June 30, 2023

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
14 Beacon Street, Suite 800, Boston, MA 02108

Re: 2023 Value Assessment Framework Proposed Changes:

Dear Dr. Pearson:

The Alliance for Regenerative Medicine (ARM) is pleased to provide comments in response to the Institute for Clinical and Economic Review (ICER) June 5, 2023, request for input on the 2023 Value Assessment Framework (VAF) proposed changes.

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis. We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 475 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

As of year-end 2022, there were 1,457 engineered cell therapy and genetic medicine developers worldwide sponsoring 1,070 clinical trials (out of 2,200 clinical trials globally, which are also sponsored by academic and government institutions) across dozens of indications, including rare monogenetic diseases, oncology, cardiovascular, central nervous system, musculoskeletal, metabolic disorders, ophthalmological disorders, autoimmune diseases, and more.[1]

The health technology assessment (HTA) evaluation issues presented in this iteration of the ICER VAF proposed changes contain three areas where ARM applauds ICER: (1) the patient engagement program, (2) clinical trial diversity considerations, and (3) real-world evidence priorities.

Patient Engagement Program

ARM commends ICER's commitment to building on the 2020 VAF to enhance the patient voice and compensate patient representatives for their time and contributions, and ARM strongly urges similar enhancement in valuing of the patient life and perspective across all components of the VAF.

[1] https://www.alliancerm.org

Clinical Trial Diversity

ARM applauds ICER's efforts on this topic and stands with the organization to focus on continued diversification of clinical trial demographics. ARM is committed to supporting all patients having access to life saving care. Inclusion of a diverse clinical trial population is key to removing biases and demonstrating benefits across demographics. With that said, in some cases, such as some rare diseases, factors that drive a diverse trial population may not be well characterized at the time of scoring. In those cases, scoring is not possible; and in all cases of scoring, more transparency related to the detailed methodology is warranted.

Use of Real-World Evidence

ARM is fully supportive of using real world evidence to evaluate gene and cell therapies and finding innovative solutions for incorporating real-world evidence into trial planning, trial endpoints, and outcomes research.

With the emergence and expansion of these therapies, we are entering an unprecedented era of potentially curative treatments for patients where no cure existed before. ICER has previously acknowledged, "[t]he 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."[2] More recently ICER has stated "[c]ell 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."[3] ARM agrees, and further suggests that while expectations are that the patient outcomes will be durable over the long-term, it is important that payment may be incurred and settled at the time of treatment in many cases.

In addition to these points of appreciation, however, ARM has critical concerns with certain proposed changes as detailed below. From a general approach standpoint, the comment period provided for these VAF revisions is inadequate. ARM recommends ICER allow at least 60 days for stakeholders to provide meaningful input on future proposals. Additionally, the proposed changes are more restrictive than prior VAF revisions, each of which creates significant barriers to ICER obtaining meaningful input.

Limitations of Traditional HTA frameworks

ARM believes that an independent scientific evaluation of the clinical and economic evidence should be conducted first, without consideration of price or payment model, in order to understand the totality of benefits of a new technology. ARM also believes that every effort should be made to ensure patients have access to transformative new therapies in a timely manner and that incentives for innovation remain in place, so that undue challenges in market access and commercialization do not hinder the pace of innovation 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 appropriately evaluate potential cures and do not capture

[2] ICER Launches International Collaborative to Develop New Methods to Guide Value-Based Pricing of Potential Cures - ICER

[3] ICER Seeks Public Comment on Proposed Methods Adaptations for Assessments of Potential Cures and Other Transformative Therapies - ICER

the full product value due to issues including: the short-term timeframe for assessing affordability versus the long-term timeframe for assessing value; variability in willingness to pay based on degree of unmet medical need addressed; and the subjectivity of incorporating contextual considerations such as caregiver and societal impacts into a quantitative framework.[4]

ARM has also noted in prior statements that an important limitation in ICER's approach is in the timing of its review of new therapies, particularly those that are first in class and the only treatment for a given condition. ICER routinely schedules the release of its evaluations to coincide with anticipated FDA approval. Conducting a value assessment prior to regulatory approval denies patients, providers, and health insurers a comprehensive understanding of a treatment's potential benefits and risks. This practice is premature and limits the amount of data and information that can be incorporated into ICER's assessment and upon which ICER can base its conclusions. Post-marketing trials, such as confirmatory studies for accelerated approval drugs, and real-world evidence from registries and other data generation methodologies can provide invaluable data on a drug's benefits and risks derived from longer-term use for a more complete picture of a drug's impact. In the absence of these data, ICER evaluations begin with a premise of insufficient evidence of clinical benefit which inherently biases the review towards a finding of low cost-effectiveness. This is especially true of accelerated approval drugs in which clinical benefit is verified through post-approval trials. ICER's decision to issue its reports and identify a value-based price benchmark at the time of a drug's approval in order to influence payer decisions and launch price reflects a narrow focus on cost constraints and access restrictions. This practice is at odds with the reality that certain data are not yet available at the time of launch and the importance of obtaining such information to yield an accurate assessment of both short and long-term value which will lead to maximizing value for patients.

ICER states that "the purpose of the value assessment framework is to form the backbone of rigorous, transparent evidence reports that, within the broader mechanism of stakeholder and public engagement, will help the United States evolve towards a health care system that provides fair pricing, fair access, and a sustainable platform for future innovation". In the spirit of fulfilling this mission, ARM suggests that ICER should endeavor to be as broad, inclusive, and fair as possible about its methods and assumptions, not less inclusive or less fair as could be suggested by current approaches in the 2023 ICER VAF proposed changes. One example of a planned approach in the 2023 VAF in direct opposition to inclusivity and fairness is the suggested use of a lower set of QALY thresholds but not higher thresholds where appropriate.[5] US payers have the ability and latitude to select the willingness to pay and cost perspective (healthcare system, societal) most appropriate to their own resource allocation decisions.[6]

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[4] See October 18, 2019 ARM letter to ICER regarding the proposed update to the ICER Value Assessment Framework. https://acrobat.adobe.com/link/review?uri=urn:aaid:scds:US:64f9e9cb-aad2-34bd-91f2-9d8d74cb8815.

[5] Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/wp-content/uploads/2023/06/Proposed-VAF-Changes-For-Public-Comment_For-Publication_06052023.pdf. Published 2023.

[6] Research by Neumann and Kim find that US CEAs increasingly cite a range of $100,000-$150,000/QALY and thresholds for oncologic CEAs are higher than non-oncologic CEAs, suggesting that "diseases associated with greater mortality and morbidity warrant higher thresholds." Newmann PJ, Kim DD (2023). Cost-effectiveness Thresholds Used by Study Authors, 1990-2021. JAMA, 329(15):1312-1314. Available at: https://jamanetwork.com/journals/jama/fullarticle/2803816;

Reducing and limiting these perspectives within value assessments and reports may reduce coverage and access to potentially valuable therapies that do not fit well into a traditional Cost/QALY framework.

Health Benefit Price Benchmarks (HBPB)

Further concerns ARM maintains with the 2023 VAF proposed adaptations are largely focused on the Health Benefit Price Benchmarks (HBPB). Under this section, for proposed change 1.b., ICER states that *for the [HPBP] of high-impact single or short-term therapies (SSTs), or of other treatments with relevant and substantial potential cost offsets, ICER will continue to consider the results of two scenario analyses:*

i. *A 50/50 shared savings model in which 50% of the lifetime health system cost offsets from a new treatment are "assigned" to the health system instead of being assigned entirely to the new treatment; and*
ii. *A cost-offset cap model in which the health system cost offsets generated by a new treatment are capped at $150,000 per year but are otherwise assigned entirely to the new treatment.*

ARM has several concerns with the direction of the discussion in this section. The first of these concerns is regarding how cell and gene therapy benefits are directly related to the treatment. These are potentially curative therapies that contain the capability to stop disease and restore partial or full quality of life. To minimize the contribution of the therapy, such as in the first scenario of a 50/50 split, and only assign half of the lifetime cost offset to the treatment will unfairly erode the actual value of the treatment. This will discourage further research into the cell and gene sector as it limits the cost offset value assigned to these important new therapies, thus unnecessarily creating inequality between cell and gene therapy and traditional medicine.

Another concern for ARM is that capping cost offsets generated at $150k per year is not feasible. As stated above, a gene or cell therapy has the potential to offer substantial cost offsets to the healthcare system. While the idea of setting a cap for healthcare system benefits is not entirely unreasonable, the cap for such benefits should be lower, thus allowing for more of the cost offset to directly be tied to the treatment. For example, if a cell or gene therapy can prevent a disease that has an ongoing cost of management of $200k per year, it is the treatment intervention that will be responsible for those cost offsets. Additional cost offsets realized by the healthcare system may exist, but the heterogeneity of diseases ARM members invest in preventing, curing, and treating requires that there be a low capitation assigned so that much of the benefit (i.e., the large majority) can be aptly attributed to the treatment.

In the discussion section following proposal 1.b., ICER mentions that *although studies have explored the willingness-to-pay thresholds for cost effectiveness from both the health care system and societal perspectives, limited research has been conducted to estimate the opportunity-cost threshold from the societal perspective. If research expanded upon the Vanness et al. study to include broader societal domains within an opportunity cost paradigm, it would show a*

In 2021, the Congressional Budget Office (CBO) used a value of statistical life year of $388,000/life year and willingness-to-pay values of $507,000/QALY, including sensitivity cases used values that were 50 percent higher and 50 percent lower. Adams, C. Herrnstadt, E. (2021). CBO's Model of Drug Pricing Negotiations Under the Elijah E. Cummings Lower Drug Cost Now Act. Congressional Budget Office. Available at: https://www.cbo.gov/system/files/2021-02/56905-Drug-Price-Negotiations.pdf.

decreasing threshold from the original estimate of $104,000 per QALY with each added broader societal element.[7]

The primary assumption of the Vanness study referenced in this section is that decision makers wish to get the most population health for what is already spent on health care. ARM takes issue with such an analytical approach when considering Single or Short-Term Transformative Therapies (SSTs) for the following reasons:

- There have been numerous published studies providing estimates of the wasteful spending on many current chronic therapies and ARM suggests that this wasteful spending for chronic therapies can and should be replaced versus expanded upon.
- A paper by Garrison and colleagues (2019) makes a compelling argument for higher cost-effectiveness thresholds for emerging gene therapies.[8] One contention is that prior research efforts to estimate the value of a statistical life provided results ranging from $4.6M to $15.0M, with a mean of $9.6M that implied a roughly $315k threshold per life-year gained. The Garrison paper also indicates that evaluations of highly specialized technologies by NICE in the UK have implied thresholds reaching $309k per QALY.
- In addition, for many one-time, potentially curative gene therapies in development, there are competitor chronic therapies being developed for similar diseases. Reimbursing one-time gene therapies can help avoid the addition of these future costs to the system, a scenario not currently addressed in ICER models.

While ARM strongly supports ICER considering the societal perspective as a co-equal case, ICER should always leverage its public reports and public comments to discuss the HBPB in the context of the co-equal case societal perspective rather than focusing public comments on proposed pricing based solely on payer perspective. This approach should also include patient and family quality of life and the potential for increased productivity into the HPBP framework.

ARM appreciates the opportunity to provide our perspective on these important issues. Please feel free to contact Brett Logan at blogan@alliancerm.org with questions.

Sincerely,

Erica Cischke, MPH
Vice President, U.S. Government Affairs
Alliance for Regenerative Medicine

[7] Vanness DJ, Lomas J, Ahn H. A health opportunity cost threshold for cost-effectiveness analysis in the United States. Annals of internal medicine. 2021;174(1):25-32. A Health Opportunity Cost Threshold for Cost-Effectiveness Analysis in the United States - PubMed (nih.gov).

[8] Garrison LP, Jackson T, Paul D, Kenston M. Value-based pricing for emerging gene therapies: the economic case for a higher cost-effectiveness threshold. *J Manag Care Spec Pharm* 2019;25(7):793-799. Value-Based Pricing for Emerging Gene Therapies: The Economic Case for a Higher Cost-Effectiveness Threshold (jmcp.org).