Alliance for Regenerative Medicine

October 18, 2019

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

Re: 2020 Value Assessment Framework Response:

Introduction

The Alliance for Regenerative Medicine (ARM) is pleased to provide our comments in response to the Institute for Clinical and Economic Review (ICER) October 18, 2019 request for inputs on the "2020 Value Assessment Framework."

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 350 leading research-based life science companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our 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 raised in the ICER press release raise critical concerns for ARM members. Cell and gene therapies have shown the potential to cure many diseases, some of which are partly or fully caused by genetic mutations. ARM member companies have shown convincing evidence of halting progression of severe and rare diseases in many of their development programs. Cell and gene therapies are complex to manufacture, can require custom processes to create individualized therapies, and in many cases are administered once or over a short course of treatment. While expectations are that the patient outcomes will be durable over the long-term, the payment may be incurred and settled at the time of treatment in many cases.

With the emergence 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." 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."

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 clinical 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 U.S. and Europe are not flexible enough to appropriately evaluate potential cures and do not 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 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[1].

ICER states that its mission to 'provide an independent source of analysis of evidence on effectiveness and value to improve the quality of care that patients receive while supporting a broader dialogue on value in which all stakeholders can participate fully'. US payers are increasingly relying on ICER evaluations in setting their cost-effectiveness thresholds, informing utilization controls and coverage policies and setting and negotiating price, including value-based arrangements (ICON, PLC 2019 Whitepaper 'Current US payer's perceptions on value-based pricing for pharmaceuticals'). In the spirit of fulfilling this mission, ARM suggests that ICER should endeavor to be as broad, inclusive and transparent as possible about its methods and assumptions, not less inclusive and transparent as suggested by the current proposed changes to the ICER value framework. One example of a proposed change to the 2020 framework in direct opposition to inclusivity and transparence is the proposed use of a narrower set of QALY thresholds in sensitivity analysis for orphan drugs. 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. 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.

In the current open comment period for the 2020 value assessment framework, ICER has solicited input on several proposed adaptations. Among these adaptations, ARM supports the following proposed changes:

- **Augment Efforts to Use Real World Evidence (RWE):** We support ICER's effort to generate RWE for value assessments and recommend that these data be made publicly available. Additional clarification on how ICER plans to collect, analyze and use RWE, however, would be informative. Transparency will be critical here for all stakeholders.

- **Expanding and Revising Voting Structure to Capture Important Potential Other Benefits and Contextual Considerations:** The addition of other important benefits and contextual considerations will allow the ICER report audience to garner a better understanding of the quantitative impacts of a treatment that are not captured in the cost-effectiveness analysis.

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

- **Creating a New Process for Re-assessing the Emergence of New Evidence:** We suggest that ICER also consider an evidence re-assessment at the 5-year mark when additional RWE is likely to be more readily available.

In addition to these areas of agreement, ARM would like to highlight several concerns with ICER's approach and proposed adaptations:

- **Timing of Review is Premature:** 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.

- **Cost-Effectiveness Threshold Ranges:** Omitting the willingness to pay (WTP) threshold up to $500K per QALY/evLYG removes important information from ICER's reports, especially for stakeholders in the United States, where different payers will consider different WTP thresholds.[2,3,4,5] The proposed framework will lessen incentives to develop transformative treatments for rare diseases, where it is more difficult to demonstrate cost-effectiveness using traditional WTP thresholds applicably to more

[2] Wang A, Halbert RJ, Baerwaldt T, Nordyke RJ. US payer perspectives on evidence for formulary decision making. Journal of oncology practice 2012;8:22s-7s.
[3] Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. New England Journal of Medicine 2014;371:796-7.
[4] Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health economics 2010;19:422-37.
[5] Weinstein MC. How much are Americans willing to pay for a quality-adjusted life year? : LWW; 2008.

widely used treatments.[6,7] With this measure, ICER departs from the path taken by other global HTAs (e.g. NICE), where higher WTP thresholds are used in order to enable innovation for rare diseases.[8] We suggest that mis-representation or mis-interpretation of the thresholds used can be mitigated by providing additional clarifying discussion in the framework document and ICER reports and statements.

ICER also states that it "*only takes $100,000 per treatment course, multiplied by a mere 10,000 patients, to provide $1 billion per year in revenue.*" However, many ultra-rare diseases impact fewer than 1,000 patients per year.[9] Furthermore, uptake among patients is often far from 100% due to unique disease, treatment and patient segment characteristics and has been consistently overestimated by ICER.[10] Non-oncology rare disease drugs that consistently generate more than $1 billion in global revenues are the exception, not the rule. As the cost to bring a drug to market has been estimated to exceed $1 billion, manufacturers will not develop new treatments if there is no way to recoup investments, leading to a high unmet need remaining for patients with rare diseases.[11] This will have a broad impact in the US, where 25 to 30 million people are estimated to suffer from a rare disease.[12]

Recognizing the inadequacy of traditional cost-effectiveness thresholds for rare disease and transformation products, NICE has adopted an innovative way of incorporating QALY weightings that have the effect of adjusting cost-effectiveness thresholds for therapies targeted for rare conditions through the Highly Specialized Technologies pathway (meeting certain criteria, including small eligible patient population and minimum QALY increases).[13] The minimum QALY criteria ensures that only therapies with substantial health benefits in rare diseases will be evaluated using the higher thresholds.

- **Contextual Considerations should be considered in calculating Value-Based Price when possible.** While we agree with ICER that including contextual considerations is important, these broader benefits typically do not influence ICER's recommended value-based price. For instance, one can readily calculate the value of reductions in caregiver burden and using approaches similarly to those used to estimate treatment impact on

[6] Pant S, Visintini S. Drugs for rare diseases: a review of national and international health technology assessment agencies and public payers' decision-making processes. . CADTH Environmental Scan 2018

[7] Shah KK. Severity of illness and priority setting in healthcare: a review of the literature. Health policy 2009;93:77-84.

[8] Tordrup D, Tzouma V, Kanavos P. Orphan drug considerations in Health Technology Assessment in eight European countries. Rare Diseases and Orphan Drugs 2014;1.

[9] Boat TF, Field MJ. Rare diseases and orphan products: Accelerating research and development: National Academies Press; 2011.

[10] Snider JT, Sussell J, Tebeka MG, Gonzalez A, Cohen JT, Neumann P. Challenges with Forecasting Budget Impact: A Case Study of Six ICER Reports. Value in Health 2019;22:332-9.

[11] Adams CP, Brantner VV. Spending on new drug development 1. Health economics 2010;19:130-41.

[12] Genetic and Rare Diseases Information Center - National Center for Advancing Translational Sciences. FAQs About Rare Diseases. 2017.

[13] Changes to NICE drug appraisals: what you need to know. 2017. (Accessed Sep 10, 2019, at https://www.nice.org.uk/news/feature/changes-to-nice-drug-appraisals-what-you-need-to-know.)

patients' quality of life.[14,15] These additional components of value can be calculated in many cases and may significantly impact a treatment's cost per QALY.[16]

- **Include an Undiscounted Approach as a Sensitivity Analysis**. While discounting is common in cost-effectiveness modelling, this approach may undervalue treatments which have large health benefits that accrue into the future. Aggressive discounting can sometimes make common-sense public health interventions appear to be of low value.[17] In some cases, discounting can lead to unreasonably low valuations that undervalue transformative innovations, a result that is at odds with society's stated preferences.[18]

- **Applying More Precise Evidence Ratings:** The proposed evidence rating matrix is unclear and subjective, and the voting record demonstrates a lack of consensus and clarity on the meaning of the ratings. The ICER framework has two dimensions of assessing the evidence: 1) level of certainty and 2) comparative benefit. We would recommend developing explicit measures for drivers of both certainty (e.g. trial size, active comparators, randomized clinical trials, single arm trials, meta-analysis etc.) and comparative benefit (e.g. relative efficacy, AEs, net clinical benefit, etc.).

  Additionally, it should be noted that surrogate endpoints used in FDA's accelerated approval pathway are not adequately accommodated for in ICER's framework when reviewing drugs that receive FDA approval through this important expedited program. The accelerated approval pathway represents a pragmatic approach to addressing the challenges and limitations presented by small, difficult to study patient populations, allowing for flexibility in the types of evidence that can be used to satisfy the full statutory standards for safety and effectiveness that apply to all drugs approved by the FDA. The key challenge in applying ICER's framework to accelerated approval drugs lies in the fact that the full extent of clinical benefit has not been established at the time of approval and it can take years to verify the anticipated clinical benefit in post-approval confirmatory studies. As Drs. Woodcock and Marks recently reinforced, accelerated approval "is especially useful when the drug is meant to treat a disease whose disease course is long, and an extended period of time is needed to measure its effect"[19] (August 27, 2019, FDA Voices).

---

[14] van denBerg B, Brouwer W, Exel Jv, Koopmanschap M. Economic valuation of informal care: the contingent valuation method applied to informal caregiving. Health economics 2005;14:169-83.

[15] Arno PS, Levine C, Memmott MM. The Economic Value of Informal Caregiving: President Clinton's proposal to provide relief to family caregivers opens a long-overdue discussion of this "invisible" health care sector. Health Affairs 1999;18:182-8.

[16] Shafrin J, Skornicki M, Brauer M, et al. An exploratory case study of the impact of expanding cost-effectiveness analysis for second-line nivolumab for patients with squamous non-small cell lung cancer in Canada: Does it make a difference? Health Policy 2018.

[17] NICE CC. How Should NICE Assess Future Costs and Health Benefits? 2011.

[18] Bonneux L, Birnie E. The discount rate in the economic evaluation of prevention: a thought experiment. Journal of Epidemiology & Community Health 2001;55:123-5.

[19] FDA. Delivering Promising New Medicines Without Sacrificing Safety and Efficacy. FDA Voices: Perspectives From FDA Leadership and Experts. August 2019. Available at: https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/delivering-promising-new-medicines-without-sacrificing-safety-and-

- **A Crosswalk Between ICER Evidence Ratings and Those of the German HTA System not currently suitable for US health technology assessments:** Although Germany is the largest pharmaceutical market in Europe, the German system for evidence rating has not been established as a uniformly and internationally accepted standard for evaluating evidence.[20,2119,20] We question the need to use the German system before an international standard has been set. We also find ICER's proposed crosswalk to the German evidence rating system to be unclear and subjective. For example, evidence rated an "A" in ICER's EBM matrix could be either "major" or "considerable added benefit" in the German system. Further, if ICER's EBM matrix rates evidence as either C+, C++, P/I, C, or I, then it would be considered to have "no added benefit proven" when cross-referenced to the German rating system, despite ICER's own assessment that these treatments have value. ICER states they will "*provide [their] own judgement of 'added benefit' within the German categories… rather than rate the evidence in the same manner as would be done in Germany.*" Using the ratings of the German system without implementing the methodology they were designed for is inconsistent and makes assessment of the ratings difficult, confusing, and ultimately incompatible with the actual results of German HTAs.

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,

Robert J. Falb
Director, U.S. Policy and Advocacy

efficacy?utm_campaign=Delivering%20Promising%20New%20Medicines%20Without%20Sacrificing%20Safety%20and%20Efficacy&utm_medium=email&utm_source=Eloqua. Accessed October 8, 2019.

[20] Mycka J, Dellamano R, Lobb W, Dellamano L, Dalal N. Orphan drugs assessment in Germany: a comparison with other international HTA agencies. Value in Health 2015;18:A550-A1.

[21] Schaefer R, Schlander M. Different Methods, Different Results? Comparing Health Technology Assessments in the United Kingdom and Germany. Value in Health 2016;19:A494.