

July 13, 2022

Dr. Steven D. Pearson  
President  
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Two Liberty Square, Ninth Floor  
Boston, MA 02109

Dear Dr. Pearson:

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to provide feedback on ICER's assessment of treatments for amyotrophic lateral sclerosis (ALS). ALS is a progressive neurodegenerative disease for which there is still a marked unmet need. There have been significant increases in scientific understanding around the physiology of ALS in recent years, and there are many ongoing studies to develop treatments and cures for ALS. Given the severity of the disease, it is imperative that patients are able to access treatments as they become available. PIPC encourages ICER to consider the following comments to ensure its assessment accurately represents the needs of ALS patients and caregivers and the potential benefits these treatments may provide.

**ICER should be weighting by severity in its models, as is becoming widely accepted by health technology assessment organizations globally.**

In recent years, many of the assumptions that cost utility analysis is built on have come under scrutiny,<sup>1</sup> particularly the assumption that every unit of health gain is equal in value.<sup>2</sup> Experts have noted that it is not reasonable that a single unit of health generates the same utility whether that health is accrued to someone who is suffering considerable disease burden, or to someone who is suffering minimal disease burden.<sup>3</sup> Several health technology assessment systems in Europe have backed away from direct use of strict cost-per-QALY estimates for this very reason and incorporate the role of severity adjacent to the results to make a more context-relevant case for, or against, a new technology.<sup>4,5</sup>

Numerous economists have made the case that a system of evaluation that treats therapeutic innovations in these disease spaces as of similar relative value for unit of health gain in less severe conditions, and

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<sup>1</sup> Beresniak A, Medina-Lara A, Auray JP, De Wever A, Praet JC, Tarricone R, Torbica A, Dupont D, Lamure M, Duru G. Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOUTCOME European project. *Pharmacoeconomics*. 2015 Jan 1;33(1):61-9.

<sup>2</sup> Sund B, Svensson M. Estimating a constant WTP for a QALY—a mission impossible? *The European Journal of Health Economics*. 2018 Jul;19(6):871-80.

<sup>3</sup> MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). *Social Science & Medicine*. 2018 Aug 1;211:359-66.

<sup>4</sup> Barra, M. and K. Rand-Hendriksen, *A missing cornerstone in the Norwegian Priority Commission's weighting scheme—Sub-treatment balancedness is a necessary property for priority setting criteria*. *Nordic Journal of Health Economics*, 2016. 4(2): p. pp. 8-23.

<sup>5</sup> Swedish Parliamentary Priorities Commission, *Priorities in health care: ethics, economy, implementation*. 1995, Stockholm: Swedish Government.

for patients who have minimal disease burden, is thought by many to be inherently unfair and skewed in the wrong direction.<sup>6,7,8</sup>

ALS is a severe condition with significant unmet need, as there are currently no effective therapies beyond symptom management. Current methodologies that factor in severity would suggest a severity multiplier of between 2-4 for a disease with this scale of relative health loss.<sup>9</sup>

### **ICER continues to rely on the Quality-Adjusted Life Year, which is known to be discriminatory.**

Multiple studies have shown that cost-effectiveness models that use the quality-adjusted life year (QALY) discriminate against patients with chronic conditions<sup>10</sup> and people with disabilities.<sup>11</sup> There is widespread recognition that the use of the QALY is discriminatory. The QALY has historically been opposed by the American public and policy makers. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.<sup>12</sup>

As we note above, the most recent work shows that due to diminishing returns, traditional cost utility methods, like those ICER uses, overvalue treatments for mild illnesses and undervalue treatments for highly severe illnesses, and as a result such studies recommend underpaying for treatment of severe illnesses. ICER should be evolving away from use of the QALY, and, instead, measuring value based on the most up-to-date science and improved health utilities reflecting the value to the patient.

### **Caregiver burden must be fully incorporated into ICER's model.**

Caregiver burden in ALS is profound. As the disease progresses, there is greater need for informal and paid caregiving.<sup>13</sup> Among 600 caregivers participating in the ALS Focus Caregiver Survey, 68% reported spending more than 30 hours per week providing care and nearly half felt unprepared for changes in caregiving responsibilities as ALS progressed.<sup>14</sup> The majority of caregivers also report a marked decline in their own physical and mental health as the patient's condition progresses.

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<sup>6</sup> Shiroiwa, T., et al., *WTP for a QALY and health states: More money for severe health states?* Cost Effectiveness and Resource Allocation, 2013. 11(1): p. 22.

<sup>7</sup> Lancsar, E., et al., *Deriving distributional weights for QALYs through discrete choice experiments.* Journal of health economics, 2011. 30(2): p. 466-478

<sup>8</sup> Richardson, J., A. Iezzi, and A. Maxwell, *How important is severity for the evaluation of health services: new evidence using the relative social willingness to pay instrument.* The European Journal of Health Economics, 2017. 18(6): p. 671-683.

<sup>9</sup> Lakdawalla DN, Phelps CE. Health technology assessment with diminishing returns to health: the generalized risk-adjusted cost-effectiveness (GRACE) approach. Value in Health. 2021 Feb 1;24(2):244-9.

<sup>10</sup> Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.

<sup>11</sup> Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.

<sup>12</sup> [https://www.ncd.gov/sites/default/files/NCD\\_Quality\\_Adjusted\\_Life\\_Report\\_508.pdf](https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf)

<sup>13</sup> Oh J, An JW, Oh S-I, et al. Socioeconomic costs of amyotrophic lateral sclerosis according to staging system. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2015;16(3- 4):202-208.

<sup>14</sup> ALS Association. ALS Focus Results from the Caregiver Needs Survey. 2022

As such, the societal perspective is a more relevant choice than the health care perspective in the case of ALS. NICE, which ICER leans heavily on for its approach to value assessment, has already included caregiver utility in its cost-effectiveness models for diseases such as Alzheimer's, Multiple Sclerosis, and Parkinson's disease.<sup>15</sup> It is also the recommended perspective for cost-effectiveness models of the second panel on cost-effectiveness<sup>16</sup> and ISPOR.<sup>17</sup>

**ICER should include estimates of the “option value” of successful treatment for interventions slowing progressive diseases with high mortality rates, like ALS.**

Innovation in medicine does not happen in a vacuum. The traditional approach to cost-utility analysis used by ICER in this report measures the value of a health innovation by comparing benefits to costs assuming no further improvements in medical technology in the future. In real terms this overlooks the fact that life-extending, or progression-delaying innovations can allow patients to live until the next breakthrough, or stay in less severe disease states longer.<sup>18</sup> Other than the obvious benefits of such an outcome, there is also the tangential benefit that these patients could ultimately access improvements in medical technology in the near future.<sup>19</sup> These benefits that would not have accrued to them, if they hadn't benefit from current innovations, or “option value” of a health innovation<sup>20</sup> should be factored into the model. As long as medical technology continues to advance, there will be option value in extended survival, or innovations that delay progression. Failing to account for this value ignores a potentially important source of benefit to patients, especially in areas of rapid innovation.<sup>21</sup>

**ICER should be placing a greater emphasis on distributive effects of new therapies.**

Rather than concentrating only on the net cost-effectiveness for a hypothetical archetypal patient, ICER should be considering the impact new treatment options may have on the ALS population writ large.<sup>22</sup>

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<sup>15</sup> Afentou N, Jarl J, Gerdtham UG, Saha S. Economic evaluation of interventions in Parkinson's disease: a systematic literature review. *Movement disorders clinical practice*. 2019 Apr;6(4):282-90.

<sup>16</sup> Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016 Sep 13;316(10):1093-103.

<sup>17</sup> Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ispor drug cost task force report—Part II. *Value in Health*. 2010 Jan;13(1):8-13.

<sup>18</sup> Philipson TJ, Becker G, Goldman DP, Murphy KM. Terminal care and the value of life near its end. NBER Working Paper. Published 2010.

<sup>19</sup> Sanchez Y, Penrod JR, Qiu XL, Romley J, Snider JT, Philipson T. The option value of innovative treatments in the context of chronic myeloid leukemia. *Am J Manag Care*. 2012 Nov 1;18(11 Suppl):S265-71.

<sup>20</sup> Snider JT, Batt K, Wu Y, Tebeka MG, Seabury S. The option value of innovative treatments for non-small cell lung cancer and renal cell carcinoma. *Am J Manag Care*. 2017 Oct 1;23(10):e340-6.

<sup>21</sup> Li M, Basu A, Bennette C, Veenstra D, Garrison Jr LP. How does option value affect the potential cost-effectiveness of a treatment? The case of ipilimumab for metastatic melanoma. *Value in Health*. 2019 Jul 1;22(7):777-84.

<sup>22</sup> Love-Koh J, Cookson R, Gutacker N, Patton T, Griffin S. Aggregate distributional cost-effectiveness analysis of health technologies. *Value in Health*. 2019 May 1;22(5):518-26.

One challenge ALS patients face is access to specialized multidisciplinary ALS clinics, which is considered standard of care for the treatment of ALS.<sup>23</sup> There are over 200 ALS clinics in the U.S., but these clinics are not geographically distributed. Several states have only one or two clinics. This is a large driver of intervention-generated inequality<sup>24</sup> in treatment of ALS. Access to oral primary care physician-prescribed treatments could considerably reduce this inequality and improve the distribution of health benefits across the ALS patient community, regardless of where patients live or their relative access to healthcare services.

### **ICER's model structure does not appropriately represent a progressive disease, like ALS.**

The model structure oversimplifies ALS, and relies too much on categorization, which likely underweights the value of small changes in the rate of progression. A better choice for comparing therapy to standard of care would be a time-to-event methodology, such as a discrete event simulation model (DES)<sup>25,26</sup> or a discretely integrated condition event (DICE) model<sup>27,28</sup> looking at changes in ALS Functional Rating Scale (ALSFRS-R).

ALS is a highly heterogeneous disease, and a known limitation of the Markov model is that it is only appropriate when the disease in question is largely homogenous. Patients, caregivers, and clinical experts emphasized to ICER the need for multiple different mechanisms of action because ALS is a heterogeneous illness with multiple molecular pathways leading to neuronal death. It is well established that generating and reporting of differential value assessment across subgroups in heterogeneous diseases leads to substantial health gains, both through treatment selection and coverage.<sup>29,30</sup> PIPC would advise ICER to move away from the assumption that all patients are the same, and the value to each can be determined by the estimation of a single point average, and move to producing ranges that are more representative of heterogeneous patient populations.

### **An ALS-specific patient-reported outcome tool should be used in ICER's model, as research has shown that the EQ-5D is insensitive to health gain in the ALS population.**

A recent study highlighted how limited the EQ-5D is as a measure of quality of life in ALS patients. It showed that there is a considerable lack of content validity and convergent validity for generic patient-

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<sup>23</sup> Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2009;73(15):1218-1226

<sup>24</sup> Lorenc T, Petticrew M, Welch V, Tugwell P. What types of interventions generate inequalities? Evidence from systematic reviews. *J Epidemiol Community Health*. 2013 Feb 1;67(2):190-3.

<sup>25</sup> Standfield L, Comans T, Scuffham P. Markov modeling and discrete event simulation in health care: a systematic comparison. *International journal of technology assessment in health care*. 2014 Apr;30(2):165-72.

<sup>26</sup> Getsios D, Blume S, Ishak KJ, Maclaine G, Hernández L. An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. *Alzheimer's & Dementia*. 2012 Jan 1;8(1):22-30.

<sup>27</sup> Moller J, Davis S, Stevenson M, et al. Validation of a DICE simulation against a discrete event simulation implemented entirely in code. *Pharmacoeconomics*. 2017;35(10):1103-1109.

<sup>28</sup> Caro JJ. Discretely integrated condition event (DICE) simulation for pharmaco-economics. *Pharmacoeconomics*. 2016;34(7):665-672.

<sup>29</sup> Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered health care. *Journal of health economics*. 2011 May 1;30(3):549-59.

<sup>30</sup> Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. *Medical Decision Making*. 2014 Nov;34(8):951-64.

reported outcome tools (PROs) in domains highlighted as important for ALS patients. It also showed that the correlation between generic PROs and disease specific ALS PROs was low.<sup>31</sup> It concluded “*generic PROs [such as EQ5D] covered only half of the domains important to individuals with ALS suggesting the need for an ALS specific preference-based measure to better reflect the health-related quality of life of this population.*”

## **Conclusion**

PIPC encourages ICER to revisit its modeling choices to ensure that the model accurately represents the needs of and treatment value to the ALS patient population.

Sincerely,



Tony Coelho  
Chairman  
Partnership to Improve Patient Care

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<sup>31</sup> Peters, N., Dal Bello-Haas, V., Packham, T., Chum, M., O’Connell, C., Johnston, W.S., MacDermid, J.C., Turnbull, J., Van Damme, J. and Kuspinar, A., 2021. Do generic preference-based measures accurately capture areas of health-related quality of life important to individuals with amyotrophic lateral sclerosis: a content validation study. *Patient Related Outcome Measures*, 12, p.191.