

## Developing a consortium for ALS clinical research: the Canadian ALS Research Network

**Clin. Invest.** (2013) 3(12), 1113–1117

Amyotrophic lateral sclerosis (ALS) is an incurable neurological disease characterized by progressive weakness resulting in death 2–5 years after symptom onset in most cases. Collaborative research initiatives have accelerated the search for effective treatments and are essential for the discovery process in a rare, terminal disease such as ALS. We describe the advantages of forming a disease specific network and chronicle the growth of the Canadian ALS Research Network. This includes forming infrastructure to perform clinical trials, building a program to conduct translational studies, partnering in epidemiological and imaging studies, and the development of quality of life and best practice guidelines. ALS research networks will continue to serve a pivotal role in improving the lives of patients with this devastating disease.

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**Keywords:** amyotrophic lateral sclerosis

• Canadian Amyotrophic Lateral Sclerosis Research Network • consortium  
• motor neuron disease

Amyotrophic lateral sclerosis (ALS) was first described in the 19th century by Charcot. It is a devastating neuromuscular disease resulting in rapidly progressive weakness and loss of function, ultimately resulting in death due to respiratory muscle failure in the majority of cases. It became well known in North America when New York Yankees baseball hero Lou Gehrig succumbed to the disease in 1941.

Prior to 1990, clinical trials in ALS patients were performed in few centers with small cohorts of patients typically treated with medications approved for other diseases. With the advent of ciliary neurotrophic factor [1] and other nerve growth factors, the approach to clinical trials in ALS changed dramatically. International collaborative trials began with new outcome measures and complex secondary end points. Although only one compound produced a successful result in the 1990s [2], the benefits associated with collaborative research networks to test the most promising compounds was realized and National ALS consortia were formed in the USA and Europe.

Instead of forming an independent Canadian network, the largest ALS clinics in Canada joined US consortia to participate in clinical trials. This resulted in the majority of Canadian ALS centers being excluded from international trials as Canada was rarely chosen to participate. With too few ALS trials globally, nations often compete to be included in international trials and the existence of an established national network is a significant advantage. In the absence of local studies, Canadian ALS patients keen to participate in a trial would travel to the USA at considerable personal expense. As tragic as it is for a patient to be diagnosed with ALS, it is also painful for patients to be deprived of the hope associated with participating in studies testing the most promising therapeutics.

There are numerous other important advantages of a national ALS network including the training of site personnel to participate in international trials in a

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timely manner, the establishment of a program for translational research to test molecules or ideas that originate from the local research community, and to support ALS multidisciplinary clinics. A national network can also facilitate key epidemiological studies that are feasible in a large country such as Canada with a universal healthcare system.

In order to contribute and collaborate in the global pursuit for effective treatments for ALS, a Canadian national research network was formed.

### Canadian ALS Research Network formation

To address the primary problem of too few clinical trials available for Canadian ALS patients, a meeting of the leaders of all 15 Canadian academic ALS clinics was arranged in December 2007 at the International Motor Neuron Disease Symposium. The challenges associated with attracting industry sponsored trials to Canada were presented. The systematic disadvantage of smaller sites being excluded from industry trials was also highlighted given that selection by pharmaceutical industry was typically based on patient volumes and catchment area sizes rather than the quality of the investigators and research staff. The obstacles associated with more collaborative studies including investigator-led clinical trials were also highlighted. A proposal was made to construct a national ALS research network with the primary purpose of attracting and conducting multicenter, ALS clinical research studies. The consortium would be not-for-profit and operated by its members.

The concept of forming a Canadian ALS Clinical Research network was unanimously endorsed by the leaders of all 15 Canadian academic ALS clinics. The concept was also supported by the ALS Society of Canada, the primary national organization dedicated to ALS research and patient support, and a seed grant was provided to undertake this initiative.

The Canadian ALS Research Network (CALS) was formed in 2008 and is registered as a nonprofit corporation with Industry Canada [101]. CALS is a national academic alliance committed to the pursuit of ALS clinical research and is created, owned and operated by its members. Its mission is to promote multicenter ALS research studies in Canada, which include investigator- and industry-initiated clinical trials, companion epidemiological studies and translational studies in collaboration with ALS basic scientists. CALS is recognized by the ALS Society of Canada as the official clinical trials network of Canada and CALS is the official ALS affiliate organization of the Canadian Neurological Sciences Federation.

CALS members include clinicians/researchers and staff from all 15 ALS academic centers in Canada

(Figure 1). Neurologists, physiatrists, respirologists, respiratory technicians, occupational therapists, physiotherapists, basic scientists, nurses and research assistants make up the more than 65 CALS members to date. Conditions of membership include a scientific and/or clinical research interest in ALS, attendance at the CALS annual general meeting conducted at the research forum held by the ALS Society of Canada and participation in expedited reviews of industry-proposed projects when requested. Another important condition of membership is for members to agree to direct all industry inquiries regarding potential ALS pharmaceutical trials to CALS headquarters. In this way, CALS can first review the proposal to determine scientific merit, feasibility and appropriateness for Canadian ALS subjects. It also affords all CALS sites the opportunity to review the proposal and apply to participate in the study if a call for sites is issued. This model is also advantageous for the pharmaceutical industry in that protocol feedback is provided by key opinion leaders during the expedited review process and CALS centralized headquarters can provide Canada-wide site metrics and contact information to assist in site selection.

In addition to attracting and conducting clinical trials, epidemiological, genetic and quality of life studies in ALS can be facilitated by a cross-Canada network of ALS researchers. These studies require multicenter and often multinational participation given the low incidence and prevalence rates of ALS [3]. CALS can form international collaborations with other ALS Consortia and researchers to pool resources and share data. In cooperation with the ALS Society of Canada, CALS can promote public and primary care education campaigns to increase ALS awareness. CALS can also help to represent Canadian ALS research initiatives at the international level.

### CALS investigator-led studies

The birth of CALS resulted in immediate success and demonstrated the benefits of constructing a consortium that can nimbly address the needs of the research community. In 2008, a small Italian trial demonstrated a dramatic effect of lithium carbonate in slowing ALS disease progression [4] and ALS patients began taking this potentially dangerous medication worldwide. The infrastructure of CALS allowed for a rapid validation study to determine if lithium was truly efficacious. In collaboration with the Northeast ALS Consortium (NEALS), CALS conducted its first clinical trial [5]. The study represented the first Canada-wide investigator-initiated clinical trial in patients with ALS and the first ALS Canada and NIH-sponsored investigator-initiated trial conducted in Canada. CALS members were coprinciple



**Figure 1. The location of the 15 amyotrophic lateral sclerosis academic centers across Canada.**

\*There are two centers in Montreal.

investigators and served on the steering committee. CALS members were directly involved in all stages of the trial including conception of the novel study design, project management and study oversight. All 15 CALS centers participated in the trial and an equal number of subjects were recruited between the CALS and NEALS consortia.

Although the study was negative and disproved the dramatic benefits of lithium carbonate demonstrated in the pilot study, the conclusion was reached expeditiously and with minimal expense. The collaborative effort between the CALS and NEALS consortia produced the most rapid recruitment ever observed for an ALS clinical trial. The investigators meeting united American and Canadian investigators and CALS centers that had never previously participated in an ALS clinical trial received training and outcome measure certification. This resulted in the participation of more Canadian ALS sites than any prior ALS study. Upon

study completion and publication, the trial was noted for its innovative design and for being the first study to dismiss lithium carbonate as a treatment for ALS [6].

Given the success of the first collaboration between the consortia, CALS was invited to participate in a second NIH-supported Phase III study testing ceftriaxone in ALS subjects [7]. A grant was received from the ALS Society of Canada to fund the project management of CALS sites for the trial and CALS members served on the steering committee. Although the study was also negative, CALS sites made an important contribution. CALS represented only eight out of 58 sites in the trial, however, half of the CALS sites ranked in the top 15 recruiting centers for the study.

In addition to clinical trials, CALS has also been successful in promoting and facilitating a number of investigator-initiated epidemiological, quality-of-life and best-practice studies. This includes an ALS Canada-supported initiative to establish a Canadian ALS

registry [8], a Public Health Agency of Canada-supported study to determine Canadian ALS incidence and prevalence rates, a multinational ALS quality of life measure validation study, the development of Home Ventilation national guidelines for ALS [9] and the development of Canadian best practice guidelines for patients with ALS. CALS has also been used to assist in the sharing of blood and tissue samples from ALS subjects to help determine disease pathophysiology and for the identification of novel genes underlying familial forms of ALS [10]. A large grant was recently obtained for a collaborative imaging study in ALS and will use CALS infrastructure and investigators.

#### ■ Future studies

The Canadian ALS Research Network provides the necessary infrastructure and expertise to test the most promising targets identified in preclinical ALS animal models. In the truest form of translational research, CALS investigators are preparing to conduct a Phase II clinical trial testing a compound found by Canadian ALS scientists to slow disease progression in two ALS animal models [11]. Funding for this ALS Canada-supported trial has been secured and CALS centers will begin recruitment in early 2014.

#### Industry studies

With a limited number of promising therapeutics for ALS patients globally, there is international competition to be included in industry sponsored trials. The presence of a national, disease-specific network such as CALS is advantageous to the pharmaceutical industry by improving trial efficiency and reducing start-up costs. With centralized headquarters and

communication, CALS is well equipped to facilitate and expedite the requirements of pharmaceutical industry in preparing for clinical trials. The start process is streamlined whereby the study sponsors negotiate directly with CALS instead of contacting each individual site. A single confidentiality disclosure agreement can be signed by the CALS Chairperson that binds all members of the consortium saving time and legal costs. The study synopsis can then be reviewed by a small group of opinion leaders charged with the task of reviewing the project's scientific merit and feasibility for Canadian sites. Feedback is provided to the sponsor and if the study is approved, a call for sites will be issued by CALS. A list of interested sites across Canada is rapidly provided to the sponsor along with local site metrics and feasibility data. The sponsor can then make an informed decision on site selection and a single budget for the study can be negotiated with CALS. These efficiencies significantly expedite the pretrial preparation phase and replace the arduous and expensive process of site selection and budget negotiations incurred by the sponsor. CALS can also help to insure the highest quality of data collection by training and maintaining outcome measure certification for evaluators at each site.

After site selection, the CALS chairperson and project managers continue to work with the sponsor in all phases of the study to improve trial efficiency and optimize patient accrual. CALS assists sites with the start-up process including facilitating ethics approval and contract execution. They also monitor enrollment during the study to insure recruitment targets are being met.

Since inception, CALS has attracted interest from a number of pharmaceutical companies interested in using the network to test cutting-edge ALS therapeutics. On the heels of a promising Phase II study of dexamipexole in ALS [12], six CALS sites were chosen to participate in the global Phase III trial. Canada was included as one of a select group of eleven countries to participate in the global trial and the existence of CALS was instrumental in securing Canada's inclusion. In addition, the number of Canadian sites included was doubled from what was originally planned after negotiations between CALS and the sponsor. The success of CALS sites in trials has attracted two new industry studies in 2013 and Canadian ALS patients are presently being enrolled in clinical trials in record numbers (Figure 2).

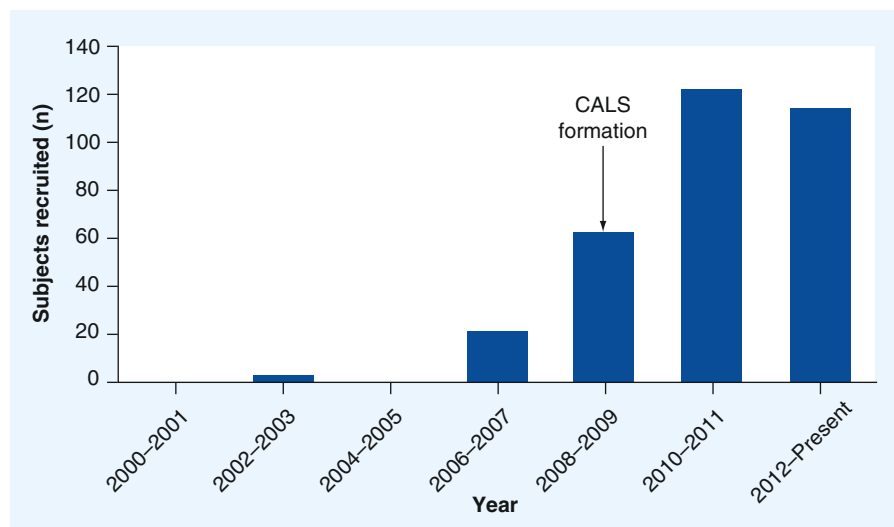


Figure 2. Canadian subject enrollment in amyotrophic lateral sclerosis clinical trials from 2000 to the present day.

CALS: Canadian Amyotrophic Lateral Sclerosis Research Network.

#### Conclusion

This manuscript has outlined the numerous advantages of forming a disease

specific network with the singular focus of improving the lives of patients with ALS. In addition to forming a foundation for national research initiatives, consortia serve a key role in facilitating international collaborations which are essential for a rare and terminal disease. ALS specific networks have accelerated the discovery process and will be instrumental in the development of effective treatments for this devastating disease.

### Future perspective

Untangling the complex pathophysiology underlying ALS and other neurodegenerative diseases will require multidisciplinary networks of researchers. Team initiatives will continue to gain favor over 'silo research' and will be prioritized by funding agencies. ALS networks will continue to accelerate the pace of discovery, and

global sharing of databases, tissue and genetic samples will produce the advances needed to turn ALS into a treatable disease.

### Financial & competing interests disclosure

*L Zinman has received honoraria from Biogen Idec, Cytokinetics and Glaxo Smith Kline and support from the ALS Society of Canada, the Canadian Institute of Health Research, the NIH and the University of Toronto. A Genge has received honoraria from Biogen Idec, Glaxo Smith Kline, Novartis, Grifols, CSL Behring, Genzyme and Cytokinetics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

### Executive summary

- The Amyotrophic Lateral Sclerosis (ALS) Society of Canada supported the establishment of a network of 15 multidisciplinary ALS clinics across Canada for the purpose of encouraging and promoting clinical research for Canadian ALS patients.
- The Canadian ALS Research Network (CALS) has a central mechanism for reviewing clinical trials that are being conducted internationally; thus industry has a straightforward mechanism to avail itself of when considering bringing a treatment trial to Canada.
- CALS has participated in five international clinical trials since 2008.
- CALS also facilitates nonindustry driven clinical research including: imaging, epidemiological and genetic studies, the establishment of a Canadian ALS Registry, the development of National Guidelines for home ventilation and the validation of ALS-specific quality of life measures.

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