

September 6, 2019

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

***Re: Comments to ICER's proposed value assessment framework to address "single or short-term transformative therapies (SSTs)"***

Dear Dr. Pearson:

The Innovation and Value Initiative (IVI) appreciates the opportunity to offer comments on the draft set of methodological adaptations to the Institute for Clinical and Economic Review's (ICER) value assessment framework to assess treatments deemed "single or short-term transformative therapies (SSTs)."

IVI is a non-profit research organization whose mission is to advance the science and improve the practice of value assessment in healthcare by adapting a more collaborative, open and tailored approach to examining value, exploring new methods and building models that can support flexible decision making.

Before offering IVI's specific comments to ICER's recommendations, at the outset, we believe it is important to reiterate a point made in our recent response to ICER's proposed changes to the 2020 Value Assessment Framework: namely, ICER's stated goal of estimating long-term value while providing short-term budget estimates in a market where decision makers are incentivized to act primarily based on short-term costs.<sup>1</sup> While this is a concern in the use of all ICER value assessments, it is particularly acute in the case of SSTs, which are more likely to involve high upfront costs with benefits arising over a long timeframe. We do not suggest that ICER is responsible for altering these incentives. We do, however, highly encourage ICER to address these issues head-on in all reports, especially related to recommendations for outcomes-based contracts and other non-traditional financing strategies.

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<sup>1</sup> Specifically, our previous response included the following: "A further challenge exists regarding the need for a long-term view when quantifying the value of a medical technology and the frequent short-term budget-driven perspective of decision making. We agree that the long-term value of a therapy is the most important consideration, and this is certainly true for patients, their families, and society at large. In a system where health plans make coverage decisions based on short-term budget impacts, however, there is little incentive for insurers and others to prioritize investments in therapies with higher short-term costs but 2 greater long-term value. This issue is acknowledged and discussed in the existing ICER value framework. We are concerned, however, that merely listing long-term value alongside short-term budget impact leaves the decision-maker with the easy option to ignore long-term value. The potential disincentives to invest in treatments with long-term societal benefits are a pressing issue that confronts our society as whole, but through the reports and policy analyses produced by ICER, there is an opportunity to educate audiences on the issue and generate discussion about potential solutions."

Please find our response to specific proposed changes below. IVI's response is organized to correspond to ICER's "Proposed Adaptations to the ICER Value Assessment Framework" dated August 6, 2019.

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

### **2.1 Cure proportion modeling: ICER proposes to make cure proportion modeling its reference case standard when relevant, but to address uncertainty we will also provide survival analysis based on other modeling approaches when feasible.**

IVI applauds ICER for considering survival analysis with multiple approaches, including using cure fraction models. If the models used to quantify value are primarily based on parametric survival functions, model averaging can be implemented in a relatively straightforward way, and we strongly recommend that ICER do so to capture structural uncertainty (beyond the parameter uncertainty). To overcome many of the practical challenges with implementing multiple structures for more complex models, we recommend syntax-based programming languages (such as R) rather using Excel spreadsheets. This also allows for efficient programming of model averaging techniques.<sup>2</sup>

When multiple studies are considered in the estimation of time-to-event outcomes, it is important to consider multivariate (network) meta-analysis and indirect comparison methods that allow for estimating time-varying treatment effects based on the complete survival distributions of the studies of interest. These methods have been developed for parametric survival functions, fractional polynomials, and splines.<sup>3</sup> However, evidence synthesis in the context of cure fraction models is not yet established. As such, defining cure-fraction modeling as the reference standard may be challenging when the findings of multiple studies need to be combined.

In the absence of mature data regarding longer term survival outcomes, formal expert elicitation methods may be considered to help inform extrapolation of outcomes over time in a more transparent and reproducible manner.<sup>4</sup>

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<sup>2</sup> Incerti D, Thom H, Baio G, Jansen JP. R you still using Excel? The advantages of modern software tools for health technology assessment. *Value Health*. 2019;22:575-579.

<sup>3</sup> Dias S, Ades AE, Welton N, Jansen JP, Sutton A. *Network meta-analysis for decision-making*. Wiley. 2018, Chapter 10.

<sup>4</sup> Cope S, Ayers D, Zhang J, Batt K, Jansen JP. Integrating expert opinion with clinical trial data to extrapolate long-term survival: A case study of CAR-T therapy for children and young adults with relapsed or refractory acute lymphoblastic leukemia. *BMC Med Res Methodol*. In press.

**2.1 Incremental cost-effectiveness scenarios at multiple time horizons: ICER’s assessments of SSTs will include cost-effectiveness analyses and associated value-based prices at multiple time horizons: at the time horizon representing the longest-available follow-up data for a significant number of treated patients; and also, at 5 years, 10 years, and the standard lifetime horizon. The official ICER value-based price benchmark will remain that generated by a lifetime horizon analysis, but other results will be provided as important context with which to assess the impact of uncertainty on cost-effectiveness results.**

Incremental cost-effectiveness analysis is performed to quantify the value, and IVI strongly agrees that value should be estimated over a lifetime time horizon. When benefits are expected to accrue over that lifetime time horizon, providing estimates over shortened timeframes may potentially bias results when outcomes are not proportional over time – for example, when costs are higher in the short term and clinical and non-clinical benefits accrue over the lifetime. In the case of SSTs with the potential to cure or transform the course of disease, this approach may be particularly likely to underestimate benefits of therapies.

We do agree that uncertainty in long-term outcomes is a significant concern in the case of many SSTs, but we also acknowledge that evidence on long-term outcomes is limited on new therapies in general. The resulting uncertainty in value estimates should certainly be explored and thoroughly reported, but this is better accomplished using methods for examining structural uncertainty (e.g., comparing results from multiple model structures<sup>5</sup>) and parameter uncertainty (e.g., using probabilistic sensitivity analysis (PSA)).

**2.3 Introducing a new economic review section on “Controversies and Uncertainties”: We propose including a new section in the “Long-Term Cost-Effectiveness” section of ICER reports which will discuss “Controversies and Uncertainties” related to the economic evaluation. Although the current layout of ICER reports includes information on these issues, we feel it will be helpful to consolidate and expand discussion of factors related to uncertainty, including lack of information on natural history, limitations of the data on patient outcomes, and difficulties translating existing data into measures of quality of life. This section will also be used to expand discussion of alternative model structures or inputs suggested by manufacturers or other stakeholders. This proposed change to ICER’s report structure will be considered for all ICER reports, not just those for SSTs.**

IVI welcomes this recommended change to ICER’s reports and supports its implementation in all ICER reports.

**2.4 Probabilistic sensitivity analysis linked to policy recommendation for outcomes-based payment: At a price at which greater than 25% of PSA simulations of the base case produce incremental cost-effectiveness ratios above \$200,000 per QALY, we propose to**

<sup>5</sup> Linthicum M. The Impact of Structural Uncertainty on Cost-Effectiveness Estimates. Value Blueprints research brief. September 3, 2019. Available at [https://www.thevalueinitiative.org/wp-content/uploads/2019/09/2019-09-03.Value-Blueprint\\_Structural-Uncertainty\\_FINAL.pdf](https://www.thevalueinitiative.org/wp-content/uploads/2019/09/2019-09-03.Value-Blueprint_Structural-Uncertainty_FINAL.pdf)



**include a policy recommendation that payers and manufacturers view outcomes-based contracting as the preferred method of payment. This methods change is proposed for all ICER reports, including SSTs.**

IVI interprets ICER’s proposed modification to mean that the cost-effectiveness of SSTs will be evaluated such that the most-likely (or average) incremental cost-effectiveness ratio across PSA simulations will still need to be less than the threshold of \$150,000/QALY for a SST to be deemed cost-effective, but that if there is a high degree of uncertainty, outcome-based contracting is recommended.

We agree with the underlying reasoning for this proposed modification, but we are concerned by specific elements of the approach. In particular, the arbitrary selection of thresholds – both the percentage of PSA iterations that must fall above the \$200,000 threshold, and the \$200,000-per-QALY threshold itself – suggests a level of consensus on thresholds that does not exist. Instead of this approach, we suggest that ICER continue to present (pairwise) cost-effectiveness acceptability curves which effectively provide the same information but for a range of different thresholds.

The range of model output estimates obtained with a PSA is directly influenced by a number of modeling decisions: e.g. the number of model input parameters considered; the upper and lower bound for each of the model input parameters; the assumed parametric distribution; the incorporating correlation between different parameters; etc. Given the potential policy implications, it is important that there be full transparency regarding the implementation of a PSA for a given model, and as much detail as possible needs to be pre-defined in the protocol/analysis plan.

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

#### **3.1 Additional elements of value: ICER proposes to add two additional domains of “potential other benefits or disadvantages” for voting by our independent appraisal committees:**

**(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.**

#### **General Response:**

We applaud ICER for examining the possibility of incorporating novel dimensions of value but wish to clarify several aspects of the discussion. According to the technical brief, ICER’s view on additional dimensions of value is 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.”

It appears that ICER views new value elements as *additive*, when in fact concepts like “insurance value” and (the misleadingly named) “value of hope” are *corrective*. ICER’s underlying assumption is that its cost-effectiveness methods produce estimates of value that are substantively correct and that align with the rank-ordering of medical technologies. This outmoded view is refuted by recent research. In their work identifying insurance value,<sup>6</sup> Lakdawalla, Malani and Reif (2017) demonstrate that traditional cost-effectiveness methods, including those used by ICER, wrongly assume that healthcare consumers are risk-neutral. For example, if consumers were risk-neutral, they would not be interested in health insurance. Thus, traditional cost-effectiveness methods themselves pose fundamental equity concerns. By properly accounting for risk-aversion, Lakdawalla, Malani, and Reif show that the traditional approach actually *overvalues* treatments for mild disease and *undervalues* treatments for severe illness. Thus, the sickest, most vulnerable patients are penalized by this analytical inaccuracy 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.<sup>7</sup> This includes incorporating realistic risk-aversion preferences. Cost-effectiveness analysis has stood apart from the rest of welfare economics in forcibly assuming that consumers are risk-neutral. Failure to incorporate insurance value into cost-effectiveness analysis 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 illness and away from milder ones.

#### Response to proposed domain additions:

We are encouraged that, though ICER does not find sufficient evidence or support for novel value dimensions to include them in quantitative analyses, ICER does acknowledge their potential importance. The addition of new domains related to these issues is an encouraging step. IVI strongly believes, however, that ignoring these developing concepts until they are fully established in the field both does a disservice to stakeholders in the U.S. healthcare system and fails to take responsibility for actively working to improve methods used in value assessment. IVI calls on ICER to take an active role in efforts to test and improve evolving methods for value

<sup>6</sup> Lakdawalla DL, Malani A, Reif J. The insurance value of medical innovation. *Journal of Public Economics*. 2017; 145:94-102

<sup>7</sup> Samuelson PA. Reaffirming the existence of “reasonable” Bergson-Samuelson social welfare functions. *Economica*. 1977;44(173):81-88.



assessment, including but not limited to application of novel value components such as those discussed. IVI would gladly collaborate with and support ICER in any such efforts.

IVI supports the addition of a domain that addresses the **“potential advantage for therapies that offer special advantages by virtue of having a different balance or timing of risks and benefits versus other treatments.”** It is important to note, however, that this domain may apply to non-SST therapies as well as SSTs, and it should therefore be included in all ICER value assessments.

Regarding the addition of a domain addressing the **“potential disadvantage for therapies that, if not successful, could reduce or even preclude the potential effectiveness of future treatments,”** IVI is concerned that meaningful inclusion of this domain may be challenging given the degree of uncertainty around both long-term clinical effects and future therapeutic developments.

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We would like to thank ICER for its willingness to make its recommended value framework alterations public and accepting feedback. IVI believes that collaboration is essential to raise the level of discussion regarding value in healthcare and finding common ground in the approach to measuring value. To that end, we appreciate ICER’s process as it seeks to update its framework and hope we have offered substantive recommendations that can be incorporated, tested and refined as the community jointly works to improve the science and implementation of value assessment analyses.

Sincerely,

A handwritten signature in cursive script, reading "Jennifer L. Bright". The signature is written in dark ink and is positioned above a thin horizontal line.

Jennifer Bright, MPA  
Executive Director  
Innovation and Value Initiative