INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value

Response to Public Comments on Draft Evidence Report

July 11, 2019

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Manufacturers		
PTC Therapeutics		
1.	*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. 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).	Thank you for this comment; we have acknowledged this label expansion in Table 1.1.
2.	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." 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. 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. These guidelines additionally acknowledge, as ICER reiterates, that deflazacort may lower risk of weight gain and behavioral problems as compared with prednisone.	Thank you for this comment.
3.	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, 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.	For ultra-rare diseases rigorous clinical trial evidence can be limited. For our evaluation of deflazacort versus prednisone, we conducted a thorough literature search which yielded three randomized, controlled trials and seven observational studies. We acknowledge that a limitation of the observational studies is that there may be variation in practice, which may obscure any differences between groups; however, for the majority of outcomes, the randomized trials also did not show significant differences in outcomes between the deflazacort and prednisone groups. Thus, there does not appear to be evidence from good quality studies that demonstrate significant differences between deflazacort and prednisone. We have carefully reviewed the wording in the report and have clarified this when necessary.
4.	*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	We acknowledge the complex quality of life profiles of DMD patients and their caregivers and agree this is an important area for future research. However, in the absence of an optimal quality of life tool to capture these complexities, we have opted to use the best available estimates of utility scores across defined DMD related health states, which are the US-

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	that DMD patients and their caregivers have a complex quality of life profile that may not be fully captured by current generic tools." 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.	based HUI proxy-assessed utilities found in a DMD modeling paper (Landfeldt, 2014). These utilities are based on a validated tool and the level of utility that the model employs is consistent with other very serious illnesses. For example, our utility in the late non-ambulatory state is 0.146 which is below that of a fully dependent Amyotrophic lateral sclerosis (ALS) patient utility of 0.35 (Busterien, 2005) reflecting the severity of the disease. Together with the assumptions on treatment effects and disutilities of SAEs in the model we believe these provide useful and quantitatively driven upward bound estimates of potential treatment effects in DMD associated with the treatments in question.
5.	*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. 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.	We recognize our model is a simplification of the reality that DMD patients and their caregivers face. All models are, by definition, a simplification of reality. We also acknowledge potential variation in disease progression of DMD patients. However, in relation to decision-making, it is the average cost-effectiveness of the relevant population that is most informative, particularly in the absence of known subgroups with differential treatment effects of specific treatments. We also acknowledge that our model averages over other critical functionalities specific to DMD patients in the ambulatory and non-ambulatory health states, but this is due to a lack of evidence of proportions of patients with those functionalities and demonstrated quality of life impacts for these critical functionalities. Further, to date there is insufficient evidence to model treatment effects (i.e., overall quality of life impacts) on these underlying critical functionalities. We agree this is a potentially important area for future research. As a result of the overall paucity of data, we incorporate data driven upper bound estimates of potential treatment effects in the assessment and conduct a wide variety of sensitivity, scenario, and threshold analyses.
6.	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 now including early and late ambulatory and non-ambulatory states in the model with age varying proportions themselves based on prior models in the literature. Given available evidence of treatment effects in the literature, we are also assuming parallel shifts in all the curves provide estimates of potential treatment effects. Data providing, we would have built in more granularity to better reflect the reality of living with DMD. However, in the absence of sufficient evidence to model more granular treatment effects, we have chosen to make very

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		favorable assumptions for both deflazacort and eteplirsen. For deflazacort we have modeled the upper end of treatment effects observed in the literature. In the absence of observed differences in randomized controlled trials between prednisone and deflazacort, we used the most favorable observational evidence of a 2.7-year delay to non-ambulatory states rounded up to 3, in addition to accounting for disutility and additional weight gain from prednisone. For eteplirsen, there was insufficient evidence to model treatment effects, therefore we explored scenarios that restored patients and their caregivers to perfect health, added on 40 years of life in perfect health, and eliminated the need for supportive care costs. These extremely favorable, even implausible assumptions for eteplirsen still exceeded standard cost-effective thresholds (see Table 4.14). We fully acknowledge and agree that it is possible to categorize patients into even more stages than those included here and that it is possible that treatments may impact the relative proportion of time patients spend in those states. However, to date there is insufficient evidence to model any such stages or treatment effects on those stages. Again in response to this we have used the most favorable treatment effects for deflazacort that have been observed in the literature (using more favorable observational evidence vs. less favorable RCT evidence) and we have explored thresholds for eteplirsen with extremely favorable (even implausible) treatment effects and our results are robust. Had we had a more granular model, the evidence needed to support this granularity would not lead to more favorable treatment effect results than the assumptions used in this simpler model presented here. Hence, while we agree that pursuit of more accurate and more granular models for DMD are an important area for future research it would not change our basic conclusions regarding the cost effectiveness of these treatments.
7.	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.	Please see above response to PTC Therapeutics, row 5.
8.	*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 relative proportion of US patients in the early and late stages in the survey that contributed to the original estimates. In doing so,	See below and PTC Therapeutics, row 6.

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	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. 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.	
9.	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.	We have updated the model in response to these comments. Please see response above in row 6.
10.	Second, there is evidence from McDonald (2017) 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.	The model parallel shifts the ambulation survivor curve and the mortality curve which directly reflects a delay in disease progression. Given available data we maintain this is reasonable assumption for projecting a likely upper bound for the impact of deflazacort on QALYs and costs.
11.	*D. Model Costs Inputs* The costs for the model are based on a single study (Landfeldt 2014). 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.	We acknowledge with improved data collection and future consistent trials based on a broader set of outcomes, that models for DMD could incorporate a broader set of health states. The current limitations in data available limit the potential treatment nuances that can be reasonably projected. Nonetheless, the loss of ambulation and mortality have large measured impacts on QALYs and Costs that allow for reasonable projections of potential cost effectiveness of existing treatments.
12.	*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	It is consistent and recommended practice to use the QALYs of only patients in measuring treatment effects in conducting a cost effectiveness analysis from a modified societal perspective. However, we also acknowledge this consideration of including care-giver QALYs and we conduct scenario analyses that incorporate consideration of changes in

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	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).	caregiver utility (specifically adding gains in modeled QALYs of caregivers to the modeled gains in QALYs of the patients) based on caregiver utilities associated with the health states in the model available in the literature.
13.	*F. Mortality Data* The reference for the mortality data on page 45 includes both Becker Muscular Dystrophy and DMD patients. 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.	The mortality curves used in the model are based on assumptions made by Landfeldt and roughly match available data in the US. Specific survival curves for DMD for patients on steroids are not available. It is certainly possible that the tails of the survival curves in the model are too long. This is acknowledged in the limitations. However, given the parallel shifts for potential treatment effects, as well as the use of discounting the impact of the tails of these curves on the incremental costs and QALYs are very small.
14.	McDonald (2017) 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) 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.	Same comment as above. We agree that it is unlikely that many DMD patients will survive until age 55. In fact, our model has 92% of the cohort exiting the model by age 40. The “fat tail” effect is a noted limitation, however the additional cost and QALYs of these unlikely survivors are minimal because of discounting. It also does not impact the incremental cost-effectiveness. Any time horizon over 35 years in our model does not impact the incremental results.
Sarepta		
1.	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	We appreciate Sarepta submitting their press release of May 23, 2019 as a public comment, although think it unfortunate that Sarepta chose not to engage more fully in ICER's review of the exon-skipping therapies eteplirsen and golodirsen. Sarepta states that ICER's model is "ill-suited to evaluate rare disease treatments", and apparently based this conclusion on ICER's reviews of a number of treatments for rare diseases. Sarepta states these included reviews of treatments for CF, hATTR, and Spinraza for SMA. Interestingly, Sarepta did not comment on ICER's reviews of other treatments for ultra-rare conditions including CAR-T therapies for relapsed/refractory acute lymphoblastic leukemia and aggressive B-cell lymphoma, emicizumab for hemophilia A with inhibitors, and Zolgensma for SMA. In each of these cases, ICER concluded that the treatments were cost-effective. Apparently Sarepta's view is that an ICER review of a treatment for an ultra-rare condition can

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	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 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. Addendum: May 23, 2019 Statement Sarepta Therapeutics Statement on ICER Draft Evidence Report for Treatments for Duchenne Muscular Dystrophy	only be appropriate if it finds the treatment to be cost-effective. In contrast, ICER's view is that ICER should follow the economics and the evidence to their appropriate conclusions. When ICER has used this latter strategy, some treatments for ultra-rare conditions have been found cost-effective while others have not. We recognize why Sarepta would be concerned about this approach for eteplirsen given that the FDA required the label to state, "A clinical benefit of EXONDYS 51 has not been established." It can understandably be difficult to demonstrate cost-effectiveness for a therapy that has not established effectiveness.

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	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	

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	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 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.	
Wave Life Sciences		
1.	*1. Economic Model Health States*	See response to PTC Therapeutics, row 6 above.

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	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. 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.	
2.	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.	Please see response to PTC Therapeutics, row 6 above.
3.	*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. 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. We request clarity on the assumptions used to adapt the published costs and utilities to align with the health states in the ICER model.	We have adapted the model; please see comment in PTC Therapeutics, row 6. We will also edit the report for clarity.
4.	*3. Alignment with Accelerated Approval* 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 does recognize the difficulties in evidence generation in this situation. Additional language was added to the Evidence Report to make this clearer.

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	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.	
5.	*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.	We agree that comparison against natural history and historical controls can shorten the time it takes to conduct studies for ultra-rare diseases, but such comparisons are also subject to confounding.
6.	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.	See above.
7.	*5. Value of Motor Function Composite as an Outcome Measure* Motor function is considered to be an important parameter to measure in DMD trials. 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). 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." The European Medicines Agency has also stated: "for ambulant boys with DMD, the disease-specific North Star Ambulatory Assessment (NSAA) that also includes timed items …can be used."	Thank you for this comment. We agree that the outcomes used in current trials may not adequately capture functional status in patients with DMD, and have discussed this limitation in the "Controversies and Uncertainties" section of the report. We hope that alternative measures of efficacy will be discussed at the public meeting.

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	The NSAA has therefore been included as a key endpoint in DYSTANCE 51.	
Patient Groups		
CureDuchenne		
1.	*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.	We agree that excessive weight gain may lead to other consequences that affect the lives of DMD patients and their caregivers. We have added language in the report in the "Insights from Patient Groups" section to reflect this concern. To the extent weight gain affects time to loss of ambulation, this would be captured in the available data that directly measures time to loss of ambulation. In addition, we assign a likely upper bound disutility of -0.05 for weight gain and additively a disutility of -.05 for becoming Cushingoid.
2.	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 psycho-social 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.	We appreciate this comment and have added language to the "Insights from Patient Groups" section of the report to reflect that delaying loss of ambulation is a critically important outcome to patients and their families.
3.	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.	The model incorporates utility scores associated with defined health states from valid published sources. The methodology of using QALYs to evaluate cost effectiveness has a long standing in published literature and is recommended by existing model guidance in the US.
4.	*Patient Heterogeneity*	We agree that the Duchenne population is heterogenous population, which brings with it

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	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.	challenges to evaluating treatments for the disease. The purpose of the clinical effectiveness section our report is to evaluate, to the best of our ability, the treatment outcomes for patients treated with deflazacort (compared with prednisone) and exon-skipping therapies, using the best data available. We acknowledge that current clinical trial data may not allow us to adequately characterize the effects of therapies in different DMD populations and may not adequately reflect the entire spectrum of outcomes for patients with DMD. We have stated in our report in the "Controversies and Uncertainties" section that there may be other outcomes that may better reflect treatment effects for DMD patients; however, until these outcomes are validated and used consistently across studies, we are unable to include such evidence in our evaluation.
5.	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.	In response to comments we will go back and include age-based proportions of early and late stages of ambulatory and non-ambulatory health states in the model, please see response above row 6.
6.	*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.	In the absence of data on treatment effects the model projects whether the treatments could be cost effective using a wide array of plausible and even implausibly large potential treatment effects. The conclusions of the model for the given prices of the drugs are highly robust.
Parent Project Muscular Dystrophy		
1.	*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	ICER does recognize the difficulties in evidence generation in this situation. Additional language was added to the Evidence Report to make this clearer. However, it would be a mistake to assume that a lack of data is evidence of efficacy.

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	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.	
2.	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.	The "I" rating for these therapies matches this concern. It says that the evidence is inadequate, not that the therapy does not work.
3.	*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.	In most modelling frameworks, including Markov models, health states are mutually exclusive, whereby patients can only be in one health state at a time. In fact, the example described could be modeled using a Markov framework (and has been modelled previously[1]) and that would require states to be mutually exclusive. We have adapted our model to incorporate additional health states to better reflect the natural progression of DMD, see response in row 6 above. Nonetheless we do assume mutually exclusive states. The early and late stages are age driven and are mutually exclusive by definition. Being early non ambulatory we believe is reasonably approximated as mutually exclusive from late ambulatory though of course in the real world there could be some back and forth in those states for some time for some proportion of patients. There are insufficient data to know whether and for how long non-ambulatory patients may regain ambulation for a period of time and adding that possibility would not change the main conclusions.
4.	*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.	Please see above responses in PTC Therapeutics, rows 5 and 6.

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5.	• *Both the Duchenne Regulatory Science Consortia (D-RSC) of the Critical Path Institute https://c-path.org/programs/d-rsc/ 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)*
		Please see above response in PTC Therapeutics, row 6.

6.	*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.	Clarification: Treatment effects were modelled as rightward shifts. SAEs were modelled as disutilities based on observed rates for which behavioral side effects were included.
7.	Assumption: Patients on prednisone transitioned between “ambulatory,” “non-ambulatory,” 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. Comment: 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.	Please see above response in PTC Therapeutics, row 6.
8.	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. Comment: Assuming that the proportion of early/late ambulatory and early/late non-ambulatory 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	There are insufficient data to establish treatment effects on these proportions. We do explore the potential impact of treatment effects that would shift these proportions in scenario analyses.

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	deflazacort, this could potentially impact the proportion of patients in early/late ambulation who are going to be in prednisone or deflazacort.	
9.	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. Comment: 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 the study by Landfeldt et al., an international data set from the Treat NMD Registry utilized data from Germany, Italy, the United Kingdom, and the United States. Mean per-patient 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/regulatory-advocacy/	We agree with the basic conclusion that supportive care costs increase as the disease progresses and this is reflected in the model. The model incorporates published evidence on caregiver costs in the modified societal perspective results in the report. It is possible these costs are underestimated, but we did not find any better estimates of the costs of supportive care associated with DMD.
10.	Assumption: Patients are diagnosed and begin treatment at five years of age.	See above response to PTC Therapeutics, row 1.

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	Comment: Emflaza is commercially available to patients ages 24 months and older.	
11.	Assumption: SAEs (weight gain, cushingoid, fractures, cataracts) related to prednisone and deflazacort resulted in a disutility of 0.05. Comment: 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	In modeling side effects, we balanced consistency in the data sources with using likely upper bound estimates for treatment effects related to deflazacort relative to prednisone. As such we found the available rates of SAEs in the McDonald study to be the best available.[2] As there are also no available estimates of disutilities associated with these SAEs we used a likely upper bound estimate of disutility of -0.05.
12.	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.	To the extent weight gain affects time to loss of ambulation, this would be captured in the available data that directly measures time to loss of ambulation.
13.	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. Comment: 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.	Please see response to PTC Therapeutics, row 6.
14.	*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.	We acknowledge the model is based on limited data. However, we believe the model provides best available measures of likely upper bound treatment effects on costs and QALYs in DMD. In addition to the base case we conduct a wide variety of sensitivity analyses, scenario analyses, and threshold analyses and our results are highly robust.
Partnership to Improve Patient Care		
1.	*ICER's Study is Premature to Evaluate the Value of Novel Therapies*	Eteplirsen was approved by the FDA in 2016. It doesn't seem unreasonable to expect evidence adequate to evaluate a therapy that has been sold

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	ICER has a concerning pattern of reviewing new drugs at earlier and earlier phases of their development and approval. This report is the most concerning to date. The report sets out to determine the value of three drugs: two – eteplirsen and golodirsen – new mutation-specific therapies known as exon-skipping therapies, and deflazacort, a corticosteroid. Corticosteroids have made up the bulk of traditional treatment for DMD, and it can ease suffering and slow progression in the disease. Exon-skipping therapies are a new, game-changing group of drugs that could have a significant effect on the disease in the near future. This report ignored this fact and set up a model for DMD based on deflazacort, and then used that same model to make far-fetched assumptions about this new form of gene therapy with almost all of the inputs from the model coming from just one study. One of the drugs under review, golodirsen, had not yet received FDA approval at the time of the study.	and administered to patients for several years. In general, ICER tries to evaluate therapies around the time of FDA approval, so the eteplirsen review is later than ICER would consider ideal. Therapies being given to humans should have evidence of benefit. In the absence of benefit, these therapies can be administered as part of clinical trials but should not be sold.
2.	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.	See above.
3.	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. 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	ICER has provided in the evidence report an analysis of the degree of benefit the exon-skipping therapies would need to have to be cost-effective. All stakeholders can decide whether it is likely that these benefits are achieved by therapies that marginally increase levels of dystrophin.

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	must be weighted against the 'certainty of doing nothing.'"	
4.	*The Model Oversimplifies the Disease* Duchenne Muscular Dystrophy is a complex condition with a very heterogeneous patient population. For this reason, it is particularly concerning that this report leaned heavily on one study that shows that there was a significant shift in progression from ambulatory to non-ambulatory status between deflazacort and prednisone. From a separate study, ICER describes its approach as digitally mapping the 'survival curve' for transitioning out of ambulatory status into non-ambulatory status (figure 4.2, page 45 in the report). It uses this as its transition probabilities between health states. It then uses this survival curve to estimate the transition rate to death and extrapolates all subsequent changes in quality of life and probability of death over a lifetime to just this one source. It is clear that taking such a complex disease and representing it with just two health states and using quality of life weights that translate across just two health states is a gross oversimplification. Patient stakeholders recognized this issue in the first round of comment letters as well, encouraging ICER to incorporate a wider range of outcomes — suggesting Daily Functional Outcomes — which would capture more nuanced data like the ability to do basic self-care activities. The simplification of a complex disease down to two health states is concerning as this type of dichotomization or over-categorization of outcomes has been shown to lead to underestimation of outcomes effects.	See above response to PTC Therapeutics, row 6.
5.	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. 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.	The underlying data that form the basis of the curves are long-term international trials of steroid treatments that directly measured time to loss of ambulation.[1,3,4] While the model may not capture with full accuracy the nuances of DMD, it does provide a reasonable first order estimate of potential treatment effects. Moreover, we include a wide variety of sensitivity, scenario, and threshold analyses and the basic conclusions are highly robust.
6.	*ICER Continues to Overlook Outcomes that Matter to Patients and Caregivers*	We appreciate this comment and agree that outcomes used in prior clinical trials may not

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	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.	adequately capture the full spectrum of functional outcomes important to DMD patients and their families. We have reflected this in the "Insights from Patients and Patient Groups" and "Controversies and Uncertainties" sections of the report. However, because many of the outcomes suggested are not used in the studies included in the report, we are not able to include them in our current evaluation. If such outcomes are validated and used routinely across studies in the future, we would welcome this development and consider including such outcomes in future reports. We maintain that QALYs are a highly useful and informative measure of patient outcomes with a broad context and long-standing applications. Importantly, the QALY reflects patient preferences for health states in a consistent and evidence-based manner and use of it rewards treatments both for improving life expectancy but also for improving quality of life.
7.	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.	Though not standard practice in cost-effectiveness analyses, we have explored the impacts on caregivers by including quality of life impacts for one and two caregivers in Scenario Analysis. Our dual base case with a modified societal perspective also includes direct and indirect costs to caregivers.
8.	*ICER Continues to Use the Flawed and Discriminatory QALY* 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. DMD falls into both of these categories.	We maintain that treatments should be rewarded for improving quality of life as well as for extending life of patients which is the purpose of the QALY. In addition, there is a large and growing body of evidence related to the QALY that provides important context for considering efficiency. We acknowledge the literature for preferences for directing healthcare resources towards patients suffering more severe diseases. This may impact what payers are willing to pay for a QALY but does not imply that QALYs should not be considered. In doing so, greater weight has been placed on the QALYs gained in populations suffering from ultra-rare diseases (which may have fewer effective therapies).
9.	This literature has uncovered a broad range of attributes across which the value of QALY gains may be expected	Please see comment above.

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	to vary. 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. 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.'	
10.	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. For example, the Netherlands has operationalized disease severity using the proportional shortfall approach. Sweden uses categories to give an indication of the level of severity. 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.	The primary purpose of our analysis is to establish likely lower bounds for the incremental costs of these drugs. We are not trying to establish a specific willingness to pay for these drugs. However, we do discuss our findings relative to existing published standards for cost effectiveness that our often used.
Patients Rising Now		
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."	Please see above response to Partnership to Improve Patient Care, row 10.
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." 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,	Thank you for this comment and we also hope that new measures that more fully capture the daily functional status of DMD patients can be developed and validated for use in future studies.

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	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." 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.	
3.	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 for – 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, and that long-term clinical improvements have not yet been definitively demonstrated from an increased presence of this protein, but our point is that there is a dramatic difference in the specificity and accuracy of those two measurements: ambulation (and other measures of disease progression) and levels of dystrophin.	Thank you for this comment. We have acknowledged in our report that functional outcomes currently used in clinical trials of DMD patients have significant shortcomings, including that they may be dependent on patient effort, and also that clinically significant improvements in dystrophin levels have yet to be defined. We agree that there is a difference in the precision of such measurements; we are only able to evaluate what was reported in the clinical trials, which appear to be standard outcome measures for patients with DMD.
4.	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:	We think the report adequately shows why these statements are not inconsistent.

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	• "…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…" • "However, as demonstrated by our extensive scenario/sensitivity analyses, our conclusions were extremely robust at the current treatment prices."	
5.	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.	Calling data imprecise requires a threshold of required precision. While the evidence on eteplirsen is not sufficiently precise to make reasonable clinical decisions since it is uncertain if it provides clinical benefits, we feel it is more than adequate to answer the question of whether its current price is reasonable.
6.	*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	Thank you for your comment. We agree that it is very difficult to project future therapies, particularly for an ultra-rare disease where there are several potential treatment pathways that are being investigated. Our review is meant to evaluate current therapies based on current evidence only; therefore, any speculation on the effect of future therapies is out of the scope of the review.

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	increasing costs. We don't know if that will happen, and neither does ICER – and that's the point.	
7.	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.	We do not usually expect patients and insurance companies to pay for experimental medicines or experimental airplanes. Neither did the Wright brothers.
8.	*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 after a second treatment is created using some of the same basic knowledge?	Development costs of a drug can affect whether or not a drug will be continued to be developed and/or marketed, as companies weigh development costs against the future potential market for the drug. Although this does not directly affect clinical efficacy of the drug, it does impact whether companies choose to pursue further clinical trials to demonstrate efficacy and safety of a drug, which in turn affects which drugs may be available for patient treatment. Additionally, drug development costs may affect pricing of a drug, which then affects access for patients, coverage decisions for payers, and the overall cost of healthcare. However, development costs of a drug are irrelevant in projecting future value for the price of a drug. What matters in calculating value is the impact of the treatment on patient's lives relative to how much it changes forward-looking costs of care in the health system and for society. Because QALYs capture impacts of treatments on both quality of life and life expectancy, and because they have a long-standing place in the science and literature with a substantial set of validity testing as well as policy context, they are considered as a gold standard.
9.	*Additional Points:* • The Draft Report provides a link to the list of stakeholders from whom ICER requested input, but not those from whom it actually received input. That list should be provided.	This list includes organizations that have provided input as well as those that have been invited to provide input.
10.	• The draft report indicates ICER requested information about "potential cost-saving	Thank you for your comment.

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	measures" that could "create headroom in health care budgets." 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. 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.	
11.	• In previous reports ICER has stated it could not find coverage policies for experimental 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." 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.	Thank you for your comment.
Project HERCULES		
1.	*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; all used a Markov approach.	We have changed the language in the model to reflect that it is a multi-state partitioned survival model. The proportions of patients in each health state by age are based directly on the survival curves found in Hill.[5] Thus our model is very much in line with existing models in the literature as our parallel shift of three years is in line with the 25% reduction of disease progression in all states, or a mean delay of 3 years that has been modelled previously.[1]
2.	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	We agree and have modelled Exponential, Weibull, Log-Logistic, and Log-Normal curves. We selected the Log-Normal as it was the best fitting model.

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	normal parametric models can be used as well as more complex and flexible models.	
3.	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 underlying survival type curves used to form the structure of the model are themselves synthesized from published Kaplan Meir curves based on results from international trials of steroid treatment in DMD. We view this as the best available evidence of proportions of patients in early and late ambulatory and non-ambulatory health states across age.
4.	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). 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.	We acknowledge that the partitioned survival model we incorporate does not explicitly specify differences in the transition to mortality from the ambulatory state versus the non-ambulatory state. The best data available to characterize health state transitions associated with patients on steroids are survival type curves for ambulation. While it is certainly true that non-ambulatory patients have higher mortality rates than ambulatory patients, those conditional hazard ratios have not been established. Our model does incorporate a relationship between loss of ambulation and death by shifting both curves as the treatment effect. In the absence of other data, we feel this is the most reasonable assumption to make. The mortality curve we incorporate is consistent with past modeling efforts and match reasonably with available survival related data on patients with DMD.
5.	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 only prognostic factor for mortality, which is incorrect.	There is insufficient data to establish the relationship between delaying ambulation and its impact on time to death. The assumption of a direct parallel shift of the mortality curve the same number of years as the ambulation curve is reasonable approximation of an upper bound treatment effect. It is also reasonable to say that there may be other predictors of mortality in DMD patients, but there are no data available of treatment effects on those predictors or of how changes in those possible predictors relate to mortality.
6.	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, which gives transition probabilities from a multi-state model, not a partitioned survival model.	The model is based on digitized curves for ambulation and mortality from Hill. In response to comments, we are further going to incorporate the proportion of patients in early and late stages of ambulation and non-ambulation by age seen in a past published study with parallel shifts in those proportions matching modeled treatment effects. As such, we agree you could refer to this as a multi-state model. However, it is also consistent to call this a partitioned survival model even though it has multiple states. The key difference as others have pointed out is that we do not specify precise

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		transition rates from ambulatory to death versus non-ambulatory to death. The model does incorporate best estimates of proportions of patients in key health states by age.
7.	*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.	Please see above responses in PTC Therapeutics, row 5 and Partnership to Improve Patient Care, row 10.
8.	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 describes nine milestone groups based on lower and upper body function that could be a potential basis for a multi-state model.	Please see above response in PTC Therapeutics, row 6. There is insufficient evidence on treatment effects however to create a nine-stage model.
9.	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.	Please see above response in PTC Therapeutics, row 6. In addition, we have scenario analyses that explore the impact of very large potential treatment effects related to maintaining patients in early versus late stages of ambulatory and non-ambulatory and the results are robust.
10.	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.	Please see above response in PTC Therapeutics, row 6 and row 12 below.
11.	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,	Please see above response in PTC Therapeutics, row 6 and row 12 below.

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	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.	
12.	*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. Note that in Hill et al only Kaplan-Meier (KM) curves for loss of ambulation were digitised. The other transitions were informed by Landfeldt et al. How transition probabilities are obtained from the project is unclear in the text. It suggests that the analysis performed in Hill et al 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.	See comments in PTC Therapeutics, rows 6 and 14. We have added language to describe these limitations and analyses done to assess the potential impact of them. While these underlying curves do have inherent limitations, we maintain they are the best available approximations of time to loss of ambulation and subsequently to mortality. The potential errors in the tails of the curves do not impact the conclusions of the model.
13.	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	Please see above response in PTC Therapeutics, row 6.

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	highly informative in a disease area with limited evidence to HTA agencies, clinicians and patients.	
14.	*Failure to address insufficient clinical data* The Modelling Analysis Plan suggests that there are inadequate data with which to perform a network meta-analysis 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. It is, however, noted that these methods require access to individual patient data in a subset of trials.	We did not have adequate data for such calculations. The treatment effect used in the model for deflazacort is likely an upper bound given all available information. Any reasonable meta-analysis of all available data would conclude a smaller treatment effect.
15.	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 only factor affecting mortality.	Please see above response in PTC Therapeutics, row 6. We also opted to always shift the mortality curve as part of the treatment effect. We have edited the report for clarity.
16.	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.	The base case model reflects a likely upper bound treatment effect in terms of a direct shift in measured time to loss of ambulation. We opted to not include treatment effect estimates based on the six-minute walk test given that currently there is insufficient data for making an accurate projection of time to loss of ambulation or to mortality from the six-minute walk test.
17.	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.	The model reflects data driven likely upper bound treatment effects. The sensitivity analyses, scenario analyses, and threshold analyses in fact confirm the results are highly robust.
18.	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	The modeled treatment effects reflect reasonable data driven upper bound treatment effects in terms of costs and QALYs. Moreover, the resulting incremental costs are highly robust across and wide

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	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.	variety of sensitivity, scenario, and threshold analyses.
19.	*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. 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 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 was conducted by experts at the School of Health and Related Research, University of Sheffield, UK. 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.	Please see above response in PTC Therapeutics, row 5. Better quality of life measures would be very beneficial to establish. Nonetheless we maintain that we are using upper bound treatment effects in the model and employing a wide variety of sensitivity and scenario analyses and our results are highly robust. Future treatment effect measures associated with the treatments being examined are highly likely to result in smaller projected treatment impacts for the drugs in question.
20.	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.	Please see above response in PTC Therapeutics, row 6.
21.	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	Please see above response in PTC Therapeutics, row 6.

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	of the currently proposed binary states of ambulatory and not ambulatory.	
Other		
Kermit Kubitz		
1.	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.	Thank you for your comment. We believe the best place to state the adoption of the ultra-rare disease framework for DMD is in the model overview section as is currently. Please note that we now also mention this in the executive summary, which is the first section of the final report.
2.	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.	The cost effectiveness model describes in detail the transitions, costs, and utilities used in the model. It also describes how the treatment effect was modelled. The treatment effect for deflazacort was a very favorable shift in time to loss of ambulation as well as a shift in time until death with corresponding shifts in the early and late stages of ambulatory and non-ambulatory. This was the largest effect seen in the published literature. For eteplirsen, the treatment effects were varied widely to explore potential cost effectiveness in the model and the conclusions were highly robust.
3.	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.	We maintain that treatments should be rewarded if they improve quality of life and also if they increase length of life which is the purpose of the QALY. Nonetheless, we also present incremental results in terms of life years gained.

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4.	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.	Thank you for this comment. As mentioned in our draft report, we discussed the state of the evidence for DMD with two clinical experts, who also reviewed and commented on the draft report prior to its release. This is the standard protocol for all ICER reports, including those for ultra-rare diseases. We also appreciate the link to the article by Thayer et al.; we have revised the report to include data from this study.
5.	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.	We will incorporate some suggested changes to the model based on the comments. See PTC Therapeutics, row 6. Given the available data we provide data driven cost effectiveness results associated with likely upper bound treatment effects. We also conduct a wide variety of sensitivity, scenario, and threshold analyses and our results are highly robust.
6.	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	We have acknowledged that our evaluation is being conducted under ICER's ultra-rare disease framework in Section 1.2.

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	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.	
7.	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."	Thank you for this comment. We have language in the report that makes clear that this is a report using the ultra-rare disease framework in Section 1.2.
8.	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.	The model incorporates a wide variety of scenario and threshold analyses. It also includes a dual base case incorporating a modified societal as well as a health system perspective analysis. In addition, given a scarcity of data, it incorporates highly favorable assumptions regarding treatment effects to examine implications of evidence based but likely upper bound treatment effects.
9.	3. COMPARATIVE CLINICAL EFFECTIVENESS, P. 21 AND OVERVIEW P. 7	Thank you for this comment. We have added comments in the background and clinical effectiveness sections, as well as the Contextual

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	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."	Considerations sections that highlight that DMD is considered an ultra-rare disease.
10.	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.	Thank you for this comment. We have added comments to add context to our review of an ultra-rare disease and have also highlighted this fact in the Contextual Considerations section of the report.
11.	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 golodirsen 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	Thank you for this comment. We appreciate that the findings in our report should be contextualized for ultra-rare diseases and have tried to do so in the report. However, the clinical effectiveness section is meant to present the current evidence in as unbiased a manner as possible, reflecting clinical outcomes and not economic ones.

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	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.	
12.	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.	Thank you for this comment. The discrepancy between the length of the sections of the report that evaluate deflazacort and prednisone and those that evaluate the exon-skipping drugs is proportional to the amount of evidence we found during our systematic search of the literature. We discuss the uncertainty of clinical significance of dystrophin levels in several places in our report (pages ES9-10, ES17, 38).
13.	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.	Thank you for this comment. Our report is meant to summarize the findings in the current literature. While we appreciate that it is possible that smaller amounts of dystrophin may be beneficial to patients with DMD, this has not been verified in clinical trials and thus is out of the scope of the clinical effectiveness section of our report. We have discussed alternative methods of gathering outcomes in the "Controversies and Uncertainties" section of the report and have added discussion about the potential of "n of 1" trials.
14.	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 methods used in the cost effectiveness projections follow best practice recommendations. The type of scenarios suggested here where the treatment is used for 10 years at which point another curative treatment are beyond the scope of this type of analysis and certainly not based on any currently available information regarding these or any other treatments in DMD.

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	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%.	
15.	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.	The results in life years and in QALYs from different shifts in the treatment effects are internally consistent but are not linear as they are impacted by discounting.
16.	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.	The cost effectiveness model incorporates the best available information regarding health state progression and associated costs and utilities related to DMD health states. There was in fact suitable evidence for generating a partitioned survival model in for this condition. Building on the available information, very favorable treatment effects were incorporated such that the results are almost certain to reflect lower bounds for likely cost effectiveness. In addition, a wide variety of sensitivity analyses, scenario analyses, and threshold analyses were undertaken. These are all described and have been edited further for clarity. In addition, the model was changed to reflect all available health states for considering supportive care costs in the US and utilities that could be combined with existing evidence on treatment effects. The results presented are highly robust across changes in input values and underlying assumptions in the model.
17.	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,	Language has been added to the report reflecting the difficulties in generating evidence around treatments for ultra-rare conditions. Lack of evidence should not be interpreted as evidence of efficacy, however.

#	Comment	Response/Integration
	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.	
18.	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	Given that this report is developed for deliberation by ICER's New England CEPAC Program, the objective of Section 2.1 is to provide a high-level overview of commercial coverage policies nationwide as well as highlight a few public payers representative of the New England area. Section 2.1 is not intended to be an exhaustive summary of every private and public policy for DMD treatments in the United States. We acknowledge that California's Department of Health Care Services may provide less restrictive coverage for eteplirsen than that of Husky Health, but inclusion of California's or other states' policies is outside of the scope of Section 2.1.

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