January 31, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

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

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[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.