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On behalf of Parent Project Muscular Dystrophy (PPMD) and the Duchenne community, we are most grateful to the Institute for Clinical and Economic Review for the opportunity to offer feedback on the Modeling Analysis Plan for the ongoing assessment, *ICER Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value*. It is imperative to PPMD that the framework ICER constructs for the valuation of these — and emerging - products be specific to Duchenne and reflective of Duchenne expert input. While the proposed methodology does reflect many of these inputs, there remain additional areas of enhancement and clarification needed in order for the foundational understanding of Duchenne and the framework upon which the modeling is built to reflect the Duchenne community’s experience.

PPMD is focused specifically on the following areas:

### Overall comment:

We are concerned about the repeated comment made throughout the oral presentation about lack of available clinical data and potential for potentially impacting ability to perform analyses and meta-analyses and again reiterate our concern as to whether this is the correct time to conduct the assessment for these products with limited clinical data. Eteplirsen was approved utilizing the Accelerated Approval pathway on the surrogate outcome measure of dystrophin. Limited clinical data for products approved through accelerated approval 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.

### Overview and Model Structure:

- Partitioned Survival Model -
  
  We are concerned that this type of model is not most appropriate for Duchenne, given the typical disease progression. As Partitioned Survival Modeling is modeling cohort of a patient through time as they move between a set of exhaustive and mutually exclusive health states. This is contrary to Duchenne
disease progression in that the health states are not mutually exclusive from one another. The health states of early ambulatory, late ambulatory, weight bearing health state (transitioning to non-ambulatory), early non-ambulatory, and late ambulatory are not mutually exclusive.

- Duchenne Disease Progression –
  It is critical that Duchenne disease progression be understood to be more nuanced than the overly-simplistic proposal of three disease stages of “ambulatory”, “non-ambulatory”, and “death”.
  
  - 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:
    - Ambulatory: Early ambulatory, late ambulatory
    - Intermediate
    - Non-Ambulatory: Early Non-ambulatory (Brooke 1), Late non-ambulatory (Brooke 2-4), Late non-ambulatory (Brooke 5)
  - Death can occur at any age in Duchenne.

Project HERCULES has incorporated this disease progression model into their health economic modeling efforts.

**Key Model Assumptions:**

**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 deflazocort), 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 deflazocort, this could potentially impact the proportion of patients in early/late ambulation who are going to be in prednisone or deflazacort.

**Assumption:** Treatment effects based on the six-minute walk test will result in a parallel shift upwards, at that age, of the patterns seen in historical data and fitted curves from a past comprehensive study on historical six minute walk test data by age will be used to project changes in number of years ambulatory defined as a six minute walk test above zero.
Comment: While we understand that the available clinical trial data may be quite limited and focused on the 6MWT, it is important to note that the 6MWT is rarely used in clinical practice to measure the physical status of a child with Duchenne. The Duchenne community has worked with regulators to reach agreement around outcome measures such as the North Star Ambulatory Assessment and 4 Stair Climb, rather than the 6 MWT.

Assumption: We feel a direct upwards shift equal to the observed treatment effect at the age where the treatment effect was found and then thereafter following historical patterns of decline, would be a reasonable assumption.
Comment: We are concerned about this assumption as it assumes that the biggest treatment effect is experienced at a single point in time at a certain age, where the patient will experience the most significant improvement in outcome at a specific age only and then it seems that the patient is assumed to decline at similar pattern of declined observed in the historical data with the assumption that during the decline patient benefit minimally from the therapy. This assumption disregards the potential continuous impact of the therapy that has been mentioned by clinicians and caregivers that some patients still noticeably experience benefit of the drug even during the decline.

Assumption: The relative proportion of modified societal perspective and health care sector perspective costs are the same in the ambulatory and non-ambulatory health states.
Comment: This assumption is unclear.

Assumption: Cataracts result is an office visit and a disutility of 0.05 for the proportion of patients experiencing a cataract each year. In addition, a small proportion of cataracts each year will be assigned a cost of surgery.
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 – in addition to disutility due to cataracts. 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
Interventions

- For the list of Interventions – We recommend also including Duchenne patients who have received no therapy at all (inclusive of those who are steroid naïve) as an additional interventional group as a comparator. This can be used to compare the value of overall steroid therapy and the value of combination of steroid and eteplirsen/golodirsen.

Discontinuation

- In addition to reflecting the high discontinuation rate of patients who become non-ambulatory, we would suggest incorporating in the model the difference in outcomes of patients who keep taking steroid even during the non-ambulatory state vs. those who stopped steroid after reaching this health state.

Adverse Events

- We suggest incorporating the impact of weight gain from steroid use in the modeling of as an adverse event as this has direct implications on mobility and daily functional outcomes.

In Conclusion

We thank ICER for the opportunity to participate in the review of the modeling analysis plan. It is our hope that ICER’s framework serves to further inform and enhance – rather than hinder – our Duchenne therapy development landscape. Please contact Annie Kennedy, SVP – Legislation & Policy at annie@parentprojectmd.org for any additional information.

Sincerely,

Founding President & CEO, Parent Project Muscular Dystrophy

Acknowledgements:

PPMD’s review of ICER’s proposed drafts and proposed models has included the following individuals:

Ryan Fischer, PPMD Senior Vice President – Community Engagement
Annie Kennedy, PPMD Senior Vice President – Legislation & Policy
Juliana Setyawan, Pharm.D., M.S. – Health Economist and Duchenne community member