ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

505 LAWRENCE SQUARE BLVD SOUTH
LAWRENCEVILLE, NJ 08648

P +1-609-586-4981
F +1-609-586-4982

info@ispor.org
www.ispor.org

February 20, 2019

Steven D. Pearson, MD, MSc
President, Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

ISPOR is pleased to respond on behalf of its membership to the call for comments on key methodological questions circulated by ICER as input for the international collaborative that has been formed to develop new methods to guide value-based pricing of cures. We strongly agree that these are important issues to address with input from a wide variety of stakeholders, and thank ICER and its collaborators for this opportunity to provide our comments.

ISPOR is a scientific and educational society with many of its members engaged in some aspect of health economics and outcomes research (HEOR) related to evaluation of pharmaceuticals. Our membership includes over 20,000 individuals across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government (including some HHS employees), and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

This response was formulated with the assistance of ISPOR's most senior and representative Council, the Health Sciences Policy Council. It was reviewed by and approved by our current President and myself. Given the 4-week response period, however, we were unable to conduct the poll of membership that we typically do for such consultations. This area is of great interest to ISPOR and its members and we would be happy to engage in further consultation in this area. We would also welcome conference submissions or other suggestions for broadening the discussion about these issues.

ISPOR would be happy to answer any questions about our response. Please consider Richard Willke, PhD, our Chief Science Officer, as the contact person in this area.

Sincerely,

Nancy S. Berg
CEO & Executive Director
ISPOR

Final response, February 20, 2019

ISPOR Comments on key methodological concerns related to value-based pricing of potential cures for the ICER-led collaboration

- *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?*

  Potential cures are not necessarily different in regard to uncertainty as to clinical safety and effectiveness. Limited information on long-term safety and effectiveness has long been a concern for new drugs, biologics and devices. Concern is also often expressed about the clinical irreversibility of potentially curative treatments. But, this too extends to other medical interventions that cannot be undone, such as gastric bypass surgery, oophorectomy (removal of ovaries), or double-mastectomy. A related and important concern applies to the costs associated with curative therapies. Upfront costs for one-time curative treatments are typically irreversible, whereas chronic treatments, if evidence becomes available that they are ineffective, can be discontinued, allowing the cost burden to be tied more closely to real world effectiveness.

  A forthcoming paper by Towse and Fenwick, to be published in Value in Health, points out the importance of ensuring that there is no bias in methods or in decision critieria that would lead to a lower value-based price for a curative therapy versus a chronically-administered therapy (assuming they deliver the same health outcomes). This would create inefficient incentives for R&D.

  As noted above, repeat dose treatments allow discontinuation if there is evidence of reduced effectiveness or cost-effectiveness. However, Towse and Fenwick and others have pointed out that phased payments for cures linked to treatment effectiveness can tackle this issue.

  HTA groups such as ICER, CADTH and NICE should consider whether to account for the impact of future patent expiration and market competition. The developer of the one-time treatment is not as susceptible to a competitor entering the market and driving down prices as a developer of a chronic treatment, although the evidence of competing DAA treatments for HCV indicates that competitive entry can impact the price of cures. When accounting patent expiration and market competition, the cost-effectiveness of a chronically-administered curative treatment would improve relative to the one-time curative treatment. Although both treatments may be priced to meet acceptable cost-effectiveness thresholds at time zero, the chronically-administered treatment could lead to reduced costs for payers over time. All else equal, accounting for these issues would reduce the value-based price for one-time curative therapies. However, it may be that accounting for additional elements of value (addressed below) to patients and family may offset the cost advantages of a chronically-administered curative treatment.

  Although including costs for formal and informal caregiving are often included in cost-effectiveness analyses, these costs may be particularly important in the context of potentially curative therapies since they tend to be focused on more severe illnesses. As discussed above, these costs could be expected to differ between an up-front curative treatment and a chronically-administered curative treatment as additional costs may be incurred with ongoing treatment even if health outcomes were the same.

- *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?*

  Our ISPOR Special Task on Value Frameworks argued that the cost-per-QALY metric, as used by ICER and NICE, provides a good starting point for economic evaluations of the value on new medicines [1]. However, the STF also argued that standard cost-effectiveness, as typically implemented, may often overlook several uncertainty-related potential elements of value [2]. Several of these appear to be pertinent to cures and, in particular, those for rare, health-catastrophic conditions, for which we are beginning to see curative gene therapies. It has been argued that for potentially curative therapies, it is likely that several of these novel elements could apply, including financial risk protection, health risk protection, value of hope, and real option value, as well as others—such as disease severity and equity [3,4]. Most of these elements need further research to inform the development of methods and data to estimate them, as well as their likely range of values and other characteristics. We have encouraged this type of research and are aware of various lines of research now being pursued (see, for example [5]). These results bear watching since they may help CEA results be more representative of patient and societal values.

  A good example is stated preference studies, such as discrete-choice experiments, that have been done or are underway to attempt to quantify the strength of patient (and other stakeholders') preferences for additional elements of value by isolating them from traditional elements of value, like survival, health status, and costs [6,7]. For instance, one could evaluate the relative importance of a one-time treatment versus ongoing treatment, holding all else equal. Alternatively, one could evaluate the relative importance of knowing when a treatment has worked by comparing levels such as 'immediately', 'in one year' or 'in 10 years'. If these additional elements have unique value above and beyond a treatment's impact on survival, health status and out-of-pocket costs, one could quantify their unique value using metrics like cost-equivalents or survival-equivalents which could potentially be included in cost-effectiveness analyses.

  Our STF argued for further research on two alternative approaches—augmented CEA (ACEA) and multi-criteria decision analysis (MCDA)—to consider a broader set of elements or criteria for value [8]. The STF also argued for the use cost=effectiveness thresholds (CETs) as part of the methodology for making coverage decisions. The STF highlighted the need for aggregating information to reach a decision whether under ACEA or MCDA. MCDA can directly deal with a diverse set of elements or criteria, while aggregation via ACEA requires either monetization or inclusion in health state utilities. Under ACEA, the QALY can be monetized applying a CET. Both ICER and NICE have acknowledged the relevance of a higher CET for orphan or rare diseases. This would argue for a higher value-based price, ceteris paribus.

- *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?*

  Simple approaches to this issue, such as varying the discount rate and observing the "time profile" of the incremental cost-effectiveness ratio (e.g., how the ICER changes as the time horizon used is 1, 5, 10, 15, etc. years) can be useful and informative. Beyond that, even though constant proportional tradeoffs are a fundamental assumption of the QALY metric, non-linearity in preferences for health benefits and their duration may deserve deeper consideration in some cases. A recent article found "strong evidence of non-linear time preferences,", with somewhat better results for hyperbolic discounting rather than standard exponential discounting – hyperbolic discount rates do not decline quite as quickly as exponential ones [9]. Similarly, it could be the case that there is non-linearity with respect to the magnitude of health benefits, related either to severity of illness or duration of gains. The case for considering non-linearities due to severity of illness has been recently studied by Taylor et al (2017), among others [10]. Some non-linearities due to duration can be handled by the discounting function, but not if there is any non-monotonicity involved (e.g., the behavioral economics behind why people buy lottery tickets); we are not aware of any recent health economics research that has addressed this particular issue.

References

1. Garrison LP Jr, Neumann PJ, Willke RJ, Basu A, Danzon PM, Doshi JA, Drummond MF, Lakdawalla DN, Pauly MV, Phelps CE, Ramsey SD, Towse A, Weinstein MC. A Health Economics Approach to US Value Assessment Frameworks-Summary and Recommendations of the ISPOR Special Task Force Report [7]. Value Health. 2018 Feb; 21(2):161-165.
2. Lakdawalla DN, Doshi JA, Garrison LP, 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 Health 2018;21:131–9.
3. Jena AB, Lakdawalla DN. Value Frameworks for Rare Diseases: Should They Be Different? Health Affairs Blog: Drugs and Innovation. April 12, 2017. Available at: https://www.healthaffairs.org/do/10.1377/hblog20170412.059563/full/. Accessed Oct. 3, 2018.
4. Garrison LP, Jackson T, Paul D, Kenston M. Value-based pricing for emerging gene therapies: the economic case for a higher cost-effectiveness threshold. Forthcoming in American Journal of Managed Care & Specialty Pharmacy. February, 2019.
5. 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. 201 Jun;122(6):607-613.
6. Lakdawalla DN, Romley JA, Sanchez Y, et al. How cancer patients value hope and the implications for cost-effectiveness assessments of high-cost cancer therapies. Health Affairs 2018; 31(4): 676-82.
7. https://healthpolicy.duke.edu/news/phrma-foundation-awards-two-grants-value-based-and-cost-effectiveness-research (accessed 2/20/2019).
8. Phelps CE, Lakdawalla DN, Basu A, Drummond MF, Towse A, Danzon PM. Approaches to aggregation and decision making—a health economics approach: an ISPOR Special Task Force report [5]. Value Health 2018;21:146–54.

9. Jonker MF, Donkers B, de Bekker-Grob EW, Stolk EA. Advocating a paradigm shift in health-state valuations: the estimation of time-preference corrected QALY tariffs. Value Health 2018: 21: 993-1001.
10. Taylor MJ, Chilton S, Ronaldson S, Metcalf H, Nielsen JS. Comparing increments in utility of health: an individual-based approach. Value Health. 2017;20(2):224-9.