PIP Digest

CCRA ACRC Canadian Cancer Research Alliance
Alliance canadienne pour la recherche sur le cancer

PIP PPP Patient Involvement in Cancer Research Program
Programme de Participation des Patients à la recherche sur le cancer

CLINICAL TRIALS: What is a Clinical Trial?

This PIP Digest will help you understand why clinical trials are conducted and how they help advance our knowledge of what works and what does not work in terms of reducing and treating cancer.

Key Concepts

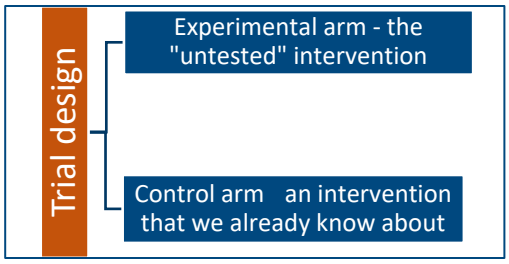
- Types and phases of clinical trials
- Role of the patient advocate

Related PIP Digests

- Clinical Trials: Finding a Clinical Trial
- Clinical Trials: Precision Medicine and Clinical Trials

A clinical trial is a research study that tests new interventions to prevent, detect, or treat disease or symptoms. Interventions might be new drugs or combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments. Clinical trials can also test other aspects of care — for example, ways to improve the quality of life after cancer treatment has been completed.

The most common kind of trial has two arms: an experimental arm, which involves testing the new or improved intervention, and a control arm, which involves the usual or standard care. (Rarely would a placebo or non-acting intervention be used in the case of cancer).



Participants are randomly assigned to a specific trial arm before the trial begins, which means that they do not know which arm they are assigned to. Randomization prevents bias. Bias is even better controlled when patients, investigators and evaluators are all unaware of which patients are assigned to which arm. (Note that there are some

trials where patient choice is built into the trial design. These are referred to as patient preference or two-step randomized trials.)[1]

Each trial has inclusion and exclusion criteria based on the characteristics and health status of participants, which can make them eligible or ineligible for the trial. A person may not be eligible if he or she has had previous treatments or has other health conditions. Age restrictions may also apply. These criteria are designed to reduce variables and ensure that researchers can interpret the results of the study and draw accurate conclusions about the interventions they are testing.

Before a clinical trial can begin, a research ethics board must approve the trial plan (also called a protocol). During the trial, review committees make sure that the plan is followed and that participants are protected. In addition, before a person decides to participate, they must be fully informed about the trial intervention, required tests, and all the known potential risks and benefits. This requirement is called **informed consent**.

"**Informed consent** is an on-going process that starts with the researcher's first contact with the individual and continues until the study is complete or the participant withdraws. Any discussion of informed consent with the participant, the written informed consent form and any other written information given to participants should provide adequate information for the participant to make an informed decision about his/her participation." For more information, see https://www.canada.ca/en/health-canada/services/science-research/science-advice-decision-making/research-ethics-board/consent-process.html

The potential benefits of clinical trial participation include:

- accessing new drugs or other interventions before they are widely available
- having health care delivered by leading clinician-researchers and being closely monitored for any side effects
- exercising more control over your healthcare
- contributing to cancer research

Potential risks include:

- receiving treatments that may be ineffective or less effective than current approaches
- experiencing side effects, some of which could be serious

A well-designed clinical trial is the gold standard for proving that a treatment or medical approach works. But clinical trials do have practical limitations. For example, researchers can't randomly assign people to live in different places or ask them to start smoking or eating an unhealthy diet.

[1]Walter SD et al. (2017). Estimation of patient preference effects in clinical trials when some participants are indifferent to treatment choice. *BMC Medical Research Methodology*, 17:29. https://link.springer.com/article/10.1186/s12874-017-0304-x

Types of Cancer Clinical Trials[2]

There are several types of cancer clinical trials, including treatment trials, prevention trials, screening trials, and supportive and palliative care trials. Each is designed to answer different research questions and help researchers learn new approaches to improving people's health outcomes and quality of life.

Treatment trials involve people who have cancer. They test new treatments or new uses or combinations of existing treatments, including drugs, immunotherapies, vaccines, surgery, and radiation therapy. These trials can explore many potential outcomes.

Many treatment trials require people to have their tumours tested for genetic changes at the outset to see if certain treatments might be more effective against specific mutations.

Treatment trials answers questions such as:

- What is a safe dose for a treatment?
- How should the treatment be given?
- Does the treatment help people with cancer live longer?
- Can the treatment shrink tumours, or prevent them from growing or spreading?
- What are the side effects of the treatment?
- Does the treatment allow a better quality of life with fewer side effects?
- Does the treatment help prevent the cancer from recurring once treatment is finished?

Cancer prevention trials involve healthy people. In most prevention trials, participants either do not have cancer but may be at high risk for developing the disease, or else they have had cancer and are at high risk for developing a new cancer. These studies look ways to reduce cancer risk.

There are two kinds of prevention trials:

- Action studies ("doing something"), which focus on finding out whether actions people take like increased exercise or eating more fruits and vegetables can prevent cancer.
- Agent studies ("taking something"), which focus on finding out whether taking certain medicines, vitamins, minerals, or dietary supplements (or a combination of them) may lower the risk of a certain type of cancer. These are also called "chemoprevention studies."

Researchers who conduct these studies want to know:

- How safe it is for a person to take an agent or engage in an activity?
- Does the new approach prevent cancer?

[2]Source: NIH Clinical Research Trials and You: The Basics at https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics.

- Does the new approach have unintended consequences?

Screening trials test new ways to find disease early when it may be more easily treated. An effective screening test reduces the number of deaths from the cancer being screened.

Researchers who conduct cancer screening studies want to know:

- Does finding disease earlier, before people exhibit symptoms, save lives?
- Are some screening tests better than others?
- Do people who receive the screening test undergo unnecessary follow-up tests and procedures?

Quality-of-life, supportive care, and palliative care trials test ways to improve the quality of life of cancer patients, especially those who have side effects from cancer and its treatment. They find new ways to help people cope with physical and psychological effects like pain, infections, fatigue, nausea, depression, cognitive issues, etc.

Trials might test drugs, such as those that help with depression or nausea, or they might test activities, such as attending support groups, exercising, or talking with a counselor. Some trials also test ways to help families and caregivers cope with their own needs.

Researchers who conduct these studies want to know:

- How does cancer and its treatment affect patients and their loved ones?
- What can mitigate side effects and improve the comfort and quality of life of people who have cancer?

Phases of Clinical Trials[3]

Clinical trials are usually conducted in phases that build on one another—especially when evaluating new drugs—and that answer different questions. Knowing the phase of a clinical trial tells you important information about how much is already known about the intervention and what you can expect to get out of participating.

Phase I: What is a safe dose?

Phase I studies of a new intervention are usually the first that involve people Usually involving between 20 and 80 people, phase I studies focus on determining the highest dose of a new intervention that is safe and without serious side effects. The intervention will already have been tested in lab and animal studies, but the side effects in people cannot always be predicted. These studies also help determine the best way to administer the new treatment. Phase I trials are sometimes referred to as "first-in-human" studies.

[3]Sources: American Cancer Society, What Are the Phases of Clinical Trials? https://www.cancer.org/treatment/treatments-and-side-effects/clinical-trials/what-you-need-to-know/phases-of-clinical-trials.html; Network of Networks (N2), It Starts With Me at http://itstartswithme.ca/; Canadian Cancer Society https://cancer.ca/en/treatments/clinical-trials/types-and-phases-of-clinical-trials.

Key points:

- The first few people in the study often get a very low dose of the treatment and are watched very closely. If they exhibit only minor side effects, the next few participants may get a higher dose. This process continues until researchers find a dose that is most effective while having an acceptable level of side effects.
- The focus is on what the intervention does to the body and how the body responds to the intervention.
- Safety is the main concern at this point as rare side effects may not be seen until later. These studies are not designed to find out if the new treatment works against cancer.
- Often, people with different types of cancer can take part in the same Phase I study.
- Overall, Phase I trials carry the greatest potential risk, but may also be helpful for some patients.

Phase II: Does the intervention work?

If a new treatment is found to be reasonably safe in Phase I clinical trials, it can then be tested in a Phase II clinical trial to find out if it does something to the cancer. Researchers look for different benefits or responses depending on the goal of the treatment. For instance, they may be trying to shrink the size of a tumour, eliminate a cancer, or extend the time to recurrence. In some studies, the benefit may be an improved quality of life. Many studies evaluate whether the new treatment allows people to live longer than they would have been otherwise expected.

Key points:

- Typically, 100 to 300 patients with the same type of cancer get the new treatment in a Phase II study. They are treated using the dose and method found to be the safest and most effective in Phase I studies.
- In a Phase II clinical trial, all the volunteers usually get the same dose. But some studies randomly assign participants to different treatment groups (much like what is done in Phase III trials). These groups may get different doses or be treated in different ways to see which provides the best balance of safety and effectiveness.
- Larger numbers of patients get the treatment in Phase II studies, making it more likely researchers will observe less common side effects. If enough patients benefit from the treatment, and the side effects are within acceptable limits, the treatment can proceed to Phase III.

Phase III: Is it better than what is already available?

Treatments that have been shown to work in Phase II studies usually must succeed in one more phase of testing before they are approved for general use. Phase III clinical trials compare the safety and effectiveness of the new treatment against current standard treatments.

A randomized controlled trial (RCT) is considered the most objective way to assess the outcome of an intervention. In the simplest case, a relevant population is identified, such as patients with a cancer that the drug is designed to treat. The population is divided by some impartial, randomizing method into intervention and control groups.

In a single blind experiment, subjects are unable to tell whether they are receiving the test intervention or the usual treatment. In a double-blind experiment, neither the subjects nor the persons administering the treatments know

which subjects are receiving the test intervention. In a triple blind experiment, the subjects, the persons administering the treatments, and the persons evaluating the results are all blinded. Triple blinding is considered the most objective way to conduct a study, although it is not always possible to achieve.

Key points:

- Most Phase III clinical trials have large numbers of patients, usually 100 to 3,000.
- These studies are often done in many places across the country (or even around the world) at the same time.
- These studies tend to last longer than Phase I and II studies.
- Placebos may be used in some Phase III studies when a standard of care is not available.
- As with other studies, patients in Phase III clinical trials are watched closely for side effects, and treatment is stopped if these side effects become unacceptable.

Phase IV: What happens long-term?

Even after testing a new intervention on thousands of people, the full effects of the treatment may not be known. For example, a drug may get approved because it was shown to reduce the risk of recurrence. But there could be rare side effects that did not emerge during trials, or common side effects that only manifest after long-term use. These types of issues may take many more years to understand. They are often addressed in Phase IV clinical trials, which are also known as post-marketing surveillance trials.

Key points:

- Phase IV studies look at the long-term safety of drugs that have already been approved. They may also look at other aspects of the treatment, such as quality of life or cost effectiveness.
- These studies may involve a very large population.
- This is typically the safest type of clinical trial because the treatment has already been well studied and may have already been used with many people.
- Because you can get the treatment used in a Phase IV trial without enrolling, participation in Phase IV trials is an altruistic endeavor that helps researchers learn more about the treatment for the benefit of future patients.

There are many differences between industry-led versus academic clinical trials. Foremost, industry trials are undertaken to meet the regulatory requirements for licensure or marketing of a new drug. This may be secondary or irrelevant in the case of academic clinical trials. Without academic trials, there would likely be no testing of different established drugs or combinations, behavioural interventions (like physical activity), dietary interventions, complementary approaches, and so on that are vital in terms of preventing cancer, preventing recurrence, and facilitating quality of life among cancer patients.

Outcome Measures

The effectiveness and safety of interventions in clinical trials are measured by endpoints or outcomes. These outcomes are ideally relevant to patients, improving their survival, quality of life, or other factors. Outcomes can also include laboratory measurements of biomarkers—biological molecules that may be found in the blood, other body fluids, or tissues that can indicate how well the body responds to an intervention.

The primary outcome measure represents the greatest benefit resulting from the intervention. Trials can sometimes have more than one primary endpoint if several measures demonstrate equal therapeutic value. Trials may also have several secondary endpoints, which assess therapeutic effects of secondary importance, side effects, and tolerability. Secondary endpoints help researchers interpret results for the primary outcome. In general, a trial with more endpoint measures requires more people to participate.

The primary and secondary outcomes for a trial must be declared when the trial is being planned. This requirement prevents researchers from cherry picking measures that show significant differences between treatment groups after the fact, helping to ensure the objectivity and credibility of the trial.

The table below shows the primary and secondary outcomes for an actual Canadian Phase I-II trial.

Trial: A Phase I-II Study of Stereotactic Body Radiation Therapy for Breast Cancer (SBRT Breast) NCT03585621
Primary Outcome: Acute toxicity: Incidence of side effects/toxicity associated with SBRT to the breast, during and in the three months following treatment using CTCAE v4.0. Time frame: 12 weeks post treatment.
Secondary Outcomes: • Breast Symptom Scores: Patient reported breast symptom scores for bleeding, discharge and odour measured on a scale from 1 (no symptoms) to 10 (worst possible/continuous symptoms) using the Visual Analogue Scale tool. Time frame: 2 years post treatment. • Patient Reported Quality of Life: Patient reported quality of life measured using the combined EORTC QLQ-C30 and QLQ-BR23 questionnaires, and VES13 questionnaire. Time frame: 2 years post treatment. • Patient Reported Pain Level: Patient reported pain levels measured using a standardized tool. Time frame: 2 years post treatment. • Tumour Response Rate: Measured on follow-up MRI or CT imaging using RECIST criteria. Time frame: 2 years post treatment.

Patient Advocacy in Cancer Clinical Trials

Beyond being involved in a clinical trial as a subject, as a patient partner, you can also play important advisory and advocacy roles, including:

- Bringing a sense of urgency to the research agenda and helping to accelerate trial start-up (for example, pushing to centralize processes like ethics reviews)
- Broadening diversity and patient eligibility criteria (for example, looking at ways to expand trials to pediatric patients)
- Identifying ways to facilitate trial access (for example, looking at how to reduce barriers to patients living in rural and remote locations who want to participate in a trial)
- Helping to ensure prospective subjects have reliable access to comprehensive, understandable, and timely information about Canadian trials.

- Ensuring that all patients are informed about relevant clinical trials and supported to access relevant trials.
- Advising on consent forms and the consent process so that patients truly understand the potential harms and benefits of participation, the scientific rationale for the trial, and their rights as patients.
- Helping to improve patient recruitment, adherence, and retention by providing input on trial protocols and identifying ways to better inform and support patients throughout the duration of the trial.
- Providing advice on relevant patient reported outcomes (PROs) and ensuring that the PROs are easy to use and understand, and that they are not burdensome.
- Helping to promote the results of the trial to the broader patient and health care community.

Use these videos to find out more about clinical trials:

- Demystifying Medicine (McMaster University). *Clinical Trials: It's not just a phase!* (YouTube) November 7, 2016 [4:11 minutes] https://www.youtube.com/watch?v=wcXbP-F_4K4
- Americans for Cures. *White Board: Clinical Trials 101* (YouTube) March 22, 2016 [4:56 minutes] https://www.youtube.com/watch?v=rrFA3lZAAuo
- Center for Information and Study on Clinical Research Participation (CISCRP). *The Impact Clinical Trials Have on All of Us.* (YouTube) May 3, 2018 [1:13 minutes] https://www.youtube.com/watch?v=sa6PswVuaDs

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