September 6, 2019

Institute for Clinical and Economic Review
Two Liberty Square
Ninth Floor
Boston, MA 02109

Re: Value Assessment Methods for "Single or Short-Term Transformative Therapies" (SSTs): Proposed Adaptations to the ICER Value Assessment Framework

Dear Dr. Pearson,

The Muscular Dystrophy Association (MDA) thanks the Institute for Clinical and Economic Review (ICER or the Institute) for the opportunity to comment on ICER's "Value Assessment Methods for 'Single or Short-Term Transformative Therapies' (SSTs): Proposed Adaptations to the ICER Value Assessment Framework."

MDA is the nation's leading nonprofit organization dedicated to transforming the lives of individuals living with muscular dystrophy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA) and other neuromuscular diseases (NMDs) through innovations in science and innovations in care. MDA fulfills its mission by funding biomedical research, providing access to expert clinical care and support through its national MDA Care Center Network which is comprised of expert medical clinics at more than 150 of the top health care institutions across the US, and by championing public policies and programs that benefit those it serves. Since inception, MDA has invested more than $1 billion in research grants to accelerate treatments and cures for neuromuscular disorders, making MDA the largest source of neuromuscular disease funding in the U.S. outside of the federal government.

One gene therapy for an NMD, spinal muscular atrophy (SMA), has already been approved by the Food and Drug Administration (FDA)—the second gene therapy for a genetic disease ever approved in the US. With a dedicated research community, and with the SMA therapy as a catalyst, many exciting gene therapy approaches, including gene editing technologies, are currently under development to treat a variety of NMDs, including Duchenne muscular dystrophy (DMD), Friedreich's Ataxia (FA), Limb-girdle muscular dystrophy (LGMD) and Facioscapulohumeral muscular dystrophy (FSHD). In fact, the future of therapeutic development for NMDs is heavily focused on "single or short-term transformative therapies."

Consequently, conversations around the economic valuation and impact of SSTs, and subsequent access strategies and considerations, are of particular importance to the NMD community and MDA. Perspectives, recommendations, and suggestions that impact when, where, how, and to whom such therapies will be made available can be significantly impacted by such discussions, and it will be important to keep the perspective of the patient and their families at the forefront of

such activities. Therefore, MDA is pleased to share our comments on ICER's proposed alterations to their value assessment methods for SSTs.

We appreciate that ICER acknowledges the unique challenges SSTs pose to access, coverage, and reimbursement systems, as well as the valuation techniques that help guide these systems. However, we find that ICER's decision to deliberately exclude certain elements of value that are important to the patient population because of their apparent complexity to quantify to be, at best, troubling. The current form of the SST framework, as acknowledged by ICER, disregards some of the most important values patients may derive from SSTs, resulting in an analysis that is not necessarily reflective of the needs of the patient community.

Single or Short-Term Transformative Therapies in Neuromuscular Diseases

In many ways, neuromuscular diseases are at the forefront of the ongoing revolution of transformative technologies. Indeed, Novartis's Zolgensma for SMA has only accelerated conversations on the promise of these groundbreaking therapies, and the challenges they pose to our coverage and payment systems.

There are many SSTs on the horizon for NMDs, only further heightening the urgency. As of October 2018, over 275 clinical trials for 195 therapies were ongoing for NMDs.[1] Of these 195 potential therapies, 14 percent are gene therapies, all of which could qualify as SSTs if approved. As explained in a recent study of the neuromuscular disease space,

> "The accessibility of muscle and the potential for its cells to amplify the impact of nuclear-targeted therapies due to their being multinucleate, make it an attractive target for gene therapy and novel genome editing technologies. Additionally, breakthroughs in targeting the motor neurons of the central nervous system have also accelerated gene therapy efforts for these diseases."[2]

With one approval already in place and with many SSTs in the pipeline for NMDs, the urgency to establish access to such therapies is pressing.

Framework Revisions for SSTs:

As ICER sets out in its report, SSTs create unique challenges to value assessments that may not be presented by conventionally administered therapies. Thus, we agree that a modified framework to satisfy the unique aspects of SSTs is in order.

ICER sets out four unique challenges with the valuation of SSTs, including: increased uncertainty and unrecoverable costs, additional dimensions of value, time divergence between costs and benefits, and affordability and economic surplus concerns. Each of these situations presented by SSTs requires an amended evaluation, and we encourage other decisionmakers and

[1] Understanding Neuromuscular Disease Care: Current State and Future Prospects (2018, October 30). Retrieved September 6, 2019, from https://www.iqvia.com/institute/reports/understanding-neuromuscular-disease-care
[2] Id., at 32

policy makers in the coverage and reimbursement space to follow ICER's lead in acknowledging the immediate necessity of considering the uniqueness of gene therapy and SST approaches.

Exclusion of Critical Additional Elements of Value:

While MDA is supportive of much of ICER's proposal, we are troubled by ICER's decision to exclude seemingly all potential unique values that patients may derive from SSTs that do not fit within classic cost effectiveness analysis. We believe this decision could strongly skew ICER's findings and exclude many values that patients derive from these innovative therapies.

Added Dimensions of Value: MDA rejects ICER's concern about "adding dimensions of value that only increase the assessed value of some forms of treatment – and thus would support higher prices for them – without creating some mechanism for balancing this when the resultant opportunity cost and attendant health losses due to other treatments foregone."

We fail to understand how unique values derived from transformative therapies should somehow be disqualified due to the opportunity cost of not taking another therapy. If this is the case, why is ICER not ignoring all unique aspects of SSTs and simply treating SSTs exactly like all other therapies? We fail to understand the distinction ICER is trying to make between excluding unique elements of value in SSTs, but including other unique considerations of SSTs, such as their potential permanence, ambiguous long-term value, and more. Without further explanation, ICER's decision appears arbitrary.

Value of Hope: ICER appears to misunderstand the "value of hope" in a way that allows the Institute to exclude this important value from its evaluations. ICER defines the "value of hope" to be the "value of having the *choice* among treatments with a different balance and timing of risks and benefits." MDA disagrees with this alternative definition. The "value of hope" is about the potential for a more healthy and happy life in the future than was previously expected. SSTs offer patients the possibility of substantially healthier lives many years into the future, and with this brings the hope of attending college, getting married, and other important life experiences. ICER's alternative definition ignores the hope for experiencing these seminal moments entirely.

Insurance Value: The exclusion of insurance value is concerning to MDA. ICER acknowledges that insurance value has been empirically measured by Lakdawalla et al. and through "explicit mathematical models of consumer utility maximization."[3] However, ICER dismisses these empirical values of SSTs by stating that insurance value, "overlaps significantly with considerations given to severity or burden of illness." We disagree; there is not enough overlap between insurance value and burden of illness to justify excluding insurance value. Burden of illness studies pertain mostly to those directly affected by the disease while insurance value pertains to those not yet affected. Insurance value, as ICER acknowledges, is about peace of mind for individuals who do not have the disease, and therefore such values are not captured within burden of illness values.

[3] Lakdawalla DN, Doshi JA, Garrison LP, Jr., Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(2):131-139.

Additionally, ICER's assertion that including insurance value within its assessments in an empirical manner would result in too substantial of an impact is discouraging. If one takes this argument to its conclusion, it can safely be assumed that all substantial values of new therapies would need to be discarded due to their financial impact, and only values that fit within ICER's vision for appropriate spending levels should be included. We view this as an incredibly subjective method for approaching value assessments.

Scientific Spillover Effects: ICER's exclusion of empirical values pertaining to scientific spillover effects is subjective and serves to skew its value assessments. ICER again acknowledges that scientific spillover effects have been empirically measured but disregards such values as duplicitous with the value the future therapies will derive, and problematic due to the opportunity costs they will create for other patients.

MDA is concerned by ICER's stance on behalf of unnamed patients that including alternative values of therapies will present opportunity costs for other patients in the healthcare system. This argument can be used for any value anywhere within our healthcare system, (or our society in general), but ICER is only applying this concern to these additional elements of value.

In general, MDA is disappointed that ICER appears to be subjectively picking and choosing which empirical values it includes within its assessments based upon opinion and insufficient reasoning. We request that ICER reconsider excluding these empirical values.

Potential Exclusion from Future Therapies:

MDA is supportive of ICER's intention to include considerations of the implication of SSTs potentially excluding patients from being able to take future SSTs due to the mechanism of action or immune response. We are aware that certain disease modifying therapies, particularly gene therapies and gene editing technologies, provide irreversible effects. These therapies may also disqualify patients from future ability to take other SSTs or disease modifying therapy.

This is a very real issue that patients today must grapple with. Including this possibility in an empirical manner within ICER's assessments is appropriate. However, including this potential harm of an SST while excluding many potential unique benefits is troubling. If ICER is to include the potential unique harms of SSTs, it must also include the potential unique benefits.

Time Horizons:

MDA encourages ICER to flexibly approach time horizons within upcoming evaluations of SSTs as each SST may require a unique variety of time horizons to be considered. Within ICER's proposal, the Institute proposes to assess cost-effectiveness scenarios, "at 5 years, 10 years, and the standard lifetime horizon." We encourage ICER to consider a flexible approach in which more than these three horizons are considered based upon the expected, or potential, duration of the effectiveness of the therapy.

Additionally, we caution ICER against deferring to "decision-makers" as they, "may wish to apply their own judgement on the time horizon for which judgements of value should be based." While decision-makers will use whichever criteria they would like, we do not encourage ICER to simply defer this choice to decision-makers (which we interpret to be private or public payers who may use ICER reports in their coverage decisions). Instead, we recommend that ICER publish a variety of time horizons, or at the very least publish the time horizons that make the most sense for the specific therapy, for public consumption and consideration. This will allow the public to consider all time horizons decision-makers may choose to use in their analysis.

Flexible Cost-Effectiveness Thresholds:

MDA believes that all orphan therapies (a category which encompasses every approved therapy for neuromuscular diseases) deserve a flexible approach to their cost-effectiveness evaluations. ICER has shown this flexibility within its ultra-orphan therapy adjusted framework by increasing the societal willingness-to-pay threshold to $450,000 per QALY compared to the lower values within its standard framework. However, ICER refuses to flexibly approach its cost-effectiveness threshold for ultra-orphan therapies by keeping the highest threshold at $150,000 per QALY.

We believe this will once again prove problematic in evaluating SSTs as they will likely all be orphan therapies and will once again have to meet the same cost-effectiveness thresholds that common disease therapies meet. This runs counter to several international agencies who have raised the cost-effectiveness threshold for orphan therapies in their evaluations as well as the increased societal willingness-to-pay.

MDA encourages ICER to revisit whether the $150,000 cost-effectiveness threshold is appropriate for SSTs, and other orphan therapies. A flexible approach to SST cost-effectiveness thresholds, as employed in other systems, could be warranted.

Controversies and Uncertainties:

MDA supports the addition of a section to identify uncertainties as ignoring them would result in an incomplete evalution. However, we caution against the use of the word "controversies" within the title of the section. There will be uncertainties in economic reviews, and within those uncertainties there may be diverging views and perspectives, but divergent thinking and analysis does not necessarily result in controversy.

Within this section, we support ICER's intention to discuss alternative model structures submitted by outside stakeholders and would urge that any considerations and/or modeling that is proposed by outside stakeholders be published and responded to in finalized recommendations by ICER. Knowing the source of outside counsel is essential in the community evaluation of the recommendation, and transparency will be essential in such valuation exercises. We encourage ICER to remain open to alternative ways of measuring the value of SSTs. By allowing for outside submissions, ICER will create a more inclusive process.

Probabilistic Sensitivity Analysis and Outcomes-Based Payments:

MDA appreciates ICER's discussion on aligning prices and payments to the value the health intervention brings. As the Institute discusses, SSTs naturally bring added ambiguity to the value of the therapy as expected values could be stronger or weaker than initially anticipated due to the lack of long-term data upon administration of the therapy. Consequently, MDA is eager to participate in deliberations on how best to reorient our payment and pricing incentives to better align with value, particularly where uncertainty of the therapy's long-term value is present.

Patient-Focused Expected Outcomes:

As ICER evaluates the long-term potential value of a new SST, the Institute will assess what "expected outcomes" can be derived from the therapy. MDA asks that ICER clarifies the definition of "expected outcomes." Will ICER only evaluate the therapy's expected outcomes using the primary or secondary endpoints from the clinical trials?

We encourage ICER to also include additional outcome measures that may be more important to patients, or outcomes derived from patients using innovative clinical outcomes assessments driven by real world evidence (RWE). MDA also encourages ICER to consider patient preference information (PPI) and patient experience data (PED) when choosing which outcomes the Institute will use to evaluate a therapy's long-term value.

These patient-focused outcomes are critical to assessing the salience of a therapy to a patient population. ICER's recent review of therapies for DMD offers a perfect example. DMD patient representatives (mostly parents of children with DMD) emphasized that the six-minute walk test, the primary endpoint for most clinical trials for FDA-approved therapies for DMD, is a poor way to measure the progression of the disease, or the efficacy of a drug. Instead, other measures are much more salient to the patient's experience. Consequently, we encourage ICER to consider patient-focused outcomes when assessing the long-term value of SSTs rather than simply clinical trial endpoints that may or may not actually matter to patients and their families.

Cure Proportion Modeling:

MDA is supportive of exploring cure proportion modeling and flag that it will be essential to engage the patient community to help define what is considered curative for this purpose.

We again thank ICER for the opportunity to comment and look forward to continuing to work with the Institute to ensure clinical and economic evaluations of transformative therapies are thorough, accurate, and beneficial and inclusive to the neuromuscular disease community. For questions regarding MDA or the above comments, please contact advocacy@mdausa.org.

Sincerely,

Paul Melmeyer, MPP
Director of Regulatory Affairs