CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

risdiplam (Evrysdi)

(Hoffmann La-Roche Ltd.)

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

December 10, 2021

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0661
Name of the drug and Indication(s)	Risdiplam (Evrysdi) Indication: For the treatment of spinal muscular atrophy (SMA) in patients 2 months and older.
Organization Providing Feedback	FWG

Reconsideration of the draft recommendation		
1. Please indicate if the stakeholder requires the expert review committee to reconsider its recommendation.		
Request for major revisions: A change in recommendation category or patient population is requested		☒
Request for minor revisions: A change in reimbursement conditions is requested		☐
For Initiation Condition 2.1, it is requested that criterion "*body weight greater than the third percentile*" be removed for consistency with other SMA drugs (i.e., this criterion is not included for other SMA drugs).		
Clarity of the draft recommendation		
2. Is the rationale for the draft recommendation clearly stated in the draft recommendation?	Yes	☒
	No	☐
3. Are the reimbursement conditions clearly stated and the rationale for the conditions provided in the draft recommendation?	Yes	☐
	No	☒
	N/A	☐
• For Initiation Condition 2.2, it may be an issue that if a patient has 3 copies of SMN2, they must wait until they're 7 months old to get risdiplam but can start at younger age if they have 2 copies. Could any additional clarity be provided in the recommendation (e.g., as discussion point) to address why risdiplam should not be started in a patient aged 2-6 months with 3 copies of SMN2?		

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Publication Date: TBC
Report Length: 2 Pages

- For Initiation Condition 2.2, could additional clarity be provided in the recommendation regarding the age cut-off of 25 years, including comments on whether there is evidence to inform use of risdiplam in symptomatic patients older than 25 years of age?

- For the Pricing Condition, the rationale of "*The economic evidence for SMA Type 1 patients suggests that risdiplam should be priced similarly to nusinersen*" could appear to imply that nusinersen is cost-effective for SMA type 1, which is not the case. As nusinersen is not cost-effective at its current price, it should be clear that risdiplam is not cost-effective.

  The Rationale for the Recommendation also states "*However, the lack of long-term comparative efficacy evidence means that incremental effectiveness, and thus cost-effectiveness, of risdiplam compared with nusinersen is highly uncertain*."

  It may be more appropriate to indicate that "The cost-effectiveness of risdiplam compared with nusinersen is highly uncertain for SMA Type 1." An optional addition could be: "There is no evidence to suggest risdiplam should be priced any higher than nusinersen."

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

- Implementation Guidance point #4 indicates that there is an evidence gap for sequencing of risdiplam relative to other medications indicated for the treatment of SMA. It also noted that children who have been receiving medications indicated for SMA and meet the initiation conditions should not be precluded from receiving treatment with risdiplam.

  - Does this also imply that a patient who failed onasemnogene abeparvovec (OA) could get risdiplam afterwards? Note that the OA rec indicates: "*Clinical experts for CADTH suggested that once onasemnogene abeparvovec is administered, no further treatment with nusinersen or other medications indicated for treatment of SMA should be expected. There are currently no data on the effectiveness of nusinersen or other medications indicated for SMA administered after onasemnogene abeparvovec*."
    If intent is to NOT reimburse risdiplam after failure of OA, should a statement to align with the above be included in the risdiplam recommendation?

- The last Discussion Point highlights that studies are ongoing for the effects of risdiplam in pre-symptomatic patients. Can a statement be included to indicate that it will be the manufacturer's responsibility to submit evidence regarding the pre-symptomatic population once it becomes available?

- Can CDEC comment on whether time-limited reimbursement should be considered for patients who meet the CDEC-recommended criteria but will age out before the review and negotiation process are complete? If yes, please provide criteria.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0661
Brand name (generic)	EVRYSDI® (risdiplam)
Indication(s)	For the treatment of spinal muscular atrophy
Organization	Hoffmann-La Roche Ltd (Roche)
Contact information[a]	[redacted]

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

Roche Canada agrees that the committee's recommendation is aligned with the evidence from the FIREFISH Part 2 and SUNFISH Part 2 studies. The populations identified in the recommendation are reflective of the populations included in the trials. However, there are elements of the recommendation that are not optimal as it relates to clinical practice. Roche's commentary[b] around these challenges are included as part of implementation challenges.

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 recommendation reflects that the clinical and economic data submitted were considered as part of the assessment.

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

The reasons for the recommendation are clearly stated and are based on the clinical trial data.

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

As previously stated, the recommendation is aligned with the available clinical trial data; however, from the perspective of clinical practice, we note some potential challenges with implementing the criteria as written in section 2.2 of the *Initiation Criteria* (*Table 1 - Reimbursement Conditions and Reasons*, page 3). These are related to issues with using clinical trial populations and data to establish reimbursement criteria.

Firstly, while SUNFISH Part 2 included a non-ambulatory SMA population, given the progressive nature of SMA it is inconsistent with the goals of treatment to wait for individuals to lose ambulation before considering initiating a therapy. As written, an individual with SMA who has not yet reached the definition of non-ambulatory would have to deteriorate further in order to meet the criteria and be eligible for funding. Clinical trials, especially in the area of rare conditions, are challenging to design and conduct. The clinical development program for risdiplam included a very broad SMA population including ambulant individuals in SUNFISH Part 1. We recognize that there is uncertainty regarding

the benefits in individuals with SMA who are ambulatory due to the trial design; however, it is generally accepted that the goals of treatment in SMA are to prevent loss of motor neurons and to preserve function. The evidence to date suggests that the earlier treatment is initiated, the better the outcome. For this reason, the criteria will pose challenges in real world practice.

Secondly, the initiation criteria limit treatment eligibility to adults with SMA up to 25 years of age. While aligned with the SUNFISH Part 2 trial population, age at treatment initiation is not the only predictor of response. There are many other SMA-related factors that may affect how an individual adult will respond to therapy. Many adults remain untreated and continue to lose motor function however, the criteria, as written, would not allow those over 25 years of age to initiate treatment even though they may benefit when considering other factors.

As noted in the recommendation, it is difficult to predict who will respond to treatment. Ambulatory status and age may not be the most appropriate predictors of response to treatment in SMA. Using the criteria for discontinuation is preferred to restricting who can initiate therapy based on age or ambulatory status for this reason. This allows a decision about continued treatment to be made based on the individual's observed response. Further, it could allow the collection of real world evidence to help make more informed decisions about appropriate care moving forward. It is not feasible to represent all individuals with SMA in a full double-blind, randomized, controlled study design.

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

The reasons for the reimbursement conditions are clear as well as the rationale.

[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.

[b] Commentary only. **Not** a request for reconsideration.

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	☐	☐	☐	☐

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.
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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.
- 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 clincian 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

New or Updated Declaration for Clinician 1	
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 2	
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 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	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0661-000
Brand name (generic)	EVRYSDI (Risdiplam)
Indication(s)	Spinal Muscular Atrophy (SMA)
Organization	The Neuromuscular Disease Network for Canada (NMD4C)
Contact information[a]	Name: Dr. Hanns Lochmüller, Senior Scientist, CHEO Research Institute, Professor of Neurology, University of Ottawa Faculty of Medicine and The Ottawa Hospital Department of Medicine [redacted]

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

Re: Table 1. Reimbursement Conditions and Reasons

Reimbursement condition: *Aged 7 months and up to 25 years who are non-ambulatory and have genetic documentation of 2 or 3 copies of the SMN2 gene.*

With respect to the proposed condition that patients be *"non-ambulatory",* we believe that CDEC has overlooked the opportunity for the use of risdiplam to stabilize disease and retain motor function such as ambulation for a subset of patients.

The importance of early treatment (of SMA) has been extensively demonstrated in both clinical trials and in real world practice. Eligibility criteria for an SMA treatment that requires deterioration of motor function before treatment can be initiated contradicts long established, evidence-based therapeutic strategies for the treatment of SMA. It is also of note that some babies in the Firefish study with SMA type 1, who would never have achieved walking (known from natural history studies), were able to achieve this motor milestone. To exclude children who have milder disease and who are walking would be counter-productive. We know that with regards to ambulatory function in SMA[i] there is gradual reduction in the 6 minute walk distance over time, most markedly in the adolescent age group. To deny these patients the potential of maintaining function would be short-sighted. NMD4C will be collecting Real World Evidence through the Canadian Neuromuscular Disease Registry (CNDR) to understand more about the effects of treatment. The other concern re: ambulation is that, for instance, when reviewing two children with SMA of equal disease severity, but one happens to be a few kilograms heavier than the other, and subsequently cannot ambulate – that child would be eligible for treatment, but his lighter, equally affected counterpart would be ineligible for treatment as he/she is still able to ambulate.

Reimbursement condition: *Aged 7 months and up to 25 years who are non-ambulatory and have genetic documentation of 2 or 3 copies of the SMN2 gene.*

In our clinician input we (NMD4C) stated (re: risdiplam): *"...it may be the preferred option for some patients, including many adults, where stabilization of the disease can mean retention of a vital motor function, avoidance of ventilator dependency, continued ability to speak and swallow, and survival."*

With respect to the proposed age range of eligibility "Aged 7 months and up to 25 years", we (NMD4C) believe that the reimbursement condition that proposes to cut off eligibility at 25 years of age is somewhat arbitrary. While we recognize that this age limit was used as the cut-off for eligibility in the clinical trial, it is important to recognize that adult SMA patients (over the age of 18) have a high unmet need for treatment. Maintaining motor function remains an important outcome for this population.

As stated in our clinician input submission: "*We recognize that there is limited evidence available for assessment of this population. However, in a rare disease such as SMA, clinical trials of sufficient size are difficult to conduct generally, and for this sub-group of adults, the problem is compounded."*

In real-world clinical practice, we believe that eligibility for initiation of therapy is not rationally determined by a rigid age cut-off. Rather, eligibility should be determined by more traditional clinical criteria along with defined conditions for discontinuation of risdiplam based on the patient's observed response to treatment.

In our clinician input, we stated:

> *"Importantly, this treatment has been tested in clinical trials for SMA patients up to age 25 years. In addition, a trial is underway in people with all types of SMA aged 6 months to 60 years previously treated with other SMA therapies."*
>
> AND
>
> *Even though the magnitude of treatment effect on older patients was not as robust, we believe the evidence supports the use of this treatment in patients that are currently ineligible for nusinersen due to age or physical ability. There is also indication of maintained swallowing ability that has not been demonstrated in other medications to date*.

Recognizing the lack of data of adult patients (> 18 years), we advise CDEC to recommend that these adult patients be given access to this therapy with the condition that provinces support the capture of outcomes data of these SMA patients in the Canadian Neuromuscular Disease Registry (CNDR) to address any existing uncertainty for this subpopulation.

Following the issuance of the draft recommendation (re: risdiplam for SMA) from CADTH, NMD4C was contacted by an Alberta physician who treats patients with SMA. His concerns, as quoted below, are largely representative of the concerns of the larger SMA-treating physician community:

> *"I have two concerns related to the restrictions ....*
>
> *My biggest concern is not allowing ambulatory patients to get it. This seems insane. Do we wait until someone is not ambulatory to institute the therapy? It seems like we are giving people permanent disability. What percentage of those children with that genotype don't eventually have significant loss of ambulation?*
>
> *My second concern is the age restriction. This hits close to home as I currently have 4 patients this would affect. I don't believe there is any a priori reason to believe those between 20 and 25 are going to behave differently than those between 25 - ?"*

Reimbursement condition: *Patients who are symptomatic and either: 2.1. Aged between 2 months and 7 months (inclusive), have a body weight greater than the third percentile, and genetic documentation of 2 copies of the SMN2 gene*.

We (NMD4C) would like to clarify with CDEC that the Health Canada approved indication does not exclude pre-symptomatic patients - only patients under 2 months. SMA-treating physicians recognize that risdiplam may be of great practical value for the treatment of pre-symptomatic (or early symptomatic) patients identified through newborn screening. While the preference would be to treat these patients with Zolgensma (AAV gene therapy), there are often significant delays in securing funding for Zolgensma. Again, in recognition of the importance of early treatment (of SMA) in these circumstances, risdiplam (or spinraza) could be used as a bridge to Zolgensma.

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	☒

It is unclear that the expert committee has given consideration to the input provided by this group of expert clinicians, specifically with respect to the use of risdiplam for stabilization of the disease with the objective to maintain vital motor function, avoid ventilator dependency, and maintain the continued ability to speak and swallow.

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. Contact information will not be included in any public posting of this document by CADTH.

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Clinician Group Information	
Name	*Hanns Lochmuller*
Position	*Senior Scientist, CHEO Research Institute, Professor of Neurology, University of Ottawa Faculty of Medicine and The Ottawa Hospital Department of Medicine*
Date	*Please add the date form was completed (27-05-2021)*
☒	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.

Note: NMD4C receives funding from CIHR and Muscular Dystrophy Canada exclusively.

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	☐	☐	☐	☐

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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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: • Dr. Jodi Warman-Chardon • Dr. Kathyrn Selby • Dr, Jean Mah • Dr. Kerri Schellenberg • Dr. Craig Campbell • Dr. Hanns Lochmuller *Note: The COI updates for Dr. Dowling and Dr. Vajsar are pending. Dr. Tarnopolsky did not provide input during the "Feedback" stage.*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician	
Name	*Bernard Brais*
Position	*Professor of Neurology and Genetics*
Date	*27-05-2021*
☒	**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	☐	☒	☐	☐

REFERENCES

[i] MontesJ,,Eugenio Mercuri et al 2018 Ambulatory function in SMA: Age related patterns of progression. PLos ONE 13(6): e0199657

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0661
Brand name (generic)	Evrysdi (risdiplam)
Indication(s)	For the treatment of spinal muscular atrophy (SMA) in patients 2 months and older.
Organization	Cure SMA
Contact information[a]	Name: Susi Vander Wyk [redacted] [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
While we are happy to see a positive recommendation, we do have some concerns of the limitations set within and would like to offer our input as we do feel there are gaps that must be addressed.		

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? We feel the committee considered the points brought forward, however there are gaps as many concerns are not reflected in the recommendation.		

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. Patients over the age of 2 may not benefit from the assessment tools recommended by the committee, without the ability to demonstrate benefit from treatment through fair outcome measures, the patient risks being removed from treatment.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
It is evident in the reimbursement recommendation that the committee members see the limitations within, as there is reference to other patients who will benefit from treatment. Surely, patients who are able to walk will benefit from the continuation of that skill, the ability for someone to feed themselves or work a full day are all valuable to the individual. There are treatments available for other diseases		

where there is later onset, we must recognize that adult SMA patients meet the basic criteria for a right to benefit from a treatment as in other progressive diseases affecting older patients.

With conditions in place for discontinuation of treatment should a patient not demonstrate benefit such as maintaining function, there is justification to increase the window of eligible patients. Concerns:

- **Limitation of eligibility to patients who are symptomatic.** Prevention of loss of function is imperative in all stages of this disease. To wait until a patient experiences this loss is limiting their ability to maintain maximum function. Preventing progression is an important goal in the treatment of SMA, the earlier we address this goal, the less loss is experienced.

- **Restricting treatment access according to SMN2 copies is an unfair method of identifying eligible SMA patients.** Patients are not falling into types according to their copies of SMN. For example; we have patients who are non ambulatory with three copies of SMN2 but also patients who are ambulatory with the same copy number. The limitation due to the number of SMN copies provides the ability for patients who meet other conditions to be denied. It is important to ensure that copy number does not limit access, we suggest increasing SMN2 copy numbers required.

- **Limiting access to patients who are non-ambulatory is greatly concerning for patients who have achieved the ability to walk.** We must not allow a patient who is ambulatory, to lose the ability and become wheelchair bound to justify access to treatment. This would be a devastating loss to the patient that would have long term negative effects both physically as well as mentally.

- **Permanent ventilation –** We know Risdiplam benefits bulbar function. To exclude patients who may reduce their dependency on permanent ventilation support, due to treatment access, would be eliminating a low number of patients who could also benefit from treatment that would affect their quality of life and longevity.

- **Patient age restriction of 25 years –** All SMA patients are experiencing a decline in function if left untreated. A patient that is able to type a thesis at 30 years old is fearful of the loss of that ability. A patient that is holding a job at 50 is worried what another year without treatment will mean in terms of earning an income and providing for their family. A mother in her 40s is losing the ability to remove her socks and pants and is dependant on her teenage son to do that for her when one year ago she was able to do it without assistance. To slip past an age limit when you are the individual is devastating. Their tomorrows are bright and full of plans, the abilities they hold today are worth holding on to because today they can achieve. Through focus groups, when patients were asked about accessing treatment, the common thread was the fear of loss of the physical abilities they have and their will to live and be productive. To lose the ability to receive an education, to hold a job, to plan a future, is not only a physical loss for the patient, it is a devastating emotional loss for them as well as their family and the community. The youth affected by SMA are important, but so are the adults, most of our adults have no other option, its this or nothing, and it can't be nothing.

[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	*Susi Vander Wyk*
Position	*Executive Director*
Date	*27-05-2021*
☒	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**
Biogen	☐	☐	☐	☒
Novartis	☐	☐	☐	☒
Roche	☐	☐	☐	☒

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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  - 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 clincian 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

New or Updated Declaration for Clinician 1	
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 2	
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**			
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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
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				
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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

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Company	Check Appropriate Dollar Range			
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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0661
Brand name (generic)	Evrysdii (risdiplam)
Indication(s)	Spinal muscular atrophy
Organization	Muscular Dystrophy Canada
Contact information[a]	Name: Homira Osman [redacted]

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

We are encouraged by the overall positive recommendation. However, we would be remiss in not acknowledging that the clinical criteria in the recommendation limits access to treatment for many patients with SMA who could potentially benefit from EVRYSDI®, a lifechanging drug therapy for SMA - a debilitating rare neurodegenerative condition.

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	☒

Removing caregiver utilities from the cost-effectiveness analysis is problematic. As mentioned in our original patient input submission, living with SMA requires a high degree of dependence on both caregivers and equipment, additional therapy, and medical appointments, all of which leads to exhaustion for both patients and caregivers as well as increased strain on mental health and relationships. Caregiver burden is significant with SMA. Our clients with SMA have reported that they often require 24-hour support with all activities of daily living. Provincial government home support programs cannot accommodate this request due to funding cap restrictions. Unfortunately, caregivers are required to provide at least 12 hours of personal care for some of our clients. Removing caregiver utilities from the cost analysis underestimates the total QALY benefits that can be observed with EVRYSDI®. Recently, MDC conducted a cost of illness and health-related quality of life study in children, adults and family members affected by SMA. Our preliminary analyses point to significant direct and non-direct health resource utilization costs and loss of productivity for informal caregivers. Removing the two informal caregivers per patient from the cost analysis is challenging because access to EVRYSDI® has potential to maintain independence, function and reduce reliance on informal caregivers.

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	☐

Restricting the recommendation for access to EVRYSDI® for those under age 25 is highly problematic. Beyond infancy, age has not been identified as an independent predictor for the response to treatment. While there is consensus that an early start of any such treatments (e.g., first year of life) provides the most dramatic results. However, an early start of treatment is usually accompanied with early symptoms and high severity occurring at an early age; hence age is not an entirely independent variable. Baseline health/motor function status and the number of SMN2 copies are the most validated surrogates/biomarkers to predict the likely magnitude of a treatment response. A few adult Canadians over age 25 are currently accessing EVRYSDI® via Health Canada's Special Access Programme with the support of their neuromuscular clinicians (i.e., neurologists, physiatrists). One of our clients, an adult in his mid-40s in New Brunswick, shared the following quote:

- "I was diagnosed with SMA at 10 months of age and all my life I have been looking forward to the day where I can access treatments and therapies for SMA. The day finally came two months ago, where I was given special access to Risdiplam. In the short period with this treatment, I have already seen minor improvements in swallowing and in motor function in all four limbs. To others, these improvements might be insignificant, but for me – minor improvements and even stability in disease has a significant impact on my quality of life."

- Another one of our adult clients in her late 30s shared: "I have been on Risdiplam for a few months and it's honestly surreal. I am able to eat more and have actually gained weight – which is great and it's all because my chewing and swallowing has improved considerably. I also have more energy. For someone who has lived with SMA all my life, I am still processing the small benefits this treatment gives me each day."

Based on the draft recommendations, access to EVRYSDI® would not be recommended for the two adult Canadians cited above. CADTH has noted that the rationale for this is because the data from clinical trials (i.e., FIREFISH, SUNFISH) is limited and evidence was only available for those under age 25. However, the lack of clinical trial data does not suggest lack of potential for positive responses/outcomes. In fact, by necessity, clinical trials in rare disorders, such as SMA, enroll small samples. This is not only because of an inherently small population, but also the high inter-individual variability in clinical course observed in SMA can diminish a study's power. Thus, researchers/industry partners opt for techniques such as tightening the inclusionary criteria (i.e., limiting age) in order to maximize data from a small and heterogeneous group of subjects.

Bearing in mind such challenges and time required for obtaining clinical trial data for adult SMA, the adult SMA community is not in a position to wait. Instead, in the interim, we need to leverage outcomes from global registries/databases, where clinically meaningful improvements in motor function as a result of EVRYSDI are well recognized.

The establishment of arbitrary age limits on access to EVRYSDI® should be discouraged. An upper age limit of 25 is problematic: age 25 vs 26 or 45 does not demarcate safety and efficacy of EVRYSDI® and instead the success of treatment varies depending on the individual patient. We propose that CADTH remove the rigid arbitrary age cut-off from its recommendations. Similar to Health Canada's Special Access Programme, if a clinician that specializes and treats SMA deems their 25+ year old patient appropriate for EVRYSDI®, they should be recommended to access it. If this cut-off is not removed, many adults affected by SMA will be left very disappointed and without

treatment options. This was clearly noted in our patient submission where 'difficulty accessing treatments due to age' emerged as a common theme from the qualitative analysis.

Restricting the recommendation for access to EVRYSDI® to those who are non-ambulatory is highly problematic. As noted in our patient input submission, it is the priority of most adults with SMA, due to the inherent weakness and functional limitations, to preserve their mobility and independence as much as possible.

- "If I could halt my SMA's progression at its current stage it would be gigantic relief."
- "I would love to regain some strength but would settle for the slowing (or outright stopping) of SMA's progression."
- "Stopping the progression is critical. I can still walk, drive and work. I would love to be able to all these things for many years to come."
- "I don't care so much about improvement as I do about being stable."

For some adults who are able to walk independently at some point (i.e. type 3 SMA), it is critical to maintain function. EVRYSDI can offer stability in disease progression. According to Wan et al. 2020: "People with SMA universally stated that maintaining stability of their current functional ability was important." In this study, fear of functional decline and premature death was noted as an emotional and social well-being consequence of living with SMA. Moreover, access to treatment for ambulatory adults affected by SMA can decrease the event of a life-threatening secondary complications i.e. pneumonia which could result in admission to ER, ICU and or acute care. Limiting EVRYSDI® to those who are non-ambulatory will be i) inconsistent with clinical judgement and emerging evidence which suggests that these patients may benefit significantly with treatment to maintain their independent ambulation; ii) significant barriers will remain for ambulatory adults with SMA who wish to access therapeutic interventions that aim to maintain stability, promote function, independence and enhance quality of life.

[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

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- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Homira Osman*
Position	*Director of Knowledge Translation & External Engagement*
Date	*28-05-2021*
☒	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

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  - Please add more tables as needed (copy and paste).
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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 clincian 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

New or Updated Declaration for Clinician 1	
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	

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
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 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				
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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

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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

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Add or remove rows as required	☐	☐	☐	☐