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

Draft Background and Scope

January 11, 2019

Background

Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin gene (*DMD*) that result in progressive loss of skeletal and cardiac function. It is the most common pediatric muscular dystrophy with a prevalence of 1 in 3,500-5,000 live male births, or about 400 to 600 boys per year in the US.[1] Rarely, females who are carriers of a *DMD* mutation can also be symptomatic.[2]

DMD is caused by one of more than 2,000 mutations in the gene *DMD* that results in loss of expression of the dystrophin protein. Dystrophin is located in skeletal and cardiac muscle; it forms an important part of the glycoprotein complex, strengthening and connecting muscle fibers. The absence or lack of functional dystrophin results in muscle degradation leading to progressive skeletal weakness and wasting, as well as cardiomyopathy. Levels of dystrophin in patients with DMD are generally less than 3% of normal.[3] The majority of patients (70%) have single- or multi-exon deletions or duplications that are amenable to detection via genetic testing.[4] Severity of disease appears to vary with mutation, resulting in differing rates of progression.[5,6]

Diagnosis of DMD usually occurs in early childhood, with symptoms beginning around age three to five years in affected children. Early symptoms include muscle weakness, clumsiness, difficulty with rising from a squatted position (Gower's sign), and difficulty going up and down stairs. If untreated, children with DMD progress to a loss of ambulation by age 10 years.[7] There may also be developmental delay, as well as impaired growth, delayed puberty, adrenal insufficiency, and gastrointestinal complications from the loss of muscle contraction (e.g., dysphagia and gastroparesis). Osteoporosis with resultant fractures can occur, primarily as a side effect of glucocorticoid therapy. Respiratory problems and cardiomyopathy develop, and death generally occurs in the second or third decade of life due to respiratory or cardiac failure. However, with improved supportive care such as assisted ventilation and new treatments, survival of patients with DMD has improved and some patients are now surviving into their 30s or 40s.[6] Importantly, costs of treating DMD rise as much as five-fold with disease progression, particularly as patients lose the ability to walk and become non-ambulatory.[8]

Quality of life

DMD affects patient and caregiver quality of life in a variety of ways. Scores on health-related quality of life surveys for children with DMD are worse than that of healthy children and children with other chronic illnesses, particularly for physical function.[9,10] Arm function, in particular, significantly influences quality of life.[11] Surprisingly however, studies of DMD patients and caregivers have suggested that although physical quality of life declines with disease progression, scores on social functioning, mental health, and vitality remain fairly stable throughout the disease course.[12] Most caregivers perceived those they cared for to be at least somewhat happy and in good to excellent health regardless of the patient's physical status, though caregiver burden was high.[9,13] Additionally, a review of quality of life studies suggests that DMD patients have a complex quality of life profile that may not be fully captured by current standard quality of life and health-related quality of life tools.[14]

Management of DMD

Care of patients with DMD is multidisciplinary, and services needed are based on disease stage (early ambulatory, late ambulatory, early non-ambulatory, late non-ambulatory). Depending on the patient's needs and disease manifestations, the disease-management team may include neuromuscular specialists, other physicians (e.g., orthopedic surgeons, cardiologists, pulmonologists, gastroenterologists, and endocrinologists), physical and occupational therapists, speech language pathologists, orthotists, psychologists, social workers, and others. Management of DMD involves supportive therapies and medication. Early initiation of treatment has been associated with prolonged ambulation, decreased contractures and deformities, and prolonged function and participation in activities of daily living.[6,15] Early screening and treatment for respiratory and cardiac complications can also improve quality of life and prolong survival.[16]

Medications

Corticosteroids are the mainstay of therapy for DMD. Steroids are usually begun early in the disease course, prior to substantial physical decline. Randomized trials show that treatment with prednisone or prednisolone improves muscle strength and function, and delays loss of ambulation.[15] Steroids have also been shown to possibly slow the development of scoliosis or lessen the need for scoliosis surgery,[17,18] improve pulmonary function,[19,20] delay the onset of cardiomyopathy,[21,22] and decrease mortality.[23] However, treatment side effects include weight gain, hirsutism, osteoporosis and fractures, and cataracts. The optimal length of treatment with corticosteroids is currently not known.

Deflazacort (Emflaza®, PTC Therapeutics) is a newer corticosteroid that was approved by the US Food and Drug Administration (FDA) for treatment of DMD in February 2017. Studies have shown that treatment with deflazacort offers similar benefits to that of DMD patients treated with

prednisone[24], but may be associated with less weight gain.[25] However, deflazacort also may be associated with an increased risk of cataracts compared with prednisone.[20,24]

Exon-skipping therapy

In patients with DMD, mutations in the exons (regions that code for the dystrophin protein) gene *DMD* cause misalignments in the transcription reading frame that lead to nonfunctional or absent dystrophin (Figure 1a). As part of RNA synthesis, exons are connected together to generate messenger RNA that encodes dystrophin, and mutations in a single exon can disrupt all downstream synthesis of protein if the reading frame is disrupted. Exon-skipping therapies are anti-sense oligonucleotides (AON) that can shade mutated exons from being transcribed, which allows downstream exons to be transcribed in the correct reading frame. The remaining exons form a shortened messenger RNA that encodes a shortened but partially functional dystrophin protein (Figure 1b). Animal models and anecdotal data suggest that restoration of small amounts of dystrophin (between 2-4% of normal) may be beneficial in slowing progression of the disease.[26,27]

Figure 1a. Exon Deletion Causing Lack of Dystrophin Production in Duchenne Muscular Dystrophy

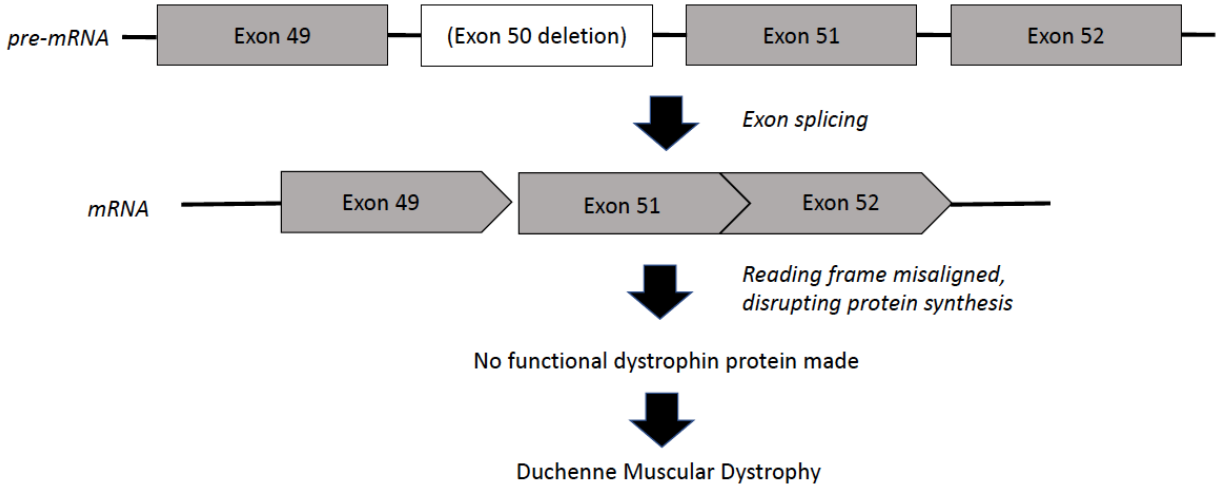
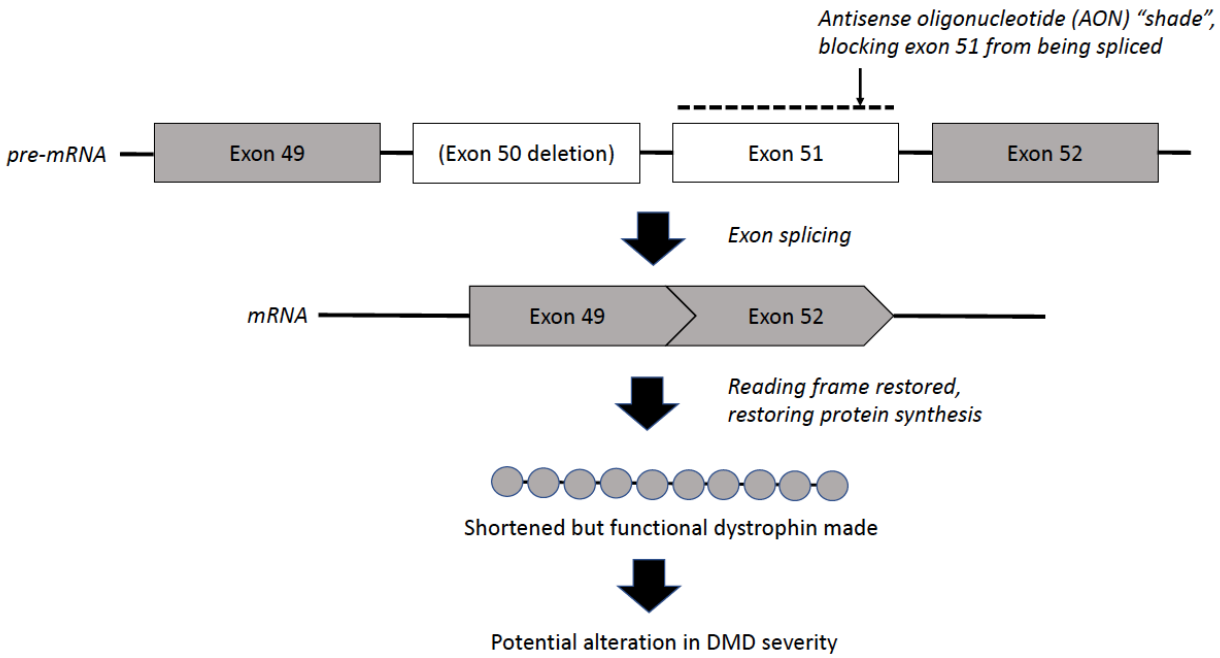


Figure 1b. Exon-Skipping Therapy Leading to Shortened but Functional Dystrophin Production



Eteplirsen (Exondys 51®) was developed by Sarepta Therapeutics and was the first exon-skipping therapy for DMD to be approved by the US FDA in September 2016 for patients with mutations amenable to exon 51 skipping (about 13% of the DMD population). Eteplirsen is delivered by a weekly intravenous infusion. Patients receiving eteplirsen infusions had an increase in dystrophin in skeletal muscle. However, clinical benefit based on increased dystrophin levels has not yet been established.[28]

Golodirsen (SRP-4053) is a new exon-skipping therapy developed by Sarepta Therapeutics for patients with mutations amenable to exon 53 skipping (estimated to be 9% of the DMD population[29]). Based on a Phase I/II study, patients taking golodirsen for one year had a statistically-significant increase in dystrophin protein in skeletal muscle. Based on these results, golodirsen is under evaluation for accelerated approval by the US FDA, with an expected decision date in mid-2019.

Other avenues of treatment are being pursued, such as symptomatic therapies to target muscle degeneration, prevent fibrosis, inhibit myostatin, and reduce inflammation, as well as gene replacement therapy and other gene-altering therapies. However, such treatments have not yet been tested clinically.

DMD has a substantial impact on quality of life and survival. New and promising treatments are emerging; however, questions remain regarding the indications, timing, safety, acceptability, and how well the cost of drug treatment for DMD aligns with potential patient benefits. Therefore,

stakeholders will benefit from a comprehensive review of the clinical evidence for deflazacort, eteplirsen, and golodirsen, and an analysis of their long-term cost-effectiveness.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A final scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Patient groups were concerned that disease-related quality of life was not being adequately measured by current metrics, and that the lack of validated disease-specific quality of life measures, as well as a lack of natural history data, impaired the community's ability to accurately assess the value of treatment interventions. Additionally, concern was expressed that research studies did not include broad enough populations or outcomes that reflect real-world patient functional status, and that non-traditional sources of data, such as videos, may be important in capturing the full spectrum of treatment benefit. Parents described the physical, financial, and emotional tolls of caring for children with DMD, highlighting the barriers to accessing exon-skipping therapies, financial burdens outside of medical costs that are not covered by insurance (e.g., obtaining wheelchair-accessible transportation, costs of renovations to make their homes accessible, travel costs to access specialty care), and the anxiety, depression, and isolation that can result from caring for a child with a severe illness. Additionally, while they hoped that new breakthrough treatments would help improve quality of life for patients with DMD, particularly by improving functional status and independence, parents were also concerned about the potential side effects, durability, and high cost of such therapies. Pharmacy benefit managers discussed the mismatch between evidence of clinical benefit and drug pricing, particularly for the exon-skipping therapies, as a significant barrier to broader access and use of therapies. Manufacturers pointed out that evidence generation, particularly for novel therapies, is a dynamic and ongoing process and thus there will be inherent uncertainty in some outcomes, particularly long-term clinical outcomes. We will continue to gather input from relevant groups during the scoping process.

Report Aim

This project will evaluate the health and economic outcomes of deflazacort, eteplirsen, and golodirsen for patients with DMD. We will assess these three treatments under an adaptation of the ICER value framework focused on treatments for serious, ultra-rare conditions because the assessment meets the following criteria:

- The eligible patient population for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.[30,31]
- There are no ongoing or planned clinical trials of the treatments for a patient population greater than approximately 10,000 individuals.

Based on population studies, the prevalence of DMD in the United States is estimated to be 0.4 per 10,000 males, resulting in approximately 6,000 affected people in the US.[32] The ICER value framework for ultra-rare conditions includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

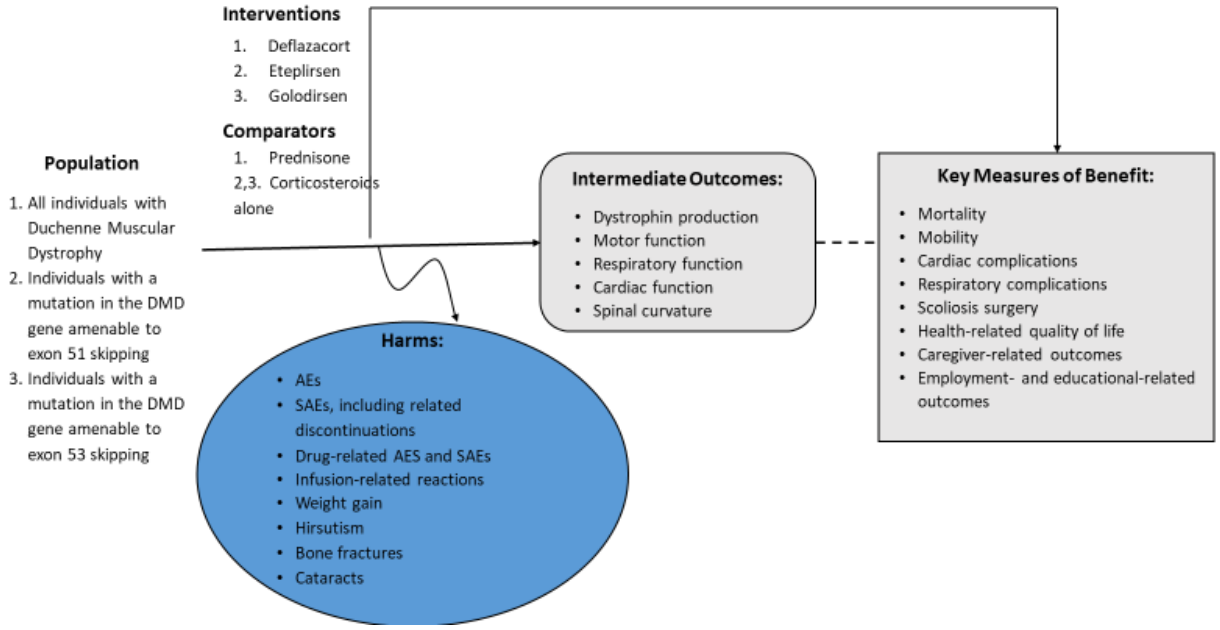
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials and nonrandomized studies as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of therapies for DMD is depicted in Figure 2.

Figure 2. Analytic Framework: Therapies for DMD



AE: adverse event, SAE: serious adverse event

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., dystrophin production), and those within the squared-off boxes are key measures of benefit (e.g., mobility). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipsis.[33]

Populations

Our review will focus on three populations, defined as follows:

1. All individuals with DMD. We will review evidence on the corticosteroid deflazacort in this population based on the FDA-approved indication.
2. All individuals with a mutation of the *DMD* gene amenable to exon 51 skipping. We will review evidence on eteplirsen in this population based on the drug's mechanism of action and FDA-approved indication for eteplirsen.

3. All individuals with a mutation of the *DMD* gene amenable to exon 53 skipping. We will review evidence on the golodirsen based on the mechanism of action and clinical trial population.

Interventions and Comparators

The list of interventions was developed with input from patient organizations, researchers, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

1. For individuals who are candidates for deflazacort, we intend to compare deflazacort to prednisone.
2. For individuals who are candidates for eteplirsen, we intend to compare eteplirsen plus background corticosteroids (i.e., those used per standard care guidelines) to supportive care with corticosteroids alone.
3. For individuals who are candidates for golodirsen, we intend to compare golodirsen plus background corticosteroids to supportive care with corticosteroids alone.

Outcomes

We will seek information on a mix of clinical and patient-centered outcomes, as well as safety data.

The key outcomes of interest are:

- Mortality
- Mobility
- Cardiac issues (e.g., cardiomyopathy, arrythmias, and heart failure)
- Respiratory complications (e.g., dyspnea, respiratory failure, hospitalization due to pneumonia or atelectasis, respiratory-induced cardiac arrythmias)
- Health-related quality of life
- Caregiver burden (e.g., parent employment, home caregiving)
- Education and employment-related outcomes (e.g., ability to attend work or school)

We are also interested in evidence on intermediate and surrogate outcomes:

- Dystrophin production
- Motor function
- Respiratory function
- Cardiac function
- Spinal curvature

Safety outcomes of interest include:

- Adverse and serious adverse events
- Serious adverse events leading to discontinuation of drug
- Weight gain
- Incidence of cataracts
- Hirsutism (unwanted hair growth)
- Bone fractures
- Deaths

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any follow-up duration.

Settings

All relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by deflazacort, eteplirsen, and golodirsen to individual patients, caregivers, the healthcare delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in Table 1.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Table 1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving the patient's ability to return to work and/or their overall productivity.
This intervention will have a significant positive impact outside the family, including communities.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of the treatments of interest (i.e., deflazacort, eteplirsen, and golodirsen). Deflazacort will be compared to prednisone, and eteplirsen and golodirsen, each with corticosteroids, will be compared to background corticosteroids alone. The model structure will be based in part on a literature review of prior published model frameworks of DMD.[34] Following the ICER methodology for treatments of ultra-rare conditions, we will present a dual base case, including both a health care sector perspective (i.e., focus on direct medical care costs only) and a modified societal perspective (i.e., taking into consideration productivity and caregiver-related costs). The target population will be determined based on the intervention of interest, as described above. Depending on available evidence, the model may consist of one or a combination of two

basic structures, one with health states including early and late ambulatory, early and late non-ambulatory, and death, or another with health states such as no-ventilation support, ventilation support and death, pending data availability. The model will likely be based on annual or biannual cycles over a lifetime time horizon, modeling patients from treatment initiation until death. A 3% annual discount rate will be applied to both costs and outcomes. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years), if deemed relevant. If we find inadequate evidence to populate a model for exon-skipping therapy, then for those therapies where the price is known we will develop a threshold analyses showing the degree of efficacy that would be required to reach standard cost-effectiveness thresholds.

Key model inputs will include clinical transition probabilities between health states, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using results from clinical trials and other published literature.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, side effects/adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of life-years and quality-adjusted life years (QALYs) gained. We will also consider available measures of clinical consequences if data permit. Quality of life weights will be applied to each health state, including quality of life decrements for AEs. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver time and productivity losses will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the incremental cost per QALY gained and cost per life-year gained. Subgroup analyses will be conducted if adequate data are available.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be

reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by DMD treatments (e.g., fewer hospitalizations, ED visits, etc.), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of DMD beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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