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

Research Protocol

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Background, Objectives, and Research Questions

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 any of more than 2,000 mutations in the gene *DMD* that result 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 a heterogeneous population with 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. Children with DMD usually progress to a loss of ambulation by age 10; treatment can delay this outcome.[7] There may also be developmental delay and behavioral issues, as well as impaired growth, delayed puberty, adrenal insufficiency, and gastrointestinal complications (e.g., dysphagia and gastroparesis) from the loss of muscle contraction. Osteoporosis with resultant fractures can occur, both from the disease itself and as a side effect of glucocorticoid therapy. Fatal respiratory or cardiac complications commonly develop in the second or third decade of life, with many deaths occurring in the setting of an acute infection such as pneumonia.[8] 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.[9]

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 those of healthy children and children with many other chronic illnesses, particularly for physical function.[10,11] Arm function, in particular, significantly influences quality of life.[12] 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.[13] 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.[10,14] Additionally, a review of quality of life studies suggests that DMD patients and their caregivers 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.[15]

Management of DMD

Care of patients with DMD is multidisciplinary, and care needed is 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.[6,16] Early screening and treatment for respiratory and cardiac complications can also improve quality of life and prolong survival.[17]

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.[16] Steroids have also been shown to possibly slow the development of scoliosis or lessen the need for scoliosis surgery,[18,19] improve pulmonary function,[20,21] delay the onset of cardiomyopathy,[22,23] and decrease mortality.[24] However, treatment side effects include weight gain, hirsutism, decreased bone density and increased risk of fracture, and cataracts. The optimal length of treatment with corticosteroids is currently not known. Deflazacort (Emflaza®, PTC Therapeutics) is a corticosteroid that was approved by the US Food and Drug Administration (FDA) specifically for the treatment of DMD in February 2017. Studies have shown that treatment with deflazacort offers similar benefits to that of DMD patients treated with prednisone,[25] but may be

associated with less weight gain.[26] However, deflazacort also may be associated with an increased risk of cataracts compared with prednisone.[21,25]

Exon-Skipping Therapy

In patients with DMD, mutations in the exons (regions that code for the dystrophin protein) of the *DMD* gene 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 small increases in the amount of dystrophin produced (between 2-4% of normal) may be beneficial in slowing progression of the disease,[27,28] though clinical correlation has yet to be established.

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

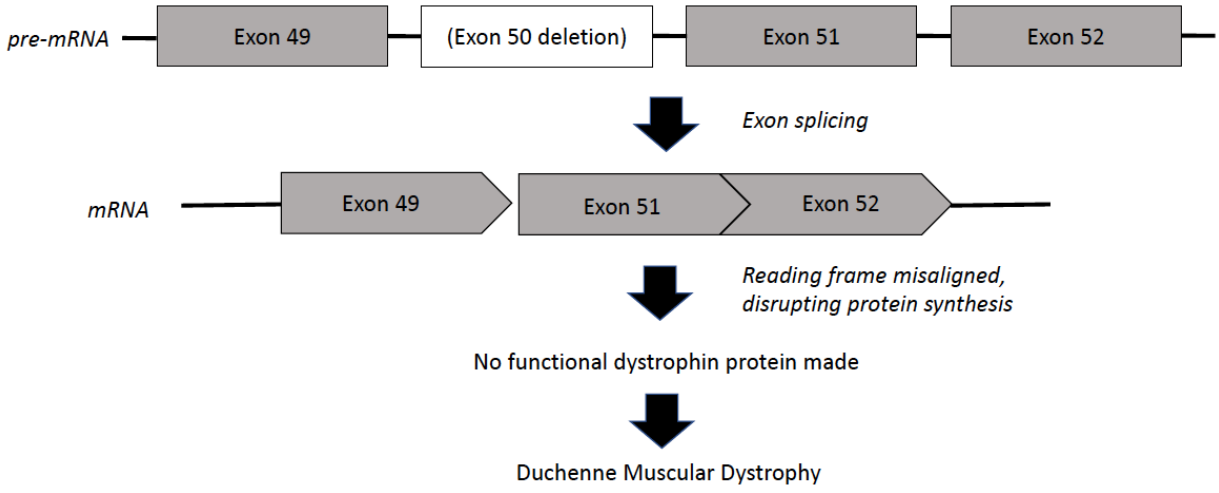
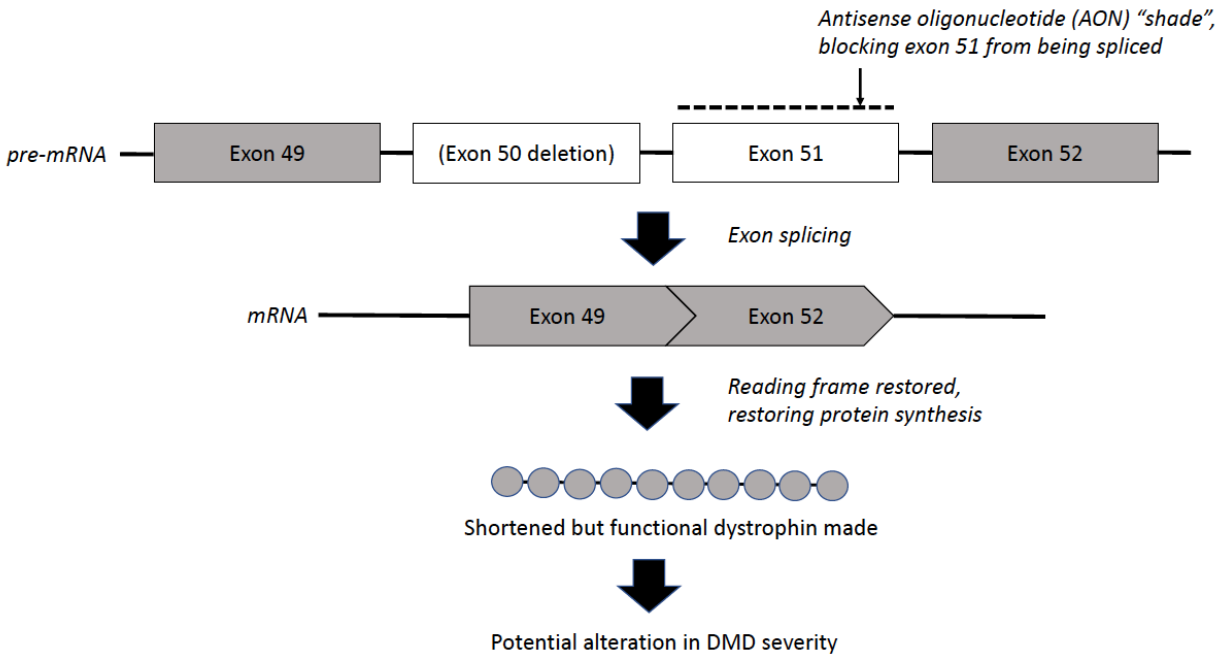


Figure 1b. Exon-Skipping Therapy Leading to Shortened but Functional Dystrophin Production



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.[29]

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[30]). 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, and acceptability of these treatments, as well as how 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.

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of deflazacort, eteplirsen, golodirsen for the treatment of DMD. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). Details on the proposed methodology and model structure for the economic evaluation will be presented in a separate document (to be published on April 9, 2019).

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts, patients, and patient groups:

- In all patients with DMD, what is the comparative efficacy, safety, and effectiveness of deflazacort versus prednisone in terms of mortality, mobility, motor function, cardiac function, respiratory function, activities of daily living, caregiver burden, quality of life, adverse events, and other key outcomes?
- In patients with a mutation of the *DMD* gene amenable to exon 51 skipping, what is the comparative efficacy, safety, and effectiveness of eteplirsen versus supportive care and corticosteroids alone in terms of mortality, mobility, motor function, cardiac function, respiratory function, activities of daily living, caregiver burden, quality of life, adverse events, and other key outcomes?
- In patients with a mutation of the *DMD* gene amenable to exon 53 skipping, what is the comparative efficacy, safety, and effectiveness of golodirsen versus supportive care and corticosteroids alone in terms of mortality, mobility, motor function, cardiac function, respiratory function, activities of daily living, caregiver burden, quality of life, adverse events, and other key outcomes?

PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

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 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 golodirsen based on the drug's mechanism of action.

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 and corticosteroids alone.
3. For individuals who are candidates for golodirsen, we intend to compare golodirsen plus background corticosteroids to supportive care and 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, and respiratory-induced cardiac arrythmias)
- Health-related quality of life
- Activities of daily living
- 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
- Deaths

Additional safety outcomes of interest specific to corticosteroids include:

- Weight gain
- Decreased linear growth
- Cataracts
- Neurodevelopmental and behavioral issues
- Hirsutism (unwanted hair growth)
- Bone fractures and their sequelae (e.g., fat embolism)
- Other complications of chronic corticosteroid therapy

Timing

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

Setting

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

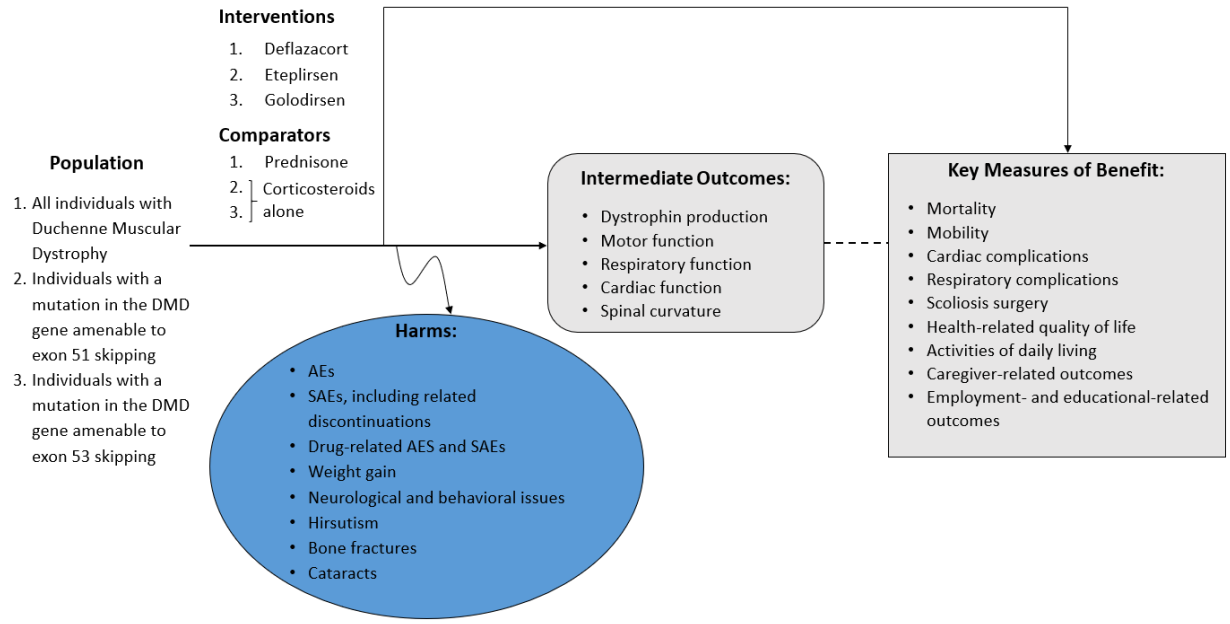
Study Design

Randomized controlled trials, non-randomized comparative studies, and single-arm studies with any sample size will be included.

Analytic Framework

The proposed analytic framework for this project is depicted below:

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.[31]

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on deflazacort, eteplirsen, and golodirsen for DMD will follow established best methods.[32,33] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[34] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include full-text articles as well as abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 1. Search Strategy of Medline 1996 to Present with Daily Update Cochrane Central Register of Controlled Trials via Ovid, March 19, 2019.

1	exp Duchenne muscular dystrophy/
2	(Duchenne muscular dystrophy or DMD).mp.
3	Exon skipping.mp.
4	OR/1-3
5	(eteplirsen OR exondys#?51 OR avi#?4658).mp.
6	(golodirsen OR srp#?4053).mp.
7	(deflazacort OR emflaza OR zamen* OR calcort OR dezacor OR cortax OR decortil OR deflanil OR MOAID OR xalcort).mp.
8	exp steroids/ OR exp glucocorticoids/
9	(steroid* OR corticosteroid* OR glucocorticoid*).mp.

10	exp prednisone/
11	(predniso* OR deltason* OR rayor OR delta-cortef OR meticorten OR orason*).mp.
12	OR/5-11
13	4 AND 12
14	(animals not (humans and animals)).sh.
15	13 NOT 14
16	(addresses OR autobiography OR bibliography OR biography OR clinical trial, phase I OR comment OR congresses OR consensus development OR conference OR duplicate publication OR editorial OR guideline OR in vitro OR interview OR lecture OR legal cases OR legislation OR letter OR news OR newspaper article OR patient education handout OR periodical index OR personal narratives OR portraits OR practice guideline OR review OR video audio media).pt.
17	15 NOT 16
18	limit 17 to English language
19	remove duplicates from 18

Table 2. Embase Search Strategy, March 19, 2019.

#1	'Duchenne muscular dystrophy'/exp
#2	'DMD protein human'
#3	#1 OR #2
#4	'eteplirsen'/exp OR 'golodirsen'/exp OR 'deflazacort'/exp
#5	eteplirsen:ti,ab OR exondys*51:ti,ab OR avi*4658:ti,ab
#6	golodirsen:ti,ab OR srp*4053:ti,ab
#7	(deflazacort OR emflaza OR zamen* OR calcort OR dezacor OR cortax OR decortil OR deflanil OR MOAID OR xalcort):ti,ab
#8	#4 OR #5 OR #6 OR #7
#9	'prednisone' OR 'prednisolone' OR 'steroid' OR 'corticosteroid' OR 'glucocorticoid'
#10	predniso*:ti,ab OR deltason*:ti,ab OR rayor:ti,ab OR delta-cortef:ti,ab OR meticorten:ti,ab OR orason*:ti,ab
#11	#9 OR #10
#12	#3 AND (#8 OR #11)
#13	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#14	#12 NOT #13
#15	#14 AND [english]/lim
#16	#14 AND [medline]/lim
#17	#15 NOT #16
#18	#17 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#119	#17 NOT #18

Eligibility Criteria

Studies meeting the PICOTS criteria will be eligible for our review. To be included, studies must assess deflazacort, eteplirsen, or golodirsen with any dose or regimen. For any study that assesses supportive care, we will accept and use the study's definition of supportive care, noting any potentially important clinically relevant differences between studies. We will exclude studies where only supportive care is assessed (e.g., comparative studies of different supportive care options or single-arm supportive care studies).

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR; a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

Data will be extracted into Microsoft Excel. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[35]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exist: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "deflazacort", "Exondys-51", "eteplirsen" and "golodirsen". We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base and (2) a synthesis of outcome results.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome, described narratively, and presented in tables in the report. Key considerations for interpreting the results will be specified and described in the Evidence Report.

Analyses are expected to be descriptive in nature only, as differences in entry criteria, patient populations, outcome assessments, and other factors are likely to preclude formal quantitative direct or indirect assessments of deflazacort, eteplirsen, and golodirsen versus each other, prednisone, or supportive care. Nevertheless, if studies are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we will conduct random effect pairwise meta-analyses and network meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator.[36] A network meta-analysis extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)). [37,38] The specific approach for any (network) meta-analysis will depend on the available evidence and will be detailed in the report.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[34] Additional explanation of each item can be found in Liberati et al. 2009.[39]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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Appendix B. Data Extraction Summary Table Shell

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes