deceased: (1) information with respect to the physical or mental health of the individual; (2) information with respect to any health service provided to the individual; (3) information with respect to the donation by the individual of any body part or any bodily substance of the individual or information derived from the testing or examination of a body part or bodily substance of the individual; (4) information that is collected (a) in the course of providing health services to the individual, or (b) incidentally to the provision of health services to the individual; or (5) registration information (HIPA).

9.3. Health Canada, Food and Drugs Act and Regulations

9.3.1. Food and Drugs Act and Regulations

Researchers conducting clinical trials (see *Section 8*) in Canada must comply with the *Food and Drugs Act*, *Food and Drug Regulations* (if doing drug trials), and *Medical Devices Regulations* (if doing device trials). The act and regulations give authority to Health Canada to regulate drugs and medical devices. The regulations define requirements for obtaining approval to market drugs and medical devices in Canada and spell out sponsors' and investigators' obligations in the conduct of clinical trials.

9.3.2. Health Canada

The *Health Products and Food Branch (HPFB)* of Health Canada is the branch that regulates drugs and medical devices. The HPFB in turn consists of seven directorates. The directorates with responsibilities regarding human clinical trials are:

- *Therapeutic Products Directorate* – regulates pharmaceutical drugs and medical devices for human use
- *Biologics and Genetic Therapies Directorate* – regulates biological drugs (products derived from living sources) and radiopharmaceuticals for human use
- *Natural Health Products Directorate* – regulates natural health products¹¹
- *Marketed Health Products Directorate* – responsible for post-market surveillance, including collecting, reviewing, and analyzing safety data for marketed health products
- *HPFB Inspectorate* – responsible for compliance and enforcement activities for the HPFB

Before a new drug can be sold, the pharmaceutical company must obtain a Notice of Compliance (NOC) and a Drug Identification Number (DIN) from Health Canada. Before a medical device can be sold, the manufacturer must obtain a medical device license from Health Canada.¹²

NOCs, DINs, and medical device licenses represent Health Canada's approval for a drug or device to be marketed in Canada. Before Health Canada will issue its approval, the pharmaceutical company or device manufacturer must provide sound evidence of the safety and effectiveness of the drug or device. The purpose of clinical trials is to provide that evidence.

¹¹ Natural health products sold in Canada are subject to the *Natural Health Products Regulations*.

¹² Class I (lowest risk) devices do not require licenses, but manufacturers must ensure that devices are designed and manufactured to be safe, as required by the *Medical Devices Regulations* (Health Canada, http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/3kit-fiche/factsheet_fiches-info_14-eng.php).

9.3.3. Qualified Investigator

At each clinical trial site, there is a *qualified investigator*. The *Food and Drug Regulations* define the qualified investigator as the person responsible for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is:

- In the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association; and
- In any other case, a physician and a member in good standing of a professional medical association.

The qualified investigator is the person who is ultimately responsible for the trial at the site. There can be only one qualified investigator at each site. There can, however, be multiple sub-investigators at a site. The qualified investigator is also referred to as the *principal investigator* (see *Section 6*).

The qualified investigator can delegate tasks to others (e.g., sub-investigator, clinical research coordinator, pharmacist), but the tasks, and corresponding delegates, should be documented (e.g., in a delegation of responsibility log). The extent of delegation should be clearly stated; e.g., who will be responsible for assessing serious adverse drug reactions and serious unexpected adverse drug reactions and reporting those reactions within the specified time limits. The document (log) should be signed and dated by the qualified investigator and the persons to whom the functions are delegated. Tasks not specified as being delegated are considered to remain the direct responsibility of the qualified investigator. (HPFB 2006)

Although the qualified investigator may delegate tasks to others, he or she is ultimately responsible for all aspects of the clinical trial at his or her site. The qualified investigator must ensure compliance with the Regulations and the guidelines for good clinical practice (see *Section 9.3.7*) by every person involved in the conduct of the trial at the site. The qualified investigator must complete a *Qualified Investigator Undertaking* form, which states that she or he will conduct the trial according to good clinical practices. The form is kept by the sponsor and must be submitted to Health Canada upon Health Canada's request.

9.3.4. Clinical Trial Applications

Before a sponsor can conduct a clinical trial, the sponsor (or sponsor-investigator, see *Section 7.2*) must obtain approval from Health Canada. To obtain this approval, the sponsor must submit a *Clinical Trial Application (CTA)*. The CTA contains information and documentation to support the objectives and goals of the proposed clinical trial. Health Canada reviews the application based on the following criteria (Lourenco 2008):

- Scientific merit: rationale, study design, patient population, dosage regimen, safety and efficacy variables
- Sufficient information to support the safety of the drug for the purposes of the clinical trial
- Adequate communication of potential risks and anticipated benefits to clinical trial participants
- Acceptable chemistry and manufacturing information

Based on its review, Health Canada issues either a *No Objection Letter (NOL)* or a *Not Satisfactory Letter* to notify the sponsor whether the trial may start. Although by regulation clinical trials can start after 30 days unless the applicant has received a Not Satisfactory Letter, it is advisable that the sponsor wait until the NOL is received before starting the trial. (Klein and Tomalin 2005)

Important: In addition to Health Canada's authorization of the CTA, the approval of a research ethics board at each participating institution must also be obtained before the clinical trial can begin (see *Section 10.4*).

Phase IV trials are exempt from the requirement to file a CTA. As defined by Health Canada, phase IV trials are studies conducted after a drug has been approved for marketing *and related to the approved indication*. If the use of the drug in the trial is outside the parameters of the NOC or DIN (i.e., outside the approved indication), the study is not considered a phase IV trial and a CTA must be filed.¹³ All of the following parameters must match the NOC or DIN for the trial to be exempt from the CTA requirement:

- Indication(s) and clinical use
- Target patient population(s)
- Route(s) of administration
- Dosage regimen(s)

¹³ An investigation of a marketed drug for a new indication is considered a Phase II or Phase III trial (Health Canada, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_frequent_outline-eng.php).

The regulatory requirements for CTAs apply not only to commercially sponsored clinical trials but also to investigator-initiated trials.¹⁴ (See *Section 7.2* for more information about investigator-initiated research.)

The following references provide valuable information about the requirements for Clinical Trial Applications (see the *References* section for links to the documents):

- Clinical Trial Applications in Canada (Klein and Tomalin 2005)
- Health Canada Guidance for Clinical Trial Sponsors: Clinical Trial Applications (HPFB 2003)
- Health Canada Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals (HPFB 2008b)

Important: Each of the Health Canada directorates (see *Section 9.3.2*) has its own unique forms and Clinical Trial Applications.

9.3.5. Clinical Trial Registration

The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS2; see *Section 10.3*) stipulates that **all clinical trials must be registered before recruitment of the first trial participant**.

Health Canada encourages sponsors (including sponsor-investigators) to register their clinical trials at either of the following websites (HPFB 2008a):

- ClinicalTrials.gov (www.clinicaltrials.gov)
- Current Controlled Trials International Standard Randomised Controlled Trials Number Register (www.controlled-trials.com/isrctn)

The International Committee of Medical Journal Editors (ICMJE) requires trial registration as a condition for the publication of research results generated by the trial. Because the ClinicalTrials.gov registry uses the World Health Organization (WHO) Trial Registration Data Set required by ICMJE, it is recommended that U of S, SHR and SCA sponsor-investigators register their trials at ClinicalTrials.gov.¹⁵

As noted in the TCPS2, registration improves researchers' awareness of similar trials so that they may avoid unnecessary duplication and thereby reduce the burden on participants. Registration also improves researchers' ability to identify potential collaborators or gaps in

¹⁴ Health Canada, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clin/cta_for_sponsors-eng.php.

¹⁵ The WHO Trial Registration Data Set, or TRDS, is the minimum amount of trial information that must appear in a register in order for a given trial to be considered fully registered by the WHO (<http://www.who.int/ictrp/network/trds/en/index.html>).

research so that they may pursue new avenues of inquiry, with potential benefits to participants and to society. Perhaps of most concern is the danger that some researchers or sponsors may only report trials with favourable outcomes (i.e., publication bias). Failing to report the outcome of a trial or withholding negative findings is more difficult when all trials must be registered.

The trial registration record must be updated within 30 days of a change to recruitment status (not yet recruiting, recruiting, completed, etc.) or completion date. Other changes or updates to the record must be made at least every 12 months.¹⁶

For help in registering a clinical trial, contact the U of S Research Ethics Office (306-966-2975, ethics.office@usask.ca).

9.3.6. Changes to Clinical Trials

After the CTA has been authorized, Health Canada must be kept informed about the clinical trial. Small changes to the trial can be made immediately, with notification to Health Canada within 15 days. Similarly, if a change needs to be made to the protocol for patient safety, then the change should be made and Health Canada can be informed within 15 days (or as soon as possible). Otherwise, significant changes to either the protocol (e.g., revised dosing regimen) or the clinical trial supplies (e.g., drug manufacturing process) are considered amendments to the CTA and require prior authorization by Health Canada before they can be implemented. (Klein and Tomalin 2005, HPFB 2003).

9.3.7. Good Clinical Practice

The principles of *good clinical practice (GCP)* provide assurance that the data submitted to regulators (e.g., Health Canada) with applications to market new drugs are credible and accurate, and that the rights, integrity, and privacy of clinical trial participants are protected. The *Food and Drug Regulations* require that sponsors of clinical trials conducted in Canada be able to demonstrate that the trials are conducted according to the principles of GCP (Health Canada 2001). Phase IV trials (see *Sections 8.1* and *9.3.4*), even though they are exempt from the requirement to file a CTA, must still be conducted according to GCP. Health Canada has adopted the International Conference on Harmonisation's *Guideline for Good Clinical Practice E6* (ICH 1996a) as a guideline for complying with the GCP requirements of the *Food and Drug Regulations*.^{17,18}

¹⁶ See <http://clinicaltrials.gov/ct2/manage-recs/how-register>.

¹⁷ The ICH GCP Guideline is available at <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php>.

¹⁸ Other practices important in the research, development and production of drugs and medical devices include good laboratory practice (GLP) and good manufacturing practices (GMP). GLP is a quality system concerned with

According to Health Canada (2001) and ICH (1996a), the principles of GCP include the following:

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
- Before a trial is initiated, foreseeable risks and inconveniences must be weighed against the anticipated benefit for the individual trial participant and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- The rights, safety, and well-being of the trial participants are the most important considerations and must prevail over interests of science and society.
- The available non-clinical and clinical information on an investigational drug must be adequate to support the proposed clinical trial.
- Clinical trials must be scientifically sound and described in a clear, detailed protocol.
- A trial must be conducted in compliance with a protocol that has received research ethics board (REB) approval prior to initiation.
- The medical care given to, and medical decisions made on behalf of, participants must always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks. Investigators should provide evidence of such qualifications through up-to-date curriculum vitae and other relevant documentation as requested by the sponsor, the REB, or regulatory authorities.
- Freely given informed consent must be obtained from every participant prior to clinical trial participation.
- All clinical trial information must be recorded, handled, and stored in a way that enables its accurate reporting, interpretation, and verification.
- The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- Investigational drugs must be fabricated, handled, and stored in accordance with applicable good manufacturing practices (GMP). They must be used in accordance with the approved protocol.

the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported (OECD 2003). Pre-clinical (e.g., animal) studies (see *Section 8.1*) must comply with GLP (Applied Clinical Trials 2009). GMP are the part of quality assurance that ensures that drugs are consistently produced and controlled in such a way to meet the quality standards appropriate to their intended use, as required by the marketing authorization (HPFB 2009).

- Systems with procedures that assure the quality of every aspect of the trial must be implemented.

GCP Training

The University of Saskatchewan and Saskatchewan Cancer Agency expect their investigators and research staff who conduct clinical trials to obtain training and certification in GCP. Similarly, the Saskatoon Health Region expects investigators and their research staff who conduct clinical trials in SHR to obtain GCP training and certification. Researchers who are affiliated with the U of S or SCA are able to take the online GCP training made available through the Network of Networks (N2). As members of N2, the U of S and SCA are able to make N2's online GCP training available to their researchers free of charge. For more information about GCP training, contact the Saskatoon Centre for Patient-Oriented Research (see *Section 3.2*).

9.3.8. Record Handling and Retention

Canada's *Food and Drug Regulations* require that **clinical trial records be kept for 25 years**.¹⁹ Clinical trial records should be handled in accordance with good clinical practice. The Guideline for Good Clinical Practice (ICH 1996a) includes the following standards:

- The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the case report forms (CRFs)²⁰ and in all required reports.
- Data reported on the CRF that are derived from source documents²¹ should be consistent with the source documents, or if there are discrepancies, they should be explained.
- Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators on making such corrections. The investigator should retain records of the changes and corrections.

¹⁹ According to Health Canada's *Guidance for Records Related to Clinical Trials (Guide-0068)* (HPFB 2006), the starting date for calculating the retention time is the date when a record is created. For example, when an informed consent is signed, the date of the signature by the subject is the starting date. The guidance further states that, in practice, it may be easier to calculate the starting date for record retention as the date of completion or termination of the trial.

²⁰ A *case report form (CRF)* is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject (ICH 1996a). See the definition of *case report form* in the *Glossary* for further information about CRFs.

²¹ Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH 1996a)

- The investigator or institution should maintain the trial documents as specified in *Essential Documents for the Conduct of a Clinical Trial* (i.e., Section 8 in the GCP guideline) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
- The qualified investigator should always consult the sponsor prior to destruction of records created during the conduct of clinical trials.
- Upon request of the monitor, auditor, research ethics board or regulatory authority, the investigator or institution should make available for direct access all requested trial-related records.

All records created during the conduct of clinical trials are subject to inspection and must be retained for the prescribed period. Examples include signed informed consent forms, medical records, office charts, laboratory reports, X-rays, participant diaries, appointment and scheduling records, adverse events and drug reactions records, pharmacy records, and other essential documents including communications with sponsors and the research ethics board, and qualifications and evidence of training of staff involved in the trial. These records should be kept in a secure location to maintain their integrity and confidentiality. (HPFB 2006)

See Health Canada's *Guidance for Records Related to Clinical Trials: Guide 0068* (HPFB 2006) for additional guidelines on meeting regulatory requirements for handling and storing clinical trial information. Also see *Section 10.7* for the University of Saskatchewan's requirements for record handling and retention.

9.3.9. Reporting of Adverse Events

Definitions

The following definitions are important for understanding the requirements for adverse event reporting:

Adverse Event (AE). Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH 1996a)

Adverse Drug Reaction (ADR). Any noxious and unintended response associated with the use of a drug in humans. (1) Before a drug is approved for marketing (e.g., during a phase I, II, or III clinical trial), an ADR is an adverse event that occurs at any dose and where a causal relationship is at least a reasonable possibility. (2) After a drug is approved for marketing,

an ADR is an adverse event that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. (ICH 1994, 1996a; Applied Clinical Trials 2009)

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction. Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (ICH 1994, 1996a).

Unexpected Adverse Drug Reaction. An adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (ICH 1994, 1996a)

Investigator Responsibilities

Investigators conducting clinical trials should report all *serious adverse events (SAEs)* to the sponsor immediately, except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports (ICH 1996a).

Investigators must also report SAEs to the REB as required. Investigators whose research is subject to review by a University of Saskatchewan REB must follow the procedures described in the *U of S Requirements for Reporting Adverse Events/Unanticipated Problems (Section 10.6)*.

Sponsor Responsibilities

Sponsors of clinical trials, including sponsor-investigators (see *Section 7.2*), are required to inform Health Canada in an expedited timeframe of serious, unexpected adverse drug reactions. Only adverse drug reactions (ADRs) that are *both serious and unexpected* are subject to expedited reporting to Health Canada. Expedited reporting of reactions which are serious but expected is not required. Expedited reporting is also not required for serious events that are considered unrelated to the study product, whether or not the event is expected. (HPFB 2003)

The guidelines for expedited reporting of serious, unexpected ADRs are described in the Health Canada/ICH guidance document, *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A* (ICH 1994).²²

Timeframes for reporting ADRs are as follows:

²² Available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>.

- Where the ADR is neither fatal nor life-threatening, within 15 days after becoming aware of the information
- Where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information
- Within 8 days after having informed Health Canada of the ADR, submit as complete as possible, a report which includes an assessment of the importance and implication of any findings.

9.3.10. Drug Accounting and Storage

The principles of GCP (ICH 1996a) require that the investigator or appropriate designee (e.g., pharmacist) maintain records of:

- The delivery of the investigational product(s) to the trial site;
- The inventory at the site;
- The use by each participant; and
- The return to the sponsor or alternative disposition of unused products.

These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants. Investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and that reconcile all investigational products received from the sponsor.

Investigational products should be stored as specified by the sponsor (e.g., storage temperatures, conditions, and times) and in accordance with applicable regulatory requirements. The investigator must ensure that investigational products are used only in accordance with the approved protocol.

9.3.11. SHR Clinical Trial Pharmacy

The Saskatoon Health Region Clinical Trial Pharmacy at Royal University Hospital (RUH) is available to assist with managing investigational products for clinical research involving outpatients or inpatients at RUH, Saskatoon City Hospital or St. Paul's Hospital. Depending on the nature of the study, use of the Clinical Trial Pharmacy may be mandatory for inpatient studies conducted at these hospitals. The Clinical Trial Pharmacy can be contacted at (306) 655-2013.

9.3.12. Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial participants and the research ethics board, and should assure that the participants receive appropriate therapy and follow-up.

If the sponsor of a clinical trial (including a sponsor-investigator, *Section 7.2*) discontinues the trial, the sponsor must (1) inform Health Canada no later than 15 days after the date of the discontinuance and (2) provide Health Canada with the reason for the discontinuance.

9.3.13. Standard Operating Procedures

Investigators must conduct clinical trials according to the protocol, the sponsor's *standard operating procedures*, good clinical practice, and applicable regulatory requirements. Sponsors of clinical trials (including sponsor-investigators, *Section 7.2*) must put standard operating procedures in place as part of their quality assurance and quality control systems. (ICH 1996a)

As defined in the *ICH Guideline for Good Clinical Practice E6*, standard operating procedures (SOPs) are “detailed, written instructions to achieve uniformity of the performance of a specific function.” Use of SOPs ensures that trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Clinical trial investigators may use the sponsor’s SOPs or they may use their own, but they must have and follow SOPs. Researchers who are affiliated with the University of Saskatchewan are welcome to adopt the SOPs made available through the Network of Networks (N2). N2, a national organization supported by CIHR, provides a comprehensive and high-quality set of SOPs for clinical research. As a member of N2, the U of S is able to make these SOPs available at no charge to its researchers. For more information about the N2 SOPs, contact the Saskatoon Centre for Patient-Oriented Research (see *Section 3.2*).

9.3.14. Health Canada Guidance Documents and ICH Guidelines

Health Canada publishes a variety of *guidance documents*, which provide guidelines for complying with the *Food and Drugs Act* and *Food and Drug Regulations*. Among these guidance documents are the guidelines that were developed by the International Conference on Harmonisation (ICH) and which Health Canada has adopted. Examples of Health Canada’s guidance documents include:

- Clinical Trials Manual (HPFB 2007)
- Guidance for Clinical Trial Sponsors: Clinical Trial Applications (HPFB 2003)
- Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals (HPFB 2008b)

- Guidance for Records Related to Clinical Trials (Guide 0068) (HPFB 2006)
- Clinical Trials for Natural Health Products (HPFB 2005)
- ICH E2A: Clinical Safety Data Management Definitions and Standards for Expedited Reporting (ICH 1994)
- ICH E3: Structure and Content of Clinical Study Reports (ICH 1996b)
- ICH E6: Good Clinical Practice: Consolidated Guideline (ICH 1996a)
- ICH E8: General Considerations for Clinical Trials (ICH 1997)
- ICH E9: Statistical Principles for Clinical Trials (ICH 2003)

Health Canada's guidance documents pertaining to clinical trials are available at <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/index-eng.php>.

9.4. U.S. Regulations

U of S, SHR and SCA researchers may, for some studies, be required to comply with U.S. regulations. Typically, compliance with U.S. regulations is necessary when the sponsor of a clinical trial intends to apply for approval to market a new drug or device in the U.S. In this case, researchers will be required to comply with U.S. Food and Drug Administration (FDA) regulations, which are comparable to Canada's *Food and Drug Regulations* and *Medical Devices Regulations*. Requirements for compliance with FDA regulations should be spelled out in the contract with the sponsor, and the sponsor should provide guidance on how to meet them.

For studies funded by the *U.S. National Institutes of Health (NIH)*, researchers must comply with regulations overseen by the *Office for Human Research Protections (OHRP)*. These regulations have to do primarily with requirements for research ethics review and protection of research participants (see *Section 10*).

10. Research Integrity and Ethics

10.1. Introduction

It is essential that researchers conduct their research with utmost integrity and ethics. The proper conduct of research is critical to its credibility, the public's trust in its outcomes, and the integrity of the published record (CCA 2010). As stated in the University of Saskatchewan's *Responsible Conduct of Research* policy (U of S Policies 2013), "Scholarly work is expected to be conducted in an exemplary fashion, be ethically sound, and contribute to the creation of and the refinement of knowledge."

U of S, SHR and SCA researchers should know the policies that pertain to research integrity and ethics and follow them where they apply. These policies include:

- The Tri-Agency Framework: Responsible Conduct of Research (CIHR, NSERC and SSHRC 2011)
- University of Saskatchewan Responsible Conduct of Research Policy (U of S Policies 2013)
- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2)
- University of Saskatchewan Policies and Procedures for Ethics in Human Research (U of S Policies and Procedures 2002, updated 2007)

10.2. Tri-Agency Framework and U of S Responsible Conduct of Research Policy

The *Tri-Agency Framework: Responsible Conduct of Research* (CIHR, NSERC and SSHRC 2011) describes the responsibilities of researchers with respect to research integrity, applying for funding, financial management and requirements for conducting certain types of research. Adherence to the Tri-Agency framework is expected of all U of S, SHR and SCA researchers. The University of Saskatchewan's *Responsible Conduct of Research* policy (U of S Policies 2013) is based on and is consistent with the research integrity policy described in the Tri-Agency framework.

Principles of research integrity described in the Tri-Agency framework and the U of S *Responsible Conduct of Research* policy include:

- Using a high level of rigour in (1) proposing and performing research, (2) recording, analyzing, and interpreting data, and (3) reporting and publishing data and findings
- Keeping complete and accurate records of data, methodologies and findings, including graphs and images, in accordance with the applicable funding agreement, institutional policies, and laws, regulations, and professional or disciplinary standards in a manner that will allow verification or replication of the work by others
- Referencing and, where applicable, obtaining permission for the use of all published and unpublished work, including data, source material, methodologies, findings, graphs and images
- Including as authors, with their consent, all those and only those who have materially or conceptually contributed to, and share responsibility for, the contents of the publication or document, in a manner consistent with their respective contributions and authorship policies of relevant publications.
- Acknowledging, in addition to authors, all contributors and contributions to research, including writers, funders and sponsors

- Appropriately managing any real, potential or perceived conflict of interest²³

Examples of breaches of research integrity described in the Tri-Agency framework include:

- *Fabrication*: Making up data, source material, methodologies or findings, including graphs and images
- *Falsification*: Manipulating, changing, or omitting data, source material, methodologies or findings, including graphs and images, without acknowledgement and which results in inaccurate findings or conclusions
- *Destruction of research records*: The destruction of one's own or another's research data or records to specifically avoid the detection of wrongdoing or in contravention of the applicable funding agreement, institutional policy and/or laws, regulations and professional or disciplinary standards
- *Plagiarism*: Presenting and using another's published or unpublished work, including theories, concepts, data, source material, methodologies or findings, including graphs and images, as one's own, without appropriate referencing and, if required, without permission
- *Redundant publications*: The re-publication of one's own previously published work or part thereof, or data, in the same or another language, without adequate acknowledgment of the source, or justification
- *Invalid authorship*: Inaccurate attribution of authorship, including attribution of authorship to persons other than those who have contributed sufficiently to take responsibility for the intellectual content, or agreeing to be listed as author to a publication for which one made little or no material contribution
- *Inadequate acknowledgement*: Failure to appropriately recognize contributions of others in a manner consistent with their respective contributions and authorship policies of relevant publications
- *Mismanagement of conflict of interest*: Failure to appropriately manage any real, potential or perceived conflict of interest, in accordance with the Institution's policy on conflict of interest in research

The University of Saskatchewan's *Responsible Conduct of Research* policy includes the following additional examples of research misconduct:

- Failure to comply with pertinent federal, provincial, international, or University guidelines for the protection of researchers, human participants, the public, and the welfare of animals; or failure to meet other legal requirements that relate to the conduct of research

²³ A conflict of interest may arise when activities or situations place an individual in a real, potential or perceived conflict between the duties or responsibilities related to research, and personal, institutional or other interests. These interests include, but are not limited to, business, commercial or financial interests pertaining to the individual, their family members, friends, or their former, current or prospective professional associates. (TCPS2)

- Failure to conduct research in the manner in which it has been approved by the University's research ethics boards
- Failure to disclose any conflict of interests when asked to undertake reviews of research grant applications or to test products for sale or distribution to the public
- Failure to disclose conflict of interests prior to any commitment or expenditure of research funds and failure to notify the respective unit head should a conflict arise at a later point
- Failure to disclose to the University any financial interest in a company that contracts with the University of Saskatchewan to undertake research, particularly research involving the company's products, or to provide research-related materials or services. Financial interest means ownership, direct or indirect beneficial interest, substantial stock holdings, a directorship, honoraria or consulting fees, but does not include minor stock holding (<\$10,000) in publicly traded corporations
- Misuse of funds acquired for the support of research
- Failure to comply with terms of research funding agreements or University policy on Research and Scholarly Activities and the Administration of Research Funds

10.3. TCPS2

The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 2nd Edition*, (TCPS2) describes principles, standards and procedures for conducting research involving human participants.²⁴

Compliance with the TCPS2 is a requirement for all research conducted under the auspices of the University of Saskatchewan and for all research conducted in the Saskatoon Health Region.²⁵

The TCPS2 covers the following key topics:

- Research Ethics Review
- The Consent Process
- Fairness and Equity in Research Participation
- Privacy and Confidentiality
- Conflict of Interest
- Multi-Jurisdictional Research

²⁴ The TCPS2 is available at <http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default>.

²⁵ The requirement for compliance with the TCPS2 is stipulated in the *Subsidiary Agreement on Human Research Ethics Review* between the U of S and the Saskatoon Regional Health Authority (2008) and the *U of S Policies and Procedures for Ethics in Human Research* (2002, updated 2007).

- Research Involving First Nations, Inuit, And Métis Peoples
- Qualitative Research
- Clinical Trials
- Human Biological Materials
- Human Genetic Research

A tutorial about the TCPS2 is available at <http://www.pre.ethics.gc.ca/eng/education/tutorial-didacticiel>. All U of S and SHR researchers are strongly encouraged to take the tutorial.

10.4. Research Ethics Review

10.4.1. University of Saskatchewan Research Ethics Boards

All research conducted under the auspices of the University of Saskatchewan and all research that involves the Saskatoon Health Region must receive research ethics review and approval by a U of S Research Ethics Board (REB) (U of S Policies and Procedures 2002, updated 2007; SHR Policies and Procedures 2011a; U of S-SRHA 2008).

Important: No intervention or interaction with human participants in research, including recruitment, may begin until the REB has reviewed and approved the research.

10.4.2. Which REB will review my ethics application?

The University of Saskatchewan has established the Biomedical and Behavioural Research Ethics Boards (REBs) to review and approve research involving humans. The determination of which REB is the most appropriate to conduct a review is based primarily on research methods.

Biomedical Research Ethics Board

The Biomedical Research Ethics Board (Bio-REB) is responsible for the review of all ethics applications involving human participants that include medically invasive procedures; physical interventions and therapies (including exercise and diet interventions); administration and testing of drugs, natural products or devices; or physiological imaging and measures (e.g. MRI or CT scans, heart rate, blood pressure). A project that is based solely on the use of medical charts or health records (no other research method is being used) will be reviewed by the Biomedical Research Ethics Board.

The Biomedical REB has two types of application forms—one for retrospective projects and the other for prospective projects—and corresponding guidance notes to assist you in preparing your submission. The application forms and guidance notes are available at: <http://www.usask.ca/research/files/index.php?id=22>.

Behavioural Research Ethics Board

The Behavioural Research Ethics Board (Beh-REB) is responsible for the review of all ethics applications involving human participants that include social, behavioural and cultural research using methods such as interviews, surveys, questionnaires, observations, psychological, social or behavioural interventions, audio or video recording.

The Behavioural REB has one form for all research projects and includes guidance notes to assist you in preparing your submission. The form is available at:

<http://www.usask.ca/research/files/index.php?id=21>.

Mixed Methods Research

An ethics application using mixed methods should be reviewed by the REB (Biomedical or Behavioural) with the best expertise in the methods that may impose the greater risk to a research participant. Where appropriate, the Biomedical and Behavioural REBs may collaborate in the ethics review of the submission. For help in determining which REB an ethics application should be submitted to, contact the Research Ethics Office (see *Section 10.4.5*).

Harmonized Review for Multi-Institution Research

Research conducted at multiple institutions requires research ethics approval from each institution before it can begin. To make multi-institution ethics approval less cumbersome, the University of Saskatchewan, University of Regina, Regina Qu'Appelle Health Region and Saskatoon Health Region have harmonized their research ethics review processes. The harmonization includes common application forms, common consent form templates and a streamlined submission process. Investigators conducting research at any or all of the four institutions need only complete one application package, which they submit simultaneously to the institutions at which the research is being conducted. Contact the Research Ethics Office (see *Section 10.4.5*) for more information.

10.4.3. Types of Review

The REB follows a *proportionate approach* to research ethics review. In other words, the level of review is determined according to the level of risk the research poses to the participant. The proportionate approach allows the REB to provide a higher level of scrutiny, and correspondingly more protection, for the most challenging research. Studies that pose more than minimal risk must be reviewed at a face-to-face meeting of the REB (*full-board review*). Review of minimal risk studies may be delegated to the REB chair or to one or more experienced REB members (*delegated review*). Full-board review is the default requirement.

Definition of Minimal Risk

Minimal risk research is defined as research in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in those aspects of their everyday life that relate to the research.

The concept of minimal risk applies to all aspects of the research protocol, and not just to the procedures entailed by the study itself. For example, an otherwise straightforward questionnaire or interview may exceed the threshold of minimal risk if the participant population involves a vulnerable group.

Full-Board Review

Research studies that involve greater than minimal risk must be reviewed by the REB at a face-to-face meeting. The REB reviews above minimal risk studies at a regularly scheduled monthly (Behavioural REB) or semimonthly (Biomedical REB) meeting. A deadline for submission precedes each meeting by approximately two weeks. Based on its deliberations, the REB may make one of the following four determinations regarding the research:

Determination	Description
Approval	Approved as submitted. Research may begin as soon as the investigator receives a Certificate of Ethics Approval (C of A) from the REB. Once the C of A has been issued, the research may begin, provided that all other institutional requirements have been met, and that approval to proceed is not withdrawn by the Vice-President Research, the Board of Governors or the President.
Proviso	The REB may decide that a protocol may be approved provided that certain conditions are met or required changes are made. A written explanation of the conditions or modifications – a Notice of Ethical Review (NER) – is sent to the investigator by the REB chair. When the investigator provides the REB with proof that the conditions have been met and the documents have been amended, the C of A is sent to the investigator.
Deferral	The REB may defer a decision on any submitted research application if it does not have sufficient information to arrive at a determination, if the REB requires extensive revisions to any part of the research or if all of the criteria for REB approval are not met. The application will be brought back before the full REB for consideration after the additional information or revisions are received.

Determination	Description
Rejection	The REB may reject any protocol which does not meet its standards for ethical or scientific review and where revision is unlikely to enable the REB to reach a positive determination. No other U of S REB or institutional official may approve a study which has been previously rejected by a U of S REB. A researcher may request reconsideration of a decision made by the REB and has the right to appeal the REB's decision pursuant to the provisions of the <i>U of S Policies and Procedures for Ethics in Human Research (2002, updated 2007)</i> .

For full-board review, researchers can normally expect an initial response from the REB within 10 working days from the meeting date.

Delegated Review

For minimal risk research and for minor changes to approved research, the REB delegates review to the REB chair or to one or more experienced REB members. Studies subject to delegated review are sent out for review as they are received. Researchers can normally expect an initial response from the REB within two to three weeks from the time of submission.

10.4.4. Annual Renewal and Study Closure

Ethics approval may last for up to one year. If the project is to continue beyond the one-year approval period, the researcher must submit a Study Renewal Form to the REB. If the renewal is not submitted and approved by the expiration date, the study will be suspended and the investigator will be advised that the study has expired. The Study Renewal Form should be submitted at least six weeks before the expiration date to allow sufficient time for review and approval. Extension without renewal will not be granted. Review of study renewals may be delegated (see previous section) when there has been little or no change in the ongoing investigation.

When the project is complete, the researcher must notify the REB by submitting a Study Closure Form. Submission of the Study Closure Form allows the REB to close its files and provides the REB with information it may use in the evaluation and approval of related studies.

Study Renewal and Study Closure Forms are available at the following U of S Research Ethics Office webpage: <http://www.usask.ca/research/files/index.php?id=15>.

10.4.5. For More Information

For more information about requirements and guidelines for obtaining U of S REB approval, visit the Research Ethics website (http://www.usask.ca/research/ethics_review/). You can also contact the Research Ethics Office at (306) 966-2975 or ethics.office@usask.ca.

10.5. Informed Consent

A critical element of ethical research is *informed consent*. All research participants must be well informed about the research in which they are being asked to participate and must be given the opportunity to freely and voluntarily decide whether to participate. Evidence of informed consent by a participant needs to be obtained prior to their participation in the research and should ordinarily be obtained in writing. Consent form guidelines and templates are available at http://www.usask.ca/research/ethics_review/guidelines.php.

Informed consent is an ongoing, interactive process rather than a onetime information session (Applied Clinical Trials 2009, TCPS2). Researchers must ensure that participants:

- Continue to understand what the research is about and what their participation involves,
- Are provided with any new information which might influence their decision to continue their participation in the research, and
- Continue to consent to participate throughout the research.

Revisiting informed consent is often done informally. However, formal reconsent (with written documentation) must be obtained from participants if there is a significant change to the study or if there is new information which might alter participants' willingness to participate in the study. (RCN 2011)

10.6. U of S Requirements for Reporting Adverse Events/Unanticipated Problems

10.6.1. Local (Internal) Adverse Events

Local (i.e., internal) adverse events (see *Section 9.3.9*) are those that occur at the principal investigator's site. The PI is required to report to the REB only those local adverse events that are deemed to be unanticipated problems. An *unanticipated problem* is defined as any incident, experience or outcome that meets all of the following criteria:

- **Unexpected** (in terms of nature, severity or frequency) given the research procedures that are described in the protocol-related documents (e.g., REB-approved research protocol, informed consent document, Investigator Brochure) and the characteristics of the research participant population being studied, and

- **Related or possibly related to participation in the research** (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the drugs, devices or procedures involved in the research), and
- Suggests that the research places **participants or others at a greater risk of harm** (including physical, psychological, economic or social harm) than was previously known or recognized.

Once an investigator is aware of a local adverse event, he or she should assess whether the adverse event represents an unanticipated problem. If the investigator determines that the adverse event represents an unanticipated problem, it must be reported to the REB. If the investigator determines that an adverse event is not an unanticipated problem but the sponsor subsequently determines that it is, the sponsor should report this determination to the principal investigator, and a report must then be submitted to the REB. The principal investigator must clearly explain how she or he determined that the event meets the definition of an unanticipated problem. The report must also describe any proposed protocol changes or other corrective actions to be taken by the principal investigator or sponsor in response to the event.

Report Timing and Process

Local (internal) serious adverse events that meet the definition of an unanticipated problem should be reported to the REB as soon as reasonably possible, but in any case no later than seven calendar days after the occurrence of the local event or the sponsor's determination that the event constitutes an unanticipated problem. Such events should be reported using the Unanticipated Problems Reporting Form²⁶, and should include:

- The status of the study and summary of participants enrolled
- A detailed description of the local event
- An opinion expressed by the local investigator that the event is both serious and unexpected and a justification of that opinion
- An opinion expressed by the local investigator that the event is related or potentially related to the study drug, procedure or device and an explanation of that opinion.
- An opinion expressed by the local investigator respecting the implications of the SAE on the continuation of the study and any further actions that may be required such as changes to the study procedure, informed consent or protocol.
- A statement of the study team response to the event and the patient outcome of the SAE

²⁶ Available at <http://www.usask.ca/research/files/index.php?id=22>.

10.6.2. Non-Local (External) Adverse Events

Non-local (i.e., external) serious adverse events are those that occur at other sites and that are reported to the local PI. Non-local AEs should be reported to the REB in the form of a *periodic safety update report*. The contents of the periodic safety update report should include at a minimum:

- A summary analysis of the significance of the AEs, or
- An analysis from an independent Data Safety Monitoring Board (DSMB) with (where appropriate) a comprehensive listing of previous similar events.

Investigators may rely on the sponsor's assessment and provide to the REB a periodic safety update report prepared by the sponsor. The format used by the sponsor for an annual safety reports is acceptable. In general, the sponsor should amend the Investigator's Brochure as needed to keep the description of safety information updated.

Single, isolated external AEs rarely meet the requirements for reporting to REBs. Individual external AEs should only be reported when a determination has been made that the event meets all of the criteria for an unanticipated problem (see *Section 10.6.1*). University of Saskatchewan REBs will ONLY accept individual case reports of non-local (external) AEs in the exceptional circumstances that they meet the definition of an unanticipated problem. Individual isolated external AEs should NOT be reported to the REB *unless they are unanticipated problems*. If such an event meets the reporting criteria, the report that is submitted must include *all* of the following information:

- Justification of the assessment that the event described is both serious and unexpected, and
- Identification of all previous safety reports concerning similar adverse experiences, and
- An analysis of the significance of the current adverse experience in light of the previous reports, and
- An outline of any proposed protocol changes, informed consent form changes or other corrective actions to be taken by the sponsor in response to the unanticipated problem.

Reports not meeting these requirements will be returned to the submitter.

Report Timing and Process

Periodic safety update reports and individual non-local (external) adverse events that represent unanticipated problems should be reported to the REB using the Unanticipated Problems Reporting Form.

Periodic safety update reports should be reported to the REB as soon as reasonably possible but in any case no later than fifteen calendar days after the principal investigator or designee has received the report from the Sponsor. At the time of submission of the application for annual renewal, the principal investigator will be expected to provide:

- A summary of the impact of all safety data that has been received from the sponsor, and
- Any new information that they have become aware of, and
- Recommendations for any proposed changes to the study, if applicable.

Investigators should append to the application any periodic safety update reports issued by the sponsor within the previous year, if they have not been previously submitted to the REB. If the sponsor is unwilling to or has been unable to provide the Investigator with an assessment of safety information at least once annually, the Investigator should report this to the REB when submitting the request for annual renewal.

In the limited circumstances where an individual external AE constitutes an unanticipated problem, the report of the AE should be reported to the REB as soon as reasonably possible, but in any event, no later than within seven calendar days after the investigator has made the determination that the event is reportable.

10.6.3. Other Unanticipated Problems

Other incidents, experiences, or outcomes not considered adverse events may meet the definition of unanticipated problems (see *Section 10.6.1*). When an investigator becomes aware of any other incident, experience, or outcome that may represent an unanticipated problem, he or she should assess whether it does constitute an unanticipated problem. If the investigator determines that it is an unanticipated problem, the investigator must report the problem to the REB.

In general, only those incidents, experiences, or outcomes that require a change to the study procedures or study documents or that require notifying the research participants of a change in the risk/benefit ratio should be reported to the REB. Examples include:

- For an "expected," serious adverse reaction, an increase in the rate of occurrence which is judged to be clinically important
- A significant hazard to the research participant population, such as lack of efficacy with an investigational product used in treating life-threatening disease
- A major safety finding from a newly completed animal study that suggests a significant risk for human participants (such as carcinogenicity)
- Breaches of privacy and confidentiality
- Protocol deviations that impact data integrity or the safety of research participants

- Acts of nature that impact the study conduct or data integrity (e.g., floods, hurricanes, earthquakes, pandemics)

Report Timing and Process

Other unanticipated problems should be reported to the REB as soon as reasonably possible but in any event within seven calendar days of awareness of the occurrence of the event or the receipt of the report of the unanticipated problem by the investigator from the sponsor. The problem should be reported using the Unanticipated Problems Reporting Form.

10.7. U of S Requirements for Record Handling and Retention

The *Procedures for Stewardship of Research Records at the University of Saskatchewan* (U of S 2010) describe record handling and retention requirements for research reviewed by the U of S Research Ethics Boards.²⁷

The document states that the principal investigator (PI) is responsible for the collection, maintenance, privacy and secure retention of research records. The PI must also ensure that all personnel involved with the research understand and adhere to appropriate practices for handling research records.

Research records are those documents and other records and materials recorded by or for a researcher that are necessary to document, reconstruct, evaluate, and validate research results and the events and processes leading to the acquisition of those results. Research records may be in many forms including but not limited to laboratory notebooks, survey documents, questionnaires, interview notes, transcripts, machine-generated data or performance outputs, recruitment materials, consent forms, correspondence, other documents, computer files, audio or video recordings, photographs including negatives, slides, x-ray films, samples of compounds, organisms (including cell lines, microorganisms, viruses, plants, animals) and components of organisms.

Research records must be retained in sufficient detail to enable the University and the involved researchers to respond to questions about research accuracy, authenticity, compliance with pertinent contractual obligations, and University of Saskatchewan and externally imposed requirements and regulations governing the conduct of the research.

Research records must be stored securely and protected with all the precautions appropriate to their sensitivity and privacy. Highly sensitive records may need to be held on computers not connected to networks and located in secured areas with restricted access. Secure storage may

²⁷ Available at http://www.usask.ca/research/ethics_review/policies.php.

mean encryption of research records sent over the internet or kept on a computer connected to the internet; adherence to guidelines on data storage on mobile drives, digital recording devices or laptop computers; the use of computer passwords, firewalls, back-ups, and anti-virus software; off-site backup of electronic and hard-copy records; and other measures that protect research records from unauthorized access, loss or modification.

Research record retention periods will vary depending on the research discipline, research purpose and type of records involved. The procedures stipulate that research records be retained for not less than:

- five years after the end of a research project's records collection and recording period;
- five years from the submission of a final project report;
- five years from the date of publication of a report of the project research; or
- five years from the date a degree related to a particular research project is awarded to a student;

whichever occurs last.

Research records must be retained for longer periods if any of the following criteria apply:

- If required to protect intellectual property rights;
- If such research records are subject to specific federal or provincial regulations requiring longer retention periods (**Health Canada requires that clinical trial records be kept for 25 years; see *Section 9.3.8* for Health Canada's requirements for record handling and retention**);
- If required by the terms of a research sponsorship agreement; or,
- If any allegations regarding the conduct of the research arise, such as allegations of academic misconduct or conflict of interest.

Research records may be retained for longer periods if retention is required for the continuity of scientific research or if the research records are potentially useful for future research by the PI or other researchers.

See *Section 9.3.8* for additional information on record handling and retention.

11. Saskatoon Health Region and University of Saskatchewan Policies

11.1. Saskatoon Health Region Research Policies²⁸

All Saskatoon Health Region employees, practitioner staff, contractors, vendors, students and volunteers who conduct research involving human participants must abide by the *SHR Research Policy*. The *SHR Research* policy (SHR 2011a) also applies to non-SHR personnel who conduct research using SHR or affiliate facilities, resources, patients, long-term care residents or staff.

The *SHR Research Policy* describes SHR's requirements for research ethics review, operational approval, regulatory compliance, liability protection, delegation of responsibility, qualifications and training, cost recovery, audits, review of non-disclosure agreements, contracts and budgets, dispute resolution and policy non-compliance.

Other SHR policies that apply to researchers include those pertaining to:

- Privacy and Confidentiality (2012);
- Critical Incident Reporting (2004, revised 2007);
- Fraud and Irregularity (2010);
- Our Values in Action/Code of Conduct (2008); and
- Speaking up - Protection of Persons Reporting Wrongdoing (2011b).

11.2. University of Saskatchewan Research Policies

Those who are involved in research at the University of Saskatchewan must abide by the University's policies pertaining to:²⁹

- Administration of Research Funds (2002a);
- Administration of Research Grants and Contracts (2002b);
- Administration of Research Overheads (2005);
- Care and Use of Animals in Research (2001);
- Centres (2004);
- Responsible Conduct of Research (2013);
- Postdoctoral Fellows (2006);
- Research Involving Human Subjects (2000); and

²⁸ SHR policies are available on the SHR Policies and Procedures website:

http://www.saskatoonhealthregion.ca/about_us/policies_and_procedures_introduction.htm.

²⁹ University of Saskatchewan policies are available on the University of Saskatchewan Policies website: http://www.usask.ca/university_secretary/policies.

- Research Publications (2002c).

12. SHR Operational Approval

Investigators conducting research that involves Saskatoon Health Region or affiliate facilities, resources, patients, long-term care residents or staff must obtain SHR operational approval before the research can begin. The requirements for operational approval are described in the *SHR Research* policy (see *Section 11.1*). Operational approval consists of the following two components:

- Proof of research ethics approval; and
- Department impact assessment.

Research ethics review for SHR research, as well as for University of Saskatchewan research, must be done by one of the University of Saskatchewan Research Ethics Boards (REBs). See *Section 10.4* for information about research ethics review by the University of Saskatchewan REBs.

Department impact assessment identifies the SHR (and affiliate) departments whose services or support will be needed for the research and determines each department's ability to provide the needed services or support. The department impact assessment allows all potentially affected SHR departments the opportunity to review the research study, assess the operational impact of the study, determine how the proposed research will affect their functions and, where appropriate, prepare a budget for cost-recovery.

The Department Impact Assessment may be conducted simultaneously with preparation and submission of the ethics application. It is not necessary to wait for ethics approval before beginning the Department Impact Assessment.

See the *SHR Research* policy and the *SHR Research Approval* website (http://www.saskatoonhealthregion.ca/about_us/research_approval.htm) for information about how to apply for operational approval.

13. Start-up of a New Clinical Research Project

Starting a new clinical study involves a number of steps, including activities such as defining the research question, obtaining funding, reviewing the study protocol, conducting a feasibility assessment, obtaining the needed ethics and regulatory agency approvals, receiving operational approval from the health region, and negotiating the contract with the sponsor.

Grant or Internally Funded Research Projects

Figure 3 summarizes the steps to start up a study that is funded by a grant or that is internally funded (i.e., funded by the U of S, SHR or SCA). The first step is to develop a thorough understanding of the topic by reviewing the literature and to define the research question. Once the research question has been defined, a source of funding must be identified. If the study will need external funding, a grant application must be completed and submitted to the funding body. It is important to determine and meet the deadlines and other requirements for application review and submission (see *Section 4*). Once notification of funding is received, the necessary regulatory, ethics and operational approvals must be obtained.

If the study is a clinical trial (see *Section 8*), there are special requirements. If the study is a phase I, II or III clinical trial, a Clinical Trial Application must be submitted to Health Canada (see *Section 9.3.4*). A No Objection Letter (NOL) from Health Canada must be received before the trial may proceed. All clinical trials must be registered on the ClinicalTrials.gov website (see *Section 9.3.5*).

Before they can proceed, all research projects involving human participants must receive approval from the research ethics board (REB), which involves submitting an application to the REB and making revisions based on the REB's feedback (see *Section 10.4*).

If the study involves facilities, resources, patients, long-term care residents or staff of a health region, operational approval must be obtained from the health region (see *Section 12*). An application for operational approval must be submitted and approval must be received by the health region departments that will be involved in the study.

Contracted Research Projects

If the study is sponsored by a company or another institution, a contract must be put in place with the sponsor (see *Section 5*). Figure 4 summarizes the steps to start up a contracted study. If the sponsor is a company, the first step is usually to negotiate and sign a confidential disclosure agreement (CDA). Once the CDA is in place, the researcher reviews the protocol and works with the sponsor to assess the suitability of the study for the researcher's site. If it is determined that conducting the study at the site is feasible, the contract is negotiated, approval from the research ethics board is obtained, and if needed, health-region operational approval is obtained. After these steps are completed, the researcher may proceed with the study once the sponsor gives the go-ahead.

Figure 3. Start-up of a Grant or Internally Funded Research Project

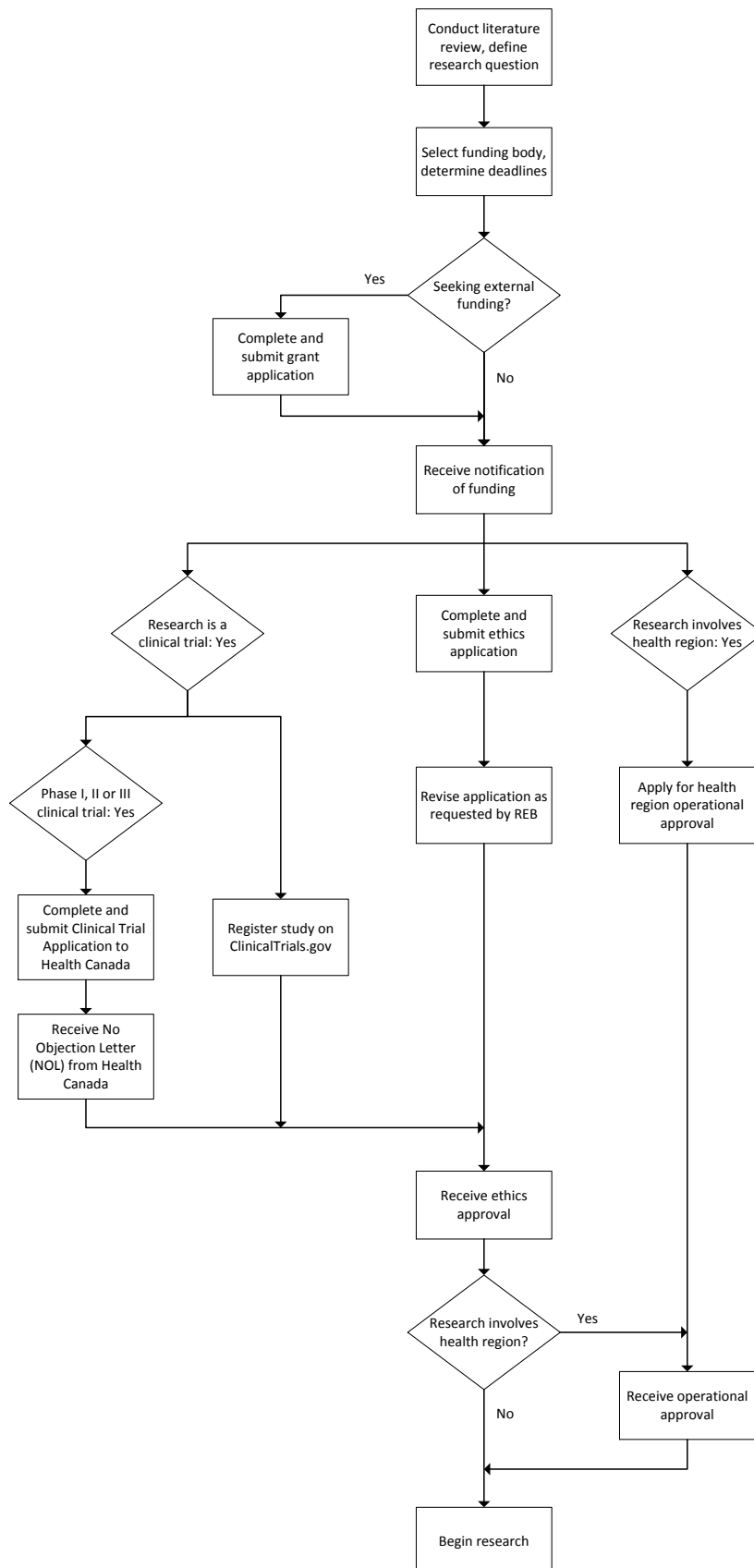
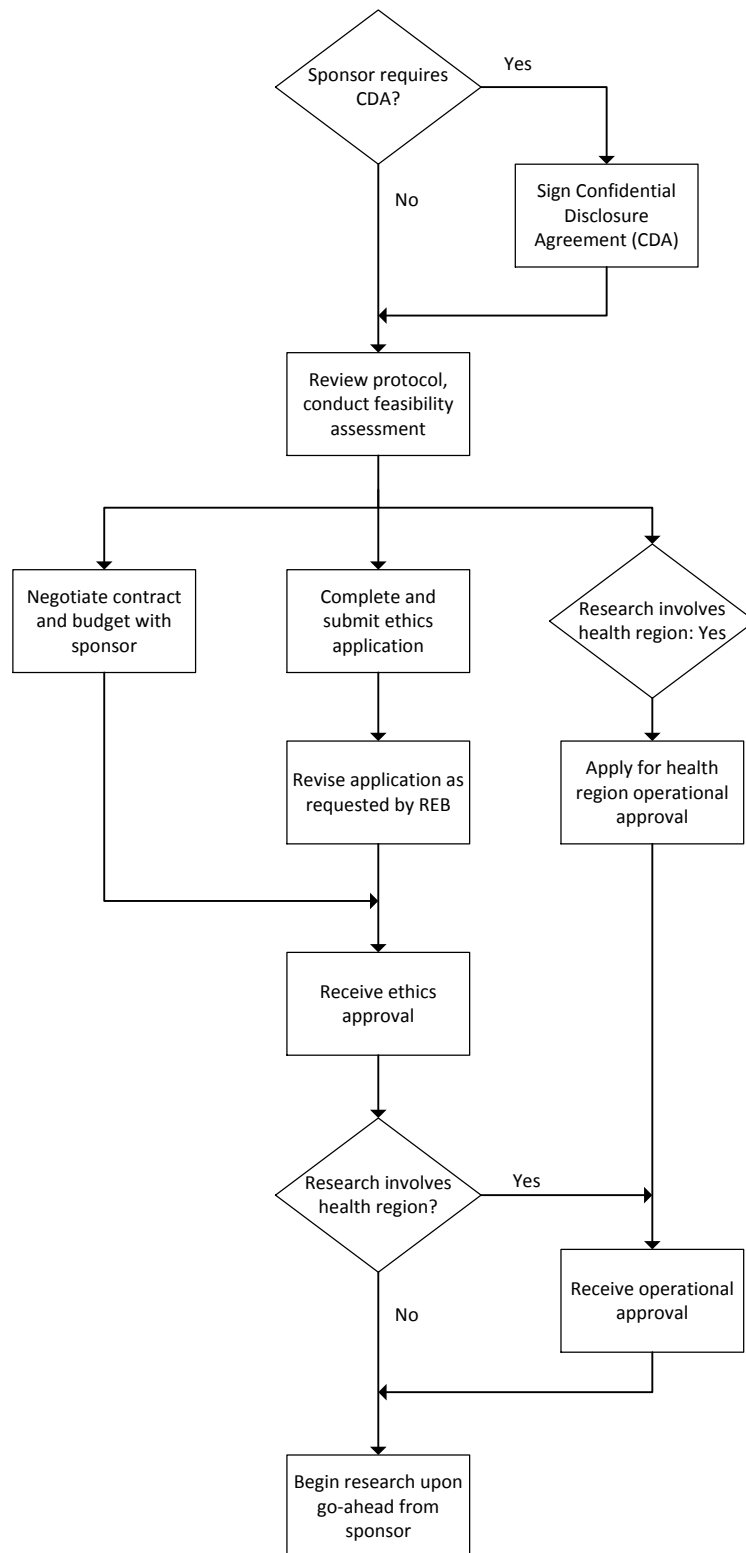


Figure 4. Start-up of a Contracted Research Project



Online Training Resources

Resource	For More Information
TCPS2 Tutorial	http://www.pre.ethics.gc.ca/eng/education/tutorial-didacticiel
N2 Online Training in Good Clinical Practice (GCP)	Contact the Saskatoon Centre for Patient-Oriented Research (see <i>Section 3.2</i>)
Protecting Human Research Participants, NIH Office of Extramural Research	http://phrp.nihtraining.com/users/login.php
McMaster University Tutorial for Researchers Conducting Retrospective Review of Health Records	https://ethics.mcmaster.ca/chart/

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