PIPC Partnership to Improve Patient Care

June 18, 2019

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

On behalf of the Partnership to Improve Patient Care (PIPC), we are writing to provide comments on the Institute for Clinical and Economic Review's (ICER) draft evidence report on treatments for Duchenne Muscular Dystrophy (DMD). Duchenne Muscular Dystrophy is a devastating genetic disorder characterized by progressive muscle degeneration. Symptoms develop in young children between the ages of 3 and 5. Until relatively recently a diagnosis of DMD meant a life expectancy of under two decades. Even with new medical innovations, DMD patients only survive into their early 30s.[1] Given the severity of this disease, it is essential that we continue working to develop novel and effective disease-altering treatments for patients. ICER's study continues to harm patients by ignoring outcomes that matter to them and shortchanging treatments that could, for the first time, be truly curative. ICER is evaluating new treatments at too early a stage to fully capture their effectiveness in the real world, and without recognition that the alternative is an early death.

We would like to highlight the following concerns with ICER's draft evidence report.

ICER's Study is Premature to Evaluate the Value of Novel Therapies

ICER has a concerning pattern of reviewing new drugs at earlier and earlier phases of their development and approval. This report is the most concerning to date. The report sets out to determine the value of three drugs: two – eteplirsen and golodirsen – new mutation-specific therapies known as exon-skipping therapies, and deflazacort, a corticosteroid. Corticosteroids have made up the bulk of traditional treatment for DMD, and it can ease suffering and slow progression in the disease. Exon-skipping therapies are a new, game-changing group of drugs that could have a significant effect on the disease in the near future. This report ignored this fact and set up a model for DMD based on deflazacort, and then used that same model to make far-fetched assumptions about this new form of gene therapy with almost all of the inputs from the model coming from just one study.[2] One of the drugs under review, golodirsen, had not yet received FDA approval at the time of the study.

[1] Muscular Dystrophy Association. Duchenne Muscular Dystrophy (DMD). Accessed June 3, 2019.
[2] Landfeldt E, Lindgren P, Bell CF, Schmitt C, Guglieri M, Straub V, Lochmüller H, Bushby K. The burden of Duchenne muscular dystrophy: an international, cross-sectional study. Neurology. 2014 Aug 5;83(6):529-36.

ICER acknowledges this lack of evidence in their report, calling the results for the exon-skipping therapies inconclusive. This result leads us to question why ICER is conducting the report at this early stage, especially considering its potential implications for access and coverage.

In ICER's haste to provide payers with results, they are doing harm to patients. We are in a time of innovation in which whole new approaches to treating rare diseases are being developed, and their complexity means that finding the ideal method of delivering this therapy may require some evolution in practice, rather than assuming providers will be immediately omniscient in their clinical knowledge. ICER is implying to their payer stakeholders that we should not openly use or pay for these drugs until they have proven to have lifelong effects on DMD patients, but we know that to produce that longitudinal data in a rare disease would take decades, while the beneficiaries of these innovations — patients — are left out in the cold. Although the bulk of such innovations will in all likelihood make their way into the health care system at some point, the delay is not without cost, in health benefits foregone and lives lost to all those patients who are waiting for access now. No decision, whether to approve or delay access, is without human cost.[3,4] Parent Project For Muscular Dystrophy summed this up concisely in their first comment letter to ICER, in which they stated, "Among the most critical contextual considerations that must be taken into account that the 'yet to be fully known' of all of the interventions detailed within this Draft Scope must be weighted against the 'certainty of doing nothing.'"

The Model Oversimplifies the Disease

Duchenne Muscular Dystrophy is a complex condition with a very heterogeneous patient population. For this reason, it is particularly concerning that this report leaned heavily on one study that shows that there was a significant shift in progression from ambulatory to non-ambulatory status between deflazacort and prednisone. From a separate study, ICER describes its approach as digitally mapping the 'survival curve' for transitioning out of ambulatory status into non-ambulatory status (figure 4.2, page 45 in the report). It uses this as its transition probabilities between health states. It then uses this survival curve to estimate the transition rate to death and extrapolates all subsequent changes in quality of life and probability of death over a lifetime to just this one source. It is clear that taking such a complex disease and representing it with just two health states and using quality of life weights that translate across just two health states is a gross oversimplification. Patient stakeholders recognized this issue in the first round of comment letters as well, encouraging ICER to incorporate a wider range of outcomes — suggesting Daily Functional Outcomes — which would capture more nuanced data like the ability to do basic self-care activities. The simplification of a complex disease down to two health states is concerning

[3] Stevens W, Philipson T, Wu Y, Chen C, Lakdawalla D. A cost-benefit analysis of using evidence of effectiveness in terms of progression free survival in making reimbursement decisions on new cancer therapies. InForum for Health Economics and Policy 2014 Jan 1 (Vol. 17, No. 1, pp. 21-52). De Gruyter.
[4] Lakdawalla DN, Chou JW, Linthicum MT, MacEwan JP, Zhang J, Goldman DP. Evaluating expected costs and benefits of granting access to new treatments on the basis of progression-free survival in non–small-cell lung cancer. JAMA oncology. 2015 May 1;1(2):196-202.

as this type of dichotomization or over-categorization of outcomes has been shown to lead to underestimation of outcomes effects.[5,6]

Furthermore, the assumption that there are straightforward linear extrapolations in transition between health states and across quality of life, level of function and risk of mortality, all encapsulated in one measure as a function of that one particular outcome is overly simplistic. It is also not clear from the Poster used to develop these transition probabilities between health states, what test this model used to derive their classification of non-ambulatory and ambulatory.[7] Most studies have used the 6-minute walk test (or 6MWT), which is known to be quite subjective and relies on the relative effort, or intention of those being tested.

Overall this model is not scientifically rigorous enough to capture the nuances and complexities of Duchenne Muscular Dystrophy.

ICER Continues to Overlook Outcomes that Matter to Patients and Caregivers

In simplifying their study to capture only two health states, ICER overlooks outcomes that matter to patients and caregivers. We would like to reinforce the comments that caregivers and patient advocacy groups submitted and suggest new measures beyond the 6MWT that better capture the nuances of patient function should be used to better assess outcomes. In their previous comment letter, Parent Project for Muscular Dystrophy encouraged ICER to add respiratory function and daily functional outcomes (DFO) to their outcomes, as they are primarily important to patients. ICER chose not to incorporate these outcomes. This is a concerning pattern. Again and again, patients and caregivers emphasize that their daily quality of life and ability to better complete simple daily tasks is of primary importance to them. ICER continues to ignore this consistent patient input in favor of using the QALYs and considerations that neatly fit into their cost per QALY estimates. We challenge ICER to be more thoughtful and strategic in incorporating outcomes that matter to patients, even if it means reports are not churned out as quickly.

Caregiver burden, both emotionally and financially, is also largely ignored. Patients with DMD gradually lose the ability to complete basic self-care and live independently. This takes both a large emotional and financial toll on families and primary caregivers. In the United States, costs of additional personal support for patients are paid largely out of pocket. With this in mind, these costs should also be considered when evaluating the value of a drug, as therapies that can increase a patient's day-to-day function have the potential to decrease caregiving costs and increase quality of life for caregivers.

ICER Continues to Use the Flawed and Discriminatory QALY

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[5] Altman DG, Royston P. The cost of dichotomising continuous variables. Bmj. 2006 May 4;332(7549):1080.
[6] Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Statistics in medicine. 2006 Jan 15;25(1):127-41.
[7] Hill M, Crowther MJ, Abrams KR. The challenges of estimating multi-state model transitions in rare diseases: Informing an economic decision model for Duchenne Muscular Dystrophy. In Value in Health 2018 Oct 1 (Vol. 21, pp. S400-S400).

PIPC continues to have concerns with ICER's use of the QALY. Not only is the metric discriminatory against people with disabilities, there is a growing literature on how people exhibit genuine preferences for healthcare resources to be directed towards patients suffering more severe disease or for those for which there are currently few effective therapies.[8,9,10] DMD falls into both of these categories.

This literature has uncovered a broad range of attributes across which the *value* of QALY gains may be expected to vary.[11] One study showed a QALY gain to younger patients or those with more severe disease may be weighted more highly than a QALY gained to older patients or those with a less severe condition.[12] This is a preference seen consistently and by the many, not the few, with a similar study recently concluding that the '*marginal willingness to pay per QALY was sensitive to severity of disease among a substantial proportion of the public.*' [13]

It's not just in academic circles that this issue has gained traction. Recently healthcare agencies have designed specific policies around approval and acceptance of new technologies that address variance in relative value across patient populations.[14,15] For example, the Netherlands has operationalized disease severity using the proportional shortfall approach.[16] Sweden uses categories to give an indication of the level of severity.[17] In both these countries severity only plays an implicit role in the reimbursement decisions, but in Belgium and France its role is more explicit in determining resource allocation in healthcare.[18]

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[8] Nord E. Concerns for the worse off: fair innings versus severity. Soc Sci Med. 2005;60(2):257–63.
[9] Green C. Investigating public preferences on 'severity of health' as a relevant condition for setting healthcare priorities. Soc Sci Med. 2009;68(12):2247–55.
[10] Dolan P, Tsuchiya A. Health priorities and public preferences: the relative importance of past health experience and future health prospects. J Health Econ. 2005;24(4):703–14.
[11] Rowen D, Brazier J, Mukuria C, Keetharuth A, Risa Hole A, Tsuchiya A, Whyte S, Shackley P. Eliciting societal preferences for weighting QALYs for burden of illness and end of life. Medical Decision Making. 2016 Feb;36(2):210-22.
[12] Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Econ. 2004;13(5):437–52
[13] van de Wetering L, van Exel J, Bobinac A, Brouwer WB. Valuing QALYs in relation to equity considerations using a discrete choice experiment. Pharmacoeconomics. 2015 Dec 1;33(12):1289-300.
[14] Wouters S, van Exel J, Baker R, Brouwer WB. Priority to end of life treatments? Views of the public in the Netherlands. Value in Health. 2017 Jan 31;20(1):107-17.
[15] Barra M, Rand-Hendriksen K. 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 Aug 13;4(2):pp-8
[16] Van de Wetering EJ, Stolk EA, Van Exel NJ, Brouwer WB. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. The European journal of health economics. 2013 Feb 1;14(1):107-15.
[17] Svensson M, Nilsson FO, Arnberg K. Reimbursement decisions for pharmaceuticals in Sweden: the impact of disease severity and cost effectiveness. Pharmacoeconomics. 2015 Nov 1;33(11):1229-36.
[18] Franken M, Stolk E, Scharringhausen T, de Boer A, Koopmanschap M. A comparative study of the role of disease severity in drug reimbursement decision making in four European countries. Health Policy. 2015 Feb 28;119(2):195-202.

Conclusion

ICER continues to overlook outcomes that matter to patients, families and caregivers in their haste to provide reports to payers. We encourage ICER to be more strategic and focus on producing complete and thoughtful analysis using high quality data incorporating a range of outcomes important to patients instead of rushing to complete reports that do not have appropriate scientific rigor.

Sincerely,

Tony Coelho
Chairman, Partnership to Improve Patient Care