

June 18, 2019

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

Submitted via email

Dear Dr. Pearson:

On behalf of CureDuchenne, I want to thank you for the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report, "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value."

We appreciate ICER's effort to bring clarity to drug pricing and share your goal of working to ensure a more effective, efficient, and just health care system. That said, my organization has some very real concerns regarding ICER's analysis of therapies for the treatment of Duchenne, a rare disease that is unique in its progression, treatment protocols and dosing, and needs of its patients and their caregivers who live with the disease every day.

While we have the deepest respect for your organization and its mission, we believe ICER's analysis is woefully out of touch with rare disease groups in general and Duchenne in particular. We fear that broad generalizations related to the cost-effectiveness of various therapies, including deflazacort (brand name EMFLAZA) and eteplirsen (brand name EXONDYS 51)—without a proper depth of understanding as to the value that these treatments bring in the *real world*—will ultimately hurt patients and their families as they seek to enhance the health and well-being of those living with Duchenne.

About CureDuchenne

CureDuchenne is the nation's leading nonprofit organization dedicated to finding a cure for Duchenne. We are recognized as the global leader in research, patient care, and innovation for improving and extending the lives of those with the disease. We fuel hope for families, enable progress for drug development, and extend ambulation for patients in collaboration with pharmaceutical companies, medical and healthcare professionals, our scientific advisory board, and our board of directors.



On a personal level, I am the mother of a 22-year-old living with Duchenne. He has taken EMFLAZA for more than 17 years. Our son is able to walk—we believe this is in large part because his weight has remained stable over the years. In other words, he has not experienced the type of weight gain associated with the steroid prednisone (which has not been approved by the FDA for the treatment of Duchenne). The fact that he has not gained weight has contributed to extension of ambulation which in turn helps avoid numerous adverse health consequences, such as scoliosis, loss of bone density, and respiratory issues. He has never had a bone fracture, and he can work outside the home—in fact, he currently has a paid internship with a major, national media company

This is the promise that these treatments bring to the lives of patients living with this disease and, we fear, the kind of real-world impact that isn't recognized by ICER in its QALY methodology, due to ICER's own lack of experience in this area.

The Cascading Impacts

Indeed, the weight gain example is illustrative. The impact of this side effect, common to users of prednisone, cannot be ignored. It has a cascading effect on the Duchenne patient, affecting everything from ambulation, to the ability of caregivers to lift and transfer the patient, to the social and psychological well-being of both the patient and his family. Yet, in the report, weight gain is treated as just another potential side-effect (see pages 4, 10 and 19 of the report, for example). In fact, the addition of 20-30 extra pounds can lead directly to some of the other side effects listed, such as osteoporosis and fractures due to weight gain loss of ambulation and other muscular and respiratory disorders. Your report notes that in Karimzadeh 2012, four patients treated with prednisone were excluded from the study at about 52 weeks of treatment due to uncontrollable weight increase, despite consulting with a nutrition specialist. In addition, dose reduction due to weight related AEs was implemented in all prednisone treated patients, compared to only 21.4% deflazacort treated patients (page 30). Yet the real-world implications of this information go unrecognized in the report.

And while 2-3 extra years of ambulation may not seem like much on paper, such an "incremental" improvement has an enormous impact on a diverse array of physical and psychosocial components of the disease. Ultimately, therapies that increase ambulation—even if only by a few years—and do not have weight gain as a side-effect (which, itself, can result in loss of ambulation) allow Duchenne patients to live better lives, longer.

How do you price such impacts? Are you properly accounting for the value of independence in instances where the parent of a patient with Duchenne does not have to quit his or her job to be



home with the patient 24 hours a day? The cost of hospital stays brought on by respiratory illness which can be delayed by EMFLAZA? More broadly: How do you assign a value to happiness? To extra months or years of quality time with loved ones? These are difficult questions, to be sure, but they reveal, beyond a doubt, factors that ICER's methodologies simply are not capturing at present.

Patient Heterogeneity

One thing we are sure of as a patient advocacy organization is the diversity of the Duchenne population. Approximately 15,000 boys are living with Duchenne in the United States, 300,000 worldwide. In this context, ICER's reliance on clinical data rather than real-world evidence presents real challenges. It is difficult to generalize about Duchenne boys when the rate of disease progression and range of severity, both of which depend on the genetic mutation, are so varied.

Moreover, ICER uses a model that doesn't follow the actual disease course. It is particularly difficult to delineate the health states of Duchenne, and even the progression from ambulatory (and its various stages) to nonambulatory (and its various stages) presents as a range. It is not accurate to suggest that 69% of patients at age 5 will have a health state equivalent to late ambulatory, but ICER has used this statistic in its analysis. The starting age, dosing regime, and length of therapy also diverge greatly from patient to patient.

Lack of Data

Finally, we note that ICER's evaluation is being done when there is not yet enough data to fully examine the treatments covered, whether it be deflazacort, eteplirsen, or golodirsen. In fact, this shortcoming is acknowledged throughout the Draft Evidence Report, and the conclusion states that "[t]he underlying evidence for evaluating the cost-effectiveness of treatments in DMD remains sparse." In this regard, ICER's analysis is not only based on incomplete data; it could in fact impede Duchenne patients' access to care. These treatments are just too new for ICER to determine long-term conclusions.

Conclusion

CureDuchenne thanks ICER for being open to comments during this time. We support ICER's mission to educate the public, protect patient access, and promote high-value care. While we are aligned with these goals, we are concerned about the lack of real-world evidence in the Draft Evidence Report, which makes it impossible to evaluate the validity of ICER's analysis. Although ICER acknowledges this lack of evidence, we believe releasing a report with these



defects negatively impact patient access to crucial treatment. At the very least, before proceeding to a final report, ICER should consider incorporating additional perspectives in its analysis—including input and information directly from the community facing the real-world impacts of this rare disease.

Should you have any questions, or need more information regarding this letter, please feel free to reach out to me at 949-872-2552.

Sincerely,

Debra Miller CEO & Founder Comments on ICER Draft Evidence Report: Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value. Dated May 22, 2017

These comments on the May 22 Draft Evidence Report are mainly provided for the purpose of ensuring transparency and full awareness of the critical nature of assumptions in modeling effectiveness and value for a rare potentially fatal, progressive disease such as Duchenne Muscular Dystrophy. In particular, any public discussion or review of the Draft Evidence Report for DMD, including at the New England CEPAC, should consider the following issues:

As ICER has recognized, adaptations to evaluation of treatments for rare diseases must be made, considering the limited patient population, the resulting difficulty of randomly controlled trials, and the ethical issues involving placebo trials, particularly for pediatric patient populations. (See: Modifications to the ICER value assessment framework for treatments for ultra-rare diseases Final Version November 2017). The fact that such modifications exist, and have only recently been adopted, is not mentioned in the DMD Draft Evidence Report until late in the report, p. 41 and should be acknowledged up front, as below.

1.. Workpapers showing detailed calculation of declines in functional ability and ultimately loss of ambulation and life were not provided, meaning the actual assumptions of how the progressive disease resulted in life years versus life years with the treatments reviewed, deflazacort, eteplirsen, and golodirsen, could not be reviewed for comment and are not obvious in the draft evidence report.

2. Use of Quality Adjusted Life Years (QALY) may be difficult, and inappropriate, for progressive diseases like Duchenne Muscular Dystrophy because to suggest a year of life is worth less than a standard year of life because of lesser quality is to devalue patient lives. Therefor caution should be used is applying discounts to life by ICER and data without any QALY discount should be presented as an alternative view which may better represent patient viewpoints. In fact, there is more recent data from Landfeldt which discusses the cost of loss of life years without a quality adjustment, see Mortality Cost of Duchenne Muscular Dystrophy, Landfeldt, Eagle, Straub, April 28, 2017. See also Key Questions for Legislators About the Institute of Clinical and Economic Review (ICER) by Dr. William Smith, the Pioneer Institute Jan 2019. The ICER review should acknowledge that there is some question about the use of QALY in terms of valuing the lives and health of patients, especially for rare diseases.

3. The Draft Evidence Report uses standards for evidence based on literature reviews, rather than asking experts in the field how they view the data and evidence for effectiveness of both intermediate biomarkers such as dystrophin production, as well as maintenance of function versus historical controls for similar untreated populations of DMD patients. This is inconsistent with the commitments made in the Nov 2017 report on adaptation of the framework for rare diseases. See comments below on necessary changes to Sec 3, Comparative Clinical Effectiveness, of the May 22 Draft evidence report. Moreover, the "evidence" in the draft evidence report is not even the most recent data. Most of the cost burden evidence is from

Landfeldt, 2014. There is more recent data in The Direct Cost of Managing a Rare Disease: Assessing Medical and Pharmacy Costs Associated with Duchenne Muscular Dystrophy in the United States, J. Manage Care Spec Pharm 2017 Jun: 23(6):633-641, Thayer, S, Bell C, and McDonald CM. **This data shows the cost and value of delaying loss of ambulation.**

4. The result of the combination of issues described above, ie the difficulty of developing and evaluating treatments for rare or ultra-rare diseases like Duchenne Muscular Dystrophy, the issues surrounding QALY adjustments; and the lack of workpapers showing detailed calculations reflecting assumptions about loss of function or life without treatment suggests that major revisions to the Draft Evidence Report are needed before any CEPAC discussion, which might be misled by apparent results whose basis is subject to substantial uncertainty and lack of specificity tied to the serious unmet medical need for defeating the harms resulting from progressive DMD.

These comments about general areas where changes are needed in the May 22 Draft Evidence Report are followed by specific proposed changes as indicated below.

1.1 BACKGROUND. NEEDS TO MENTION DMD AS **FATAL RARE DISEASE SUBJECT TO ADAPTATIONS OF EFFECTIVENESS AND VALUE FRAMEWORK** AND SPECIAL CONSIDERATIONS IN FUNDING

RECOMMENDATION: INSERT REFERENCE TO SPECIAL CONSIDERATION UP FRONT This section should mention that Duchenne Muscular Dystrophy (DMD) should note that given the population of mostly boys subject to DMD, less than 10,000 in the United States, DMD should be considered an ultra-rare disease. See draft evidence report, p. 1, 400-600 boys per year, and p. 7, eligible patient population fewer than 10,000 individuals. It is therefore necessary to make adjustments in evaluation of the evidence, cost effectiveness and certainty associated with treatments for such a limited population. In the first 3 pages of background, the Draft Report should note that,

"For rare diseases like DMD, decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments"

See: Final Modifications, Nov. 2017 which should be a footnote at least acknowledging the need for such adaptations.

"ICER will use a modified approach to value assessment for treatments for "ultra-rare diseases" (URDs). This modified approach will be used when: •An eligible patient population for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals. •There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals. "

RECOMMENDATION; NOTE REASONS FOR DIFFICULTY ASSESSING VALUE OF ORPHAN DRUGS

There are reasons given for the need for adaptation of the evaluation and cost effectiveness report in the November 2017 report on final modifications which should be highlighted at the outset in the background of the DMD Draft Evidence Report. These should be presented either in the body of the DMD Draft Evidence Report or as a major footnote: From page 7 of the November 2017 Final Modifications report:

"..there are two major reasons given for altering the assessment of value of orphan drugs compared to other treatments: 1) small patient numbers make it very hard to conduct the types of studies that would usually be required to demonstrate with the same level of certainty the safety, effectiveness, and comparative effectiveness of an emerging drug; and 2) small patient numbers may make it impossible to recoup development costs unless prices exceed those that would be commensurate with traditional cost-effectiveness thresholds."

Both of these reasons are valid considerations in assessing effectiveness and value for treatments for DMD. Failure to include this existing commitment to adaptation of ICER's methodology for rare diseases, especially at the outset, discounts the difficulty of developing treatments, and therefore, imposes an opportunity cost which is simply ignored in the current May 22 draft evidence report. Moreover, it is not clear how ICER actually used the adaptations to which it committed in November 2017 in developing its May 22 report. SEE DRAFT EVIDENCE REPORT, P. 41.

3. COMPARATIVE CLINICAL EFFECTIVENESS, P. 21 AND OVERVIEW P. 7

The discussion of clinical effectiveness lacks any reflection of the adaptations to which ICER committed in Nov 2017 on evaluation of rare diseases. See the following, from the Nov 2017 report:

"For assessment of the comparative clinical effectiveness of treatments of ultra-rare diseases, ICER will not change its approach to rating evidence according to the ICER EBM matrix, nor will there be different "standards" of evidence. Instead, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. **The commonly used approach of evaluating treatments for ultra-rare diseases against historical controls will be highlighted**. This added contextual language will be **highlighted through special formatting in ICER reports** and retained throughout press releases, executive summaries, and other versions of ICER reports."

Where, in the May 22, is this "specific context" regarding the potential challenges of generating evidence for these treatments, including issues with RCT's. surrogate outcome

measures, and long term safety and durability of clinical benefit. There is no "highlighted" language in the Section 3 discussion except at the outset which talks about small quantities of dystrophin , nor is there "special formatting" in the report which reflects these issues and provides context. Although there is bold language on p. 32, it is not presented in the context of a rare disease, or as a potential major advance to avoid loss of ambulation.

At a minimum, there should be additional language which refers to the Evaluation of Rare Diseases report in Section 3, including the discussion of Exon-Skipping Therapies at page 32. While the discussion emphasizes the "very small increases in dystrophin" in bold type at page 32, it does not discuss the "potential challenges of generating evidence" and other context-providing matters to which ICER committed in November 2017. Page 32 Exon Skipping Therapies bold intro should be rewritten as:

Eteplirsen and golodirsent treatment results have been show to increase dystrophin by 3 methods of analysis (IHC, WB, PCR). Although the increases are small, there is uncertainty about the amount of dystrophin needed to provide a benefit to patients. Compared to a historical control group, which is appropriate given the rare disease nature of DMD, eteplirsen patients showed less decline in 6MWT and notably, a lower incidence of loss of ambulation, 17% v. 77%. See Table 3.5 Because loss of ambulation results in significantly higher costs of care, this difference if durable and verified, is a significant clinical and cost effectiveness benefit.

At a Minimum, Section 3 on Comparative Clinical Effectiveness, beginning at page 21-41 should be substantially rewritten to provide the rare disease context promised in 2017. Among the changes required are rewriting the conclusions about Eteplirsen on page 40 to read:

"Data on patient-important outcomes with eteplirsen are extremely limited. Studies of dystrophin levels show increases, but the clinical and biologic significance of the levels of dystrophin are uncertain, although lack of dystrophin is a primary cause of DMD, and therefore any increase should be beneficial. There is limited evidence demonstrating improvements in function with eteplirsen, as the long term data are observational with matched or historical controls. This may be appropriate for a rare disease such as DMD given the adaptations previously adopted to ICER methodology for such rare disease in November 2017, recognizing the challenges of clinical trials and analysis for such limited populations of patients. The main outcome reported, 6MWT, shows a substantial benefit in terms of both walk length and loss of ambulation, all there may be less precision in a small unblended study. There are no concerning safety signals with eteplirsen, but long term followup must continue to confirm this. Overall the evidence is of low certainty, although the benefit of exon-skippping is substantial if it can be confirmed. "

The above would be a more accurate representation, and a more honest commitment to the rare disease context to which ICER committed in November 2017, than the current "We consider the evidence to be insufficient."

RECOMMENDATION

That is, 3.1 Overview, should include references to the rare disease nature of DMD the limited population available for clinical trials, and the difficulty of assessing the long term benefits of a progressive disease. Moreover, to the extent that the Draft Evidence Report talks about Eteplirsen and Golodirsen, it does so in a simplistic and superficial manner. There are 9 pages of discussion of deflazacort studies, and then two paragraphs, one each on eteplirsen and golodirsen, on page 40. There should at least be a mention that there is uncertainty about how much dystrophin production is necessary for an improvement in patients with DMD.

At the FDA, there was discussion of how patchy dystrophin could provide benefits to surrounding cells, and how dystrophin production was essential to improvement of the lives of DMD patients. Some patient advocates summarized this in the phrase, A little dystrophin is better than no dystrophin. And regarding the number of patients in trials, one boy had a T shirt that said N = 1, meaning his experience was meaningful in assessing the benefits of any eteplirsen treatment, just as a small amount of dystrophin might be clinically meaningful for boys subject to the otherwise progressive loss of function of DMD. This is the kind of contextual discussion to which it appears ICER committed in November 2017 but did not reflect in the draft report.

Finally, although it is obvious from the points above that the Draft Evidence Report needs to be substantially rewritten, there is the issue of presenting results as Quality Adjusted Life Years. Perhaps the most pernicious nature of the cost effectiveness report of May 22 is presenting results only for QALY which discount and diminish the value of DMD patient lives. Put another way, the report does not emphasize the fact, as shown in Table 4.16 that if eteplirsen provides 37 QALYs, it meets the \$500,000 threshold.

Because 37 is a number based on a number of other assumptions, the report is not transparent. What if the cost of eteplirsen is only a transition to a perfect cure, ie the cost of eteplirsen is for ten years and then gene therapy provides a complete cure. Such a scenario is not evaluated, or even discussed. There is an opportunity cost to dying for DMD patients, because they may not survive until a complete cure is available, but eteplirsen provides that opportunity to 13% of DMD patients and golodirsen provides that opportunity for life extension and next generation therapies to another 9%.

As indicated, the workpapers are not presented directly with Table 4.17, but it is not clear from the results that the calculations are internally consistent. Why does a 10 year shift produce only 5.15 additional life years, which are then discounted to 3.55 QALYs, producing a cost of \$5,160,000. If a ten year shift in additional years of life, gives ten years, then the cost per year of life is \$1.8 million. If there is a 20 year shift, the cost per year of life is a little over \$1 million, and if there is a 40 year shift, at a cost of \$26.5 million, the cost

goes down to \$\$660,000 very close to the arbitrary \$500,000 threshold suggest as an upper limit by ICER.

Quite simply, the cost effectiveness evaluation is superficial and cannot be reasonably used to evaluate the costs, effectiveness and benefits of exon-skipping. The Draft Evidence report need to be substantially rewritten before presentation to any Commission which will not have the time or insight to understand it at a more than shallow level. ICER should fulfill its Nov 2017 commitment to adapt its analyses of cost effectiveness for rare diseases like DMD by providing more context, more recognition of the challenges of rare diseases and potential therapies, and more acknowledgement of the uncertainty of its conclusions about efficacy and cost effectiveness, given the serious unmet medical need of DMD.

In sum, it is clear that the process of evaluating clinical effectiveness and cost benefit of innovative treatments for rare diseases continues to progress. ICER should ensure that it does not impede progress in developing new approaches to treating disease, including rare and orphan diseases, by focusing on simplistic cost effectiveness criteria and reports which do not provide adequate context about challenges of new treatments and uncertainty in the results of literature reviews, rather than patient and expert testimony and experience.

ICER appeared to recognize these issues in 2017, but has not fulfilled its commitment to such transparent, context-supported, and adapted analysis in the May 22 report. It is to be hoped that a revised report before CEPAC discussion would be more reflective of the developing state of rare disease evaluation practices.

Finally, and as an example of the overall problem with the quality of the draft evidence report, I note that the discussion of Cost Coverage is incomplete. Section 2.1 ignores, or simply did not do enough research to find, the Feb. 22, 2017 State of California Department of Health Care Services Notice Letter 02-2017, Subject: Eteplirsen (Exondyst 51 tm) That Feb 2017 letter states that Effective the date of this letter, Eteplirsen is a CCS Program Benefit when the following criteria are met: Lists 5 lettered criteria including identification with exon 51 amenble dystrophy gene mutation. Signed Patricia McClelland, Chief, Systems of Care Division. This California coverage is less restrictive than Husky Health. California Dept of Health Services coverage is not mentioned in Section 2.1 or shown in Table 2.1

Please let me know if you have any questions about these comments, or require further aid to access the newer sources referenced.

Kermit R Kubitz mesondk@yahoo.com



June 18, 2019

Catherine Koola, Program Manager Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

On behalf of Parent Project Muscular Dystrophy (PPMD) and the Duchenne community, we appreciate the opportunity to again offer feedback on *ICER Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value*. As we have stated previously, we believe that it is imperative that the framework ICER constructs for the valuation of these – and emerging – Duchenne products be specific to Duchenne and reflective of Duchenne expert input. While the report does reflect some of these inputs, there remain additional areas of clarification needed in order for the foundational understanding of Duchenne and the framework upon which the modeling is built to reflect the Duchenne community's experience and the input provided to date. We remain concerned that the report fails to reflect that – within the Duchenne community - slowing or halting of disease progression through treatment intervention is significant¹. The impact of such - on the lives of both patients and caregivers - should be reflected in the modeling.

PPMD's concerns are focused specifically on the following areas:

Concern about the ICER Assessment Timing for Products Approved via the Accelerated Approval Pathway

The FDA Accelerated Approval Program was established in 1992 to allow for products that meet regulatory rigor based on efficacy of a surrogate endpoint that is reasonably likely to have clinical benefit for select patient communities in which there is significant unmet need. By definition, limited clinical data for products approved through accelerated approval will exist at the time of approval and in early stages of the phase IV environment. In these circumstances, this lack of clinical data is not a reflection of the robustness of the therapy, but rather the regulatory review pathway agreed upon by the product developer and the Food and Drug Administration.

PPMD has articulated our concern about the timing of ICER's assessment for products approved utilizing this pathway in several occasions: a) In November of 2015 and

¹ Peay HL, Hollin I, Fischer R, Bridges JF; A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. Clin Ther. 2014 May; <u>https://www.ncbi.nlm.nih.gov/pubmed/24852596</u>





including our formal engagements as a member of the working group at the ICER Orphan Drug Assessment & Pricing Summit; b) in our 2 public comments regarding *"Modifications to the ICER value assessment framework for treatments for ultra-rare diseases" (November 2017)* and; c) our series of engagements surrounding the current Duchenne-product specific ICER assessment now underway.

We remain concerned about the lack of available clinical data that may potentially impact the ability to perform an appropriate value assessment. Eteplirsen was approved utilizing the Accelerated Approval pathway on the surrogate outcome measure of dystrophin, and Golodirsen is utilizing the accelerated approval pathway, and is not yet approved. Thus, the valuation of these products is compromised as the ICER Evidence Rating Matrix is dependent upon the availability of clinical data including data on long term outcomes and the level of certainty in the evidence. In the case of these products, this lack of data may not necessarily be a reflection of the robustness of the therapy, but rather the regulatory review pathway agreed upon by the sponsor and the FDA.

Concerns regarding the ICER economic model structure, assumptions, and input parameters

Concerns about the Model Structure

The selection of the partitioned survival model structure to model DMD is inappropriate, since this framework typically models a cohort of patient through time as they move between a set of exhaustive and mutually exclusive health states. This modeling framework is not reflective of the natural progression of the Duchenne disease state, since in DMD the health states are not mutually exclusive from one another. In fact, the patients experience each health state in a consecutive linear manner, where the current health state is dependent on the previous state.

Concerns about the Model Assumptions

Concerns about the Duchenne disease states assumptions

- It is critical that Duchenne disease progression be understood to be more nuanced than the overly-simplistic assumption of three disease stages of "ambulatory", "non-ambulatory", and "death" in the current draft report.
- Both the Duchenne Regulatory Science Consortia (D-RSC) of the Critical Path Institute <u>https://c-path.org/programs/d-rsc/</u> has established a disease progression model that includes 6 stages of Duchenne progression (this model is incorporated into the Project HERCULES HE model):
 - Ambulatory: Early ambulatory, late ambulatory; Intermediate;
 - Non-Ambulatory: Early Non-ambulatory (Brooke 1), Late non-ambulatory I (Brooke 2-4), Late non-ambulatory (Brooke 5)





Concerns about the Key Model Assumptions Outlined in Table 4.1

Assumption: Treatment effects were modeled as rightward shifts of the survival curves for losing ambulation and death and/or if there was evidence of having different rates of SAEs.

Comment:

It is possible that a SAE may not influence the right ward/left ward shift of the survival curve in instances where the AE experienced does not impact ambulation. A common example would include behavioral side effects.

Assumption: Patients on prednisone transitioned between "ambulatory," "nonambulatory," and "death" health states following the survival curves originally projected in a prior analysis, which was based on international clinical trial data and historical data for patients diagnosed with DMD and receiving steroids. <u>Comment:</u> This is an over-simplification of the real world experience of Duchenne patients and does not reflect current community consensus around the Duchenne disease progression model as being led by coalitions such as the Critical Path Institute's Duchenne Regulatory Science Consortium (D-RSC) and Project HERCULES.

Assumption: Hence, the relative proportion of ambulatory patients in early and late ambulation and in early and late non-ambulation after losing ambulation is assumed to be the same in all treatments.

<u>Comment:</u> Assuming that the proportion of early/late ambulatory and early/late nonambulatory patients is the same across treatment may be an oversimplification. This is the case because even with steroids (i.e., prednisone and deflazacort), the proportion of patients who can tolerate these 2 drugs are very different. By tolerance alone, if let's say a lot of patients discontinue prednisone by a higher number at the early ambulatory state than those who are on deflazacort, this could potentially impact the proportion of patients in early/late ambulation who are going to be in prednisone or deflazacort.

Assumption: The proportion of supportive care costs from a societal perspective made up by supportive care costs from a health care sector perspective was the same in the ambulatory and non-ambulatory health states.

<u>Comment:</u> While evidence development around caregiver spillover in Duchenne is in nascent stages, the impact of progression in relationship to the need for increasing supportive care needs has been well established. To date several Burden of Disease studies have been conducted in Duchenne yielding similar overall economic analyses. In

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the study by Landfeldt et al.², an international data set from the Treat NMD Registry utilized data from Germany, Italy, the United Kingdom, and the United States. Mean perpatient annual direct cost of illness was 7 to 16 times higher than the mean per capita health expenditure in these countries. In addition to direct costs, Duchenne was also associated with large productivity losses, for both patients and caregivers. This study further stratified costs across the progression of the disease and found that households caring for a boy with Duchenne carry a large economic burden that increases markedly with disease progression. It should be noted that outcomes for only one primary caregiver were included in these calculations and thus these estimates will be underestimates for the majority of families in which additional family members (second parent, grandparent, sibling, etc) contribute to the informal care of the individual with Duchenne. For this reason, the existing Burden of Disease study results should be considered conservative. In addition - in 2018 PPMD conducted an externally-led Patient Focused Drug Development meeting in collaboration with the FDA and other federal agency partners. Throughout the meeting panels stratified by disease stage testified and live polling was conducted, including questions intended to assess resource gaps, disease burden, and economic impact of Duchenne. The full data set from the Compass meeting polling, as well as the Compass meeting white paper, a downloadable pdf of this report, and the recording of the live stream from the meeting are available at: https://www.parentprojectmd.org/advocacy/our-strategy-and-impact/regulatoryadvocacy/

Assumption: *Patients are diagnosed and begin treatment at five years of age.* <u>Comment:</u> Emflaza is commercially available to patients ages 24 months and older.

Assumption: SAEs (weight gain, cushingoid, fractures, cataracts) related to prednisone and deflazacort resulted in a disutility of 0.05.

<u>Comment:</u> We believe that additional side effects that have been demonstrated to have significant impact on patients' drug tolerance, health, and quality of life should also be considered. Side effects that should be considered include:

- Neurodevelopmental considerations certain genetic variants associated with DMD are now known to result in atypical dystrophin expression in the brain
- Fracture-induced Fatty Embolism Syndrome
- Diminished or halted linear growth, and impacts on self-image

² The burden of Duchenne muscular dystrophy An international, cross-sectional study Erik Landfeldt, Peter Lindgren, Christopher F. Bell, Claude Schmitt, Michela Guglieri, Volker Straub, Hanns Lochmüller, Katharine Bushby First published July 2, 2014, DOI: https://doi.org/10.1212/WNL.00000000000669



Lack of assumption and modeling of the impact of adverse effects (AEs) of long term corticosteroid use:

• Since patients with DMD are typically on corticosteroids on a long term basis and gain weight and lose muscle mass at the same time, this will potentially impact ambulation and functional activities of daily living We suggest ICER incorporate the modeling of the impact of major weight gain from steroid use as an AE.

Assumption: In establishing the survival curve, the model assumed that treatments may extend time to loss of ambulation, but they did not change the proportion of time spent in "early" versus "late" ambulation, and similarly affected the non-ambulatory state. <u>Comment:</u> If treatment is assumed to extend time to loss ambulation, then the proportion of patients in early ambulation would be higher than the proportion of patients in late ambulation compared to the group that do not have treatment. Thus, this assumption over simplifies the DMD disease complexity and potential drug effect.

Concerns about the Transition Probabilities and Input Parameters

Most of the transition probabilities and key model inputs have been extracted from an ongoing project, a scientific poster, and a single study. PPMD is concerned that the use of the transition probabilities, and key costs and utility estimates from limited sources impacts the credibility of the model results.

In Conclusion

We thank ICER for the opportunity to participate in this review. We believe that the above expressed concerns may raise questions about the credibility of the cost-effectiveness model results among all stakeholders. It is our hope that our comments will be taken into consideration and that ICER's framework serves to further inform and enhance – rather than hinder – our Duchenne therapy development landscape. Please contact Annie Kennedy, SVP – Legislation & Policy at <u>annie@parentprojectmd.org</u> for any additional information.

Sincerely,

Founding President & CEO, Parent Project Muscular Dystrophy



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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 farfetched 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 nonambulatory 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 selfcare 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**

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

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,

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Tony Coelho Chairman, Partnership to Improve Patient Care



June 18, 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 "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: 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 May 22nd draft report, "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy." Our comments about the draft report are organized below into sections concerning: Patient and Family Perspectives and Issues; Assumptions of Future Effectiveness; ICER's Framework for Ultra-Rare Diseases; and Additional Points.

Patient and Family Perspectives and Issues

Duchenne Muscular Dystrophy (DMD) is clearly a devastating progressive disease as described in the draft report. And families and patients need new treatments since "Untreated children with DMD usually progress to a loss of ambulation by age 10-12 years.... Children may also have developmental delay and behavioral issues, as well as impaired growth, delayed puberty, and gastrointestinal complications (e.g., dysphagia and gastroparesis) from the loss of muscle contraction. Orthopedic complications such as contractures and scoliosis occur in most patients, typically after loss of ambulation. Bone health is a major long-term problem, as osteoporosis frequently occurs in later-stages of the disease, with a high risk of fractures. Fatal respiratory or cardiac complications commonly develop in the second or third decade of life, with many deaths occurring in the setting of an acute infection such as pneumonia or after surgery. However, treatment with corticosteroids and advanced supportive care such as assisted ventilation (noninvasive and invasive), spinal surgery, and prevention and management of cardiomyopathyrelated heart failure have led to delays in disease progression and improved survival of patients with DMD such that some patients are now surviving into their 30s or 40s."¹

¹ "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. 1.

Because DMD affects children into young adulthood, it also has major implications for their parents and family members, so it is troubling that there are not good quality of life measures for caregiver impacts, i.e., "there is not currently a standard instrument that is used across studies and that DMD patients and their caregivers have a complex quality of life profile that may not be fully captured by current standard tools."²

The draft report notes those and other challenges in monitoring disease progression and evaluating the effectiveness of treatments because of the variability of the clinical parameters used to determine disease progression. For example, ambulation is effort-based and scoring can be subjective, and "Caregivers and patient groups expressed that, in terms of impact on quality of life and caregiving, the time a patient requires to complete the 6MWT may not be as important as whether the patient can complete the test at all."³ We also appreciate the draft report's discussion about the potential for using videos for monitoring ambulation, which should provide greater real-world assessments of function and improve the current analytical fuzziness, e.g., "...there appears to be a gap between currently reported trial outcomes and video evidence shared by patients, particularly for eteplirsen. Videos of patients on eteplirsen appear to show clinical improvement in function that was not reflected in the clinical trial outcomes. The reasons for this discrepancy are unclear, but possibilities include flaws in study design and execution, flaws in data collection during the trial, non-systematic collection, and scoring of video data, the fact that a subset of patients may benefit substantially from the drug while others do not benefit at all, or choice of clinical outcomes during trials that are not sensitive enough to detect subtle changes in clinical status."⁴ We are hopeful that such tests will become better standardized and validated for DMD (and potentially other neuromuscular conditions), and could be an opportunity for the use of artificial intelligence for analyzing such videos to quantify various aspects of ambulation, activities of daily living, and quality of life – particularly in real-world situations and through longer-term observations.

We are also struck by how the challenges in determining disease progression (and treatment effectiveness) contrast so markedly with the scientific underpinnings of the exon-skipping treatments. Not only are exon-skipping treatments a very cutting edge and fascinating scientific intervention – modifying RNA's translation into an amino acid sequence that is different than what the underlying DNA codes for⁵ – but it also produces a very specific and measurable biologic response, i.e., a change in the presence of the dystrophin protein. We realize that eteplirsen currently only produces very low levels of dystrophin,⁶ and that long-term clinical improvements have not yet been definitively demonstrated from an increased presence of those two measurements: ambulation (and other measures of disease progression) and levels of dystrophin.

² "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. 2.

³ Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. 38.

⁴ Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. 38.

⁵ Lim et al., "Eteplirsen in the treatment of Duchenne muscular dystrophy," Drug Design, Development and Therapy, February 28, 2017, pp. 533–45.

⁶ "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. 34.

We raise that comparison because it illustrates a serious and fundamental flaw in ICER's draft report arising from the very limited and imprecise measurements and data of disease progression and treatment effectiveness for DMD. That is, because of the rarity of DMD and the imprecision of the measures of clinical effectiveness of existing treatments, ICER's analysis in this draft report is by necessity overwhelmed by uncertainty and assumptions. Basically, plugging numbers based upon very little data and extensive assumptions into a model means that the results are only as valid as the uncertainty of the underlying data, which in this case are very, very uncertain. And the inconsistency between the lack of robustness of the available data and ICER's assurance of its own conclusions are exemplified by two statements from the draft report:

- "...there is a lack of long-term data for exon-skipping therapies and thus the potential long-term benefits and harms of these drugs is unknown..."⁷
- "However, as demonstrated by our extensive scenario/sensitivity analyses, our conclusions were extremely robust at the current treatment prices."⁸

The challenge for ICER – and others looking to evaluate disease progression and treatment effectiveness of DMD at the population level (as opposed to for individual patients and their families engaged in shared decision making with their care team) – is to synthesize the available data within the context of its limitations. The draft report distinctly oversteps that threshold. As James Collins, the author of "Good to Great" said, "The signature of mediocrity is chronic inconsistency." This is true for ICER's dogmatic framework process overall, and how in the draft report ICER attempts to quantify results based on models and algorithms despite the immense imprecision of the underlying data.

Assumptions of Future Effectiveness:

We appreciate that the limited expression of the dystrophin protein from eteplirsen represents a quandary for analysis since it is a below normal level of a not fully functional protein. And, in the same vein we appreciate the "Future Therapies" section of the draft report providing a brief overview of potential treatment approaches being investigated. That brief discussion is very important in the context of this draft report since it illuminates the challenges of modeling into the distant future, (i.e., beyond 5 years), since patients, their families and clinicians are all hoping that better treatments will be coming out of that research pipeline. We believe this is a very important contextual consideration since the clinical situation with DMD is similar to the early days for developing new and better treatments for other complex diseases where initial improvements were small, but they provide insights that are then built upon – sometimes with combination treatments acting in unison or synergistically. That has been the historical nature of finding better treatments for common and rare conditions. In addition to the interventions described in the Future Therapies section of the draft report, we could speculate that in the future, the addition of an adjuvant agent – perhaps an already approved small molecule drug – could increase the amount and effectiveness of the dystrophin protein and thus dramatically increase the clinical effectiveness of the exon-skipping treatments without significantly increasing costs. We don't know if that will happen, and neither does ICER – and that's the point.

⁷ Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. 62.

⁸ Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. 62.

Declaring the initial efforts as low value is like concluding that the Wright brother's first airplane was not worthy of pursuit because it would only fly hundreds of feet – and was not capable of supersonic speed. Failure to recognize the step-wise progress of science and technology will result in stagnation and lack of improvement for clinical care, which would be detrimental to patients and society.

ICER's Framework for Ultra-Rare Diseases:

Concerning ICER continuing to ask companies about input development costs for specific treatments (which is part of its dogmatic ultra-rare framework modification), we would appreciate ICER responding to these questions:

- How do development costs affect the clinical value of a treatment to a patient, payer, or society?
- How do development costs affect the economic value of a treatment to a patient, payer, or society?
- Where in ICER's economic modeling would input/development costs be inserted as part of the calculation of the economic value of "long-term value for money"?
- How would ICER propose that any research and development costs for a second generation treatment such as a second exon-skipping treatment be allocated if such an analysis would be conducted? That is, should the knowledge and the costs of acquiring that knowledge through research and analysis be attributed to the first such treatment, or should it be divided between the first and any subsequent treatments that were based upon that knowledge base? And if the costs should be divided, in what ratio, and what would be the process for retrospectively adjusting the modeling "input costs" for the first treatment <u>after</u> a second treatment is created using some of the same basic knowledge?

Since we continue to be baffled by why ICER thinks that R&D or input costs are a valid facet for exploration in determining economic value – or acceptable price – of treatments, we look forward to ICER's responses to those questions.

Additional Points:

- The Draft Report provides a link to the list of stakeholders from whom ICER requested input,⁹ but not those from whom it actually received input. That list should be provided.
- The draft report indicates ICER requested information about "potential cost-saving measures" that could "create headroom in health care budgets."¹⁰ However, we challenge ICER's use of the term "headroom" since it implies a fixed ceiling of health care spending. We recognize that other countries have more pre-determined national budgets for government run health care programs, but the only examples of that in the United States are in the Departments of Veterans Affairs and Defense, which comprise less than 5% of U.S. health care spending.¹¹ Since words do have meaning, and the imagery of the word "headroom" in association with "health care budgets" is misleading, we urge ICER to recognize this reality and change its rhetoric accordingly.
- In previous reports ICER has stated it could not find coverage policies for experimental

⁹ "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. iv.

¹⁰ "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. 14.

¹¹ CMS, 2017 National Health Expenditures.

agents not yet approved by the FDA. We are glad that ICER has finally recognized the inherent futility of such research and has stated that "At the time this report was published, the FDA had yet to issue a decision on golodirsen, precluding a survey of its coverage policies."¹² Similarly, the description of the coverage policies in the draft report (pages 15-17) illustrates the complex multi-payer reality of the U.S. health care financing and reimbursement system. We would hope that ICER will expand its inclusion of this reality into its overall work by not implying that there are national payment policies or an overall fixed budget for all health care services or for any subtype of treatment options such as FDA approved biopharmaceuticals.

Conclusions & Recommendations

Patients Rising Now believes that ICER's Draft Report on DMD attempts to reflect patients' and caregivers' perspectives, but because of the lack of available data and insights about those perspectives, the draft report's analysis and conclusions are flawed because it attempts to assert precision via modeling when the underlying data is very imprecise. This inconsistency makes the draft report's conclusions misleading and inaccurate. Thus, we are forced to conclude that ICER's draft report on DMD ventures into the realm of fiction when its "analysis" is essentially a series of "What If" propositions, stuffed with assumptions about possible long-term clinical outcomes, and its process is gilded by an economically-driven aspirational world view.

We hope ICER recognizes the fundamental inconsistencies in the draft report's analyses and conclusions during its public discussion, explores it more fully and forthrightly in its final report, and somehow can bring itself to incorporate the realities of data uncertainty – and the pluralistic nature of the U.S. health care financing system – into any future updates to its framework process.

Sincerely,

Tenny M. Wilcon

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

¹² "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy" Draft Report, May 22, 2019, p. 15.

The Project HERCULES economic./; methodology team have serious concerns regarding the approach taken in this review and believe that the results from the cost effectiveness modelling will be wholly inaccurate and should not be used to inform decision making in DMD therapies.

In summary: The partition survival model approach is inappropriate for use in a disease such as DMD, particularly with respect to the morbidity and QOL changes within the proposed states and mortality occurring from any state; the states in the model are inadequate; there is over reliance on single evidence sources; the use of the transition probabilities is unverified; use of the 6MWT is not linked to meaningful outcomes; utility measurements are from one source, using the HUI, demonstrated to be ineffective in DMD, and these utilities from early and late stages of ambulation and non-ambulation respectively are inappropriately combined.

The model states are overly simplistic and completely inadequate to represent or capture the patient pathway. Whist we recognize the paucity of appropriate available data, the assumptions made are simply inappropriate. DMD is not a binary condition defined by ambulation and loss of ambulation. DMD is associated with a progressive loss of function including loss of ambulation, but also loss of ability to weight-bear, loss of upper body capability, scoliosis and contractures, loss of hand to mouth function, loss of cardiac function due to cardiomyopathy, and loss of respiratory function. Mortality can occur at any stage of the disease. Quality of life and costs are affected by every aspect of the functional losses.

The health states in ICERs model suggest no clinical, HRQL or cost benefit associated with treatments which delay step-changes within ambulatory and non-ambulatory stages: delaying loss of the ability to stand from supine, the loss of the ability to self-transfer, to self-feed, to breathe unaided. Our work to date, suggests that such benefits are highly likely to impact patient survival, quality of life, resource use and cost. Therefore, we consider this omission to be the most serious limitation of the proposed model.

In conclusion we do not consider the proposed approach to be valid, and therefore believe this will render no meaningful results on which to base a decision with such a large potential impact on both health systems and patients, and strongly do not endorse or advocate pursuing said approach.

Project HERCULES Economic Team

Professor Keith Abrams (University of Leicester), Professor Ron Akehurst (ScHARR, University of Sheffield), Fleur Chandler (Duchenne UK), Emily Crossley (Duchenne UK), Professor Jalpa Doshi (University of Pennsylvania), Josie Godfrey (JGZebra Consulting), Micki Hill (University of Leicester), Juliet Mumby-Croft (SOURCE HEOR), Phillip Powell (ScHARR, University of Sheffield)

1.1. Inappropriate Model structure

A partitioned survival model (PartSA) is proposed, which is a departure from the methods used in previously published economic evaluations. A systematic literature review (SLR) of cost-effectiveness analyses was undertaken for Project HERCULES in January 2019. Two publications were identified, which reported four economic models (1, 2); all used a Markov approach.

The PartSA uses time-to-event data to evaluate the proportion of patients in a number of finite health states over time. Trial data are typically extrapolated beyond the time horizon of the study using survival analysis. Exponential, Weibull, Gompertz, log-logistic or log normal parametric models can be used as well as more complex and flexible models.

The PartSA approach is more commonly used to evaluate the cost-effectiveness of oncology therapies, defined by a limited number of health states. However, Kaplan Meier data are not frequently reported in clinical trials of DMD therapies due to their short term nature and primary end-points.

The PartSA approach assumes that the survival functions modelled are independent. The limitations of this have previously been described by the NICE decision support unit (DSU) (3). Assuming survival functions are independent is problematic, as intermediate events in the proposed model are prognostic of later events. As patients transition to the non-ambulatory state, the mortality risk increases. A therapy that delays progression to the non-ambulatory state might reasonably be expected to increase survival. This is not captured within the PartSA framework. Figure 1 in the Model Analysis Plan is therefore not an accurate representation of model transitions; the risk of death will not be modelled separately for patients in the ambulatory and non-ambulatory states.

The approach uses 'direct rightwards shifts in the non-ambulation survival curve ...with or without equivalent shifts in the mortality curve based on years gained during ambulation...' This assumes that loss of ambulation is the <u>only</u> prognostic factor for mortality, which is incorrect.

The use of the PartSA approach is not suitable to answer the decision problem. A Markov approach, which explicitly models transitions between health states is recommended. It is not clarified if this is the chosen approach as it appears the model is based on digitising plots from Hill (4), which gives transition probabilities from a multi-state model, not a partitioned survival model.

1.2. Inadequate and unrepresentative model health states

The current health states comprise ambulatory, non-ambulatory and death. These health states are considered inadequate and an oversimplification of the natural history of DMD, and the sequelae of DMD which impact resource use and HRQL utilities. DMD is not a binary condition defined by ambulation and it's loss. DMD is associated with a progressive loss of function including loss of ambulation, but also loss of upper and lower body mobility, scoliosis and contractures, loss of hand to mouth function, loss of respiratory function, and cardiomyopathy leading to loss of cardiac function. There are major quality of life impacts and costs associated with every aspect of the disease, and a significant impact on families and society.

In the SR of previous cost-effectiveness analyses, the number of health states ranged from 4 to 25; health states most commonly included early ambulatory, late ambulatory, early non-ambulatory, late non-ambulatory and death. Ventilation status was also considered to be an important factor in determining health states. Although not proposed as health states in a multi-state model, McDonald et al (5) describes nine milestone groups based on lower and upper body function that could be a potential basis for a multi-state model.

The model structure makes it impossible to capture changing progression through states and its implications and "averaging" times in early and late stages in each state denies the possibility of exploring better scenarios.

By adopting a binary approach centred on ambulation only, information about other aspects of relative improvement is not considered; there is no attempt intended to explore the evidence of intermediate outcomes acting as surrogates for later ones. This is deserving of exploration, if only to indicate the uncertainty in any projections made, particularly given the assumption that the survival curve retains its shape after loss of ambulation irrespective of what happened before loss of ambulation.

The current health states suggest no clinical, HRQL or cost benefit associated with treatments which delay step-changes within ambulatory and non-ambulatory stages: delaying loss of the ability to stand from supine, the loss of the ability to self-transfer, to self-feed, to breathe unaided. Our work to date, suggests that such benefits are highly likely to impact patient survival, quality of life, resource use and cost. Therefore, we consider this omission to be the most serious limitation of the proposed model.

1.3. Incorrect interpretation of data

Unverified transition probabilities

The Model Analysis Plan states that survival curves for time to non-ambulation and time to death for patients on steroids will be obtained from a recent research project (6). Note that in Hill et al (4) only Kaplan-Meier (KM) curves for loss of ambulation were digitised. The other transitions were informed by Landfeldt et al (2). How transition probabilities are obtained from the project is unclear in the text. It suggests that the analysis performed in Hill et al (4) will be repeated by ICER, which is contradictory to the caption in Figure 2, and the KM curves from the poster appear to have been used directly. The authors made it clear the analysis was proposing a methodology, using only a limited sample of data, and noted in their analysis there were overly optimistic predictions with some steroid patients remaining ambulant at implausible ages. This was due to poor replication of the KM curves with overestimation in the tails of the curves. If space had allowed, this considerable limitation would have been discussed further and it would have also been made clearer that the chosen multi-state model was not advocated *per se*, but used as an example of the methods adopted, the poster intention was to demonstrate the difficulties in modeling rare disease with limited data. These limitations are informing the ongoing work in Project HERCULES. For the methodology to be used to inform an economic model, the methodology should be repeated with substantially more data, that is then verified with patients and clinicians. We recommend a systematic literature review be undertaken in order to obtain KM curves for the relevant transitions. The three-state approach is too simplistic for such a multi-faceted disease.

We recognize the limitations of appropriate available data and the need to make strong assumptions. However, for an analysis with such a large potential impact on both health systems and patients we would expect methods to be both rigorous and for quality control procedures to be in place. By collapsing the disease states, the methodology also gives no possibility to determine the value of information, which would be highly informative in a disease area with limited evidence to HTA agencies, clinicians and patients.

Failure to address insufficient clinical data

The Modelling Analysis Plan suggests that there are inadequate data with which to perform a network metaanalysis of trials and observational data. It is noted that the team is exploring the possibility of conducting a meta-analysis of trials and observational data to estimate the relative efficacy and safety of deflazacort and prednisone. It is unclear from the methods whether naïve comparisons are proposed. We refer the development team to the NICE Decision Support Unit, Technical Support Document 18: Methods for population-adjusted indirect comparisons, and the use of matching-adjusted indirect comparisons (MAIC) and simulated treatment comparison (STC) to control for imbalances in "baseline characteristics" in the trial evidence (7). It is, however, noted that these methods require access to individual patient data in a subset of trials.

Treatment effects on time to non-ambulation will be modeled using direct rightward shifts (i.e., parallel shifts) in the non-ambulation survival curve with and without equivalent shifts in the mortality curve based on years gained during ambulation found from the literature. Further clarification is required regarding this method. We also note, that loss of ambulation is not the <u>only</u> factor affecting mortality.

Further clarification is also recommended on the proposed methods for linking changes in the six-minute walk test and time to the non-ambulatory state. The use of this single metric is also highlighted as a weakness of the proposed methods, capturing only one dimension of the natural history of DMD and of potential treatment effects and was discussed at length in the NICE HTA review of ataluren (1)

It is noted that where there is an absence of clinical data for a comparator, threshold analysis will be used to estimate the minimum treatment effect for the treatment to be considered cost-effective. This is not considered a suitably robust approach to determine the likely cost-effectiveness of treatments and which may impact patients access to these therapies for the following reasons.

Firstly, it appears that the threshold analysis will be performed based on a delay in loss of ambulation. This is not usually an outcome in clinical trials (typically outcomes relate to 6MWD or timed functional tests), and therefore whether a therapy is likely to attain this threshold cannot be directly confirmed or refuted based on clinical trial data. Secondly, assuming a parallel shift in the time to loss of ambulation and time to death curves is overly simplistic. Thirdly, the estimation of cost-effectiveness based on a single outcome (loss of ambulation) is considered to inadequately capture the potential benefits of treatment. Finally, the oversimplification of DMD within the proposed model and the assumptions required in the absence of data, result in a framework that is insufficiently robust to draw conclusions on the potential cost-effectiveness of treatments.

Inadequate Utility Measures

There is justified concern that existing generic preference-based quality of life instruments, such as the EQ-5D, are insufficient to assess quality of life (QoL) in the Duchenne population, based on the aspects of QoL that matter to people living with Duchenne (8). Any resulting utility values relying on these measures are thus subject to error. In their model, ICER rely on patient utilities derived from a single 2014 study (9) which used the Health Utilities Index (HUI) for patient quality of life data (and the EQ-5D for caregiver data). A recent systematic review of QoL instruments used in Duchenne and a quality assessment of those instruments using up-to-date COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines (10) was conducted by experts at the School of Health and Related Research, University of Sheffield, UK. (11) The researchers reported that the HUI performed unsatisfactorily on all domains of content validity, and had an indeterminate structural validity, with a very low quality of evidence supporting its use in the Duchenne population.

Health state utilities appear to be based on a weighted average for the ambulatory and non-ambulatory states based on the proportion of patients in the US that are in the 'early' and 'late' ambulatory and non-ambulatory 'sub-states' respectively. This highlights that HRQL varies between patients in the 'early and late' ambulatory and non-ambulatory states respectively and the inadequacy of the currently proposed binary states of ambulatory and not ambulatory.

Health-state specific costs have been derived from a previous cross-sectional cost study that included US costs. In a similar approach to the estimation of health state utilities, costs were derived in early and late ambulatory and non-ambulatory health states and then weighted. This further highlights the resource and cost differences between the sub-states, and the inadequacy of the currently proposed binary states of ambulatory and not ambulatory.

Incorrect Assumptions for 'Modified' Societal Perspective

In the currently proposed plan, it is assumed that the relative proportion of 'modified' societal perspective and healthcare sector perspective costs are the same in the ambulatory and non-ambulatory health states. However, broader societal costs may be expected to increase in the non-ambulatory state as the requirement for home and school adaptations, wheelchair and equipment provision, physiotherapy and occupational therapy, educational provision, social care support and non-family care givers increases.

Conclusion

In conclusion we do not consider the proposed approach to be valid, and not representative of the disease progression. Therefore we believe this will render no meaningful results on which to base a decision with such a large potential impact on both health systems and patients, and strongly do not endorse or advocate pursuing said approach.

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ⁱ About Project HERCULES

Project HERCULES is an international multi-stakeholder collaborative project set up by Duchenne UK to develop tools and evidence to support Health Technology Assessments (HTA) and reimbursement decisions

for new treatments for DMD. It brings together world leading economists, clinicians, academics, HTA agencies and patient organisations, supported by nine pharmaceutical companies to develop and build a better evidence base for DMD to aid the pricing and reimbursement stage of drug development.

The outputs of Project HERCULES will include a natural history model (NHM) using real-world data, a novel health-related quality of life (HRQL) instrument, and a burden of illness study providing estimates of resource use, cost and utilities. These activities lead to the final deliverable of a flexible, core economic model to evaluate the cost-effectiveness of new therapeutic interventions in DMD, which will be completed in 2019.

The Project HERCULES team began work in 2017, in this time gaining access to real-world data sets through collaborations and gaining input from clinical experts, patients and parents of boys affected by DMD. The team therefore have an in-depth understanding of the available data, natural history and essential components of the economic argument for interventions in DMD.



June 18, 2019

BY ELECTRONIC DELIVERY

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

Re: Comments on ICER's Draft Evidence Report on "Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value"

Dear Dr. Pearson:

PTC Therapeutics appreciates the opportunity to provide comments on the Institute for Clinical and Economic Review's (ICER) draft evidence report for *"Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value"* ("Draft Evidence Report"). Our comments focus primarily on ICER's review of deflazacort (Emflaza[®]), as well as issues we have identified in the methodology used for the review. While we share ICER's interest in bolstering access to high-value care for patients with Duchenne muscular dystrophy (DMD), we are concerned about ICER continuing to conduct this review based on the methodological gaps and issues raised in these comments.

As ICER is aware, the United States (U.S.) Food and Drug Administration (FDA) approved the first treatment for DMD only three years ago, in 2016. As of 2019, only two drugs are FDA-approved for DMD treatment, but therapeutic pipelines across the country hold great promise for revolutionizing treatment in this area. ICER should proceed with extreme caution in taking action that may impact any future advances in treatments for patients with this ultra-rare, progressive degenerative disease where patients need access to all available treatment options.

I. Introduction to PTC Therapeutics

PTC Therapeutics is a biopharmaceutical with U.S. headquarters in South Plainfield, New Jersey. The company was founded over twenty years ago, with a mission to create a patient-centric approach to treating rare diseases. In addition to our efforts on deflazacort, the company is currently conducting clinical trials on several other rare diseases. PTC continues to fuel innovation by re-investing in research to develop new treatments for rare diseases leveraging our platform technologies in gene therapy, alternative splicing, nucleotide repeat, protein modification, transcript regulators, and nonsense readthrough.



II. Draft Evidence Report Considerations for Deflazacort

PTC Therapeutics is the manufacturer of deflazacort, which is FDA-approved for the treatment of DMD in patients two years of age and older.ⁱ Notably, the FDA approved an expansion in deflazacort's label for treatment of children ages five and older to children ages two and older on June 7, 2019 (*i.e.*, since the release of the Draft Evidence Report).ⁱⁱ

As ICER indicates in its summary of the American Academy of Neurology (AAN) treatment guidelines, "[d]eflazacort has . . . been shown to improve strength and timed motor function tests, and delays loss of ambulation by up to 2.5 years."ⁱⁱⁱ In addition to showing benefits for cardiac and respiratory outcomes, the guidelines also indicate there is observational evidence that deflazacort may extend survival after 5 to 15 years of follow up.^{iv} Further, as set forth in the Duchenne Muscular Dystrophy Care Considerations, the benefits of glucocorticoid therapy are considered to be well-established in the treatment of DMD.^v These guidelines additionally acknowledge, as ICER reiterates, that deflazacort may lower risk of weight gain and behavioral problems as compared with prednisone. ^{vi}

We also appreciate ICER's recognition in the Draft Evidence Report that the use of prior authorization and/or demonstration of failure on prednisone before patients are able to access deflazacort "creates an additional barrier" for patients in obtaining the medication.^{vii} These utilization management techniques are particularly concerning based on the fact that prednisone is not approved by the FDA for the treatment of DMD. We encourage reiteration of these key points in the Final Evidence Report.

PTC Therapeutics is concerned, however, about the disconnect throughout the Draft Evidence Report between ICER's *evaluation* of evidence in support of deflazacort versus prednisone and its statements that instead claim there is a *lack* of such evidence. More specifically, ICER cites Griggs 2013 to argue that there is a lack of clear evidence to support any one glucocorticoid therapy regime over the other, ^{viii} but then appears to conflate variations in practice with a lack of comparative evidence of benefit for these drugs in other portions of the Draft Evidence Report. We recommend that ICER use clearer and more descriptive language in these instances in the Final Evidence Report.

III. Methodology Concerns

A. Quality of Life Data Gaps

As ICER acknowledges in the outset of the Draft Evidence Report, "DMD affects patients and caregiver quality of life in a variety of ways . . . [A] review of qualify of life studies suggests that there is not currently a standard instrument that is used across studies and that DMD patients and their caregivers have a complex quality of life profile that may not be fully captured by current generic tools."^{ix} This lack of basis for constructing a patient-centered model to



incorporate health care quality of life considerations raises serious concerns about the ability of ICER's assessment to measure the value of treatments in this disease state.

B. Lack of Patient-Centric Approach in Partitioned Survival Model

The Draft Evidence Report fails to represent the spectrum of diversity of DMD patients in its model. The rate of disease progression and severity varies greatly for each person with the disorder. For example, even siblings with the same gene mutation may experience vastly different symptom progression.^x ICER's *de novo* multi-state partitioned survival model, which divides health states into ambulatory, non-ambulatory, and death, is too simplistic to capture the nuances of DMD disease progression. It also treats these health states as mutually exclusive. As a result of this overly simplistic approach, inadequate weight is given to maintenance of upper limb strength and pulmonary function, with undue recognition of the quality of life impacts for patients related to critical functionalities, such as remaining free from pulmonary support, being able to operate a wheelchair joystick, retaining the ability to stand without assistance, or being able to transfer to a wheelchair without full-scale aid.

Project HERCULES and the Duchenne Regulatory Science Consortia of the Critical Path Institute, instead, divide DMD progression into a minimum of the six phases set forth below, with recognition that death can occur at any age:

- Ambulatory: Early ambulatory, late ambulatory
- Intermediate
- Non–ambulatory: Early Non-ambulatory (Brooke 1), late non-ambulatory (Brooke 2 4), late non-ambulatory (Brooke 5).

We are concerned that ICER's model fails to recognize the individualized nature of this progressive, multi-systemic condition and, ultimately, may result in access limitations to life-preserving medications.

C. Key Model Assumptions

In Table 4.1, Key Model Assumptions, ICER states:

[W]e combined the early and late [ambulatory/non-ambulatory] values based on the <u>relative proportion</u> of US patients in the early and late stages in the survey that contributed to the original estimates. <u>In doing so, we assumed that the relative proportion of ambulatory patients in early and late ambulation and in early and late non-ambulation after losing ambulation was the same in all treatments.^{xi}</u>

In the discussion of Health State Utilization, on page 47, ICER describes these proportions:

Hence, we combined the utilities for the early and late ambulatory state into a utility score for the ambulatory state in the model by weighting the utility scores based on



the proportions of patients seen in these two health states in the surveyed population, specifically 30.38% in early and 69.62% in late ambulatory states. The same was done for the non-ambulatory states using weights of 38.89% and 61.11% for early and late non-ambulatory states, respectively.^{xii}

There are two problems with this assumption. First, this assumes that, at the age of 5 (when patients enter the model), 69% of patients will have a health state equivalent to late ambulatory. This does not follow the disease course. We would recommend that ICER change this percentage weighting to be time dependent for the ambulatory state. We would make a similar recommendation for the non-ambulatory state.

Second, there is evidence from McDonald (2017^{xiii}) that deflazacort does have a benefit on delaying the progression of the intermediate endpoints associated with the differences from early ambulatory to late ambulatory and from early non-ambulatory to late non-ambulatory (see Table S2). Therefore, ICER's use of the same percentages across time and across treatment could be underestimating the treatment effect of deflazacort.

D. Model Costs Inputs

The costs for the model are based on a single study (Landfeldt 2014^{xiv}). These data were based on survey results from patients and caregivers which may be less accurate due to recall. There are published treatment guidelines that provide a breakdown for nearly every aspect of the management pathway for DMD patients. This presents an opportunity for model development taking these additional health states and patient/caregiver impacts into consideration.

E. Societal Perspective

The societal perspective should include additive caregiver utilities (not disutilities) in its base case. As almost no DMD patients live independently, these patients are highly dependent on caregivers for their entire lives. A favorable change in deflazacort over prednisone incremental cost per QALY gained across scenarios 1 - 4 occurs as increasing weight is given to the family/caregiver impact of DMD. Given the life expectancy of DMD patients and the high costs associated with caregiving, not including the caregiver utilities as part of societal analysis produces a model that has confusing results (*i.e.*, results from the societal perspective are typically lower than the payer perspective).

F. Mortality Data

The reference for the mortality data on page 45 includes both Becker Muscular Dystrophy and DMD patients.^{xv} The extrapolation of the survival data in Figure 4.2 has a small percentage (possibly as high as 5%) of DMD patients surviving beyond the age of 55. Based on available data, this seems unlikely. Additionally, from the best that we can assess based on the Draft



Evidence Report, the variation of transition probabilities for time to non-ambulation and time to death were not tested in sensitivity analyses.

McDonald (2017^{xvi}) followed three different groups and the oldest median age at transition to FVC < 1L was 24.40. For the patients with a FVC < 1L, the 5-year survival rate according to Phillips (2001^{xvii}) is approximately 8%. Therefore, it seems unlikely that any patients with DMD would be alive at age 55. Given the high cost of disease, it is possible that the tail of the distribution is overestimating the costs. This suggests that the benefit of deflazacort versus prednisone is underestimated and the cost of therapy is overestimated.

Conclusion

PTC Therapeutics appreciates this opportunity to submit comments on the Draft Evidence Report. Although we are aligned with ICER on the goal of supporting patient access to highvalue care and demonstrated benefits on preservation of ambulation and forestalling of decline and mortality for deflazacort over prednisone, we are concerned about ICER moving forward with its review in this treatment area based on the gaps and other issues identified in these comments. We urge ICER to carefully take these comments into account in determining its next steps in this review, such lack of appreciation to details clearly important to the life of patients suffering with DMD puts into question the integrity of the entire report. We would be pleased to answer any questions regarding the issues raised above.

Sincerely,

Marcio Souza Chief Operating Officer PTC Therapeutics, Inc.



ⁱ PTC Therapeutics, Emflaza® (deflazacort), Prescribing Information (rev'd 06/2019). ⁱⁱ Press Release, PTC Therapeutics, PTC Therapeutics Receives FDA Approval for the Expansion of the EMFLAZA® (deflazacort) Labeling to Include Patients 2-5 Years of Age (June 7, 2019), <u>http://ir.ptcbio.com/news-releases/news-release-details/ptc-therapeutics-receives-fda-</u> <u>approval-expansion-emflazar</u>.

ⁱⁱⁱ Institute for Clinical and Economic Review, Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value, Draft Evidence Report at 19 (May 22, 2019) [hereinafter "Draft Evidence Report"].

^{iv} Id.

^v Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol.* 2018;17(3):251-267.

^{vi} Draft Evidence Report at 20.

^{vii} *Id.* at 13.

^{viii} *Id.* at 4 (*citing* Griggs RC, Herr BE, Reha A, et al. Corticosteroids in Duchenne muscular dystrophy: major variations in practice. *Muscle & Nerve*. 2013;48(1):27-31). ^{ix} *Id.* at 2.

^x Parent Project Muscular Dystrophy, What is Duchenne Muscular Dystrophy?, <u>https://www.parentprojectmd.org/about-duchenne/what-is-duchenne/.</u>

^{xi} Draft Evidence Report at 42-43 (emphasis added).

^{xii} *Id*. at 47.

^{xiii} McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet (London, England)*. 2018;391(10119):451-461.

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^{xv} Draft Evidence Report at 45.

^{xvi} McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet (London, England)*. 2018;391(10119):451-461.

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June 18, 2019

BY ELECTRONIC DELIVERY

Steven D. Pearson, MD, MSc President Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109 publiccomments@icer-review.org

Re: Draft Evidence Report – Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value

Dear Dr. Pearson:

I am writing in response to the Institute for Clinical and Economic Review (ICER) May 22, 2019 publication of the Draft Evidence Report for Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy. Sarepta Therapeutics (Sarepta) submits the enclosed statement issued on May 23, 2019 upon the release of the draft report for inclusion in ICER's public record.

As specified in our May 23, 2019 statement, we believe ICER's model is ill-suited to evaluate rare disease treatments and have chosen not to participate in reviews by ICER until flaws in its framework are addressed. We reached this position after careful deliberation informed by ICER's assessments of other rare disease treatments, as well as our own direct engagement with ICER dating back to more than two years ago. We first conveyed our methodological concerns to ICER in 2017 as a participant in ICER's working group focused on updating its ultra-rare value assessment framework and in submitted comments. Unfortunately, ICER's updates were inconsequential in addressing the underlying flaws in its framework. Nowhere is this more evident than in ICER's recent assessments of treatments for cystic fibrosis (Symdeko[®], Orkambi[®], Kalydeco[®]), hereditary transthyretin-related amyloidosis (Onpattro[®], Tesedi[®]), and spinal muscular atrophy (Spinraza[®])—all innovative treatments addressing unmet needs for rare disease patients where ICER untenably recommended discounts upwards of 90 percent. ICER continues to fail to accurately, responsibly, and fairly capture the full value these innovative medicines hold for rare disease patients.

When ICER announced its intent to review eteplirsen and golodirsen, Sarepta reiterated in detail in our January 8, 2019 comment letter our concerns with ICER's approach as applied to pediatric rare disease treatments – to include limitations in its methods, process and timing, which are even more acute in the context of drugs that receive accelerated approval. We communicated from the start that we would not participate in a process that introduces fundamental misunderstandings of value, has proven to significantly undervalue innovative rare disease treatments, and has a predetermined outcome. Instead, we would continue to direct our efforts at fulfilling our commitment to the Duchenne community, with a focus on generating evidence for our current and future therapies and providing accurate information to

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help patients, doctors, and payers make informed treatment and coverage decisions. We remain steadfast in keeping this promise.

Sarepta believes value assessment frameworks can serve as informative tools if developed and implemented properly and with an end goal of doing what is in the best interest of patients, not with a narrow focus on cost constraints and access restrictions. We stand willing to work with ICER if it adapts its model to address the inherent limitations and biases that compromise its evaluations of therapies intended to treat patients with serious, often fatal and debilitating, rare diseases. These patients face challenges at every step of their journey and deserve meaningful solutions, not more barriers that could put treatment options out of reach.

Sincerely,

Diare Be

Diane Berry, Ph.D. Vice President, Global Policy, Government, and Patient Affairs

Addendum: May 23, 2019 Statement

Sarepta Therapeutics Statement on ICER Draft Evidence Report for Treatments for Duchenne Muscular Dystrophy

CAMBRIDGE, Mass., May 23, 2019 -- Sarepta Therapeutics, Inc., the leader in precision genetic medicine for rare diseases, released the following statement on the report from the Institute for Clinical and Economic Review ("ICER") on treatments for Duchenne muscular dystrophy:

Sarepta is committed to appropriately pricing therapeutics so that they are cost effective and believes that, done properly, evaluations such as those conducted by ICER could serve a valuable purpose. With that said, however, ICER's approach is fatally flawed as it relates to rare and genetic disease for a number of reasons. As a result, we have chosen not to participate in reviews by ICER until it adapts its model to address the inherent limitations and biases that compromise its evaluations of therapies intended to treat patients with serious, rare diseases.

First, ICER's model is unfit to evaluate rare disease populations in a manner that would encourage innovation to bring profound treatments to patients living with, and far too often dying from, rare disease. There are 7,000 rare diseases, most of which are genetically based, and today only about 5% of those diseases have any treatment available. Great human suffering and death results from these rare diseases. Half of all those who suffer from rare disease are children. Rare disease is responsible for a third of all deaths in the first year of life and a third of children with rare diseases will not reach their fifth birthday.

After decades of extraordinary scientific advancement, biomedical innovation is bringing treatments to rare disease patients and their families who have been without any hope for far too long. ICER's model stands to halt these advancements. Consider that prior ICER evaluations have concluded that for diseases such as spinal muscular atrophy – a death sentence for those children who have it; cystic fibrosis -- a disease that robs one of the ability to breathe and then of life, and hereditary transthyretin amyloidosis – a devastating and life-limiting rare disease, proposed therapies are only cost effective if offered at discounts upwards of 90%. That is not a typographical error.

To the extent ICER's evaluations are taken seriously, no company would be able to attract investment to fund the development and manufacture of treatments for these rare diseases. Through its conclusions, ICER sends a clear message to innovators that developing rare disease therapeutics is not worth the effort, and to patients – often children who are dying with no other treatment options – that their lives are not worth the investment.

Second, the ICER model is unequipped to accommodate the FDA accelerated approval process for new therapy approvals. Nearly 30 years ago, the FDA created an accelerated approval pathway to ensure faster approval of safe and effective drugs for serious conditions that fill an unmet medical need. The pathway relies on surrogate endpoints that are reasonably likely to lead to clinical benefit and ensure that life changing therapies for very serious diseases are sped to the medical community to ensure that patients do not suffer and die while longer clinical trials are conducted. As a reminder, this is the pathway that spurred tremendous advancements in treatments for HIV and cancer. The ICER model attempts to negate that pathway by failing to properly align with the goals of, and accepting the evidence set that supports, accelerated approval.

Third, if the goal is to support a cost effectiveness approach that promotes true innovation while acting as a watchdog for waste in the system, ICER is failing. ICER has focused nearly all its reports on evaluating

June 18, 2019 Page 4

and generally undermining innovative new therapies, often for rare disease. The bulk of pharmaceutical expense lies in legacy therapies, and much of the waste in the system lies in old, high-volume drugs with price increases that have historically exceeded increases in the Consumer Price Index (CPI). ICER spends little time doing the difficult but important work of evaluating waste in the large segment of healthcare spend, instead choosing to evaluate innovative new therapies that may garner headlines but do little to relieve non-innovative expense from the system.

Sarepta's mission is to find new treatments and cures for those suffering from genetic disorders and we remain focused on bringing those advances to patients as quickly as possible. We will continue to work directly with clinicians, payers, and other stakeholders to inform treatment and coverage decisions, and identify real and meaningful solutions to the challenges of patient access and sustainable innovation. And if and when ICER adapts its model to thoughtfully support investment in therapies for rare disease and the FDA's accelerated approval of those therapies, we stand ready to work with ICER as well.

About Sarepta Therapeutics

Sarepta is at the forefront of precision genetic medicine, having built an impressive and competitive position in Duchenne muscular dystrophy (DMD) and more recently in gene therapies for 5 Limb-girdle muscular dystrophy diseases (LGMD), Charcot-Marie-Tooth (CMT), MPS IIIA, Pompe and other CNS-related disorders, totaling over 20 therapies in various stages of development. The Company's programs and research focus span several therapeutic modalities, including RNA, gene therapy and gene editing.

Sarepta is fueled by an audacious but important mission: to profoundly improve and extend the lives of patients with rare genetic-based diseases. For more information, please visit www.sarepta.com.

Internet Posting of Information

We routinely post information that may be important to investors in the 'For Investors' section of our website at www.sarepta.com. We encourage investors and potential investors to consult our website regularly for important information about us.

Source: Sarepta Therapeutics, Inc.

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To the Institute for Clinical and Economic Review:

Wave appreciates the opportunity to comment on the Duchenne muscular dystrophy (DMD) draft Evidence Report from the Institute for Clinical and Economic Review (ICER).¹ We recognize the importance and challenge of ICER's work to evaluate the clinical and economic value of health care interventions.

Background

Wave is a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. Wave aspires to develop best-in-class medicines using PRISM, the company's proprietary discovery and drug development platform that enables the precise design, optimization, and production of stereopure oligonucleotides. Preclinical studies have demonstrated that our stereopure oligonucleotides may achieve superior pharmacological properties compared with mixture-based oligonucleotides.²

Our lead DMD program is suvodirsen, an investigational stereopure oligonucleotide intended for the treatment of boys with DMD who are amenable to exon 51 skipping. In an in vitro study suvodirsen demonstrated 52% dystrophin restoration in patient derived cells as compared to approximately 1% seen in drisapersen and eteplirsen analogs that were synthesized by Wave for the purposes of the experiment³. Suvodirsen is currently being evaluated in an open label extension (OLE) study and is open to patients from the completed phase 1 clinical trial, where initial safety and tolerability were demonstrated after administration of single doses.⁴

In July 2019, Wave expects to initiate DYSTANCE 51, a global, multicenter, randomized, double-blind, placebo-controlled phase 2/3 efficacy and safety clinical trial of suvodirsen in DMD patients amenable to exon 51 skipping. This trial is targeted to enroll 150 patients.⁵

It is important to note that the DYSTANCE 51 trial has been selected by the US Food and Drug Administration (FDA) for the agency's pilot program for complex innovative trial designs, and was designed with input from the FDA, other global regulatory authorities and the global physician and patient DMD communities. In addition, suvodirsen has been granted orphan drug designation for the treatment of DMD by the FDA and the European Commission, as well as a rare pediatric disease designation by the FDA.

The trial will collect dystrophin protein levels, a surrogate endpoint likely to predict clinical benefit, in addition to measures of patient strength and function. An interim analysis based on dystrophin expression in muscle may provide an opportunity for accelerated approval by the FDA.

Wave also has an exon 53 skipping clinical candidate and we are exploring programs targeting DMD exons 44, 45, 52, 54 and 55.

Overview of Comments

1. A three state economic model does not capture important treatment effects in DMD. For future evaluations, ICER should use a more granular economic model framework.

2. Additional information is required on the assumptions used to adapt costs and utilities from the source publication to the health states used in ICER's model.

3. ICER should align its assessment approach for drugs that, because they are addressing devasting diseases like DMD with significant unmet needs, have been approved under FDA's Accelerated Approval pathway.

4. ICER should provide greater contextualization regarding the importance of using natural history comparisons to detect treatment effects in DMD.

5. ICER should consider motor function as a key measure of patient benefit.

Detailed Comments

1. Economic Model Health States

We believe that future evaluations of DMD treatments should use a more granular model framework, such as health states based on 'early' and 'late' ambulatory and non-ambulatory status. This would provide the opportunity to capture additional clinical and economic benefits. Published data demonstrate both a substantial decrease in utility and substantial increase in costs when progressing from early ambulatory to late ambulatory, or from early non-ambulatory to late non-ambulatory health states.^{6,7,8} Exclusion of these states in the current model does not capture the benefits provided by DMD treatments that delay such progression. We understand that, in this case, there was no evidence available to demonstrate such a treatment effect. However, ICER's allowance of these additional health states in evaluations supported by such evidence would be beneficial to patient access to future treatments.

The inclusion of the additional early and late states in future models is also clinically justified. Published treatment guidelines in 2018 demonstrated different care considerations for DMD patients in the early and late stages of the ambulatory and non-ambulatory health states.⁹

2. Adaptations of Cost and Utility Data to ICER Model

We were unable to identify several cost and utility input values in the ICER report from the source publication.¹⁰ For example, we were unable to identify health-state specific costs for different cost categories (e.g. Direct Medical-Nonmedication). We were also unable to identify utilities that have been aggregated across early and late stages of the ambulatory and non-ambulatory health states, respectively. Indeed, the reference publication reported separate utilities for early ambulatory, late ambulatory, early non-ambulatory and late non-ambulatory.¹¹ We request clarity on the assumptions used to adapt the published costs and utilities to align with the health states in the ICER model.

3. Alignment with Accelerated Approval

DMD is a devastating progressive disease with limited treatment options. The FDA has developed an Accelerated Approval pathway precisely for diseases like DMD.¹² This statutory provision under §21 CFR 314, Subpart H, allows the FDA to approve a new drug based on its effect on a surrogate endpoint or intermediate clinical endpoint when there is scientific evidence that endpoint is reasonably likely to predict clinical benefit. A confirmatory study(ies) is then required to verify clinical benefit for the patient. This

provides an essential route to more rapid regulatory approvals based on a sound scientific basis with the potential to benefit those with serious diseases like DMD where there are limited treatment options.

The FDA has accepted increased dystrophin protein levels as a surrogate endpoint likely to predict clinical benefit in DMD as evidenced by regulatory policy and established guidance for clinical development of therapies aimed to treat DMD. In FDA's guidance, they state: "Deficiency of functional dystrophin appears to be the proximate cause of the symptomatic and functional consequences of dystrophinopathies, justifying particular interest in dystrophin as a biomarker and as a potential surrogate endpoint for accelerated approval."¹³

Dystrophin protein levels were used in the FDA approval of eteplirsen. ICER evaluated dystrophin, pulmonary function and the 6 Minute Walk Test (6MWT) data in its assessment of the clinical benefit of eteplirsen and golodirsen. Because of the very small patient numbers, the challenges of interpreting patient benefit from the 6 Minute Walk Test (6MWT), and difficulties in characterizing a meaningful change in dystrophin protein levels, ICER concluded that the clinical evidence is "insufficient" for eteplirsen and golodirsen. ¹⁴ In the case of the DYSTANCE 51 study, it has been designed to deliver dystrophin results in parallel to conclusive clinical results by using innovative statistical methods to analyze and adapt the study based upon the results of interim analyses. Nonetheless, the potential for Accelerated Approval in the setting of an increase in dystrophin production remains an essential route to making the drug available to patients as soon as possible, while confirmatory clinical data are gathered in a timely manner.

It is critical for ICER to align its assessment process with the FDA's statutory Accelerated Approval pathway under Subpart H. The current process is heavily critical of the clinical evidence arising for drugs approved under Accelerated Approval, yet the underlying premise of this pathway is that there is persuasive evidence that the chosen surrogate endpoint will influence clinical outcomes based on an in-depth scientific understanding of the disease. If the timing of an ICER evaluation is such that only biomarker data and limited functional data are available, then allowance for, and acknowledgement of, that challenge should be explicit in its reports. Ideally, ICER should time its evaluations such that adequate longer-term clinical data are available for these drugs. This misalignment between Federal statute and the ICER process, unless resolved, will continue to frustrate access to treatments of serious diseases like DMD.

4. Comparison to Natural History

Comparison of treatment effects against natural history data and historical controls, which include placebo datasets, is often necessary in rare diseases with significant unmet need, such as DMD. This can be done to shorten the time period patients are on placebo as well as minimize the number of patients required in the placebo arm.

Comparisons against historical controls must be conducted carefully with prospectively defined analysis plans to better ensure the comparability of the comparator population and to minimize bias and type 1 errors. We agree that comparisons against previously published data alone are problematic. Statistical methods that incorporate historical control patients using clinical and patient variables that are important to disease progression, in the setting of appropriate means to minimize bias and type 1 error, can be effective tools in the

development of treatments for rare diseases. Greater contextualization of the appropriate use of natural history controls in DMD should be provided in the final ICER report.

Wave's application for the complex innovative trial design pilot program includes a plan to leverage DMD historical control data to augment the placebo arm of the suvodirsen phase 2/3 clinical trial. Our intention is to reduce the number of patients required to deliver conclusive clinical efficacy results, and thereby minimize the number of patients required in the placebo arm and accelerate study completion.

5. Value of Motor Function Composite as an Outcome Measure

Motor function is considered to be an important parameter to measure in DMD trials.¹⁵ However, we agree with ICER that the 6MWT, although historically used in DMD trials, has limited use in characterizing a DMD patient's functional status.

A more relevant measure for DMD treatments may be the North Star Ambulatory Assessment (NSAA).¹⁶ The NSAA was specifically designed to measure functional ability in ambulatory patients with DMD. The NSAA is a comprehensive assessment of functional ability and includes assessments of standing, walking, standing up from a chair, standing on one leg, rising from the floor, jumping, hopping, running, etc. In short, activities that any developing boy will want to conduct. The FDA has stated: "The NSAA is a comprehensive outcome measure, and arguably more fully reflects function in DMD than the 6MWT."¹⁷ The European Medicines Agency has also stated: "for ambulant boys with DMD, the diseasespecific North Star Ambulatory Assessment (NSAA) that also includes timed items ...can be used."¹⁸ The NSAA has therefore been included as a key endpoint in DYSTANCE 51.

Summary

Thank you for the opportunity to comment on the draft Evidence Report for DMD. Despite the number of clinical advances in this rare disease, there continues to be an enormous unmet need. Wave is committed to advancing therapeutic innovations and to engaging with ICER as they evaluate therapies for DMD patients. Equally important to us and the patients we aim to serve is our commitment to provide broad access to our therapies once approved. We hope these comments are useful to the current and future evaluations of treatments for this devastating disease.

Sincerely,

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