CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

nusinersen (Spinraza)

(Biogen Canada Inc.)

Indication: For the treatment of 5q Spinal Muscular Atrophy (SMA).

June 3, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0713-000
Brand name (generic)	Spinraza (nusinersen)
Indication(s)	Spinal Muscular Atrophy: Adult type II & type III patients older than 18 years of age regardless of ambulatory status
Organization	IRDPQ-CIUSSSCN, Québec City
Contact information[a]	Name: Dr Xavier Rodrigue, Head of Service PM&R, CIUSSSCN

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Recommendations are only based on RCT and didn't consider real world experience (RWE) especially the experience of province of Quebec.

Doing a new RCT would be virtually impossible and unethical.

- There would be a selection bias since this therapy is accessible in Quebec and reimbursed by the private insurance of many patients in the rest of Canada.
- The experience in Quebec demonstrates the effectiveness of the product. We simply cannot recommend such an avenue (RCT).

CADTH's argument is based solely on RCTs. On the other hand, in Quebec, there are 3 years of experience. RWE must be taken into account. CADTH considers the RCT data to be heterogeneous but did not even consider the data from Quebec that are homogeneous of Canadian population. The Quebec experience relies entirely on data from **public** systems.

1- "The maximum follow up time across studies was 14-months, which was considered insufficient to assess clinically meaningful change in outcomes in adult patients, due to the slowly progressing nature of the disease, as well as natural history."

- RWE: at IRDPQ our team as a 3 years of long-term follow-up experience with spinraza (April 2022). There are 16 patients treated with spinraza.
  - All patients decided to continue treatment.
  - All patients either maintained or improved their functional/motor ability and quality of life.

2- "The clinical experts also noted that the natural history of SMA has a variable manifestation of functional decline and improvement and over time"

- This claim is surprisingly **false.** There is no description in the literature of an improvement in function over time. After nearly 10 years of clinical follow-up, none of our patients have ever shown improvement over time but only a noticeable year-to-year decline.
- Our experience of 10 years of follow-up in multidisciplinary clinics demonstrates that there are no sustained gains in physiotherapy. Our patients just don't have the energy to pursue a long-term program. After 3 years of experience with spinraza, it is impossible to speak of a placebo

effect or an influence of physiotherapy or any other equivalent approach. Our clinical experience shows that our results are attributable to spinraza treatment only.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

Decision-making is only based on RCTs. Clinical experience in Quebec only demonstrates favorable results, and what is more, in a public system.

The Canadian SMA expert community was not consulted. There is a consensus of clinicians (ex: NMD4C) in favor. We strongly recommend that the CADTH meet with its specialist clinicians across Canada to avoid opinion bias.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

The statements are clear. However, some are based on misperceptions that do not represent our clinical experience and literature.

For example, as mentioned previously, our experience of 10 years follow-up does not show at any time an improvement in the clinical picture.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

The recommendations aren't strong enough to help clinician in Canada to explain why this medication, which is accepted in Québec, recently in Australia and in more than 20 others countries, cannot be giving to their patients…RWE haven't been consider.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐

Not applicable

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Xavier Rodrigue*
Position	*PM&R and head of service CIUSSSCN*
Date	*29-05-2022*
☒	**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

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.

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	☐	☒	☐	☐
Novartis	☒	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0713-000
Brand name (generic)	Nusinersen
Indication(s)	
Organization	Undersigned Investigators of the Canadian Neuromuscular Disease Registry
Contact information[a]	Name: Dr. Lawrence Korngut

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

As Canadian neuromuscular specialists caring for adults with spinal muscular atrophy (SMA), we write to express our opinions in response to CADTH's draft opinion regarding Biogen's request for reimbursement for Spinraza to be expanded to include adult type II & type III patients older than 18 years of age regardless of ambulatory status.

We believe CADTH's decision stands apart from the increasing global recognition of- and use of real-world evidence (RWE) to inform such decisions and undervalues RWE as a current and ongoing methodology for demonstrating therapeutic effectiveness particularly in rare disease populations. The result is an insurmountable barrier to access of an important therapy resulting in considerable inequity of access for adults with SMA between Canadian provinces outside of Quebec and 25 countries around the world.

1) Heterogeneity of Disease:

As was cited in the draft opinion, the clinical experts described the natural history of SMA types II and III in adults as one of "substantial heterogeneity in the degree of disability and motor function". While this is true, spinal muscular atrophy is one disease, caused by loss of a single gene product (SMN1), and a single treatment target. Additionally, while it is true that SMA has a variable rate of functional decline over time, it has been demonstrated to be true that patients progress in motor weakness and decline over time. Published natural history studies report progression on average of ≥ 0.5 pts./year on the Hammersmith Functional Motor Scale- Expanded (HFMSE) (Wadman, 2018). Potential learning biases in motor outcome testing may limit the interpretation of improved scores, however, on average, the evidence of stabilization and improvement is vastly different than the natural history of decline on these same measures over a similar time frame (wherein learning would also occur). Additional objective measures, including use of ventilatory support, feeding tube support, and frequency and duration of hospitalizations provide additional insight into potential therapeutic effectiveness in this population.

2) Lack of Trial Feasibility:

We strongly believe that the condition of a randomized, intrathecal sham-controlled clinical trial in SMA adults is not feasible. While nusinersen is available in certain regions of Canada (i.e., Quebec), virtually no patient is likely to enroll in a year-long intrathecal sham-controlled trial, that has already demonstrated clinical trial benefit in their disease, when they could move to Quebec to access treatment. We strongly believe that the available RWE is sufficient to demonstrate benefit in this patient population rather than a clinical trial that is not feasible and in our view is ethically dubious.

3) Real-world Evidence:

The analysis cites concerns in biases of published real-world data from adults on nusinersen (without randomization and blinding), and appears, on this basis, to discount the evidence for nusinersen clinical

value. We agree that uniform study methodologies and comparable eligibility criteria are ideal, however, given adults with SMA represent a small subgroup of a rare disease the inherent limitations of study design need to be considered. If strict eligibility and methodologies are used the resulting subgroup sample sizes shrink and conclusions are just as challenging to interpret. Biases, notwithstanding, we believe it more appropriate to look at the consistency of demonstrated benefits across multiple real-world studies in comparison to the known natural history of decline.

Although we understand the concerns around bias in published real-world data, the totality of the real-world evidence supports broader access than the CADTH decision reflects. In alignment with the totality of real-world data, many other jurisdictions internationally have reviewed the same real-world evidence and have supported decisions to reimburse therapy for adults based on this data. Most recently, Australia released the following public listing to fund nusinersen for adults with symptom onset prior to 19 years (primarily Types II and III): *"The PBAC is satisfied that nusinersen provides, for some patients, a significant improvement in efficacy over standard care."* (PBAC).

Additionally, there are currently at least 25 countries that fund nusinersen for adults. Importantly, to ensure rapid access in a degenerating disease with urgent need for intervention, 16 of the 25 nations have pharmacovigilance plans in place, the majority of which leverage national registries for real-world evidence (personal communications, and SMA UK). For example, the UK, Germany, Switzerland, the Netherlands, and Belgium are among European countries leveraging established national registries to evaluate population-based outcomes in a standardized fashion (Facey, 2021, and personal communications). Additionally, of note, with the novel PMPRB benchmarking nations, 9 of these 11 PMBRB countries are reimbursing Spinraza for all ages (with the exception of Norway and Sweden). (Personal communications, and TREAT-NMD).

With the emergence of novel treatments in SMA, the CNDR undertook a multi-stakeholder, iterative dataset expansion process in 2018 to expand the clinical data collection program for SMA to incorporate data items supporting analyses of safety and effectiveness of novel therapies in the real-world. (Hodgkinson, 2020). The CNDR, with 37 specialty neuromuscular clinics across the country participating (18 pediatric and 17 adult) (Hodgkinson 2021a), is well positioned to support post-marketing surveillance and pharmacovigilance. Importantly, patient registries, such as the CNDR provide an important platform to not only monitor clinical outcomes in a real-world environment, but also to benchmark national standards, monitor trends in patient characteristics, and support consensus building and standardization of patient monitoring nationwide. In addition to registry readiness, the CNDR also facilitated consensus building for outcome measure assessments in adults (Slayter, 2021) and monitoring recommendations (Hodgkinson, 2021b). The CNDR SMA work is supported by Biogen, Roche, and Novartis, however all scientific evidence and results are collected and published independently from industry partner oversight. The CNDR could serve as an independent third party to collect SMA outcomes for individual reimbursement purposes, and support Canada-wide evidence generation.

While we are in agreement with the committee discussion that more conclusive evidence to evaluate the benefit of nusinersen in this population would be of utility, supporting outcomes-based managed access would enable patients' urgent access to potentially life-altering therapy and support Canada's alignment with the emerging international consensus.

References

Wadman RI, Wijngaarde CA, Stam M, Bartels B, Otto LAM, Lemmink HH, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. *Eur J Neurol*. (2018) 25:512–8. doi: 10.1111/ene.13534

https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-made-by-the-pbac-march-2022

Facey KM, Espin J, Kent E, et al. Implementing Outcomes-Based Managed Entry Agreements for Rare Disease Treatments: Nusinersen and Tisagenlecleucel. *Pharmacoeconomics*. 2021;39(9):1021-1044. doi:10.1007/s40273-021-01050-5

https://smauk.org.uk/progress-with-access-to-nusinersen-in-european-countries-for-adults-who-have-sma

Hodgkinson VL, Oskoui M, Lounsberry J, et. al. A National Spinal Muscular Atrophy Registry for Real-World Evidence. Can J Neurol Sci. 2020 Nov;47(6):810-815. doi: 10.1017/cjn.2020.111.

Hodgkinson V, Lounsberry J, M'Dahoma S, et. al. The Canadian Neuromuscular Disease Registry 2010-2019: A Decade of Facilitating Clinical Research Through a Nationwide, Pan-Neuromuscular Disease Registry. J Neuromuscul Dis. 2021;8(1):53-61. doi: 10.3233/JND-200538.

Slayter J, Hodgkinson V, Lounsberry J, et. al. A Canadian Adult Spinal Muscular Atrophy Outcome Measures Toolkit: Results of a National Consensus using a Modified Delphi Method. J Neuromuscul Dis. 2021;8(4):579-588. doi: 10.3233/JND-200617.

Hodgkinson VL, Chapman K, Izenberg A, et. al. Response to Provincial Governments' Decisions Regarding Monitoring for Adults with Spinal Muscular Atrophy. Can J Neurol Sci. 2021 Mar;48(2):201-203. doi: 10.1017/cjn.2020.161.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☒
As part of the NMD4C physician opinion submission, the CNDR provisioned data analyses on a treated cohort of patients that were not discussed or mentioned in the draft recommendation. Data is being collected on this cohort of patients to help inform safety and effectiveness, however this RWE was not addressed.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Lawrence Korngut*
Position	*Associate professor, Neurology, University of Calgary; National PI, Canadian Neuromuscular Disease Registry*
Date	*02-06-2022*
☒	**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				
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.				
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	☐	☐	☐	☒
Novartis	☐	☐	☐	☒

New or Updated Declaration for Clinician 2	
Name	*Aaron Izenberg*
Position	*Assistant professor, Department of Medicine, University of Toronto*
Date	*02-06-2022*
☒	**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				
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.				
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	☐	☒	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Jodi Warman-Chardon*
Position	*Associate Professor, Faculty of Medicine & Cellular and Molecular Medicine, University of Ottawa; Director, NeuroMuscular Centre, the Ottawa Hospital; Co-Director, Eric Poulin Centre for Neuromuscular Disease, uOBMRI*
Date	*02-06-2022*
☒	**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
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.

New or Updated Declaration for Clinician 4	
Name	*Erin O'Ferrall*

Position	*Assistant Professor, Clinical, Department of Neurology, Neurosurgery, and Pathology, McGill University*
Date	*02-06-2022*
☒	**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

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.

Conflict of interest statement:

I have participated in Clinical Trials funded by Sanofi Genzyme, Roche, Harmony Biosciences, Grifols and Acceleron. I received no personal compensation for these trials.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Stephanie Plamondon*
Position	*Clinical Associate Professor, Physical Medicine and Rehabilitation, Clinical Neurosciences, University of Calgary*
Date	*02-06-2022*
☒	**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

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.

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	☒	☐	☐	☐

New or Updated Declaration for Clinician 6	
Name	*Colleen O'Connell*
Position	Medical Director and Research Chief, Stan Cassidy Centre for Rehabilitation
Date	*03-06-2022*

☒	**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

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.

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	☐	☐	☒	☐

New or Updated Declaration for Clinician 7	
Name	*Gerald Pfeffer*
Position	Assistant Professor, Clinical Neurosciences, University of Calgary
Date	*03-06-2022*
☒	**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

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.

No disclosures to report.

New or Updated Declaration for SCIENTIST	
Name	*Victoria Hodgkinson-Brechenmacher, Ph.D.*
Position	*Scientific Director, Canadian Neuromuscular Disease Registry; Chair, Global TREAT-NMD SMA Registries Network*
Date	*02-06-2022*
☒	**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

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.

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	☐	☒	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0713-000
Brand name (generic)	Spinraza (nusinersen)
Indication(s)	Spinal Muscular Atrophy: Adult type II & type III patients older than 18 years of age regardless of ambulatory status
Organization	Montreal Neurological Institute & Hospital (The Neuro), McGill University
Contact information[a]	Name: Erin K. O'Ferrall and Bernard Brais

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We strongly disagree with the CADTH recommendation since it contradicts the peer-reviewed literature, the recommendations of approval agencies in more than 25 jurisdictions including INESSS in the Province of Quebec, the consensus of international experts and Canadian SMA experts who are members of NMD4C and our experience in treating 31 adult SMA patients with nusinersen.

We are convinced that it would be unethical to propose a Randomized double-blind sham-procedure controlled Clinical Trial (RCT) of the efficacy of nusinersen in adult SMA patients considering that the proof of therapeutic value in SMA lead to the arrest by the FDA of the first ENDEAR trial in November 2016. The only way forward since has been to collect quality data in Real World Evidence (RWE) studies, as it has been done with increasing longer follow-up data that continue to confirm benefit in most adult patients.

It is impossible to support the CADTH recommendation since it does not match our understanding of the contemporary SMA literature and practice, nor our experience of treating SMA patients with nusinersen.

In late 2019 we introduced nusinersen treatment for adult SMA patients at the Montreal Neurological Hospital in close coordination with the multidisciplinary Clinique des Maladies neuromusculaires of the Centre de réadaptation Lucie-Bruneau (Centre Intégré Universitaire Santé Service Sociaux du Centre-Sud-de-l'Ile-de Montréal) which has cared for adult SMA patients for more than 40 years and presently follows more than 59 5q SMA patients. We have presently 30 patients treated with nusinersen, 23 of whom have been on treatment for more than 2 years now. All had extensive batteries of tests prior to the initiation of treatment that are repeated minimally every 12 months.

Our McGill University Health Center central pharmacy compiled the one-year post-initiation clinical data and approved that we continue to prescribe in all cases. Our experience

matches the published RWE experience of the larger Hagenacker et al. and Maggi et al. published 2020 studies.

Based on the analysis of the 12-month data from the Montreal Neurological Institute completed in December 2020, 31 patients were started on nusinersen. Three have chosen to discontinue (two due to technical difficulties or patient intolerance of the lumbar puncture procedure and one based on patient choice).

In terms of the baseline characteristics of the 26 patients for which data was available, the age range was 20-71 (average 37.5 years) and 14 patients were male. There were roughly equal numbers of type 2 and 3 SMA patients. Eight patients had 4 SMN2 copies, 15 had 3 SMN2 copies and 3 had an unknown SMN2 copy number. Four patients were ambulatory and 8 used non-invasive ventilation at night only (less than 8 hours per night).

After 12 months of nusinersen treatment, 5 out of 16 patients (31%) had a clinically meaningful response (i.e. improved by 3 points or more) on the revised Hammersmith (rHFMSE) scale. Seven of 15 patients (47%) had a clinically meaningful response (i.e. improved by 2 or more points) on the RULM. Two out of 2 patients had an improvement exceeding 30 meters on the 6MWT. In summary, 10 out of 16 patients (63%) were responders on at least one scale. Two patients that had become non-ambulatory gained the ability to walk (one of which was 71 years old and had stopped walking 18 months prior). Many patients reported improvements not captured by the scales: increased voice strength allowing the patient to work longer hours, less need for BIPAP at night (able to skip a night without fatigue), less fatigue, and improvement in dysphagia among other reported improvements.

Most patients experienced either injection site pain or headaches, but these were rarely severe and diminished over time. No other major side-effects have been recorded that were clearly related to nusinersen. All cases at two years have chosen to continue treatment with nusinersen despite the availability of risdiplam (an oral agent).

The 24-month data is currently being analysed.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

The summary of the consultations that serve as the basis of CADTH Reimbursement Recommendation, despite apparently having been systematic and abundant, do not provide strong evidence that International or Canadian Adult SMA experts were extensively consulted. Furthermore, some of the statements do not match our understanding of contemporary SMA literature, such as on neuronal survival in SMA, differences in composition of the published adult treated SMA patients and the Canadian SMA population, and the suggestion that physical therapy is sufficient to maintain function. All of these do not match or our clinical experience that has come from following adult SMA patents for 10 and 22 years respectively.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification. They are in general terms, though the reasons presented in our opinion would not meet with a wide support from SMA experts, including the ones consulted that led to the approval of nusinersen for adult SMA patients in more than 25 jurisdictions.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. It is unclear how CADTH's recommendation that no adult Canadian SMA patients should have access to nusinersen can be implemented when some provinces already offer access as is also the case in more than 25 jurisdictions based on the same literature?		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. The present CADTH's *Rationale for the Recommendation* does not allow Canadian SMA experts to explain to patients, their families, patient organisations or insurance companies why CADTH disagrees with the great majority of other international approval agencies. An added statement that CADTH has based its recommendation on different data sets than the other national organizations would be appreciated if this is the case.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☐

D. New or Updated Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Erin K. O'Ferrall • Bernard Brais		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Erin Kathleen O'Ferrall*
Position	*Assistant professor, Depts of Neurology, Neurosurgery and Pathology, Montreal Neurological Institute and Hospital, McGill University*
Date	*03-06-2022*
☒	**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	

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.

Conflict of interest statement:

I have participated (as site investigator or subinvestigator) in Clinical Trials funded by Sanofi Genzyme, Roche, Harmony Biosciences, Grifols and Acceleron. I received compensation for performing EDSS (neurological exam) assessments for the Multiple Sclerosis trials only. I received no other personal compensation for these trials.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Sanofi Genzyme	☒	☐	☐	☐
Roche	☒	☐	☐	☐
Harmony Biosciences	☒	☐	☐	☐
Grifols	☒			
Acceleron	☒			

New or Updated Declaration for Clinician 2	
Name	*Bernard Brais*
Position	*Professor of Neurology, Director of the Rare Neurological Diseases Group, The Neuro, McGill U.*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**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

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.				
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**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				
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.				
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**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				
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.				
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	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0713-000
Brand name (generic)	Spinraza (nusinersen)
Indication(s)	Spinal Muscular Atrophy: Adult type II & type III patients older than 18 years of age regardless of ambulatory status
Organization	The Neuromuscular Disease Network for Canada (NMD4C)
Contact information[a]	Name: Dr. Hanns Lochmüller with Dr. Aaron Izenberg, Neurologist, Sunnybrook Health Sciences Centre, Toronto Dr. Jean Mah, Professor, Department of Paediatrics, Alberta Children's Hospital Dr. Colleen O'Connell, Medical Director and Research Chief, Stan Cassidy Centre for Rehabilitation, Fredericton Dr. Kerri Schellenberg, Neurologist, University of Saskatchewan Dr. Jiri Vajsar, Neurologist, The Hospital for Sick Children, Toronto Dr. Jodi Warman-Chardon, Neurologist, Clinician Scientist, The Ottawa Hospital and Children's Hospital of Eastern Ontario

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Expert physicians from across Canada who treat adult SMA patients disagree with the CADTH Canadian Drug Expert Committee (CDEC) recommendation because:

- we believe the RWE supporting the use of nusinersen is compelling and sufficient to inform a positive reimbursement recommendation
- we disagree with CDEC that there was selection bias (re: included populations) in the included studies
- we strongly disagree with CDEC's apparent belief that adults with SMA (type 2 and type 3) do not have progressive worsening of their motor function. There is strong evidence that adults with SMA do experience ongoing progression.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

The draft recommendation made no mention of the Real World Evidence submitted by NMD4C of 12 Canadian patients (in Quebec) that initiated nusinersen after the age of 17 and had at least 12 months of follow-up post-nusinersen initiation. Overall, the data submitted, in contrast to the natural history of disease progression, demonstrated that patients derive positive benefits of therapy in either stabilization or functional gains regardless of age of therapy initiation, ambulatory status, spinal fusion status, or SMA type/SMN2 copy number.

In the recently released CADTH Strategic Plan (2022-2025), one of the stated strategic pillars is to "Innovate" described as: *Unleash the Value of Technology Across Its Lifespan*. In describing how CADTH will deliver on this ambition, CADTH states it will: *Innovate and collaborate on the use of real-world evidence (RWE).* CADTH describes this further: *To unlock the potential of new products where the evidence is still evolving through understanding the impact in the real world, including drawing on patient-level experiences, we will identify new ways of bridging the evidence gaps. CADTH will*

actively shape the pan Canadian discussion on how best to generate, gather, and optimize the use of RWE, drawing on our methods, knowledge, experience, and expertise, including from a wide range of domestic and international partners.

The real-world evidence (RWE) supporting the use of nusinersen in adults with SMA continues to build, and while Canadian experience with nusinersen for adult SMA patients is predominantly in Quebec, there are adults on nusinersen in Nova Scotia and Saskatchewan. CADTH had/has a tremendous opportunity to draw on these patient-level experiences. RWE by definition uses a different approach from double-blind, placebo-controlled trials; it is less restricted to narrow inclusion criteria, small numbers and limited observation periods. We reject the notion of the CADTH reviewers that the presented RWE is "per se" biased, uncontrolled and therefore not valuable. The RWE from countries such as Germany that our group has provided is strong and has led authorities and payers in many countries with similar health care systems to Canada to conclude to reimburse nusinersen in adults with SMA.

Given the strength of the existing and emerging RWE that demonstrate the benefit of Nusinersen in adults with SMA, CDEC should reconsider this reimbursement recommendation.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

There seems to be a general misconception in the review that adults with SMA (type 2 and type 3) do not have progressive worsening of their motor function. There are several natural history studies that clearly demonstrate that adults with SMA do, in fact, experience ongoing disease progression. Though this progression may seem gradual over time, when compounded over multiple years and involving multiple motor regions, this would result in a very meaningful decline in patients' level of functioning. Moreover, the reviewers argue that there are no motor neurons left which would benefit from increased levels of SMN protein (the mechanism of action of nusinersen). This statement may be based on some controversial data in animal models, but has not been studied in adult humans with SMA. It is highly improbable that there would be either no motor neurons remaining, or that the remaining moto neurons became independent of SMN. Clinical reasoning based on progression of weakness into adulthood, in adults, or even adult-onset disease, suggests that there are motor neurons in adults with SMA which rely on and benefit from SMN protein.

On page 10 of the draft recommendation CADTH states that: *"…selection bias in the included populations was noted as key limitation. Patients enrolled in the included studies consisted of mainly type III SMA (62% to 100%), with few type II patients (11.2% to 36%), which was noted by the clinical experts to be higher than what they see in clinical practice. The patients included in the 4 studies were considered higher functioning SMA patients based on the high prevalence of type III disease, with most patients having 3 or 4 copies of SMN2, and proportion of ambulatory patients (37% to 56.03%). Moreover, baseline motor function scores were considered high, suggesting a population with less severe disease. As such, the included study populations were unrepresentative of the reimbursement request (lack of type II SMA patients), and the results may not be generalizable to adult patients with type II and III SMA in Canada."*

We believe this comment is inaccurate. In the referenced real-world studies, all treated adults (both SMA type II and type III) were included during a certain period (for a number of sites or a country), there was no attempt to "recruit" the same number of SMA type II and type III. Both SMA type II and III would most likely have 3 SMN2 copies (most SMA type I has 2 SMN2 copies), so there is

absolutely nothing wrong or unrepresentative with that. There is also no reason to assume that adult Canadians with SMA would be any different from the patients described in these studies.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
It is unclear how CADTH's **recommendation that no adult Canadian SMA patients should have access to nurinersen** can be implemented when some provinces already offer access (as is also the case with more than 25 countries based on the same evidence). Also, is CADTH suggesting that children and teens who are started on nusinersen are discontinued once they hit a certain age?		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
The present CADTH *Rationale for the Recommendation* does not equip SMA experts with a suitable justification to explain to patients, their families and patient associations how come CADTH disagrees with the great majority of other international HTA agencies. An added statement that explains how CADTH has come to a different recommendation than other national HTA organizations is needed.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☐

D. New or Updated Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

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  - Please 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.
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  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0713
Name of the drug and Indication(s)	Nusinersen (Spinraza) for adult type II & type III SMA patients older than 18 years of age regardless of ambulatory status
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	x
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification. Request clarity around the “current” unmet need in the rationale. In discussion point 2, suggest rephrasing as the sentences imply that SMA can improve over time.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Re: CADTH Reimbursement Recommendation Draft
for Nusinersen (Spinraza) for Type 2 and Type 3 older than age 18

Dear CADTH,

I am writing this email, pleading for a new decision from your CADTH Reimbursement Recommendation Draft for Nusinersen (Spinraza) for Type 2 and Type 3 older than age 18. The recommendation is horrible, it's heartbreaking and it isn't good enough.

What you are missing is that the drug is really working in Adults. Look beyond just the labs, the controlled studies, the data,and go talk face to face to adult patients that have paid out of pocket, remortaged, fundraised and done everything they can do to access this drug. Do our Canadian citizens need to move to Europe and flee like the Ukraine's living with SMA did to Poland to access a drug no questions asked or move around the globe to Australia just to access a drug that will change their life forever.

It is easy to look at paper and write no, get curious, speak to more Doctors that have administered and witnessed the change in their patience after receiving the drug Spinraza.

Our plea is that you change this recommendation for our patients. Allowing them choice for a life saving and changing drug. Let them decide with your medical team what is best between Risdaplam and Spinraza. I will leave you with this one story.

A female adult patient who received the first 4 doses of Spinraza (paid out of pocket) saw drastic change in her own strength. We have flown together and on each flight support was required to help the patient not fall into the seat in front of her during landing in the past. After 4 doses of Spinraza she no longer required support to stay solid in her seat. She no longer required additional help.

Please change your draft recommendations, give patients a choice and the opportunity to succeed.

A very frustrated and discouraged patient group.

With gratitude and thanks,

Jessica Janzen
Executive Director

May 31, 2022

Attention: Members of the CADTH CDEC

Re: Negative recommendation: Nusinersen for adult patients

Cure SMA Canada – Patient group feedback

Dear Members of the Drug Expert Committee,

This feedback is in response to the negative recommendation received for Nusinersen for adult type 2 and 3 patients.

Canada's Spinal Muscular Atrophy community does not support the recommendation issued by the Expert Committee. There is strong evidence and need for a revision. We encourage the committee to take the feedback that is provided through the various entities into account and provide a positive recommendation that will save the lives of Canada's adult SMA patients.

The draft reimbursement recommendation included points that we would like to address, and we would like to bring other information to your attention.

1. **The lack of randomized clinical trials (RCT) in submitted data.**
   Some Canadian patients, (Quebec, and others through various avenues) along with patients from other jurisdictions were fortunate to access Nusinersen based on the original supporting clinical trial data. Because there is experience with the benefits and safety of this medication, it would be unethical for an RCT to now be held, forcing participating patients to wait even longer to access a treatment that will halt the progression of their disease. The submitted studies, providing the real world evidence (RWE) that supports adult access must be taken into account as viable evidence. How would we possibly justify a patient to take part in an RCT when even the patient is aware of the benefit of treatment access. From a patient perspective, we wonder what hoops we must jump through to provide proof to the Canadian government that an existing treatment that patients are clearly benefitting from, and sharing their life changing experiences, is obviously beneficial to others in the very same position.

2. **Sources of information - 2 clinical specialists**
   The Patient community feels it is critical to utilize the expertise of clinicians who are actively treating adult patients with this particular treatment as they are able to give the most robust input of their patients' response to treatment.

3. **Existing patient access**
   We must take into consideration the fact that patients who are not able to access treatment in their own province may consider moving to a province where they can. Patients are placed in the position of making a decision between no treatment in their own province (and experience all the consequences of disease progression), or move to a province where they can ultimately save their lives. To desperately move to another province, a patient must leave their extended families, friends, communities, jobs, all their support systems and comfort of home towns. Do we really want to put provinces who value their constituents' lives and support their better health by providing access to life saving treatment, to be the recipients of other province's responsibilities? If Quebec and Saskatchewan are able to find a viable pathway for their SMA patients, the other provinces must be able to offer support as well. We must value adult lives as much as we do children and work together to ensure these patients receive life saving treatments in all provinces in Canada.

4. **Stopping Criteria**
   The SMA patient community has expressed its support of the inclusion of stopping rules in the event they are accessing treatment and are not responding to it. We must remember the goal of treatment for SMA is to halt progression, if a patient continues to decline in function despite receiving treatment (outside experiencing illness or surgery for limited time) we support the removal of a patient from treatment. In focal groups held in BC, AB and ON in 2019, patients were asked if they would agree to being removed from treatment should they not respond to it. 100% of patients stated they would agree to being removed from treatment, but all felt they would like to be provided the opportunity to access treatment to stop their disease progression and improve their quality of life. This submission includes the video recording of patient responses to the posed question, "Would you agree to being removed from treatment if it wasn't working."

5. **Quebec/Saskatchewan**
   We are very fortunate to have the experience of patients and clinicians right here in Canada to provide the supporting evidence of adult patient access to Nusinersen. In our efforts to provide feedback on patient experience, we reached out to request that information for you. Due to the tight time constraints of supplying feedback to respond to this recommendation, we were unable to poll patients broadly. We would like to express the challenge of continually

requesting the small patient population, who are able to access, for their experiences as well as the ones who aren't accessing, to share their desires, needs and feelings. However, with that said, we did reach out to those that stated that they would be willing to be contacted further. These are not tactically selected patients for the purpose of this response, these are all patients who were contacted.

a) Saskatchewan patient – 41 – type 3 – accessed through EAP – has been receiving Spinraza since July 2019. Prior to treatment, her husband cooked meals and provided most of her personal care. Because of treatment, she now cooks all meals, bakes for her family, rolls over in bed after 20 years of not being able to do so, transfers herself, performs her own personal care, she volunteers in her community, and it has greatly affected her mental health. The impact on the entire family is profound. Supporting letter attached.
Dr. Shellenberg is her physician

b) Saskatchewan patient - 35 - type 2 – accessed through EAP – started Spinraza in June 2019, noticed some improvements even during loading dosing. Prior to initiating treatment, he experienced sleep apnea, this stopped completely after receiving treatment. He experienced a stronger voice, was able to feed himself more easily, was able to engage in social activities with friends, can now lift a glass to his mouth, he also stopped needing to take breaths often while speaking, has more stamina for a full day and became able to adjust himself in bed also became less dependent on his care givers due to these changes. His physician told him he has "clinically significant improvement."
Dr. Shellenberg is his physician.

c) Alberta patient – type 2 – 28 – accessed through private insurance – started Spinraza in 2019 – Noticed more energy shortly after starting treatment. She has much more energy in her days, she has more flexibility, leg movement and strength. Prior to initiating treatment, she experienced a great deal of muscle pain, since starting treatment, she has no pain in her muscles at all. Mentally, she has a great deal of relief, and she has experienced no disease progression at all. She is now engaged in her community and has started her own business. Her physician is Dr. Korngut.

d) Quebec patient – type 3 – 76 – has been receiving Spinraza for one year, health is much more stable now, able to stand much longer than before treatment, is retired. No progression in any area since starting treatment. Dr. Genge is her physician.

e) Quebec patient – 25 - type 2 – prior to treatment, he was coughing a great deal, all day, after starting treatment, the coughing has stopped completely. Before treatment he went to bed between 6:00-7:00, now 11:00 as he isn't as exhausted. He has a much more positive mindset, feels completely stable. Prior to initiation of treatment, his physician stated that he would need to move to bipap during the day, because of his treatment, this didn't need to happen, he just uses it at night. His physician told them that his strength and lung function have increased in his evaluations. Spinraza has had a marked improvement on his quality of life. Supporting letter attached. His physician is Dr. Donald Rivest

f) Quebec patient – 42 – type 2 – Has been receiving Spinraza since December 2019. By six months of receiving treatment, she noticed an increase in energy, stronger core and arm strength. She used to have chronic shoulder pain which has ceased completely. Being pain free has had a large impact on her life, as she is subsequently able to work long hours on her computer now. She has been told her voice is stronger and is easier to hear and understand. She also experienced an improvement in her stamina during her day. Her physician is Dr. O'Ferrall.

g) Two of the above patients independently requested to provide letters to share their experiences. Those letters are submitted as separate documents.

6. Real World Evidence

The clinical evidence that has been submitted through the collection of data through RWE must be included as valuable in the decision-making process. The studies from treating clinicians offers ground breaking data collected through means of existing patients accessing this particular treatment. Adult patients here in Canada have been accessing Nusinersen for 3 years now, their experience also clearly demonstrates the clinical and personal value of the treatment to the patient. Even though SMA is a rare disease, it has a great deal of evidence to support the benefit of treatment. Cure SMA Canada participated in the Best Brains Exchange to contribute to the incorporation of RWE in drug approval by utilizing this additional evidence for a disease like SMA. This disease and this treatment is the perfect opportunity for CADTH to implement the plan to incorporate RWE. Safe, effective, utilized in multiple countries, published studies to support and even experience within Canada is in your hands, here is your opportunity to base a decision that will have great impact on patient's health and lives.

7. Patient mental health decline

Cure SMA Canada has been supporting patients since the year 2000. Since treatment has been developed and has come available, the already struggling mental health of our patients who were not accessing treatment has plummeted substantially. I personally have the experience of supporting a type 3 adult artist whose decline in function resulted in the loss of the ability to paint. This loss impacted her so severely that she ended up taking her own life.
I can not express to you how it feels to watch and support patients who are losing function daily. These are people with active lives, hold jobs, have families, and have everything to live for. To lose abilities when others are stabilized and even improving deeply affects the mental health of a patient. I can share with you that the mental health decline is rampant. We are supporting multiple patients who have a great deal to lose and the consequences of not accessing treatment are negatively life changing and life limiting.

This treatment saves lives, a fact we know. Please listen to the treating clinicians, hear the words of our Canadian patients who generously shared their personal experiences, and hear the

words of the ones who are still waiting. Ultimately its their lives that you hold with the power of your pen.
I am submitting a video that Cure SMA Canada provided to CADTH and other members of government in 2019. It is important to note that 3 years later, most of the patients in this video are still not accessing treatment. They have continued to decline in spite of the fact that the treatment was accessed by others.

With this response, I also add a personal letter from a patient who has been waiting for access. At 29, he is losing his ability to walk. With that loss, he will not be able to perform his career in health care, he will need to move homes to an accessible one, he becomes dependant on others for his care, and his mental health is dangerously declining. You hold the power to change his outcome, to turn it all around for him. Please see your decision as the purity of this outcome. With stopping criteria in place, where can you go wrong? These patients have a right to try to save their lives, to change the outcome of their disease, and to plan their tomorrows.

Please revise your decision. As always, Cure SMA Canada offers to work cohesively with government bodies to ensure the best outcome for Spinal Muscular Atrophy patients, and welcome the opportunity to provide the patient input on this decision.

Sincerely

[redacted]

Susi Vander Wyk
Executive Director
Cure SMA Canada
curesma@telus.net

Links to two videos for the committee to view

1. “Would you agree to being removed from treatment if it wasn’t working.”
   https://youtu.be/Mq9RRnFvuQk

2. “Dear Canadian Government: Please Don't Let Us Down”
   Three years after the making of this video, most people in the videos are still waiting for access to treatment.
   https://youtu.be/DD_nTpCXfwk

June 1, 2022

Cure SMA Canada

Dear members of the CADTH Drug Expert Committee,

Cure SMA Canada initiated a petition after hearing the negative recommendation for Biogen's submission for Spinraza for adult patient.

Please see the attached link for access to this petition.
Clearly, Canadians are sending a message for a revision in the recommendation. Many have signed this petition in a very short period to send you that important message of disagreement to the draft recommendation.

https://www.change.org/p/adult-sma-patients-need-treatment-stop-their-disease-progression?utm_content=cl_sharecopy_33393746_en-CA%3A5&recruiter=1266557361&utm_source=share_petition&utm_medium=copylink&utm_campaign=share_petition&fbclid=IwAR1qLWMsR5Ra70IY4pFEN1z5cdTFuOcIfjWIAwo5vGZWwcsKWd4oDwrs_BA

Sincerely,
Susi Vander Wyk
Executive Director
Cure SMA Canada

Dear CADTH expert committee,

When we first heard about the application to change the recommendations to include Type 3's and adults, I felt hopeful for the first time in a long time.

I've always been very self-conscious speaking publicly about my disease, and it felt like my effort was finally paying off.

I found myself hopeful, because this incredible treatment has been approved in more than 25 other countries for Type 3's and adults. Canada, being known for its inclusive healthcare, should surely be part of that equation.

However, when the recommendation came back negative, I was crushed. Heartbroken, even. I had finally started to see a brighter future for myself, and it was taken from me. I felt utterly betrayed by our healthcare system once again.

I personally know of other adults in Canada with SMA type 3 that are receiving Spinraza. They've shared their stories with me of how much it's improved their lives for the better. They've shared that it's real. They've shared that it works.

How could this life-changing treatment, that has so much real world evidence, be denied?

This has had a severe impact on my life personally. My life as I know it is on a countdown clock. I'm sitting here watching not only my physical endurance slip away but, my mental health deteriorate.

I'm scared for the future of my career, as I've dedicated my life to help others in healthcare, and here I am unable to access the help I need to continue doing so. My independence in my career is one of the few things that make me feel whole.

Without my ability to work and provide, my entire self is lost to severe depression and atrophy.

I won't be able to hold my future child in my arms. I want to show them a normal life; where their dad goes to work, comes home to play catch, and help support the family.

Not a future where their mother is their father's caregiver more than a partner.

These are my dreams. The longer I can't access treatment, the more faded they become because I can't picture my life in a wheelchair. I want to be able to teach my kids to dream.

In the past couple years alone, I've seen my quality of life drop drastically due to my SMA growing exponentially. I can no longer do things I love, like nature walks, as I can only walk on flat surfaces for short periods of time. One thing that's kept me sane is my passion for music, especially playing guitar. It has been my vice for most of my life. I used to teach it, but due to the decline in dexterity, I'm very quickly losing the ability to play, let alone teach.

I have three beautiful nieces, whom I love dearly, that I can no longer hold for fear of dropping them, and it breaks my heart.

The future I want is slipping away, and it's completely out of my control, and I'm not the only one.

So I'm writing this to beg you to reconsider your recommendation because my life, along with many others, is counting on you to make the right decision.

Sincerely,

[redacted]

May 31, 2022

Attention: CADTH

My name is [redacted], I'm 41 years of age, and I have Spinal Muscular Atrophy type 3. This letter is in response to the recent draft recommendation made by CADTH regarding approval of Spinraza for Canadian adults living with SMA.

I currently live in Saskatoon, Saskatchewan, with my husband of 20 years, and our 13-year-old daughter. I'm one of very few adults who have been fortunate enough to access Spinraza, ever since July 2019. I gained access to this treatment through the Exceptional Drug Status though my province of Saskatchewan. My neurologist is [redacted].

While I am extremely thankful to have access to treatment, I also feel guilty as others are not receiving this life changing treatment.

I want to briefly tell you about what life was like prior to access to Spinraza. It's difficult to put into words what it feels like to live in a constant state of fear, worry, loss and grief, not knowing when the next loss would happen or what I'd lose next. As I progressed, so did the equipment I required – first a manual wheelchair, then a scooter, and now an electric wheelchair. I've now been in a wheelchair for approximately 30 years!

I would often think that if I was able to still walk or do the things I used to, that life would be so different. Because when you are in a wheelchair, every single moment of every day is filled with obstacles. And they aren't just physical barriers either. It's a mental and emotional battle daily, and most days I'd lose that battle. Living with SMA *USED TO* mean living in fear every single day - until Spinraza.

I never expected that this drug was going to do miraculous things, but it truly has. It has saved my life, my marriage, my future, and has given me hope back. Since being on this drug for almost three years, the changes in my life have been substantial. I'm able to drive independently again and take my daughter to different activities. There was a point in my relationship when I questioned whether our marriage would survive the progression of this disease but having access to this treatment has allowed us to focus on our relationship as husband and wife instead of wife and caregiver.

I've taken back the control over my care. I do most things independently again. I cook meals and bake for my family once again. For years I struggled with depression. I no longer feel like a burden or dependant on others, especially my husband. My muscles are waking up, my arms and core are getting stronger. I can brush my own hair and teeth. I can grocery shop, run errands on my own, contribute to my family and manage our household, and I have the strength and energy to exercise daily. I also now have the energy to volunteer within the health care community.

But… I'm truly saving the best for last. Because of access to Spinraza, and after 25 years of losing specific abilities, I've now slowly regained some of what I'd lost. For the first time in over two decades, I can now roll over independently! I can sit up independently! I can get on my hands and knees independently and move from my wheelchair to my bed independently!

So, with so many amazing changes in my life, why am I feeling burdened and guilty? Because there are still adults within our community who do not have access to Spinraza within Canada - within a country that prides itself on caring for one another regardless of their age, who they are or where they live within our beautiful country. Every life has value; a life is a life, regardless of being a child or adult, whether you are born with a rare disease or born completely healthy. There are adults who are losing physical abilities daily. There are adults who are progressing from being able to walk to now needing wheelchairs. There are adults who were once able to feed themselves, who are now dependant on others. There are adults who will lose this battle not to the natural progression of the disease necessarily, but due to mental health and all the loss associated with having this disease.

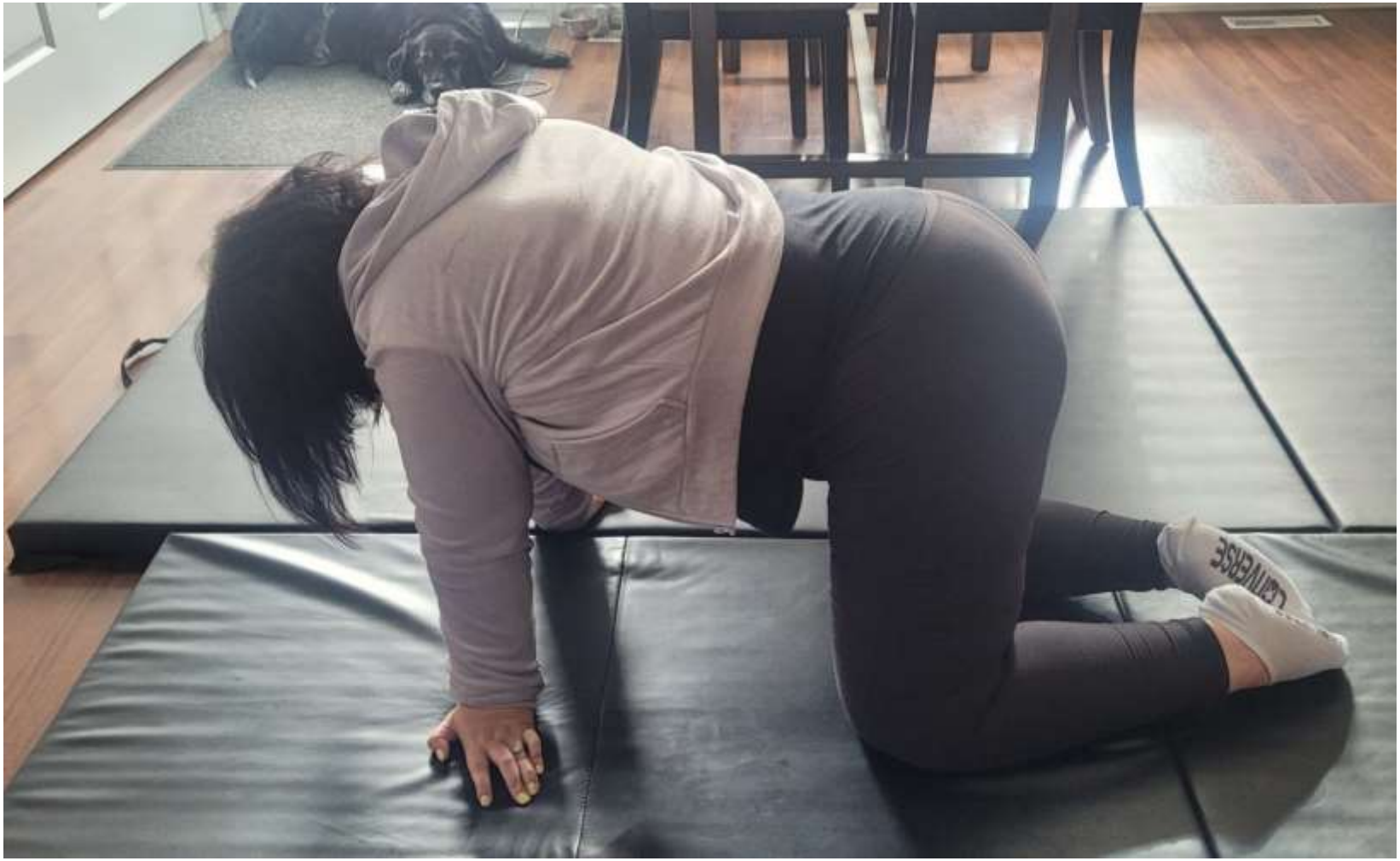
So, for now, until there is access for all within our country, I keep my amazing achievements to myself. I keep the joy and my success story close to my heart, to not only protect the feelings of those without treatment, but because I still mourn. I no longer mourn about my own progression because I have access to Spinraza. Instead, I mourn for all who are still unable to have access to a treatment, who are still losing and progressing. I cry for each of them because I've been there, and I know that loss and grief all too well.

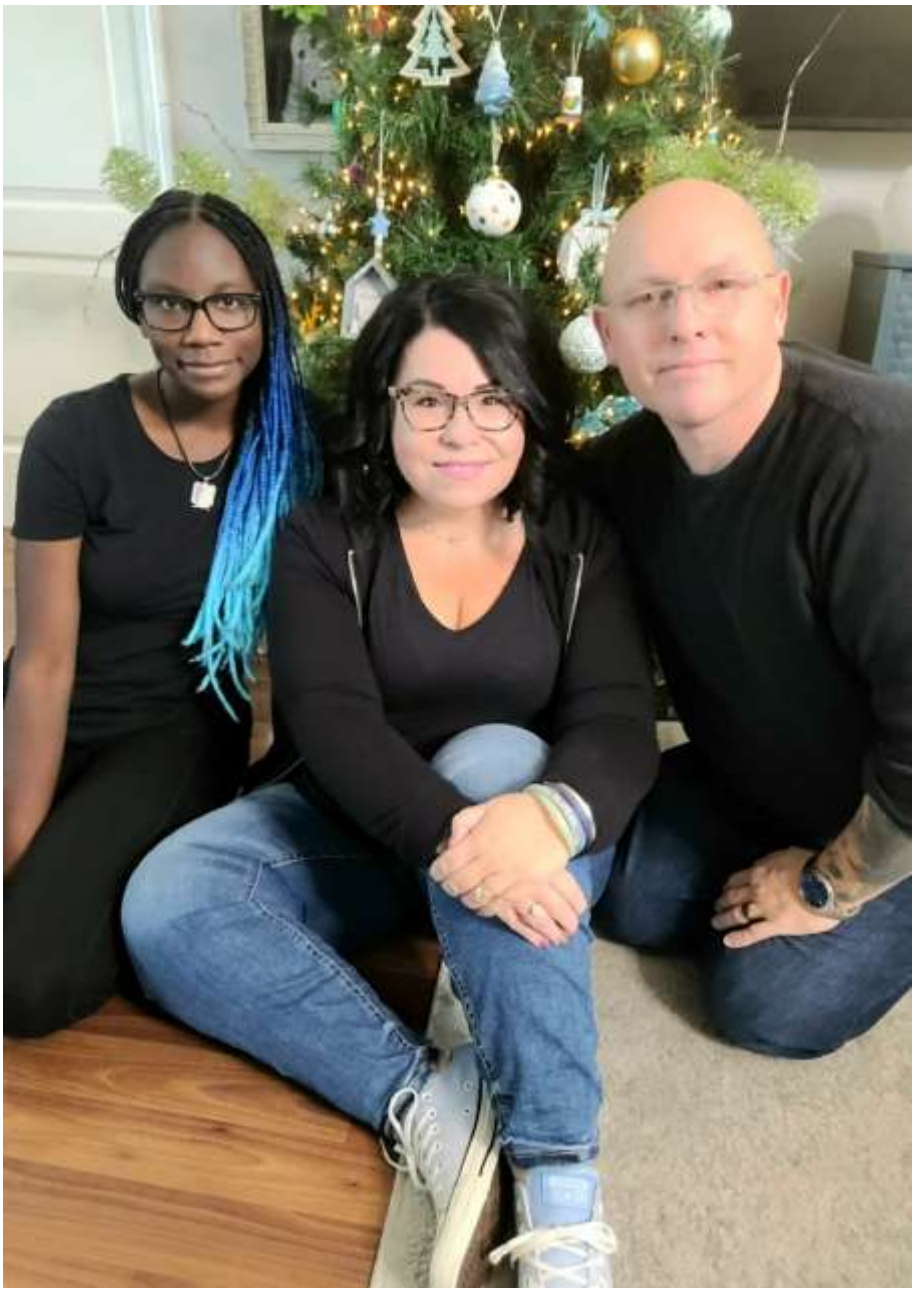
Everyone deserves the opportunity to a future filled with joy, hope, and the ability to not have to face ongoing loss and uncertainty. For the first time in my life, I feel like I am living a life I could have never imagined. How amazing it would be to be able to witness firsthand what this treatment could do in the lives of all other adults within Canada. A treatment and drug that is truly a miracle; that is changing lives daily.

Warm regards,

[redacted]

Saskatoon, Saskatchewan
[redacted]





May 30, 2022

Bonjour,

Nous sommes du Québec et notre fils de 25 ans à la chance d'avoir le traitement de Spinraza. Son médecin vient de nous informer que le reste du Canada n'a pas accès à ce médicament et qu'il y a possibilité de témoigner des améliorations que le traitement a eu sur notre fils pour soutenir vos démarches. Nous avons aussi fait parvenir ce témoignage à Dystrophie musculaire Canada.

Je vous fais parvenir notre témoignage :

Mon fils, [redacted], à 25 ans et a eu le diagnostic d'amyotrophie spinale (trois copies du gène SMN2) à l'âge de 2 ans mais depuis ses 6 mois que les spécialistes cherchaient pourquoi il n'avait pas beaucoup de force. Il n'a jamais marché seul et à 4 ans il doit se déplacer en fauteuil manuel et a un fauteuil motorisé un an plus tard. Jusqu'à l'âge adulte il a perdu progressivement de la force et de l'endurance. Le tout se faisait par plateau, période de perte plus prononcée sur quelques mois et ensuite la situation restait plus stable pendant quelques mois. Vers la vingtaine il s'est mis à perdre beaucoup plus rapidement de la force et sa capacité pulmonaire diminuait aussi mais on ne vivait plus de plateau ou la maladie progressait moins vite. Il n'avait presque plus de force dans les mains et les bras, a peine pour lui permettre de conduire son fauteuil motorisé et devait être prudent pour ne pas faire de mauvaises manœuvres. Sa capacité pulmonaire était en diminution et il utilisait un Bi-pap la nuit. Son pneumologue commençait à parler de lui mettre quelques heures durant la journée. Il s'est installé une toux persistante qui l'épuisait physiquement et qui l'obligeait à se coucher très tôt car il était fatigué. Son neurologue nous avait expliqué que ses forces dans la gorge diminuaient et que ce n'était pas de bon augure pour [redacted].

[redacted] a commencé son traitement avec le Spinraza en septembre 2020 et quelques semaines plus tard sa toux qui lui empoisonnait la vie a cessée. Il a beaucoup plus d'énergie, fini les couchers à 18 h 30 car trop fatigué. Maintenant il peut jouer à ses jeux de consoles jusqu'à 23 heure. Il a plus de force pour manger, il est maintenant capable de se moucher, de cracher, de tousser (un gros avantage pour éviter les infections respiratoire) et plus de force pour la conduite de son véhicule. Ça c'est les améliorations qu'on a observé dans la vie quotidienne.
Mais lors de ses évaluations au CRDP les intervenants ont confirmé une augmentation de force et d'endurance au niveau des bras, des mains et des membres inférieurs. Sa force dans la voie et sa bouche a eu une grande amélioration. C'est aussi le cas pour sa force et sa capacité pulmonaire.

Depuis presque deux ans que [redacted] a le traitement et sa situation s'est améliorée alors qu'il perdait des forces depuis plusieurs années. Le traitement n'a pas seulement arrêté la maladie mais lui a redonné des forces et une meilleure qualité de vie.

[redacted]

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0713-000
Brand name (generic)	Spinraza (nusinersen)
Indication(s)	Spinal Muscular Atrophy: Adult type II & type III patients older than 18 years of age regardless of ambulatory status
Organization	Muscular Dystrophy Canada (MDC)
Contact information[a]	Name: Homira Osman (MDC) [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

While we recognize that the data supporting nusinersen for adults is imperfect and more robust RCE-type studies are needed, we disagree with the CADTH Canadian Drug Expert Committee (CDEC) recommendation. This recommendation neglects the growing real-world evidence, the clinical input provided by expert neurologists in Canada and the value of shared-decision making between a patient and their physician. This recommendation also further promotes 'postal-code healthcare' and health inequities and undermines the patient-level experiences. As per the CADTH Strategic Plan (2022-2025), one of the stated strategic pillars is to "Innovate" described as: "*Innovate and collaborate on the use of real-world evidence (RWE). To unlock the potential of new products where the evidence is still evolving through understanding the* ***impact in the real world, including drawing on patient-level experiences, we will identify new ways of bridging the evidence gaps.****"*

We specifically disagree with the following statements in the recommendation:
"Several potential confounders were identified that may impact motor function, such as prescribed physical activity (which maintains neuronal connectivity and muscle function) and potential learning and training effects for functional outcomes scales."

- We believe this rationale can also apply to pediatrics.

"Although the studies generally suggested that treatment with nusinersen had a positive effect on motor function (measured by the HFMSE, RULM, and 6MWT), key limitations including the uncontrolled nature of the studies and a high degree of selection bias, resulted in a patient population that was not considered representative of adult patients with SMA in Canada."

- We believe the real-world evidence supporting the use of nusinersen is compelling and sufficient to inform a positive reimbursement recommendation. In fact,
- We disagree that there was selection bias (re: included populations) in the included studies. Also, there was data submitted from Quebec by NMD4C, which aligns with these other studies and is in fact from a Canadian patient population. This data demonstrated results similar to other studies which initiated nusinersen after the age of 17 and had at least 12 months of follow-up post-nusinersen initiation.

"It was also discussed that routine physical activity alone can have a profound effect on patients' physical function."

- While this is a true statement, physical activity on its own is not a sufficient treatment option for adult patients affected by SMA. Many adults affected by SMA engage in intensive physiotherapy, aqua therapy and exercise programs. MDC has supported clients with funds to access such services. However, such rehabilitation-based services are not enough to manage the progression of disease and reduce the rate

of functional loss or make meaningful changes to their lives, which is why access to treatment is important.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

No, the CADTH Reimbursement Recommendation seems to have not considered the rich, poignant, detailed, valued lived experience input of adult patients affected by spinal muscular atrophy. In fact, it appears the current set of recommendations is in contrast with the patient input provided. It is not clear whether the patient input submission were taken into consideration by the Committee – which is problematic especially as the input submission incorporates the perspectives and experiences of Canadians living with documented/known SMA age 18+ who have accessed nusinersen in Quebec and those who are still working towards access in other provinces. While the patient input was summarized as "patients and caregivers identified a need for treatments that stabilize disease progression, improve HRQoL through greater independence, and improve strength (primarily in the arms and respiratory function)," it is not clear how the CDEC committee weighed the input and request from the patient community which was to **lean on the existing and growing real-world evidence in combination with the real-life impact on Canadians' lives.**

In response to the draft recommendation, we connected with the respondents from our initial patient input submission and asked: *(i)* What are your thoughts on the draft recommendation? *(ii)* How do you feel? *(iii)* What would you like the CDEC Committee to know/consider when finalizing their decision? *(iv)* What questions do you have?

We heard the following key themes and messages:

Disappointment

*"As I read the draft, I felt hope. Most of the evidence quoted in the document is strong, auspicious—for the most part a bright outlook on SMA. However, the dismal direction this committee's draft is going—Do Not Reimburse—reverted me back to **hopelessness**. There is a dissonances between the content of the document and the draft recommendation arrived at by the committee, which is **dispiriting**."*

*"For years now, I've been advocating for myself and other people with SMA to be approved to access life-changing treatment for our condition. This recent denial, it's **deflating**."*

*"I am shocked, **disappointed** and disheartened."*

*"Inherently, SMA has been a lifelong **disappointment** for me and others. Every neurologist I have seen throughout my entire life had the same prognosis: nothing could be done about the atrophy that will consume your body, gradually, inexorably. By age 30, I consciously discontinued seeing neurologists, since their visits had become irrelevant. I accepted the prognosis, and like everyone, I had a life to undertake. No time to dwell on my body's process of rapid and premature weakening or waiting for an improbable SMA treatment. There would be no cavalry. In 2017, nusinersen offered optimism. Ever since I was age 6, I consciously forbade myself to imagine about such a day. Fortuitously, that day arrives. Yet, this narrative remains unchanged. Your recommendation as it stands will be used by reimbursement programs as another bogus reason to deny coverage and to justify its negligence. It will assure an even steeper uphill battle for I and others to gain access to this treatment. Your choice will have this impact on lives."*

Ageism

*"There is a bureaucratic depersonalization that institutions use to sort of let go of the responsibilities they have to the most vulnerable people in the population. All the things that all of us need to live and thrive are harder to access because **we're a minority**."*

*"It is **ageism**. Who wouldn't want to see the kids saved? People in their 40s, 50s, 60s doesn't count and isn't worth stabilizing."*

Real-life consequences

*"**Real life consequences of SMA are incalculable** and perhaps difficult for anyone who is unaffected or is not closely treating an afflicted person. Its impact on my activities of daily living, things such as getting in and out of bed, using the bathroom, bathing, dressing, eating, etc. are (at the time of writing) either near impossible or soon to be. The use of my limbs and hands are in constant decline. I require ever more expensive specialized mechanical equipment and/or caregiver aide."*

"Every day between the time I open my eyes in the morning and have breakfast, I have already spent 60-70% of my day's energy and pain threshold. Merely 10% of my body's generalized muscle strength is what I have left now. That 10% is precious to me, and with it I still manage to accomplish a great deal. I use every last drop every day. This week, however, my strength performance has been below average. How do I know? Because basic activities of daily life that are plainly grueling have been exceptionally grueling. Is this strength erosion permanent? In my experience, probably."

"My wife is looking for jobs with the federal government. This way I can be added as a dependent on her federal drug plan which actually covers nusinersen."

"We are exploring options to move to Quebec – that would mean moving away from family, our community, our jobs, our friends, our lives… all to access treatment."

"I now need to seriously consider moving to Quebec. I am losing function and I need to at least try treatment to see if it would help slow down the rate of decline."

Mental Health

*"The **mental health toll** of living with SMA is a daily challenge. I am fortunate to be in robust mental health, yet experiencing your body constantly deteriorating damages ones 'espoir' and hope for the future. More often than I wish, I stare into dark nihility, considering the basic functions of life and how they've been whittled away from me. It is incumbent upon me to put extra effort to maintain relationships. Since I was a child, I had to be left behind when I was unable to follow my peers, which became more and more often. I still experience this regularly today in my daily life. The **mental strain** of mustering confidence against the ever diminishing and downward spiral of the body."*

*"The **mental health aspect** is a huge component with dealing with not accessing treatment and what it's doing to our community and how it's dividing our community: one accesses the drug and the other does not. For some, if they don't access treatment by this time, they're not going to live and their disease has progressed so they choose to end their lives.*

*"I don't think people don't understand the **toll of having to fight to prove you deserve this treatment**, while you're waiting while you know the realities of SMA."*

*"Not being able to access treatment for 3 years, on top of everything else that we have to deal with, from not only a disability standpoint, but from the life point that every other person has to deal with; it's so **taxing mentally**. I don't want to be doing this again, a year from now."*

Inconsistent with Medical Advice/Recommendation

"The members of my medical team agree unwaveringly that nusinersen treatment would be beneficial to me, and the evidence supports that opinion."

"My neurologist is world-renowned – she does research on SMA and teaches physicians – she is evidence-based in her practice and has recommended nusinersen – yet her medical recommendation based on her clinical expertise, review of my chart and case does not matter."

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒

	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. It is unclear how CADTH's recommendation that no adult Canadian SMA patients should have access to nurinersen can be implemented when some provinces already offer access (as is also the case with more than 25 countries based on the same evidence).		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by CADTH.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Homira Osman*
Position	*Vice-President, Research & Public Policy*
Date	*2022-06-01*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

[redacted]

May 26, 2022

Canadian Agency for Drugs and Technologies in Health
865 Carling Ave., Suite 600
Ottawa, ON Canada K1S 5S8

CADTH Committee:
Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed,

As I read the draft, I felt hope. Most of the evidence quoted in the document is strong, auspicious—for the most part a bright outlook on SMA. But the dismal direction this committee's draft is going—**Do Not Reimburse**—reverted me back to hopelessness. There is a dissonances between the content of the document and the draft recommendation arrived at by the committee, which is dispiriting.

Inherently, SMA has been a lifelong disappointment for me and others. Every neurologist I have seen throughout my entire life had the same prognosis: *nothing could be done about the atrophy that will consume your body, gradually, inexorably.* By age 30, I consciously discontinued seeing neurologists, since their visits had become irrelevant. I accepted the prognosis, and like everyone, I had a life to undertake. No time to dwell on my body's process of rapid and premature weakening or waiting for an improbable SMA treatment. There would be no cavalry. In 2017, nusinersen offered optimism. Ever since I was age 6, I consciously forbade myself to imagine about such a day. Fortuitously, that day arrives. Yet, this narrative remains unchanged. Your recommendation as it stands will be used by reimbursement programs as another bogus reason to deny coverage and to justify its negligence. It will assure an even steeper uphill battle for I and others to gain access to this treatment. Your choice will have this impact on lives.

To be clear, I do not share the following information freely. I also am not trying to garner pity, I am giving you an example of my experience to meet a deficit of understanding of a type III SMA profile. This is too important, so it is vital that I articulate myself clearly, vigorously, and completely.

Real life consequences of SMA are incalculable and perhaps difficult for anyone who is unaffected or is not closely treating an afflicted person. I will share a small part of my experience with you, the CADTH Committee, how a life is effected by this rare disease. Its impact on my activities of daily living, things such as getting in and out of bed, using the bathroom, bathing, dressing, eating, etc. are (at the time of writing) either near impossible or soon to be. The use of

my limbs and hands are in constant decline. I require ever more expensive specialized mechanical equipment and/or caregiver aide.

As my body crumbles, I have had to struggle with other health issues as a result, Type 2 Diabetes, double scoliosis, posture issues, respiratory problems, aches, sores, leg and foot edema, social isolation, just to name a few. These chronic health problems are a direct result of SMA, and will progress in lock step. In actuality, every day between the time I open my eyes in the morning and have breakfast, I have already spent 60-70% of my day's energy and pain threshold. Merely 10% of my body's generalized muscle strength is what I have left now. That 10% is precious to me, and with it I still manage to accomplish a great deal. I use every last drop every day. This week, however, my strength performance has been below average. How do I know? Because basic activities of daily life that are plainly grueling have been exceptionally grueling. Is this strength erosion permanent? In my experience, probably.

The mental health toll of living with SMA is a daily challenge. I am fortunate to be in robust mental health, yet experiencing your body constantly deteriorating damages ones 'espoir' and hope for the future. More often than I wish, I stare into dark nihility, considering the basic functions of life and how they've been whittled away from me. It is incumbent upon me to put extra effort to maintain relationships. Since I was a child, I had to be left behind when I was unable to follow my peers, which became more and more often. I still experience this regularly today in my daily life. The mental strain of mustering confidence against the ever diminishing and downward spiral of the body.

The financial burden to living with SMA is immoral. My ongoing needs include a wheelchair, its maintenance, lifts, slings, a highly specialised vehicle, various medical costs, various medicines, home care, personal assistants, an array of home modification, specialized toilet, shower, the list is endless. I must pay for most of these myself, since I inherited SMA at birth, that load is mine and mine alone, therefore no insurance settlement to offset any of these costs. No insurance company would ever insure me or my life for any reasonable cost, viewing my mere existence as an unbearable liability. This is where most of my meager income goes.

Now, I ask the members of this committee, if you were in my position and there was a known therapy, would you not want access to it to limit further deterioration of your body? What kind of a coward would you be if you did not try to receive that treatment? If your answers are anything other than, "of course" you'd be lying to me, but worse, you'd be letting down your family, friends, and yourselves. Passively accepting this fate is spineless. I don't do spineless and nor does anyone who knows anything about SMA.

I have been actively seeking nusinersen since 2019. Request after request to the New Brunswick Drug Plan have been denied on the flimsiest grounds or based on vague statements. In fact, my denials do not cohere with other cases that are being reimbursed while having similar profiles. I know this through well-placed sources. The only conclusion we can draw: I am being barred access to the treatment uniquely. If this committee's **Do Not Reimburse** recommendation stands, New Brunswick Drug Plan will exploit it to automatically shut down any chance I and

others have at ever accessing nusinersen. Only the NB Drug Plan and similar bodies will celebrate your **Do Not Reimburse** decision.

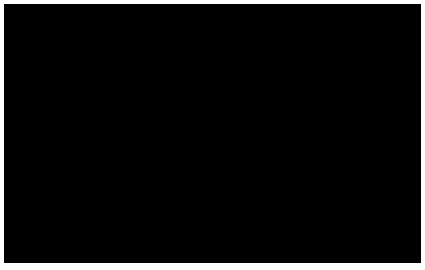
While ALL genuine SMA experts and specialists, those who are dedicate to helping with people with SMA—the neurologists, physiotherapists, occupational therapist, rehabilitation specialists—agree nusinersen has changed the game, heedless of SMA type or age. With an issue as complex as this and making a discission as significant as this, I expect the members of this committee to understand SMA a great deal. I also expect the member to grasp at what point this scenario is horrendous for people with SMA. I've read each and every one of your biographies at: https://www.cadth.ca/canadian-drug-expert-committee-cdec. Each of you seem to be genuinely accomplished in your fields and together make up a veritable body of intelligence. Please demonstrate leadership.

To reiterate, the members of my medical team agree unwaveringly that nusinersen treatment would be beneficial to me, and the evidence supports that opinion. This committee states its concern with a body of evidence regarding nusinersen treatment that is smaller than is desired. Is this not inherent with rare diseases? Should issues surrounding rare diseases not be scrutinized by the proper experts? This committee's draft recommendation appears to be cautious. Cautious for whom? This committee's stated risk-benefit profile of administering nusinersen to adults is adorable. Between a life with unchecked SMA vs. the described risk profile, I relish those odds. The more I read the document, the more it loses coherence. And at the very end, the one part that does cohere with the draft recommendation "**Do Not Reimburse**" is the last paragraph:

> ***…In the CADTH base case, the anticipated budget impact for reimbursing nusinersen for the treatment of adult patients with SMA Type II and III is $23,240,632 in year 1, $44,044,233 in year 2, and $65,387,990 in year 3, for a three-year total of $132,672,855.*** *… Uncertainty remains in this estimate due to the true prevalence rate of Type II and Type III SMA in Canada being unknown, as well as the availability of risdiplam.*

In this very last paragraph is your case: it's expensive.

A last word. If this letter seems cynical, it's because I am. I have not known one day since 1975 that SMA has not stepped in and spoiled it. Then I read your draft which amounts to an all-out green light for reimbursement programs, to neglect and to be derelict, and restricting even more an already restrictive pathway to nusinersen treatment. This is exactly what they want from CADTH, seems like it is exactly what CADTH will deliver. Dismal.



Mon fils, [redacted], à 25 ans et a eu le diagnostic d'amyotrophie spinale (trois copies du gène SMN2) à l'âge de 2 ans mais depuis ses 6 mois que les spécialistes cherchaient pourquoi il n'avait pas beaucoup de force. Il n'a jamais marché seul et à 4 ans il doit se déplacer en fauteuil manuel et a un fauteuil motorisé un an plus tard. Jusqu'à l'âge adulte il a perdu progressivement de la force et de l'endurance. Le tout se faisait par plateau, période de perte plus prononcée sur quelques mois et ensuite la situation restait plus stable pendant quelques mois. Vers la vingtaine il s'est mis à perdre beaucoup plus rapidement de la force et sa capacité pulmonaire diminuait aussi mais on ne vivait plus de plateau ou la maladie progressait moins vite. Il n'avait presque plus de force dans les mains et les bras, a peine pour lui permettre de conduire son fauteuil motorisé et devait être prudent pour ne pas faire de mauvaises manœuvres. Sa capacité pulmonaire était en diminution et il utilisait un Bi-pap la nuit. Son pneumologue commençait à parler de lui mettre quelques heures durant la journée. Il s'est installé une toux persistante qui l'épuisait physiquement et qui l'obligeait à se coucher très tôt car il était fatigué. Son neurologue nous avait expliqué que ses forces dans la gorge diminuaient et que ce n'était pas de bon augure pour [redacted].

[redacted] a commencé son traitement avec le Spinraza en septembre 2020 et quelques semaines plus tard sa toux qui lui empoisonnait la vie a cessée. Il a beaucoup plus d'énergie, fini les couchers à 18 h 30 car trop fatigué. Maintenant il peut jouer à ses jeux de consoles jusqu'à 23 heure. Il a plus de force pour manger, il est maintenant capable de se moucher, de cracher, de tousser (un gros avantage pour éviter les infections respiratoire) et plus de force pour la conduite de son véhicule. Ça c'est les améliorations qu'on a observé dans la vie quotidienne. Mais lors de ses évaluations au CRDP les intervenants ont confirmé une augmentation de force et d'endurance au niveau des bras, des mains et des membres inférieurs. Sa force dans la voie et sa bouche a eu une grande amélioration. C'est aussi le cas pour sa force et sa capacité pulmonaire.

Depuis presque deux ans que [redacted] a le traitement et sa situation s'est améliorée alors qu'il perdait des forces depuis plusieurs années. Le traitement n'a pas seulement arrêté la maladie mais lui a redonné des forces et une meilleure qualité de vie.

[redacted]

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0713-000
Brand name (generic)	Spinraza® (nusinersen)
Indication(s)	Spinraza® (nusinersen) is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA)
Organization	Biogen Canada
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Biogen strongly disagrees with the draft recommendation. The totality of real-world evidence (RWE) submitted to CADTH for Spinraza® in adults is extensive for a rare disease and clearly demonstrates statistically significant clinical benefits seen with Spinraza® in all studies, as well as experiences of treating physicians and patients in Canada and worldwide. The extensive RCT data in younger patients and the RWE in adults demonstrates the benefit of Spinraza® in all patients based on its mode of action. Spinraza® is backed by multiple double-blinded RCTs in younger SMA patients, highlighting the clear disease-modifying nature of Spinraza®. Regardless of age, ambulation status, or performance on motor function scales, all patients with 5qSMA have the same disease, resulting in the same molecular effect - a reduction in SMN protein. Spinraza® increases the production of SMN protein, ultimately targeting the underlying molecular pathology of SMA While RCTs have traditionally been the basis for decision making at CADTH, CADTH's 2022-2025 Strategic Plan emphasizes the important role and use of RWE to inform decision making. The same collection of robust RWE has led many countries to approve and HTA to recommend Spinraza® for adults, including most recently, the UK and Australia. Biogen has submitted a request for reconsideration.

The key points below are of significant concern:
1. Reference: pg 3, second paragraph, last sentence; pg 4, third bullet, first sentence; pg 12, first paragraph, last sentence. **The effectiveness of Spinraza® in these studies is highly uncertain.**

- The totality of RWE submitted all show the same significant benefit with Spinraza®. Statistically, if the data were highly uncertain, there would be discordance in the data to reflect this. In addition, the studies were put through various quality tools as requested by CADTH which confirms the data is of a high quality and the conclusions drawn can be certain. Biogen would like to highlight the resoundingly consistent results of the RWE evaluated. 12-14-month HFMSE change in adults on Spinraza® indicate statistically significant increases of 3.12, 2.85, and 1.60 points by Hagenacker, Maggi, and the EU Registry Study, respectively. 12-14-month RULM changes were also statistically significant, with increases of 1.09, 0.86. and 0.64 points, respectively. 6MWT scores in ambulatory adults experienced a similarly consistent improvement in all the RWE studies. These improvements are further validated by the results of the Coratti et al. meta-analysis. With the comparative EU Registry study, Spinraza®-treated patients consistently experienced a statistically significant improvement on HFMSE, RULM, and the 6MWT, while the untreated cohort consistently did not improve on any of these 3 scales. Further, when the above 55-week results are compared to the 12- or 14-month results from Hagenacker et al, 2020; Maggi

et al, 2020; and Pera et al., 2021, the magnitude and direction of HFMSE, RULM, and 6MWT change remain consistent for the treated Spinraza cohorts between the EU Registry study and all other RWE studies.

2. Reference: pg 3, "…several potential **confounders** were identified …"

- The potential confounders and treatment effect modifiers mentioned are highly unlikely to be major drivers influencing the results of the RWEs submitted. There is no published literature to suggest that interventions such as physiotherapy or occupational therapy yield sustained benefit on motor function scales in adults with SMA as they do not treat the underlying disease vs active treatment with Spinraza®. Additionally, "training for the outcomes of interest" is unlikely a potential confounder, due to the lack of published evidence of a training effect with motor function scales used in adults with SMA. Further, in the context of natural history studies of SMA in adults, the training effect is further invalidated as a concern. Natural history studies of HFMSE and 6MWT have consistently demonstrated worsening of function in untreated adults with SMA, despite repeat testing with these motor function scales.

3. Reference: pg 3, "The clinical experts described the known **natural history** …"

- Published natural history studies uniformly show functional decline over time. A 2017 cross-sectional study by Wadman et al. concluded that **HFMSE** declines by a consistent 0.5 points per year, stated by authors to be an underestimation of the true rate of decline. In contrast to the statistically significant benefits seen with Spinraza®.
- Montes et al., 2018 provides further evidence of consistent deterioration of function in adults with SMA. In this natural history study, patients with SMA aged ≥ 20 years old experienced an annual reduction in **6MWT** distance of 9.7 metres. Coratti et al., 2021, resulted in statistically significant pooled 10-14-month improvements of 1.87 points on HFMSE, 0.64 points on RULM, and 20.28m on 6MWT.
- Therefore, as per multiple motor function endpoints, the evidence clearly outlines that untreated adults with SMA experience a steady and persistent worsening of their disease over time with impact on their functional status, quality of life and reducing their independence. Coratti et al., 2021, provides a clear and comprehensive view on all the available evidence for the use of Spinraza® in adults with SMA. The HFMSE change point estimates for all the included RWE studies for Spinraza®-treated patients were above zero showing consistency in benefit.

4. Reference: pg 10, "The included studies….they were **non-comparative**…"

- The EU Registry Study includes a comparison of an adult Spinraza®-treated cohort (n=235) to an untreated cohort of 17 adults with SMA. The 17-patient untreated arm represents an appropriate-sized comparator group for the Spinraza®-treated cohort for a rare disease where treatment options exist and are readily available in Germany, Italy and Spain. This untreated group of adults, captured within the same set of registries as the Spinraza®-treated adults, provides adequate data to conduct a methodologically-sound real-world comparison of treated versus untreated adults with SMA. As these three countries are where the study's registries are based, the proportionally lower number of untreated adults is a direct result of a limited pool of potential untreated adults, and not a result of selection bias. Additionally, Biogen would like to reiterate that population sizes on this scale are common in rare disease studies. Similar cohort sizes have been able to inform CADTH's decision-making in recent rare disease reimbursement reviews.

5. Reference: pg 3, "…results in the patient population…**not representative** of adult patients with SMA in Canada" pg 3, "… substantial **heterogeneity** in the degree of disability and motor function.";
The critical review and meta-analysis published by Coratti et al. in 2021 provides a clear and comprehensive view of all of the available evidence for the use of Spinraza® in adults with SMA. The HFMSE change point estimates for **all** the included RWE studies for Spinraza®-treated patients were above zero. In addition, HFMSE changes in various untreated adult cohorts with SMA were also included. In stark contrast to the treated cohorts, the average HFMSE changes in untreated cohorts were **all** below zero, representing worsening of function (Fig. 2A of Coratti et al., 2021). Biogen would

like to clarify that, in the adult meta-analysis, **no pooled estimates crossed the zero-meridian in contrast to what is documented in the draft recommendation**. Further analyses have been submitted in the reconsideration to address the heterogeneity concern.

- Additionally, epidemiological, Global, and local studies (CNDR data and Biogen's Patient Support Program), all show more Type III patients than Type II patients in Canada.

6. Reference: pg 3, "…high degree of selection **bias**…" pg 11, under Other Sponsor Submitted Evidence, "no interpretation on the quality of studies, however, as all studies were observational, most studies were noted to suffer from a high level of bias in selection of participants."

- In the RWEs submitted, various techniques were used to minimize the impact of selection bias on the interpretation of Spinraza®'s benefits.
  - Hagenacker et al., 2020 included an exploratory subgroup analysis, which determined that Spinraza® initiation in adults with SMA resulted in a statistically significant improvement in HFMSE at 14 months regardless of SMA type (i.e., II and III), ambulation status, baseline HFMSE (i.e., ≥ 35 and <35), or history of spondylosis
  - Maggi et al., 2020 stratifies patients by ambulation status, where it was shown that both ambulatory and non-ambulatory Spinraza®-treated, type III adults experience an improvement in HFMSE at 14 months.
  - The EU Registry Study also employed various methods to counter the threat of selection bias. First, the analyses in the study were adjusted for various potential confounders, like age, baseline motor function scores, SMN2 gene copy number, and registry, among others. In addition, inclusion criteria ensured that the untreated cohort was as similar as possible to the treated group. For example, untreated patients were excluded if they had any record of conditions that may have precluded intrathecal treatment with Spinraza®, such as scoliosis. Finally, two sensitivity analyses were conducted with EU Registry Study data, one using the Last Observation Carried Forward (LOCF) approach and one with the Multiple Imputation method. The final results for each of these two imputation methods were similar, suggesting that selection bias caused by missing data is not a concern in the EU Registry Study.
- In any critical appraisal, biases must be raised and considered. These biases however, are highly unlikely to account for the overall consistent pattern of findings, of stabilization and improvement of motor function across multiple studies of 100's of patients in this rare disease with Spinraza.

Biogen remains committed to standing behind the efficacy of Spinraza® in adults with SMA and in finding a sustainable solution for Spinraza for SMA adults. We recognize that there must be a balance reached between equitable access of Spinraza® for patients in need and maintenance of economic sustainability of publicly funded health programs. Biogen proposes a multi-faceted solution that will ensure access to Spinraza® for Canadian adults who need it the most. Firstly, having a national panel of Canadian SMA experts who would identify adults with SMA that would benefit the most, as per expert clinician consensus. Secondly, establishment of pre-defined initiation and stopping criteria to guide the panel in assessing patient cases. Lastly, CNDR's infrastructure should be leveraged as a central mechanism to collect essential data in Canadian adults treated with Spinraza®.

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

The recommendation does not reflect the totality of RWE clinical evidence submitted as part of the reassessment nor PAG/Clinician input from SMA Adult treaters. It is also unclear why the comparative EU registry did not fulfil the additional data needs to assess the clinical evidence of Spinraza® in a comparative treated vs untreated manner.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

References to key RWE that supports Spinraza® for adults with SMA

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