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September 6, 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 proposed adaptations to your value assessment framework for Single or Short-Term Transformative Therapies. 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, 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, as well as our Institutional Council and members of our recent Special Task Force on US Value Assessment Frameworks. 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

ISPOR's comments below are provided by section of the "Proposed Adaptations" document:

## **1. Determining those treatments for which adapted assessment methods will be used**

ISPOR supports the definition of these therapies and their need for additional consideration in economic evaluation. However, it is important to delineate the potential reasons for doing so. From a pure welfare maximization approach, there is no clear need for a "new" model for economic evaluation of these therapies: standard CEA/threshold-based decision approaches are still relevant, given their understood limitations. Nevertheless, single and short-term transformative therapies (SSTs) do involve a few unique considerations, both practical and conceptual. On the practical side, the potential for major health gains as well as large cost offsets, and their inherent uncertainty, call for additional care in those calculations. Similarly, the financial and affordability risk due to large upfront payments for lifetime benefits, or the alternative of staged payments, distinguish this class of drugs, leading to concerns about what may constitute a viable pricing and payment system for them consistent with their economic value. Finally, on the conceptual side, is the controversial concern about whether pricing of drugs for very small populations should explicitly consider R&D costs in some systematic way (Drummond & Towse, 2019).

We also encourage ICER to provide clear inclusion and exclusion criteria for potential SSTs, at least to the extent that these adaptations will only be applied to those included in this definition. For example, some oncologics clearly qualify, some clearly don't, but there are certainly some that may or may not.

## **2. Assessing and Describing Uncertainty**

Cure proportion model: The cure proportion modeling technique fits better than other models to survival data with a cured portion. To accurately estimate the cure rate and the survival probability of the uncured patients, long-term follow up is normally needed. ICER acknowledges this as the condition to apply the cure proportion models and we agree with its adoption as a reference case when appropriate.

In cases where long-term follow-up data are not available, ICER's position is that "the presentation of results from several types of survival models can be used to develop a range around estimated long-term survival until more data become available". We would like ICER to elaborate on what types of survival models are acceptable in such situations. We would recommend the finite mixture model or other latent class mixture models as options to capture heterogeneity of response in a more general way than simply cure/non-cure proportions. Even when there are no long-term data showing the survival curve plateaus after certain time, there may be good reason to believe that the patients are heterogeneous (they respond to the treatment differently), so mixture models may fit the data better than other single population parametric models. We recognize that such models may be difficult to fit in some cases, but when they do fit they can help inform the modeling of longer-term survival.

Time horizon threshold analyses for durability of effect: We understand that estimating cost-effectiveness ratios at specific time horizons is a recognized type of sensitivity analysis on this dimension of cost-effectiveness calculations. However, it is an indirect approach to capturing uncertainty in the durability of a treatment effect—isn't it better to model that uncertainty directly? Using specific time horizons, especially to calculate an array of value-based prices, has little clinical rationale, risks creating greater confusion about results, and could disproportionately impact curative and transformative therapies for children and adolescents; this approach should be used with great caution.

Probabilistic sensitivity analysis linked to policy recommendation for outcomes-based payment: We also understand that PSA is a standard tool for measuring uncertainty in CEA results, and that uncertainty in outcomes is a reason for considering outcomes-based agreements (eg, Cohen et al, 2019). However, this is another indirect connection that should, at best, be used cautiously, given the probably-pragmatic-but-still arbitrary “25% over 200K” threshold proposed. Should recommendations for payers be based on this particular criterion before more consensus is developed about it? And what about the flip side of this story—if a new medicine/ intervention is most likely cost-effective (based on PSA), should it be recommended that payers grant open access to all patients with low co-pays and no prior authorization criteria, using value-based insurance design principles?

### **3. Additional Elements of Value**

In its technical brief on “Methods for Potential Cures,” ICER considers including additional elements of value, including “insurance value.” We appreciate ICER’s interest in this concept and wish to clarify several aspects of their discussion. The brief summarizes its views as follows: “a major overriding factor that would argue against the inclusion of additional value domains cannot be overstated: their inclusion would raise fundamental equity concerns. Higher spending on certain SSTs (or other treatments) that get extra credit for these additional value domains would lead to opportunity cost effects either inside or outside the health system.”

ICER views all these new value elements as additive, when in fact “insurance value” is *corrective*. ICER’s underlying assumption is that “classical” cost-effectiveness methods produce estimates of value that are substantively correct and that align with the rank-ordering of medical technologies. This view is not supported by recent research. In their work identifying insurance value, Lakdawalla, Malani, and Reif (2017) demonstrate that traditional cost-effectiveness methods, including those used by ICER, wrongly assume that healthcare consumers are risk-neutral. This is incorrect for numerous reasons. For example, if consumers were risk-neutral, they would not be interested in health insurance! By properly accounting for risk-aversion, Lakdawalla, Malani, and Reif show that the traditional approach overvalues treatments for mild disease and undervalues treatments for severe illness. Thus, the sickest, most vulnerable patients are penalized by this analytical error in traditional cost-effectiveness methods.

Similarly, ICER argues that “it is also not clear that willingness to pay for ‘peace of mind’ would not apply equally to societal spending in areas other than health care.” In fact, deploying insurance value aligns cost-effectiveness analysis with well-accepted welfare economics approaches that are used in the rest of the economy. For at least 80 years, economists have recognized that consumer preferences must be

accurately incorporated when valuing governmental programs and social spending (Samuelson 1977). This includes incorporating realistic risk-aversion preferences. CEA has stood apart from the rest of welfare economics in assuming that consumers are risk-neutral. Failure to incorporate insurance value into CEA perpetuates this misalignment and may systematically undervalue health spending compared to spending on other programs. Moreover, “insurance value” has implications for how medical technologies are rank-ordered, not just for the total level of healthcare spending. Put differently, even if we held healthcare spending fixed, insurance value would alter the way those fixed dollars are allocated; it would shift dollars toward more severe illnesses and away from milder ones.

There are two specific domains that are recommended for consideration by the independent appraisal committee:

- (1) A potential advantage for therapies that offer special advantages by virtue of having a different balance or timing of risks and benefits versus other treatments; and
- (2) A potential disadvantage for therapies that, if not successful, could reduce or even preclude the potential effectiveness of future treatments.

The first one, also known as “value of hope” (a preference for positively skewed outcomes), now has enough empirical support to be given serious consideration, and we agree with its inclusion. We are not sure the new label is an accurate or better description; it does not seem specific enough to the situation. If value of hope is too non-specific as well (though we still like it), maybe call it something like “preferential weighting of highly positive outcomes.”

The second one appears to be a “negative” aspect of “real option value,” in that a therapy may reduce or eliminate the potential benefits of a future therapy. If this is to be included, however, it seems inconsistent not to include the “positive” side of real option value, i.e., that some additional survival due to a therapy increases the potential to be further treated by a new therapy that may become available during that survival time. We agree, however, that there is some risk of double-counting, and that further research is needed to sort that out.

Finally, curative and transformative treatments can have a very significant impact on the family of the patients in terms of productivity and quality of life. Since ICER is very interested in the societal and health system impact of SST, and in keeping with the recommendations of the 2<sup>nd</sup> Panel, we encourage further consideration of these broader societal elements of value and their impact to the health system and society.

#### **4. Time Divergence Between Costs and Benefits**

Discounting: We understand and endorse the 3% standard for discount rates. However, given ICER’s propensity to consider sensitivity analyses for many other factors, we are not sure it’s consistent to rule out sensitivity analysis on the discount rate used for these therapies, especially when over a lifetime it can make quite a difference (e.g., a fully healthy 75 years of life expectancy becomes 30.6 years at a 3% discount rate, but is 39.5 years at 2% and 24.6 years at 4%).

## 5. Affordability and Fair Sharing of Economic Surplus

ICER's presentation of the concept and application of the concept of "shared savings" is a great starting point for beginning a discussion about appropriate rewards for innovative so-called SSTs. On a minor terminological point, the section heading refers to "Fair Sharing of Economic Surplus", but "fair" is never defined or explained. In health economics, "fair" is most commonly used in discussion of equity issues (which are not being discussed here) or about a "fair market", where participants compete on a proverbial "level playing field." In this case, the use is probably closer to the latter meaning, but the term "appropriate" (as used on p. 9) would be better. And by "appropriate", we would mean a system that aims to promote "dynamic efficiency", viz., the optimal amount and mix of medicines innovation across different types of medicines—small molecules, biologics, and SSTs.

As noted, under the current regulatory and legal system, innovative small molecules and biologics in the U.S. have a net exclusivity period of approximately 12 years. The expectation is that the generics or biosimilars will enter the market after 12 years, and the price of these substitutes will eventually be considerably lower than that of the branded originator product. One might think that creating a level playing field for SSTs would apply a similar rule, as ICER proposes. However, as ICER notes, not all SSTs are the same and some could be "cures" in very small (ultra-orphan) population. There is a case for running the proposed shared savings as a scenario analysis—but not as the base case for the VBP.

As we have noted elsewhere, ignoring several potential "novel" elements of value related to uncertainty could seriously bias the assessment of some technologies (Lakdawalla and Phelps, 2019)—and particularly in the case of health-catastrophic ultra-orphan conditions. There is likely to be an interaction among severity of disease, financial risk protection, health risk protection, and the value of hope (for a cure) (Jena and Lakdawalla, 2017; Garrison et al., 2019). Under conventional CEA, this would imply a higher cost-effectiveness threshold for QALY gains. Or using a net monetary benefit estimate from augmented CEA, this would imply adding value beyond cost-offsets and the QALY gain times the standard threshold.

A calculation of "shared savings" based only 12 years of exclusivity and the QALY gains would ignore these factors. We would urge ICER to give this more thought before launching without further study of the impact on different types of SSTs—and particularly those for health-catastrophic ultra-orphan conditions.

## Conclusion

We congratulate ICER on its thorough and very well-written recommendations and are pleased to be able to provide the comments above. One final comment may be about the general relevance of many of these considerations—would they change final recommendations about the products, at least for the purposes of payers, who are a primary audience for ICER's scenarios? Based on the examples shown in section 5 of the Technical Brief, very few of the scenarios shown would have caused the incremental CER to cross a \$150K/QALY threshold. On the other hand, the differences in the value-based price were

sometimes large, which could matter if they were implemented. On the whole, however, these proposed adaptations do address – perhaps with some potential modifications – many of the issues that arise in the economic evaluation of SSTs.

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