January 31, 2019

AveXis, a Novartis company, appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) draft evidence report of treatments for spinal muscular atrophy (SMA). We thank ICER for delivering a complex model and thorough analysis in such a short time. We found the model used appropriate health states that accurately capture the clinical progression of SMA Type 1; including a separate permanent ventilation health state was especially important given the implications for patients. Using a short-term and long-term approach effectively captured the key data available. We agree with the survival data used to model transitions, and for those patients who achieve sitting and walking milestones, using SMA Type 2 and SMA Type 3 data, respectively, was a reasonable approach. Similarly, avoiding the transition from sitting or walking to permanent ventilation was a valid assumption and supported by clinical experts. In addition, the use of a mixed approach for utilities is pragmatic given a lack of disease-specific utilities, and the cost data adequately captures the health state burdens. Finally, the well-thought-out sensitivity and scenarios analyses highlighted key data gaps and provided additional value for decision making.

Detailed Comments and Recommendations

We appreciate ICER's evaluation and willingness to engage stakeholders during the review process. In our review, we identified some methods that we recommend be reconsidered, specifically:

1. We disagree with ICER's base case model assumption that 1/6 of sitting ZOLGENSMA patients return to the not-sitting state at the end of the short-term model, and with ICER's assumption that these patients "required" Spinraza. This assumption is not grounded in evidence and is inconsistent with those made for Spinraza. We acknowledge scenario analysis #6 reports results assuming no loss of milestones, and removing this assumption lowers the ICER by $17,000 to $230,000 per QALY for ZOLGENSMA vs BSC. However, we request the modeling team remove this loss of sitting milestones assumption for ZOLGENSMA in the base case. We also request the removal of the word "required" when referencing patients who did receive Spinraza after ZOLGENSMA as there is no evidence to support this language.

    - There is no clinical evidence to support the milestone loss. Importantly, no patients who received the therapeutic dose in the ZOLGENSMA CL-101 24-month study, or the long-term study (maximum follow-up of 30 months) experienced any loss of milestones or worsening disease.[1,2]
    - There is no evidence that Spinraza was "required" or beneficial for ZOLGENSMA patients in the trial. It is highly implausible that any ZOLGENSMA-treated patient would receive additional benefits by commencing chronic treatment with Spinraza.

      ZOLGENSMA is a gene replacement technology based on Adeno Associated Virus (AAV) Serotype 9 as vectors, which has demonstrated long-term gene expression in several pre-clinical and clinical trials. ZOLGENSMA was designed for rapid onset and long-term gene expression utilizing self-complementary DNA technology for rapid gene expression as well as a modified Chicken B-Actin promoter for high-level, robust expression in a wide variety of cell types including motor neurons. Preclinical data support the expectation of long-term gene expression following administration of ZOLGENSMA. In a mouse model of SMA, gene therapy resulted in survival of greater than 250 days, compared to control-treated animals who did not survive past

22 days; this suggests continued expressions.[3] Gene therapy vector-derived DNA and RNA were detected in tissues from mice examined at 24 weeks post-injection, indicating persistence of expression. In non-human primates, quantitative RT-PCR was used to demonstrate gene therapy vector-derived mRNA 6 months post-injection, indicating persistence of expression.

The addition of an SMN-enhancing agent more than two years after treatment with ZOLGENSMA lacks therapeutic rationale and biologic plausibility. Swoboda *et al.* demonstrated a precipitous decline in viable motor units over the first few months of life amongst infants with SMA Type 1.[4] For patients with SMA Type 1, without disease-modifying treatment, over 95% of motor neurons are permanently lost by age one. Following treatment with ZOLGENSMA, a significant majority of motor neurons are expected to take up the vectors and thus express continuously sufficient SMN protein. Motor neurons that fail to take up vectors are effectively untreated and will thus be lost. For this reason, the addition of an SMN2-enhancing agent months to years following ZOLGENSMA dosing lacks biological plausibility – the only motor neurons left, by definition, already express adequate levels of SMN protein. In contrast, there is a plausible mechanism to support administering ZOLGENSMA to patients who have previously received Spinraza (i.e. using Spinraza as a "bridge therapy"). This approach should be regarded as different from a sequential strategy (Spinraza post ZOLGENSMA) modelled in the base case.

- Because there was no evidence of clinical deterioration in the CL-101 trial, it is our contention that the decision to initiate Spinraza post ZOLGENSMA was driven by parental desire, rather than by clinical indication or biological plausibility. It is understandable that parents would have considered additional options, regardless of the lack of scientific evidence to support the plausibility of additional effectiveness (see above). And, while the specific motivations that underlay the decision to initiate use of Spinraza is a private matter between patient's guardians and physician, these motivations **should not be used** as a foundational assumption that patients were deteriorating or that Spinraza was required. Further, the following points are important:
  1. Among four new milestones reported among participants in the long-term follow-up, three occurred among patients only receiving ZOLGENSMA.
  2. Two of the five subjects who initiated Spinraza discontinued use due to lack of benefit (i.e., no new motor milestones).
- ICER's approach to ZOLGENSMA milestone persistence, which was modeled as a decline in the absence of evidence, is contradictory to ICER's approach to Spinraza milestone persistence, which was modeled as consistent despite published data showing a decline in the proportion of sitting patients. Table 4.2 (page 56) of the ICER report states: "In the short-term model for Spinraza, we assumed that the numbers of patients sitting cannot decrease over time". This is explained in Table E2 and page 158: "The numbers of patients sitting are monotonically increased with time, except for the last time point where the number of patients sitting is lower than the previous time point. It is not clear if this is due to administrative censoring or patients losing milestones. We assumed that this was due to administrative censoring, and in step three, the number of patients sitting at the last time point was set as equal to those in the previous time period." This assumption's importance can be observed in the one-way sensitivity analysis for

Spinraza (Figure 4.4, page 72), Scenarios 7a-c for Spinraza vs BSC (Table 4.21, page 75), and where ICER reports 64% of Spinraza QALYs are from the sitting (Table E12, page 168).

- The loss of milestones assumption was not mentioned in the original model analysis plan. Based on the report, it is unclear whether clinical, SMA or gene therapy experts were consulted about this assumption, and a discussion with experts or AveXis may have benefitted this assumption.
- If the assumption is not removed, for the purposes of balancing the analysis, we request the modeling team conduct a scenario analysis where responders are restored to full health.

2. We request the modeling team conduct a new value-based price (VBP) analysis for the threshold prices in Table 4.26 using the "no milestones lost" assumption for ZOLGENSMA.
3. As discussed in earlier consultations, we recommend ICER's "Report at a Glance" should include all relevant thresholds **including** the VBP analysis using a willingness-to-pay of $500,000 per QALY. This short version report is more accessible for decision makers than long-form reports, and including this figure would be consistent with ICER's stated objectives for ultra-rare diseases. This request is also supported by a £100K- £300K per QALY threshold for ultra-orphan drugs by NICE.[5]
4. We find the "ZOLGENSMA vs Spinraza" scenario (Pages 77-8, Tables 3, and 4.23-24) misleading.
   - We recommend this scenario should be removed given the lack of clinical and biologic plausibility for sequential treatment with Spinraza (Point 1), and an unaddressed uncertainty of whether Spinraza would be covered for ZOLGENSMA-treated patients by US insurers.
   - If this scenario is not removed, we request the scenario be relabeled as "ZOLGENSMA *followed by* Spinraza vs Spinraza" for clarity, as this reflects the true comparison.
   - Further, it would be appropriate for ICER to modify the scenario and report the scenario where ZOLGENSMA (monotherapy) is the comparator against the sequential treatment. The current ICER of $202,000 (Table 4.23, page 78) shows the incremental benefit of ZOLGENSMA as a bridging therapy to Spinraza treatment, an indication for which ZOLGENSMA has not been studied, nor follows clinical rationale. ZOLGENSMA as the comparator shows the incremental benefit of adding Spinraza post-ZOLGENSMA. Based on current values in the reports, we have calculated this ICER for ZOLGENSMA *followed by* Spinraza vs ZOLGENSMA to be $1,415,323/QALY (($5,240,000 - $3,485,000) / (12.57 – 11.33) = $1,755,000 / 1.24). Adding Spinraza to ZOLGENSMA-treated patients would not be clinically justified nor cost-effective.
   - We also request the modeling team report an additional scenario analysis of "ZOLGENSMA monotherapy (without milestone loss) vs Spinraza monotherapy" so that the committee, and subsequent audiences, can more fully consider the long-term value for money.
   - In the event ZOLGENSMA *followed by* Spinraza vs Spinraza scenario is not removed, based on recent data from the ZOLGENSMA managed access program (MAP) (16 out of 20 =80% MAP patients received Spinraza prior to ZOLGENSMA), we request ICER to conduct a switch strategy scenario (1 to 3 doses of Spinraza *followed by* ZOLGENSMA) and report the ICERs for switch strategy vs BSC and Spinraza monotherapy.
5. To match current recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine, NICE, and HTA agencies in The Netherlands and Belgium,[6-12] and given the long-term

health benefits provided by ZOLGENSMA, we request the modeling team conduct additional scenario analyses using differential discounting (i.e., 3% for costs and varying utilities from 0% - 3%). Also, as recommended by the Second Panel,[12] we request that the modeling team include discounting as part of the one-way sensitivity analysis for all treatments.

- There is broad agreement that in cost-effectiveness analysis (CEA), future outcomes should be discounted, and their present values calculated so that cost-effectiveness ratios will be appropriately adjusted for the differential timing of costs and consequences. However, there is disagreement over the appropriate discount rate to use. The Second Panel noted that the appropriate discount rates for costs and health will depend, among other things, on fixed health care budgets, the social objective of maximizing welfare vs health, and social time preferences (which may be different for health vs consumption).[12] The Second Panel recognized the uncertainty around the appropriate discount rates from societal and health care sector perspectives. The Panel noted that "since the goal of the Reference Cases is to promote comparability across studies, we recommend that a 3% interest rate be used for both costs and effectiveness from both the societal and the health care sector perspectives."[12] We recognize this rate was used in the ICER model. However, the Second Panel stated it is always advisable to perform sensitivity analyses for any baseline discount rates used, especially when the costs and benefits are incurred at different times for different interventions. More recently, other have argued, based on theoretical and empirical evidence, that the Second Panel's recommended discount rate of 3% per annum is too high, resulting in systematic bias against health technologies with upfront costs and long-term health effects.[6]
- We note ICER is preparing its framework for curative therapies and hope ICER will consider the merits of differential discounting in its assessment. As the standard practice in the US is to discount benefits at the same rate as costs, the benefit of potentially curative medicines may be severely misrepresented. In the meantime, given the considerable public attention to ICER reports beyond the field of health economics, it would be beneficial to patients and members of the public for an undiscounted survival benefit to be published, as well as a VBP based on undiscounted benefits. This is demonstrated well by an example from the published draft report. Table E10 (page 167) reports a gain of 32.4 undiscounted life years for the ZOLGENSMA cohort. To test the ICER per QALY, we multiplied the corresponding utility value for each health state (using 0.88 as an average for walking) by the undiscounted LYs (by health state) for ZOLGENSMA to yield the undiscounted QALYs. Our calculations show ZOLGENSMA yields 22.4 undiscounted QALYs; in the base case (3% discounting) ZOLGENSMA yields 11.33 QALYs. Removing discounting nearly doubles the QALYs. Using costs from Table 4.13 (page 70) shows the benefit of differential discounting (3% costs, 0% utilities), as the ICER for ZOLGENSMA vs BSC lowers to $123,000 / QALY from the base case of $247,000 / QALY.

6. We appreciate HTA bodies outside the US frequently use stopping rules in CEA. We disagree with the base case 24-month stopping rule assumption for Spinraza, as this is not likely to be indicative of US clinical practice. We request that the modeling team report the results from scenario analyses where different Spinraza stopping rules are tested (e.g. 36 months, 48 months).

- Insurance guidelines for Spinraza suggest that Spinraza can be continued if it helps to improve, maintain, or slow the disease progress.[13] Spinraza is indicated for life-long treatment. Therefore,

even if patients do not achieve a milestone (i.e., not sitting to sitting), it is expected that they would continue treatment. Understanding how the stopping rule affects the Spinraza vs BSC ICER results will be important when assessing long-term value for money.

7. We request the modeling team remove the "Drug X" pre-symptomatic analysis. We enthusiastically agree that there is promise for treating SMA patients early. However, there is little clinical evidence to support these analyses, thus the "Drug X" analyses are premature and speculative. Also, as the results rely heavily on patient mix, they are not generalizable. The patient mix does not match the ongoing pre-symptomatic study AveXis is conducting which means ICER's results are unlikely to reflect how ZOLGENSMA will be used in practice. Further, it is unclear how SMA patients may be identified pre-symptomatically as not every US state has a compulsory newborn SMA screening program. Therefore, the source and validity of pre-symptomatic prevalence assumptions are unclear.
8. We request optimistic versions of scenarios 7a-7c (i.e., assume 10/20/30% of sitting [or not sitting] patients transition to walking [or sitting] at the end of the short-term model) to test uncertainties.
9. We request the modeling team conduct a scenario analysis accounting for a blended Spinraza price: 60% with $127,500 (Table 4.7, page 66) and 40% with the hospital markup ranging from 8% to 60%. In Table 4.7, ICER assumes no hospital markups for Spinraza. However, in calculating the total administration cost for Spinraza, ICER assumes 40% of patients receive Spinraza in inpatient settings (Table 4.8, page 5). If 40% of patients receive Spinraza in inpatient settings, it would be reasonable to account for the hospital markup costs for Spinraza. Our range recommendation is from clinical experts who have advised hospital markups could range between 8%-60% per dose.
10. Intubation in the US is more common. We request ICER conduct a scenario using pooled survival curve of non-invasive and tracheostomy patients (PV to death[14]) with a survival limit (e.g. 22 years).
11. There are several important considerations for ZOLGENSMA that should be added to Section 5 – Potential Other Benefits and Contextual Considerations. We list these below.
    - ZOLGENSMA is a one-time, one-hour IV treatment that should eliminate patient and caregiver anxiety, inconvenience, and complexity associated with repeated lumbar punctures needed for Spinraza while improving patient outcomes.[15]
    - The benefits of ZOLGENSMA extend beyond improved patient survival and quality of life. These children will have the potential to attend school and require substantially reduced levels of care, allowing family to return to work, with subsequent mental health and financial benefits.
    - Due to its mode of action and its one-time dosing, ZOLGENSMA may reduce the existing burden on caregivers by helping to eliminate the need to continuously navigate complex and often-changing health insurance coverage policies.

In summary, we largely agree with ICER's findings and analysis. This is a challenging disease to model, but the findings are generally in agreement with our expectations. ICER highlights the milestones achieved by ZOLGENSMA patients, who otherwise would have experienced rapidly progressing and lethal disease. We believe that incorporating the important issues highlighted above will further improve the scientific validity and usefulness to audiences of the evaluation.

1. Mendell J, Al-Zaidy S, Shell R, et al. AVXS-101 Phase 1 Gene Replacement Therapy Clinical Trial in SMA Type 1: Continued Event Free Survival and Achievement of Developmental Milestones. Paper presented at: American Academy of Neurology Annual Meeting; April 21-27, 2018, 2018; Los Angeles, California.

2. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med.* 2017;377(18):1713-1722.

3. Foust KD, Wang X, McGovern VL, et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. *Nature biotechnology.* 2010;28(3):271.

4. Swoboda KJ, Prior TW, Scott CB, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. *Ann Neurol.* 2005;57(5):704-712.

5. NICE. *Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes.* April 2017.

6. Paulden M, O'Mahony JF, McCabe C. Discounting the recommendations of the second panel on cost-effectiveness in health and medicine. *PharmacoEconomics.* 2017;35(1):5-13.

7. NICE. *Discounting of health benefits in special circumstances.* 2011.

8. Postma MJ, Parouty M, Westra TA. Accumulating evidence for the case of differential discounting. *Expert Rev Clin Pharmacol.* 2013;6(1):1-3.

9. Ultsch B, Damm O, Beutels P, et al. Methods for Health Economic Evaluation of Vaccines and Immunization Decision Frameworks: A Consensus Framework from a European Vaccine Economics Community. *Pharmacoeconomics.* 2016;34(3):227-244.

10. Attema AE, Brouwer WBF, Claxton K. Discounting in Economic Evaluations. *Pharmacoeconomics.* 2018;36(7):745-758.

11. O'Mahony JF, Paulden M. NICE's selective application of differential discounting: ambiguous, inconsistent, and unjustified. *Value Health.* 2014;17(5):493-496.

12. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. *Cost-effectiveness in health and medicine.* Oxford University Press; 2016.

13. Biogen. *Navigating insurance and support programs for Spinraza® (nusinersen).* 2018.

14. Gregoretti C, Ottonello G, Chiarini Testa MB, et al. Survival of patients with spinal muscular atrophy type 1. *Pediatrics.* 2013;131(5):e1509-1514.

15. La Foresta S, Faraone C, Sframeli M, et al. Intrathecal administration of Nusinersen in type 1 SMA: successful psychological program in a single Italian center. *Neurological Sciences.* 2018;39(11):1961-1964.

January 30, 2019

Dear Dr. Steve Pearson,

Thank you for the opportunity to comment on ICER's SMA Draft Evidence Report. Outlined below are **six** key issues with ICER's assessment that have the potential to significantly affect the results presented to the New England CEPAC. A large amount of research, analysis, and data with significant uncertainties have been distilled into a clinical value assessment and incremental cost-effectiveness ratios for each treatment that will form the basis of New England CEPAC's votes on evidence and value. We strongly encourage ICER to ensure that any presented conclusions fully capture clinically meaningful improvements observed in studies and adequately account for uncertainties and current limitations.

Biogen values credible, reliable scientific and economic evidence that is based on robust and extensive data packages, valid assessment methodologies, and meaningful input from subject matter experts and patient communities. After careful review, Biogen believes that the current ICER report fails to meet these standards. As a result, we believe there are important questions about the validity of the draft assessment and risks to its use in healthcare decision making.

Our primary comments and recommendations are outlined below:

1. The rationale for ICER's evidence ratings are unclear, appear to be applied inconsistently, and do not capture significant differences in strength of evidence. ICER should strongly reconsider these ratings.
2. ICER's report makes no attempt to adjust the economic value comparison of Spinraza vs. investigational AVXS-101 despite significant and clinically relevant differences in baseline characteristics of populations and trial designs in ENDEAR and CL-101.
3. ICER's assumptions around durability of treatment effects for investigational AVXS-101 do not take into account potential uncertainties associated with gene therapies. ICER's new initiative to develop methods to guide value-based pricing of potential cures highlights the need for a more robust approach.
4. Key assumptions in the draft assessment unduly disadvantage Spinraza, and important areas of uncertainty are not adequately addressed. Incremental cost-effectiveness ratio values are inappropriately presented as absolute numbers instead of ranges or intervals to account for uncertainty.
5. The importance of Spinraza's approval and evidence supporting the ability to treat broad and diverse patient populations is not accurately captured in the ICER assessment.
6. The ICER draft report contrasts sharply with the outcomes of numerous HTA assessments globally and does not capture the real-world value experienced by SMA patients.

DETAILED COMMENTS AND RECOMMENDATIONS

1. **The rationale for ICER's evidence ratings are unclear, appear to be applied inconsistently, and do not capture significant differences in strength of evidence. ICER should strongly reconsider these ratings.**
   - Page 51: The rationale for assigning investigational AVXS-101's uncontrolled, single-site, open-label Phase I CL-101 trial, which enrolled only 12 patients in the proposed therapeutic dose cohort, an evidence rating of an "A" is unsubstantiated. The ranking of CL-101 in infantile-onset SMA eliminates the large difference in evidence between investigational AVXS-101 and the robust Spinraza clinical trial data. As stated by ICER on Page 51: *"Despite the limitations of the single-arm, open-label design in which 12 infants received the proposed therapeutic dose, we have **high certainty** that Zolgensma provides a substantial net health benefit, and rate the evidence base as "superior" to standard care (A)."*
     - According to ICER's evidence rating matrix, an "A" rating requires high certainty in level of evidence and a substantial comparative net benefit effect. In reference to investigational AVXS-101,

we believe that the net health benefit is currently **uncertain**, particularly given **lack of data on the durability of investigational AVXS-101**. The long-term efficacy of investigational AVXS-101 is unknown, with data limited to a single-site, open-label, uncontrolled study of a small population of infants with SMA treated for just over 24 months as of the last report.[i] Furthermore, public reports indicate that ~47% of investigational AVXS-101 treated patients in CL-101 received Spinraza after this trial ended.[ii]
    - ENDEAR, a randomized, multi-center, international, double-blind, sham-controlled Phase III study, with a total of 121 participants,[iii] should not receive the same rating as an uncontrolled trial with only 12 participants. Furthermore, patients with infantile-onset SMA who were treated with Spinraza in ENDEAR have been followed for nearly 3 years in the SHINE extension study, during which additional improvements in motor milestones and general motor function have been observed.[iv]
- There were two patients (N=2/12 or 17%) in the high dose cohort of CL-101 who were treated soon after birth (0.9-1.9 months) and had CHOP INTEND scores at baseline (~46-50) that were similar to what would be expected for healthy infants as opposed to infants with SMA Type I (see Figure 1 from Mendell et al. [2017]).[iv] This raises questions on the sponsor's ability to select appropriate patients for an SMA Type 1 study and why these two patients were included in the proposed therapeutic cohort.
- Page 25-26: 17 out of 19 publications meeting PICOTS criteria were Spinraza studies, which points to its solid evidence base while also underscoring the prematurity of the ICER analysis of investigational AVXS-101.
- An ICER report from October 2018 assigned a "C+" rating to the evidence for investigational inotersen for hereditary transthyretin amyloidosis (hATTR) based on NEURO-TTR, a Phase III, randomized, controlled trial with 172 total patients followed for over 15 months after treatment. Similarly, in a report from February 2018, ICER assigned a "B+" rating to voretigene neparvovec for biallelic RPE65-mediated retinal disease, based in part on a Phase III randomized control trial (Study 301) with 31 participants. This represents a large inconsistency in ICER evidence ratings across evaluations.

2. **ICER's report makes no attempt to adjust the economic value comparison of Spinraza vs. investigational AVXS-101 despite significant and clinically relevant differences in baseline characteristics of populations and trial designs in ENDEAR and CL-101.**
    - Although ICER did not assign an evidence rating comparing investigational AVXS-101 versus Spinraza for infantile-onset SMA in the Comparative Clinical Effectiveness section of its report (Section 3.5), the foundation of ICER's economic modeling in Section 4 is the clinical data, for which ICER makes no adjustments to account for differences in baseline characteristics between study populations, as recommended by ISPOR's Good Research Practices.[v]
    - Page 51: ICER notes *"Differences in trial populations related to age at treatment initiation and disease duration limit our ability to adequately distinguish the net health benefit of investigational AVXS-101 versus Spinraza for infantile-onset SMA. We therefore rate the evidence to be insufficient (I)."*
    - Page 31: Key baseline characteristics of ENDEAR and CL-101 indicate that the patient populations have clinically relevant differences, with patients in ENDEAR having a comparatively less favorable profile in terms of potential to respond to therapy:
        - Treatment with Spinraza was initiated later after disease onset compared to investigational AVXS-101: Patients treated with Spinraza in the ENDEAR study **(mean age: ~5.3 months)** were older at study initiation compared to investigational AVXS-101 patients in the high dose cohort of CL-101 **(mean age: ~3.4 months)**.
        - Patients treated with Spinraza in the ENDEAR study had a longer disease duration (3.3. months) compared to patients treated with investigational AVXS-101 in the high-dose cohort of CL-101 (approximately 2.0 months).
        - There was a greater proportion of patients treated with nusinersen in the ENDEAR study (26%) who required respiratory intervention at baseline than those in the high-dose cohort of CL-101 (17%),

which could have an important impact on clinical outcomes, such as event-free survival and respiratory outcomes. Table 3.1 incorrectly transposes numbers from those reported in Table 1 of the Mendell et al 2017 publication.[vi]

- Page 36: As noted in the previous point, two patients (N=2/12 or 17%) in the high dose cohort of CL-101 were treated soon after birth (0.9-1.9 months) and had CHOP INTEND scores at baseline (~46-50) that were similar to what would be expected for healthy infants as opposed to infants with SMA Type I (see Figure 1 from Mendell et al. [2017]).[iv] Due to early treatment and higher baseline motor function, these patients may have had more opportunity to respond compared to patients treated with Spinraza in ENDEAR who received initial treatment at a later age and had lower baseline motor function.
- Page 78: Of great concern, ICER estimates an incremental cost-effectiveness ratio comparing Spinraza and investigational AVXS-101 in the infantile onset patient population based on a naïve, **unadjusted** comparison of trial data. In contrast, HTA bodies such as NICE in the UK and the TLV in Sweden are cautious to conduct such cost-effectiveness evaluations based on naïve comparisons and ask for adjusted comparisons also in areas where such comparisons are challenging to conduct, as exemplified by their evaluations of CAR-T therapies such as Yescarta and Kymariah.[vii,viii,ix]

3. **ICER's assumptions around durability of treatment effects for investigational AVXS-101 do not take into account potential uncertainties associated with gene therapies. ICER's new initiative[x] to develop methods to guide value-based pricing of potential cures highlights the need for a more robust approach.**
   - Lack of consensus exists on appropriate methods to assess the substantial uncertainty around long-term safety and effectiveness of gene therapies.
   - In the absence of a consensus on appropriate methodology, ICER should utilize durability assumptions for its evaluation of investigational AVXS-101. One consideration would be to use what was previously applied for durability assumptions for the gene therapy voretigene neparvovec for inherited retinal disease.[xi] In this previous assessment, treatment effect was assumed to be maintained for 10 years, followed by a 10-year waning of effect, after which the rate of decline in vision was the same as SOC. There are significant unknowns in the long-term efficacy of investigational AVXS-101, further amplified by the extremely limited number of patients who have received this treatment to date. In addition, public reports indicate that ~47% of investigational AVXS-101 treated patients in CL-101 received Spinraza after this trial ended. [iii]
   - In either the base case analysis or in the scenario analyses, ICER should assume that SMA patients treated with Spinraza will continue to improve (e.g., *increase* motor function) as observed in clinical trials results, such as the ENDEAR/SHINE analysis[xii], and reports from real-world practice. In ICER's current analysis, improvements observed in clinical trials and real-world practice are ignored and replaced with the incorrect assumption that patients do not improve from the health state they are in at the end of short-term clinical trials.
   - The present ICER model fails to adequately capture clinically meaningful improvements and quality of life changes and relies on arbitrary assumptions about long-term efficacy. The proposed model health states are based on binary motor milestone achievements and are not sensitive enough to differentiate between changes in clinical or quality of life improvements that affect QALYs. ICER should alter its methods to allow for more sensitivity in QALY estimates for patients in different SMA health states reflecting 'no milestones', 'mild milestones', and 'moderate milestones'. For the long-term model, the base case analysis assumes that motor milestones achieved at the end of follow-up in clinical trials are sustained until death. This assumption is biased, as it conflicts with the trend of continuous improvement observed in patients treated with Spinraza and confers a durability of efficacy to investigational AVXS-101 that has yet to be proven.

4. **Key assumptions in the draft assessment unduly disadvantage Spinraza, and important areas of uncertainty are not adequately addressed. Incremental cost-effectiveness ratio values are inappropriately presented as absolute numbers instead of ranges or intervals to account for uncertainty.**
    - Motor Milestones Achieved on Spinraza, Page 58: The estimated proportion of 'sitting' patients at different time points was based only on participants in SHINE who attended those study visits. Because the ENDEAR study was terminated early due to the favorable benefit/risk profile established at the interim analysis, not all patients were followed long enough to make it to latter study visit days in ENDEAR and SHINE. ICER disadvantages Spinraza in the multi-stage calculation process as shown in Table E2 and underestimates the proportion of patients in the 'sitting' health state by incorrectly using the number of patients at baseline as the denominator instead of the number of patients at the study visit (e.g. Day 698). ICER's current approach does not produce an accurate estimate of patients achieving the ability to sit in the SHINE study.
    - Long-term Assumptions, Page 61: ICER's assumptions on QALY weights for different health states inadvertently apply a downward bias in the value of Spinraza while also overstating the value of investigational AVXS-101. In ICER's current assessment, the 'not sitting' health state assumes the same overall survival of the ENDEAR sham control arm which recognized no treatment benefit. The 'walking' health state is also assumed to have the same overall survival of the US general population. Since a higher proportion of patients were in the 'walking' health state for the investigational AVXS-101 model, these optimistic assumptions were applied to benefit the incremental QALYs and cost-effectiveness ratio of investigational AVXS-101.
    - Time Horizon of Long-Term Model, Page 55: ICER mentioned that the extrapolation of motor function milestones was conducted for the long-term model over a lifetime horizon. However, ICER excluded the exact number of years (e.g. 10 years, 20 years, etc.) that was defined as the lifetime horizon.
    - Patient Utility Values, Page 64: The patient utility values for the different health states are key drivers of uncertainty and drastically impact the incremental QALY results. Patient utilities have the largest impact on cost-effectiveness results, especially for the later-onset model. ICER decided to use patient utility values from multiple references versus one study. ICER did not discuss or evaluate the key utility data (for Type I and II) from the Lloyd vignette study[xiii] in its sensitivity analyses. Of the 3 available utility sources, the ERG preferred the vignette study according to the NICE committee papers August 2018.[xiv]
    - Treatment Costs, Page 65: Since investigational AVXS-101 is not yet approved by the FDA, its final market price is not yet available and remains highly uncertain. Many long-term costs of investigational AVXS-101 are unknown and sensitivity analyses should be conducted to understand the potential impact of downstream costs on treatment value. There is also large uncertainty regarding the long-term durability and safety of investigational AVXS-101. As there are limited data for investigational AVXS-101 with only 15 patients total, of which 7 have been reported to receive Spinraza post CL-101 trial, total treatment costs should consider inclusion of Spinraza as reported in the real-world.
    - As suggested by ISPOR and NICE guidelines, robust methodologies include performing extensive sensitivity and scenario analyses to explore the impact of structural and input parameter uncertainty.[xv,xvi,xvii]

5. **The importance of Spinraza's approval and evidence supporting the ability to treat broad and diverse patient populations is not accurately captured in the ICER assessment**.
    - **Later-onset (Types II/III):** The safety and efficacy of Spinraza has been studied in patients with later-onset SMA (likely to develop Type II/III) in a randomized sham procedure-controlled Phase 3 trial (CHERISH).[xviii] We believe the evidence rating of CHERISH should be ranked as an "A" (similar to ENDEAR) due to the significant and clinically meaningful efficacy of Spinraza that was demonstrated on measures of motor function (HFMSE, RULM) in a rigorously designed clinical study of N=126.

- Page 42-43: It is a failure and limitation of the ICER economic model to not capture any of the benefits of Spinraza versus SOC, as demonstrated in the CHERISH study, and acknowledged in ICER's own clinical assessment for later-onset SMA. These include a significant treatment difference of 5.9 points in total HFMSE score at 15 months in the interim analysis, and a clinically meaningful increase in RULM score from baseline to 15 months (4.2 vs. 0.5) for patients treated with Spinraza vs. SOC. These outcomes should be included in the ICER model as these assessments measure motor ability across domains that are meaningful to patients and important for activities of daily living. The current ICER model is incomplete without including these outcomes.
- Page 88: As mentioned by ICER and recognized by a key HTA body, the Type II/III model submitted by Biogen to NICE resulted in an incremental QALY difference for later-onset SMA: 16.88 and 14.52 QALYs for Spinraza and BSC, respectively, in the base case.

- **Pre-symptomatic:** Patients with genetically diagnosed pre-symptomatic SMA (most likely to develop Type I/II) have been studied in the ongoing Phase II, open-label, multi-center NURTURE trial. The study has been presented at three different sources/conference proceedings.[xix,xx,xxi]
  - Presymptomatic patients treated with Spinraza who were most likely to develop SMA Type I/II (median follow-up = 27.1 months) demonstrated unprecedented outcomes in the context of SMA natural history on event-free survival, motor function, and motor milestone endpoints.[xxii]
  - NURTURE, a Phase II, open-label, **multi-center trial of N=25** pre-symptomatic infants, was determined as a "B+", a lower rating than open-label CL-101 for investigational AVXS-101.

6. The ICER draft report contrasts sharply with the outcomes of numerous HTA assessments globally and does not capture the real-world value experienced by SMA patients.

- Spinraza is used to treat over 6,000 patients worldwide and has become the foundation of care for individuals with SMA. Individuals with SMA live with an uncertain future and are among society's most vulnerable patients. Denying access to treatment can be life-threatening to patients.
- Spinraza has been approved for use in over 40 markets worldwide as of January 2019. The clinical benefit of Spinraza has been rigorously evaluated and validated by numerous other HTA bodies.[xxiii]
  - **Germany:** First orphan drug ever with major added benefit & third product with major added benefit since AMNOG exists, out of 246 assessments.[xxiv]
  - **France:** One of the few rare drugs to be recognized as bringing a high level of medical innovation, receiving an ASMR III for Type I and Type II.[xxv]
- Economic modeling in rare disease is often challenging and frequently does not portray the full picture of the unmet medical needs of the community or adequately address how to objectively assign monetary value to quality of life.[xxvi,xxvii] Many orphan medicines are not deemed cost-effective (determined by cost per quality of adjusted life year) based on standard accepted cost-effective thresholds. However, many key **HTA markets** (Germany, France, Australia, Sweden, Scotland, Canada/INESS) **recognize Spinraza's value** and have ensured access driven by clinical benefit and the robustness of the clinical data.

In addition to these points, we have outlined a total of 16 specific technical concerns and/or errors that we ask ICER to address in its revised report. Please see the Appendix for details related to these specific issues. Biogen thanks ICER for the opportunity to comment on the draft report. We would be happy to discuss any of the outlined concerns in more detail if needed.

Sincerely,
Chris Leibman
Sr. Vice President, Value and Access
Biogen

Genentech
A Member of the Roche Group

January 30, 2019
Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Dear ICER Review Panel,

Genentech, a member of the Roche Group, appreciates the opportunity to respond to the ICER Spinal Muscular Atrophy Draft Evidence Report. Spinal Muscular Atrophy (SMA) is a progressive disease that has a profound impact, not only on those with the condition, but also on their caregivers. Despite recent clinical advances, there remain significant unmet needs in SMA. Genentech, in collaboration with PTC Therapeutics and the Spinal Muscular Atrophy Foundation (SMAF), is developing risdiplam, an investigational drug designed to modify survival motor neuron 2 (SMN2) splicing for the treatment of patients in all ages and stages of SMA.

Genentech believes the economic models in ICER's draft evidence report do not accurately reflect the totality of available data. We provide the following suggestions for your consideration:

1. The economic models should be revised in order to prevent oversimplification of the disease course and better capture treatment benefits important to patients.

2. Model assumptions should be revised to adequately reflect high uncertainty due to lack of long-term outcomes data and limited evidence on utility and cost.

3. Caregiver productivity and quality of life (QoL) should be included in all economic SMA models in order to reflect the true impact of disease and treatment to society.

We provide detailed comments and evidence supporting our key recommendations in the remainder of this document.

1. The economic models should be revised in order to prevent oversimplification of the disease course and better capture treatment benefits important to patients.

We believe the model structure, health states and assumed utility and cost values should be reconsidered in order to more accurately reflect outcomes meaningful to patients.

Infantile-Onset Model:

- The current model is based on permanent ventilation, death, and motor milestone achievement. Unless 'sitting' or 'walking' were achieved, the utility and health-state cost are assumed to be the same. Given the majority of patients in the ENDEAR trial did not achieve 'sitting' or 'walking', this model construct essentially ignores the benefits of delayed or circumvented permanent ventilation on patient and caregiver QoL.[1] Literature has showed that patients requiring ventilation had a lower utility score than patients who did not, despite not achieving any motor milestones.[2]

- In the base case of infantile-onset model, improvements in bulbar function and minor motor function improvements (e.g., head control, rolling, crawling, and standing) are not reflected. In clinical trials, an increase of ≥4 points in the CHOP-INTEND score is considered clinically meaningful and this was achieved by a large majority of treated patients in the ENDEAR and START trials.[1,3] Even when the 'sitting' or 'walking' milestone is not reached, improvements in other motor abilities (e.g., head control and rolling), bulbar function (e.g., eating and speaking) and activities of daily living (e.g., moving and dressing) are clinically meaningful and are associated with QoL improvements for both patients and caregivers.[4]

Genentech encourages ICER to adjust the health state cost and utility value in the base case model. Applying different assumptions for permanent ventilation and 'not sitting' will reflect the lower level of support required as well as the improved QoL for patients not requiring permanent ventilation. To the extent possible, ICER should also apply additional utility benefit for improved bulbar function, achieving interim milestones (e.g., head control, rolling), and other functional improvements due to treatment.[1,3,5,6]

Later-Onset model:

- The model structure includes only three motor milestones: 'not sitting', 'sitting', and 'walking'. Although these milestones are convenient for linking to available data on health state utilities, these were not the primary endpoints in clinical trials. For example, none of the treated patients in the CHERISH trial achieved walking without assistance.[7] However, an increase of ≥3 points in HFMSE is considered clinically meaningful and this was achieved in 57% of treated patients in the CHERISH trial.[7,8] Such improvements would translate into improved functional ability and QoL, thus should be captured in the model. In addition, the ICER report concludes that Spinraza® (nusinersen) is dominated by best supportive care, with higher costs but no improvement in quality-adjusted life years (QALYs) or life years (LYs). This model result lacks clinical validity. Natural history suggests that as SMA progresses, patients lose motor functions and their ability to remain independent decreases over time.[9]

- Even in the absence of stark improvement in motor milestones such as 'walking', disease stabilization or prevention of further deterioration are important

improvements.[4,10] A qualitative study demonstrated avoiding declines in function are important for patients and even small changes make a substantial difference for patients to function and thrive. As noted by a clinician in the study, "*the difference between not being able to move a finger and being able to move a finger by half an inch can mean the difference between being able to operate a motorized vehicle or not, and that can make a huge impact on their quality of life and on their ability to be independent*."[10]

- Additionally, the mean age of patients with later-onset SMA in the economic model was assumed to be 2 years. While this mean age was based on the CHERISH trial population, it is not representative of the population in the real world. The Cure SMA membership database may be a better source for the age used in the model.[11]

Genentech encourages ICER to explore an alternative model structure for later-onset SMA. The health states should be defined by patient functional levels that are meaningful to patients and caregivers (e.g., level of independence) and reflect the benefit of treatment. In addition, we also recommend revising the mean age of later-onset patients in this model to be more in line with the real-world population.

2. Model assumptions should be revised to adequately reflect high uncertainty due to lack of long-term outcomes data and limited evidence on utility and cost.

- While it takes time for the long-term effects for any new therapy to emerge, the optimistic assumptions around the durability of effect have created bias in favor of Zolgensma® (onasemnogene abeparvovec). This is likely due to the one-time administration frequency and the large magnitude of effect observed in a Phase I, single-arm study with a highly selected patient population (N=15). There are multiple key assumptions built into ICER's base case evaluation, given the "*unknown duration of expression of the gene therapy*".[12] Most notably, ICER assumed motor function milestones achieved at the end of the trial period are sustained until death. Additionally, it was assumed that Type I patients who achieved 'sitting' or 'walking' had mortality similar to Type II and Type III patients, respectively. However, despite motor milestone improvements, 5 out of 12 (42%) patients in the START trial (cohort 2) still required ventilation, an intervention not common for Type II or Type III patients.[3,12] Moreover, 5 out of 12 patients treated with Zolgensma also went on to receive Spinraza after the end of the study period indicating a need for additional therapy in some patients.[12]

- In ICER's model, key drivers of uncertainty are (1) monthly cost, (2) utility values for 'sitting', 'non-sitting', and 'walking', and (3) the length of survival associated with the 'sitting' and 'walking' health states for infantile-onset patients. Of note, none of these estimates are from clinical trials or robust observational studies. In many cases, proxy estimates and assumptions were used. These may have led to a low level of precision in parameter estimates, leading to further uncertainties surrounding model results.

- Lastly, cost and disutility of treatment-related adverse events should be captured in the model as those events are well characterized and distinct from disease-related complications. Similarly, cost and disutility associated with intrathecal administration should be accounted for. Specifically, facility costs associated with intrathecal administration, in both inpatient and outpatient settings, should be included.

Genentech recommends that ICER make the following adjustments to the models:

(1) The short-term and long-term model results would be more meaningful, if presented separately. For the long-term model, it would be more conservative to adopt a 5-year or 10-year model horizon as the base case rather than lifetime horizon. A shorter time horizon would also be in line with ICER's last evaluation of a gene therapy (Luxturna™ [voretigene neparvovec-rzyl]) which applied a 10-year model horizon as the base case.[13] Additionally, the lack of nationalized healthcare in the US makes the shorter-term horizon more relevant in payer decision making.

(2) Revise the base case to assume a proportion of Zolgensma patients lose motor function over time based on the fact that ~40% of patients from the START trial subsequently received Spinraza.

(3) Vary utility and cost parameter values by 20% instead of 10% in sensitivity analysis given the high level of uncertainty in the model.

(4) Include the cost and disutility related to adverse events and the facility cost and disutility associated with intrathecal administration in the model.[14]

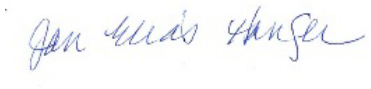
3. Caregiver productivity and QoL should be included in all economic SMA models in order to reflect the true impact of disease and treatment to society.

We believe that caregiver burden should be included in any cost-effectiveness analysis determining societal value. The impact of SMA on caregiver productivity and QoL is well documented in published literature.[15] In this draft report, caregiver burden is excluded because ICER believes its inclusion may "*lead to counter-intuitive results due to prolonged negative productivity effects and unknown quality of life effects on caregivers when children who need substantial care live longer*".[12] However, in a cost-effectiveness assessment of pediatric interventions, incremental cost-effectiveness ratios on average decreased by 31% when family spillover effect was included.[16] Genentech strongly recommends that ICER include caregiver burden by including productivity and QoL impact in the infantile-onset, later-onset, and pre-symptomatic models.

In closing, we thank you for the opportunity to comment on the draft evidence report for SMA. Despite the number of clinical advances in this rare disease, there continues to be a high unmet need due to ongoing challenges with access, logistics, and lack of clinical data in the broader SMA population.[17] Genentech remains committed to therapeutic innovation

and engaging with ICER as they evaluate therapies for SMA patients. We hope these comments will contribute to a more robust assessment of the current and future therapies.

Sincerely,



Jan Elias Hansen, Ph.D.
Vice President, Evidence for Access Medical Unit
Genentech US Medical Affairs

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Comment to ICER on the draft evidence report: “Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value”

This detailed analysis relies on many assumptions and a very small sample size with limited duration of observation under treatment. The conclusions made in this report are fraught with uncertainty. While the goal of this ICER evidence report is certainly of high merit, it is premature to endorse the conclusions drawn by the authors. Later analysis of a larger sample of treated patients who are observed over a longer period of time will be of greater value.

Richard S. Finkel, MD
Nemours Children’s Hospital

Memorandum

Date: January 31, 2019

To: Institute for Clinical and Economic Review

From: Professor Emeritus Louis Garrison, PhD, The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, Department of Pharmacy, University of Washington, Seattle WA 98195

Subject: Comments on Draft Evidence Report on Spinal Muscular Atrophy

Dear Colleagues,

Thanks for the opportunity to comment on ICER's draft evidence report on spinal muscular atrophy (SMA).

I am a health economist and Professor Emeritus in The CHOICE Institute at the University of Washington. I have participated as an independent consultant in a one-day health economics advisory board sponsored by AveXis, Inc., where high-level issues related to onasemnogene abeparvovec (Zolgensma®, Novartis AG/AveXis) were discussed. I have not seen or reviewed any models that AveXis has developed for this product. I also received support from AveXis to prepare a conceptual, general thought piece on cost-effectiveness thresholds (CETs) for products for ultra-rare diseases with catastrophic health consequences, such as SMA. This article—coauthored with three colleagues, who are also consultants to AveXis—will soon be published as a viewpoint article in the Journal of Managed Care & Specialty Pharmacy.

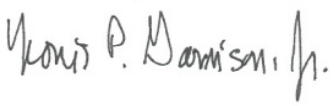
I have long believed that welfare economic theory could provide a basis for a higher threshold for these ultra-rare, health catastrophic diseases, and that, in theory, the optimal threshold might vary among different diseases more generally. ICER has recently initiated a new effort on the topic of cures, and ICER staff interviewed me earlier this month, where I outlined my views. As I explained, this argument is related to the additional "novel elements of value" that were outlined in our recent ISPOR Special Task Force on Value Assessment Frameworks. In particular, I think that the additional elements—beyond the cost per quality-adjusted life years (QALYs)—of insurance value and severity of disease are key.

With regard to this SMA report, these arguments would suggest that ICER is being too conservative in applying a cost-per-QALY threshold of $150,000 per QALY in projecting a "value-based price" (VBP) for onsemnogene abeparvovec. ICER does recognize a broader range for rare diseases of up to $500,000 per QALY, and should consider, in this instance, either not making a specific projection for a VBP based on $150,000 per QALY, or presenting it at a higher level or as a range with a higher upper bound. Given that onsemnogene abeparvovec has not been launched, the device of using "placeholder price" of $2,000,000 is understandable. However, it may create misleading benchmark: for example, the U.S. Government values lives at closer to $10 million (https://www.transportation.gov/regulations/economic-values-used-in-analysis).

Furthermore, given the grave, negative implications of having a child with SMA Type 1 for parents and caregivers, ICER should emphasize the societal perspective. It was not clear to me whether the "Modified Societal Perspective" alternative in the report captures the "family spillover" effect, e.g., on the (dis-)utility of parents and caregivers. Of course, as outlined in our ISPOR report, augmenting cost-effectiveness analysis—beyond the cost-per-QALY—affects the calculation and/or interpretation of the appropriate CET.

I hope these comments are helpful. Please let me know if you have any questions. I would be happy to discuss further.

Sincerely yours,



Louis P. Garrison, Jr., Ph.D.
Professor Emeritus, The CHOICE Institute

Make today a breakthrough.

On behalf of Cure SMA, the largest patient group dedicated to the treatment and cure of spinal muscular atrophy (SMA), we appreciate the opportunity to comment on the Institute for Clinical and Economic Review (ICER)'s Draft Evidence Report entitled *Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value.*

We believe there is an important role for this type of analysis, which can assist in finding the right balance between preserving the incentives that are essential to attract investment and innovation to an orphan disease and not restricting access to approved treatments. We also believe such an analysis should place high value on the patient voice and perspective. It should contain accurate data from clinical trials and should be based on educated assumptions and knowledge about the disease under review. A selection of errors and issues that we have observed are presented in the categories below.

We request that ICER prominently and clearly include the specific disclosure of what they consider fair market value to be in an ultra-rare disease like SMA, as this is critical to interpreting this analysis. According to the framework for considering ultra-orphan drugs (such as Zolgensma and Spinraza) ICER adopted in 2017, this value is up to $500,000 per Quality Adjusted Life Year (QALY).

Lack of Understanding About SMA:

Within the report are multiple errors showing a lack of basic understanding of the disease. For instance, the report states that "there remains considerable uncertainty in the generalizability of the results" (page 48). However, Spinraza clinical trials were completed in patients with SMA types I-III. SMA types I-III represents approximately 95% of patients with SMA. Due to the genetic homogeneity of SMA, the mechanism of action for Spinraza and Zolgensma is the same across the disease spectrum.

Additionally, this report does not seem to understand the basic biology of SMA stating on page 27 that "Overall, we noted some differences in baseline characteristics between the Spinraza and sham control arms of both ENDEAR and CHERISH that suggest more severe SMA symptoms in the Spinraza arm. The direction of potential bias in results is unclear as the patients receiving Spinraza may be at higher risk of death and other complications but may also have a greater potential to improve." The progressive loss of motor function is due to loss of motor neuron innervation. An important consideration for therapeutic efficacy is that motor neurons cannot be restored after being lost and this limits the time window allowing for maximal improvement.

The lack of SMA natural history understanding is reflected in the statement "we do not know how the 15 patients would have progressed if they had not been treated with Zolgensma." The most recent natural history studies consistently describe the progressive motor weakness and progression to respiratory failure and death without achieving the motor milestone of sitting (Finkel et al, Neurology, 2014; Kolb et al, Ann Neurol, 2017; De Sanctis et al, NMD, 2016). In stark contrast, 11/12 infants treated with high dose Zolgensma achieved independent sitting and all have survived without permanent ventilation (Mendell et al, NEJM, 2017).

The long-term extrapolation model for non-sitters is flawed. The long-term model utilizes a lower mean survival of 1.55 years for non-sitters compared to a mean survival of 5.3 years for permanent ventilation

thus assuming significantly poorer survival for non-sitters compared to permanent ventilation, even though the non-sitter group has showed better outcomes and improvements following treatment with Spinraza. The ENDEAR trial demonstrated a 47% reduction in the risk of death or permanent ventilation in the Spinraza treated group compared to control (Finkel et al, NEJM, 2017). The life years for the SMA type I not sitting Spinraza treated model is severely underestimated.

Inaccurate Clinical Trial Data:

Throughout the report, clinical trial data is misinterpreted in the ICER models, which has a major impact on the determination of cost effectiveness of the therapies under evaluation. Table 3.4 of the report correctly indicates that maximally 29% of patients had the ability to sit independently towards the end of the SHINE extension study (Castro et al, NMD, 2018). However, in section 4 of the report a value of only 11% is used. This lower value appears to be calculated using the total number of patients receiving Spinraza in the ENDEAR trial (n=81, Finkel et al, NEJM, 2017), rather than the number of patients being assessed at that particular time point (n=31, Castro et al, NMD, 2018). By doing so, the model unfairly assumes unfavorable outcomes for the unassessed 50 patients, i.e., none would have sat if assessed. Meanwhile, the actual reason that many in the full cohort were not assessed at this time or beyond is that they had not yet reached this point in the study (meaning that they had been on drug less time than the actual timepoint under evaluation).

Furthermore, there are major flaws in framing the outcomes of pre-symptomatic treatment with Spinraza, which downplay the dramatic impact on survival and function in this situation compared to natural history. Trial data demonstrate that most infants treated proactively, when free of symptoms, achieve the motor milestones of walking and standing. In fact, 22 of 25 were able to walk with assistance and 17 of 25 were able to walk independently (Swoboda et al, WMS, 2018). To date, no pre-symptomatic SMA infant treated with Spinraza in this study has died or required permanent ventilator support. The assessment of pre-symptomatic treatment benefit is wrongly framed by a comparison to the development of healthy children. Natural history outcomes regarding individuals with the same SMN2 copy number should be used for comparison, not outcomes in unaffected children.

Finally, as with any treatment whose approval is based on clinical trials of a feasible and ethical duration, there is always ongoing uncertainty about longer-term outcomes. However, the report has a lengthy section (3.4) about clinical trial controversies that seems unwarranted. These would be better framed as important issues that would ideally now be examined using real world data capture on drug efficacy and safety. We believe ICER should frame long-term uncertainties in a more balanced manner, leaving open the possibilities of both pessimistic and optimistic scenarios for future results. Currently, for example in tables 4.21 and 4.22, there are only 2 and 3 positive scenarios modeled out of the total in each table.

Lack of Patient Perspective:

This analysis is further weakened by its lack of patient perspective. This lack of patient perspective is vastly different from current approaches to the drug approval processes and safety protocols at the FDA, research priorities and protocols at the NIH, and the philosophy reflected in recent milestone legislation, the 21st Century Cures Act.

ICER assigns benefit to the patient only if the drug allows for obtaining milestones such as sitting or walking. Meanwhile patients have reported, and the FDA has recognized, the great value in abilities that

allow for more independence and activities of daily living (McGraw et al, BMC Neurol, 2017; and Rouault F et al, NMD, 2017). For some patients and their families, simply not getting worse is an improvement and a meaningful outcome. It should also be noted that even incremental increases in a patient's motor abilities may alleviate the stresses and challenges involved in caregiving by allowing patients greater ability for self-care.

These meaningful and valued milestones are not factored into this analysis; however, the complete set of clinical trial data from the early open label studies to the pivotal ones demonstrates these improvements in SMA type I, II, and III participants.

Infants who received Spinraza in the ENDEAR study showed statistically significant improvements in HINE-2 response compared to sham control at both the interim analysis (21/51 [41%] of Spinraza and 0/27 of sham control group; $p<0.001$), and in the final analysis (37/73 [51%] of Spinraza and 0/37 sham control patients). In the Spinraza group, 22% of the infants achieved full head control, 10% were able to roll over; in the control group no infants achieved these milestones at the end of the entire study. The percentage achieving head control increased to 45% on day 578 for those continuing into the SHINE extension study.

There were also improvements in participants' CHOP-INTEND scores in this study. Seventy-one percent of infants treated with Spinraza achieved an increase of ≥4 points in CHOP-INTEND score between baseline and their end-of-trial visit (Table 3.3); compared to just 3% in the sham control arm who achieved improvement.

In the CHERISH study, the prespecified interim analysis from baseline to month 15 showed a 4 point increase in the HFMSE score in the Spinraza group and a 1.9 point decrease in the control group (Mercuri et al, NEJM, 2018). This represents a difference in ability to perform three items on the Hammersmith scale between the treatment and sham groups, whose items have been shown to be correlate to activities of daily living. In the final analysis, 57% of the children in the Spinraza group as compared with 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points.

We know that most patients show clinically meaningful improvement with Spinraza, yet ICER ignores these when constructing this analysis. This lack of patient perspective about the value of these milestones and incremental improvements seriously weakens ICER's models, and therefore, the analysis of value and efficacy is incomplete. It is a disservice to all with SMA that a report which could impact access to life saving treatments for some of the most vulnerable members of society does not include their perspective.

The ICER models show that only 1% of SMA patients gain any meaningful benefit from Spinraza. This ignores and contrasts with:

- 51%, vs 0% untreated, HINE Responders.
- 45%, vs 0% untreated, with Head Control.
- 71%, vs 3% untreated, CHOP Responders.
- 57%, vs 26% untreated, HFMSE Responders.

The process of determining QALYs for patients permanently on ventilators and those who are non-sitters appears arbitrary and does not take into account the wide range of patient outcomes in between these two statuses. The analysis also fails to take into account the advances in technology that have made it possible for physically limited individuals to meaningfully contribute to society in ways never before possible. Many patients who have not achieved the arbitrary ICER chosen milestones are productively employed.

Moreover, incorrect assumption and subsequent erroneous modeling occurred around the fact that some subjects who received Zolgensma in the START trial were subsequently treated with Spinraza. The assumption that Spinraza was added after Zolgensma due to a deteriorating health status led to modeling that "half of the patients would lose a milestone in the absence of Spinraza. We therefore assumed that a sixth (33% * 50%) of the patients in the sitting health state at the end of the short-term model in the Zolgensma arm dropped a milestone (i.e., to not sitting) to reflect those patients who apparently required Spinraza after the study period." There is no evidence to support this assumption. The more likely explanation is that families' expectations are high for best outcomes and families will do everything possible to get their child every available treatment in order to eliminate as many symptoms as possible.

Bias in ICER Model for Financial Discounting of Life Years:

For a pediatric and typically fatal disease such as SMA, now with transformative and impactful treatments, the ICER model of financially discounting life years has a significant effect. The controversial approach of using a financial model for discounting life years (prior to any utility discounting) should be clearly disclosed and have scenario analyses to indicate the impact on any conclusions.

These groundbreaking treatments for SMA are taking an untreated lifespan of less than 2 years up to over 30 years for Zolgensma, and also up to over 60 years for Spinraza in pre-symptomatic patients. ICER does a present value financial reduction on these actual life years to drastically reduce these extraordinary results to 18 and 27 discounted life years respectively.

In addition, as ICER states, the use of QALY can discriminate, and we agree: "…and viewing results of both the cost per LY gained and the cost per QALY gained will ensure that policymakers can feel confident that they are considering information that poses no risk of discrimination against this patient group."

The conclusions in this report will change significantly based on the above notes and whether an actual life years are discounted or not.

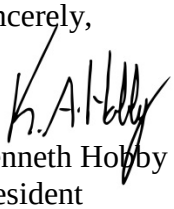
Summary:

This report is based on assumptions from ICER that the currently approved treatment for SMA provides a meaningful benefit to only 1% of the SMA population. It should be noted that this is separate from any analysis of whether any benefits are worth the related costs. This is in stark contrast to the FDA analysis and approval for 100% for all ages and all types of the disease. ICER decides that SMA types II, III and IV gain no benefit at all from the only currently approved treatment for this devastating disease.

Make today a breakthrough.

As currently drafted, including numerous and substantial errors in both data and assumptions and modeling, and a disregard for the SMA patient and caregiver perspective, we believe that this report should not be used by any groups or individuals for SMA treatment related decisions.

Sincerely,



Kenneth Hobby
President

Make today a breakthrough.

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Muscular Dystrophy Association

January 31, 2019

Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Submitted electronically to: publiccomments@icer-review.org

Dear ICER Review Panel,

Thank you for the opportunity to provide comments on the *Institute for Clinical and Economic Review's Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value Draft Evidence Report* as published December 20, 2018, hereinafter "the draft report".

As an organization with a mission of transforming the lives of individuals affected by SMA and other neuromuscular diseases through innovations in science and innovations in care, the Muscular Dystrophy Association (MDA) is committed to funding groundbreaking research; accelerating the development of treatments and cures; promoting early identification, diagnosis and treatment; and improving health outcomes. For more than 65 years, MDA has been on the frontlines of research for SMA and other neuromuscular diseases. We funded foundational work in SMA and invested in the early-stage development of nusinersen (brand name Spinraza). We also helped to connect SMA patients with clinical trials for onasemnogene abeparvovec (brand name Zolgensma), and we are encouraged by the promise of this innovative new gene therapy, the first of its kind for neuromuscular disease treatment.

This is a pivotal time for the SMA community. Only a few years ago, there were no treatments for SMA. Now, we are on the cusp of having more than one treatment option. This paradigm shift is a reason for hope and excitement. In the absence of therapy intervention, death or the need for constant ventilation to breathe before the age of two years is the outcome for more than 90% of individuals diagnosed with SMA Type 1. Considering that SMA is the number one genetic cause of death for infants, affecting approximately 1 in 10,000 newborns in the U.S. each year, and accounting for the severity of the disease, the recent therapy developments and potential advancements mark important progress for not only the SMA community, but for society as a whole.

The importance of the evolution from having no treatments to having treatment options cannot be overstated, and any effort to evaluate the respective therapeutic approaches must

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be thoughtful and measured and should help support access to novel and life-changing and -saving therapies.

SMA is a lethal disease that affects the motor nerve cells in the brain stem and spinal cord and carries a significant burden. The age at which SMA symptoms begin roughly correlates with the degree to which motor function is affected: the earlier the age of onset, the greater the impact on motor function. For this reason, MDA advocated for SMA to be added to the national Recommended Uniform Screening Panel and continues to work with states to encourage them to add SMA to their list of diseases for which infants are screened at birth. With the implementation of newborn screening for all babies born in the US, infants with SMA will have the opportunity to receive treatment early, before critical motor function is lost, allowing the future of the disease course and clinical care approaches to be altered.

For MDA and the patient community that we represent, the development of therapies for rare diseases like SMA is of paramount importance. We appreciate that there is a value framework from which to consider therapies and appreciate ICER's intent to provide a value-focused lens through which to consider therapies for SMA and other neuromuscular disorders.

With regard to the value of treatments for SMA as set out in the draft report, we would note that the evaluation of milestones may not fully reflect the experiences and needs of the patient community. For example, gains in mobility, such as the ability to sit or to reposition unassisted, can represent significant, positive change in the life of an individual living with SMA and their caregivers. Improvements in mobility, however small they may be deemed, often represent major improvements in quality of life and the value of these gains cannot be discounted. In addition to health improvements that may be associated with increased mobility, increases in mobility are directly related to independence, which is a critical factor for those living with neuromuscular disease. Similarly, respiratory function is also major concern for the SMA community. The significance of what one may consider even relatively small gains for SMA patients in this area must be reflected in any evaluation. Further, with SMA being classified as not only a rare disease, but as an ultra rare disease with a significant burden, the QALY applied in the report is likely insufficient. This is important as such determinations may impact access to treatment. Additionally, while the report notes that there are "common limitations" in applying the framework in rare diseases, there are further limitations in the draft report as Zolgensma has not yet received FDA approval. Thus, for example, it does not yet have a price. Similarly, and as noted in the report, there are no coverage policies associated with Zolgensma to evaluate.

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Given the importance and potential impact of a value framework on the SMA community, including the role that such findings may have on payor determinations and behavior, we appreciate the opportunity to comment, and look forward to the opportunity to engage with you further as you finalize the report.

Sincerely,

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January 31, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
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RE: Draft Evidence Report "Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value"

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases for them to have access to vital therapies and services. Access is a matter of survival for those patients, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers, and others to foster realistic, patient-centered, solution-oriented discussions for particular conditions and the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's December 20th Draft Report, "Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value."

Before commenting on specific aspects of the Spinal Muscular Atrophy (SMA) Draft Report, we want to revisit some past ICER reports and comments – and particularly responses to some of our previous comments, since they provide critical insights into ICER's approach to health care challenges, and ICER's perceived role in attempting to inform decisions about innovations.

Because imprecise language can lead to misleading conclusions, the specific issue we want to address is ICER's decisions about choices regarding word usage and phrasing to describe its work. The danger of such rhetorical imprecision is well summarized in this quote: "[Language] becomes ugly and inaccurate because our thoughts are foolish, but the slovenliness of our language makes it easier for us to have foolish thoughts."[i]

Specifically, in responding to our comments on the Opioid Use Disorder Draft Report, ICER noted that its use of the term "healthcare" rather than "health care" "does not affect the conclusions of our report."[ii] While in that specific instance the meaning is likely the same, that is not always true. For example, the two phrases "mental healthcare" and "mental health care" have two distinct and different meanings. And we are very concerned that ICER apparently fails to recognize that such differences can lead to misinterpretation of data or results.

This concern is even more problematic in the Final Report about OUD treatments where ICER equivocates on the definition of MAT, declares that its assessment MAT can have two different

meanings, and that ICER will use them interchangeably.[iii] In that report ICER also misconstrues and misrepresents the meaning of the statement from the FDA: "Because OUD is a chronic illness, we should consider treating it much like we would any other chronic condition. We do not think of the medications used to treat diabetes or hypertension as 'medication assisted treatment.' We simply call it 'treatment.' OUD should be viewed similarly." [iv] First ICER fails to understand that the FDA is not questioning the meaning of the definition of MAT - the heading for the article in fact is "Medication Assisted Treatment."

Second, ICER fails to appreciate that the FDA is reinforcing the point that "It is important to remember that MAT is broader than just the use of medication," which is completely contrary to the meaning of narrower term, "Medications for Addiction Treatment."

Third, the point the FDA is making in comparing treatment of OUD to diabetes and hypertension is that RESPONSIBLY treating people with OUD, diabetes, or hypertension should ALWAYS involve not just medications, but also counseling of some sort. For example, clinician who prescribes a medicine to control blood sugar levels for a person with diabetes without support or counseling regarding diet, weight loss (or control), and exercise would be grossly negligent. ICER's failure to recognize what the FDA is saying and the fundamental difference between "Medication Assisted Treatment" and "Medications for Addiction Treatment" – reflects ICER's siloed (and flawed) vision that focuses on pharmaceuticals both clinically and economically without putting that information into a comprehensive patient-centered context, is of course, extremely troubling and should cause all decision makers to have grave concerns about ICER's entire activity-set.

And finally, ICER's straw-narrow approach is retrograde to the movement of the U.S. health care system that is seeking to incorporate more comprehensive, integrated, and systemic analyses and innovations in care delivery, financing, and reimbursement as part of the broad trend to align all components of health care for better patient-centered clinical and economic outcomes for the benefit of patients, payers, and society.

ICER's approach reflects a top-down centralized-control mentality that is reminiscent of the Soviet Union or a government agency with strict silo budget allocations that cannot be adjusted based upon clinical needs or new information. And history has shown the adverse outcome from this type of centralized and siloed thinking, planning, and management leads to society's needs not being met because of inefficiencies, and mismatched production and distribution activities.[v]

It is hard to know where to start in commenting on the specifics of the Draft Report for SMA since it includes 1 FDA approved medicine (Spinraza) that is given repeatedly, 1 potential treatment (Zolgensma) that could be curative (i.e., possibly a 1-time gene therapy treatment) that has not yet been approved by the FDA and acts through a different biological mechanism, and a "Drug X"[vi] that is completely hypothetical with conjectured "data" and scenarios. We agree that "naïve comparisons should be avoided,"[vii] but by producing a report about two distinctly different treatment approaches, ICER seems to be doing exactly that.

As we've previously stated, "evaluating the clinical and market potential of medicines prior to

approval – and by definition prior to the final FDA label of indications and warnings – is extremely difficult."[viii] In the Draft Report ICER has taken an additional leap to include a completely fictional construct. Therefore, we think it would be analytically and socially responsible for ICER to reissue an updated Draft Evidence Report that includes actual data for Zolgensma after FDA approval when its labelled indications and warning will be known, as well as the list price – and of course separately publish any fictional constructs of potential medicines in more appropriate publications.[ix]

Our more specific comments about the December 20th Draft Report are organized below into sections concerning: Patient and Family Perspectives and Issues; Relationships Between Payment Policies and R&D Investments; ICER's Pricing and Market Assumptions, and Additional Points.

Patient and Family Perspectives and Issues

Families and patients with SMA should welcome new treatments since if SMA if untreated "causes irreversible degeneration of motor neurons, which clinically manifests as progressive muscle weakness such that patients may have difficulty moving, swallowing, or breathing,"[x] and life expectancy can be as short as 2 years depending on the severity of the disease. In addition, as the Draft Report describes, SMA is a disease with many forms based upon the specific genetic variations and the presence of the number of copies of the SMN2 gene that is associated with modulated severity and age of onset of SMA.

We also note that SMA does not affect cognitive functioning. Therefore, the preservation of motor function – or reversal of lost function – is important for self-care and autonomy of individuals with SMA, and ultimately their ability to earn a living and be productive members of society. In this regard, we agree that in ICER's analytical scheme the "utility value" for individuals able to walk should be the same as the general population.[xi]

While the genetic cause of SMA is known, and tests for determining a patient's status are available, we share ICER's concern about the limited data available about Spinraza and Zolgensma. However, models or projections based on uncertain data is inherently an error prone process and a fundamental flaw in this Draft Report, as well as many other ICER activities. The 189-page Draft Report[xii] contains numerous references to this uncertainty, including the admission on page 183 that "the true uncertainty is likely to be more than that represented in our probabilistic analyses." Nevertheless, the Draft Report makes economic declarations that it clearly recognizes others will rely upon for decisions affecting patients and families.[xiii]

We also appreciate the complications of modeling based upon clinical trials that are single armed or limited in duration. However, for certain innovations, single arm trials are the appropriate structure and research methodology. As has been written, "Such comparisons [in a single arm study to the natural history of the disease] are meaningful only when the expected outcomes in the absence of the intervention are well-known, and the expected effect size from the intervention is large,"[xiv] which clearly is the situation with Zolgensma.

Similarly, projecting long-term outcomes from trials of limited duration is a well-recognized issue in clinical research. However, this issue has largely been settled, since waiting for lifetime

results (i.e., 60+ year trials) is impractical, would deny patients access to treatment that have demonstrated short or intermediate term benefits, and would also effectively terminate any investments in such research.

Overall, the objections ICER raises about the sparsity of data are due to the self-determined timing of ICER's activities (i.e., before or shortly after FDA approvals) rather than the realities of the data itself. This is akin to a paraphrase of the Heisenberg Uncertainty Principle,[xv] i.e., the sooner you get the data, the more uncertainty there will be, and conversely the more you demand certainty of data the longer you will have to wait - and more people and society will be denied the benefits of the resulting innovations.

Thus, while families and patients with SMA would clearly benefit from better treatment options, we believe that ICER's Draft Report – both its technical aspects and overall approach – are counterproductive to that goal.

Relationships Between Payment Policies and R&D Investments

We have previously commented to ICER about the relationship between payment policies (which include pricing and reimbursement schemes from payer) and R&D investments.[xvi] While we continue to be befuddled that ICER's framework does not consider how payer decisions effect R&D priorities and resource allocations, we would like ICER to comment on the perspectives of two economists in an article[xvii] in a Boston-based publication that notes how some funders of early and cutting edge research areas have greater flexibility for reassigning funding among potential types of projects and companies, including specific disease areas or patient populations, which they describe as "mobility of investment capital."

While we await those comments from ICER, we continue to be concerned about ICER's lack of attention to this relationship because if policies and reimbursement practices fail to recognize it, the long-term consequences would be fewer treatment options, and higher morbidity and mortality. For example, observers of biomedical innovations and access to medicines have noted the recurrent problem about the availability of new antibiotics, (i.e., every 15 years or so there has been another call for the development of new antibiotics as resistance rises for older classes), but with little recognition that appropriate payment amounts and practices for new antibiotics should be part of the discussion. In this vein, the development of new antivirals likely took a step backward because of the rhetoric around the new treatments/cures for chronic hepatitis C infection in 2014, which interestingly almost never include information about how manufactures of two medicines approved by the FDA in 2011 for chronic hepatitis C infection took them off the market after only a few years because they had become clinically irrelevant.[xviii] Extending this discussion, we also hope that ICER will incorporate this knowledge into its processes for ultra-rare conditions by eliminating the pointless request for information about R&D and manufacturing costs since that information only has a relationship to the price of a medicine in a fictional "truthy" world."[xix]

ICER's Pricing and Market Assumptions

ICER's assumption filled process fundamentally risks incorrectly modeling the real world. For example, it is widely recognized that modeling of uptake and usage of new medicines can be very far off from what actually occurs once a treatment is approved by the FDA. This was

evident from the actual usage of the first new medicines to treat hepatitis C (which had initial usage much greater than had been projected), and those to treat very high cholesterol because of PCSK9 protein variants (which had initial usage that was much less than projected). What is also interesting in both those cases was that over time, there was dramatic decline in the net prices paid by payers, although what patients paid may not have fallen to the same extent – which is of course an ongoing concern – and a factor ICER also does not address in its framework process.

We would appreciate ICER's comments about how its methodology does not account for such real-world market dynamics that effect prices and overall costs to payers, patients, and society.

Additional Points:

- The Draft Report provides a link to the list the stakeholder from whom ICER requested input[xx], but not those from whom it actually received input. That list should be provided.
- The Draft Report only lists one "Expert Reviewer," and that individual appears to have only a few years of experience since finishing her doctorate.
- The Draft Report states that "Harvard Pilgrim and UHC specify that the patient seeking coverage must have at least two copies of the SMN2 gene; Humana states that patients may have no more than two copies."[xxi] Can you explain the rationale for why different insurers would have such opposite prior authorization criteria? Also, Humana appears to have updated their criteria so that individuals with Delayed Onset SMA can have "no more than three copies of SMN2"[xxii]
- It seems the 100% survival rate for Zolgensma has now been reported at 24 months.[xxiii]
- One source for health care costs used for the scenario analyses are from the Department of Defense,[xxiv] which are likely very different from overall U.S. health care costs.

Conclusions & Recommendations

Patients Rising Now remains concerned that ICER's activities will continue to lead policy makers, and others (including payers and clinicians) to focus on limited data and suspect economic analyses to erect barriers to patients accessing FDA approved treatments, which would contribute to more adverse outcomes for patients. Such an outcome is compounded by ICER's lack of transparency about its modeling, which includes an overly simplified and homogenized construct of the U.S. health care financing, delivery, and innovation systems and organizations.

Patients Rising Now believes that ICER's Draft Report on SMA inadequately reflects patients' perspectives, misunderstands how investment decisions for biomedical R&D are made, and by ignores market processes. Because the outputs from models are only as valid as the certainly of the data and the assumptions used to build the modes, the Draft Report's conclusions are warped and inaccurate. Thus, the Draft Report's "conclusions" have serious flaws and misleading, and ICER should reissue the Draft Report once more substantive and certain data is available.

Sincerely,

Terry M. Wilcox

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

[i] "Politics and the English Language," George Orwell, 1946.
[ii] ICER's Response to Public Comments on Draft Report, "Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder," October 25, 2018, p. 20
[iii] "Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder," Final Evidence Report, December 3, 2018, p. 1
[iv] "CDER Conversation: Treatment for Opioid Use Disorder," https://www.fda.gov/Drugs/NewsEvents/ucm611659.htm (page last updated July 18, 2018)
[v] "Soviet food shortage not for lack of output. Distribution, waste blamed for problem," Baltimore Sun, December 20, 1990, https://www.baltimoresun.com/news/bs-xpm-1990-12-02-1990336114-story.html
[vi] "Spinraza® and Zolgensma® for Spinal Muscular Atrophy," Draft Report, December 20, 2018, p. 86
[vii] "Spinraza® and Zolgensma® for Spinal Muscular Atrophy," Draft Report, December 20, 2018, p. 49
[viii] Patient Rising Now's Comment Letter to ICER about "Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value" Draft Evidence Report, September 20, 2018
[ix] We would suggest "Weird Tales" (https://www.weirdtales.com/), or "Asimov's Science Fiction" (https://www.asimovs.com/)
[x] "Spinraza® and Zolgensma® for Spinal Muscular Atrophy," Draft Report, December 20, 2018, p. 8
[xi] "Spinraza® and Zolgensma® for Spinal Muscular Atrophy," Draft Report, December 20, 2018, p. 64
[xii] "Spinraza® and Zolgensma® for Spinal Muscular Atrophy," Draft Report, December 20, 2018, pages 11, 22, 48, 49, 68, 72, 73, 81, 83, 86, 88, 90, 91, 93, and 183. In addition, there are numerous assumptions made in the report that add to the uncertainty of the Draft Report's conclusions.
[xiii] https://icer-review.org/morning-view/04-27-18/
[xiv] "Role of Single Group Studies in Agency for Healthcare Research and Quality Comparative Effectiveness Reviews, AHRQ Publication No. 13-EHC007-EF, January 2013
[xv] https://www.britannica.com/science/uncertainty-principle
[xvi] Patient's Rising Now Comment Letters about ICER Draft Reports, "Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value" Draft Evidence Report, September 20, 2018, "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value," April 12, 2018, and "Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value," August 17, 2018
[xvii] "Drug pricing conversations must take the cost of innovation into consideration," Garthwaite and Ippolito, STAT, January 11, 2019. https://www.statnews.com/2019/01/11/drug-pricing-conversations-include-cost-innovation/
[xviii] Incivek (approved by the FDA in May 2011) removed by Vertex in October 2014, and Victrelis (approved by the FDA in May 2011) removed by Merck in January 2015
[xix] Stephen Colbert has been credited with giving new meaning to the word "truthy," i.e., "concepts or facts one wishes to be true, rather than concepts or facts known to be true." https://www.americandialect.org/truthiness_voted_2005_word_of_the_year, also see https://www.nytimes.com/2010/10/17/magazine/17FOB-onlanguage-t.html
[xx] "Spinraza® and Zolgensma® for Spinal Muscular Atrophy," Draft Report, December 20, 2018, p. iv
[xxi] "Spinraza® and Zolgensma® for Spinal Muscular Atrophy," Draft Report, December 20, 2018, p. 19
[xxii] http://apps.humana.com/tad/tad_new/Search.aspx?criteria=spinraza&searchtype=freetext&policyType=both (Accessed Jan 7, 2019)
[xxiii] https://www.novartis.com/news/media-releases/novartis-announces-fda-filing-acceptance-and-priority-review-avxs-101-one-time-treatment-designed-address-genetic-root-cause-sma-type-1
[xxiv] Armstrong EP, Malone DC, Yeh W-S, Dahl GJ, Lee RL, Sicignano N. The economic burden of spinal muscular atrophy. Journal of medical economics. 2016;19(8):822-826.

Institute for Clinical and Economic Review
RE: Public Comments (Spinal Muscular Atrophy)

To the ICER SMA group and other interested parties:

Today, for the first time, our son Max rolled over (unassisted) from his back to his side. Most babies do this when they are a few months old. Max is five. He has SMA type I. Max started receiving Spinraza in April of 2017. Since then, he has made significant gains:

- an eighteen point gain on the CHOP-INTEND (measured in clinic)
- louder vocalizations
- stronger wrist movements and greater hand and finger dexterity (allowing him to consistently control his communication devices and pilot his power wheelchair)
- being able to roll his head and slide his legs up and down when lying
- being able to turn up both corners of his mouth into the slightest hint of a smile

Since first receiving Spinraza, Max completed preschool and began attending kindergarten, all from home via a telepresence robot (which he pilots using two adaptive switches on his power wheelchair). Currently, in school, he is mastering his letters, learning basic arithmetic, writing stories, and exploring science and social studies. Meanwhile, in physical therapy, he is working on using his biceps and shoulders to lift his arms off the ground, using his neck to prevent his head from falling, and more.

Since Max began receiving Spinraza, we have seen greater energy and a boost in his ability to achieve the goals set for him in physical therapy. For us as his parents, this is deeply heartening. We have elected to schedule an orthopedic surgery (a bilateral screw hemiepiphysiodesis) that has recently become a part of the standard-of-care for SMA type 1 due to long-term benefits over a span of time previously considered well out-of-reach for the typical SMA type 1 patient—another example of the changes in care and opportunity brought about by the first wave of treatments for SMA.

As parents of a child with a rare, life-threatening disease, we had long reconciled ourselves to the importance of not taking the future for granted and making the most of each day. When a treatment first came within reach, we did everything in our power to ensure that Max began receiving it so he could reap the benefits as soon as possible. To us, the potential for long-term health and strength more than justifies the effort required to keep up with his Spinraza treatments. Ensuring that Max receives Spinraza is part of our definition of doing everything possible to give our child every opportunity. Significantly, it also gives us hope that when the

next, better treatment comes along, Max will be in a better place to derive benefits from it as well.

We hope these comments are helpful and thank you for the work you are doing to quantify the effectiveness and value of SMA treatments.

Sincerely,

Jonathan* and Kristen Lasko
maxstrength.org

*Jonathan Lasko serves on the Events and Family Support Committee of Cure SMA.

Hello,

August 10, 2011 was the first time we ever heard the words Spinal Muscular Atrophy (SMA). This would be a date that forever changed our family. Those three letters shattered our world and gave us no hope for our future. On that date there was no treatment or cure for SMA, only a death sentence, often delivered by doctors as a "take him home and love him, as he won't see his second birthday" type of message. This was the message we were given to our then 1-month old first born, Mateo, who is now 7 years and 6 months old!

The first year of Mateo's life was full of tears, 911 calls and constant fear of losing him. By his second year we were more comfortable with our new life with SMA and began traveling and getting more involved in things. SMA would rob Mateo of many things, including his ability to swallow, breathe on his own, move and smile. Mateo had surgery at 3 months old for a g-tube as he could no longer safely eat orally. At 7 months old Mateo had a tracheostomy as he could no longer breath on his own and we had nearly lost him more times than any person should ever encounter. Over the months, Mateo would slowly start losing his ability to move his hands and feet. Mateo never had any head control and was often described as "floppy" by the doctors. Mateo's cry was very weak and soft. Despite Mateo losing the ability to move he never lost the ability to fight. He continued to prove doctors wrong every time we celebrated another birthday. Mateo started school at 3 years old as cognitively he functioned right at his age level. Today Mateo is thriving in 1st grade where he loves being the center of attention.

We eventually decided we wanted to add to our family and decided to risk the 1 in 4 chance we would have another SMA child.

On January 24, 2016 Javier entered the world and he would help change SMA. A clinical trial was recruiting with a drug called Nusinersen. This drug would be delivered via lumbar puncture to replace the missing protein in SMN2. We took the chance of the unknown and Javier was enrolled in a trial at Johns Hopkins Hospital in Baltimore, receiving his first injection at 12 days old. Javier began meeting milestones that SMA type 1 children could never do. Javier drank from a bottle without choking, he maintained oxygen saturations, he eventually learned to roll over, sit up, crawl and eventually walk! We were originally told Javier would most likely be very similar to Mateo. What we have experienced is quite the opposite thanks to Spinraza. My husband and I had to learn to baby proof the house, something that was not needed for Mateo as he can't move. We got to hear the words "Mama" and "daddy" for the first time, something Mateo has never been able to do as he cannot talk.

Javier still has development delay as he has poor core strength, making it harder to get up from the ground on his own. He can not jump or run. He receives weekly PT and OT sessions as well as wears braces on his feet. Javier does at times struggle with maintaining his oxygen above 92 when he is sick. He wears a bipap when ill. This compares nothing to what we've been through with Mateo.

On December 23, 2016 this drug was FDA approved. Despite it being FDA approved Javier's trial is still open for another two years, therefore he continues to travel to Baltimore every 4 months for injections. The down fall to this treatment is the every 4 month spinal injections. Javier has great anxiety when around doctors or hospitals. He is now at an age where he knows when we get to the hospital he will be getting an injection. I can only hope this will not be a lasting trauma response for him and he will understand when he is a bit older how important these injections are to him.

Mateo began receiving this drug on October 3, 2017. He has begun to get movement back in his hands and feet and a small curl of his mouth his back to indicate he is smiling! Mateo's oxygen levels have been consistently higher. He is able to recover from illnesses faster.

With all the excitement we were seeing in our boys we decided our family was not complete and we yet again rolled the genetic dice and got pregnant with our 3rd SMA baby. Amelia entered the world on March 30, 2018. Amelia began treatment of SMA at 11 days old. She is developing on target for her age and at this time needs no medical intervention. She can current sit unassisted, army crawl and is bearing weight on her legs. Amelia makes sounds and loves to try new foods. She has battled two colds at home with no concerns.

All our children are thriving due to research and advancements made in the last 7 plus years. It has been amazing to see how far the treatments for SMA have come as we get to experience them on a daily basis.

Thank you,

Amy M.

Date: 01/16/2019

1. Briefly describe your disease experience, including your diagnosis, treatments you've used, etc. Be as specific as you feel comfortable with.

My son was diagnosed with Type III, Spinal Muscular Atrophy (SMA) at the age of two. Overtime, he began losing the ability to walk. By four years old, he had his first manual wheelchair. He started Spinraza over a year and a half ago when he was five years old.

2. How do the disease/condition and the available treatments affect your day-to-day life?

Before we started treatment a year and a half ago, we observed our son losing the ability to walk. He was not able to lift his legs up while laying down nor was he able to stretch his leg outward while sitting. While standing, he was not able to bend his knees (squat) without falling. He fatigued easily (three to four hour naps were common) and fell frequently.

Since my son started Spinraza, he has gained and maintained strength. Before he started treatment, he was only able to walk 50 meters in a 6-minute walk test and fell six times during the test. Just over a month ago however, in the same 6-minute walk test, he was able to walk 150 meters without falling. This is incredible because by definition, SMA individuals (without treatment) loose muscle strength over time.

This translates to everyday living with respect to being independent. It means my son does not need an aide at school to take notes or use the restroom. Likewise, it means he can be independent at home preforming daily tasks such as getting dressed, eating, using the bathroom and brushing his hair and teeth.

Spinraza has not only given my son the strength he desperately needed but the treatment has also given him more energy which allows him to stay focused during school.

3. What impact does the disease have on family or caregivers?

As a mother, I am continuously worried about my son's physical and mental health. I worry my son was left behind at recess again because he cannot keep up with the other children. I worry about how he carries his hot lunch. I worry about him navigating field trips and Halloween parades at the school. I worry about him breaking a bone, which could mean he may never walk again.

Aside from the worry, my husband and I have taken off several days from work to attend doctor appointments and school functions so that our son can participate as normally as possible in activities like field days, classroom parties, school fundraisers etc.

There are many costs associated with a disability, which is emotionally and financially stressful. Whether it be paying for new equipment, doctor visits, therapy visits, getting an adaptive bike, building or buying an accessible home and vehicle.

4. What else should ICER know about living with the disease or condition (e.g. impact on your ability to work, exercise, care for family, etc.)?

There are many things we take for granted like being able to participate in the same activities as others, choosing any seat at a sporting event or concert, taking a hike, or even wearing snow boots (our son cannot wear many snow boots because they are too heavy for him). Logistics and accessibility are always in the forefront of our mind when planning anything whether it be a family vacation, play date or field trip.

5. What outcomes are most important to patients? For example, is the top priority improved quality of life, longer survival, or relief of a specific symptom?

Improving or maintaining any strength…no matter how little it may seem. Because until you live with SMA, you do not realize how every little bit of strength maintained or gained helps to improve the quality of life.

6. Are there new/emerging treatments that the patient community is anticipating? What are the benefits or disadvantages of the new treatments (e.g. more or fewer side effects, convenience, effectiveness, etc.)? Do you think the benefits will outweigh side effects or risks?

My son is on a relatively new treatment (Spinraza) that requires an intrathecal administration of the drug. The benefits my son receives from this treatment outweighs the short-term effects he experiences. Because Spinraza is a relatively new drug, the long-term side effects are unknown however; it is a risk we are willing to take for the sake of our son's quality of life.

There are a few additional drugs in the pipeline that look promising for SMA patients however I do not have enough information to comment more on them.

7. Do patients have trouble getting insurance coverage for treatment? Do costs affect patients' choice of treatment, or their ability to access treatment?
Getting approval for Spinraza has been a painfully slow process for many however, we were fortunate to get approval from our insurance relatively quickly.

8. Please share any other information that you think is important for us to know from a patient perspective.

Saving a life is as important as improving the quality of life – both are priceless. It is also essential that each person be given the right to choose what is important to him or her with respect to treatment and treatment options.