Clinical Trials Q&A

Last updated February 2017

ALS Canada’s vision is that “by 2024, ALS is a treatable, not terminal disease.” To achieve this vision, new therapeutics that can slow down the progression of ALS will need to undergo clinical trials on humans to ensure that they are both safe and effective before they are approved for widespread availability. Clinical trials need human participants who agree to be involved, and in many cases, they will not likely be beneficial, but to do so is an offer of generosity to help others who will someday be diagnosed by helping researchers bring us closer to a therapy. One day, a clinical trial will test a therapeutic that slows progression of ALS and those participants might directly benefit from taking part.

The two best resources for clinical trial information are your clinician (preferably at an ALS clinic) and the website www.clinicaltrials.gov, where all legitimate, recognized studies are registered globally. However, as ALS Canada wishes to facilitate a better understanding of the clinical trial process, this document is designed as a supplement to those resources.

Questions answered in this document are as follows:
1. **What is a clinical trial?**
2. **Why get involved in clinical trials?**
3. **Who sponsors clinical trials?**
4. **How long does the clinical trial process take? Why does it take so long?**
5. **How are clinical trials run in Canada?**
6. **Where can I find out what clinical trials are happening for ALS?**
7. **How do I get involved in a clinical trial?**
8. **Why have clinical trials not led to a new therapy for ALS in over two decades?**
9. **What if the trial/treatment I’m considering is not on clinicaltrials.gov?**

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1. **What is a clinical trial?**
   A clinical trial is a research study that involves human participants. In most cases, 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). Others are observational, to learn more about the disease.

   When a potential therapeutic is discovered in the laboratory and has proven enough to be continued in human testing, it then moves to clinical trial. There are stages of clinical trial to get the drug from the testing phase to market (ie. widely available in the clinic):
• **Pre-clinical:** Testing of a potential therapeutic in the laboratory to prove it’s a strong enough candidate for human testing; involves molecular studies, cell and animal experiments

• **Phase I:** Testing on a small number of people, typically to assess safety through determination of any side effects or adverse events, and identification of appropriate dosing levels

• **Phase II:** Testing on a larger number of individuals for safety using the dose regimen determined from Phase I; 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 to move to Phase III; often therapies already approved for other conditions can move straight to Phase II because safety and dosage information already exists

• **Phase III:** Potential therapeutic is tested in a large number of people designed to determine if it will slow progression of ALS while still assessing safety

• **Health Canada approval:** If a drug passes Phase III and significantly shows an effect on ALS progression, drug developers (either academic study leaders or a pharmaceutical company) will apply for approval to market with Health Canada; typically process takes one year to be approved for market (those with private insurance coverage or ability to pay), though ALS Canada has advocated for any ALS therapeutic to go through Priority Review, which takes 6 months; further advocating at the provincial level to have a therapy covered by universal health care likely takes a minimum of two years to reach decision after a positive Phase III. ALS Canada will also advocate to ensure any possible Special Access Programme abilities are utilized for Canadians living with ALS

• **Phase IV:** Often, therapies need to be monitored once they are on the market and accessible to the wider population; Phase IV ensures continued safety and efficacy for Canadians

2. **Why get involved in clinical trials?**
   There are multiple reasons why someone would want to participate in a clinical trial, but ultimately the decision to do so is yours. Without participants and trials, no drugs to effectively treat ALS will ever come to market, so it is philanthropic in assisting research to help others who will be diagnosed with the disease in the future. Additionally, there is always the possibility that an experimental therapeutic will positively effect your disease course allowing for personal benefit from the experience.

3. **Who sponsors clinical trials?**
   Typically clinical trials for potential ALS therapeutics are sponsored either by pharmaceutical companies or by academic researchers receiving funding from government agencies, private donors or health charities like ALS Canada. Phase I and II trials often cost several hundred thousand dollars at minimum and Phase III trials cost millions. For example, the 900+ person, multi-national Phase III clinical trial for the drug dexpramipexole run by Biogen Idec in 2011/2012 cost approximately $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. The drive of the pharmaceutical companies might be the bottom line, but that drive will also help to push for as accelerated process as possible.

4. **How long does the clinical trial process take? Why does it take so long?**
   Typically it can be 5-10 years before a drug can go from the first clinical trial to being submitted for approval by Health Canada (should it pass Phase III). One of the biggest delays is obtaining all the appropriate permissions from Health Canada’s Therapeutic Products Directorate (TPD) to perform the study in humans. This can sometimes take more than a year for each new trial.

   Coupled with the time of recruitment and execution of the trials, followed by design of subsequent studies after successful trials, the process is lengthy, but it is necessary to ensure that Canadians are prescribed therapeutics that are truly safe and effective.

5. **How are clinical trials run in Canada?**
   To access a clinical trial, you will need to be attending an ALS clinic and ask the neurologist or physiatrist (in the event there is no neurologist) if there is anything available to you. A list of ALS clinics in Ontario and their contact information can be found here. To find out about Canadian ALS clinics outside of Ontario, please contact your local ALS Society.

   The [Canadian ALS Research Network](https://www.calsnetwork.ca) (CALS) is an entity that is designed to increase the number of clinical trials for ALS coming to Canada. CALS consists of 16 ALS clinics from across the country including: Vancouver, Calgary, Edmonton, Regina, Winnipeg, London, Hamilton, Toronto, Kingston, Ottawa, Montreal (3 clinics – Montreal Neurologica Institute, University of Montreal and Rive Sud), Quebec City, Halifax and Fredericton.

   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. CALS provides a single entity for all of Canada that a company would have to deal with as opposed to having to seek out information for each clinic individually. Not only is this advantageous in bringing more/better trials to Canada because it is easier and hence, more attractive for the pharmaceutical companies to deal with a single entry point, but it also provides a higher likelihood for sites to be chosen that otherwise might not get access to multi-national studies and top experimental therapeutics. For example, the Phase IIb clinical trial of tirasemtiv, a multi-national study, involved an unprecedented 12 CALS sites.

   Canada also has a second world class tool for optimizing clinical trials in ALS called the [Canadian Neuromuscular Disease Registry](https://www.cnndr.ca) (CNDR). This registry gathers medical information from people living with ALS across Canada to help match people up with clinical trials. As we move more to the possibility of personalized therapeutics and more stringent inclusion/exclusion criteria (see below information about [www.clinicaltrials.gov](http://www.clinicaltrials.gov)), tools like
the CNDR can help to recruit suitable people into trials which will hopefully also entice more exciting experimental therapeutics to Canada. It might also someday be a valuable resource to match people to experimental treatments that they would likely have a good shot at benefiting from based on specific aspects of their disease.

In addition, the **Canadian Clinical Trial Asset Map** is a new resource that was just launched by Health Canada in attempt to increase the number of clinical trials in Canada. This will be an online clinical research community where clinic sites can add their information and capabilities so clinical trial sponsors, like pharmaceutical companies, can have another central resource to determine what sites would be valuable to contact for participation in testing their therapeutic.

6. **Where can I find out what clinical trials are happening for ALS?**

All valid clinical trials will be registered with the website [www.clinicaltrials.gov](http://www.clinicaltrials.gov). You can type the term “amyotrophic” into the search box to find all trials related to ALS. You can further click on “Modify this search” to select for certain parameters including trials that are Open (not yet recruiting participants or actively recruiting) or Closed (active and running or completed).

There are several key things you can look for in a study listed on this website. Using the most recent **Phase II study of the drug tirasemtiv (CK-2017357)** as an example, here are some of the things to look for:

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**Study of Safety, Tolerability & Efficacy of CK-2017357 in Amyotrophic Lateral Sclerosis (ALS)**

**Purpose**

The purpose of this research study is to evaluate the safety and effectiveness of **CK-2017357** when taken with or without riluzole (also called Rilutek®) in patients with Amyotrophic Lateral Sclerosis (ALS).

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<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Drug: CK-2017357 Other: Placebo tablets</td>
<td>Phase 2</td>
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You will see this is listed as a Phase 2 (same as Phase II) trial and that it is Interventional. That means it is a trial to try and affect the disease course rather than manage symptoms or to gain information observationally. It also states that the primary purpose is treatment.

Often you will see the term ‘double blind, randomized, placebo-controlled’. This means that both the participant and the clinician are blinded as to who randomly (by computer) receives placebo (fake therapy, "sugar pill") and who randomly receives the actual therapeutic. Only the clinic pharmacy has the information. This blinding prevents the participant from being biased about how they are feeling when in the study and prevents the clinician from being biased in their evaluation. There is a natural desire to be testing an effective treatment and this can cloud judgement of both the participant and the clinician.

On the screenshot above you will also see that there are Primary Outcome Measures and Secondary Outcome Measures. The primary measure is the main means of evaluating the trial. In this case, it is a measure called the ALSFRS-R, which is an estimate of an individual’s degree of functional impairment based on 12 questions and ratings on a five-point scale from 0 = can’t do, to 4 = normal ability. Scores are summed to produce a reported score between 0 = worst and 48 = best. The slope of decline in this score is the main method used to assess the effectiveness of tirasemtiv in this trial. Secondary outcomes are measures that are of interest, but that the trial might not have the statistical power to get a definitive answer. In the case of this trial, there was no significant difference in the ALSFRS-R, but there was in the secondary measure of slow vital capacity (SVC – amount of air you can slowly exhale after inhaling deeply). As a result, a new Phase III trial of tirasemtiv will be executed, with SVC as the primary outcome measure.
In this portion, you will see the **Estimated Enrollment** number, as well as the dates of start and completion. There is also an indication of the type of drug (tablets in this case), the dose and a description of the treatment regimen.

Of note, enrollment number is key in determining how much can be interpreted from clinical trial results. If this number is low (often for Phase I or small Phase II it can be only 10-20 participants), very little, if anything, can be interpreted. This is common to any statistical evaluation, but is even more prominent in ALS because of the variability of the disease from person to person. For example, if there are 20 participants (10 on therapeutic, 10 on placebo) and you have 6 slow progressing participants in the therapeutic branch and only 1 on the placebo, it might end up looking like there is a significant slowing of disease progression in the study even if the therapy does nothing. That is why to truly see efficacy, as in the study displayed here where the SVC measure was enough to stimulate a Phase III trial, there must be high enough enrollment (the above study had 680 participants) to prevent data from being skewed as at higher numbers it would be assumed that both the placebo and the treatment groups would have approximately the same percentage of fast and slow progressors.

Thus, it might be valuable to consider this when you research further information on certain trials. For example, **GM604, a drug from the company Genervon, had 12 participants**, making the efficacy of that treatment virtually impossible to interpret from that particular trial.
Under **Eligibility**, you will see the criteria for being able to participate in the trial. The reason this criteria exists is because the study must have participants that will allow for the best chance of getting a real answer about whether the therapy works. For example, in the above study, anyone using non-invasive positive pressure ventilation might confound the results with respect to the respiratory secondary endpoints, so they are excluded. Another example is that anyone who does not score a 2 or a 3 on at least four questions of the ALS-FRS-R would not be included in the study. This shows the desire to have participants that have some impairment, but have also not lost too much function. In this case, the investigators feel participants meeting those criteria provide the best chance to see if the therapy works.

7. **How do I get involved in a clinical trial?**
Ask your clinician to either refer you to an ALS clinic or if you are already attending an ALS clinic, ask your neurologist/physiatrist. They will inform you if you fit the criteria for inclusion in any of the trials being run at your clinic. Often they may be able to assist you in options available at another clinic if there is something you qualify for.

If you are interested in a particular trial, and you qualify, you will be asked to fill out a printed form providing informed consent. This will outline the details of the study, as well as potential risks, benefits or side effects. You have the right to ask questions throughout the study and withdraw your consent at any time.

8. **Why have clinical trials not led to a new therapy for ALS in over two decades?**
ALS is a disease where the journey is different for everyone. While the average lifespan after diagnosis is 2 to 5 years, some will progress very rapidly, while others will live with ALS for more than a decade. This “heterogeneity” as it’s called in science, is possibly part of the reason we have no other therapies for ALS other than riluzole. The other major reason is that we just have not been able to understand this complex disease well enough yet to develop the right therapies.
When testing a new therapy in clinical trial and the study has participants who are both slow and fast progressors, there needs to be a high enough number of total participants to prevent either from skewing the data. For example, consider a trial with 20 participants (10 on therapeutic, 10 on placebo) and you have 6 slow progressing people in the therapeutic branch and only 1 on the placebo, it might end up looking like there is a significant slowing of disease progression in the study even if there was no effect because of the larger number of slower progressors in the treatment group. Conversely if it was the other way around, we might miss a potential protective effect of the therapy because of the excess slow progressors in the placebo group. However, when the number is 200, for example, the chances of a significantly skewed group after randomization is much lower.

Another area of improvement in clinical trials that have been executed in the past is that investigators have not been able to tell if the intended mechanism of action for a therapeutic was properly targeted and affected. This means when a therapeutic fails to show efficacy, it is not possible to know if it’s the biological mechanism that is not beneficial or simply the particular therapeutic.

It is also entirely possible that the heterogeneity of ALS has caused us to miss some therapies that might have slowed disease progression in some specific individuals. Beneficial effects in a small number of individuals could be lost when lumped into the bigger group.

These possibilities have caused two courses of action:

• First, some investigators are going back into data after the trial has finished to examine if perhaps any subset of individuals might have received a benefit. In that case, they then will attempt to determine what about those individuals might make them unique and propose a subsequent trial using participants that are screened for these unique factor(s) (biomarker). This is an example of what the company Neuraltus did with their drug NP001. In a Phase II trial, Neuraltus found that while overall there was no benefit of the drug, a subset of participants on NP001 appeared to have little or no ALS progression over 6 months. Further analysis of those individuals revealed specific biomarkers that the company is now proposing as a means of pre-screening people who would likely benefit in a new clinical trial. It must be stated that this is not exactly common practice and many researchers are quite skeptical about the concept, but it also demonstrates the commitment that everyone feels to not overlooking something with potential merit in some people living with ALS.

• Second, ALS researchers are working very hard to determine how new clinical trials can be more intelligently designed. This involves using the knowledge we’ve obtained with regard to being able to predict the progression of individuals and match trial treatment/placebo groups with participants with similar ALS functional decline. The CNDR is designed to assist in matching the right people to the right clinical trial. In addition,
most new trials in ALS will require a biomarker to examine whether or not the biological target is being affected.

Altogether, one of the biggest advancements in ALS research over the past few years is the huge improvements in clinical trial design. With such tremendous hope in what laboratory research will discover in the foreseeable future, it will be important that clinical trial design and infrastructure are optimal when new treatments reach the point of human testing.

9. **What if the trial/treatment I’m considering is not on clinicaltrials.gov?**
If you are considering a therapy that is not listed as a registered trial on clinicaltrials.gov, the first step would be to ask your clinician for advice about what you’re considering. Alternative resources 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 not officially being studied in a Health Canada/FDA governed clinical trial (these treatments are called off-label).

Unfortunately, there are a lot of dubious people and treatments out there. 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.

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 to further examine.

For additional clarification on any item, please contact Dr. David Taylor, Vice-President of Research at dt@als.ca.