# What are clinical trials?

## Define in simple terms

* Clinical trials are research studies that look at new ways to prevent, find and treat cancer. They can help us understand cancer better or discover what works best for particular types of cancer or groups of people”
  + This is from the Canadian cancer society and the way they define what clinical trials seems like it targets the lay audience
  + <https://cancer.ca/en/treatments/clinical-trials>

## Why are they important?

* <https://www.nih.gov/health-information/nih-clinical-research-trials-you/why-should-i-participate-clinical-trial>
* Clinical trials are vital because they drive medical advancements by testing new ways to prevent, detect, and treat diseases.
* These trials may involve new drugs, drug combinations, surgical techniques, medical devices, or innovative uses of existing treatments.
* The primary goal of clinical trials is to ensure that new tests or treatments are effective and safe. They also explore ways to improve the quality of life for people with chronic illnesses.
* People participate in clinical trials for different reasons. Healthy volunteers often join to contribute to scientific progress and help others. Those with illnesses may participate to access the latest treatments and benefit from the extra care provided by trial staff.

## Where are they done

* [**https://cancer.ca/en/treatments/clinical-trials/understanding-the-clinical-trial-and-informed-consent#:~:text=A%20clinical%20trial%20usually%20takes,results%20will%20be%20scientifically%20accurate**](https://cancer.ca/en/treatments/clinical-trials/understanding-the-clinical-trial-and-informed-consent#:~:text=A%20clinical%20trial%20usually%20takes,results%20will%20be%20scientifically%20accurate)**.**
* [**https://www.cancer.gov/research/participate/clinical-trials/how-trials-work#:~:text=Cancer%20clinical%20trials%20take%20place%20in%20cities%20and%20towns%20across,Updated:%20November%208%2C%202024**](https://www.cancer.gov/research/participate/clinical-trials/how-trials-work#:~:text=Cancer%20clinical%20trials%20take%20place%20in%20cities%20and%20towns%20across,Updated:%20November%208%2C%202024)
* [**https://ised-isde.canada.ca/site/canadian-life-science-industries/en/biopharmaceuticals-and-pharmaceuticals/clinical-trials-environment-canada#**](https://ised-isde.canada.ca/site/canadian-life-science-industries/en/biopharmaceuticals-and-pharmaceuticals/clinical-trials-environment-canada)
* [**https://clinicaltrials.gov/study-basics/learn-about-studies**](https://clinicaltrials.gov/study-basics/learn-about-studies)
* **Hospitals and Medical Centers**
  + **Major Academic and Research Hospitals**: Many clinical trials take place at large hospitals affiliated with universities or research institutions (e.g., Toronto General Hospital, BC Children’s Hospital).
  + **Specialized Treatment Centers**: Some hospitals have dedicated clinical trial units for conditions like cancer, cardiology, or rare diseases.
* **University Research Institutions**
  + Many Canadian universities conduct clinical trials in collaboration with pharmaceutical companies and health agencies (e.g., McGill University Health Centre, University of Toronto).
  + These institutions often have dedicated clinical research units.
* **Private Clinics and Physician Offices**
  + Some clinical trials are run in private medical offices or specialized clinics, particularly for outpatient treatments such as dermatology, neurology, or endocrinology trials.
  + Physicians involved in clinical research may conduct smaller-scale studies in their own practices.

## An Example of Trials Specific to Brain Tumours

### **Phase 1**

### **Summary**

* **Title:** DSC-MRI With Ferumoxytol and DCE-MRI With Gadolinium in Imaging Vascular Properties in Younger Patients With Brain Tumors
* **ClinicalTrials.gov ID:** NCT00978562
* **Sponsor:** OHSU Knight Cancer Institute
* **Study Completion:** December 2018
* **Trial Phase**: Phase 1

### **Overview – What Was This Study About?**

This **Phase 1 clinical trial** tested a new way to **visualize blood vessels in brain tumors in children and young adults** using two different MRI contrast agents:

* **Ferumoxytol (iron-based contrast agent)**
* **Gadolinium (standard contrast agent used in MRIs)**

The goal was to see if **ferumoxytol** could provide **better images of brain tumors and their blood supply** than gadolinium, which is commonly used. Researchers hoped this could lead to **more accurate diagnosis and treatment planning** for pediatric brain tumors.

### **Why Was This Study Done?**

Brain tumors in children and young adults are challenging to diagnose and monitor. Doctors often use **MRI scans with contrast agents** to see the tumor and how much blood it receives (vascularity).

* **Gadolinium is the standard contrast agent**, but it does not always provide the clearest image of **blood vessels within tumors**.
* **Ferumoxytol, an iron-based agent, stays in the bloodstream longer** and may provide **better imaging of tumor blood supply**.
* This study tested whether using **both contrast agents in the same MRI session** could provide **more detailed and accurate images**.

### **What Happened in the Study?**

* **Participants:** 14 patients aged **5 to 18 years** with suspected or diagnosed brain tumors.
* **Study Design:**
  + Each patient received **both contrast agents** in the same MRI session.
  + First, **ferumoxytol was injected**, and a **DSC-MRI (Dynamic Susceptibility Contrast MRI)** was performed to measure **blood volume in the tumor**.
  + Then, **gadolinium was injected**, and a **DCE-MRI (Dynamic Contrast-Enhanced MRI)** was performed to measure **how "leaky" the blood vessels were** in the tumor.
  + Some patients underwent **up to four MRI scans over two years** to monitor changes in their tumors.

### **Key Findings**

* **Ferumoxytol Provided More Detailed Blood Vessel Imaging**
  + **Ferumoxytol-based MRI showed a clearer view of tumor blood supply** compared to gadolinium.
  + It helped **better differentiate tumors from normal brain tissue**.
* **Dual-Contrast MRI Provided More Comprehensive Information**
  + **Using both ferumoxytol and gadolinium together** gave **a more complete picture of tumor blood flow and vessel permeability**.
  + This could help doctors **better understand how aggressive a tumor is** and guide treatment choices.
* **Safe to Use, but Enrollment Was Low**
  + **Ferumoxytol was well tolerated**, with **no severe side effects** reported.
  + **However, the study had a small number of participants (14 total)**, which limited the ability to draw broad conclusions.
* **Potential for Improved Diagnosis and Treatment Planning**
  + The findings suggest that **ferumoxytol could improve brain tumor imaging**, but more research with **larger studies** is needed before it can become a standard practice.

This **Phase 1 trial successfully showed that ferumoxytol-enhanced MRI can provide clearer images of blood vessels in pediatric brain tumors**. If confirmed in larger studies, this approach could **improve diagnosis and treatment planning for children with brain cancer**

### **Phase 2**

### Summary:

* Title: Radiation Therapy in Treating Young Patients with Gliomas
* Sponsor: Children's Oncology Group
* ClinicalTrials.gov ID: NCT00238264
* Trial Phase: Phase 2

### Overview:

This clinical trial studied a specialized form of radiation therapy to treat young patients (ages 3 to 20) with gliomas. The goal was to test whether this targeted radiation therapy could effectively shrink tumors while causing less damage to healthy brain tissue.

### Why Was This Study Done?

Gliomas are brain tumors that can affect children and young adults. Standard radiation treatments can sometimes harm healthy brain tissue, leading to long-term side effects. This study tested a more precise form of radiation therapy to see if it could effectively treat the tumor while minimizing risks.

### What Happened in the Study?

* Patients received radiation therapy five days a week for six weeks.
* Researchers tracked:
  + How many patients had tumors that did not grow back (marginal-failure rate).
  + Survival rates—how long patients lived without the tumor returning.
  + Quality of life, including brain function, emotional well-being, and daily activities.
* Patients were monitored for several years after treatment to check for any tumor regrowth or health issues.

### Key Findings:

* The study successfully tested this specialized radiation therapy.
* Researchers collected important data on tumor control, survival, and quality of life.
  + **Tumor Control**: The study showed that the targeted radiation therapy **effectively controlled tumor growth** while minimizing damage to surrounding brain tissue.
  + **Survival Rates**: Patients demonstrated **promising survival rates**, including **progression-free survival and overall survival** improvements.
  + **Reduced Side Effects**: The specialized radiation method led to **lower toxicity and fewer long-term cognitive effects** compared to broader radiation techniques.
  + **Long-Term Monitoring**: Follow-ups over several years confirmed that the treatment remained effective while preserving the quality of life.
* This Phase 2 trial provided critical information on using a safer, more precise type of radiation therapy for young brain tumor patients. The goal was to improve treatment effectiveness while reducing side effects, giving children and young adults a better chance at a healthy future.

### Phase 3

### **Summary**

* **Title:** An Investigational Immuno-therapy Study of Temozolomide Plus Radiation Therapy With Nivolumab or Placebo for Newly Diagnosed Patients With Glioblastoma (GBM, a Malignant Brain Cancer) – CheckMate 548
* **ClinicalTrials.gov ID:** NCT02667587
* **Sponsor:** Bristol-Myers Squibb
* **Study Completion:** April 9, 2024
* **Trial Phase**: Phase 3

### **Overview – What Was This Study About?**

Glioblastoma (GBM) is the most aggressive and common type of brain cancer in adults. Standard treatment includes **surgery, radiation therapy (RT), and chemotherapy with temozolomide (TMZ)**. However, the cancer often comes back.

This **Phase 3 clinical trial** investigated whether adding **nivolumab (NIVO)**, an immunotherapy drug, to the standard treatment **would improve survival for patients with a specific type of glioblastoma** (those with an MGMT-methylated tumor, which makes them more responsive to chemotherapy).

### **Why Was This Study Done?**

Despite surgery, radiation, and chemotherapy, **nearly all glioblastoma patients experience a relapse**, and the average survival time is only about **12–15 months**.

* **Previous research suggested that immunotherapy drugs like nivolumab** (which boosts the body's immune system to attack cancer cells) could be effective in brain tumors.
* This study aimed to **see if nivolumab, when added to standard treatment, could extend survival** or delay cancer progression.
* Researchers focused on patients with **MGMT-methylated tumors**, which respond better to chemotherapy.

### **What Happened in the Study?**

* **Participants:** 716 newly diagnosed glioblastoma patients
* **Groups:**
  + **Nivolumab Group** → Received **radiation therapy + temozolomide + nivolumab (immune checkpoint inhibitor)**
  + **Placebo Group** → Received **radiation therapy + temozolomide + a placebo (inactive drug)**
* **Treatment Plan:**
  + **Radiation therapy** was given over **6 weeks**
  + **Temozolomide** was taken **daily during radiation, then in cycles**
  + **Nivolumab** was given **every 2 weeks for 8 doses, then every 4 weeks**
* **Main Study Goals:**
  + **Progression-Free Survival (PFS)** – How long patients lived before the cancer started growing again.
  + **Overall Survival (OS)** – How long patients lived after starting treatment.
  + **Side Effects and Safety** – Monitoring for adverse reactions.

### **Key Findings**

* **Nivolumab Did Not Improve Survival**
  + **Overall Survival (OS):**
    - **Nivolumab group:** 28.9 months
    - **Placebo group:** 32.1 months
    - **Conclusion:** Nivolumab did **not** help patients live longer.
  + **Progression-Free Survival (PFS):**
    - **Nivolumab group:** 10.6 months
    - **Placebo group:** 10.3 months
    - **Conclusion:** The cancer returned at nearly the same time in both groups.
* **Higher Side Effects in the Nivolumab Group**
  + **52.4%** of patients in the nivolumab group experienced **severe treatment-related side effects**, compared to **33.6%**in the placebo group.
* **No Unexpected Safety Issues**
  + While nivolumab **increased side effects**, there were **no unexpected safety concerns**.
* **Standard Treatment Remains the Best Option**
  + The study confirmed that **radiation + temozolomide remains the most effective treatment** for patients with MGMT-methylated glioblastoma.
  + Nivolumab **may still have potential** in future research, but it **did not improve survival in this study**​​​.

The study **did not show** that nivolumab improves survival in glioblastoma patients.Standard treatment (**radiation + temozolomide**) **remains the best option** for newly diagnosed glioblastoma patients with MGMT-methylation. **Nivolumab may still have potential** in combination with other treatments in future research.

While this trial **did not find a benefit** from adding nivolumab, it provided **important insights** into glioblastoma treatment. Researchers continue to look for new ways to improve survival for patients with this aggressive brain cancer​

### **Phase 4**

* **Title:** Multihance at 3 Tesla (3T) in Brain Tumors
* **ClinicalTrials.gov ID:** NCT00395863
* **Sponsor:** Bracco Diagnostics, Inc
* **Study Completion:** March 2008
* **Trial Phase**: Phase 4

### **Overview – What Was This Study About?**

This **Phase 4 clinical trial** tested **two different MRI contrast agents**—**Multihance (gadobenate dimeglumine)** and **Magnevist (gadopentetate dimeglumine)**—to see which one was better for **detecting brain tumors** using **MRI at 3 Tesla (3T)**.

Doctors use **MRI (Magnetic Resonance Imaging)** scans with contrast agents to **see brain tumors more clearly**. This study compared the effectiveness of the two contrast agents to determine which provided **sharper, more detailed images** of brain tumors, which can help doctors make better treatment decisions.

### **Why Was This Study Done?**

MRI contrast agents help **highlight brain tumors** by making them stand out from normal brain tissue. Multihance was believed to be **superior to Magnevist** due to its higher ability to enhance contrast, but this had not been proven in large clinical studies at **3 Tesla (3T) MRI machines**.

* The main goal was to **compare the quality of brain tumor images produced by the two agents** to determine:
  + **Which agent provided clearer images?**
  + **Which agent made tumors more visible?**
  + **Which agent was preferred by radiologists?**

### **What Happened in the Study?**

* **Participants:** 46 patients with suspected or confirmed brain tumors.
* **Study Design:**
  + Each patient received **both contrast agents** in separate MRI scans (crossover study).
  + The order in which they received the contrast agents was **randomized**.
* **MRI scans were performed at 3 Tesla (3T),** a high-power MRI machine that provides **high-resolution images**.
* **Three blinded radiologists** (who didn’t know which agent was used) compared the images to determine which contrast agent was better.

The images were evaluated for:

* **Global Preference** – Which contrast agent made the images clearer overall?
* **Lesion Border Delineation** – Which agent better defined the tumor edges?
* **Lesion Contrast Enhancement** – Which agent made tumors stand out more?
* **Lesion-to-Brain Ratio (LBR)** – How well tumors were distinguished from healthy brain tissue?
* **Contrast-to-Noise Ratio (CNR)** – How much contrast the agent provided against background noise?

### **Key Findings**

* **Multihance Provided Clearer Images**
  + Multihance was **preferred over Magnevist** by the radiologists in **more than half of the cases**.
  + Tumors appeared **brighter and more distinct** with Multihance.
* **Better Tumor Visibility and Border Definition**
  + Multihance provided **better delineation of tumor borders**, making it easier to see the exact tumor shape.
  + This helps doctors determine **tumor size and spread** more accurately.
* **Stronger Contrast Enhancement**
  + Tumors appeared more **enhanced** (brighter) in the images with Multihance.
  + Multihance **improved visibility by 45-50%** compared to Magnevist.
* **Improved Lesion-to-Brain and Contrast-to-Noise Ratios**
  + Multihance had a **higher lesion-to-brain ratio (LBR)**, meaning tumors stood out more clearly.
  + It also had a **higher contrast-to-noise ratio (CNR)**, meaning **less background noise** in the image.
* **Safe to Use**
  + Both contrast agents had **similar safety profiles**, with only minor side effects reported (e.g., mild nausea, headache).

This **Phase 4 trial confirmed that Multihance is superior to Magnevist** for **MRI scans of brain tumors** at 3T. It provided **clearer, more detailed images**, helping doctors diagnose and assess tumors more accurately.

For patients, this means that **using Multihance can lead to better tumor detection and treatment planning**, improving overall care for brain tumor patients​

# Types of clinical trials

* \*\*\* for this section the Canadian cancer society was a great resource that provided detailed information that was appropriate for lay audience to understand

Preamble: Clinical Trials are heterogeneous and can be divided into three main formats of organization; by purpose, methods, and phases.

## Types of Clinical Trials by Purpose

#### **1. Treatment Trials**

Treatment trials evaluate new therapies or seek to improve existing treatments for cancer. These trials may involve:

* **New drugs**: Investigating novel chemotherapy, immunotherapy, or targeted therapies.
* **Surgical methods**: Testing minimally invasive techniques or new approaches to tumor removal.
* **Radiation therapy**: Exploring different dosages, combinations, or delivery methods to enhance effectiveness while minimizing side effects.
* **Combination therapies**: Assessing how multiple treatments (e.g., chemotherapy + immunotherapy) work together to improve outcomes.

Since treatment trials directly involve cancer patients, they often require multiple phases of testing to confirm safety and effectiveness before new therapies become standard practice.

#### **2. Prevention Trials**

Prevention trials focus on reducing the risk of developing cancer or preventing cancer recurrence in individuals who have already been treated. These trials may study:

* **Medications (chemoprevention)**: Evaluating drugs or supplements that could lower cancer risk (e.g., aspirin for colorectal cancer prevention).
* **Lifestyle interventions**: Examining the impact of diet, exercise, or other behavioral changes in reducing cancer risk.
* **Vaccines**: Testing vaccines that may prevent cancer (e.g., HPV vaccine to prevent cervical cancer).
* **Genetic risk reduction strategies**: Investigating preventive measures for high-risk individuals, such as prophylactic surgery in people with BRCA gene mutations.

These trials often involve long-term follow-ups to determine their effectiveness in reducing cancer incidence.

#### **3. Screening Trials**

Screening trials aim to improve early detection of cancer in the general population, particularly in asymptomatic individuals. These trials investigate:

* **New screening tools**: Testing the accuracy of new imaging techniques (e.g., MRI vs. mammogram for breast cancer screening).
* **Blood or biomarker tests**: Assessing non-invasive tests that detect cancer earlier through biomarkers in blood, urine, or saliva.
* **Screening frequency and effectiveness**: Evaluating whether screenings should start earlier or be done more frequently for certain populations.

Successful screening trials can lead to new national screening guidelines that help detect cancer at earlier, more treatable stages.

#### **4. Diagnostic Trials**

Diagnostic trials seek to refine how cancer is identified and staged, ensuring more accurate diagnoses. These trials may test:

* **New imaging techniques**: Comparing PET, CT, or MRI scans to determine which provides the most precise cancer detection.
* **Advanced biopsy methods**: Investigating liquid biopsies (blood tests that detect tumor DNA) as a less invasive alternative to traditional biopsies.
* **Genetic and molecular testing**: Examining how tumor profiling can provide more precise diagnoses and guide personalized treatment plans.

A more accurate diagnosis allows doctors to select the most appropriate treatments, improving patient outcomes.

#### **5. Supportive Care Trials**

Supportive care (also called **palliative care**) trials explore ways to enhance the comfort, well-being, and quality of life for cancer patients and survivors. These trials study:

* **Pain and symptom management**: Testing new pain relief strategies or treatments for nausea, fatigue, or neuropathy caused by cancer treatment.
* **Mental health and emotional support**: Evaluating the effectiveness of psychological interventions, such as therapy, mindfulness, or peer support groups.
* **Rehabilitation and survivorship programs**: Assessing exercise, nutrition, or lifestyle interventions that help cancer survivors regain strength and reduce long-term treatment side effects.
* **Alternative and integrative therapies**: Investigating complementary treatments like acupuncture, massage therapy, or meditation for symptom relief.

These trials focus on improving day-to-day life for patients and helping survivors' transition back to normal activities after treatment.

## Types of Clinical Trials by Study Design or Methodology

#### **1. Randomized Controlled Trials (RCTs)**

RCTs are the **gold standard** for evaluating treatment efficacy and safety. Participants are randomly assigned to different groups to reduce bias and ensure reliable comparisons.

* **Intervention group** receives the new treatment.
* **Control group** may receive a placebo or standard treatment.
* Randomization ensures that external factors do not influence results, making the study more scientifically valid.

#### **2. Blinded Trials (Single-Blind, Double-Blind)**

Blinded trials reduce **bias** by keeping participants and/or researchers unaware of group assignments.

* **Single-blind**: Participants do not know whether they are receiving the treatment or placebo.
* **Double-blind**: Neither participants nor researchers know who is receiving the treatment, preventing unconscious influence on results.

#### **3. Crossover Trials**

In crossover trials, **each participant receives multiple treatments** in a specific sequence, allowing for direct comparisons within the same individual.

* Example: A patient receives Treatment A, followed by a washout period, then Treatment B.
* This design minimizes variability between individuals, requiring fewer participants to achieve statistically significant results.

#### **4. Adaptive Trials**

Adaptive trials allow researchers to **modify aspects of the study** based on interim results, improving efficiency and patient safety.

* Modifications may include **adjusting dosage, changing group assignments, or ending ineffective treatments early**.
* These trials accelerate drug development while maintaining scientific rigor.

#### **5. Observational Studies (Cohort, Case-Control, Cross-Sectional)**

Unlike interventional trials, **observational studies do not assign treatments** but analyze existing health data to identify trends and associations.

* **Cohort Studies**: Follow groups over time to examine risk factors and outcomes (e.g., tracking smokers vs. non-smokers for lung cancer rates).
* **Case-Control Studies**: Compare people with a disease to those without to identify potential causes (e.g., studying genetic links to cancer).
* **Cross-Sectional Studies**: Analyze health data at a single point in time to assess prevalence or correlations (e.g., survey on diet and heart disease).

Observational studies are essential for identifying risk factors and guiding future clinical research but cannot establish direct causation like RCTs.

## Phases of clinical trials + a detailed explanation of each phase

* <https://cancer.ca/en/treatments/clinical-trials/types-and-phases-of-clinical-trials>
* <https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-clinical-trials-are/phases-of-clinical-trials>
* <https://ctontario.ca/learn-about-trials/#:~:text=Why%20are%20clinical%20trials%20done,healthcare%20dollars%20should%20be%20allocated>.
* <https://www.imperialcrs.com/blog/clinical-trial-writing-and-design/drug-approval-process-four-clinical-research-phases/>
* **Preclinical Research**

Before testing a new treatment in humans, researchers perform preclinical studies in laboratories. These studies involve cells, tissues, and animal models to evaluate how the treatment functions and assess its potential safety. If the results are promising, the treatment advances to clinical trials in humans.

* **Phase 1 Trials**  
  These are the very first studies where a new treatment is tested in humans. The main goal of Phase 1 trials is to find out if the treatment is safe to use and to figure out the right dose to give to people. Since this is the first time the treatment is being used, researchers focus closely on safety and monitor participants for any side effects. Phase 1 trials are typically small, involving about 15 to 30 participants. They are often offered to people with advanced cancer that hasn’t responded to other treatments or who don’t have any other options left.
* **Phase 2 Trials**  
  Once a treatment passes Phase 1 and is shown to be safe, it moves on to Phase 2. Here, the focus is on seeing how well the treatment works for a specific type of cancer. Researchers still keep a close eye on safety and look for possible side effects, but the main question they’re asking is, "Does this treatment actually help people?" Phase 2 trials usually involve fewer than 100 participants, so they’re still relatively small but larger than Phase 1. Sometimes phase 2 studies are divided into phases 2a and 2b:

**2a (Proof of Concept):** Assess the drug’s mechanism of action and its effects on the body to demonstrate its effectiveness in individuals with the target disease. If the results do not indicate promising efficacy, additional testing will not proceed.

**2b (Dose-Response Studies):** Identify the optimal dosage(s) for use in subsequent research.

* **Phase 3 Trials**  
  If a treatment looks promising in Phase 2, it advances to Phase 3. This phase is much larger and involves comparing the new treatment to the standard treatment that is already being used for the condition. Researchers want to know if the new treatment is better – does it improve outcomes, help people live longer, or have fewer side effects compared to the usual approach? Phase 3 trials often involve hundreds or even thousands of participants, sometimes from countries around the world. These trials play a big role in deciding if a treatment should be approved for wider use. Sometimes, Phase 3 studies are divided into **3a and 3b**:

**3a (Pivotal Trials):** Evaluate the drug’s safety and effectiveness in a larger population, providing evidence to support the sponsor’s claims for regulatory approval. This phase occurs before the drug receives its first indication approval, confirming its safety and efficacy for the intended use.

**3b (Post-3a Studies):** Collect additional data on aspects such as real-world usage, effects on specific patient subgroups, long-term outcomes, and impact on quality of life. This phase begins after the first regulatory approval but before final marketing authorization and accurate labeling.

* **Phase 4 Trials**  
  Even after a treatment is approved and starts being used by the public, research doesn’t stop. Phase 4 trials are conducted to gather more long-term information about the treatment. Researchers look for any rare or delayed side effects and continue to assess its overall benefits. These studies are often large, involving hundreds or even thousands of participants, and help ensure the treatment remains safe and effective as it’s used in everyday healthcare settings.
* These phases work together to carefully study new treatments, making sure they are both safe and effective before they become widely available to patients.

## The journey of vorasidenib from preclinical research to public availability

### Drug Discovery (2007-2008)

* IDH1 mutations were first discovered around 2007-2008.
* A group of researchers analyzing genetic mutations in glioblastoma found that around 12% of glioblastomascarried an IDH1 mutation.
* Further studies found that 70% of lower-grade gliomas (grade 2 and 3) had either an IDH1 or IDH2 mutation.
* These tumors, which typically appeared in younger patients, had a better prognosis than IDH wild-type tumors.
* This discovery suggested that IDH mutations played a key role in tumor development and could be a potential drug target.

### Drug Development & Preclinical Testing

* IDH1 and IDH2 are enzymes involved in cellular metabolism. Mutant IDH1/2 produces 2-hydroxyglutarate (2HG), an "oncometabolite" that disrupts normal cell function and promotes tumor growth.
* Researchers sought to develop a drug that could block IDH1 and IDH2 mutations and stop the production of 2HG.
* The first two IDH inhibitors developed were:
  + Ivosidenib (AG-120) – IDH1 inhibitor
  + Enasidenib (AG-221) – IDH2 inhibitor
* However, scientists wanted a single drug that could target both IDH1 and IDH2 mutations effectively.
* After testing several modifications of the initial IDH inhibitors, researchers developed Vorasidenib (AG-881), a dual IDH1/IDH2 inhibitor.
* Mouse studies (orthotopic mouse models) showed that Vorasidenib:
  + Effectively entered the brain (important for brain tumors).
  + Lowered 2HG levels significantly in IDH-mutant gliomas.
  + Had a tolerable safety profile.
* With positive preclinical results, Vorasidenib moved to human clinical trials.

### Clinical Trials (Phase 1, Phase 2, and Phase 3 Trials)

A. Phase 1 Trials (Dose Finding Study)

* Goal: Find the maximum tolerated dose (MTD) and recommended Phase 2 dose.
* Small study (less than 30 patients) tested different doses:
  + Started at 25 mg once daily.
  + Gradually increased up to 300 mg daily.
  + Some patients experienced liver enzyme elevations, leading to adjustments.
  + 50 mg daily was chosen as the optimal dose.
* Results:
  + Drug was well tolerated.
  + Reached the brain effectively.
  + Reduced 2HG production in tumor tissue.

B. Phase 2 Trial (Pre-Surgery Window of Opportunity Study)

* Goal: Confirm Vorasidenib’s ability to penetrate the brain, reduce 2HG, and show clinical benefit.
* Patients with IDH1-mutant gliomas received Vorasidenib for one month before surgery.
* Tumor samples collected during surgery showed:
  + High drug concentration in brain tumors.
  + Significant reduction in 2HG levels.
* Some patients continued Vorasidenib after surgery to monitor long-term efficacy.
* Results:
  + Patients showed long-term tumor control.
  + Minimal side effects.

C. Phase 3 Trial – INDIGO Study

* Large-scale, randomized, placebo-controlled trial with 331 patients across multiple countries.
* Patients had IDH-mutant grade 2 gliomas with residual tumor after surgery, but no prior radiation or chemotherapy.
* Half received Vorasidenib, half received a placebo.
* Primary outcome: Progression-Free Survival (PFS).
* Key results:
  + Vorasidenib significantly extended progression-free survival:
    - 27.7 months vs. 11.1 months in the placebo group.
  + Patients on Vorasidenib delayed the need for chemotherapy and radiation.
  + Well-tolerated safety profile, with mild liver enzyme elevations being the most common side effect.
  + Time to next intervention (radiation or chemotherapy) was much longer in the Vorasidenib group.
* Outcome: The strong positive results led to FDA approval consideration.

### FDA Drug Review & Approval (2024)

* New Drug Application (NDA) submitted to the FDA.
* The FDA reviewed:
  + Preclinical data, clinical trial results, safety profile, and effectiveness.
  + Inspected clinical trial sites for accuracy and compliance.
* Final Decision:
  + Vorasidenib was approved in 2024 for adult and pediatric patients (12+ years old) with grade 2 IDH1/IDH2-mutant gliomas.
  + Recommended Dose: 40 mg (equivalent to previous 50 mg formulation), once daily.

### Postmarket Monitoring

* Even after approval, the FDA continues monitoring the drug for any long-term side effects or safety issues.
* Patients and doctors can report side effects via the MedWatch system.
* The Sentinel Initiative tracks data from electronic health records to detect potential issues.
* Ongoing research into combination therapies:
  + Vorasidenib + immunotherapy (e.g., pembrolizumab).
  + Vorasidenib for more aggressive tumors (IDH-mutant glioblastomas).

### Summary

* Vorasidenib (Vorasidnib) is a groundbreaking drug that offers longer tumor control and delays aggressive treatments in IDH-mutant grade 2 gliomas.
* The approval process took nearly 15+ years from IDH mutation discovery to FDA approval.
* Future research aims to explore:
  + Combination therapies (e.g., Vorasidenib + immunotherapy).
  + Use in more aggressive gliomas.

## Other types of trials\*\*\* (section revised above)

* <https://cancer.ca/en/treatments/clinical-trials/types-and-phases-of-clinical-trials>
* The information below is directly from the Canadian cancer society
* **Treatment trials** test new treatments or ways to make existing ones better. Maybe it’s new drugs or methods of surgery and radiation. This is the most common type of clinical trial involving people with cancer.
* **Prevention trials** look at new ways to lower the risk of getting cancer or stop it from coming back.
* **Screening trials** look for ways to find cancer early in populations of people, before they have any symptoms.
* **Diagnostic trials** look for better ways to diagnose or stage cancer.
* **Supportive care trials** study how to improve comfort and quality of life for people with cancer or cancer survivors.

## What is randomization

* <https://cancer.ca/en/treatments/clinical-trials/types-and-phases-of-clinical-trials>
* Clinical trials often involve different groups of participants. Most trials have two main groups, but sometimes there are more.
  + **Placebo group**: This group does not receive the treatment being studied but instead receives the standard of care or a neutral substitute to compare outcomes.
  + **Experimental group**: This group receives the treatment being studied.
* To make the comparison between groups fair, participants are randomly assigned to a group using a computer.
* This process is called **randomization**, and everyone has an equal chance of being placed in either group.
* There are two types of randomization:
  + **Blinded randomization**:
    - The researchers know which participants are in each group.
    - However, the participants themselves do not know which group they are in.
    - This helps prevent participants from doing things that could unintentionally affect the study results.
  + **Double-blinded randomization**:
  + Neither the researchers nor the participants know which group the participants are in.
  + This design is considered the most reliable because it minimizes bias, ensuring that neither the participants’ actions nor the researchers’ expectations influence the results.

# Eligibility

## Who can participate in clinical trials?

* Participation in clinical trials is open to individuals who meet specific eligibility criteria, which are carefully defined to ensure participant safety and the integrity of the study results.
* Eligibility criteria vary depending on the trial's goals and the condition being studied. These criteria help researchers ensure that the results are scientifically valid and that participants are not put at undue risk. Common factors that determine eligibility include:
* <https://www.nhlbi.nih.gov/research/clinical-trials/participating#:~:text=Eligibility%20criteria%20are%20different%20for,you%20have%20other%20health%20problems>.
* [https://www.kidney.org/kidney-topics/who-can-participate-clinical-trial#:~:text=This%20is%20called%20“eligibility.”,such%20your%20gender%20or%20age](https://www.kidney.org/kidney-topics/who-can-participate-clinical-trial#:~:text=This%20is%20called%20).
* [https://www.abbvieclinicaltrials.com/resources/what-are-eligibility-criteria-clinical-trials/#](https://www.abbvieclinicaltrials.com/resources/what-are-eligibility-criteria-clinical-trials/)
* **Medical Condition** – Participants must have the specific disease or condition being studied (e.g., cancer, diabetes, heart disease).
* **Age & Sex** – Some trials may be open to all adults, while others are designed for specific age groups (e.g., pediatric, elderly) or a particular sex.
* **Health Status** – Trials may require participants to be in a certain stage of the disease, have specific biomarkers, or meet general health requirements.
* **Previous Treatments** – Some studies require participants to have already tried standard treatments, while others look for treatment-naïve individuals.
* **Medication Use** – Eligibility may depend on whether participants are currently taking specific medications that could interact with the treatment being tested.
* **Lifestyle Factors** – Some studies may exclude participants based on lifestyle choices such as smoking, alcohol use, or physical activity levels.
* **Genetic Factors** – Some trials focus on individuals with specific genetic markers or hereditary conditions.

## How are patients selected for participation?

* <https://clinicaltrials.gov/study-basics/learn-about-studies>
* <https://nashbio.com/blog/clinical-trials/understanding-patient-selection-in-clinical-trials-considerations-and-implications/>
* <https://www.nia.nih.gov/health/clinical-trials-and-studies/what-are-clinical-trials-and-studies#:~:text=After%20you%20consent%20to%20participate,will%20be%20excluded%20from%20another.&text=If%20playback%20doesn%27t%20begin%20shortly%2C%20try%20restarting%20your%20device>.
* **Pre-Screening**
  + Researchers review applications or referrals to determine if the individual meets the basic eligibility criteria.
* **Informed Consent**
  + Potential participants receive detailed information about the study, including risks, benefits, procedures, and their rights. They must provide written consent before proceeding.
* **Screening and Baseline Assessments**
  + More in-depth medical evaluations, including blood tests, imaging, or genetic screening, are conducted to confirm eligibility.
* **Randomization (if applicable)**
  + In randomized trials, eligible participants may be randomly assigned to different study groups (e.g., treatment vs. placebo).
* **Ongoing Monitoring**
  + Even after enrollment, participants are continuously monitored to ensure they remain eligible and do not experience severe adverse effects that would require withdrawal.

## A note on trials for the pediatric population

* [https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/pediatrics.html#](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/pediatrics.html)
* <https://www.who.int/clinical-trials-registry-platform/clinical-trials-in-children#:~:text=Why%20perform%20clinical%20trials%20in,the%20best%20medical%20treatment%20available>.
* <https://www.pfizerclinicaltrials.com/our-research/pediatric-clinical-trials#:~:text=Pediatric%20clinical%20trials%20and%20safety,child%20have%20about%20the%20study>.
* Importance of Pediatric Clinical Trials
  + Children have unique developmental and physiological needs that differ from adults, making it essential to conduct pediatric clinical trials rather than relying solely on adult studies. These trials help identify the safest and most effective medical treatments specifically for children.
* Conducting Pediatric Clinical Trials
  + Pediatric clinical trials follow the same fundamental process as adult trials but include special considerations for children. They are regulated by authorities like the U.S. FDA and monitored by institutional review boards or independent ethics committees. Additionally, they require informed consent from both the child (when appropriate) and their parents or guardians.
* Key Aspects of Pediatric Clinical Trials
  + Determining the appropriate medication dosage for children
  + Developing liquid formulations to improve ease of administration
  + Evaluating new treatments or therapies
  + Optimizing dosages and delivery methods for pediatric patients

# Why consider a clinical trial

## Potential benefits

* Clinical trials play a crucial role in advancing healthcare by testing how safe and effective new medical treatments are. They also give participants the opportunity to learn more about their condition and take an active role in their own healthcare journey.
* <https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/understanding-the-benefits-of-clinical-trials-for-cancer>
* <https://cancer.ca/en/treatments/clinical-trials/clinical-trial-benefits-risks-and-costs>

## Benefits for Participants

* **Access to new treatments**: By participating in clinical trials, individuals may gain early access to innovative and advanced treatments that are not yet available to the general public. These treatments could potentially provide better results than existing standard options.
  + <https://www.kidneyfund.org/treatments/clinical-trials/advantages-and-disadvantages-participating-clinical-trials#:~:text=Possible%20benefits%20to%20participants:,your%20disease%20or%20health%20condition>
  + [https://www.pancreaticcancer.org.uk/information/clinical-trials/advantages-and-disadvantages-of-clinical-trials/#:~:text=Possible%20advantages%20of%20clinical%20trials%20\*%20You,reassuring%20and%20may%20identify%20any%20problems%20early](https://www.pancreaticcancer.org.uk/information/clinical-trials/advantages-and-disadvantages-of-clinical-trials/#:~:text=Possible%20advantages%20of%20clinical%20trials%20*%20You,reassuring%20and%20may%20identify%20any%20problems%20early).
* **Potential for fewer side effects**: Many new treatments are designed to improve upon existing therapies, which may mean fewer or milder side effects. Participants have the opportunity to benefit from these advancements while helping researchers understand how the treatment impacts patients.
  + [https://www.pancreaticcancer.org.uk/information/clinical-trials/advantages-and-disadvantages-of-clinical-trials/#:~:text=Possible%20advantages%20of%20clinical%20trials%20\*%20You,reassuring%20and%20may%20identify%20any%20problems%20early](https://www.pancreaticcancer.org.uk/information/clinical-trials/advantages-and-disadvantages-of-clinical-trials/#:~:text=Possible%20advantages%20of%20clinical%20trials%20*%20You,reassuring%20and%20may%20identify%20any%20problems%20early).
* **Frequent health monitoring**: Participants in clinical trials often receive more frequent tests, check-ups, and detailed monitoring of their health. This close observation helps identify any health issues early and ensures that participants are supported throughout the process.
  + [https://www.pancreaticcancer.org.uk/information/clinical-trials/advantages-and-disadvantages-of-clinical-trials/#:~:text=Possible%20advantages%20of%20clinical%20trials%20\*%20You,reassuring%20and%20may%20identify%20any%20problems%20early](https://www.pancreaticcancer.org.uk/information/clinical-trials/advantages-and-disadvantages-of-clinical-trials/#:~:text=Possible%20advantages%20of%20clinical%20trials%20*%20You,reassuring%20and%20may%20identify%20any%20problems%20early).
* **Greater understanding of their condition**: Being part of a clinical trial allows participants to learn more about their specific condition, including its causes, progression, and ways to manage or even prevent it. This knowledge can empower them to make more informed decisions about their health.
  + <https://www.nia.nih.gov/health/clinical-trials-and-studies/clinical-research-benefits-risks-and-safety#:~:text=There%20are%20many%20possible%20benefits,active%20role%20in%20your%20health>.
* **Active role in healthcare**: Many participants feel a sense of purpose and involvement by contributing to medical research. Being part of a clinical trial allows individuals to take an active role in improving their own care while potentially helping others who face similar health challenges.
  + <https://www.nia.nih.gov/health/clinical-trials-and-studies/clinical-research-benefits-risks-and-safety#:~:text=There%20are%20many%20possible%20benefits,active%20role%20in%20your%20health>.

## Benefits for Society

* **Development of better treatments**: Clinical trials are critical in identifying new therapies that are more effective or safer than current treatments. These findings lead to improved options for patients, helping to advance overall medical care.
  + https://www.clinicaltrials.astellas.com/why-is-clinical-research-important/#
* **Advancing medical knowledge**: Each clinical trial contributes valuable data to the scientific community. This knowledge helps researchers better understand diseases, their treatments, and the human body, paving the way for future discoveries and medical advancements.
  + <https://www.australianclinicaltrials.gov.au/participants/what-you-should-know#:~:text=Clinical%20trials%20are%20essential%20for,with%20the%20disease%20or%20condition>.
* **Improving health and well-being**: The results of clinical trials directly impact public health by providing more effective and targeted treatments. These advancements lead to better health outcomes and an improved quality of life for people worldwide.
  + <https://ctontario.ca/learn-about-trials/#:~:text=Why%20are%20clinical%20trials%20done,healthcare%20dollars%20should%20be%20allocated>.
* **Accelerating availability of new treatments**: When more people participate in clinical trials, it speeds up the research and approval process, making new and effective treatments available to the public faster. This can be especially important for conditions where current options are limited or ineffective.
  + <https://www.australianclinicaltrials.gov.au/participants/what-you-should-know#:~:text=Clinical%20trials%20are%20essential%20for,with%20the%20disease%20or%20condition>.

## Potential Risks of Clinical Trials

* While clinical trials are essential for medical advancements, they also come with certain risks. These risks vary depending on the trial, the type of treatment being tested, and an individual’s health condition.
* **Side Effects and Health Risks**
  + **Serious or life-threatening side effects** – Since new treatments are still being studied, there may be unexpected or severe reactions, some of which could be harmful.
    - <https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics#:~:text=other%20health%20professionals.-,Risks,stays%2C%20or%20complex%20dosage%20schedules>.
  + **Worse side effects than standard treatments** – The new treatment may cause more intense or difficult-to-manage side effects compared to current treatment options.
    - <https://cancer.ca/en/treatments/clinical-trials/clinical-trial-benefits-risks-and-costs>
  + **Treatment may not work** – There is no guarantee that the experimental treatment will be effective for all participants. Some people may see improvement, while others may not benefit at all.
    - <https://cancer.ca/en/treatments/clinical-trials/clinical-trial-benefits-risks-and-costs>
* **Increased Medical Visits and Time Commitment**
  + **More frequent doctor visits and testing** – Clinical trials require careful monitoring, which may involve regular blood tests, scans, or other medical procedures.
    - <https://www.cancer.gov/research/participate/clinical-trials/why-participate#:~:text=have%20any%20treatment?-,Possible%20risks%20and%20benefits%20of%20joining%20a%20clinical%20trial,%2C%20housing%2C%20and%20childcare%20costs>.
  + **Possible hospital stays** – Some trials require hospitalization for observation, which can be inconvenient and time-consuming.
    - <https://www.cancer.gov/research/participate/clinical-trials/why-participate#:~:text=have%20any%20treatment?-,Possible%20risks%20and%20benefits%20of%20joining%20a%20clinical%20trial,%2C%20housing%2C%20and%20childcare%20costs>.
  + **Strict dosage schedules** – Participants may have to follow complex medication schedules, which can be difficult to maintain.
    - <https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics#:~:text=other%20health%20professionals.-,Risks,stays%2C%20or%20complex%20dosage%20schedules>.
  + **Time-consuming participation** – Attending frequent appointments, keeping health records, and following trial protocols may require a significant time commitment.
    - <https://cancer.ca/en/treatments/clinical-trials/clinical-trial-benefits-risks-and-costs>
* **Unforeseen Risks**
  + - [**https://www.roswellpark.org/clinical-trials/risks-benefits**](https://www.roswellpark.org/clinical-trials/risks-benefits)
  + **Unknown long-term effects** – Because the treatment is still in the experimental phase, researchers may not yet know about potential long-term health risks.
  + **Unexpected complications** – Some participants may react differently to the treatment, leading to unforeseen health issues.
* **Financial and Logistical Challenges**
  + - <https://www.nhlbi.nih.gov/research/clinical-trials/safety-benefits-risks>
  + **Travel and accommodation costs** – If the trial is conducted far from home, participants may need to cover expenses for travel, lodging, or food.
  + **Childcare and work disruptions** – Time spent participating in the trial may interfere with work, childcare, or daily responsibilities.
  + **Additional healthcare costs** – While some trials cover medical expenses, others may not fully cover treatments, tests, or hospital stays.
* **Psychological and Emotional Challenges**
  + - <https://www.nhlbi.nih.gov/research/clinical-trials/safety-benefits-risks>
  + **Uncertainty about treatment outcomes** – The uncertainty of whether the treatment will work can cause anxiety or stress.
  + **Emotional strain** – Dealing with side effects, frequent medical visits, or the possibility of treatment failure can be mentally and emotionally exhausting.
  + **Receiving a placebo** – In some studies, participants may be given a placebo (a treatment with no active medication), meaning they may not receive any actual treatment.
* **Ethical and Personal Concerns**
  + - [**https://www.cancer.org/cancer/managing-cancer/making-treatment-decisions/clinical-trials/what-you-need-to-know/who-does-clinical-trials.html**](https://www.cancer.org/cancer/managing-cancer/making-treatment-decisions/clinical-trials/what-you-need-to-know/who-does-clinical-trials.html)
  + **Withdrawal from standard treatments** – Some trials may require participants to stop their current treatment, which could lead to worsening symptoms if the new treatment is ineffective.
  + **Potential conflicts of interest** – Some clinical trials may be funded by pharmaceutical companies, leading to concerns about bias in research findings.
* **Risk of Dropping Out**
  + **Difficulty maintaining trial requirements** – Some participants may struggle to follow strict protocols, leading to them dropping out of the study.
  + **Health changes during the trial** – If a participant’s condition worsens, they may need to withdraw from the study, which could impact their treatment plan.

## Ways to Reduce Risks in Clinical Trials

* <https://pmc.ncbi.nlm.nih.gov/articles/PMC3943957/>
* <https://ohrpp.research.ucla.edu/assessing-risks/#:~:text=Risks%20to%20subjects%20are%20minimized%20by%20using,the%20subjects%20for%20diagnostic%20or%20treatment%20purposes>.
* <https://www.australianclinicaltrials.gov.au/participants/what-you-should-know#:~:text=Potential%20risks&text=Some%20possible%20risks%20of%20taking,even%20life%2Dthreatening%20side%20effects>
* <https://pmc.ncbi.nlm.nih.gov/articles/PMC8498219/#:~:text=Risk%20Identification%20Process.%20The%20quality%20feature%20of,is%20how%20to%20define%20a%20certain%20risk>.
* <https://pmc.ncbi.nlm.nih.gov/articles/PMC9829217/#:~:text=A%20risk%20assessment%20can%20help%20determine%20which,on%20inclusion%20and%20diversity%20during%20trial%20enrollment>.
* Choose the Right Trial for You
  + Consult with your doctor – Talk to your healthcare provider before joining a clinical trial to understand if it is the right choice based on your medical history and condition.
  + Research the trial – Learn as much as possible about the study, including its purpose, the treatment being tested, and past research results.
  + Understand your options – Compare the trial treatment with standard treatments to see if it offers potential advantages or if the risks outweigh the benefits.
* Understand the Risks and Benefits
  + Read the informed consent document carefully – This document explains the potential risks, benefits, and expectations of the study. Don’t hesitate to ask questions before signing.
  + Clarify any uncertainties – If you’re unsure about any part of the study, ask the research team for explanations. You have the right to fully understand what you’re signing up for.
  + Know your rights – You can leave the trial at any time if you feel uncomfortable or if the risks become too high.
* Ensure Proper Medical Supervision
  + Choose a reputable research center – Opt for a clinical trial conducted by a trusted medical institution or hospital to ensure high safety standards.
  + Stay in close contact with the research team – Regular check-ins with doctors and researchers can help catch and address any side effects early.
  + Follow all safety guidelines – Adhering to the trial’s instructions, such as dosage schedules and dietary restrictions, can help reduce risks.
* Monitor Your Health Closely
  + Report side effects immediately – Inform the research team about any unusual symptoms, discomfort, or changes in your health as soon as they occur.
  + Keep a personal health journal – Tracking symptoms, side effects, and how you feel throughout the trial can help detect problems early.
  + Have a support system – Keep family members or friends informed about your participation in the trial so they can support you and help monitor any health concerns.
* Minimize Financial and Logistical Struggles
  + Ask about cost coverage – Some trials provide financial support for travel, accommodation, and medical expenses. Clarify these details before enrolling.
  + Plan for time commitments – Be aware of the required visits, tests, and procedures, and plan accordingly to reduce stress.
  + Check for alternative trials – If a study seems too demanding, look for other trials with similar treatments but fewer logistical challenges.
* Be Prepared for Unexpected Outcomes
  + Understand that the treatment may not work – Be mentally prepared for the possibility that the experimental treatment may not be effective or may have side effects.
  + Know your exit options – If you experience severe side effects or feel the risks are too high, you can withdraw from the trial at any time without penalty.

# Patient safety and rights

* Informed consent: detailed explanation of what it is and why it matters, note that consent is an ongoing process, right to withdraw at any time
* <https://www.cancer.org/cancer/managing-cancer/making-treatment-decisions/informed-consent/clinical-trial-consent.html>
* <https://pmc.ncbi.nlm.nih.gov/articles/PMC5980471/#:~:text=Informed%20consent%20is%20a%20procedure,participate%20in%20a%20clinical%20trial>.
* <https://www.cancer.gov/research/participate/clinical-trials/safety#:~:text=Informed%20Consent%20in%20Clinical%20Trials,-Patient%20Safety%20in&text=Informed%20consent%20is%20an%20essential,research%20team%20will%20inform%20you>.
* <https://cancer.ca/en/treatments/clinical-trials/understanding-the-clinical-trial-and-informed-consent>
* <https://www.canada.ca/en/health-canada/services/science-research/science-advice-decision-making/research-ethics-board/consent-process.html>
* <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html#:~:text=The%20informed%20consent%20process%20is,study)%20and%20continuing%20until%20the>

## ****What is Informed Consent?****

Informed consent is a fundamental ethical and legal requirement in clinical trials. It is the process by which potential participants receive comprehensive information about a study, enabling them to make a voluntary and informed decision about whether to participate. The goal is to ensure that individuals understand the risks, benefits, procedures, and their rights before enrolling in the trial.

Informed consent is not just about signing a document; it is an **ongoing process** that continues throughout the participant's involvement in the trial.

## ****Key Components of Informed Consent****

* **Study Purpose and Objectives**
  + Participants must be informed about the purpose of the trial, the medical condition being studied, and the goals of the research.
* **Study Procedures**
  + A clear explanation of what participation involves, including medical tests, treatments, frequency of visits, and any lifestyle changes required.
* **Potential Risks and Benefits**
  + Participants must be made aware of all known risks (e.g., side effects, complications) and any potential benefits (e.g., improved condition, contribution to scientific knowledge).
* **Alternative Treatment Options**
  + If standard treatments exist for the condition being studied, participants must be informed about these options and how they compare to the trial.
* **Confidentiality and Data Protection**
  + Information on how personal and medical data will be collected, stored, and used in compliance with privacy regulations (e.g., HIPAA in the U.S., PIPEDA in Canada).
* **Compensation and Costs**
  + If applicable, details on compensation for participation, reimbursement for expenses (e.g., travel, accommodation), and whether any medical costs are covered.
* **Right to Ask Questions**
  + Participants are encouraged to ask questions before and during the trial, ensuring they fully understand their involvement.
* **Voluntary Participation and Right to Withdraw**
  + Participation is completely voluntary, and individuals have the right to withdraw from the study **at any time** without penalty or loss of standard medical care.
* **Informed Consent as an Ongoing Process**
  + Informed consent is **not a one-time event** but a continuous dialogue between researchers and participants. This includes:
  + **Re-consenting** if there are changes to the study (e.g., new risks discovered, changes in treatment protocol).
  + **Ongoing communication** to ensure participants understand what is happening at each stage of the trial.
  + **Reaffirming voluntary participation** throughout the study.
  + Researchers must **regularly check in** with participants to confirm their willingness to continue, answer questions, and provide any new information that may affect their decision.
* **Right to Withdraw at Any Time**
  + Participants in a clinical trial have the **absolute right** to withdraw for any reason, at any stage, without facing negative consequences. Reasons for withdrawal may include:
  + Personal discomfort with procedures or side effects.
  + Change in health status.
  + Desire to pursue another treatment option.
  + Any other personal or medical reasons.
  + If a participant withdraws, researchers may ask for permission to continue collecting follow-up data for safety monitoring, but participants can refuse. Their withdrawal does **not affect their standard medical care**.

## ****Why Informed Consent Matters****

* **Protects Participants' Rights** – Ensures individuals are treated with respect and autonomy.
* **Enhances Ethical Research** – Upholds principles of medical ethics, including autonomy, beneficence, and justice.
* **Promotes Transparency** – Provides clear, honest information about the study.
* **Builds Trust in Medical Research** – Encourages ethical participation in clinical trials.

## The role of IRBs and data safety

* Institutional Review Boards (IRBs) play a critical role in safeguarding the rights, safety, and well-being of participants in clinical trials. They provide ethical oversight, ensure regulatory compliance, and monitor data safety both during and after the study.
* <https://www.fda.gov/about-fda/cder-offices-and-divisions/institutional-review-boards-irbs-and-protection-human-subjects-clinical-trials#:~:text=Under%20FDA%20regulations%2C%20an%20Institutional,who%20are%20subjects%20of%20research>.
* <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/institutional-review-boards-frequently-asked-questions#:~:text=The%20fundamental%20purpose%20of%20IRB,has%20complied%20with%20applicable%20regulations>.
* <https://pmc.ncbi.nlm.nih.gov/articles/PMC4631034/#:~:text=Institutional%20review%20boards%20(IRBs)%20or%20research%20ethics,ethical%20acceptability%20of%20proposals%20for%20human%20research.&text=IRBs%20are%20charged%20with%20providing%20an%20independent,and%20laws%20designed%20to%20protect%20human%20subjects>.
* <https://www.nia.nih.gov/health/clinical-trials-and-studies/clinical-research-benefits-risks-and-safety>
* <https://research.oregonstate.edu/ori/irb/what-institutional-review-board-irb#:~:text=Protection%20Prog...-,What%20is%20the%20Institutional%20Review%20Board%20(IRB)?,periodically%20involved%20in%20protocol%20review>.
* <https://pmc.ncbi.nlm.nih.gov/articles/PMC3272525/#:~:text=The%20IRB%20must%20review%20the,each%20potential%20subject%20or%20a>
* <https://www.wcgclinical.com/insights/the-role-of-irbs-in-research-oversight-information-for-potential-participants-in-clinical-research/#:~:text=Plays%20a%20key%20support%20role,understandable%20information%20to%20research%20participants>.
* <https://www.advarra.com/blog/beginners-guide-to-institutional-review-boards/#:~:text=While%20most%20of%20the%20heavy,opportunity%20to%20exit%20the%20trial>.
* **Key Responsibilities of IRBs**
  + **Ethical Review**
    - Evaluating the research proposal to determine if it adheres to ethical principles such as those outlined in the **Belmont Report** (respect for persons, beneficence, and justice).
    - Ensuring compliance with **federal regulations** like the Common Rule, FDA regulations, and **Good Clinical Practice (GCP)** standards.
  + **Risk Assessment**
    - Analyzing **potential risks and benefits** to participants.
    - Ensuring that risks are minimized and **justified by the study's potential benefits**.
    - Recommending study modifications to improve participant safety when necessary.
  + **Informed Consent Process**
    - Reviewing and approving the **informed consent document** to ensure clarity and transparency.
    - Ensuring participants fully understand study details, potential risks and benefits, and their **right to withdraw at any time**.
  + **Study Design Oversight**
    - Examining research methodology, including:
    - **Participant selection criteria** to ensure fairness and inclusivity.
    - **Data collection procedures** to maintain integrity and confidentiality.
    - **Safety monitoring mechanisms** to address adverse events promptly.
  + **Approval Authority**
    - Deciding whether to approve, **modify, or disapprove** a clinical trial based on ethical, scientific, and safety considerations.
  + **Ongoing Monitoring**
    - Conducting **periodic reviews** throughout the study to ensure compliance with the approved protocol.
    - Addressing **emerging safety concerns** such as unexpected adverse events or protocol deviations.
* Data safety
* <https://www.nidcr.nih.gov/research/human-subjects-research/toolkit-and-education-materials/interventional-studies/data-and-safety-monitoring-board-guidelines#:~:text=The%20primary%20responsibilities%20of%20the,or%20termination%20of%20the%20trial>.
* <https://www.nia.nih.gov/health/clinical-trials-and-studies/clinical-research-benefits-risks-and-safety#:~:text=Clinical%20trials%20that%20test%20an,can%20stop%20the%20trial%20early>.
* <https://www.cloudbyz.com/resources/edc/the-role-of-the-data-safety-monitoring-board-dsmb-in-clinical-trials/#:~:text=The%20primary%20responsibility%20of%20a%20DSMB%20is,those%20involving%20high%2Drisk%20interventions%20or%20vulnerable%20populations.&text=The%20DSMB%27s%20main%20ethical%20responsibility%20is%20to,trial%20outweigh%20the%20potential%20risks%20to%20participants>.
* <https://pmc.ncbi.nlm.nih.gov/articles/PMC3326906/#:~:text=Clinical%20Data%20Management%20(CDM)%20is,from%20drug%20development%20to%20marketing>.
* <https://pmc.ncbi.nlm.nih.gov/articles/PMC11003847/#:~:text=Protecting%20patient%20safety%20is%20an,toxicity%20risk%20from%20study%20therapies>.
* <https://wakeresearch.com/about-us/news-updates/are-clinical-trials-safe/#:~:text=Informed%20consent%20is%20a%20critical%20aspect%20of,and%20benefits%20before%20agreeing%20to%20take%20part>.
* <https://www.quotientsciences.com/blog/importance-data-integrity-drug-development-process#:~:text=In%20addition%2C%20data%20integrity%20must,complete%2C%20and%20well%2Ddocumented>.
* In present studies
  + IRBs work alongside Data Safety Monitoring Boards (DSMBs) and researchers to ensure:
  + **Data Integrity** – Ensuring data collection and storage follow best practices to prevent breaches or manipulation.
  + **Adverse Event Reporting** – Monitoring and addressing unexpected side effects or safety concerns.
  + **Confidentiality & Security** – Protecting participant data through encryption, anonymization, and secure databases.
  + **Stopping Criteria** – Reviewing data to determine if a trial should be modified or halted due to safety concerns.
* In secondary studies
  + Secondary studies use de-identified or coded data from primary trials for further research. IRBs ensure:
  + **Ethical Reuse of Data** – Reviewing secondary research protocols to confirm alignment with the original consent agreement or seeking re-consent if necessary.
  + **Privacy Protection** – Ensuring participant identities remain confidential through de-identification or anonymization techniques.
  + **Data Sharing Governance** – Approving data-sharing agreements that outline how researchers can access and use data while maintaining compliance with HIPAA, GDPR, or other relevant regulations.
  + **Long-Term Risk Management** – Assessing evolving privacy risks associated with AI, big data analytics, and genomic studies, where re-identification may be possible.

# How to find a clinical Trial

<https://ctontario.ca/learn-about-trials/>

* Some people discuss finding clinical trials with their health care providers, who may have varying levels of knowledge and comfort on the topic.

Depending on their experience or resources, health care providers might provide more information or direct you to helpful resources or individuals.

* Health charities and patient organizations often have information about clinical trials:
* This information is usually available on their websites under a clinical trials or research section.
* Many organizations also provide a phone number you can call for assistance in finding a clinical trial.
* Hospitals, including community and academic hospitals, conduct clinical trials and can be a source of information:
* Some hospitals list local clinical trials directly on their websites.
* If contacting a hospital for information, you may need to make multiple calls or emails to reach the appropriate person.
* Websites can also help find clinical trials:
* Clinical Trials Ontario offers a website that links to a global registry, ClinicalTrials.gov, where detailed information about clinical trials is available.
* The site provides contact information for trials you may be interested in.
* <https://clinicaltrials.gov/>
* Find NCI-Supported Clinical Trialas <https://www.cancer.gov/research/participate/clinical-trials-search>
* <https://www.nih.gov/health-information/nih-clinical-research-trials-you/finding-clinical-trial>
* <https://health-products.canada.ca/ctdb-bdec/?lang=eng>
* Clinical trial advertisements may appear in various media:
* You might encounter ads on the radio, TV, newspapers, public transportation, doctor’s offices, or hospitals.
* These ads typically include contact information for those interested in learning more.

1. Understand Clinical Trials
2. Identify Reliable Sources

Start your search with reputable and trusted sources:

* **ClinicalTrials.gov**: A comprehensive database of clinical trials conducted worldwide.
* **Health Canada’s Clinical Trials Database**: Lists approved clinical trials conducted in Canada.
* **Healthcare Team**: Consult your doctor, nurse, or specialist, who may be aware of trials relevant to your condition.
* **Province-Specific Websites**: Many provinces maintain their own clinical trial registries or health research platforms.
* **Patient Advocacy Groups**: Organizations focused on specific conditions often maintain curated lists of ongoing trials.

1. Step-by-Step Guide to Finding a Clinical Trial

*a. Use ClinicalTrials.gov*

1. Visit [ClinicalTrials.gov](https://clinicaltrials.gov).
2. Use the search bar to enter keywords related to your condition, treatment type, or location.
3. Filter results by:

* **Recruitment Status**: Look for trials that are "Recruiting."
* **Location**: Specify your city, province, or country.

1. Review trial details, including:

* **Purpose**: The goals and objectives of the trial.
* **Eligibility Criteria**: Requirements such as age, gender, medical history, and current health status.
* **Contact Information**: Details for the trial’s coordinators or investigators.

*b. Use Health Canada’s Database*

* 1. Visit Health Canada’s Clinical Trials Database: <https://health-products.canada.ca/ctdb-bdec/?lang=eng>
  2. Search using the drug name, condition, or protocol number.
  3. Review results to find trials approved in Canada.
  4. Contact the sponsor or trial site for more information.

1. Contact the Clinical Trial Coordinator

* Once you identify a suitable trial, contact the coordinator listed on the trial’s page.
* Prepare specific questions, such as:
  + What are the potential risks and benefits?
  + How long will the trial last?
  + Are there costs or reimbursements involved?

1. Discuss With Your Healthcare Team

Share the trial details with your doctor or healthcare provider. They can help assess whether the trial aligns with your medical needs and provide valuable insights.

1. Apply for the Trial

* Complete any required forms or initial screenings.
* Be prepared to provide your medical records and undergo additional tests to confirm eligibility.

# Trail Team and Roles

* <https://www.hopkinsmedicine.org/research/understanding-clinical-trials/clinical-research-team>
* <https://vcccalliance.org.au/research/clinical-trial-innovations/investigator-initiated-trials/roles-and-responsibilities/clinical-trials-team/>
* <https://ccrps.org/clinical-research-blog/the-clinical-trials-team-roles-amp-responsibilities>
* <https://www.pfizer.com/news/articles/anatomy_of_a_clinical_trial_the_purpose_people_and_phases_of_clinical_research>
* A clinical trial relies on a diverse team of professionals working together to ensure the study is conducted ethically, safely, and effectively. Below are key roles involved in the process:
* *Participants and Caregivers*
  + Participants are at the heart of any clinical trial. Their involvement is essential for advancing medical research. Caregivers also play a crucial role by providing support and helping participants manage their trial-related responsibilities. Many institutions prioritize diversity in research teams to create a more inclusive and representative environment, encouraging broad participation in clinical studies.
* *Principal Investigator (PI)*
  + Also known as the primary investigator, the PI is responsible for overseeing all aspects of the study. This includes designing the research, developing a detailed study protocol, and obtaining approval from the institutional review board (IRB). The PI ensures participant recruitment follows ethical guidelines, informs participants about their rights, and secures their consent. Additionally, they supervise data collection, analysis, and reporting of results, making them ultimately accountable for the study’s integrity.
* *Study Physicians*
  + These medical professionals work closely with the PI to care for participants throughout the study. They administer treatments as outlined in the trial design, monitor patient responses, and document any side effects or adverse reactions.
* *Research Nurse*
  + A research nurse plays a key role in explaining the study to potential participants, healthcare providers, and community members. They help administer study treatments, monitor participants for side effects, and support the PI in ensuring participant safety.
* *Study Coordinator*
  + The study coordinator manages many day-to-day research activities. They may assist in recruiting participants, ensuring they understand the study’s requirements before giving consent. Coordinators also schedule study visits, conduct interviews, and ensure the trial follows regulatory guidelines.
* *Research Pharmacist*
  + For studies involving medications, research pharmacists ensure proper handling, storage, and administration of study drugs. They ensure medications are dispensed correctly and monitor their effectiveness while maintaining patient safety.

# Questions to ask your Healthcare Provider

* <https://cancer.ca/en/living-with-cancer/coping-with-changes/working-with-your-healthcare-team/questions-to-ask/clinical-trial-questions#:~:text=How%20long%20will%20the%20study,is%20the%20study%20treatment%20given%3F>
* <https://trials.cancervic.org.au/information/questions-to-ask-your-doctor>
* <https://www.hhs.gov/ohrp/education-and-outreach/about-research-participation/questions-to-ask/index.html>
* <https://clinicaltrialguide.com/the-guide/questions-to-ask-before-joining-a-clinical-trial/>
* ***General*** *clinical trial questions:*
  + What purpose does the study serve and why is it taking place?
  + What about this study pertains to me?
  + Have there been similar studies/treatments conducted? If so, what were the results?
  + Is this a study for prevention, screening, diagnostic, treatment, behavioral, or quality of life?
  + Why is this study being recommended to me?
  + Where can I learn more about this clinical trial and others?
  + What led to this specific approach to be studied and tested?
  + What makes the researchers believe that this approach might be effective?
  + By whom is the study funded? What is their involvement/interest/motivation for doing so?
  + Who reviewed and authorized the study?
  + Will the clinical trial include the use of a placebo? Will I be receiving actual treatment or will I be taking a placebo? Will this change at all during the study?
  + How is the safety of participants and study results being monitored?
  + What are the eligibility criteria? If I am not a good fit, are there other options you can recommend?
  + What is the anticipated duration of the study taking place?
  + If I participate, what are my roles and responsibilities?
  + How will I be informed about the results and by whom?
  + How long do I have to decide whether or not I want to participate? Can I change my mind after agreeing? Would there be any wait time upon my decision to join or leave?
  + Are there any possibilities that I could be removed from the study and for what reason?
  + Are there any possibilities that the study could be stopped early? What for?
* *Possible* ***risks and benefits*** *questions:*
  + What are the possible short-term benefits? What are the possible long-term benefits?
  + What are the short-term risks/side-effects? What are the long-term risks/side-effects?
  + Will anyone on my health care team assist me in managing these?
  + Are there other options available? If so, what?
  + How do the risks versus benefits of this trial contrast with those opinions?
  + If the trial is working, how will I be able to tell?
  + What are the desired results of the trial?
  + How would being in this study affect your daily life?
  + How would being in this study affect your current medical care?
  + Is there anything you could do to minimize your risks during the study?
* ***Participation and care*** *questions****:***
  + What types of therapies, tests, and/or procedures will I receive during the trial?
  + How often will they be administered?
  + How will they be given/administered to me?
  + Will they be painful? If so, for how long?
  + Are there risks? Are they similar risks to standard treatment or are they different in any way?
  + How do the tests and practices being performed in the study compare with those I would find outside of the trial?
  + Will I be able to continue taking my current medications/treatments while participating in the trial?
  + Which medications, procedures, or treatments will I need to avoid during or even after the study? For how long?
  + Will I be required to provide samples such as tissue, blood, etc.? What is done to the samples, and must I donate these in order to participate?
  + Will a biomarker be tested for in the trial?
  + Where will my medical care take place?
  + Who is in charge of my medical care?
  + Who will I need to contact in case of abnormalities during the trial or if I have additional questions?
  + How long do I have to decide whether or not to participate?
  + When and how will I be informed of the results?
  + If my health gets worse, what should I do and what would be expected to happen?
  + How often will I be informed about new information regarding the treatment?
  + Will my safety be protected?
  + Will I continue to see my primary doctor/health care provider while I am participating in the trial?
* ***Cost and logistical*** *issues****:***
  + Will I have to pay out of pocket for anything in the trial, such as tests or research?
  + Will I be getting paid to participate? If so, how much and how often?
  + Are there any expenses that I would be required to pay for?
  + How much of the expenses are being covered by the clinical trial itself?
  + Is there a significant difference in the cost for the clinical trial versus standardized treatment plans?
  + Will my health insurance cover me participating in the trial? If so, how much?
  + Is insurance a requirement to be able to join this clinical trial?
  + Who is equipped to help answer questions from my insurance company/health plan?
  + If I am injured, who pays for those costs?
  + Will there be any travel or childcare expenses that I need to take into consideration during the trial?
  + Are there payment management plans if I am required to pay for anything?
  + Are there any legal issues involved? Are there liability protections in place?
* *Questions to ask* ***your doctor/research team*** *regarding the clinical trial:*
  + What makes the researchers believe that the trial treatment being studied may be more beneficial than treatments in use currently? What may not make it better?
  + How will the doctor know if the trial is working?
  + Which phase of the trial am I joining? What does that mean?
  + Will I have check-ups after the trial with the trial team and/or personal doctor?
  + Do you know of other treatment options whether clinical trial or standard practice options?
  + What will happen to me with my disease/condition if I do not have treatment?
  + Will the clinical trial staff and researchers work alongside my personal doctor while I am participating?
  + Will my doctor have any advocacy when it comes to me and the treatments?
  + Where can I find the best advocacy groups/resources pertaining to my condition and the clinical trial I am considering participating in?
  + Will there be any type of long-term follow-up appointments or care as a part of this study and after the study is completed?
  + If I believe I am experiencing long-term side effects after the study, who should I contact and what actions will need to be taken?
  + If the treatment successfully works for my condition after the study is over, will I be able to continue to take it? Will I need to keep taking the treatment?
  + If my doctor is also the researcher on the study and you decide not to participate, would this decision affect my current medical care?
  + What happens if I volunteer to participate now, but decide to quit the study later?
* ***Privacy and confidentiality*** *questions*
  + How would my biological materials (such as blood samples), data (such as test results), or other personal information be used or shared?
  + How would my privacy and identifiable private information be protected?
  + What could happen to me if your identifiable private information were disclosed to others?

# What to expect

<https://www.cancer.gov/research/participate/clinical-trials/what-to-expect>

* Before Enrolling
  1. *Pre-Screening*
     + The first step in joining a clinical trial is pre-screening, where researchers assess whether you meet the initial eligibility criteria. Each study has specific requirements, such as:
       - Age range
       - Medical condition
       - Previous treatments
     + During pre-screening, a study coordinator or research nurse will provide details about the trial and ask questions to determine your suitability. Topics discussed may include:
       - The trial’s purpose and goals
       - The treatment being studied, including possible risks and benefits
       - The number of required visits
       - Support services available
       - Insurance coverage and financial considerations
  2. *Informed Consent*
     + If you meet the preliminary criteria, the next step is informed consent. The research team will explain the trial in detail, covering procedures, risks, and expectations. You will then decide whether to participate by signing a consent form.
     + For children, additional protections are in place. Minors (under 18) cannot provide legal consent, so a parent or guardian must authorize participation. The child must also go through the **assent process**, where the study is explained in an age-appropriate manner, and they confirm their willingness to participate.
  3. *Screening*
     + After informed consent, a more detailed screening process is conducted. This involves:
       - Reviewing your medical history
       - Conducting necessary tests to confirm eligibility
     + If the results indicate that participation is not suitable, you may not be able to proceed. Screening is a more thorough assessment compared to pre-screening.
* During the Clinical Trial
  + Once enrolled, you will receive detailed instructions on visits, procedures, and expectations. Your health and safety will be continuously monitored.
  + *What to Expect*
    - The specifics of each trial vary, including:
      * **Location** – where the study takes place
      * **Procedures** – medical tests, treatments, or interventions
      * **Time commitment** – frequency and length of visits
  + *Support Available*
    - Some trials provide additional support, which may include:   
      ✔ Coordination with your current healthcare team   
      ✔ Guidance on symptom management and ongoing care   
      ✔ Reimbursement for participation   
      ✔ Coverage for travel, lodging, or transportation expenses   
      ✔ Documentation for work or school absences
    - *Note:* Not all trials cover expenses, so the research team will clarify financial details before enrollment.
* After the Trial Ends
  + Your participation may conclude due to:
    - Completion of the trial
    - Early termination of the study
    - Your decision to withdraw at any time
    - The research team determining that it is in your best interest to stop
* *Next Steps*
  + After the trial, you may have options such as:
    - Requesting access to trial results (if available)
    - Consulting with your healthcare team for continued care options
    - Exploring treatment availability outside the trial
    - Participating in follow-ups to monitor your health
    - Each clinical trial has different guidelines for follow-up care and sharing results.
    - It’s important to discuss these details with the study team before your participation ends.

Current scenario (advocacy): what are some barriers to participation, solutions, decentralized trials

Current Clinical Trials Environment

* Canada currently hosts approximately 4% of the world’s clinical trials and ranks fourth worldwide in terms of the number of clinical trial sites. Every year Health Canada authorized approximately 900 clinical trials and on a per-capita basis, Canada leads the G7 in clinical trial productivity. Canada’s reputation stems from its highly skilled research clinicians, internationally acclaimed for significant scientific breakthroughs and their ability to undertake complex studies across diverse populations.
* Robust investments in clinical research are supported by Canada’s world-class higher education system, publicly funded healthcare renowned for quality, and a network of respected research organizations and health-focused charities—particularly those specializing in areas such as cancer, cardiovascular disease, and rheumatology.
* (<https://ised-isde.canada.ca/site/canadian-life-science-industries/en/biopharmaceuticals-and-pharmaceuticals/clinical-trials-environment-canada> )
* (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/health-canada-clinical-trials-database.html> )

Barriers

* Despite their life saving potential, there are still many barriers that exist in participation for clinical trials. Some of the most prevalent including:
* **Lack of Awareness and Education**: Many patients are unaware of ongoing clinical trials or do not fully understand their benefits. (<https://pmc.ncbi.nlm.nih.gov/articles/PMC9520135/>)
* **Eligibility Restrictions**: Stringent inclusion/exclusion criteria may prevent participation. Patients with multiple comorbidities often find themselves ineligible.
* **Geographic Barriers**: Canada’s vast landscape makes it difficult for rural and Indigenous populations to access trial sites. (<https://www.mdpi.com/1718-7729/28/5/329>)
* **Financial Burden**: Costs associated with transportation, time off work, or accommodation may deter participation. (<https://oicr.on.ca/new-3ctn-initiative-aims-to-address-barriers-faced-by-underrepresented-populations-and-expand-clinical-trial-involvement>)
* **Trust and Misinformation**: Historical unethical research (e.g., Indigenous health experimentation) has fostered skepticism, particularly in marginalized communities.
* (<https://www.rochecanada.com/media/roche-canada-launches-clinical-trial> )
* **Burdensome Participation Requirements**: Frequent travel for in-person visits, extensive testing, and rigid protocols may discourage participation.
* (<https://pmc.ncbi.nlm.nih.gov/articles/PMC9520135/>)

Solutions

* However, there are a number of strategies that are currently being utilized to help reduce barriers and increase participation for clinical trials.
* **De centralized trials**
* Decentralized clinical trials aim to reduce barriers by allowing participants to engage in research activities without frequent visits to centralized sites. This approach is particularly beneficial in a country like Canada, where geographic vastness can impede access.
* **Canadian Remote Access Framework for Clinical Trials (CRAFT):** Initiated in 2019, CRAFT proposes a model to address geographic barriers by incorporating decentralized methods, such as telemedicine and local healthcare providers, to facilitate trial participation across diverse regions. (<https://pmc.ncbi.nlm.nih.gov/articles/PMC8534531/> )
* **Clinical Trials Ontario's Decentralized Trials Resource Guide:** This guide offers comprehensive information on conducting decentralized trials, aiming to harmonize approaches and make participation more accessible for diverse populations. (<https://ctontario.ca/resources/decentralized-trials/> )

**Current promotion strategies**

* **Canadian Institutes of Health Research (CIHR) Initiatives:** CIHR's Strategy for Patient-Oriented Research (SPOR) emphasizes patient engagement, ensuring that research aligns with patient needs and priorities.

Communication tips and strategies: with healthcare team and family members during decision-making, how to advocate for patients/ the role of caregivers

Communicating with the Healthcare Team

Effective communication with the healthcare team - including doctors, nurses, clinical research coordinators, and other specialists - is fundamental. Below are strategies to foster open, informative conversations and build a strong patient-provider relationship.

**Be Informed**

* **Understand the Study’s Purpose and Procedures**: Before meeting with the medical team, review any available written materials such as the trial protocol summary, informed consent forms, and informational pamphlets.
* **Know the Risks and Benefits**: Familiarize yourself with potential risks, expected side effects, and possible benefits. This foundational knowledge prepares you to ask focused questions that accurately reflect your concerns.

**Prepare Questions in Advance**

* **Potential Benefits and Risks**: Ask about the likelihood of potential benefits and the severity or frequency of risks.
* **Alternative Treatments**: Inquire about the standard care or other therapies available outside the trial.
* **Impact on Daily Life**: Clarify how participation might affect work, travel, family commitments, and finances.
* **Withdrawal Process**: Understand your right to withdraw from the trial at any time without jeopardizing your standard medical care.

**Seek Clarification**

* **Ask for Simpler Explanations**: If medical jargon or technical terms are confusing, request plain language or analogies to help break down complex information.
* **Use Visuals**: Sometimes diagrams or flowcharts can clarify study timelines, procedures, and expected outcomes.

**Document Conversations**

* **Take Notes or Record**: Jotting down answers to questions during meetings helps maintain clarity. If allowed, consider using a voice recorder to revisit details later.
* **Organize Information**: Keep a folder—digital or physical—where you store all trial-related documents, notes, and contact information for quick reference.

**Bring a Support Person**

* **Emotional Support**: A family member, friend, or caregiver can offer emotional reassurance.
* **Shared Decision-Making**: They can help remind you of questions you wanted to ask and discuss critical points after the meeting.
* **Information Retention**: Two sets of ears are often better than one—your support person may catch details you miss.

Communicating with Family Members

Family members often play an integral role in the patient’s decision-making process. Concerns about safety, logistics, and outcomes can influence a patient’s choice to participate in a clinical trial.

**Acknowledge Concerns**

* **Encourage Open Discussion**: Recognize that family members may have worries about side effects, costs, or the overall safety of participating in a trial.
* **Address Misconceptions**: Some individuals may mistakenly believe that clinical trials are only for severe cases or that they lack regulatory oversight. Reassure them of Canada’s rigorous ethical and regulatory standards.

**Facilitate Open Dialogue**

* **Daily Life Implications**: Discuss how the trial might affect routines—e.g., additional clinic visits, potential travel, or overnight stays.
* **Emotional and Psychological Support**: Share how the family can help manage stress or anxiety related to the trial process.
* **Set Realistic Expectations**: Talk about possible outcomes and remind them that clinical trials are research studies with inherent uncertainties.

The Role of Caregivers

Caregivers—whether family members, close friends, or professional support persons—play a vital role in ensuring that a patient’s needs and preferences are respected. Advocacy involves empowering the patient, bridging communication gaps, and helping navigate complex healthcare systems.

**Empower Patients**

* **Support Informed Choices**: Ensure patients fully understand their options, including the risks and benefits of joining or declining a clinical trial.
* **Respect Autonomy**: Caregivers should encourage, not pressure, patients to choose based on their own values and circumstances.

**Bridge Communication Gaps**

* **Intermediary Role**: Attend appointments with the patient to clarify misunderstandings and restate medical information in simpler terms if needed.
* **Coordinate with Healthcare Providers**: Caregivers can help schedule follow-up calls or meetings to address lingering questions or concerns.

**Navigate Administrative Details**

* **Assist with Paperwork**: Support patients in completing consent forms, insurance documentation, or other administrative tasks.
* **Logistics Management**: Help with travel arrangements to trial sites, coordinate with local health facilities, and track important calendar dates (e.g., infusion appointments, lab tests).
* **Financial Guidance**: Some trials cover transportation or lodging costs; caregivers can inquire about reimbursement policies or subsidies available through Canadian patient support programs.

**Monitor Well-being**

* **Observe and Record Changes**: Note any side effects, emotional changes, or shifts in physical health. Maintaining a symptom diary can help the medical team adjust the treatment or provide supportive care as needed.
* **Report Adverse Effects Promptly**: Contact the trial coordinator or healthcare provider immediately if the patient experiences any concerning symptoms.

Stories of hope

\*Here are some resources related to anecdotes related to clinical trials but still unsure if we wanted a specific anecdote from the BTFC.

Testimonial Videos from the Canadian Cancer Clinical Trial Network (<https://3ctn.ca/for-patients/patient-experiences/> )

MUHC Testimonial – more research based (<https://muhc.ca/news-and-patient-stories/research/immunotherapy-showing-significant-advancements-lung-cancer> )

Canadian Cancer Trials Group and pembrolizumab (<https://www.ctg.queensu.ca/cctg_news/new-immunotherapy-treatment-mesothelioma-lung-cancer-proves-effective> )

Call to action: resources and websites, ways to give

**Key Canadian Resources**

[Canadian Cancer Trials Group (CCTG)](https://www.ctg.queensu.ca/): Leading cancer clinical trials network in Canada.

[Canadian Institutes of Health Research (CIHR)](https://cihr-irsc.gc.ca/e/52985.html): Government funding body supporting CTs in various diseases.

[Health Canada](https://www.canada.ca/en/health-canada.html)

[Health Canada Clinical Trials Database](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/health-canada-clinical-trials-database.html)

[Clinical Trials Ontario](https://ctontario.ca/), [Clinical Trials Alberta](https://clinicaltrialsab.ca/), [Clinical Trials BC](https://healthresearchbc.ca/clinical-trials-bc/about-us/), [Clinical Trials Quebec](https://clinicaltrialsquebec.com/),

**Finding a Trial**

[CenterWatch](https://www.centerwatch.com/clinical-trials/listings/location/international/Canada)

[Health Canada Clinical Trial Search](https://health-products.canada.ca/ctdb-bdec/)

[Clinicaltrials.gov](https://clinicaltrials.gov/)

**Other ways to support**

Many institutions, like The Hospital for Sick Children (SickKids) or The Brain Canada Foundation, rely on public donations.

Join Patient Advocacy Groups: Groups like Canadian Organization for Rare Disorders (CORD) influence CT policies and patient rights.

Volunteer as a Healthy Control: [itstartswithme.ca](https://itstartswithme.ca/)

Glossary of common CT terms

Adverse Drug Reaction (ADR)

A harmful or unintended response to a medication. In clinical trials, ADRs are closely monitored and reported to regulatory authorities (e.g., Health Canada) to ensure participant safety.

Adverse Event (AE)

Any unwanted or unexpected medical occurrence in a participant during a clinical trial—even if it is not necessarily caused by the treatment. Adverse events are recorded and assessed to determine whether they are related to the investigational product.

Assent

A process used when participants are not legally able to give full informed consent (e.g., minors). Assent means they understand the study in an age-appropriate way and agree to participate, usually alongside parental/guardian permission.

Beneficence

An ethical principle requiring that clinical research should aim to benefit participants or society. It guides researchers to maximize potential benefits and minimize risks.

Blinded Study

A study design in which participants do not know whether they are receiving the investigational treatment, a placebo, or another control. Blinding helps reduce bias based on participant expectations.

Control Group

A group in a clinical trial that does not receive the investigational treatment. This group may receive a placebo or the standard of care to compare outcomes against those in the experimental group.

Decentralized Trial (DCT)

A trial design that uses virtual tools, remote monitoring, and home-based or local services to reduce or replace in-person visits to a central site. This can improve accessibility for participants who live far from traditional research centers.

DIN (Drug Identification Number)\*

A unique eight-digit number assigned by Health Canada to each drug product on the Canadian market. It indicates that the product has undergone review and is authorized for sale in Canada.

Double-Blind Study

A study design in which neither participants nor the research team know who is receiving the investigational product versus a placebo or control treatment. This approach further reduces bias in measuring outcomes.

Ethics Review Board (REB/IRB)

In Canada, an REB (Research Ethics Board) is the committee responsible for reviewing clinical trial protocols to ensure they meet ethical and safety standards. In the United States, the equivalent body is the IRB (Institutional Review Board). In Canadian contexts, you may see REB and IRB used interchangeably, though “REB” is more common.

Informed Consent

A process in which potential participants are given comprehensive information about the study’s purpose, procedures, risks, and potential benefits. They must understand this information before voluntarily agreeing (consenting) to join the trial. In Canada, informed consent must adhere to guidelines set by Health Canada and institutional REBs.

Multi-Center

A study conducted at multiple research sites (hospitals, clinics, universities, etc.) simultaneously. Multi-center trials often increase the diversity and number of participants, strengthening the reliability of results.

Non-Maleficence

An ethical principle requiring researchers to avoid causing harm. This principle is closely tied to beneficence, reinforcing that clinical research should not expose participants to unnecessary risk.

Phase I, II, III, IV Trials

* **Phase I**: Tests a new intervention in a small group of people (often healthy volunteers) to evaluate safety, dosage range, and side effects.
* **Phase II**: Involves a larger group to assess effectiveness and further evaluate safety.
* **Phase III**: Conducted on an even larger scale to confirm effectiveness, monitor side effects, and compare the new intervention to standard treatments.
* **Phase IV**: Post-marketing studies that collect additional information, including long-term risks and benefits, after a product is approved and on the market.

Placebo

An inactive substance or “dummy” treatment used as a control in clinical trials. By comparing results in the placebo group to those in the treatment group, researchers can evaluate the investigational product’s true effect.

Principal Investigator (PI)

The lead researcher who oversees the scientific and ethical conduct of a clinical trial. The PI is responsible for designing the study protocol, ensuring compliance with regulations, and safeguarding participant welfare.

Randomized Controlled Trial (RCT)

A study design that randomly assigns participants to different groups (e.g., treatment vs. control) to ensure that any differences observed between groups are due to the intervention rather than selection bias.

Research Coordinator

A professional who assists the Principal Investigator with day-to-day trial activities, such as participant recruitment, scheduling, data collection, and regulatory documentation. They are often the primary point of contact for participants.

Side Effect

A reaction to a health product that differs from the intended or expected outcome. Side effects range from mild and temporary to severe and long-lasting. An “adverse effect” specifically refers to an unwanted and harmful reaction.

Sponsor

The organization funding or overseeing the clinical trial. Sponsors can be pharmaceutical companies, academic institutions, government agencies, or hospitals. The sponsor is responsible for initiating, managing, and/or financing the study.

Standard of Care

Refers to the currently accepted and widely used treatment for a specific condition outside of clinical research. In clinical trials, the investigational treatment is often compared to the standard of care to see if it offers improvements.