August 21, 2023

Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Blvd.
Baltimore, MD 21244

Re: (PROPOSED) CMS National Coverage Analysis Evidence Review

Dear Coverage and Analysis Group,

In service of the neuromuscular disease (NMD) patient community, the Muscular Dystrophy Association (MDA) thanks the Centers for Medicare and Medicaid Services (CMS) for the opportunity to comment on the proposed guidance document entitled, "CMS National Coverage Analysis Evidence Review". We are grateful for CMS's efforts to articulate their expectations on the evidence necessary to successfully support a national coverage determination.

MDA is the #1 voluntary health organization in the United States for people living with muscular dystrophy, ALS, and related neuromuscular diseases. For over 70 years, MDA has led the way in accelerating research, advancing care, and advocating for the support of our families. MDA's mission is to empower the people we serve to live longer, more independent lives.

Neuromuscular diseases are a group of rare, serious, progressive, mostly irreversible conditions that, while each unique, are collectively defined by progressive muscle weakening and degeneration leading to physical disabilities and, for many, early mortality. Clinical interventions for NMDs are particularly difficult to test within traditionally structured clinical trials for several reasons. First, each NMD is a rare disease, and most would be considered ultra-rare. Consequently, often there are simply not enough patients to power to a traditionally-run clinical study. The inherent heterogeneity of the diseases often confound results and endpoints are not only difficult to choose, but also challenged in measuring what's truly impactful for the community.

With this in mind, it is incredibly important for decisionmakers to act with flexibility and understanding of these inherent challenges in rare neuromuscular disease clinical testing. Unfortunately, this draft guidance is incredibly rigid, and ignores the realities of clinical testing in rare diseases.

The Realities of Clinical Testing in Rare Diseases is Largely Ignored

CMS throughout this proposed guidance outlines the ideal mechanisms and features of evidence generation to justify a national coverage determination, and by focusing on the ideal, completely ignores the challenges associated with ultra-rare disease clinical testing.

Numerous examples exist. CMS states,

> "In general, some of the methodological attributes of clinical studies that are associated with stronger evidence include the following:"
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> - Use of randomization (in allocation of patients to either an intervention or a control group) to reduce bias.
> - Use of contemporaneous control groups (rather than historical controls) to ensure comparability between the intervention and control groups.
> - Prospective (rather than retrospective) studies to ensure comparability through a more thorough and systematic assessment of factors related to outcomes.
> - Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant and clinically meaningful improvements in health outcomes."

Concurrent controls are not always possible in ultra-rare disease clinical testing, and instead historical or other non-concurrent controls may be necessary. Moreover, larger sample sizes are impossible in diseases of only a handful individuals. How does CMS plan to consider evidence from studies that do not meet these expected methodological attributes?

CMS's description of methods to maintain internal validity also bias against rare disease clinical studies. Participating in a clinical trial can be challenging for those with rare diseases for a number of reasons, including travel difficulties for those with chronic diseases and disabilities, few trial sites resulting in hundreds of miles of travel, and more. Consequently, selection and attrition biases can occur, but are manageable. Still, CMS must expect these difficulties within rare disease clinical trials to occur, and must not deter CMS from considering the evidence.

This proposal argues that "to interpret and generalize conclusions to the Medicare beneficiary population, studies may need to match or stratify their intervention and control groups by patient age, co-morbidities, disabling conditions, etc". CMS also states that "Evidence that provides accurate information about a population or setting not well represented in the Medicare program might be considered, but their applicability may suffer from limited generalizability." When only a handful of individuals are able to participate in a clinical study, and even fewer are within the standard Medicare beneficiary population, it may be impossible to stratify groups to satisfy this expectation. How will CMS consider evidence from an ultra-rare condition in which only a handful of the study participants are over 65 or otherwise qualify for Medicare?

Later, CMS suggests "Ensuring adequate sample size so that a study has sufficient power to detect clinically meaningful outcome differences between the treatment and control group, with acceptable precision". At the risk of redundancy, this again ignores the inherent small samples sizes of rare disease, particularly ultra-rare disease, populations.

CMS continues, stating, "CMS can draw more confident conclusions about effectiveness when multiple studies report findings in the same direction for a particular health outcome." Often only one study is difficult enough to conduct in rare diseases let alone two or more. This is at least in part why the Food and Drug Administration (FDA) considers the substantial evidence of

effectiveness threshold to be met if one well-controlled trial plus confirmatory evidence is submitted to FDA for approval. Conducting multiple studies may not be possible in many ultra-rare diseases and could pose a barrier to evidence generation occurring at all if the evidentiary bar is too high.

Finally, CMS discourages studies to rely too heavily on academic medical centers, stating, "Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings." This again is likely unrealistic in rare neuromuscular diseases. Clinical trials are often run by the handful of clinical specialists in the field who are almost always housed at an academic medical center. Therefore most of rare disease clinical research inherently happens at these centers. CMS should not punish evidence generated from rare disease clinical studies due to it being collected at academic medical centers.

Randomized Clinical Trials Feature Unique Confounding Biases in NMDs

Many hold the belief that randomized controlled trials (RCTs) are the ideal method for collecting clinical data to serve as evidence for informed decisionmaking. Within this proposed guidance, CMS appears to agree, stating, "In general, but not absolutely, the hierarchy of evidence dictates that randomized controlled trials (RCTs) represent the most credible evidence because they are the least subject to biased estimates of outcomes; even so, observational studies can be more representative of actual clinical practice and may answer questions that RCTs cannot answer."

We appreciate CMS's acknowledgement that often observational studies can be more representative of actual clinical practice as not only can this be true within NMDs, but RCTs also carry their own confounding challenges in NMDs. For example, many RCTs in NMDs rely on subjective clinical outcome assessments that can confound results. The diseases are heterogenous and progressive, sometimes leading to an overperforming or underperforming placebo group, thus skewing results. RCTs within NMDs can fall victim to the same sampling challenges as other forms of trials.

In conclusion, RCTs in NMDs are not the panacea many would hope. Instead, they include the very same if not greater sampling, testing, validation, and other biases compared to other forms of clinical testing.

Benefits to NMD Population Are Hard to Capture

CMS also largely fails to recognize the difficulty of capturing the benefits or effectiveness of rare disease, particularly neuromuscular disease, treatments. For example, CMS says, "A wide confidence interval does not permit a confident conclusion regarding the effects of treatment." While in an ideal world, this is indeed true, sometimes miniscule confidence intervals can be difficult to generate in small clinical trials of progressive, heterogenous diseases.

Moreover, CMS states,

> "An intervention's benefits should generally be clinically meaningful and durable rather than marginal or short-lived. When making NCDs, CMS generally places greater

> emphasis on health outcomes important to patients and their caregivers, such as quality of life, functional status, duration of disability, morbidity, and mortality, and less emphasis on outcomes in which patients often have a less direct interest, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses."

CMS again is stating the ideal while ignoring the realities in rare diseases. Often short-lived benefits are still incredibly impactful to those with severe, often terminal, diseases such as amyotrophic lateral sclerosis (ALS). Often only clinical trials that use intermediate or surrogate outcomes are feasible with slowly progressive neuromuscular diseases. The benefit may not appears significant, perhaps only extending the life of an individual by a few months, or allowing an individual to walk or reach a cabinet for just a bit longer. But these benefits can be incredibly meaningful for those with neuromuscular diseases and should not be discounted.

In short, CMS must not be so careful with the benefit it perceives of certain interventions as to someone who is not living with the disease, they may not appear to be meaningful. While patient preference information can help emphasize what is important to different communities, such data may not always be available due to the rarity of the disease and the lack of investment into collecting such outcomes.

As we have asked throughout our comments, we request CMS to flexibly consider where these expectations may not be met for rare diseases and consider alternative approaches to coverage under national coverage determinations.

In conclusion, we are grateful for the opportunity to comment on CMS's efforts to articulate the evidence necessary to justify a national coverage determination. For questions regarding MDA or the above comments, please contact us at advocacy@mdausa.org.

Sincerely,

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