

Clinical Trials

What is a Clinical Trial?

Clinical trials are experimental research studies conducted on human subjects. Clinical trials are often utilized to help researchers determine new ways to prevent, diagnose or treat medical conditions or diseases by allowing safety and efficacy data to be collected for new drugs or devices. The World Health Organization's (WHO) definition of a clinical trial is listed as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.

Clinical trials can be broken down into five (5) types:

- *Prevention Clinical Trials* are proactive and look to explore better ways at preventing subjects from developing a specific medical condition or disease (primary prevention) or look to prevent a specific medical condition or disease from reoccurring (secondary prevention).
- *Screening Clinical Trials* are used to determine the most effective way in detecting certain medical conditions or diseases.
- *Diagnostic Clinical Trials* are utilized to find better-quality tests or procedures for diagnosing a particular medical condition or disease.
- *Treatment Clinical Trials* are used to test investigational and/or marketable drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes, as well as to test the effectiveness of new combinations of treatments.
- *Quality of Life Clinical Trials* are often used to seek out new ways to improve the comfort and quality of life for patient subjects with a chronic medical condition or disease.

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The Different Phases of a Clinical Trial?

Clinical trial phases can be best broken down into four simple questions: Is the treatment safe? Is the treatment effective? Is the new treatment more effective than existing treatments? Is there a better way to use this new treatment? The first three questions involve clinical trials that are investigational, meaning that the treatment has not been approved by any governing regulatory agencies for use in the general public: the treatment is only accessible to those subjects who are volunteering to participate in the clinical trial.

Phase 1 Clinical Trials: Is the treatment safe?

The first step in a clinical trial is to test the safety, dosage levels and response to a new treatment. Phase 1 clinical trials are often conducted in a small number of healthy volunteer subjects (20 to 100 individuals) for the first time to evaluate the safety of a treatment by identifying the best way to administer the treatment (i.e. by mouth, intravenous infusion or injection), to determine a safe dosage range (i.e. how much to administer, how often to administer), and to identify possible side effects across the dosage range. In the case of a clinical drug trial, the drug is examined to determine how it is absorbed, metabolized, and excreted, and in some cases obtain early evidence on the drug's effectiveness.

Phase 2 Clinical Trials: Is the treatment effective?

Once a treatment has been proven to be safe and well tolerated in healthy volunteer subjects, the next step is to test the treatment in patient subjects with specific medical conditions or diseases in which the treatment is expected to work. In addition to further testing the safety of the treatment in the patient population, Phase 2 clinical trials are also designed to evaluate the effectiveness of the treatment and to determine the correct dosage of treatment that will produce the least number of side effects with the most effective results. For that reason, Phase 2 trials are often called "dose-ranging studies". These clinical trials can last from a few weeks to a few months to a few years. These clinical trials, usually involving several hundred participants, are often designed as well controlled, randomized trials: meaning that one group of patient subjects receive the experimental treatment and the other group of patient subjects receive a control

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treatment which can consist of a standard treatment already used in this specific patient population or a placebo. Placement of a patient subject into the experimental or control treatment is by random chance (like a flip of a coin). Often Phase 2 clinical trials are double-blinded, meaning that both the patient subject and researcher (i.e. investigators and research staff) are unaware of which specific treatment group a patient subject has been assigned to. Typically only a small portion of Phase 1 and Phase 2 clinical trials are successful and eventually go onto a Phase 3 clinical trial.

Phase 3 Clinical Trials: Is the new treatment more effective than existing treatments?

Phase 3 clinical trials are mostly used to determine if a new treatment is more effective than the standard treatment options that currently are being utilized in a specific patient population by increasing the survival and quality of life of patient subjects and to reducing the side effects (fewer and milder) and possible risk of reoccurrence in patient subjects suffering from a specific medical condition or disease. In this type of clinical trial, the new treatment is tested in several hundred to several thousands of patient subjects with the medical condition or disease of interest. Most Phase 3 clinical trials continue to be randomized and double-blinded studies. This large-scale testing allows for a more thorough understanding of the treatment's effectiveness, associated benefits and risks, and range and severity of possible adverse side effects, thereby allowing governing regulatory agencies (i.e. Health Canada, United States' Food and Drug Administration) to determine if the treatment is marketable and should be allowed to be used in the general public.

Phase 4 Clinical Trials: Is there a better way to use this new treatment?

Phase 4, or more commonly known as "post-marketing surveillance studies", primarily examine the long-term efficacy, safety and toxicity of already approved marketed treatments that might not have been apparent during the testing of the Phase 3 clinical trial. The goal of these types of clinical trials is to get a better understanding of the treatment that has already been proven to work. Thousands of patient subjects usually participate in these types of clinical trials. A Phase 4 trial can also be used to show that a specific treatment is more effective if it's given for a longer period of time, or that a lower dose of the treatment works as well as a higher dose, but with fewer side effects.

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Source Documentation?

Source documentation serves a number of purposes: it substantiates the integrity of the clinical trial data, it confirms observations that are recorded during a clinical trial, and it confirms the existence of subjects who have participated in a clinical trial. It is important that source documents are standardized in order to ensure that results are captured and documented similar for all subjects participating a clinical trial. It is important that when participating in an industry-sponsored clinical trial, researchers keep their own personal source documents that are independent of the documents required to be completed by the industry (i.e. case reports forms).

Source documents are original documents, data, and records. Some examples include:

- hospital records;
- clinical and office charts;
- laboratory notes and results;
- memos or letters to physicians/specialists;
- subject diaries;
- evaluation checklists;
- drug dispensing records;
- recorded data from instruments or machines (i.e. ECG machine);
- copies or transcriptions certified after verification as being accurate and complete;
- microfiches, photographic negatives, microfilm or magnetic media;
- x-rays, CT scans, and MRI reports;
- subject files created during a clinical trial by researcher;
- other records kept at the clinic, pharmacy, laboratories, or other medical departments involved with a clinical trial.

Sample templates for source documents commonly used in clinical trials are attached:

- Concomitant Medications
- Non-Drug Treatments
- Non-Serious Adverse Events
- Serious Adverse Events
- Screening Visit

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Standard Operating Procedures (SOPs)?

Standard operating procedures (or SOPs for short) are official, detailed, written instructions for the management of clinical trials at your specific site. SOPs are required to ensure that clinical research is conducted in a manner that protects the rights and safety of human subjects participating in research, guards the integrity of the research data being collected, and adheres to all federal and provincial policies, laws, and regulations. Any deviation of a SOP during a clinical trial must be documented and justified for auditing and monitoring purposes. The Network of Networks (N²) is a national strategic initiative of the Canadian Institutes of Health Research (CIHR) and several partner organizations. It brings together multiple existing disease networks and other stakeholder with the objectives of enhancing Canada's clinical research capability and capacity, as well as translation of the results of this research into practice and policy. The Kingston General Hospital has adopted the N² SOPs for Clinical Research (see KGH policy 11-152: *Standard Operating Procedures for Clinical Research*).

Adverse Events and Reporting?

An adverse event (AE) is any change in a subject's health or physical status or any "side-effect" that occurs while participating in a clinical trial when the subject is receiving a treatment. Adverse events are monitored not only while a subject is receiving the treatment but also within a pre-specified period of time after their treatment has been terminated.

A serious adverse event (SAE) is any adverse event that causes death, disability, deformity, requires hospitalization, is life threatening or in the opinion of the researcher is considered "serious". All SAEs need to be reported to the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board, the industry sponsor and to the regulatory authorities *immediately*.

AE's and SAE's are usually categorized as expected (known already with the use of the treatment) or unexpected (not known) and a causality of the treatment is assessed (i.e. Is the treatment definitely responsible for the adverse event? Is the treatment possibly

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related to the adverse event? Is the treatment definitely not related to the adverse event?)

The Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board has its own *Adverse Events Policy and Reporting Guidelines* (<http://www.queensu.ca/ors/researchethics/REB.html>) for SAEs. Whenever a SAE occurs, an *Adverse Event Report Form* (<http://www.queensu.ca/ors/researchethics/REB.html>) needs to be completed. All known SAE's that occurred at your site and those that occurred at other sites participating in a multi-centre clinical trial that were reported by the industry sponsor to you need to be reported to the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.