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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 public comment on the *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 draft scoping document 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 community’s experience. PPMD is focused specifically on the following areas:

**Background:**
- While steroid use does exacerbate osteoporosis, patients are -1 to -3 SD in bone density at baseline\(^1\)
- It is important to note that current BOD data does not account for costs associated with impacts on siblings and family caregivers, and significant costs associated with support through educational systems, etc.
- With respect to the comment on caregiver QOL, we felt this was an oversimplification of this finding and propose another perspective (ICER draft citation 12): Parents of children with Duchenne must develop long-term resiliency and adapt to ever-changing circumstances in order to survive.

**Stakeholder Input:**
- In reference to the mismatch between evidence in clinical benefit and drug pricing as expressed by PBMs, parents view this mismatch from a different perspective than reflected in the Draft Scope. Stability and maintaining activities of daily living are critical and meaningful to patients and their caregivers. These real world outcomes are also relevant and meaningful to the overall healthcare system.

**Interventions and Comparators**
- It is important to be aware that the Duchenne patient community is heterogeneous and disease progression, due to the underlying genetic variations and epigenetic factors at play in Duchenne, is variable. This impacts the ability to make comparisons within the general population in a single model.
Additionally, as we continue to learn more about the nuances of our Duchenne community, the definitions of outcomes may differ among subsets of patients.

- Example 1: For the broad population (Population #1 as described in the Draft Scope), there will be patients with all mutations representing a broad range of severity extending from very mild to very severe, who will be taking either prednisone or deflazacort.
- Example 2: Patients who are candidates for either eteplirsen or golodirsen (population #2) may have a more severe phenotype within the Duchenne spectrum based on their mutation. This could influence the outcomes measured within each respective dataset and trial. Emerging therapies may potentially yield improvement above baseline as the upper bound of the outcome, in addition to slowing or preventing functional decline or progression for patients who are more severely impacted.

- For Population #3 (candidates of Golodirsen), it will be important to distinguish which steroid background is used as a comparator.
- 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.

Outcomes
Related to the key outcomes of interest:

- Respiratory Complications – We recommend adding ability to maintain respiratory function (FVC, PEF, FEV1) and duration of maintaining the patients in respiratory function that allows for daily life activities.
- We suggest adding an additional outcome: “Daily Functional Outcomes” (DFO - which is different from "HRQoL") – The ability to do functional basic self-care activities of daily living such as feed, bathe, self-groom, brush teeth, etc. Improvement/decline could be measured by gaining/losing the ability to do these things over time.
- DFO could be more highly correlated with severity and long-term gradual decline in muscle mass than the HRQoL. This is the case, because HRQoL sometimes does not really reflect disease progression, since patients/caregivers are developing adaptations to changes and losses.

- Related to Caregiver Burden and Home Caregiving –
- The gradual loss of patient's ability to independently transfer or perform ADLs are key factors that drive caregiver burden to the family, and cause the family to need personal support for patients. In the US, the cost of this care is largely funded out of pocket. Thus, we can potentially link these functional outcomes to cost of caring for Duchenne patients long term.
Therapies that maintain functional activities of daily living can potentially improve patient independence and reduce caregiver burden.

Related to Intermediate and Surrogate Outcomes:
- Maintenance of Status Quo – In a progressive disease where function is lost over a period of years, stability or no change from baseline, should be considered improvement.
- In measuring Motor Function, it is important to measure muscle strengths that provide a sense of functional use context in daily life (the ability to lift objects, open doors, use a joystick or keyboard, eat/drink, etc).

Related to Safety Outcomes:
- We recommend adding the following Safety Outcomes:
  - Neurodevelopmental considerations - certain genetic variants associated with DMD are now known to result in atypical dystrophin expression in the brain.ii iii iv
  - Fracture-induced Fatty Embolism Syndromev
  - Diminished or halted linear growth, and impacts on self imagevi

Table 1 – Potential Other Contextual Considerations
- We suggest adding: “This intervention is intended for the care of individuals with a pediatric-onset condition that is fatal and shortens life expectancy.”

In Conclusion
We thank ICER for the effort to seek Duchenne expert input to date. That said, patients and providers must continue to have access to all therapies approved for the treatment of Duchenne and valuations should be seen as an additional resource to empower individual patient/provider decision-making. Valuations should not be utilized as a tool for policy-makers to limit access; such actions could have catastrophic ramifications for children with Duchenne. Among the most critical contextual considerations that must be taken into account that the ‘yet to be fully known’ of all of the interventions detailed within this Draft Scope must be weighted against the ‘certainty of doing nothing’. Maintaining strength and function, slowing disease progression, reducing chance of infection, and optimizing potential outcomes for potential future interventions are all of extreme value to patients and providers within the Duchenne community. 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
REFERENCES


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