ALS Society of Canada
Société canadienne de la SLA
www.als.ca

Clinical Trials Frequently Asked Questions

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The ALS Society of Canada's (ALS Canada) vision is a future without ALS. To achieve this vision, new treatments that can help with symptom management and slow down and someday stop the progression of amyotrophic lateral sclerosis (ALS) need to undergo clinical trials on humans to ensure that they are both safe and effective before being approved for widespread availability. Clinical trials need human participants who volunteer to be involved, and in many cases, the treatment being tested will not be beneficial, but to participate is a generous offer to advance ALS science in a way that will someday help others who have yet to be diagnosed. However, inevitably there will be clinical trials testing a treatment that does help manage symptoms or genuinely slows progression of ALS and those participants might directly benefit from taking part.

The best resource for clinical trial information is an individual's ALS specialist clinician, as they will know how trial participation relates to them from a medical standpoint. Aside from the clinician, there are several resources available to provide information on clinical trials in Canada and around the world. Three online resources for Canadians seeking ALS clinical trial information are www.clinicaltrials.gov, the ALS Signal database and the ALS Canada website, which highlights active studies within the country. The ALS Canada Research Team (research@als.ca) are also up-to-date with knowledge of the global clinical trial landscape and trial information across Canada.

Information on clinical trials is far more detailed and nuanced than can be covered in this FAQ. If you have any suggestions of questions you'd like to see added, please contact us at research@als.ca.

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Questions answered in this document are as follows:

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What is a clinical trial?

A clinical trial is a research study that involves human participants. In most cases, ALS clinical trials involve testing of a potential therapy to either slow down the progression of ALS or to improve management of symptoms in ALS (provide better clinical care). This requires the study to measure the effect of the treatment on disease over a period of time. Proof of value in humans is the only way any treatment will be considered by government organizations like Health Canada or the US Food & Drug Administration (FDA) for use by doctors in treating their patients. Other trials are observational, to learn more about the disease.

When a potential therapeutic is discovered in the laboratory and has proven enough value to be continued in human testing, it may then be advanced to clinical trials for testing in people. For something to be tested in clinical trial, it requires a researcher or company willing to put the effort and financial support into pursuing human testing. Some potential treatments with promising data in the laboratory never make it to clinical trial and some treatments in clinical trial may have little or no laboratory evidence of benefit in ALS, but a company is willing to invest in directly trying them for human ALS. The latter is particularly common for treatments that a company has pursued for another condition and wishes to examine if there is an effect in ALS as well.

There are multiple stages of clinical trial that are often utilized to provide proof of safety, tolerability, and efficacy, which are all needed to apply for approval with Health Canada. The use of these stages is at the discretion of the company or researcher attempting to get the treatment into the clinic and steps can be skipped or merged to achieve these results. The following outlines the standard pathway:

- **Pre-clinical:** This represents all work using laboratory tests, cellular and animal models of ALS to test the safety and potential value of a treatment prior to human testing. This is also critical for identifying the mechanism of action for the treatment, which is important for successful clinical trials. New treatments that have never been tested in humans

before require more extensive work prior to reaching clinical trial including safety studies in multiple animals, dosing analysis to properly escalate from laboratory cells and animals to humans, and a detailed understanding of how the treatment moves through the body including reaching the disease location, often past the blood-brain barrier and into the central nervous system.

- **Phase 1:** Often these trials represent the first time a treatment has been tested in humans. Testing is usually on a small number of people, typically to assess safety and tolerability through determination of any side effects or adverse events. Phase 1 trials often involve multiple dosing regimens or levels to identify the ideal dose or route of administration to move forward into further studies. Early-stage trials may also be used to identify or confirm key biomarkers for use in later stages.

- **Phase 2:** These trials involve testing on a larger number of individuals for safety and tolerability using the optimal dose regimen determined from Phase 1; they often don't have the statistical power to truly determine if a therapeutic is effective, but a positive indication of possible effect is usually needed for confidence to invest in a Phase 3 study; often therapies already approved for other conditions can move straight to Phase 2 because safety and dosage information already exists. The purpose of Phase 2 for a company is to get everything needed to de-risk investment in a very expensive Phase 3 study by gathering as much information as possible. Phase 2 may be skipped if the company or researcher is confident in all of the parameters needed to go straight to Phase 3.

- **Phase 3:** The potential treatment is tested in a large enough number of people considered to be sufficient for determining if it will slow progression or effect symptoms of ALS while still assessing safety and tolerability. These are often called "registration" or "pivotal" trials because they are aimed at proving or disproving the value of a treatment for use in the ALS population.

- **Health Canada approval:** If a drug passes Phase 3 and significantly shows an effect on ALS progression or symptoms, drug developers (usually a pharmaceutical company who owns the treatment) can apply for approval to market with Health Canada. Canada is generally considered a secondary market to the United States and Europe so there is often a delay between positive results and Health Canada application though advocacy efforts are always ongoing to build relationships that can reduce this timeframe. Once applied to Health Canada, if accepted, review can go through multiple pathways of different duration and there are several steps in Canada between Health Canada approval and equitable access across the country. Please refer to ALS Canada's work on access to therapies for more information.

- **Phase 4:** These trials may be mandated by Health Canada, FDA, or other regulatory body, or can be voluntarily undertaken by a company or researcher to confirm the efficacy of their treatment. In 2022, it is common for companies and researchers to seek real world

evidence (RWE) to confirm efficacy through monitoring people accessing the treatment outside of clinical trial.

Why get involved in clinical trials?

There are many reasons why someone would want to participate in a clinical trial, but ultimately the decision is up to the individual. Without participants and trials, no drugs to effectively treat ALS will ever come to market, so it is a philanthropic endeavour in assisting research to help others who will be diagnosed with the disease in the future. There is always the possibility that an experimental therapeutic will positively affect someone's disease course, allowing for personal benefit from the experience, but it is important to note that the reason for a clinical trial is to understand if a treatment has value so expectations should take this into account.

Who sponsors clinical trials?

The majority of ALS clinical trials in 2022 are sponsored by pharmaceutical companies, also termed industry-sponsored. Some trials are considered investigator-initiated, which are completely run by academics, typically ALS specialist clinicians, with financial support through research grants from sources like government, private donations, or health charities.

Phase 1 and 2 trials often cost several hundred thousand dollars at minimum, and many can require several million dollars to complete. Phase 3 trials usually cost more than $10 million and many ALS trials may exceed $50 million. This is not a cost that government grants or a health charity can absorb so the partnership between academia and the pharmaceutical industry is a very important part of drug development for ALS.

It is important to remember that while most pharmaceutical companies care deeply about bringing effective treatments to people living with ALS, they are also businesses who must satisfy investors and the ultimate drive is to market a treatment for return on investment. However, that drive to expedite research to prove or disprove a treatment also means the work is moving as fast as possible.

While only a handful of companies were invested in developing experimental treatments for ALS a decade ago, hundreds of companies are working towards this currently. This is a testament to the advancements made in our understanding of ALS, which have come a long way in recent years.

How long does the clinical trial process take? Why does it take so long?

The process from discovery to clinical trial has traditionally taken more than 10 years, but recent advancements have allowed some experimental treatments to reach human trials within five years of their initial testing in the lab. Further investment from industry has created an

environment where good targets and treatment ideas are more readily advanced from lab to clinical trial.

The time from first-in-human Phase 1 trials to proof of efficacy varies, but often can take 5-10 years or more. The startup for every new trial phase requires time for design, setup (usually at multiple sites and in multiple countries), approvals for each site to run the trial locally, and more. Once the trial begins, time is required to recruit the target number of participants into the study and then each participant needs to be observed for the duration of the study, which often ranges from 6-18 months. By the time results are compiled, Phase 2 and Phase 3 trials are frequently several years long.

Given the nature of ALS, a lot of effort has gone into expediting trial processes. One evolution that has emerged in recent years is the platform trial, which is setup for multiple treatments to be tested in parallel and to allow new treatments to be added without tearing down and rebuilding the trial infrastructure. The first platform trial to launch in ALS is the HEALEY ALS Platform Trial, but others like the MND-SMART platform and the MAGNET platform from TRICALS have also started. It is expected that more will be considered, but it is unlikely they will be able to eliminate the need for standalone trials.

How does someone participate in a clinical trial?

Most clinical trials are run at ALS specialist clinics. To participate, an individual should ask the clinician at an ALS clinic about the availability of any trials they might be eligible for. Resources listed in this FAQ can be used to locate trial sites in Canada and internationally. If someone would like to participate in a clinical trial that is not located at their clinic, they should contact a host clinic found in those resources and ask for more information. They may also ask their clinician to refer them to another clinic with a trial of interest. The ALS Canada Research Team is also a resource for information on clinical trials in Canada and globally (research@als.ca).

Why are placebos necessary in ALS clinical trials?

To determine if an experimental treatment is effective in slowing down ALS progression, people being treated need to be compared to a parallel group who are receiving fake treatment to eliminate as much bias as possible from the result. Current measures used to determine disease progression in ALS are subject to unintentional bias that can mask the true effect of a treatment. As a result, the gold standard clinical trial design is a randomized, double-blind, placebo-controlled study where neither the evaluating clinician or medical team, nor the participant, are aware of whether they are receiving treatment or placebo. Every effort is made to reduce the number of participants on placebo without sacrificing the statistical requirements to ensure the trial will get an interpretable answer in the end.

The unintentional biases in current trial measurements unfortunately prevent conclusion from being drawn from individual experiences with a treatment. It is not uncommon in ALS for people

to experience benefits while on placebo and the natural course of disease varies from person-to-person, with periods of stabilization and modest reversal of symptoms also occurring.

Comparing treated individuals to control groups used in previous clinical trials (historical controls) is also susceptible to large error in interpretation as the clinic and care conditions in those trials are not the same and will undoubtedly skew the results one way or the other. Without reliable data at the end of the trial, the whole study could end up being wasted, further delaying a potentially effective treatment from getting to the wider population.

It is common for current ALS clinical trials to offer significant open label extension (OLE) portions to clinical trials where everyone who finishes the placebo-controlled portion is offered the opportunity to receive the active treatment for a duration of time. This is both seen as reciprocation for the sacrifice of participation in the placebo-controlled portion of the study and can provide valuable additional data for the sponsor regarding the treatment.

The ALS research field is working very hard to determine more objective measurements (biomarkers) that can avoid the biases of human reporting. Achieving these reliable biomarkers may eventually remove the need for placebos in clinical trials.

Why are clinical trials not open to everyone?

Clinical trials are studies paid for by a sponsor with the aim of getting a result that will help move an experimental treatment closer to being widely available for people living with ALS. In the case of pharmaceutical companies, they are designed to get answers with a mind of obtaining sufficient proof for marketing to recuperate money spent on this research process (return on investment). As a result, clinical trials often have very specific parameters designed to maximize the potential of getting those answers.

Amongst these parameters are inclusion/exclusion criteria, which should be considered early for anyone interested in participation in a particular trial. Often, key criteria will limit the study to people earlier in their disease progression, who are not being treated with anything other than standard of care drugs like riluzole and Radicava (in Canada), and who may be progressing at a particular rate. For some targeted treatments, participants may be limited to those with a specific genetic background or with a particular biomarker that is considered most hopeful to benefit from the treatment. Slower progressing individuals are often excluded from clinical trials as the measurement of an effect requires participants to have expected progression over the duration of the trial.

Efforts are ongoing between ALS clinicians, the ALS community and industry to find better ways of making clinical trial participation more inclusive. Consideration and inclusion of expanded access opportunities to provide some level of treatment to a portion of individuals who are ineligible to participate in the trial are evolving.

What is the cost of participation in a clinical trial?

Access to the treatment or placebo in a clinical trial is free and is financially covered by the sponsor of the study (usually a pharmaceutical company). The participant is volunteering to help the sponsor test their treatment, for which they hope someday to sell widely for treating people living with ALS. However, only a handful of studies will provide sufficient (or any) reimbursement for travel and accommodation expenses to participate. As most clinical trials require multiple visits to the study site/clinic, these expenses are not always trivial.

Why are some clinical trials not available in Canada?

When a pharmaceutical company wants to run a clinical trial of a potential therapeutic, they search for academic sites (clinics, usually housed in university-affiliated hospitals) where the study can be completed. Often sponsors are looking for sites where they can get strong, reliable data as quickly as possible as the faster the trial is executed, the less it costs. This is why most clinical trials are run in countries, and at specific clinics with a proven track record.

Fortunately, Canada has a good track record of running effective clinical trials. The Canadian ALS Research Network (CALS) is a group of ALS clinicians from across the country that collaborate and share best practices around care and research. It consists of 23 clinics with active trial sites in Calgary, Edmonton, Saskatoon, London, Hamilton, Toronto, Ottawa, Montreal (three sites), Quebec City, and Fredericton. Historically, clinical trials have also been available in Vancouver, Winnipeg, Kingston, and Halifax. The CALS network is constantly working alongside ALS Canada to advocate for trial access in underserved areas.

Despite participating in far less clinical trials than the United States, Canada is regularly amongst countries like the UK, Australia, and Italy, with the second highest access to trials. The vast majority of countries in the world do not have access to ALS clinical trials, though international efforts are underway to expand trial-ready sites in areas underserved globally as well.

In many cases, sponsors may decide to only perform their clinical trial in the United States or Europe, as these are the two primary regions for marketing proven treatments for return on investment. Sometimes Canadian clinicians may choose not to participate in a particular trial for various reasons. It is important to know that ALS Canada and Canadian ALS clinicians are constantly advocating for access to the most promising clinical trials. If there are any questions about why there are no Canadian sites participating in a particular clinical trial, the ALS Canada Research Team (research@als.ca) can provide more information.

Why doesn’t ALS Canada invest more in clinical trials?

ALS Canada has invested in clinical trials as part of its Research Program, but at present that only occurs when a trial, or more commonly a portion of a clinical trial, is applied to our Discovery Grant competition for funding. Often these are small, early phase trials or enhancements to

existing clinical trials through supporting biomarker work or other add-on studies. Supporting a Phase 2 or 3 clinical trial is outside the scope of ALS Canada's funding and multimillion-dollar investments in one experimental treatment with no indication of efficacy, can be a risky investment. Pharmaceutical companies who intend to eventually market a treatment for profit are the appropriate source of financial support for these expensive studies.

ALS Canada provides a lot of indirect support to help make Canada a primary destination for the most promising clinical trials. Active collaboration with the CALS network, constant advocating with pharmaceutical companies to consider Canada for future studies, supporting the next generation of ALS research clinicians through the Clinical Research Fellowship, and helping to establish and maintain key national initiatives like the Canadian Neuromuscular Disease Registry (CNDR) and the Comprehensive Analysis Platform To Understand, Remedy & Eliminate ALS (CAPTURE ALS), all keep this country on the radar of sponsors when considering their next steps.

How do we know if something worked in clinical trial?

If something is still in clinical trial, its ability to affect ALS progression remains unknown or unconfirmed, despite what someone might read through various sources.

The only reliable way to determine if a treatment is effective is through data obtained from well-designed clinical trials. The data collected to make these assessments is an extensive topic. In brief, trials typically have a primary outcome measure, which is the main method the sponsor is using to compare a difference between participants on treatment and those on placebo. Each trial will also have several secondary and/or exploratory outcome measures that are designed to provide supporting information about the effect of the treatment, including measuring critical biomarkers. The most common primary outcome measure in ALS clinical trials at present is the ALS Functional Rating Scale-Revised (ALSFRS-R), but work is being done globally to find alternative and complementary measures as there are aspects of the scale that are far from ideal. A detailed description of the common and exploratory outcome measures is beyond the scope of this FAQ.

Clinical trials where there is no placebo arm, termed "open label", are not designed to evaluate efficacy of a treatment, despite some sponsors attempting to use the data for this purpose. The subjectivity of current outcome measures, the potential for unintended biases where both participants and clinicians want a positive outcome, and the extremely variable natural progression of ALS from person-to-person make these conclusions impossible until we can establish better, more objective biomarkers of clinical effect.

In clinical trials that have limited size and representation of the overall ALS population, it is often very difficult to know with certainty whether a treatment was effective and requiring a level of subjective expert opinion. Across diseases, scientific and clinical consensus is generally the best mechanism to determine if a treatment has proven efficacy. Fortunately, the global ALS research community is connected enough to establish a reasonable understanding of the belief in the data supporting any treatment and there are a significant number of in-person conferences where key

discussions happen. While individual opinions may vary, scientific and clinical consensus also avoids the problem of individual biases. Currently, while confidence in the statistical analysis of clinical trial of data is still the most important factor, most experts in the research community weigh it against the unmet need of ALS and attempt to find a compassionate balance that considers many factors. The ALS Canada Research Team (research@als.ca) can help explain the current landscape of scientific and clinical consensus around any particular treatment.

What are biomarkers? Why are they important?

Biomarkers in ALS is a huge and rapidly evolving topic. In brief, biomarkers are objective measurements that can be made to better understand how a treatment is acting in the body. Currently and historically, most experimental treatments for ALS have been assessed based on subjective reporting of effect and assumption that the treatment acted on the expected biological pathway(s) in the participants.

There are many types of biomarkers involved in clinical trials. Some are aimed at being a reliable measurement of disease progression or objectively indicating that a treatment is working. For example, if a biological substance could be measured to reliably change in the blood as the disease progresses and that is reversed in the presence of a particular treatment, but not in placebo, it might represent a valuable biomarker. Finding these will reduce the need for subjective measurements of function like the ALSFRS-R scale or others that may have variability due to human error, like measuring breathing capacity or muscle strength. Other biomarkers may be used to determine eligibility for a clinical trial, as those individuals might be suggested, based on previous understanding, to more likely benefit.

Currently, it is also important for sponsors to consider biomarkers that demonstrate the treatment is affecting the targeted biological pathway(s). If this “target engagement” is not shown, researchers are unable to determine if a positive effect is due to the intended biology, which could slow down discovery of new and better treatments, and perhaps more importantly, whether a failure to affect disease progression can rule out biological pathways that can expedite new treatments and eliminate unnecessary duplication of trials with no chance of success from the outset.

Why have clinical trials not led to effective treatment options for ALS that are comparable to other diseases?

The simplest answer as to why we don’t yet have more effective treatment options for ALS is that we still don't fully understand the biology of the disease. There are two major reasons why this is the case.

First, ALS is incredibly complex. Like other neurodegenerative diseases, the complicated science of the central nervous system is vastly more difficult to tackle than most other organs of the

body. While we have come a long way in the past 5-10 years in terms of our understanding of ALS biology, slowing or repairing the internal dysfunction of very specialized cells like motor neurons, which are the wiring connecting our brain to our muscles, is very different from shrinking a tumour, removing a pathogenic virus or bacteria or repairing more accessible systems like the heart, lungs, or liver. Among many other layers of complexity, ALS is very different from person-to-person (heterogeneity), has an as-yet not understood overlapping biology with frontotemporal dementia and may require earlier treatment to rescue motor neurons while time to diagnosis remains a challenge that often allows the disease to progress for many months to years after symptom onset.

As a result of this still evolving understanding, most treatments currently in clinical trials could be described as somewhat generic for ALS, in that they are targeting systems we know are probably affecting the disease process but are not based on rigorous ALS-specific science. However, that is changing, and the field is on the cusp of more promising treatments, such as genetically targeted antisense oligonucleotides, that certainly hold more promise than what has been tested to date. There is far more optimism in the scientific and clinical ALS community than ever before.

Second, ALS is a massively underfunded disease by comparison. Financial support for research to better understand the disease is a fraction of a percent of more treatable diseases like cancers, HIV, cardiovascular disease, etc. The influx of pharmaceutical company investment, our evolving understanding of the disease and identification of more promising treatment targets, and advancements in treatment delivery technology that is more amenable to central nervous system diseases will help. Discovery of the first truly significant disease-modifying treatments will also undoubtedly increase investment in ALS research in a manner that should accelerate future discoveries.

What if the trial/treatment being considered is not on clinicaltrials.gov or other resource?

If you are considering a treatment that is not listed as a registered trial on clinicaltrials.gov or other resource, the first step would be to ask your clinician for advice about what you're considering. The ALS Canada Research Team is also a source of information on any treatment, whether alternative or traditional.

Alternative resources of information include, ALSUntangled, a database of open access manuscripts where a consortium of scientists and clinicians take an unbiased look at treatments that are receiving a lot of attention on the internet or elsewhere, but are typically not officially being studied in a scientifically-designed clinical trial. These treatments are usually called off-label.

Unfortunately, there are a lot of dubious individuals, businesses and treatments selling false hope to people living with ALS. It is best to at least ask someone who knows the field of ALS well for more information when considering alternative options. Most researchers are open-minded

to the fact that there are no effective marketed therapies for ALS and are mostly concerned with your safety and financial security. You should never have to pay for a clinical trial. Also, anyone running a trial should not be able to tell you that you will benefit because the exploration of that possibility is why it is a clinical trial to begin with, and if done properly, they should not be able to guarantee you will not be on placebo. A resource for outlining things to be aware of when considering off-label treatments can be found here.

If a treatment existed anywhere in the world that truly appeared to be having a positive effect in people living with ALS, scientists and clinicians in the field would do everything they could to properly confirm the benefits through clinical trials and get it to people with the disease as soon as possible. ALSUntangled is constantly exploring alternative possibilities for further examination.

Why aren't experimental treatments available widely when there is so little to help people with ALS?

There are many reasons why experimental treatments are not widely available to everyone, but the primary reason is that they are experimental, with no proven indication of safety or efficacy. For clinicians, there can be concerns over safety for their patients, if it has not been firmly established. However, noting that there is often a higher tolerance for risk in the ALS community, clinicians may be willing to consider opportunities for access of unapproved treatments, though many are also careful about providing false hope by asking for access to treatments that have no solid indication of efficacy.

Health Canada has a pathway called the Special Access Programme, where a Canadian clinician can request an unapproved treatment for their patient living with ALS. In most cases, if sufficient safety data exists, Health Canada approves the request and defers the decision to the owner/sponsor/company.

Many of the hurdles in accessing unapproved treatments is through the owner/sponsor/company. There are several reasons why a company would not be willing to provide access to their treatment including liability if there is a significant side effect that could derail their ongoing clinical trial process, the inability to afford provision of their treatment widely for everyone in a fair and equitable manner and more. In most cases, pharmaceutical companies have built strong reputations on providing safe, tolerable, and effective treatments for various conditions and do not believe in treating a broad population of people with something unproven. However, current practices are evolving towards consideration and potential provision of Expanded Access Programs (EAP), or equivalent regional terminology, to provide some level of access to individuals who don't meet the criteria to participate in a clinical trial. Such programs will be more controlled than just simple provision of treatment, to account for the aforementioned concerns, and can be quite complex to execute in a fair manner.

Why doesn't Health Canada approve a promising experimental treatment and seek proof of efficacy after it is available more widely?

There are several reasons why approving a treatment without sufficient data to support efficacy and/or without scientific and clinical consensus supporting its value, can be problematic. First, if clinician support is not evident, the treatment will not be widely prescribed, so approval would not necessarily equate to access. For those willing to prescribe, the lack of convincing data would also affect insurance coverage, whether through private insurance companies or national healthcare programs, leaving people living with ALS to pay huge, often unaffordable, out-of-pocket costs for a treatment that has no solid proof of value.

Clinical trials also require participants to be able to access standard of care treatments in addition to the experimental treatment. For most current studies, this means use of both riluzole and Radicava are allowed, though Radicava may be excluded from some studies located in regions where it is not widely approved, such as European-only trials. If Health Canada were to approve a treatment that is not widely embraced by the scientific and clinical community, anyone taking the unproven treatment would be excluded from trial participation and Canadian sites would become far less attractive to companies looking to setup their new studies. Wide approval of multiple unproven treatments would likely derail the whole clinical trial system in a way that massively delays the discovery of truly effective treatments by years or even decades.

One must also consider the source of the assessment that something is promising. Often the treatments most desired by the ALS community are based on companies with the least tempered messaging. For Health Canada to approve treatments before obtaining sufficient data and academic support would reward the sponsors who promote a biased interpretation of results to a lay audience and encourages others to follow suit.

Clinical trials in ALS have come a very long way over the years and are continually evolving through collaboration of ALS scientists and clinicians, pharmaceutical companies, and regulatory bodies like Health Canada. All are very motivated to bring effective treatments to people living with ALS as quickly as possible and while there are no easy answers in a disease of clear unmet need like ALS, there is an immense effort ongoing globally.

For additional clarification on any item, please contact the ALS Canada Research Team at research@als.ca.