Protocol for Proposed Evidence in Focus: Delandistrogene Moxeparvovec Gene Therapy in Individuals with Duchenne Muscular Dystrophy

Proposal of the Guidelines Subcommittee of the American Academy of Neurology

Authors (Listed alphabetically, with the exception of the project lead; final order to be determined later in the guideline development process)

Maryam Oskoui, MD, FAAN[1], Jyoti Bharadwaj[2], Russell Butterfield, MD, PhD, BS[3], Tracie Caller, MD, MPH, FAAN[4], James J. Dowling, MD, PhD[5], Julie Parsons, MD[6], Sean Rose, MD, FAAN[7], Laurent Servais, MD, PhD[8], Benjamin Tolchin, MD, MS, FAAN[9]

1. Departments of Pediatrics and Neurology & Neurosurgery, McGill University, Quebec, CA
2. Muscular Dystrophy Association, Chicago, IL
3. Department of Pediatric Neurology, University of Utah, Salt Lake City
4. Department of Neurology, Cheyenne Regional Medical Center, WY
5. Division of Neurology, Hospital for Sick Children, and Departments of Paediatrics and Molecular Genetics, University of Toronto, Canada.
6. Department of Child Neurology, Children's Hospital Colorado, Aurora
7. Nationwide Children's Hospital, Columbus, OH
8. Department of Pediatrics, University of Oxford, UK
9. Department of Neurology, Yale School of Medicine, New Haven, CT

Full name	Role	Guidelines Subcommittee member (Yes/No)	Representing (If representing an external organization)
Maryam Oskoui, MD, FAAN	Lead author, methodologist	Methodologist	
Tracie Caller, MD, MPH, FAAN	Facilitator	Yes	
Sean Rose, MD, FAAN	Co-author (Clinician)	Yes	
Benjamin Tolchin, MD, FAAN	Co-author (Clinician)	Yes	
Russell Butterfield, MD, PhD, BS	Co-author (Clinician)	No	
Julie Parsons, MD	Co-author (Clinician)	No	
James Dowling, MD, PhD	Co-author (Clinician)	No	
Laurent Servais, MD, PhD	Co-author (Clinician)	No	
Jyoti Bharadwaj	Co-author (Patient/caregiver representative)	No	Muscular Dystrophy Association

Correspondence to

American Academy of Neurology:

guidelines@aan.com

Approved by the Guidelines Subcommittee on July 13, 2024.

STUDY FUNDING

This Evidence in Focus protocol was developed with financial support from the American Academy of Neurology (AAN). Authors who serve as AAN subcommittee members (TC, SR, BT), or as methodologists (MO), or who are AAN staff members (KPH), may be reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts are reviewed.

DISCLOSURE

Dr. Oskoui has received personal compensation in the range of $500–$4,999 for serving as an officer or member of the Board of Directors for the Association des Neurologues du Quebec. The institution of Dr. Oskoui has received research support from Roche Genentech. The institution of Dr. Oskoui has received research support from Muscular Dystrophy Canada. The institution of Dr. Oskoui has received research support from Canadian Institutes of Health Research. The institution of Dr. Oskoui has received research support from Santhera. Dr. Oskoui has a non-compensated relationship as a Member of the Medical and Scientific Advisory Committee with Muscular Dystrophy Canada that is relevant to AAN interests or activities.

Dr. Caller has nothing to disclose.

The institution of Dr. Rose has received research support from Dale Earnhardt Jr. Foundation and the National Institute of Neurological Disorders and Stroke.

The institution of Dr. Tolchin has received research support from C. G. Swebilius Trust.

Mrs. Bharadwaj has nothing to disclose.

Dr. Butterfield has received personal compensation in the range of $5,000–$9,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Sarepta. Dr. Butterfield has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Scholar Rock. Dr. Butterfield has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Reata. The institution of Dr. Butterfield has received research support from the FSHD Society. The institution of Dr. Butterfield has received research support from the NIH. The institution of Dr. Butterfield has received research support from Ionis. The institution of Dr. Butterfield has received research support from the CDC.

Dr. Dowling has received personal compensation in the range of $500–$4,999 for serving as a Consultant for GLG. Dr. Dowling has received personal compensation in the range of $500–$4,999 for serving as a Consultant for Ikaika Therapeutics. Dr. Dowling has received personal compensation in the range of $500–$4,999 for serving as a Consultant for Bain Consulting. Dr. Dowling has received personal compensation in the range of $500–$4,999 for serving as a Consultant for Guidepoint. Dr. Dowling has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory board for the RYR1 Foundation. Dr. Dowling has received personal compensation in the range of $10,000–$49,999 for serving as an Expert Witness for Dechert LLP. The institution of Dr. Dowling has received research support from Astellas. The institution of Dr. Dowling has received research support from the NIH. The institution of Dr. Dowling has received research support from the CIHR. Dr. Dowling has received personal compensation in the range of $5,000–$9,999 for serving as an advisor with the Ontario Ministry of Health.

Dr. Parsons has received personal compensation in the range of $5,000–$9,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Biogen. Dr. Parsons has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory or Data

Safety Monitoring board for Pfizer. Dr. Parsons has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Sanofi. Dr. Parsons has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Ultragenex. The institution of Dr. Parsons has received research support from AveXis. The institution of Dr. Parsons has received research support from Biogen. The institution of Dr. Parsons has received research support from Scholar Rock. The institution of Dr. Parsons has received research support from Biohaven. The institution of Dr. Parsons has received research support from PTC Therapeutics. The institution of Dr. Parsons has received research support from Novartis.

Dr. Servais has received personal compensation in the range of $5,000–$9,999 for serving as a Consultant for Biogen. Dr. Servais has received personal compensation in the range of $5,000–$9,999 for serving as a Consultant for Roche. Dr. Servais has received personal compensation in the range of $10,000–$49,999 for serving as a Consultant for Novartis. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving as a Consultant for Astellas. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving as a Consultant for Pfizer. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving as a Consultant for Sarepta. The institution of Laurent Servais has received personal compensation in the range of $500–$4,999 for serving as a Consultant for Evox. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving as a Consultant for PTC. Laurent Servais has received personal compensation in the range of $10,000–$49,999 for serving as a Consultant for Sysnav. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving as a Consultant for BioHaven. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving as a Consultant for Dyne. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving as a Consultant for Zentech. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving as a Consultant for MitoRx. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Lupin. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Fibrogen. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Alltrana. Laurent Servais has received personal compensation in the range of $500–$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Illumina. Laurent Servais has received personal compensation in the range of $10,000–$49,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Roche. The institution of Laurent Servais has received research support from Roche. The institution of Laurent Servais has received research support from Novartis. The institution of Laurent Servais has received research support from Biogen. The institution of Laurent Servais has received research support from Zentech. The institution of Laurent Servais has received research support from BioHaven. The institution of Laurent Servais has received research support from PerkinHalmers. The institution of Laurent Servais has received research support from Scholar Rock.

DESCRIPTION OF AAN DOCUMENT TYPES

This protocol is the planning document for an AAN Evidence in Focus document, which is an accelerated, focused document intended to assist neurologists, other clinicians, and patients and caregivers to contextualize available evidence on newly approved treatment options. Other AAN document types include focused systematic reviews, comprehensive systematic reviews, practice advisories (based on a systematic review), or practice guidelines (based on a systematic review). The Guidelines Subcommittee oversees the development of all of these AAN evidence-based documents. Because it is for planning purposes only, this protocol document is not a substitute for the complete Evidence in Focus document.

EVIDENCE IN FOCUS PROJECT PROTOCOL

Project development plan

This proposed Evidence in Focus project will be developed in accordance with the processes described in the 2017 edition of the AAN clinical practice guideline development process manual,[1] as amended by the Guidelines Subcommittee's more recently adopted processes related to the development of Evidence in Focus documents.

Project timeline

Following is the tentative timeline for development of this Evidence in Focus.

Stage	**Projected completion**
Author panel formed	5/28/2024
Author contracts executed	6/24/2024
Guidelines Subcommittee (GS) approval of protocol	7/13/2024
Literature search completed	8/02/2024
Abstract review completed	8/9/2024
Full text review completed	8/23/2024
Risk of bias (ROB) rating completed	8/20/2024
Data extraction completed	9/6/2024
Data synthesis completed	9/20/2024
Manuscript drafted	10/4/2024
GS approval of EIF manuscript	10/19/2024
Quality Committee approval of EIF manuscript	11/19/2024
First submission to journal	11/19/2024
Second submission to journal	1/23/2025
AAN Board of Director approval	3/28/2025
Publication	5/23/2025

Composition of the author panel

In May 2024, the AAN Guidelines Subcommittee (GS) recruited a multidisciplinary panel consisting of 9 clinicians and patient advocates to develop this Evidence in Focus protocol. The panel includes content experts (RB, JD, MO, JP, and LS), a methodology expert (MO), AAN GS members (TC, BT, and SR), and a patient advocate (JB). All potential authors were required to submit AAN relationship disclosure forms and copies of their curriculum vitae (CV). The panel leadership, consisting of the lead developer and methodologist (MO), guideline facilitator (TC) and AAN staff persons (KPH, KBD), reviewed the disclosure forms and CVs for financial and intellectual conflicts of interest (COI). These documents were specifically screened to exclude those individuals with a clear financial conflict in this topic and those whose professional and intellectual bias would diminish the credibility of the review in the eyes of the intended users. Serving on a speaker's bureau for, being employed by, or holding significant ownership interest in an affected healthcare company (as defined in the 2017 AAN Clinical Practice Guideline Development Process Manual) precluded participation on the author panel. Authors who personally or whose immediate family member(s) received compensation in other capacities from companies of interest in this topic over the past 2 years were determined to have a financial conflict of interest and have a limited role on the author panel.

As required by the AAN, a majority (at least 51 percent) of the members (MO, TC, JD, BT, SR, JB) of the author panel and the lead author (MO) are free of COI relevant to the subject matter of this guideline. Three of the author panel members (LS, JP, RB) were deemed to have financial conflicts of interest and will not be permitted to review or rate the evidence. These authors will be consulted in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles to validate the literature search. The panel members with conflicts of interest will also contribute to the sections of the manuscript concerning clinical context and suggestions for future research. The lead author (MO) and AAN staff (KPH, KBD) recommended the final panel composition to the AAN GS leadership, who reviewed the list of members and the panel leaders' relationship disclosure forms and provided final approval. This entire panel will be solely responsible for the final decisions about the design, analysis, and reporting of the proposed systematic review and practice guideline. The document will then be submitted for approval to the AAN GS, the AAN Quality Committee, and the AAN Board of Directors.

Introduction to proposed Evidence in Focus project topic

Rationale for this Evidence in Focus

Duchenne muscular dystrophy (DMD) is an X-linked childhood onset progressive muscle disease due to pathogenic variants in the *DMD* gene resulting in absence of functional dystrophin protein. Prognosis for affected individuals has improved with multidisciplinary care and use of corticosteroids.[2,3] Novel disease modifying therapies have reached regulatory approval, including several mutation-specific antisense oligonucleotide therapies (ASOs). The first gene therapy, delandistrogene moxeparvovec, gained initial, provisional approval by the FDA on June 22, 2023, with a label expansion (and removal of provisional restriction) on June 20, 2024. The

purpose of this Evidence in Focus is to assess all high-quality clinical studies that evaluate the efficacy of delandistrogene moxeparvovec for improving outcomes in individuals with DMD and the risks associated with its use. The results of the evidence review will then be used to provide clinical considerations for the use of delandistrogene moxeparvovec in clinical practice.

Clinical questions

This Evidence in Focus will address the following questions:

1. In individuals with DMD, is delandistrogene moxeparvovec more effective than placebo or standard care in improving functional motor outcomes?
2. In individuals with DMD, what is the safety profile of delandistrogene moxeparvovec?

Population, Intervention, Comparator, and Outcome (PICO) Table

Question (type)[a]	Population	Intervention	Comparison	Outcome
1. Therapeutic	Individuals with DMD	Delandistrogene moxeparvovec	Placebo, standard care, no treatment	Functional motor outcomes
2. Therapeutic	Individuals with DMD	Delandistrogene moxeparvovec	Placebo, standard care, no treatment	Safety profile

[a] Question type refers to one of the following categories: screening, diagnostic, therapeutic, prognostic, natural history, and frequency.

Rationale for the clinical questions

Delandistrogene moxeparvovec is an adeno-associated virus (AAV)-based microdystrophin gene transfer therapy—the first to receive FDA approval for children with DMD. To help guide clinicians, patients, and families in treatment decisions, an evidence-based synthesis of available information on the effectiveness and safety of this therapy is needed. As DMD is primarily a muscle disease, the impact on motor function was chosen as the clinically relevant measure of efficacy.

Consideration of patient preferences

Interviews of individuals with DMD or their caregivers have highlighted a tolerance of risk when there is a lack of other available disease modifying therapies, advocating for a patient-centered risk-benefit assessment. Functional motor outcomes, as well as quality of life and pulmonary and cardiac function, are the key outcomes highlighted of value to patients and their families, including maintenance of stability across these outcomes.

Relevant special populations and multiple morbidities

The care guidelines in DMD, revised in 2018, address multiple comorbidities including cardiac, respiratory, endocrine, psychological, orthopedic, and gastrointestinal.[4,5,6] They enumerate general care principles for DMD, and also specific recommendations by stage of disease progression, suggested as ambulatory, early non-ambulatory, and late non-ambulatory. Treatment response and potential side effects can vary by age, ambulatory status, concurrent health conditions, or other variables. Special populations of relevance to this Evidence in Focus who present potentially unique circumstances and treatment response(s) include non-ambulatory patients (for whom a large unmet need remains[7]), as well as patients with neurodevelopmental co-morbidities (such as autism spectrum disorder or intellectual disability), cardiomyopathy, liver disease, and respiratory insufficiency. Although these populations are often under-represented in clinical trials, we will ensure that where available, we will include results by age, ambulatory status, and comorbidity.

Another important variable that we will specifically evaluate is prior corticosteroid exposure. Corticosteroids are the cornerstone of pharmacologic treatment in DMD, with a requirement to be on a stable dose of an approved corticosteroid for several months prior to meeting eligibility criteria for most disease modifying therapy clinical trials in DMD. Furthermore, administration of gene therapy requires co-administration of corticosteroids to lower the immune system response.[8] Corticosteroids have been shown to improve strength, timed motor function, pulmonary and cardiac function, delay progression of scoliosis and improve survival in DMD.[2] However, dosing regimens may vary, and the amount and extent of steroid exposure prior to receiving treatment represents an important confounding variable. Careful consideration of differences in corticosteroid exposure between treatment and comparison groups will be needed to ensure comparability of groups.

Study screening and selection criteria: inclusion and exclusion criteria for article selection

Types of participants

Disease	Include/exclude	Rationale (Q#)
Duchenne muscular dystrophy	include	1, 2
Becker muscular dystrophy	exclude	1, 2

We will not restrict the selected studies by age, motor function, or exposure to corticosteroids in the population. However, these variables will be specifically captured for all participants.

Types of intervention

Delandistrogene moxeparvovec is approved as a single-dose treatment. The dose used in each treatment arm will be captured.

Intervention	Include/exclude	Rationale (Q#)
Delandistrogene moxeparvovec	Include	1, 2

SRP-9001	Include	1, 2
Elevidys	Include	1, 2

Comparison group

Comparison group	Include/exclude	Rationale (Q#)
Placebo	Include	1, 2
Standard of care	Include	1, 2
No treatment	Include	1, 2

Standard of care will be defined per study protocol. Standard of care typically refers to care in alignment with the established consensus statements on the care of individuals with DMD. Differences in corticosteroid exposure between treatment and comparison groups will be noted.

Types of outcome measures

Outcome	Include/exclude	Rationale (Q#)
North Star Ambulatory Assessment (NSAA)	Include	1
Performance of Upper Limb (PUL)	Include	1
10-Meter Walk/Run (10MWR)	Include	1
Time to Rise (TTR)	Include	1
Treatment Emergent Adverse Events (TEAEs)	Include	2
Serious Adverse Events (SAEs)	Include	2
Adverse Events (AEs) of Special Interest	Include	2

In addition to the above specific outcome measures, we will also report all primary outcome measures included in the studies.

Literature search strategy

We will conduct a systematic review of the literature for clinical studies of delandistrogene moxeparvovec in individuals with DMD. Two non-conflicted panel members will independently review abstracts for inclusion. Then, two panel members will independently review the full text articles of the selected abstracts for inclusion. Data from posted results on clinicaltrials.gov and in available FDA documents will also be reviewed. For evidence-based information about adverse reactions, warnings, and precautions, we will include all study types of original reports

and consult the Lexicomp database and FDA drug labels, as complete information is not available from randomized clinical trials due to their comparatively short length.

Inclusion and exclusion criteria

Study type	Include/exclude	Rationale (Q#)
Randomized controlled trial	Include	1,2
Cohort – Prospective	Include	1,2
Cohort – Retrospective	Include	1,2
Case control	Include	1,2
Case series	Include	2
Review papers/Systematic reviews	Exclude	1,2
Meta-analyses	Exclude	1,2
Population-based epidemiological studies	Include	1,2
Gray literature	Include	1,2

Terms and databases to be used in the literature search

Databases to search: PubMed and Cochrane

1. Muscular Dystrophy, Duchenne/ or duchenne
2. SRP-9001
3. elevidys
4. Delandistrogene moxeparvovec
5. 2 or 3 or 4
6. 1 and 5
7. limit 6 to non-animals (humans only)

Gray literature from Clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP), and any available FDA documents will also be searched for available data on Delandistrogene moxeparvovec and related substance naming conventions. Studies in all languages will be included.

Risk of bias assessment

Selected studies will be evaluated for internal risk of bias using the AAN 2017 classification system for therapeutic studies.[1] Patient reported outcomes and functional motor scales will be considered non-objective. Laboratory findings, death, and hospitalizations will be considered as objective outcomes. Each selected study will be independently rated for risk of bias by two nonconflicted raters who have passed the AAN's evidence rater test (TC, SR, BT). Any disagreement will be arbitrated by a third reviewer who will be the methodologist (MO). We will include all classes of studies.

Data extraction and analysis

Data extraction will be done by authors without conflict of interest (TC, SR, BT, JD) and reviewed by the study methodologist (MO), who will be tasked with the synthesis of results. We plan to report the study findings directly and not provide a meta-analysis.

Discussion

The clinical context section will include a discussion on the FDA label and any gaps between the available evidence, challenges in measuring efficacy of treatment including clinically important effects on functional motor scales and biomarkers, infrastructure needs, and safety monitoring. The future directions will include a discussion on remaining questions in dosing, expected durability of treatment, combination therapy, timing of treatment, and wearables as outcome measures.

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews and other guidance published by the American Academy of Neurology (AAN) and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information: 1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; 2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

CONFLICT OF INTEREST

The AAN's Relationships and Conflicts of Interest Policy is available at AAN.com/disclosures. All AAN guideline authors must meet the stipulations outlined in the policy in order to participate on a guideline development panel. This policy and specific requirements related to guidelines are further described in the 2017 AAN Clinical Practice Guideline Development Manual, available at *AAN.com/practice/what-are-clinical-practice-guidelines.*[1]

REFERENCES

[1] Gronseth GS, Cox J, Gloss D, et al. Clinical Practice Guideline Process Manual. Minneapolis: The American Academy of Neurology; 2017. Available at: https://www.aan.com/siteassets/home-page/policy-and-guidelines/guidelines/about-guidelines/17guidelineprocman_pg.pdf. Accessed July 2, 2024.

[2] Gloss D, Moxley RT 3rd, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016 Feb 2;86(5):465-72. doi: 10.1212/WNL.0000000000002337. PMID: 26833937; PMCID: PMC4773944.

[3] McDonald CM, Mayer OH, Hor KN, Miller D, Goemans N, Henricson EK, Marden JR, Freimark J, Lane H, Zhang A, Frean M, Trifillis P, Koladicz K, Signorovitch J; PRO-DMD-01 consortium investigators. Functional and Clinical Outcomes Associated with Steroid Treatment among Non-ambulatory Patients with Duchenne Muscular Dystrophy1. J Neuromuscul Dis. 2023;10(1):67-79. doi: 10.3233/JND-221575. PMID: 36565131; PMCID: PMC9881035.

[4] Birnkrant, D. J., et al. (2018). "Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management." *Lancet Neurol* 17(3): 251-267.

[5] Birnkrant, D. J., et al. (2018). "Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management." *Lancet Neurol* 17(4): 347-361.

[6] Birnkrant, D. J., et al. (2018). "Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan." *Lancet Neurol* 17(5): 445-455.

[7] Schuster ALR, Crossnohere NL, Fischer R, Furlong P, Bridges JFP. Unmet Therapeutic Needs of Non-Ambulatory Patients with Duchenne Muscular Dystrophy: A Mixed-Method Analysis. Ther Innov Regul Sci. 2022 Jul;56(4):572-586. doi: 10.1007/s43441-022-00389-x. Epub 2022 Mar 24. PMID: 35325439; PMCID: PMC8943787.

[8] Sack BK, Herzog RW. Evading the immune response upon in vivo gene therapy with viral vectors. Curr Opin Mol Ther. 2009 Oct;11(5):493-503. PMID: 19806497; PMCID: PMC3584155.