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Proceedings of the 2019 Canadian Inflammatory Myopathy Study Symposium: Clinical Trial Readiness in Myositis

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ABSTRACT. The Canadian Inflammatory Myopathy Study (CIMS) is a multicenter prospective cohort recruiting in 8 centers across Canada. One of the aims of CIMS is to conduct and participate in clinical trials in autoimmune inflammatory myopathies (AIM). Conducting clinical trials in rare diseases such as AIM presents challenges. During this symposium, experts in the field presented different solutions to successfully conduct clinical trials in AIM, including the importance of collaboration and careful trial design, as well as training and mentoring of young investigators.

Key Indexing Terms: clinical trials, dermatomyositis, inclusion body myositis, polymyositis

The Canadian Inflammatory Myopathy Study (CIMS) group held its second national symposium in Montreal, Canada, on December 6, 2019. The goal was to develop capacity to conduct and participate in clinical trials in autoimmune inflammatory myopathies (AIM). The meeting was organized by Drs. Marie Hudson (chair), Océane Landon-Cardinal, and Valérie Leclair. The event was attended by 11 rheumatologists, 1 neurologist, 1 pediatric rheumatologist, 1 pediatric neurologist, 1 neuropathologist, 1 respirologist, 1 physiotherapist, 1 nurse clinician, 2 patient research partners, 2 non-medical scientists, and 3 representatives of the pharmaceutical industry. The symposium was sponsored by a Canadian Initiative for Outcomes in Rheumatology cAre (CIORA) grant, the McGill Interdisciplinary Initiative in Infection and Immunity (MI4), and industry.

The CIMS cohort was inspired by a strong Canadian commitment to collaborative research in rheumatic diseases. It was created and enrolled its first subjects in 2014. This pan-Canadian multicentered prospective cohort has now recruited more than 230 AIM subjects from 8 sites across Canada. Data are collected annually and entered into a central database for the purpose of epidemiological and discovery research[1,2,3,4,5]. The next goal for the study group is to develop capacity to conduct and participate in clinical trials in AIM.

Martin Jarry and Suzan McNamara, 2 patient advocates, opened the symposium. They emphasized the importance of patient advocacy in rare diseases and how this could shape the research agenda, even that of industry[6]. With an overall incidence of 8–18 cases/million/year and a prevalence of 14–30 cases/100,000, AIM is a rare disease[7]. At the moment, most industry-sponsored clinical trials in adult AIM do not include Canadian sites. Canadian patients with AIM are thus at a considerable disadvantage regarding early access to potentially novel therapeutic interventions. Yet Canada has strengths that could help attract industry, including a favorable exchange rate. The challenges of conducting clinical trials in Canada and possible solutions were examined throughout the symposium and are summarized in Table 1.

Collaboration facilitates translational research and accelerates access to clinical trials for patients with neuromuscular diseases. TREAT-NMD is an example of a global network in neuromuscular diseases offering an infrastructure to connect

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researchers, clinicians, patients, and industry worldwide[8]. The chair of the TREAT-NMD Global patient registry, Dr. Craig Campbell, outlined its multifaceted approach to clinical trials facilitation including training and education as well as guidance for study planning. The global registry also serves as a link to easily locate centers that could be sites for any given trial, benefiting both patients and industry. A key message from this session was that it is important for research groups to identify common goals and to build their network infrastructure around them, because a desire to cover too much ground can lead to failure.

Dr. Brian Feldman, a pediatric rheumatologist and clinician-researcher, shared his experience conducting clinical trials in AIM. The pediatric rheumatology community has been a leader in successful collaborative networks such as the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the Pediatric Rheumatology International Trials Organisation (PRINTO) and has played a major role in the International Myositis Assessment and Clinical Study group. Those groups were key in developing outcome measures and standardizing treatments in juvenile dermatomyositis[9,10,11]. One of the main points of Dr. Feldman's presentation was the benefit of "thinking outside the box" when designing clinical trials in AIM. He presented alternative study designs and analytic methods such as pragmatic trials and the inverse probability of treatment weighting of observational data that are cost-effective and leverage existing research infrastructure[12,13].

Dr. Rohit Aggarwal, an adult rheumatologist and clinician researcher, discussed trial design and outcome measures in AIM. He presented the strengths and limitations of the 2016 American College of Rheumatology/European League Against Rheumatism criteria for clinical response in dermatomyositis and polymyositis[14]. Notably, he discussed the pitfalls of the core set measures including the manual muscle testing (operator dependent, ceiling effect) and global activity visual analog scales (subjective, assessing several constructs at once). Dr. Aggarwal discussed newer outcome measures that could be easier to implement in a busy clinical practice such as physical activity monitors, physical function testing (e.g., Sit-to-Stand, 6-minute walk test, and timed up and go) as well as devices to obtain more objective measures of muscle strength, such as handheld dynamometers)[15,16]. Dr. Aggarwal proposed the idea of a Myositis Clinical Trial Consortium that would have as a primary goal facilitating multicentered clinical trials in AIM. In a similar manner as TREAT-NMD, this consortium would facilitate planning and collaboration between different centers and would support clinical trial readiness by mentoring junior investigators, sharing standard operating procedure, and developing classification criteria/outcome measures.

Table 1. Challenges of conducting autoimmune inflammatory myopathies (AIM) clinical trials in Canada.

Challenge	Possible Solution
Limited resources	Consider innovative trial designs (e.g., pragmatic trials, patient-centered outcomes). Facilitate recruitment using established AIM registries.
Regulatory agencies	Partner with regulators to develop and validate outcome measures that meet their requirements.
Inexperienced investigators	Mentor young investigators to increase capacity. Create and maintain easily accessible training resources.
Complex outcome measures	Develop and validate AIM subset-driven outcome measures that can be easily interpreted.

Dr. Nick Bansback, a health economist, described emerging methods to co-design trials in collaboration with patients. The need for alternatives to traditional trial design has emerged from the increasing recognition that a lot of resources are invested in trials investigating treatments that many patients do not want, either through the treatment characteristics (mode of delivery, side-effect profile) or trial outcomes that are not sufficient to guide a patient's treatment decisions. In AIM, where patients and resources are scarce, patient-centered approaches could ensure optimal management of resources. While patient-reported outcomes are important and of interest for regulatory agencies, they do not always reflect patient preferences or priorities. Dr. Bansback explained the basis of patient-centered trial designs using examples from studies in rheumatoid arthritis and systemic sclerosis[17,18].

Finally, Dr. Barbara White, chief medical officer for Corbus Pharmaceuticals, gave an industry perspective on conducting clinical trials in rare diseases. Dr. White acknowledged the need for new treatments in AIM, but pointed out that the rarity of the disease, the lack of consensus on classification criteria, and the complexity of the outcome measures were major challenges for industry sponsors as well as regulators. Dr. White emphasized that well-trained and committed site investigators and research personnel were key to raising industry interest and conducting successful trials. The importance for the AIM community to develop valid outcome measures that are meaningful to the patient and regulatory agencies was also discussed.

Some main points should be considered to achieve clinical trial readiness in AIM. First, collaboration was mentioned throughout the presentations and the speakers gave several examples of successful networks facilitating clinical trials in rare diseases. Second, planning and trial design, both traditional and innovative, were mentioned as crucial for successful clinical trials. Third, training and mentoring young investigators to provide them with the tools to meet sponsors' expectations and encourage them to invest in research were deemed to be essential.

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