INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Value Assessment Methods for "Single or Short-Term Transformative Therapies" (SSTs)

Proposed Adaptations to the ICER Value Assessment Framework

August 6, 2019

Proposed adaptations will be subject to a Public Comment Period until 5pm EST on September 6, 2019. Please submit all comments to publiccomments@icer-review.org

Introduction

This paper presents a set of proposed adaptations to the ICER value assessment framework methods when the topic under review is a "single or short-term transformative therapy," or SST. Once posted, these proposals will be open for a 1-month public comment period, following which ICER will reflect on comments received, pursue additional feedback from stakeholders, and post a final version of adapted methods before the end of 2019.

In the future, the formal update to this set of adapted methods specifically for SSTs will be performed simultaneously with the updates to the overall value assessment framework. The proposed adaptations are meant to complement and build upon the upcoming update to the overall ICER value assessment framework that will guide ICER's methods of evidence analysis and stakeholder engagement beginning with reports in 2020 (available at https://icerreview.org/methodology/icers-methods/icer-value-assessment-framework/).

The proposed methods adaptations are the result of an eight-month process, seeking input from multiple sources. We conducted a systematic review of methods considered for "cures" or "potential cures;" sought input from CADTH, NICE, and other international health technology assessment (HTA) bodies; and performed interviews with leading methods experts and stakeholders, including patient advocacy groups, payers, plan sponsors, and life science companies. From this work ICER has developed and is posting along with this document a separate technical brief that serves as background to the proposed set of adapted methods presented here. The technical brief includes empirical analyses to evaluate the impact of different methodological adaptations across three cure scenarios. As part of seeking further comment on these proposals, ICER will host a multi-stakeholder meeting in September 2019 to gather further input on broader methodological issues related to the assessment of SSTs and on ICER's specific draft proposals for a set of modified methods.

ICER acknowledges the important insights gained from discussions with patient groups, drug manufacturers, payer organizations, health economists, and international HTA collaborators in the development of these proposed methods. Assessing the value of SSTs often presents important challenges, including increased uncertainty at the time of launch paired with high upfront costs and the risk of unrecoverable costs, questions regarding additional dimensions of value for patients or the health system, time divergence between costs and benefits, and concerns about affordability and fair sharing of economic surplus. For all stakeholders, it is critical that the methods that guide assessment and recommendations for fair value-based pricing of SSTs are ready for these challenges and are well adapted to foster innovation of transformative new therapies that are affordable to individual patients and to the health system. We look forward to receiving and considering public comment on these proposals from a broad range of perspectives.

Proposed Methods Adaptations

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

1.1. ICER will use an adapted approach to value assessment for "single and short-term transformative therapies" (SSTs). These are defined as *therapies that are delivered through a single intervention or a short-term course of treatment that demonstrate a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes*. SSTs include two subcategories:

- ***Potential cures*** **that can eradicate a disease or condition; and**
- ***Transformative therapies*** **that can produce sustained major health gains or halt the progression of significant illnesses.**

1.2 Scoping: ICER will include in its initial draft scoping document a statement on whether a therapy is judged to meet the above definition. Following formal public comment, ICER will make a final decision on whether the therapy meets these criteria and will be assessed using an adapted approach.

Discussion

There have been various attempts to define the term "cure," with divergent views on what constitutes a cure and on how long it is necessary to wait before declaring a treatment is a cure. For HTA purposes, it is most important to decide which characteristics of a new treatment would raise distinctive evaluation challenges such that alternative assessment methods should be considered. We believe it will be useful to consider alternative methods not just for potential cures, but also for certain disease-modifying treatments that produce a transformative health gain from short-term treatment, as many of the issues related to greater uncertainty and the disconnect between cost and longer-term benefits will apply.

This focus on single or short-term treatments also implies that we do not believe that treatments taken on a chronic basis, even if they may be true cures that eradicate disease, warrant consideration of special assessment methods. We believe that current assessment methods are adequate for these kinds of treatment and that it is the combination of short-term treatment with the potential for substantial long-term gain that generates the key challenges meriting consideration of alternative assessment approaches.

From a procedural standpoint, when beginning the scoping process for a new drug, ICER will review available information in the literature and from stakeholders regarding the nature of the treatment to make a preliminary judgment whether it should be considered as an SST. ICER will seek

consultation during the scoping process with manufacturers, the patient community, clinical experts, and others on the anticipated impact of the treatment. Following formal public comment on the draft scope, ICER will make a final decision on whether the treatment meets the criteria for SSTs and will be evaluated using the adapted assessment methods described below.

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.

Discussion

As discussed in the technical brief, the use of cure proportion models may help to better fit survival data in certain cases, and may be especially relevant for SSTs, where a proportion of patients may be expected to be cured or benefit from a complete halt in the progression of a serious illness. For SSTs, traditional parametric curves may not adequately fit the available survival data due to the heterogeneity of the population (with some patients cured and others not). We will model SSTs that show evidence of plateaus in survival data with newer techniques such as flexible parametric and other cure proportion analyses, using model fit statistics to determine the best fit to the available data. Where data are not mature enough to determine if the survival curve actually shows a sustained plateau, scenario analyses using various survival analytic techniques will help to characterize the range of potential results that may plausibly fit the available data to date. In such cases, 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.

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.

2.2 Time horizon threshold analyses for durability of effect: When the SST price is known or can be estimated, assessments of SSTs will also include a scenario with a threshold analysis determining the duration of beneficial effect (e.g. cure) for those patients receiving short-term benefit that would be needed to achieve standard cost-effectiveness thresholds (e.g., $150,000/QALY).

Discussion

ICER believes these additional analyses, which we have performed in an ad hoc fashion in the past, would be useful to add as a standard feature in the evaluation of SSTs. At the time of regulatory approval, SSTs will very rarely have data on patient outcomes beyond a relatively short period of time, and analyses at different time horizons of 5, 10, and 15 years will provide information on how cost-effectiveness and value-based prices would be impacted under various assumptions about durability of effect. While ICER will retain the base case at the lifetime horizon as the basis for its value-based price benchmark, decision-makers may wish to apply their own judgment on the time horizon for which judgments of value should be based. The scenario using only the longest-available follow-up data will show the intervention's estimated value when we assume nothing about outcomes beyond the data collected. This analysis may in some regards be considered the most conservative scenario, whereas some decision-makers will regard the lifetime horizon as the most optimistic scenario. Similarly, in judgments of value when the price of the SST is known, decision-makers may find it helpful to know the number of years that the benefits of a drug would need to be sustained in order to reach certain cost-effectiveness benchmarks. Knowing the results of this kind of threshold analysis may help decision-makers judge whether it is reasonable to assume that the treatment will be effective for that span of time or not. These analyses may also help inform the time horizon for outcomes-based contracts should payers and manufacturers wish to use a cost-effectiveness threshold as a target for establishing fair value.

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.

Discussion

ICER's technical brief on SSTs explored various options for adapting standard assessment methods to address uncertainty, including the feasibility of providing plausible conservative and optimistic scenarios as alternatives to the base case analysis. We believe that opting for formal designation of specific scenarios as optimistic or conservative would raise important challenges. Any designation of a scenario as a specific plausible alternative to the base case might limit appraisal committee exploration of multiple different scenarios. In addition, the choice of how to frame a "plausible"

conservative or optimistic scenario would be highly subjective. Instead, the new proposed section on "controversies and uncertainties" would be able to explore many different scenario variations that could be viewed as more or less conservative or optimistic. In particular, we intend to expand discussion of any alternative model structures or inputs suggested by manufacturers or other stakeholders that differ importantly from the base case.

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 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.

Discussion

It could be argued that every treatment with significant residual uncertainty regarding longer-term safety and effectiveness should ideally be paid for through an outcomes-based payment mechanism that helps share the risk between payers and manufacturers if long-term safety and effectiveness of a treatment does not meet expected outcomes as hoped for based on short-term data. The case for outcomes-based contracts is even stronger for SSTs given that otherwise, the entire cost of treatment would be paid "upfront" and therefore would be unrecoverable.

Payers speak of intuitively factoring in uncertainty when they make judgments about fair pricing, and we considered whether it would be useful to include in our reports a scenario in which the value-based price estimate was linked directly to uncertainty through application of a secondary cost-effectiveness criterion. This secondary criterion, as discussed in the technical brief, would require that a certain percentage of PSA simulations have incremental cost-effectiveness ratios below a given threshold, potentially lowering the value-based price recommendation from that at which the point estimate of the base case meets certain willingness to pay thresholds.

As noted in the technical brief, this is an approach proposed by the JCVI group in the UK that assesses vaccines. Our current position, however, is that this approach is not yet ready for implementation. The PSA is just one way to evaluate uncertainty, and it is unclear if it is the best way to capture the uncertainty related to duration of effect that is so central to the assessment of SSTs. Any criterion for the percent of PSA runs that would need to be below a certain threshold in order to satisfy decision-makers would be arbitrary and would need to vary across payers to accurately reflect their risk attitudes.

Therefore, we are proposing instead to evaluate the results of the PSA of the base case and identify the price at which a relatively high percentage (75%) of PSA results would fall below an incremental cost-effectiveness ratio of $200,000/QALY, modestly higher than that used for our usual value-

based price range. If less than 75% of PSA simulations are below this incremental cost-effectiveness ratio, we propose not to change the ICER value-based price benchmark, but instead will include a policy recommendation in our report that outcomes-based payment arrangements should be preferred under these circumstances to share the risk of uncertain outcomes between payers and manufacturers. As discussed above, there is no principled way to decide how to select the specific threshold for this kind of uncertainty criterion and these decisions should reflect the relative risk attitudes of decision-makers, which could vary across different SSTs depending on their specific characteristics.

In the technical brief we describe the results of applying a criterion requiring that the results of 90% of PSA simulations be less than $150,000/QALY. We discovered that applying this criterion would require a very high level of certainty that few SSTs might achieve, and might be considered too stringent a requirement. Upon reflection on these results, we have opted to propose a requirement that 75% of PSA simulations be below a higher cost/QALY and have decided not to propose that a formal "uncertainty-adjusted" value-based price be suggested. We look forward to public comment on this approach given the strong interest expressed by payers for some explicit mechanism for consistent reductions in value-based prices in the setting of substantial uncertainty.

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.**

This change is proposed for all ICER reviews, including SSTs.

Discussion

Our review of additional elements of value that are not traditionally included in cost-effectiveness analyses identified some that could be viewed as especially relevant for SSTs: the value of hope (often confused with the value for patients of treatments that have not demonstrated a chance for any benefit), insurance value, scientific spillover effects, and real option value. However, as described in the technical brief, there are important conceptual counterarguments for the inclusion of these additional elements of value as a quantitative element in value assessment. For several of the considered additional elements, we believe that there are significant risks of double counting within the QALY or within existing "other benefits" or "contextual considerations" that ICER already includes as part of its value framework.

A second counterargument against inclusion of additional elements of value is that they are all unidirectional: they all "add" value to treatments, and none have negative scores that would help balance out added value within an opportunity cost framework for determining the cost-effectiveness threshold. As discussed in the technical brief, many health economists believe that should any of these additional elements of value be incorporated quantitatively in determinations of cost-effectiveness, the operative cost-effectiveness threshold used for value-based pricing would need to be lowered, but by how much it is impossible to determine.

A third concern with these additional elements of value is that the methods for measuring them consistently across different types of treatments are not mature and the only consensus among health economists seems to be that further research is needed before it can be determined how to measure them.

We have considered these concerns and have decided to propose no quantitative integration of additional elements of value into the value assessment framework for the assessment of SSTs. However, interviews with patient groups and other stakeholders leads us to propose two additions to our list of potential other benefits and disadvantages that are important components of ICER's value framework. The first captures the basic idea of what others have called the "value of hope," but that we have chosen to call the value of having the *choice* among treatments with a different balance and timing of risks and benefits. This dimension of value can be appreciated if considering treatment options for patients facing a life-threatening condition. Best current treatment might offer a 2% chance for a five-year survival. A new treatment, however, might offer a different clinical profile: a higher chance of serious short-term side effects and death, but a 10%-15% chance of five-year survival. The total average QALYs gained for the two treatments might be the same, but for some patients there would be a special advantage in having the choice of accepting a higher short-term risk in order to have a greater chance at long-term survival. We propose to seek patient input on this potential other benefit during the review process for SSTs and have this issue debated during the public meeting and put to a vote of the appraisal committee in order to have its salience recognized by policymakers.

We also propose to include a new potential disadvantage: the disadvantage that some SSTs might have if, by their mechanism of action or triggering of immune responses, could lead to a decreased chance at effective treatment by a future generation of therapies in the pipeline. This concern has already been raised with some treatments for hemophilia and childhood blindness, and we feel it is important to consider this potential disadvantage as part of a broader judgment of long-term value for money within the ICER value framework.

4. Time Divergence Between Costs and Benefits

4.1 Discounting: ICER proposes to continue its use of a 3% discount rate as standard for both costs and outcomes.

Discussion

The use of a 3% discount rate as standard for both costs and outcomes has been standard practice for most cost-effectiveness analyses in the Unites States, as recommended by the 2nd Panel on Cost-Effectiveness.[1] This rate is based on estimates of the real consumption rate of interest and data on real economic growth, which are thought to reflect the social rate of time preference. The technical brief discusses in detail some of the arguments ongoing in HTA groups around the world over the basis for discount rates and whether there should be any deviation from a standard for certain kinds of treatments, such as SSTs. While some have criticized the use of the 3% discount rate (or of discounting *per se*), we have made the judgment that there is no persuasive evidence for the use of another rate at this time. We also see no convincing rationale for using a different discount rate or scheme for SSTs as opposed to non-SSTs, or for using differential discount rates for costs and outcomes. The use of a single, uniform discount rate for all assessments will allow for consistent comparisons across different or prior evaluations. We also do not propose presenting sensitivity analyses that vary the discount rate, as we do not believe this would provide additional information that is useful to decision-makers in this context. ICER encourages continued research into the appropriate discount rate to use for health economic evaluations, as well as periodic updates of the appropriate discount rate, as necessary.

5. Affordability and Fair Sharing of Economic Surplus

5.1 Shared savings: ICER proposes to provide a "shared savings" scenario analysis for SSTs as an adjunct to the base case. For this scenario analysis cost offsets will accrue to the innovator during the first 12-year period in the model, a time frame intended to approximate the average time to loss of exclusivity for new prescription drugs in the United States. The scenario will assume that all cost offsets following year 12 in the model will accrue to the health system, i.e. cost offsets will be set to zero in the model after year 12. The overall goal is to produce a different incremental cost-effectiveness ratio and related value-based price benchmark that reflect an alternative sharing of the economic surplus of treatment between innovators and the health system.

Discussion

Several factors lead us to believe that shared savings scenarios will provide useful information to stimulate a broader societal discussion on the use of cost-effectiveness to guide value-based pricing for SSTs. As discussed in ICER's accompanying technical brief, SSTs have the potential to lead to

very large cost offsets which translate into cost-effectiveness findings that would suggest value-based prices of extreme levels – for example, more than $80 million for a cure for one severe form of hemophilia. Importantly, standard cost-effectiveness methods assume that the innovator captures most of the economic surplus produced by a new therapy, but the background landscape of drug pricing includes an expectation that all new drugs will eventually face the equivalent of generic competition, after which the price is expected to drop closer to marginal costs of production and the drug enters an extended phase in which the health system captures nearly all the economic surplus.

SSTs may provide exceptional QALY gains and therefore have exceptionally high one-time value-based prices, but we propose an alternative pricing scenario that does not compound that pricing structure by granting the innovator a far greater share of the economic surplus driven by cost offsets generated by successful treatment. Many SSTs, particularly cell and gene therapies, due to the nature of their mechanism of action, may never face the equivalent of generic competition of the kind that has led to some balance in the sharing of the economic surplus between innovators and the health system. As Towse and Fenwick have recently elucidated, there are reduced gains to payers from competitive entry and loss of exclusivity for SSTs relative to chronic treatments.[2]

We are therefore proposing to include a shared savings scenario analysis, with associated value-based price calculations, for all ICER reviews of SSTs. Of note, we are not proposing to use a shared savings analysis as the base case for value-based price benchmarks, but are proposing that we include this analysis as a separate scenario for both the value-based price and budget impact analyses. The presentation and discussion of shared savings scenarios could provide policymakers with information to stimulate a broader dialogue on what the "appropriate" sharing of the economic surplus should be between innovators and the health system, which will be a critical issue as the number of SSTs entering clinical use increases, and the cumulative cost creates greater concerns about short-term affordability for patients and the health system.

Conclusion

We undertook our exploration of potential adaptations to our assessment methods for SSTs with an open mind and a desire to ensure that we evolve our methods to keep pace with that of innovation in treatments and the needs of decision-makers. Our analysis has concluded that the core elements of ICER's assessment methods are suitable for SSTs, but that key adaptations may help address the distinctive issues posed by SSTs related to increased uncertainty, additional elements of value, and the appropriate sharing of economic surplus between innovators and the health system. The purpose of these proposed adaptations to value assessment methods is to provide additional views of the relationship of uncertainty to value; to acknowledge relevant elements of value not captured by standard cost-effectiveness and bring those elements consistently and transparently into the decision-making process; and to stimulate a broader societal discussion of how to share economic surplus in situations in which there is a very large long-term cost offset anticipated from a single or short-term transformative therapy.

We look forward to receiving and reviewing public comments on these proposals. ICER will also host a multi-stakeholder meeting in September 2019 to gather further input on whether and how to adapt its standard assessment methods for assessments of SSTs. Following review of the comments received, ICER will revise and post a final version of adapted methods before the end of 2019.

References

1. Neumann PJ SG, Russell LB, Siegel JE, Ganiats TG, editors. *Cost-effectiveness in Health and Medicine.* New York: Oxford University Press; 2016.
2. Towse A, Fenwick E. Uncertainty and Cures: Discontinuation, Irreversibility, and Outcomes-Based Payments: What Is Different About a One-Off Treatment? *Value in Health: the Journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2019;22(6):677-683.