CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

risdiplam (Evrysdi)

Hoffmann-La Roche Ltd

Indication: For the treatment of spinal muscular atrophy (SMA) in patients 2 months and older.

December 10, 2020

CADTH

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**SR0661-000**
Generic Drug Name (Brand Name)	**Risdiplam (EVRYSDI)**
Indication	**Spinal Muscular Atrophy (SMA)**
Name of the Clinician Group	**The Neuromuscular Disease Network for Canada (NMD4C)**
Author of the Submission	Dr. Hanns Lochmüller, Neurologist, CHEO Research Institute and Dr. Bernard Brais, Neurologist, Montreal Neurological Institute and Hospital Dr. Jodi Warman-Chardon, Associate Scientist, Neuroscience Program Ottawa Hospital Research Institute, Dr. James Dowling, Pediatric Neurologist, The Hospital for Sick Children, Toronto Dr. Craig Campbell, Pediatric neurologist, Children's Hospital – London Health Sciences Centre Dr. Kathryn Selby, Pediatric Neurologist, BC Children's Hospital Research Institute, Vancouver Dr. Mark Tarnopolsky, Neurologist, McMaster Children's Hospital/Hamilton Health Sciences Dr. Jiri Vajsar, Neurologist, The Hospital for Sick Children, Toronto Dr. Jean Mah, Pediatric Neurologist, Alberta Children's Hospital, Calgary, Alberta Dr. Colleen O'Connell, Staff Physiatrist/Research Chief, Stan Cassidy Centre for Rehabilitation, Moncton Dr. Kerri Schellenberg, Associate Professor Neurology, University of Saskatchewan
Contact information	Name: Hanns Lochmüller Title: Senior Scientist, CHEO Research Institute, Professor of Neurology, University of Ottawa Faculty of Medicine and The Ottawa Hospital Department of Medicine [redacted]

1. About Your Clinician Group

https://neuromuscularnetwork.ca/

The Neuromuscular Disease Network for Canada (NMD4C) is the new pan-Canadian network that brings together the country's leading clinical, scientific, technical, and patient expertise to improve care, research, and collaboration in neuromuscular disease.

Launched in January 2020 with funding from the Canadian Institutes of Health Research (CIHR) and Muscular Dystrophy Canada (MDC), NMD4C builds on existing national initiatives such as the Canadian Neuromuscular Disease Registry (CNDR), the Canadian Pediatric Neuromuscular Group (CPNG), and the former neuromuscular network CAN-NMD. The mission of NMD4C is to improve the care, research and treatment of NMDs for all Canadians. Its vision is to be a comprehensive, inclusive, open and enduring network through which Canadian stakeholders can share expertise and data, and collaborate on joint activities and research for the benefit of Canadian patients.

The network's goals are to:

- Formalize and sustain a network of NMD stakeholders united around a cohesive three-year work plan
- Train and educate the next generation of NMD stakeholders (clinicians, scientists, and patient advocates)
- Raise the standard of care for NMD and enable access to therapies across Canada
- Strengthen biomedical and clinical infrastructure to build research capacity in Canada

2. Information Gathering

Please describe how you gathered the information included in the submission.

Clinicians with experience treating SMA, including clinicians with experience with Risdiplam were asked to contribute to this submission. These expert clinicians contribute to the knowledge of SMA and its treatments and are involved in clinical and observational research, clinical guidelines development and health technology assessment. The clinicians contributing herein are familiar with the data from clinical trials on treatments for SMA, and, specifically, for Risdiplam.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Response:

5q SMA (hereafter referred to as SMA) is a genetic disorder caused by biallelic mutations in the SMN1 gene. There are different clinical subtypes of SMA based on age of onset, function, and outcome. The most common subtype is SMA Type 1, which presents with symptoms in the first 6 months of life, and untreated results in death typically before the age of 2. SMA subtype is correlated with the number of genetic copies of a modifier gene called SMN2. Both SMN1 and SMN2 encode for SMN protein. Patients with SMA Type 1 most commonly have 2 copies of SMN2, while patients with Type 2 typically have 3 copies, though can have 2 or 4. Therapeutic strategies for SMA have centred on increasing the amount SMN protein, either by acting on SMN2 (Spinraza, Risdiplam) or SMN1 (Zolgensma).

Nusinersen (Spinraza), has been approved by Health Canada since July 2017 for the treatment of 5q spinal muscular atrophy (SMA). It is a synthetic anti-sense oligonucleotide (a type of genetic material)

that enables the *SMN2* gene to produce more full-length SMN protein thereby correcting the molecular abnormality of the disease which is necessary to help relieve the symptoms of the disease. If commenced early enough, it is possible that it may prevent the severe loss of motor neuron function and profound progressive weakness. This treatment has been recommended for reimbursement by Canadian Drug Expert Committee CDEC and as such most children with SMA are receiving nusinersen as a part of their treatment regimen. Nusinersen is injected into the spinal fluid every four months after an initial four loading doses that occur closer together during the first two months of treatment. The procedure is typically done under sedation at an experienced pediatric centre.

One main study[1] of nusinersen, involving 121 babies (of an average age of 7 months at treatment onset) with SMA, showed that it is effective in improving motor function, reducing the need for assisted ventilation, and greatly extending survival, when compared to placebo (sham injection).

SMA-treating clinicians consider the approval of nusinersen to be a significant advancement in the treatment of patients with SMA.

Onasemnogene abeparvovec (Zolgensma) is an adeno-associated virus (AVV) vector-based gene therapy for the treatment of children less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene and with two copies of *SMN2* gene. This treatment is currently under review by the Common Drug Review and has been granted Priority Review status by Health Canada. There is a managed access plan globally and a very limited number of Canadian children have been able to access this drug via that pathway.

Onasemnogene abeparvovec is a one-time intravenous infused treatment that has been shown[2] to reduce the need for assisted ventilation and extend survival in infants with SMA type 1.It has also been shown to help improve motor developmental, including sitting without support for at least 30 seconds, a motor milestone not obtained in untreated babies with SMA type 1.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Response:

For patients with early onset SMA, preservation of motor neurons, improving survival, improving motor function, delaying or alleviating the need for assisted ventilation, delaying or alleviating loss of ability to speak, and delaying other secondary complications (such as failure to thrive, scoliosis, recurrent pulmonary infections, etc.), and reducing burden on caregivers are goals that new treatments would ideally address.

For individuals with late onset SMA, treatment goals would be to maintain current level of motor function and strength (prevent further loss of motor function), achieve disease stabilization (prevent disease progression, including avoidance of need for ventilation), promote independence, and improve overall health-related quality of life.

[1] Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, Chiriboga CA, Saito K, Servais L, Tizzano E, Topaloglu H, Tulinius M, Montes J, Glanzman AM, Bishop K, Zhong ZJ, Gheuens S, Bennett CF, Schneider E, Farwell W, De Vivo DC; ENDEAR Study Group. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017 Nov 2;377(18):1723-1732. doi: 10.1056/NEJMoa1702752. PMID: 29091570.

[2] Dabbous O, Maru B, Jansen JP, et al. Survival, Motor Function, and Motor Milestones: Comparison of AVXS-101 Relative to Nusinersen for the Treatment of Infants with Spinal Muscular Atrophy Type 1. Adv Ther. 2019;36(5):1164-1176. doi:10.1007/s12325-019-00923-8

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Response:

While nusinersen has significantly changed the standard of care for children and youth with SMA, this treatment is not suitable (or accessible) for all patients with SMA. In some jurisdictions children who have ever walked-that is any child with type 3 disease- are excluded from reimbursement. Additionally, in the clinical trials conducted for nusinersen, not all patients with Type 1 and 2 SMA, responded to treatment.

Use of nusinersen in some patients is also limited by its invasive intrathecal route of administration. For patients who have severe scoliosis or who have undergone a spinal fusion, this treatment is much more challenging and requires interventional radiology approaches. There are a number of children who do not tolerate lumbar puncture procedures due to respiratory fragility or poor access to the spine. Some patients may experience side effects from repeated lumbar punctures which limits further nusinersen therapy. Additionally, access to specialists and facilities who can administer the treatment is not universal, and barriers such as travel long distance are a reality for many in Canada.

Nusinersen is reimbursed for children in most provinces, with few provinces providing coverage for this treatment for adults.

In the U.S., the FDA has required that onasemnogene abeparvovec be administered before two years of age. In Europe eligibility is determined by a weight limit as well as number of *SMN2* copies. The administration of this drug is also limited by the fact that patients cannot have antibodies to AAV-9 and a fairly high proportion of patients have potentially serious elevations of liver transaminases. A reimbursement recommendation by the Common Drug Review is anticipated very soon for this treatment.

While the therapies discussed above produce the missing SMN protein (although in different ways), there is a need for more convenient (and less invasive) treatments as well as a need for more effective treatment options for adults with SMA.

As well, while treatments that address the root cause of SMA by producing the missing protein are changing care, other therapies that help improve muscle functions are greatly needed and are expected to play a pivotal role in patient care.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Response:

- This treatment is particularly important for SMA patients with contraindications for nusinersen or Zolgensma.
- This treatment fills a need where oral therapy is preferred or required for all types of SMA instead of sustained intrathecal therapy -- which has its own side effects and an additional economic impact. Oral therapy is particularly required for those children (<18 years) unable to receive intrathecal nusinersen by simple lumbar puncture due to severe scoliosis or post spinal fusion (even under radiological guidance)
- Adult SMA patients (over the age of 18) have a high unmet need for treatment. We recognize that there is limited evidence available for assessment of this population. However, in a rare disease

such as SMA, clinical trials of sufficient size are difficult to conduct generally, and for this sub-group of adults, the problem is compounded. For adult patients (> 18 years) given access to this therapy, we advise that provinces support the capture of outcomes data of SMA patients in the Canadian Neuromuscular Disease Registry (CNDR) to address any existing uncertainty for this subpopulation. (Please see section 7.1 for further information about the CNDR)

Comment:

Clinical trial data supporting nusinersen in older children and young adults (including those with severe scoliosis, feeding dysfunction and severe contractures) is limited.

Patient preferences should factor heavily into decisions about access to drug therapies, especially in a rare degenerative disease. For SMA patients who have a tremendous burden of illness and have a high level of health care resource use, having choice in therapy, based on strong evidence and matched to their preferences and values, should be the goal. In the context of providing true evidence-based care in real world context, risdiplam could be an additional option in the armamentarium to treat SMA, with treatment decisions guided by more structured choice awareness (facilitated in centres with expertise in SMA care).

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Response:

We believe risdiplam is an important new treatment option that may provide substantial treatment benefit for patients across the SMA disease continuum. Its oral administration has significant advantages for both patient and caregivers; it does not require specialized procedures to administer treatment, and allows patients to take the medication at home, avoiding the burden of frequent travel and reducing health care utilization costs. Intrathecal injections themselves have a risk profile as an invasive procedure, and as described, are not an option for all patients due to underlying scoliosis.

We expect risdiplam to be used as one of the options in first line treatment for early onset Type 1 SMA.

Further, risdiplam, having demonstrated to be well tolerated in patients with previous exposure to SMN splicing modifiers, could be used as a second line treatment for patients who have not responded sufficiently, or who have progressed on first-line treatment such as nusinersen.

In patients with later onset SMA (Type 2 and 3), clinically meaningful improvements in motor function were shown across a broad population. However, the size of effect was more pronounced in younger patients. Even though the magnitude of treatment effect on older patients was not as robust, we believe the evidence supports the use of this treatment in patients that are currently ineligible for nusinersen due to age or physical ability. There is also indication of maintained swallowing ability that has not been demonstrated in other medications to date.

Importantly, this treatment has been tested in clinical trials for SMA patients up to age 25 years. In addition, a trial is underway in people with all types of SMA aged 6 months to 60 years previously treated with other SMA therapies.[3]

[3] https://www.clinicaltrials.gov/ct2/show/NCT03032172?term=jewelfish&draw=2&rank=1

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

Response:

Onasemnogene abeparvovec (Zolgensma), currently under review by the Common Drug Review, may be the preferred initial treatment for babies (under the age of two) if it is approved and reimbursed in Canada. Advantages of onasemnogene abeparvovec include that it is a single, one-time intravenous (IV) infusion and, that the systemic (IV) delivery route allows for distribution throughout the CNS and peripheral tissues, which is particularly important for infants with type 1 SMA as high levels of SMN protein are required very early in life in peripheral tissues.

There remains uncertainty whether children with SMA would derive more benefit from nusinersen or from risdiplam, as there are no head-to-head comparisons. Recognizing that nusinersen has been approved in Canada, and in many other countries, there is more experience (real world data) with thousands of patients world-wide. However, risdiplam may be a preferred treatment option for certain patients. For instance, risdiplam may be preferred in circumstances where the intrathecal administration (of nusinersen) is not possible. Recognizing also that the oral route of administration for risdiplam allows for distribution and increase of SMN protein in both the central nervous system and peripheral tissues, it may be the preferred option for some patients, including many adults where stabilization of the disease can mean retention of a vital motor function, avoidance of ventilator dependency, continued ability to speak and swallow, and survival.

6.3. How would this drug affect the sequencing of therapies for the target condition?

Response:

Risdiplam would potentially be first line therapy for patients who are not eligible for zolgensma or nusinersen based on the drug label or reimbursement criteria.

For instance, it may be preferred first-line therapy: ‘

- When patients cannot receive nusinersen for safety reasons such as scoliosis, allergies, or bleeding disorders.
- When children experience adverse effects to nusinersen
- Where there is lack of access to nusinersen
- Based on patient preferences (avoid intrathecal injections, remote area of the country)
- In individuals who have antibodies to AAV9 (so cannot receive zolgensma) and also cannot receive nusinersen

It could be considered as second line therapy for patients where first-line treatment has been unsuccessful or worn off.

With respect to nusinersen, the intrathecal route of administration may limit its effects on the CNS because it may not distribute equally along the spinal cord. While the issue of distribution of nusinersen requires more study, it is hypothesized[4] that nusinersen does not reach motor neurons in the upper spinal cord as effectively as motor neurons in the lower spinal cord (the injection site is at the lumbar spine) and therefore bulbar functions (eg swallowing) are not adequately treated.

[4] Ramos DM, d’Ydewalle C, Gabbeta V, Dakka A, Klein SK, Norris DA, Matson J, Taylor SJ, Zaworski PG, Prior TW. et al. . Age-dependent SMN expression in disease-relevant tissue and implications for SMA treatment. J. Clin. Invest. 2019; 129:4817–4831.

Contributors to this submission, along with The Neuromuscular Disease Network for Canada (NMD4C) recommend that decision aids be developed to guide choice. The Knowledge Translation group at NMD4C is working on such a tool to be available in Q2 2021.

6.4. Which patients would be best suited for treatment with the drug under review?

Response:

Generally, all three treatments seem to work best the younger the children and the earlier the treatment starts. Patients benefitting the most from risdiplam are probably not different from those benefitting the most from nusinersen. The biggest need would be for children who cannot receive nusinersen for the reasons mentioned above and for adults (outside of Quebec where nusinersen is reimbursed).

For many adults living with SMA, their life course with the disease is associated with progressive losses of motor function, leading to deterioration in health and reduced independence. Stabilization of the disease can mean retention of a vital motor function(s), avoidance of ventilator dependency, continued ability to speak and swallow, and survival.

6.5. How would patients best suited for treatment with the drug under review be identified?

Response:

The diagnosis is secured through genetic testing and confirmed by the absence of normal copies of the SMN1 gene. A major disease modifier is the number of SMN2 gene copies, with fewer copies associated with earlier-onset and more severe SMA.

The identification of SMA affected infants via newborn screening presents an unprecedented opportunity for achievement of maximal therapeutic benefit through the administration of treatment pre-symptomatically.

Children and adults with SMA are typically followed and managed by specialized clinical teams, and genetics testing to confirm diagnosis and SMN2 gene copies can be readily obtained if not already documented. Patients with the “SMA 0” form of 5q SMA (infantile onset with 0 copies of SMN2) are unlikely to benefit, and patients with other genetic types of SMA, unrelated to SMN deficiency, are also not expected to benefit.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Children who have been identified through newborn screening and treated with Zolgensma or Nusinersen in a pre-symptomatic stage may show normal development, in which case they may not require treatment with risdiplam.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

Response:

Most patients will benefit from the drug, apart possibly from severely affected cases who are on permanent ventilation. In general, the youngest patients should benefit more.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Response:

Outcomes tests vary according to age and functional state and include lung function (Forced Vital Capacity), Revised Upper Limb Module (RULM) and 6-Minute-Walk-Test (6MWT). In small children also there are tests that have different sensitivity with respect to the achievement of motor milestones. Revised Hammersmith Scale (RHS) is a specifically designed outcome measure for people affected by SMA. However, because that scale might lack sensitivity and has "floor effect" the 32-item Motor Function Measure (MFM32) may be a preferred measure in younger individuals particularly aged 2–5 years, and in non-ambulant individuals with Types 2 or 3 SMA, aged 2–25 years. However, in Canadian clinical practice the RHS is widely used and accepted as the tool to measure motor function. The tests will vary according to age and functional state and include lung function (Forced Vital Capacity), Revised Upper Limb Module (RULM) and 6-Minute-Walt-Test (6MWT). In small children tests will also vary on whether they achieve motor milestones. These measures require trained practitioners and are outside of the bounds of a traditional clinic visit.

Clinician experts generally agree that Patient Reported Outcomes (PRO) instruments would be useful, however, while there are no internationally validated and agreed upon PRO instruments yet, data is being developed to inform the selection of such a measure.

In 2020, Canadian experts in adults with SMA undertook a modified Delphi process exercise to determine a consensus-based recommendation for outcomes measures to be used in adults with SMA at different functional stages. Through the CNDR and the NMD4C, it is anticipated that all clinics can prospectively collect such measures, allowing a rich pool of real-world outcomes data. Below is the abstract from the manuscript that will be submitted shortly to the Journal of Neuromuscular Diseases:

> Title: **A Canadian Adult Spinal Muscular Atrophy Outcome Measures Toolkit: Results of a National Consensus using a Modified Delphi Method**
>
> Authors: Jeremy Slaytera, Victoria Hodgkinson, Josh Lounsberry, Bernard Brais, Kristine Chapman, Angela Genge, Aaron Izenberg, Wendy Johnston, Hanns Lochmüller, Erin O'Ferrall, Gerald Pfeffer, Stephanie Plamondon, Xavier Rodrigue, Kerri Schellenberg, Christen Shoesmith, Christine Stables, Monique Taillon, Jodi Warman-Chardon, Lawrence Korngut, Colleen O'Connell
>
> Abstract: BACKGROUND: Spinal Muscular Atrophy (SMA) is a rare disease which affects 1 in 11,000 live births. Recent developments in the treatment of SMA have included the study and approval of new disease-modifying therapies which require large amounts of high quality data to inform decisions around initiation and continuation of therapy. In Canada, there are currently no nationally agreed upon standard outcome measures (OM) used in the management of adult SMA. The standardization of OM is an essential step in obtaining high quality data which is comparable among neuromuscular clinics. In rare disease, with limited patient numbers, the ability to pool and analyze data among clinics is essential to facilitate the study of natural disease progression and evaluate treatment response. Additionally, more robust and standardized data can help develop best practice recommendations.
>
> OBJECTIVE: To develop a recommended toolkit and timing of outcome measures for the assessment of adults with SMA.

METHODS: A modified Delphi method was used to determine consensus among a panel of expert clinicians treating adult SMA across Canada. The modified Delphi process consisted of 2 virtual voting rounds, followed by a virtual conference to discuss and finalize the toolkit.

RESULTS: A recommended toolkit of 8 OM across three domains of function, with an optional additional 3 measures. The recommended toolkit will be revisited within 2 years. An optimal assessment frequency was determined to be 12 months for most patients regardless of therapeutic access, while patients in the first year of receiving disease-modifying therapy could be assessed more frequently.

CONCLUSIONS: Implementation of the consensus-derived OM toolkit will lead to improved monitoring and assessment of adult SMA patients, contributing to an enriched pool of real-world evidence. Regular updates to the toolkit must be considered as new measures are developed. Adult SMA-specific Patient Reported Outcome Measures (PROM), and Quality of Life OMs should be developed to better capture status and changes in these important domains.

For complete manuscript, please contact: Colleen O'Connell, Stan Cassidy Centre for Rehabilitation, Fredericton, New Brunswick, E3B 0C7. ([redacted]

6.9. What would be considered a clinically meaningful response to treatment?

Response:

In children: achievement of motor milestones, ventilation-free survival, improvement or stabilisation of motor function.

In adults: stabilisation of motor and respiratory function, less disability with maintenance of independence and fewer hospitalisations. Maintaining ability to speak and avoiding need for ventilation support have profound impacts on patient quality of life, autonomy, ability to maintain vocational and social roles.

6.10. How often should treatment response be assessed?

Response:

With new therapies for SMA being introduced into clinical practice, it is important to monitor their effectiveness and to collect evidence to help determine which therapy should be chosen for any given patient. However, the current provincial government monitoring requirements are too frequent and there is significant variability between the provinces. In addition, quantitative outcome measures require specially trained practitioners, are time consuming, and are not currently covered with provincial funding as part of the expense of therapy.

A group of Canadian neuromuscular disease specialists, most of whom are involved in NMD4C, have written a letter to the provincial governments outlining their concerns and recommending an alternative timeline for outcome measurements in patients receiving SMA therapies. The summary is below:

SMA Therapy Outcome Measures

Written by: Victoria Hodgkinson (NMD4C collaborator) and Kerri Schellenberg (NMD4C member)

Reviewed and approved by: Kristine Chapman, Aaron Izenberg (NMD4C member), Hanns Lochmüller (NMD4C lead investigator), Colleen O'Connell, Erin K. O'Ferrall, Maryam Oskoui (NMD4C investigator), Gerald Pfeffer (NMD4C member), Stephanie Plamondon (NMD4C member), Xavier Rodrigue (NMD4C member), Christen Shoesmith, Jodi Warman Chardon (NMD4C steering committee member), Bernard Brais (NMD4C investigator), and Lawrence Korngut (NMD4C investigator)

Frequency of monitoring

The natural history of SMA is a slowly progressive functional decline. Patients' function decreases by a statistically significant amount in the matter of years, not months. As such, any decline in outcome measure scores in the span of months is more likely to be due to inter- or intra-examiner variability (i.e., the normal statistical range of error) or variability in patient effort (i.e., SMA patients have "off days" and "good days" just like anyone else) than due to a true effect of the therapy. This potential artificial decline in outcome measure scores could lead to inappropriate termination of therapy provision.

Human resource strain and patient burden

Motor outcome assessments are time-consuming and personnel-intensive, requiring significant time from physical therapists and/or respiratory therapists with specialized training. As such, there are ethical concerns around mandating that these scarce resources be utilized to provide frequent monitoring for largely stable patients for whom such frequent monitoring is not clinically relevant or evidence-based. Frequent clinic visits can also be fatiguing, time-consuming, and costly for patients.

Collection of real-world evidence and proposition for appropriate monitoring

The Canadian Neuromuscular Disease Registry (CNDR) has a clear plan to assess the effectiveness of novel therapies in a broad population. The CNDR's SMA working group of expert investigators has evaluated specific outcome assessments by way of a Delphi model to determine best practices (manuscript in preparation). They recently agreed that the best timing for outcome measurements is: at baseline, 6 months later, then annually thereafter. This timing is appropriate for clinical monitoring, congruent with available evidence in treated adults, and does not put undue burden on provincial and clinical resources or on patients and families.

The shared goal of the health care system is to provide a standard of care which is acceptable for patients, maintains appropriate resource allocation for all populations, and is feasible for the clinics. The proposed monitoring system achieves these goals.

6.11. What factors should be considered when deciding to discontinue treatment?

Response:

Factors to consider when deciding to discontinue treatment (and switch to other SMN splicing modulating treatment):

1. Accelerated deterioration in clinical status while on Risdiplam for 12 months
2. Allergic reaction and critical SAEs.
3. Patients with primary retinal disease may need special protocol/ assessments

Comment: A variety of Biomarkers are being investigated which may help to predict the variability of response to treatment and allow for a more individualized treatment pathway.

6.12. What settings are appropriate for treatment with the drug under review?

Response:

Risdiplam offers the convenience of orally administration, which can take place in the home.

Risdiplam may also be appropriate in the following settings:

- When patients cannot receive nusinersen for safety reasons

(such as spine-related factors (scoliosis, orthopedic hardware), allergies, or bleeding disorders).

- When children experience adverse effects to nusinersen
- Where there is lack of access to nusinersen
- Based on patient preferences (avoid intrathecal injections, remote area of the country)
- Individuals with contra indications to receiving zolgensma (such as positive AAV9 titers)

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

Response:

Neurologists/Pediatric Neurologists/Physiatrists

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

In Canada, the Canadian Neuromuscular Disease Registry (CNDR) and its network of site investigators and research coordinators has become an ideal model for rare neuromuscular disease (NMD) registries globally. The registry has recruited 4,000 patients with various NMDs since its launch in 2010. It has facilitated 35 trials and 75 additional data inquiries and research projects.

Through the resources of NMD4C, FAIR data principles (Findable, Accessible, Interoperable, Reusable) are incorporated into CNDR functions in order to make the data more amenable to research queries. The registry will be further developed by updating existing disease modules to ensure they capture the information useful for the diseases in question and by adding new disease modules for congenital myasthenic syndrome and congenital myopathies. The registry will continue to support academic and industry-led research including quality-of-life, burden of illness and preference studies.

The contributors to this submission recommend that provinces support the capture of outcome data of SMA patients (regardless of which treatment they receive) in the CNDR. The CNDR is happy to work with regulatory bodies to provide RWE to drive decisions and explore how outcomes perform at a population based level in Canada.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

This submission content was completed exclusively by the named authors of this submission, with the Neuromuscular Disease Network for Canada (NMD4C) facilitating collaboration and editing.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No outside help was used to collect or analyze information used in this submission.

See Section 2 “Information Gathering” for details on how information in this submission was developed.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinicians:

Clinician Information	
Name	*Hanns Lochmüller*
Position	*Senior Scientist, Professor of Neurology*
Date	*01-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Biogen	☐	☒	☐	☐
Roche	☐	☒	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Clinician Information	
Name	*Kathryn Anne Selby*
Position	*Pediatric Neurologist BC Children's Hospital*
Date	*06/11/2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Biogen	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Clinician Information	
Name	*Dr. Jiri Vajsar*
Position	*Neurologist, The Hospital for Sick Children, Toronto*
Date	*See highlighted note below*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. NOTE: Dr. Jiri Vajsar reports that CADTH has on file an up-to-date COI declaration and that CADTH has waived the requirement for a new COI as there is no change.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Clinician Information	
Name	*Dr. Mark Tarnopolsky*
Position	*Neurologist, McMaster Children's Hospital/Hamilton Health Sciences*
Date	*See highlighted note below*

☐ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
NOTE: Dr. Mark Tarnopolsky reports that CADTH has on file an up-to-date COI declaration and that CADTH has waived the requirement for a new COI as there is no change.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Clinician Information	
Name	*Bernard Brais*
Position	*Neurologist and Professor, Montreal Neurological Institute and Hospital McGill University*
Date	*19-11-2020*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Biogen	☐	☒	☐	☐
Roche	☐	☒	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Clinician Information	
Name	*Colleen O'Connell*
Position	*Research Chief, Stan Cassidy Centre for Rehabilitation*
Date	*13-11-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Roche	☒	☒	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Clinician Information	
Name	*Craig Campbell*
Position	*Pediatric Neurologist*
Date	*2020/11/13*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Roche(site investigator, advisory board chair, consultant)	☐	☒	☐	☐
Biogen (site investigator, advisory board chair, consultant)	☐	☒	☐	☐
Novartis (consultant)	☒	☐	☐	☐

Note: Site investigator for other industry with SMA activity cytokinetics, acceleron, scholar rock

Clinician Information	
Name	James Dowling
Position	Staff clinician and senior scientist, Hospital for Sick Children
Date	01-12-2020
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Deep Genomics	☒	☐	☐	☐
Dynacure	☒	☐	☐	☐

Clinician Information	
Name	Jean K. Mah
Position	Pediatric Neurologist, Alberta Children's Hospital, Calgary, Alberta
Date	11-11-2020
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Biogen – Research grant for clinical trial	☐	☐	☒	☐
Biogen – Consulting / Speakers fee	☒	☐	☐	☐
Roche – Research grant for clinical trial	☐	☐	☒	☐
Roche – Consulting fee	☒	☐	☐	☐

Clinician Information	
Name	*Jodi Warman Chardon*
Position	*Neurologist, The Ottawa Hospital/Children's Hospital of Eastern Ontario*
Date	*Please add the date form was completed (11/11/2020)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Clinician Information	
Name	*Kerri Schellenberg*
Position	*Associate Professor Neurology, University of Saskatchewan*
Date	*Please add the date form was completed (23-11-2020)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Biogen	☒	☐	☐	☐
Roche	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐