



September 6, 2019

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

Re: Value Assessment for Single or Short-Term Transformative Therapies

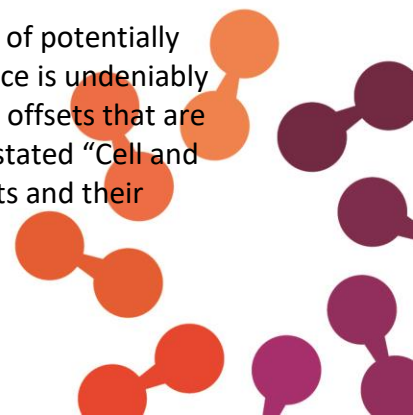
Introduction

The Alliance for Regenerative Medicine (ARM) is pleased to provide our comments in response to the Institute for Clinical and Economic Review (ICER) August 6, 2019 request for inputs on the “Value Assessment Methods for ‘Single or Short-Term Transformative Therapies (SSTs).”

ARM is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 300 leading life sciences companies, research institutions, patient groups and other stakeholders that represent the regenerative medicine and advanced therapies community. Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of investigational new drug (IND) applications, and Biologics License Applications (BLA) for such products to the FDA. ARM takes the lead on the sector’s most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

The HTA evaluation issues for SSTs raised by ICER are critical ones for ARM members. Cell and gene therapies have shown the potential to cure many diseases, including those partly or fully caused by genetic mutations. Other therapies developed, or in development, by ARM member companies have shown evidence of halting progression of severe and rare diseases, significantly improving the quality of life of patients with serious unmet medical needs. Cell and gene therapies are complex and costly to manufacture, can require custom processes to create individualized therapies, and in many cases are administered once or over a short course of treatment. Typically, under current U.S. reimbursement systems, more of the payer cost of the therapy is ‘up front’ in nature (given it is not administered on a chronic basis). Initial results from late stage clinical trials and post-launch experience suggest that the relevant outcomes of these therapies can be profound, durable and observed over the long-term.

With the emergence of these therapies, we are entering an unprecedented era of potentially curative treatments for patients. ICER has previously acknowledged, “The science is undeniably exciting” and can “reflect extreme magnitudes of lifetime health gains and cost offsets that are far beyond those generated by traditional therapies.” More recently, ICER has stated “Cell and gene therapies are starting to provide truly transformative advances for patients and their



families, particularly those with conditions for which there has not been any effective treatment before.”

ICER Value Assessment Methods Inadequate to Fully Reflect Long-Term Value of SSTs

ARM believes that independent scientific evaluations of clinical and economic evidence supporting the utilization of Food and Drug Administration (FDA) approved SSTs is critical. However, such analyses should focus on the unique benefits of a new technology before considering issues of short-term costs and/or the need for innovative payment models. Such an approach maintains the priority of patient access to the most appropriate therapy to treat their disease, a goal that we believe ARM and ICER share. Ideally, all interventions should be first appraised based on their clinical merit for patients and benefits to families and caregivers. Discussions around society’s willingness and ability to pay should take place subsequently and should be considered/determined by those paying, not by third-party observers such as ICER. Collectively, we should make every effort to ensure patients have access to innovative new therapies in a timely manner, especially in the case of severe or life-threatening conditions, and that incentives for innovation remain in place, so that the pace of innovation is not hindered by undue challenges in market access and commercialization for this new class of transformative therapies.

In prior public statements, ARM has been clear that traditional HTA frameworks in both the U.S. and Europe are not flexible enough to accommodate potential cures and do not allow the ability to capture the full product value due to issues including: the short term time frame for assessing affordability versus the long-term timeframe for assessing value; variability in ability and willingness to pay (and applicability of ICER threshold) based on degree of unmet medical need addressed; and the subjectivity of incorporating contextual considerations such as caregiver and societal impacts into a quantitative framework¹.

ARM believes that ICER can play an important role by advocating for balanced evidence assessment as well as updates in economic evaluation methods that reflect the unique and broad benefits of SSTs. Reserving the public dissemination of proposed value-based payment benchmarks until a more comprehensive data set (including real world evidence) is adequate to support the validity of the underlying assessments, as well as rigorously updating assessments as evidence that reflects clinical outcomes, patient and caregiver benefits and societal impacts becomes available should be more formally reflected in ICER methods and processes.

Speculating prematurely on the ‘fairness’ of the price of highly innovative therapies for which evidence on the duration and full spectrum of benefits is not yet available does not serve patients, their families, caregivers or society, especially if it results in undue barriers to patients receiving potentially life changing treatments. ARM believes it is important to separate methodological issues from affordability and policy considerations. ICER could also play an important role in advocating for new payment models and systems that accommodate

¹ See March 29, 2017 ARM letter to ICER regarding the proposed update to the ICER Value Assessment Framework.

uncertainty in long-term outcomes for SSTs while also rewarding unprecedented long-term performance and innovation.

In releasing the draft framework to value SST transformative treatments, ICER stated it had collaborated with methodological experts in addition to HTA bodies such as NICE and CADTH that employ similar methodologies to assess incremental cost effectiveness. We appreciate ICER's interest in engaging with these experts, but we also note that broader engagement is necessary to obtain input from expert bodies, especially in the nascent field of HTA for potentially curative therapies. ARM has had interactions with experts from methodological bodies such as the International Society of Pharmacoeconomics and Outcomes Research (ISPOR), Health Technology Assessment International (HTAi) and the Second Panel on the Cost-Effectiveness in Health and Medicine². These organizations have published extensively on key methodological issues in evaluating new therapies. ARM hopes that ICER will continue to seek participation from these experts when evaluating new issues to consider for SSTs, including those highlighted above.

Comments on Proposed SST Adaptations

In its current open input period for its framework to value SSTs, ICER has solicited input on several areas of proposed adaptations. ARM would like to highlight several concerns with ICER's proposed adaptations.

ICER's proposed SST value assessment method adaptations address only the uncertainties, but not the unique benefits of SSTs. Based on the ICER proposed adaptations, there appears to be no benefit of being considered an SST and only a detriment (e.g. PSA for OBA and 12-year sharing of economic surplus). These treatments would have a better result if they were considered under the standard framework. The interpretation is that ICER is penalizing SSTs with the result of favoring chronic therapies. SSTs that deliver substantial survival and health gains with no ongoing treatment burden directly benefit patients, families, and society. We expected the intention of these adaptations to also encourage manufactures to pursue SSTs instead of penalizing them by signaling to payers that lower launch prices for SSTs might be appropriate due to uncertainty.

Assessing and Describing Uncertainty (cure proportional models, time horizon analysis, duration of effect scenario analysis)

Regarding ICER's use of cure proportional models, time horizon analysis, and duration of effect scenario analyses, we support ICER's decision to continue to use a lifetime time horizon for the base case value-based price analysis as shorter time horizons may not capture the full potential scope of benefits for SSTs. If durability of effect scenarios are to be conducted, they should be biologically plausible, e.g. consistent with the mechanism of the product and the pathophysiology of the disease being treated. For example, although a product's effects may start to wane, it may remain clinically beneficial to the patient by having already altered the natural history of the disease. Therefore, a gradual rather than abrupt waning of effect would

² Peter J. Neumann et al, *Cost-Effectiveness in Health and Medicine* (Oxford Scholarship Online, November 2016).

be appropriate to model. In cases where better evidence is NOT available, a panel of true scientific/technical experts (e.g. Delphi panel process) could be convened that would deliberate and reach consensus on the scientific rationale for durability of effect, only. Evidence could include both clinical outcomes and surrogates suggestive of durable clinical effect such as targeted changes in gene expression, cellular function, or tissue physio-anatomy, or even non—clinical data from an appropriate animal model. The panel could provide likelihood estimates of the long-term benefit over a range of time horizons. Future outcomes could then be weighted based on the elicited probabilities.

In the case of SSTs targeting ultra-rare diseases (URDs), this issue is exacerbated given that these products are likely to have less overall revenue potential than typical specialty or primary care products over a product lifecycle. It has been recognized by ICER that some SSTs targeting URDs are likely to have a small budget impact given the size of the eligible population. This dynamic, along with the current paradigm of one-time payment, poses challenges and uncertainty for innovators for recovering the substantial, fixed R&D, overhead and manufacturing investments that are often required to launch these products, despite their orphan status. SSTs targeting URDs might often not reach traditional cost-effectiveness thresholds under current evaluation methods. Other global HTAs acknowledge the potential for unique benefits of SSTs through higher thresholds or guaranteed approval (e.g., NICE HST)³, through QALY weighting, or through differential discounting⁴.

We recommend that ICER continue to follow the lead of other global HTAs, which are seeking to reward and encourage investment in SSTs that may not otherwise be approved using their legacy cost-effectiveness frameworks and methods, by adapting its own methods in a similar way. ARM believes that the uniform application of cost/effectiveness thresholds in value assessments across all product and disease types is not appropriate. At minimum, continued use of \$500,000/QALY (or more, as appropriate) in ICER sensitivity analysis informing ICERs VBPs for URDs and SSTs is encouraged by ARM. We suggest that a wider range in the sensitivity analysis could provide appropriate context to help payers make informed decisions regarding coverage of both SST and URD products, due to differential willingness to pay among US payers.

ARM disagrees with the characterization of SSTs as lacking the potential for competition, both during and after loss of intellectual property protection, specifically the statement: *“Many SSTs, particularly cell and gene therapies, due to the nature of their mechanism of action, may never face the equivalent of generic competition of the kind that has led to some balance in the sharing of the economic surplus between innovators and the health system.”*

³ National Institute for Health and Clinical Excellence (2017): *Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes*. Available at <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf>

⁴ National Institute for Health and Clinical Excellence (2011): *Discounting of health benefits in special circumstances*. Available at <https://www.nice.org.uk/guidance/ta235/resources/osteosarcoma-mifamurtide-discounting-of-health-benefits-in-special-circumstances2>

Manufacturing techniques and costs are changing over time in ways that will likely facilitate biosimilar entry and market share erosion for innovator products upon loss of intellectual property protection, especially where the revenue potential (and correlated budget impacts on payers are largest). In addition, there is already direct competition in several areas of SST research (e.g., sickle cell, hemophilia, DMD) among innovator firms and no reason to suppose that there may not be competition in these areas by biosimilar SSTs as well once the innovator firm faces loss of intellectual property protection or next-generation products. The level of competition for each SST will depend on many factors, including the FDA approval requirements and associated costs, safety and efficacy data, patient population, ease of administration, post-approval monitoring requirements, availability of alternative treatments and costs, and the insurance and reimbursement environment. Certainly, the “mechanism of action” related to SSTs in and of itself does not constitute a certain barrier to biosimilar (or pioneer) SST competition.

Furthermore, we are concerned with the following proposal to include calculation of a “shared savings” cost-effectiveness scenario in ICER’s assessments, which is based primarily on the assumption of lack of competition for SSTs, as addressed above: *“Producing an alternative “shared savings” cost-effectiveness scenario in which the economic surplus of SSTs is shared in different proportions between the innovator and the health system. For example, one scenario will demonstrate the impact on recommended value-based prices if 100% of cost offsets from successful treatment in the economic model accrue to the innovator during the first 12 years, after which 100% of cost offsets accrue to the health system. This approach is modeled to reflect the likelihood that many SSTs will not face the equivalent of generic competition and will therefore allow upfront prices to allocate a much greater share of the economic surplus to innovators compared to chronically delivered therapies.”*⁵

Recent high-profile SST launches have not been priced such that the innovator fully captures all potential cost savings to the system but reflect a split of projected “shared savings” from launch onward. There are likely to be unintended consequence of dis-incentivizing curative therapies in favor of chronic therapies by encouraging pricing to long-term “shared-savings” at the outset. As this assessment method would likely not be imposed upon chronic therapies, manufacturers could be less incentivized to pursue investments in SSTs versus chronic therapies in the same indication or disease area.

In addition, reducing future medical expenditure delivers real savings to the health system and traditional cost-effectiveness assessment methods are not capable of fully capturing these gains. For example, patients who previously would have to be hospitalized for long periods of time may no longer require such an intensive and expensive level of care after using an SST, nor require future chronic treatments. Under the proposed scenario, savings delivered by the SST after 12 years would be fully realized by the “health system,” which in this case is comprised of

⁵ Institute for Clinical and Economic Review (2019): *ICER Seeks Public Comment on Proposed Methods Adaptations for Assessments of Potential Cures and Other Transformative Therapies*. Available at https://icer-review.org/announcements/draft_valuing_cure_methods/

providers and payers. This policy may be interpreted as a way of redistributing profits to the insurance industry, who did not partake in the risk of bringing the original innovation to market.

Lastly, 12 years appears to be an arbitrary number for determining the 'shared savings' as the actual commercial lifecycle of most products, especially high value biologics, will not necessarily be tied to 12 years of intellectual property protection or market exclusivity. The lifecycle of a product may be more or less than 12 years, with the duration highly dependent on regulatory review and launch timing, the size of the market opportunity, the type of technology, competitive intensity, and other highly variable factors. We ask ICER to explain its rationale for selecting a 12-year cutoff.

Probabilistic Sensitivity Analysis (PSA)-triggered Outcomes Based Agreement (OBA)

While we welcome the use of PSA to account for uncertainties as a principle and understand the intention of the PSA-triggered OBA, we do not think that the current proposal adds value to the proposed value assessment, as: (i) manufacturers are presently seeking entry OBAs without this assessment in place, as appropriate to the product and target patient population; (ii) the recommendation for an OBA is devoid of any context of the feasibility for implementing an OBA for a specific treatment; and (iii) the PSA probability values do not fully capture the magnitude or source of variability in treatment value.

First, OBAs should be decided depending on the balanced needs of payers, providers and manufacturers, and ought to be based on the unique outcomes and economics related to specific treatment benefits (e.g. death, clinical response, loss of effect). Second, agreeing on common outcome definitions, ability to measure outcomes, cost of implementing an OBA all factor into the feasibility of an OBA beyond just a value-based price. Third, PSAs have a number of limitations. PSAs lack the ability to designate what the OBA should be based upon because the PSA does not identify the drivers of the variation. Furthermore, some audiences for the ICER evaluation report may not understand the details of PSA analysis but will see that ICER recommends an OBA. It may be unclear how the PSA results and thresholds relate to an OBA. Also, the 25% cut-off focusing on the downward risk for payers, while ignoring a potential upside for the payer seems to be an arbitrary method for determining the point at which an OBA should be pursued.

While we disagree with this proposal, we ask that ICER explain the rationale for selecting the 25% cut-off above \$200K and to make the connection from the PSA result to specific product related factors and attributes that support the need for an OBA. Lastly, given that there are other potential triggers for OBAs beyond product performance (e.g. the budget impact), we question if this complex and confusing method is optimal and truly meets ICER and ARM's shared goal of encouraging payment model innovation. ARM would like to reiterate that it is important to separate policy considerations from an HTA assessment and we consider OBA recommendations for individual products and indications to be outside of the scope of an ICER report.

Time Divergence Between Costs and Benefits

While we agree with ICER that using a 3% discount rate for costs and benefits is most commonly done in the field of value assessment, we question ICER's decision not to include differential discounting in some scenario analyses. As a majority of SST costs are incurred up-front and benefits accrue over a much longer timeframe, we believe that benefits ought to be discounted at a smaller rate than costs. Relying on a preference-based approach to measuring health benefits such as QALYs further exacerbates this issue as patients may implicitly discount future health outcomes already in their willingness to pay estimates, thus leading to double-discounting⁶. In consequence, we therefore urge ICER to consider differential discounting as part of its standard sensitivity analyses.

Quantifying Additional Dimensions of Value

We acknowledge and appreciate ICER's inclusion of additional dimensions of value and agree with these being placed on the list of voting questions on Potential Other Benefits/Disadvantages and Contextual Considerations. Failing to incorporate additional components of value into the price recommendations, however, necessarily ensures that value-based price recommendations are inaccurate as not all societal benefits and costs are incorporated. For example, with a potentially curative therapy, the health care system will not only achieve cost offsets related to 'existing' treatments but will not have to pay for any of the chronic treatment advances that would likely reach the market in future years and be more expensive than today's standard of care.

Furthermore, health care providers no longer need to worry about their patients' level of compliance with existing treatment. Published studies have shown poor compliance with treatment across a wide range of chronic diseases. On a related point, there are individuals living with serious and rare diseases that function in a poor socio-economic environment. These individuals face substandard access to medical care services and often to not have adequate caregiver support. The ability of a one-time treatment to cure their disease can help minimize the health-related impact of their socioeconomic status.

ICER's current approach relies largely on QALY-based cost-effectiveness models. Researchers have suggested using multi-criterion decision analysis (MCDA) to address this limitation.⁷ Developed from the field of systems engineering, MCDA measures how different treatments perform across a variety of attributes and explicitly asks the decision maker to weigh these different attributes. MCDA can be used to quantify these contextual considerations and decision makers can use MCDA to examine how different prioritization affects treatment recommendations. MCDA may be useful when some key attributes of MCDA-informed value include cost or benefits received by society, but that are not captured by individual decision making or within ICER's CEA model. ARM encourages ICER to continue to collaborate with the health economic field to monitor the potential future inclusion of these dimensions.

⁶ Attema, A.E., Brouwer, W.B. and Claxton, K. Discounting in economic evaluations. *Pharmacoeconomics*, 2018. 36(7), pp. 745-758

⁷ Phelps CE, Madhavan G. Valuing Health: Evolution, Revolution, Resistance, and Reform. *Value in Health*. 2019 May 1;22(5):505-10

ARM appreciates the opportunity to provide our perspective on these important issues. Please do not hesitate to contact me if you have any questions.

Sincerely,

A handwritten signature in black ink that reads "Robert J. Falb". The signature is written in a cursive, flowing style.

Robert J. Falb
Director of Policy and Advocacy