

Understanding Pediatric Rare Disease Clinical Trials

A glossary of terms for parents and families



This glossary explains some of the words you may hear if your child is involved in rare disease research or a clinical trial. It is designed to make medical and research language easier to understand, helping families follow what doctors, nurses, researchers, and study staff are saying. While created primarily for families, it may also be useful for others in the rare disease community, including health professionals, educators, and advocates.

This glossary was developed in Canada, and some terms reflect the Canadian healthcare and research context. Words, organizations, processes, or requirements may be different in other countries or regions.

The language used in the rare disease community continues to evolve. As research advances, treatments emerge, and families and advocates share their perspectives, the meanings of terms may shift. This glossary is meant to be a supportive tool to promote understanding.

In Canada, there is no single official definition of a **rare disease**. For the purposes of this glossary, we are using a commonly accepted working definition: a condition that affects fewer than 1 in 2,000 people.^{1,2} Many rare diseases start in childhood and are caused by changes in genes. While each rare disease might impact a smaller number of individuals, together they affect many families across the country and beyond.

Can't find a word?

We welcome your feedback and continue to update this. Feel free to reach out to by emailing us to rkengage@mcmaster.ca

For more information about RareKids-CAN: Pediatric Rare Disease Clinical Trials and Treatment Network, contact rarekidscan@micyrn.ca

What is RareKids-CAN?

Vision: To ensure that every child, adolescent, and young adult in Canada affected by rare diseases has access to effective and innovative treatments.

RareKids-CAN (RKC), Canada's Pediatric Rare Disease Clinical Trials and Treatment Network, is a diverse coalition of partners focused on simplifying and speeding up clinical trials and access to innovative treatments for pediatric (children and youth) rare diseases across Canada. RKC is anchored around three strategic priorities:

- Strengthening Pediatric Rare Disease Clinical Trial Capacity and Advanced Therapy Medicinal Product Readiness.
- Optimizing Participant/Site/Trial Matching.
- Driving Regulatory Reform and System Innovation.

The RareKids-CAN network has a Patient and Family Engagement Sub-Platform dedicated to supporting the integration of diverse children, youth, and families with lived and living experiences of pediatric rare diseases across the network and in clinical trials research. This sub-platform builds capacity, promotes community, and supports meaningful patient and family engagement.

To help you find information more easily, this glossary is organized into the following sections or you can search for words using the [A-Z list](#).

Learn more about RKC's patient and family engagement work, email rkengage@mcmaster.ca or visit rarekidscan.com/patients-and-families

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To make information easier to find, this glossary is organized into sections. You can also use the A-Z Glossary to look up a specific word.

Terms in both the Table of Contents and A-Z Glossary are hyperlinked, so you can click or tap them to go directly to the definition.

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Helpful Resources

This material may include content that some individuals find sensitive or distressing. Readers are encouraged to engage with the material in a way that feels comfortable for them and to seek support if needed. For additional information and support, a collection of trusted Parent and Family Resources has been prepared by the RareKids-CAN Patient and Family Engagement Sub-Platform and can be accessed through [Patient and Family Resources](#), or via rarekidscan.com/patients-andfamilies

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How Rare Disease May Impact Children and Their Families

Advocacy

Speaking up for children and their families' needs and rights, making sure their voice is heard in health care, education, and the community. For example, advocacy can include asking for treatment/care/services, influencing policy, or raising awareness about rare diseases and challenges accessing clinical trials.

Caregiver

Someone who provides essential physical, emotional, or practical support to an individual with an illness, disability, and/or age-related needs. They can assist with daily activities (for example, dressing, eating), companionship, and/or medical monitoring (for example, complex care needs).

This help can come in many ways, such as managing complex care needs, emotional support, and many more. This support might be given by a parent, family member, friend, community member, or more formally through a paid caregiver.

Caregiver Burden

Refers to the strain that people can experience when caring for a loved one or family member. This could be tiredness, worry, and financial strain, among others things.³

Developmental Outcomes

The skills children acquire as they grow, such as walking, talking, and playing. Tracking these skills helps to check if children are growing and developing as expected.

Diagnostic Odyssey

The often long and stressful journey of searching for a diagnosis. For many children with rare conditions, this can mean years of tests, medical appointments, and uncertainty.

Some families may never receive a clear diagnosis, while others find that finally getting one brings relief, answers, and hope. Even without a diagnosis, learning these terms can help families understand what doctors, nurses, and researchers are saying along the way.

Family Spillover Effects

How a person's illness affects the whole family, including stress, time off work, and extra costs.

Financial Impact

The costs related to care, travel, time off work, job loss, and treatments not covered by insurance. It may also include hidden expenses such as additional childcare or other unexpected needs.

Health-Related Quality of Life (HRQoL)

How health affects a person's daily life, including how they feel, move, and connect with others.

Patient's Diary

A paper notebook or digital app used during a study to track how the patient feels, including symptoms and treatment effects. Families can choose the format that works best for them.

**Sibling
Impact**

Siblings of children with rare diseases may sometimes feel worried about their sibling's health, as well as their own, and may feel left out or experience stress. They may also develop resilience, a sense of pride, and advocacy skills through their experiences.

**Social
Isolation**

Families might feel alone or left out when others do not understand their situation.

Support

The emotional, practical, and social help that families give and receive. Support can come from friends, family, healthcare providers and/or networks of other families who share similar experiences. It helps families feel less alone and more empowered.

Wellness

A person's overall quality of life and ability to live well. It includes lifestyle choices, mental and spiritual well-being, and the environment around them.

Wellness is an active process, meaning it involves making choices that support health and well-being over time.⁴

Read more about wellness at <https://www.cma.ca/healthcare-for-real/whats-difference-between-health-and-wellness>

Understanding Rare Disease

**Antisense
Oligonucleotides
(ASOs)**

Short pieces of modified DNA that have therapeutic potential for some patients with rare diseases. They act like precise instructions that block the body from following harmful genetic directions.

Biomarkers

Measurable signs in the body that give doctors important information about a person's health. They can be found in blood, other body fluids, or tissues, and can reveal whether a disease is present, if the body has been exposed to something harmful, or how well a treatment is working.

Examples of biomarkers:

- Urine phosphoethanolamine and plasma pyridoxal-5- phosphate are in hypophosphatasia.
- Serum carnitine in fatty acid oxidation disorders.

Cell Therapy

The transfer of cells into a patient with the goal of improving a disease.

Cells

All living things, including people, are made up of cells. Cells group together to form tissues, organs, and body systems (e.g., nervous system, digestive system) that each do special jobs.

Inside every cell are genes, which are parts of DNA that work like tiny instruction manuals (or blueprints), telling the body how to grow and function.

Clinical Geneticists

Doctors who diagnose and explain conditions caused by gene changes. They help plan care and support for children and families, and often work as part of a team with other specialists such as genetic counselors and lab scientists.

Clinical Genetics

A specialty of medical genetics that refers to direct patient care, including finding out if a health problem is caused by a specific genetic change.

Healthcare professionals specializing in clinical genetics take a detailed family history, order and help interpret specialized tests, for the child and family and provide advice regarding management.

DNA (Deoxyribonucleic Acid)

DNA is the set of instructions inside our bodies that tell cells how to grow and work. It is found in almost every cell and is passed from parents to children.

DNA is what makes each person unique and can sometimes play a role in health or disease.

**Gene
Therapy**

A treatment that changes genes to help treat or cure a disease. It can fix or replace a gene that is not working properly.

At present, gene therapy is only available for a few conditions, often through clinical trials, and access may be limited. It is a growing and promising therapeutic approach.

Genes

Genes are pieces of DNA found inside cells that act like instruction manuals. They provide the information cells use to make proteins or help control how the body works.

These processes are important for growth, development, and staying healthy.

**Genetic
Counseling**

Support for families to understand conditions passed down through genes. Genetic counselors explain test results, answer questions, and help with care or planning for the future.

They also guide families on whether other relatives should be offered genetic testing.

**Genetic Variant
(previously called
a Genetic Mutation)**

A genetic variant is a change in the instructions of a gene. Scientists in the past used the word “mutation,” but “variation” is now widely used. These changes can sometimes affect how the body grows or works and can be, but are not always, harmful. Some variants are inherited and run in families, while others happen for reasons we do not fully understand. What is most important to know is that these changes are never caused by anything a person or family does or does not do.¹⁰

Genetic variants can lead to conditions in different ways:

a) Single-gene disorders

Caused by a change in just one gene.

- **Autosomal dominant:** Only one a variant in the gene is enough to cause the condition.
- **Autosomal recessive:** A child must inherit two changed copies of the gene (one from each parent) to have the condition. Parents are usually healthy “carriers.”
- **X-linked:** The gene change is on the X chromosome. Boys and girls have different sex chromosomes, so these conditions can affect them differently. Because boys have only one X chromosome, conditions linked to to the X chromosome tend to affect them more strongly.

Continued to next page

**Genetic Variant
(previously called
a Genetic Mutation)****b) Chromosomal disorders**

Caused by changes in number of whole chromosomes (the packages that hold our genes) or in their structure. Chromosomes typically come in pairs, but there are some genetic conditions where there is only one of a particular chromosome (monosomy) and some where there might be three copies of a particular chromosome (i.e. trisomy).

Examples of structural changes include missing pieces of a chromosome (i.e. deletion), extra (i.e. duplications), or rearranged pieces of chromosomes (e.g. translocations).

c) Multifactorial disorders

Caused by a combination of genetic and other factors, such as environment or lifestyle. No single gene alone explains the condition; it's the result of many influences working together.

d) Epigenetic disorders

Caused by changes in how genes are “switched on” or “switched off,” rather than changes in the gene’s code itself. These changes can still affect how the body grows and functions.

**Genetic
Variation**

The difference in genetic makeup across a population. In other words, – what makes each person unique at the genetic level. For example, genetic variation means some people have brown eyes, others blue or green.⁹

Genome

The complete set of genetic information in a person. It includes all of their DNA, containing thousands of genes that act like instructions for how the body grows, develops, and functions.⁷

Genomic Sequencing

A test that reads and analyzes a person's genetic information (their genome). It may identify changes in genes that may cause or contribute to a disease.

This test can support diagnosis, guide treatment decisions, and help families better understand a condition.⁸

iPSCs (Induced Pluripotent Stem Cells)

Scientists can take regular cells (like skin cells) and reprogram them to become stem cells or cells from another organ such as liver or brain. Doctors and scientists use iPSCs to study how diseases develop and to explore possible new treatments.

Orphan Drug

A medicine developed specifically to treat a rare disease. Because these medicines serve only a small number of patients, governments might provide special support or incentives to help with their development and approval.

Canada does not offer incentives like those available in some other countries.

Prognosis

A doctor's educated prediction about how a disease may affect someone over time. This helps families know what to expect.

Risk Factor

Something that might make it more likely for a person to get a disease. It could be related to their genes or their surroundings, like exposure to pollution.

Having a risk factor does not mean someone will definitely get sick, only that their chances are higher than normal.

Stem Cells

Special cells in the body that can develop into many different types of cells. They can also make copies of themselves.

Stem cells play an important role in growth, healing, and repairing damaged tissues. In some rare diseases, stem cells may be used as a treatment to replace or repair unhealthy cells.^{5,6}

**Variant of
Unknown
Significance
(VUS)**

A change in a gene found through gene testing, where it is not yet clear if the change actually causes disease. In rare diseases, this uncertainty often happens because there is not enough known.

As research progresses, the meaning of a VUS might become clearer, and families can sometimes be contacted with updated information.

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Zebra

Doctors are trained to think of common illnesses first. This idea comes from the saying, “When you hear hoofbeats, think of horses, not zebras,” meaning the most likely cause is something common.

But sometimes, the real cause is something rare, like a zebra instead of a horse. In medicine, “zebra” is a reminder not to overlook something that might be rare.

Just as no two zebras share identical stripes, each rare disease and every patient is unique.¹¹ You can also refer to the [American Society of Gene + Cell Therapy Glossary of Terms](#) to complement this section.

Understanding Health Research

Basic Research (also called Fundamental Research)

When scientists study important questions to learn more about how the world works. It is not about making something new right away, but about learning things that can help make new discoveries later.

For example, learning things that can help create new drugs or treatments in the future. Within the health sciences, basic research is often done in a laboratory setting.

Data

Data are information that scientists collect during their research. It can be numbers, words, pictures, or anything they can see, measure, or record. Scientists use data to help answer questions, test ideas, and learn new things.

For example, if scientists are studying a rare disease, they might collect data like how patients' symptoms change over time, results from blood tests, images from medical scans, or notes about how different treatments affect each patient.

Delphi Survey

A structured way to collect ideas or opinions from a group by asking questions using several rounds of questionnaires. After each round, people can see a summary of the group's responses and update their answers if they want to. This process is repeated for a few rounds until the group starts to agree (reach "consensus").¹²

External Controls

Information from patients outside the current study (for example, from past studies, registries, or medical records), natural history studies, used as a comparison group instead of enrolling a separate control group in the trial.¹⁷

Feasibility Study

A small study done first to see if a larger one is possible. It helps check if people will join the study and if the plan will work.

Health Innovation

New ideas, tools, or ways of improving health. This can include new medicines, treatments, or technologies.

**Knowledge Translation
(also called
KT, knowledge
mobilization,
knowledge sharing,
research use,
evidence use)**

The process of sharing the findings of research in a way that is easy to understand and use. The goal is to help people use new evidence to improve health and care.

Integrated Knowledge Translation (iKT)

A way of doing research that includes the people who will use the results — like patients, families, healthcare providers, or policy makers — right from the start or at different stages of a project. For example, they might help choose the research questions, plan the study process, help review study findings and/or stay involved all the way through. Working together like this helps make sure the research is useful, relevant, and more likely to be used in real life.

End-of-Grant Knowledge Translation

Sharing research results after a study is finished so they are clear, accessible, and useful. This can include presentations, reports, or other activities that help people understand and apply the findings.

**Natural History
Study**

Research that watches how a disease changes over time without treatment. It helps plan future studies or care. Natural history studies are also used as external comparator to evaluate the efficacy of new therapies.

Patient Engagement

Patient engagement means actively involving patients and families as partners in research, programs, and decision-making. By sharing their lived experiences, they help ensure that priorities, projects, and outcomes reflect what matters most to patients and families.

Engagement can range from providing feedback on a specific project to being a long-term member of a research team.¹³

Preclinical Research

Studies done in cells or animals before testing a treatment in people. This help check if the treatment might be safe and useful before moving to studies in humans.

Principal Investigator (PI)

The person leading a research study. They make sure the study is done safely and correctly.

Qualitative Data

Qualitative data are the kind of information you can't measure with numbers. Instead, they describe people's thoughts, feelings, experiences, or what's happening in a situation.

This type of data often comes from things like one-to-one interviews, group discussions, written notes, photos, or watching what people do.

Quantitative Data

Information that can be counted or measured. This type of data uses numbers, like how many people were in a study, how long something took, or how often something happened.

Real- World Data

Information about people's health and the care they receive that is collected in everyday settings (not in a research study).

Data can come from sources like patients themselves, healthcare providers (e.g., doctors, nurses), health registries, or electronic medical records.¹⁴

Real-World Evidence (RWE)

Information about how treatments work in everyday life, not in research settings.

Registry-based Clinical Trial

A type of clinical trial that uses information collected in a patient registry (a database of people with a specific condition).

Researchers use this data to study treatments, outcomes, or patterns of disease more efficiently, often reducing the need for extra visits or tests.¹⁵

Scoping Review

A type of research that looks at many studies to see what is already known about a topic.

Single Arm Control

A study design where all participants receive the same treatment, and there is no separate comparison (control) group.

Researchers may compare results to past data or data collected through natural history studies.¹⁶

Systematic Review

A type of research that carefully reviews and combines all relevant studies to answer a specific research question.

Translational Research

When researchers use what they have learned from basic research to develop new tests, treatments, or ways of providing care. Translational research helps move discoveries from the laboratory into real-world use so they can benefit patients and families.

For example, using knowledge about how a disease works to create and test a new drug, therapy, or diagnostic test.

Value of Information Analysis

A way researchers use numbers and information to help decide if doing another study is a good idea. It compares the possible benefits of learning more with the time and money it would take to do the study.¹⁸

Ethics, Rights, and Safety in Research

Assent

A person's agreement to take part in a study when they are not legally able to give full consent on their own. This is most often for children or individuals with limited decision-making capacity. It is a way of respecting the person's wishes; the researcher explains the study in simple, age-appropriate language, and the person agrees (or declines) to participate.

Assent is often needed in addition to permission from a parent, guardian, or legally authorized representative.¹⁹

Compensation

A way to thank people for taking the time to be part in a meeting, project and/or study. This can include money, gift cards, or small gifts given in appreciation for their time and effort.

In some cases, compensation may also follow Indigenous ways of giving thanks, such as offering traditional gifts (e.g., tobacco, cloth, or food), depending on cultural context.

Conflict of Interest

When a researcher might benefit personally or financially from a study, they must say so. This helps keep the research fair and honest.

Fair Subject Selection	Making sure people are invited into studies fairly and respectfully.
Free, Prior, and Informed Consent (FPIC)	A principle that protects the rights of Indigenous peoples in decisions that affect their lands, resources, and communities. “Free” means voluntary and without pressure, “Prior” means before any project begins, and “Informed” means with full understanding of risks and benefits. “Consent” recognizes the right of Indigenous peoples to say yes or no, and to have their decision respected.
Informed Consent	Giving permission to join a study after learning what it’s about, including any possible risks and benefits. It’s about making a free and informed choice.
Minimal Risk	A term used in research ethics to mean the study is not expected to be more risky than everyday life or routine medical care.
OCAP Principles (Ownership, Control, Access, and Possession)	Guidelines that support First Nations communities in managing their own data. These principles ensure that communities have control over how their information is collected, used, and shared. ²⁰
Parental Decision-Making	How parents decide if their child should join a study, often involving the child in the choice.
Pediatric Ethics Frameworks	Guides to help researchers make safe and fair decisions when working with children.

**Privacy,
Confidentiality,
and Data
Ownership**

Researchers must protect personal health information. What families share in a study is kept private and used only as allowed. Increasingly, there is also recognition that families and communities have rights over how their data is stored, shared, and used, and that their ownership of this information should be respected.

A glossary of health data and related terms was created by the Health Data Research Network and can be found at: <https://www.hdrn.ca/en/news/health-data-glossary-promotes-public-trust-transparency/>

Reimbursement

Repaying participants for expenses they have because of taking part in a study. This can include costs such as travel, parking, meals, or childcare.

**Research
Ethics Board
(REB)**

A group of people with different kinds of expertise and experience who review research studies to make sure they are safe, fair, and respectful to participants. Members may include those with knowledge in medicine, health care, law, ethics, and research, as well as people who bring community perspectives and/or lived/living experience.

The REB ensures that studies follow ethical principles, protect the rights and well-being of participants, and meet all required guidelines and regulations. Families can also contact the REB directly if they have questions or concerns about a study.

**Right to
Withdraw**

Participants can leave a study at any time, for any reason. They don't need to explain why, and it won't affect their regular care.

**Risk and
Benefit**

Research teams explain possible risks and benefits before a study begins. Risks might include side effects or discomfort, while benefits may include access to care or contributing to future treatments.

Access to Treatment

Early Diagnosis Program

A health strategy finds serious conditions (e.g., cancer) early so treatment can start right away and be more efficient.

Expanded Access (Compassionate Use)

A potential pathway for an individual with a serious or life-threatening illness to obtain access to an experimental treatment that has not yet been approved, outside of a clinical trial, when no other treatment options are available.

In Canada, this is typically requested by a healthcare provider through [Health Canada's Special Access Program](#).

Health Technology Assessment (HTA)

A process used to understand the benefits and costs of new health treatments (like medications or devices) approved for market authorization by the Regulator (Health Canada). HTA helps decision-makers decide whether a treatment should be publicly funded.²¹

Long-Term Follow-Up Studies

Studies that check in with people for many years after treatment to see how they are doing and to watch for any long-term effects.

Market Authorization

Health Canada's official approval that allows a treatment to be sold. This decision is based on evidence showing the treatment is safe and effective.²⁴

**Pan-Canadian
Pharmaceutical
Alliance (pCPA)**

A group of Canadian provinces, territories, and the federal government that work together to negotiate drug prices. Their goal is to improve access to medications and make them more affordable.²³

**Patented Medicine
Prices Review Board
(PMPRB)**

A Canadian government agency that helps to make sure the prices of patented medicines are not excessive, helping protect patients and the healthcare system.²²

**Post-Trial
Access**

Deciding if people can keep using a treatment after the study ends.

**Special Access
Program (SAP)**

A Canadian program that allows doctors to request access to unapproved treatments when no other treatment options are available. It is often used for therapies not approved in Canada, including those approved in other jurisdictions but not yet marketed here.²⁵

Tests and Procedures in Rare Disease Research

Clinical Scales

Standardized tools or questionnaires used by healthcare professionals to measure symptoms, abilities, or quality of life (for example, pain levels or mobility). These scales help track changes over time and evaluate treatments.²⁶

Biopsy Test

Taking a small sample of tissue to check for disease under a microscope.

Blood / Urine / Stool Tests

Common tests to check your health using blood, urine (pee), or stool (poop).

Colonoscopy / Sigmoidoscopy

Tests using a camera tube to look inside the large intestine.

CT scan (Computed Tomography)

A special kind of X-ray that takes many pictures to show detailed views of bones, lungs, or other parts of the body. It uses a safe, small amount of radiation.

Echocardiogram

A test that uses sound waves to show how the heart is beating and pumping blood. It helps find problems with heart structure or function.

Electrocardiography (ECG)

A test that records the heart's electrical signals to check how it is working.

**Electroencephalography
(EEG)**

A test that checks how the brain is working by measuring its electrical activity. It helps doctors understand brain function and find possible problems.

Endoscopy

A medical procedure where a doctor uses a thin, flexible tube with a camera to look inside the body (for example, the stomach or lungs). It helps diagnose or monitor certain conditions.²⁷

Genetic Testing

A test that looks at genes to help find the cause of a rare disease. This might involve the collection of blood, saliva, hair, or skin cells. In pregnant people, amniotic fluid or placental tissue may be collected.²⁹

**Hearing Test
(Audiometry)**

A test to check how well someone hears sounds. It can help find hearing problems early.

**Lumbar Puncture
(Spinal Tap)**

A test where a small amount of fluid is taken from the spine with a needle. It helps check for problems in the brain or nervous system. Some children may feel worried or find this procedure uncomfortable, but numbing medicine is used to help with the pain.

**Metabolic
Screening**

Blood or urine (pee) tests that look at how the body breaks down and uses food and nutrients, such as sugars and fats. These tests can help detect rare metabolic conditions.

**MRI
(Magnetic
Resonance
Imaging)**

A type of imaging test that uses magnets and radio waves to create detailed pictures of the inside of the body. It does not use radiation and is often used to look at the brain, muscles, and organs.²⁸

**Newborn
Screening**

The process of testing babies very soon after birth to identify rare genetic and other serious disorders before symptoms appear.

Finding these conditions early helps families and healthcare teams start treatment, monitoring, and support as quickly as possible.

**Pulmonary
Function Test**

A test that checks how well the lungs are working by measuring how much air a person can breathe in and out.

**Vision
Screening**

A test that checks for problems with eyesight.

X-ray

A test that uses a small amount of radiation to take pictures of bones or internal organs (for example, the lungs).

Clinical Trials: Planning a Trial

Clinical Trial Protocol	A detailed plan that explains how a clinical trial will be done, who can join, and how safety is protected.
Clinical Study Agreement / Contract	An agreement between those working on the study that explains roles, responsibilities, funding and tasks.
Clinical Trial	A research study that tests treatments, devices, drugs or procedures to see if they are safe and work well. ³⁰
Clinical Trial Application (CTA)	An application submitted to Health Canada to begin a clinical trial for a drug or other therapy, including safety and study details. Approval is required before the trial can start. ³²
Clinical Trial Monitoring Plan	A document that explains how a clinical trial will be checked to make sure it is running safely and correctly. It includes how data will be reviewed and how participant safety will be protected. ³¹
Data Monitoring Committee (DMC)	A group of experts who check on the trial's safety and progress.

Data Quality and Management Plan (also called Data Safety and Monitoring Board (DSMB))

A plan to keep study data correct, complete, and organized.

Investigational Testing Authorization (ITA)

Permission from Health Canada to test a new medical device in people during a clinical trial. This ensures that the study meets safety and regulatory standards before it begins.³¹

SPIRIT / CONSORT for Children and Adolescents; TIDieR for Children

Checklists and guides that researchers use to make sure studies with children are planned, described, and reported clearly.³³

Standard of Care

The best and most widely accepted treatment currently available for a condition. New treatments are usually compared to the standard of care to see if they work better.

Clinical Trials: Designing the Study

**Adverse Event (AE) /
Serious Adverse Event
(SAE)**

An adverse event is any unwanted health change that happens during a clinical trial, whether or not it is caused by the study treatment.

A serious adverse event is more severe, for example, one that requires hospitalization, causes lasting problems, or is life-threatening. Researchers track these events closely to help keep children safe.

Bias

Bias happens when the way a study is set up or carried out gives an advantage to certain results over others, making the findings less fair. This can happen by accident or because of systematic influences built into the study.

For example, if a study only includes children from big cities, the results might not show what would happen for children living in small towns. Research teams design studies to reduce bias as much as possible.

Blinding / Masking

When people in a study do not know which treatment is being given. This may include participants, clinicians, or those assessing outcomes.

In a double-blind study, both the participants and the study team do not know which treatment is being given. Blinding helps keep the results fair and unbiased.

Clinical Trial Staging Variability

Some trials combine steps or end based on early results or safety concerns.

Clinical Trials Phases

Steps used to test new treatments, from small safety studies to large tests of how well the treatment works.

- **Phase 1 – Safety.**

Tests the treatment in a small number of people to check if it is safe and what side effects it may cause.

- **Phase 2 – Does it work?**

Looks at whether the treatment helps the condition. Still tests in a small group, but with more focus on how well it works.

- **Phase 3 – Compare with standard treatment.**

Tests the treatment in a larger group to compare it with standard treatments and look for more side effects.

- **Phase 4 – Long-term safety.**

Happens after the treatment is approved. It looks at long-term effects and how well it works in everyday use.

Comparator

The treatment or approach that a new treatment is measured against. A comparator might be the standard of care, another existing treatment, or sometimes a placebo (inactive treatment).

In many rare disease studies, researchers may compare results to data collected in the past (like from registries) or natural history studies instead of using a separate control group in the study at the same time.

Composite Outcome

A way of combining several outcomes into one measure. For example, instead of only measuring survival, a trial may also look at hospital visits and quality of life together as one result.

Control

The group in a clinical trial that does not receive the new treatment being tested. The control group may receive the standard of care, another treatment, or a placebo.

Researchers compare results from the treatment group and the control group.

Core Outcome Set

A list of key things all studies on a topic should measure to make results easier to compare.

Efficacy and Effectiveness

- **Efficacy** shows how well a treatment works in the carefully controlled setting of a clinical trial.
- **Effectiveness** shows how well the treatment works in everyday life, when people may have different health needs and routines.

Endpoints	Main results used to see if a treatment works.
Exploratory Outcome	An outcome that researchers study to learn more about a condition or treatment, but that is not the main focus of the trial. These findings can help guide future research. ³⁷
Intervention	The treatment or action being tested in a study.
Measurement Properties	Qualities that show if a tool measures what it is supposed to.
Minimal Important Change (MIC)	The smallest improvement in a symptom or test result that feels meaningful to a patient or family.
Minimal Important Difference (MID)	The smallest difference between two treatments in a trial that patients or families would notice as meaningful.
Outcome	Something measured in a study to see how a treatment affects health.
Outcome Measurement Tool	A way to measure results, like blood tests or surveys.
Patient or Caregiver-Reported Outcome (also called Patient Reported Outcome Measures (PROM))	Information provided directly by a patient, or their caregiver, about their health, symptoms, or quality of life. It reflects the patient's own experience and perspective, rather than being interpreted by a clinician or researcher.

Placebo

A treatment that looks like real medicine but doesn't have medicine in it. It doesn't hurt you and helps researchers test how well the real medicine works. Placebos are only used when it's safe and ethical to do so.

Sometimes people feel better simply because they believe they are receiving treatment (this called the placebo effect). Including a placebo helps researchers determine whether improvements are truly due to the treatment itself. It also provides a comparison group, so researchers can see if people receiving the actual treatment do better than those receiving the placebo. This makes the study stronger and the results more reliable.

Primary Outcome

The main result a study is designed to measure, like improvement in symptoms, physical milestones, or slowing disease progression.

Proxy-Reported Outcome

When someone else shares how a patient is doing because the patient can't speak for themselves.

Randomization

Randomization means placing people into different groups by chance to make the study fair. It helps make sure the groups are similar at the start, reduces bias, and makes the results more reliable.

This way, any differences in outcomes are more likely due to the treatment rather than other factors.

Sample Size	The number of participants included in a study. Choosing the right sample size is important to ensure the results are reliable and meaningful. ^{35, 36}
Secondary Outcome	Other results that help researchers learn more about the treatment.
Statistical Analysis Plan	A detailed plan created before analyzing study data. It describes how researchers will examine the data and which methods they will use to answer the study questions. ³⁶
Study Arms	Groups in a study that get different treatments or no treatment.
Surrogate Endpoint	A substitute measure used in a clinical trial to predict a real health outcome. For example, biomarkers might be used instead of waiting to see long-term effects like survival or disease progression. ³⁸
Unblinding	The process of revealing which treatment a participant received in a clinical trial. This is usually done after the study ends, but may happen earlier if needed for safety reasons. ³⁴

Clinical Trials: Deciding Who Can Join

Baseline	The first health check at the start of a study to show how someone is doing before treatment.
Eligibility Criteria	Specific requirements on who can or cannot join a study. Inclusion criteria are the things a person must have to take part, such as a certain age, diagnosis, or health condition. Exclusion criteria are the things that prevent someone from joining, such as another illness or a treatment that might interfere with the study.
Registry	A collection of information about children with a specific rare disease, gathered over time. In clinical trials, a registry can track health details, symptoms, and treatments, helping researchers understand the disease better, find participants for studies, and measure long-term outcomes.
Screening	Health checks and tests done before the trial starts to see if someone qualifies to join.
Stratification	Sorting participants into smaller groups based on things like age or disease progression. This helps researchers compare how treatments work for different kinds of patients.

Clinical Trials: Types of Trials

Adaptive Trial

A flexible study that can be adjusted as new information comes in to make it more effective and efficient, like adjusting the number of participants or which treatments are tested, based on early results.

Adaptive trials can make studies faster and more efficient, reduce how many people get treatments that don't work as well, and let researchers improve the study as they go based on what they are learning.³⁹

Basket Trial

A study that tests one treatment on different diseases that have something in common, like a similar gene change.

Bayesian approach

A specific way of doing statistics, by learning and making our predictions better using new information. Take predicting the weather as an example. We make a first guess about how likely it is to be sunny based on historical data.

As new information becomes available, such as weather patterns, the Bayesian approach updates our guess using both the historical and the new information.⁴⁰

Decentralized Approach

A trial done partly or fully outside clinical settings, such as at home, nearby clinics, or through remote visits.

Delayed Start Trial

A study where one group starts the treatment right away and another starts later. This helps researchers compare how timing affects results.

Factorial Trial

A study that tests two or more treatments at the same time, in different combinations, to see how they work alone or together.

Historically Controlled Trial

A study that compares a new treatment to information from past patients, instead of using a current control group.

Parallel Arm Trial

A study where different groups each get a different treatment, and they stay in the same group throughout the trial. The results of each group are compared at the end.

Pediatric Adaptive Trial Design

An adaptive trial designed to be safe and useful for children.

Pilot Trial

A pilot trial is a small early study that tests whether a bigger study will work properly.

Platform Trial

A flexible study that tests several treatments at the same time using one overall plan. New treatments can be added or removed as the trial goes on.

Platform trials can be useful because they are faster, more flexible, and more efficient than running many separate studies.

Pragmatic Clinical Trial

A study that tests how well a treatment works in everyday, real-life settings, not just in strict research conditions.

Randomized Controlled Trial

A study where people are placed into groups by chance to compare different treatments or compares a treatment to a placebo and see which one works best.

Randomized Crossover Trial

Each person tries different treatments one after the other. This helps compare how each treatment works for the same person.

Registry-Based Multi-Centre Randomized Controlled Trial

A study across different places that uses registry data to compare treatments.

Registry-Based Crossover Randomized Controlled Trial (R-RCT)

A crossover study that uses patient registry data to track treatments.

Single Patient Study (SPS) and N-of-1 Trial

Single-patient study and N-of-1 trial both focus on a single individual. A single patient study (SPS) is used to understand how a specific treatment affects that person, often when the condition is very rare or when treatments need to be personalized.

Continued to next page

Single Patient Study (SPS) and N-of-1 Trial

Results from a single patient study may help guide that individual's care and can sometimes provide insights for treating others with identical or similar conditions. A single patient study is also called Open Label Individual Patient Study (OLIPS).

An N-of-1 trial specifically uses randomized, multiple-crossover (alternating investigational drugs and placebo in the same patient), and controlled periods to both prove efficacy and safety.

Umbrella Trial

A study that tests different treatments for the same disease. Each treatment is matched to specific features, like a person's genes or symptoms.

Clinical Trials: After the Trial

Conference

A gathering of researchers, healthcare providers, patients, families, and others to share knowledge. Conferences can include presentations on new research findings, discussions of treatments in development, and opportunities to work together to improve care and advance studies.

Data Sharing and Results Reporting

Providing access to the information and findings from a trial for the public, researchers, and participants. Sharing results in this way supports learning, transparency, and better planning for future studies. Families can also ask how and when results will be shared with them.

Dissemination

The process of sharing research findings widely so they can be understood and used. Dissemination can include publishing in journals, presenting at conferences, creating plain-language summaries, or using other methods to reach the people who can benefit from the information.

Final Report / Clinical Trial Report

A document that shares how the study was done, what happened and what was learned in a clinical trial.

Lay Summary

A short, easy-to-understand summary of the trial results written for the public. This may be shared as a short article, video, or infographic.

**Long-Term
Follow-Up
Studies**

Studies that follow patients for years after treatment to see how it affects their health over time. This helps show if the treatment stays safe and works in the long run. May be referred to as a longitudinal study.

**Open-Label
Extension**

Gives participants the option to keep using the treatment after the main part of the study ends. This helps researchers gather more information about how it works overtime. While some trials offer open label extensions, it is not always an option.

**Post-Trial
Access**

Deciding whether people can continue using a treatment after a study ends, especially if it was helping them.

Publication

Publishing study results in a medical/academic journal so others can review and learn from them.

**Regulatory
Submission**

A formal request sent to Health Canada. It can be done to get approval to run a clinical trial, or to get approval to sell a treatment. It can also be used to request changes to how an approved treatment is used, such as a new condition it treats, a different dose, or updates to its label.

**Return of
Results**

Giving participants or families access to the results of the study, including what was learned and how it might affect their care or condition. Sometimes results are only shared at the end of the whole study, which may take time.

Transition to Care

Planning for how participants move from being in a study to receiving regular care. This is especially important when the treatment is not yet widely available.

Trial Discontinuation

When a study is stopped earlier than planned. This can happen for several reasons, such as safety concerns, harmful side effects, lack of clear results, or new information showing the study treatment is not likely to help.

Sometimes a trial may also be discontinued if another, more effective treatment becomes available. The decision to stop a trial early is always made to protect participants and to ensure research is done responsibly.

Withdrawal

Withdrawal from a clinical trial means a participant stops taking part before the study is finished. This can happen for many reasons, such as side effects, personal choice, or other circumstances.

Families always have the right to withdraw at any time. If someone chooses to leave the study, staying in contact with the research team can still be helpful, as it supports safety follow-up and helps make sure the study results are as complete and reliable as possible.

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