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Institute for Clinical and Economic Review

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The Alliance for Regenerative Medicine (ARM) is pleased to provide our comments in response to the Institute for Clinical and Economic Review (ICER) January 23, 2019 request for inputs on the “evaluation of potentially curative treatments and for translating the results of cost-effectiveness analyses into recommendations for value-based price benchmarks.”

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, investors, and patient groups 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 raised in the ICER press release are critical ones 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. Other therapies developed (or in development) by ARM member companies have shown evidence of halting progression of severe and rare diseases. 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. Typically, more of the cost of the therapy is 'up front' in nature (given it is not administered on a chronic basis). It is expected that the relevant outcomes of these therapies will be 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 acknowledges, "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." We should make every effort to ensure patients have access to them in a timely manner and that incentives for innovation are in place. Independent scientific evaluations of clinical and economic evidence should be conducted first and independently of any price consideration in order to understand the unique benefits of a new technology. Ideally, all interventions should be first appraised based on their clinical and economic merit; discussions around societies' willingness and ability to pay should take place subsequently.

In its press release ICER states it plans to collaborate with methodological experts in addition to HTA bodies such as NICE and CADTH that employ similar methodologies to assess incremental cost effectiveness. 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 Medicine¹. 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 potentially curative therapies.

In prior public statements, ARM has been clear that traditional HTA frameworks in both 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 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 framework². ICER's current open input period, however, is focused on 3 specific questions. ARM believes it is important to first provide context to our responses to these questions.

Challenges with the Existing HTA Model

To start, we note an inherent limitation and challenge of HTAs is the attempt to impose a single evaluation structure across therapies with different magnitudes of clinical benefit, that treat different patient populations, and in the context of different healthcare delivery and payment systems.

¹ Peter J. Neumann et al, *Cost-Effectiveness in Health and Medicine* (Oxford Scholarship Online, November 2016).

² See March 29, 2017 ARM letter to ICER regarding the proposed update to the ICER Value Assessment Framework.

Additionally, a fundamental challenge with HTA is that it demands the impossible: perfect information about the burden of illness, safety, and efficacy of a new therapy (and the incremental efficacy thereof), and of all potential subpopulations, at launch before a product has been made available for wide adoption. In fact, ARM is concerned that ICER may have overlooked the extent to which the UK and other HTA markets do not pay the true long-term cost of denying access for therapies that are eventually proven to be cost effective. Population data collected in markets in which coverage is not governed solely by strict HTA analyses (e.g., the U.S.) is sometimes subsequently used for successful HTA resubmissions in the more restrictive countries.³ This limitation of HTA is most stark in the case of potentially curative therapies whose primary incremental value compared to standard of care lies in the durability of treatment effect, which is delivered within one or a few treatment sessions and which is likely not fully known at launch. This is the practical result of the fact that the durability of the treatment effect is expected to persist for years if not decades, given what is understood about the underlying mechanism of disease and treatment, but it would not be responsible to delay approval of such a therapy, and therefore patient access, after safety and efficacy have been demonstrated to FDA's standard.

Making coverage and reimbursement decisions based on HTA cost-effectiveness analyses alone will threaten access to patients who could

³ For example, Prevnar 7 gained wide adoption in the U.S. after FDA approval and U.S. launch in 2000, but the vaccine was initially rejected in the UK on a strict cost-effectiveness basis, despite EMA approval in 2001. After several years of real-world data generation and vaccine adoption in the US, Prevnar 7 CEA models were updated with new evidence from the real world that demonstrated strong herd immunity effects on reducing invasive pneumococcal disease in non-vaccinated persons, which resulted in the vaccine being vastly more cost-effective than originally anticipated (Initial 2000 estimate of \$110k per life-year saved vs. revised 2009 estimate of \$10k per life-year saved). It was eventually covered in the UK for all children in 2006, after five years' delay, during which unnecessary child deaths would have continued, see Ray *et al.* 2009. *Vaccine*. 27: 6483 – 6494; Isaacman *et al.* 2008. *Clinical Therapeutics*. 30(2): 341 – 357; UK coverage in The Independent 3 February 2006, available here: <https://www.independent.co.uk/life-style/health-and-families/health-news/children-to-get-jabs-against-most-lethal-form-of-meningitis-465446.html>.

significantly benefit from these therapies in the short and long term. Instead, coverage and reimbursement decisions following new product launch should follow the balance that the U.S. Congress has attempted to instill in drug review and approval: specifically, Congress has, again and again, renewed the commitment to ensuring that drugs that reach the market are safe and efficacious, but it also has committed to speeding safe and efficacious therapies to market where they can reach the greatest number of patients who may benefit from them.⁴

ARM believes that the solution to these fundamental HTA challenges lies not in incremental changes to HTA methods but in the evolution of contracting mechanisms (including data collection) that balance the need to incentivize innovation with the desire to avoid payments that are seemingly divorced from a therapy's true value. ARM has written extensively on this subject, and we urge ICER to review these comments as the organization pursues the current initiative around curative therapies.⁵

While contracting mechanisms are not within ICER's or other HTA organizations' purview, ARM argues that all HTA organizations should strive to incorporate sufficient flexibility to take into account these—and other—challenges to the greatest extent possible. Our comments throughout the remainder of this letter are an important start to doing so. Payers must recognize and account for the limitations of HTA analyses when using them in the process of making coverage and reimbursement decisions; ultimately, final decisions should be made not on the basis of HTA alone but on the basis of what is best for each individual beneficiary based on their clinical circumstances. Payers also should account for the fact that existing HTA

⁴ Most recently evidenced by the establishment of a Regenerative Medicine Advanced Therapy (RMAT) designation to improve the efficiency of drug development and review for regenerative medicines, see 21st Century Cures Act, Section 3033.

⁵ For a full account of ARM's work on this topic, see ARM's Three-Part White Paper Series, Published in *In Vivo* in November 2016, July 2017, July 2018, respectively, available here: <https://alliancerm.org/market-access-and-value/>.

frameworks do not account for societal impact or broader market dynamics that can influence the allocation of investment resources. Thus, payers at the regional and national level should make decisions—including how much weight they place on any HTA framework—to drive true innovation in treatments, not disadvantage it.

Questions and Responses

Each specific question included in the ICER press release is provided below, along with our response. ARM does not have answers for all the issues we raise in our response but believes the expert methodologists in the field should be cognizant of these issues and that ICER should work them in a collaborative and transparent approach to address them. Given the critical importance of this topic to the future of medical innovation, ARM requests that ICER be transparent not only in its processes, but in the responses it has received to this solicitation for input. We encourage ICER to publish all responses it receives as well as the process it uses to evaluate the comments.

1. How should value-based prices for potential cures reflect substantial uncertainty regarding clinical safety and effectiveness due to limitations in study design, outcome measures, and the size and duration of clinical trials?

Overall ARM believes strongly that any uncertainty should be addressed using sound quantitative methods. After all, the absence of data should not be judged as data disproving an initial hypothesis. Treating uncertainty as a subjective risk factor will make potentially curative therapy evaluations inconsistent in both application and outcome.

ARM recognizes there are unique aspects of trial design for potentially curative cell and gene therapies that may lead to increased uncertainty on actual effect size at time of launch. These include:

- Head-to-head trial design may not be feasible due to ethical concerns (e.g. treatment with a placebo may lead to irreversible damage to a patient whose disease progresses rapidly during the trial period), or due to the lack of an actual comparator (e.g. no approved therapies exist for the disease in question; no appropriate comparators exist given the therapeutic approach and outcomes being studied).
- The complex administration and the individualized approach of cell and gene therapies may make masking a challenge (e.g. a sham procedure may not be feasible or ethical, for example, ARM members are aware of experiences in which an Institutional Review Board (IRB) may raise greater concerns with the safety of placebo injections than sham injections).
- Due to the often orphan or ultra-orphan nature of the target diseases, sample sizes are small, heterogeneity is high and the power to detect the statistical significance of benefits may be low, even if the treatment effect is observable and clinically meaningful.

Response #1. ARM recognizes that, relative to traditional chronic therapies, potentially curative therapies that are administered one time or over a short course may have relatively high upfront costs. Several manufacturers have already stated publicly that they are willing to participate in outcomes agreements with payment over time at risk. Given this scenario, the option for such outcomes agreements need to be incorporated into any value-based HTA assessments. As shown in the NICE mock appraisal of CAR T-cell therapy, the inclusion of different payment schemes can have a direct and noticeable impact on the resulting cost-effectiveness ratios.

Response #2. ARM views the use of real-world evidence (RWE) as an increasingly important and credible source of relevant comparator data for potentially curative cell and gene therapies. Year over year there are improvements in the tools and methodological rigor to mine and analyze RWE. For many of the rare diseases that are the targets of cell and gene therapies, RWE such as an historical cohort is the only available data source; with the only other option being prospective, long term natural history studies (which may not always be feasible due to time and cost considerations). Thus, ICER should establish the re-evaluation of curative therapies based on RWE at regular intervals post-approval as a permanent fixture of its process. This should include an acknowledgement in any first-time HTA review that more information collecting after approval will have an impact on ICER's value assessment. Creating a concrete path for re-evaluation will better take into account the reality that evidence around the benefits and costs of curative therapies will evolve, potentially rapidly, as it is used in real-world settings.

Several factors need to be considered in order to 1) enhance the use of RWE in economic models and 2) increase the acceptability of these inputs by HTAs and other relevant stakeholders:

- The methods for appropriate matching (and reduced confounding) between RWE-derived populations and trial subjects;
- Assessment of the level of homogeneity/heterogeneity of the population and related impact on outcomes;
- The degree to which patient management is well established and standardized;
- The degree to which the primary endpoint is objective and robust;

- The effect size of the potentially curative therapy versus historical cohort (i.e., is it large and very meaningful from clinical perspective); and
- Generalizability and transferability of clinical data to clinical practice are.

Response #3. The choice of outcome measures utilized in cell and gene therapy trials may not always differ from more traditional, chronic therapies (i.e. are not necessarily unique), but the durability of those outcome measures will be a unique aspect for cell and gene therapies that are administered once or have a short course of treatment. ARM believes that a range of results should be admissible and reported in assessments using various durability assumptions, acknowledging the inherent uncertainty (e.g., the use of measures beyond best-corrected visual acuity (BCVA) for ophthalmological assessments that involve treatments for patients with severely degraded vision).

ARM may support the idea of future HTA assessments incorporating a step where a panel of true scientific/technical experts (e.g. Delphi panel process) is convened that would deliberate and reach consensus on the scientific rationale for durability of effect, only in cases where better evidence is NOT available. 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. 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. Additionally, these individuals are better positioned from an expertise perspective to weigh in on the full set of measures of a treatment's benefit in instances in which there are limitations with using (or only using)

'most accepted measures.' ARM strongly recommends collaboration with manufacturers in confirming which individuals truly are experts in the science of the product technology and disease state.

Nevertheless, for fatal diseases, early access for patients to curative therapies should outweigh the uncertainty regarding long-term durability of response to treatment.

Response #4. ARM supports the argument that discount rates utilized in health technology assessments should be lower for potentially curative therapies that can offer large, incremental gains in health benefits over a long-time horizon.

There are a number⁶ of published studies and expert commentaries that provide support for such an approach. ARM recommends that, to identify an appropriate discount rate for curative therapies, ICER consider various approaches for utilizing different discount rates based on treatment and time horizon scenarios.

Response #5. For some potentially curative therapies, the data packages will be generated largely from single-arm trials. Issues of uncertainty, as well as difficult methodological issues in evaluating clinical benefit, have already been addressed and solutions established. These include statistical methods such as Weibull life data analysis, survival modeling (e.g. as used in oncology assessments). ICER should ensure that these have been carefully reviewed and considered.

⁶ For example, see Claxton et al 2011; The Green Book, the UK OHE response to NICE mock appraisal, Severens and Milne (2004).

Continuing advancements in pragmatic trial design and execution (including use of RWE) will provide additional avenues of evidence for potentially curative therapies. This is particularly important when evidence standards can be set specific to each technology with early HTA scientific advice.

2. How should value-based prices for potential cures reflect uncertainty regarding inclusion of additional elements of value that may be important for potential cures, but which are not part of standard cost-effectiveness methods?

ARM's view is that there are some elements of value that ARE already part of standard cost-effectiveness methods (e.g. those proposed by the 2nd Panel on Cost-Effectiveness in Health and Medicine) but ARE NOT given enough weight in 'base case' HTA decision making. A clear example is the use of the societal perspective that incorporates a broader set of health utility and economic considerations than the more widely used payer perspective. The large gains in health benefits attributable to potentially curative therapies can have immediate and long-lasting positive benefits for caregivers and broader segments of society. ICER should consider privileging the societal perspective for base-case decision making (or at a minimum provide equivalent weighting of the societal perspective in its decision-making process). ICER should also ensure that caregiver QALY gains are added to patient QALY gains for the base case analysis.

In terms of elements of value that ARE NOT currently part of standard cost-effectiveness methods, ARM would highlight the following:

1. Future economic efficiency – in traditional cost-effectiveness analysis the incremental benefits of a new therapy can be captured in improved

health gains (e.g. quality-adjusted life years or QALYs) and potential cost offsets related to 'existing' treatments or healthcare resource use associated with disease-related medical events. The 'existing' treatments are the comparator and the assumption in most models is that these treatments remain relatively constant for duration of the model. With a potentially curative therapy, however, 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 far more expensive than today's standard of care, especially if it is supportive care only.

2. On a related point to (1) above, there are individuals living with serious and rare diseases that function in rural areas or poor socio-economic environments. These individuals face substandard access to medical care and services and often do 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 location or socioeconomic status.
3. Value of a cure – ARM posits that the traditional approaches to elicit health utility gains with new therapies will not be adequate to fully capture the value of a cure. As an example, the EQ-5D is the most common measure used in trials to estimate health utility gains. The recall period for the EQ-5D is one week and the questions relate to an individual's view of their current health state. It is unlikely that this set of questions will adequately capture the psychological impact of a cure on a patient (e.g., in cases of severe diseases without current treatments, patients and their caregivers may not be able to

accurately envision and rate their future possible health state(s), if that future health state is not currently possible due to lack of therapies.). ICER should evaluate whether a utility multiplier should be implemented when evaluating a potentially curative therapy and what factors would drive different levels of that multiplier.

4. Related to (3), ICER should consider more holistic valuation approaches instead of the EQ-5D, with standardized methods to ensure comparability between studies for different diseases. ICER should also consider the application of different weights to QALYs, or different valuations for specific groups of patients.
5. Different time horizons considered depending on therapy (e.g. lifetime most relevant for one-time curative therapies)
6. In more common diseases, there is a larger evidence base and common structures to draw upon for economic modeling. For potential cures, it is important to note that any framework developed by ICER should be adaptable to future learnings and developments, specifically in the space of rare diseases, where burden, endpoints, and health states may be highly unique to the disease.
7. Finally, as more innovative and value-based priced for products come to market, indication-based pricing⁷ is an approach discussed by payers, institutions, and policymakers as an opportunity to establish a more sustainable healthcare system. Although ICER is not responsible for allowing or imposing indication-based pricing or payment

⁷ Indication-based pricing considers several factors including the impact and duration of product benefit for each FDA-approved indication (based on clinical studies and ongoing clinical experience), as well as the commercial availability and outcomes data of other approved treatment options for the same indications.

mechanisms, the organization and other HTA bodies should consider how this reimbursement mechanism can facilitate a more specific analysis of a therapy's cost effectiveness for a specific patient population. This may be an issue that the organizations comment on in the context of the broader framework that they intend to establish in response to this initial comment period.

3. How should value-based prices for potential cures reflect extreme magnitudes of lifetime health gains and cost offsets that are far beyond those generated by traditional therapies?

Response #1. ARM appreciates that ICER's press release recognized the substantial health gains that may accrue with potentially curative cell and gene therapies. Published data across a wide spectrum of diseases demonstrate the unique ability of these therapies to greatly impact patients' health and quality of life. Traditional thresholds used by many HTA bodies will not be adequate to capture the substantial health gains that can accrue with potentially curative cell and gene therapies. ARM believes that some HTA bodies have already moved in a positive direction in addressing this question by raising their thresholds for determination of value (i.e. the cost-effectiveness threshold) when considering potentially curative therapies. ICER should evaluate different approaches for matching estimated health gains with varying threshold levels and determining probabilities of achieving cost-effectiveness.

Response #2. ARM recognizes that the likelihood of a payer or health system realizing cost offsets and the magnitude of those offsets depends on several factors, including treatment compliance, treatment efficacy, patient comorbidity status, and the specifics of the health care delivery system in which the patient is obtaining treatment, to name a few. However, we also

recognize that certain types of cost offsets may have a higher probability of accruing than others. For example, the probability that a curative therapy will immediately obviate the need for an ongoing, expensive chronic treatment may be higher than the probability that the curative therapy will help avoid a major complication event in 5 years. Thus, one may weigh the probability of those offsets differently in an analysis.

ICER should consider the inclusion of a 'cost offset probability analysis' in its assessment process.