



**Modifications to the ICER value assessment framework
for treatments for ultra-rare diseases**

Final Version

November 2017

Introduction

Following a process of stakeholder engagement and two rounds of public comment, this paper presents the final adopted modifications to the ICER value assessment framework for 2017-2019 when the topic under review is a treatment for an “ultra-rare” disease.

These modifications complement and build upon the update to the general ICER value assessment framework that will guide ICER’s methods of evidence analysis and stakeholder engagement during the two year report cycle 2017-2019 (available at <https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/>). As noted during that update process, ICER was aware of the importance of distinguishing methods for assessments of treatments for rare conditions. To provide a basis for stimulating early discussion of these issues, ICER produced a white paper on the evidentiary and ethical challenges associated with evaluation of treatments for rare conditions (available at <https://icer-review.org/material/odaps-briefing-paper/>). ICER then hosted an all-stakeholder meeting on May 31, 2017 to gather further input on whether and how to adapt its standard assessment methods. Proposed modifications were posted in July 2017 for a 60-day period of public comment, during which ICER received comments from over 50 organizations and individuals. These comments have contributed to further reflection and consequent changes that now constitute the final set of modifications that are described in detail in this document.

ICER acknowledges the important insights gained from discussions with patient groups and many other stakeholders throughout the process during which these modifications have been developed. Stakeholders recognize that in any health system there is no perfect, universally accepted solution to the distinctive tensions that can arise among commonly shared goals of providing incentives for innovation, assuring access to new treatments offering life-saving or life-improving outcomes, managing uncertainty regarding clinical and economic impact, and achieving affordability for patients, the health system, and the nation. These tensions take unique and often magnified form in the value assessment of treatments for ultra-rare diseases. The modifications to value assessment methods presented here do not seek to address the challenges by establishing an entirely separate structure for the assessment of treatments for rare diseases. Instead, the goal is that ICER reports be able to provide specific context and additional information so that decision-makers will be adequately informed of the distinctive character of the evidence and the broader considerations that should be part of policy decisions regarding these treatments.

Ultimately, the purpose of these modifications to the ICER value framework is to provide a backbone for rigorous evidence reports that, within a broader mechanism of stakeholder and public engagement, can help the United States find the best balance between incentives for innovation, access, and affordability through an open, collaborative process. ICER looks forward to further experience with these methods and ongoing input from the entire stakeholder community. The next formal update to these methods will be launched in 2019.

Proposed and Final Modifications

Proposed Modifications July 2017:

- 1.1 ICER will consider using an adapted approach to value assessment for treatments that will be called a “potential major advance for a serious ultra-rare condition” if the three following criteria apply:
- The treatment is envisaged for a patient population of fewer than 10,000 individuals
 - There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals
 - The treatment offers a major gain in improved quality of life and/or length of life
- 1.2 ICER will include in its initial draft scoping document a recommendation on whether a treatment meets the above criteria. Following formal public comment, ICER will make a final decision on whether the treatment meets these criteria and will therefore be appraised using an adapted approach.

Final Modifications: Significant Changes From Proposed Modifications

- 1.1 **ICER will use a modified approach to value assessment for treatments for “ultra-rare diseases” (URDs). This modified approach will be used when:**
- **An eligible patient population for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.**
 - **There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.**
- 1.2 **ICER will include in its initial draft scoping document for all topics a draft recommendation on whether the intervention will be assessed as a treatment for a URD. Following formal public comment on this recommendation, ICER will make a final decision on whether the treatment will be assessed under the modified methods presented here.**

Discussion

Definitions of “orphan” or “rare” and “ultra-rare” conditions vary widely across organizations around the world. In the United States, the Orphan Drug Act of 1983 established a definition for use by the Food & Drug Administration (FDA) based on a prevalence of <200,000 patients, which today would represent approximately 61 cases per 100,000. The European Union’s definition for rare diseases, is somewhat lower (50 per 100,000).¹ Other countries have yet different thresholds, such

as Japan, which considers diseases to be rare if they affect fewer than 50,000 patients, or <40 per 100,000 given current population estimates.

Public comment included many expressions of concern with the proposal to create a dividing line between “rare” and “ultra-rare” diseases. We continue to feel there are compelling reasons to do so for health technology assessment. First, as expressed in the ICER white paper, there are two major reasons given for altering the assessment of value of orphan drugs compared to other treatments: 1) small patient numbers make it very hard to conduct the types of studies that would usually be required to demonstrate with the same level of certainty the safety, effectiveness, and comparative effectiveness of an emerging drug; and 2) small patient numbers may make it impossible to recoup development costs unless prices exceed those that would be commensurate with traditional cost-effectiveness thresholds. We believe that neither of these factors are operative for drugs with patient populations larger than approximately 10,000. We feel this view is supported by a historical view of the Orphan Drug Act. When it was passed in 1983, a rare disease was considered to be one that “occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from the sales in the United States of such drug.”² But given the evolution of launch drug prices for orphan drugs in the United States since 1983, recovering the cost of developing drugs is rarely of concern unless the treatment is a one-time “cure” and/or the patient population is far smaller than 200,000.

Second, it is ICER’s experience, as confirmed in discussions with HTA agencies around the world, that the ability to mount RCTs with adequate outcome measures, duration, and follow-up appears to be maintained until the candidate population size drops below a prevalence of approximately three per 100,000 population (about 10,000 individuals in the US). There is, of course, no absolute reason why 10,000 is the perfect dividing line, but neither was there any perfect reason why 200,000 was selected as the original threshold for orphan diseases in the US.

ICER also considered the prevalence thresholds adopted by the many countries that have established separate health technology assessment procedures for treatments of patient populations that are much smaller than the standard upper bound of orphan population size.³ For example, the health technology assessment agency in Italy considers a disease prevalence of one per million to represent an ultra-rare disease, while the National Institute for Health and Care Excellence (NICE) in England restricts entry into a separate assessment track to diseases with a prevalence of two per 100,000 or less, a threshold also recognized by the EU.^{3,4,5} The number 10,000 that we are adopting equates to approximately three patients per 100,000 overall population in the United States. Thus, the ICER threshold for ultra-rare disease is modestly higher than the threshold used in the EU.

From a procedural standpoint, when beginning the scoping process for a new drug, ICER will use epidemiologic and other sources to estimate whether the size of the eligible population for the

indications included within the review falls near or under 10,000. ICER will also seek consultation during the scoping process from manufacturers, the patient community, clinical experts, and others on the anticipated eligible population. The clinicaltrials.gov database will also be searched to determine whether there are any clinical studies underway suggesting that the treatment's future eligible population may be far larger than 10,000. ICER does not believe that the conceptual reasons justifying a modified approach to value assessment should be applied to drugs whose patient base has a reasonable likelihood of expanding far beyond the 10,000 threshold, even if the first indication is for an ultra-rare population. Therefore, if ongoing or planned research trials point to a much larger effective overall population, ICER will not recommend application of the modified assessment methods for ultra-rare diseases.

Dropped from the set of initial proposals is the idea that ICER will only apply modified methods if we believe a new treatment represents a "major gain in improved quality of life and/or length of life." Public comment was persuasive in highlighting the subjectivity of this judgment, and in questioning whether this criterion was necessary to distinguish those treatments that should merit a modified approach to value assessment.

Proposed Modification July 2017:

2.1 For assessment of the comparative clinical effectiveness of potential major advances for serious ultra-rare conditions, ICER will not change its approach to rating evidence according to the ICER EBM matrix, nor will there be different "standards" of evidence. Instead, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. The commonly used approach of evaluating major advances for severe ultra-rare conditions against historical controls will be highlighted.

Final Modification: Minor Change from Proposed Modification

2.1 For assessment of the comparative clinical effectiveness of treatments of ultra-rare diseases, ICER will not change its approach to rating evidence according to the ICER EBM matrix, nor will there be different "standards" of evidence. Instead, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. The commonly used approach of evaluating treatments for ultra-rare diseases against historical controls will be highlighted. This added contextual language will be highlighted through special formatting in ICER reports and retained throughout press releases, executive summaries, and other versions of ICER reports.

Discussion

Following initial stakeholder input and public comment, ICER is making only a minor change to this proposed modification. Public comment was mixed on whether it would be preferable to develop a completely different approach to rating the strength of evidence for treatments of ultra-rare diseases. We continue to believe that decision-makers will be best served if ICER maintains consistency in the application of ICER's EBM matrix and its approach to judgments on the magnitude of health benefit and level of certainty. But we will develop specific language highlighting the context within which we believe the body of evidence should be viewed. This will include discussion of the challenges of conducting RCTs in many cases, as well as the need to develop *de novo* surrogate outcome measures. The historical pattern of FDA requirements will also be addressed, including information on whether single arm trials have been accepted for this kind of condition/treatment.

ICER will also include language to highlight that the goal of consistency in no way diminishes the responsibility of decision-makers to consider broader aspects of value and the differential weight often given to these aspects of value in the case of ultra-rare diseases that best reflect society's broader goals.

The minor change to this modification is that we will create special formatting to emphasize the additional contextual information that will convey with all versions of the ICER report.

Proposed Modifications July 2017:

- 3.1** For assessment of cost-effectiveness of a potential major advance for a serious ultra-rare condition, ICER will seek to produce a cost-effectiveness model for every new treatment, acknowledging and highlighting additional uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures.
- 3.2** For these treatments, ICER will adapt its analyses to provide willingness-to-pay threshold results for a broader range, from \$50,000 per QALY to \$500,000 per QALY. No special quantitative weighting system will be applied to different magnitudes of QALY gains or to baseline severity of the condition.
- 3.3** ICER will calculate a value-based price benchmark for these treatments using the standard range from \$100,000 to \$150,000 per QALY, but will add language in all report formats indicating that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions

about other treatments.

- 3.4 When ICER judges that it is not feasible to translate measures of patient outcome into QALYs, ICER will provide analyses of the potential costs and consequences of treatment, and will not produce a value-based price benchmark. Instead, ICER will provide a crosswalk to a cost-consequence price for a treatment and condition pair that is the closest clinical analogue that can be found.

Final Modifications: Significant Changes to Proposed Modifications

- 3.1 For assessment of cost-effectiveness of a treatment for ultra-rare diseases, ICER will seek to produce a cost-effectiveness model for every new treatment, acknowledging and highlighting additional uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures.
- 3.2 For these treatments ICER will adapt its analyses to provide willingness-to-pay threshold results for a broader range, from \$50,000 per QALY to \$500,000 per QALY. No special quantitative weighting system will be applied to different magnitudes of QALY gains or to baseline severity of the condition.
- 3.3 ICER will calculate a value-based price benchmark for these treatments using the standard range from \$100,000 to \$150,000 per QALY, but will add language in all report formats indicating that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.
- 3.4 When the impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial and these costs are large in relation to health care costs, ICER will present its base case health system perspective model results in tandem with the results of a scenario analysis inclusive of broader societal costs. Similarly, a value-based price benchmark (VBPB) linked to the societal perspective analysis will be presented alongside the standard VBPB.
- 3.5 When there are challenges translating the outcome measures used in clinical trials and available patient-reported data into QALYs, ICER will conduct a search for “mapping” studies that may allow translation of surrogate outcomes into quality of life measures. The validity of these mapping studies will be discussed with manufacturers, clinical experts, the patient community, and other stakeholders in order to get their input on the most feasible way to

translate these other measures of patient outcome into QALYs.

Discussion

Public comment was also mixed on the relevance and possible modifications of cost-effectiveness analysis for assessments of the value of orphan/ultra-rare diseases. ICER has decided to retain cost-effectiveness as a component of its assessment framework. Even though some countries do not include cost-effectiveness analysis as a core element in the assessment of treatments for ultra-rare conditions, many countries do, and input from US payers and purchasers over time has confirmed to ICER that decision-makers in the US feel that the information can be helpful. To address the distinctive nature of decision-making for these treatments, ICER proposes to broaden the cost-effectiveness range analyzed for willingness-to-pay thresholds and to add information highlighting the added importance of other potential benefits and contextual considerations for policy decisions regarding these treatments.

Some public comment encouraged ICER to consider enlarging the cost-effectiveness range used for its value-based price benchmark, specifically, to enlarge it to meet the full range of willingness to pay thresholds from \$50,000 to \$500,000 per QALY that will now be provided in the report. However, some stakeholders preferred to keep the value-based price benchmark range unchanged, and ICER has decided that this approach has important merits. Consistency in the range will help highlight when treatments for ultra-rare conditions are priced similarly with other treatments in proportion to their added clinical benefits to patients. Moreover, keeping the price benchmark range the same, while adding language regarding the potential heightened importance of contextual factors and considerations about return on investment, will help emphasize what ICER and others agree is most important: that decision-makers explicitly consider other potential benefits and the broader contextual considerations that are central to decisions regarding these treatments. We do not believe that increasing the upper bound of the value-based price benchmark to \$500,000 per QALY would be able to serve this purpose without implying falsely that this number is the “right” number to use.

The most significant change from proposed to final modifications in this section is item 3.4, which is related to consideration of broader, “indirect” costs related to the impact of treatment. Significant public comment recommended inclusion of these costs within the ICER base case cost-effectiveness model. Although ICER continues to believe that the health system perspective is most valid and relevant for decision-making by purchasers and payers within the US health care system, it is undeniable that some treatments are likely to have a greater impact on costs outside of the health system than within it. In particular, some treatments may appear expensive within the health care setting, but offer the potential for substantial cost offsets, or even cost savings, when the impact on productivity costs, education, and other costs are considered. Health economists sometimes call inclusion of these additional costs as reflective of a partial “societal” perspective.

In reviews of treatments for ultra-rare diseases, when contextual considerations and other benefits may be viewed as having particular salience, ICER has decided to retain the health system perspective for its standard base case, but when there are substantial cost effects outside the health system, and these costs represent are also large in relation to health care costs, we will link our base case results with those from a scenario analysis using a broader societal perspective. The base case will not be altered, but in all ICER report formats it will be shown alongside the results from an analysis that tries to consider all major relevant societal costs for which reasonable estimates can be made. The goal of this approach is to maintain consistency in the ICER base case while ensuring that decision-makers understand that special consideration for ultra-rare disease treatments should include considerations of substantial impacts of these treatments on benefits and costs outside the health system.

Lastly, the modifications in this section have been changed to eliminate the effort to identify cost-consequence “analogues” for comparison with the treatment under review when translation of available outcome measures into QALYs is not feasible. ICER already includes cost-consequence findings in all its reviews, and public comment made it clear that this proposal would not lead to methods that would feel transparent and reliable to many stakeholders.

Proposed Modification July 2017:

4.1 For report sections on “other benefits and disadvantages” and “contextual considerations,” ICER will include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community. Information will also be sought on the potential impact of new treatments on the infrastructure for screening and care of the affected individuals.

Final Modification: Minor Change to Proposed Modification

4.1 For report sections on “other benefits and disadvantages” and “contextual considerations,” ICER will include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community. ICER will develop a specific template for the patient community and others to facilitate input on these elements of value that will have a meaningful role in the report and voting in the public meeting. Information will also be sought on the potential impact of new treatments on the infrastructure for screening and care of the affected individuals.

Discussion

Public comment was largely favorable to the steps proposed to enhance and broaden the role of considerations of other benefits and contextual considerations as a part of ICER reports. ICER received some comment recommending that we quantify these elements as part of the cost-effectiveness analysis, but experience and prior public comment on our previous proposals to quantify these elements for all assessments have led us to retain a more qualitative approach for this report cycle.

ICER will seek input (and evidence wherever possible) on the potential impact of treatments for ultra-rare diseases on families, schools, and communities. In addition, in situations where no treatment has been available in the past, ICER reports will seek input from patients and clinical experts on the potential impact of a new treatment on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.

Proposed Modification July 2017:

5.1 ICER will conduct over the coming year a collaborative process through which it will seek to develop a template for providing information in its reports on the research, development, and other relevant costs related to new treatments for serious ultra-rare conditions. Until this template is completed, ICER will work with individual manufacturers of treatments under review to determine what, if any, information related to the costs of development can be shared as part of the public deliberation regarding the value of these treatments and their appropriate pricing.

Final Modifications: Major Changes to Proposed Modification

5.1 ICER will postpone all efforts to develop a formal template for research and development costs. Further discussion will be sought with stakeholders on the prospects for forming a multi-stakeholder workgroup to evaluate the options for development of some kind of formal template.

5.2 In lieu of a formal template, ICER will invite every manufacturer of a treatment under review to submit whatever information the company may wish to submit on development or manufacturing costs for inclusion in a new dedicated section of the ICER report. If the manufacturer believes that development or manufacturing costs are important considerations in justifying the price for their product, it is hoped they will submit

information to support this assertion. No editing, judgment, or analysis will be performed by ICER on any information submitted.

Discussion

As noted in the proposed modification document, comment from patient groups, policy makers, and some life science companies has supported the relevance of knowing more about the development and manufacturing costs as a piece of information relevant to a judgment of fair pricing and of value of treatments for ultra-rare diseases.

In proposing to work with manufacturers and other stakeholders to develop a formal template for information on development costs, ICER was aware that there are many fundamental questions about what the scope of information would need to be, how this information would be obtained, and how it should be interpreted. As noted in our proposed modification document, there is a significant risk of false assumptions and unintended consequences.

Public comment was not universal but did emphasize the many conceptual and practical hurdles to any effort to obtain and present useful information. We have decided that the best decision now is to postpone any attempt to seek stakeholder engagement in a process aimed at developing a formal template for development costs. ICER will continue to observe the efforts by state governments and others who are seeking development cost information, and we hope to revisit with stakeholders at some future point the question of whether a formal template for ICER reports would be feasible.

In the meantime, we have decided to offer to manufacturers of treatments for ultra-rare diseases an open invitation to submit any information about development and manufacturing costs that they feel may be useful in a broad judgment of the value or fair pricing of their treatment. We are hopeful that companies that wish to assert that these costs are substantial and important elements in the company's own thinking about pricing and value will be able to supply some quantitative information on these costs. ICER will create a section of its reports for this information and note whether any material has been received. No editing, judgment, or analysis of this material will be performed by ICER.

Proposed Modification July 2017:

6.1 During public meetings of ICER's independent appraisal committees, votes on the "long-term value for money" of treatments for serious ultra-rare conditions will be done according to the same procedures for other interventions, i.e. if the base case estimate falls between \$50,000-\$175,000 per QALY. However, for treatments of ultra-rare conditions, ICER will not assign any designation of value if the base case cost-effectiveness ratio is above \$175,000 per QALY.

Final Modification: Significant Change from Proposed Modification

6.1 During public meetings of ICER’s independent appraisal committees, votes on the “long-term value for money” of treatments for serious ultra-rare conditions will be modified from the process for other interventions by having appraisal committee votes on value even if the base case cost-effectiveness results fall outside of the standard \$50,000-\$175,000 per QALY voting range.

Discussion

As part of ICER’s 2017-2019 update to its overall value assessment framework, it was established that independent appraisal committees would only vote on the “long-term value for money” of a treatment if the base case cost-effectiveness ratio fell between \$50,000 and \$175,000 per QALY. Otherwise, treatments with a cost-effectiveness under \$50,000 per QALY would automatically be determined to be of “high” long-term value, whereas treatments above \$175,000 per QALY would be designated as “low” long-term value. Our original proposal was not to change this approach for treatments of ultra-rare diseases but to rely on the added language about the distinctive approach to weighing different components of value.

We are appreciative of the public comment that has led us to reflect further on this issue. We still believe there are strong reasons to believe that the higher boundary of this cost-effectiveness range can and should apply to orphan drugs, and even to treatments for ultra-rare diseases. But as we have also made clear, we acknowledge the reasonableness of arguments that pricing for these treatments may require higher cost-effectiveness thresholds to achieve adequate return on investment and to reflect differential weighting of “other benefits” and “contextual considerations” for treatments of particularly severe diseases with no prior available treatment.

Therefore, ICER has decided to include a vote on “long-term value for money” by the appraisal committee during the public meeting, following the discussion and public comment. There is less guidance available from health economics literature or other sources to guide votes on value when incremental cost-effectiveness ratios exceed \$175,000 per QALY, so we would expect greater variation in committee votes. Nonetheless, the process of public discussion and voting may serve to help inform policy decision-makers as they make their own judgment in light of the findings of the ICER report.

Conclusion

As noted in the ICER white paper, questions around whether there should be a “different” approach to assessing the value of treatments for rare conditions involve a mixture of practical and ethical considerations. Ultimately, the policies of health technology assessment often reflect the attempt to balance competing ethical interpretations of “fairness” in the context of spending on expensive treatments for rare and ultra-rare conditions.

There is no simple solution to this tension; many, but not all, ethicists argue that some preference, some premium, is due to treatments for very rare conditions. But no ethicist, or manufacturer, or clinician, or insurer, or citizen, would argue that treatments for rare conditions should command an unlimited premium. To decide how much preference, how high the price for a treatment should go, is a question whose answer requires us to find an elusive balance between two different views of fairness.

This final version of the modifications to the ICER value assessment framework for treatments for ultra-rare diseases represents ICER’s attempt to craft methods that will allow all stakeholders and the broader public to engage in a more transparent, evidence-based effort to find that balance. We appreciate and acknowledge the thoughtfulness of the public comments we have received throughout the course of this process. We look forward to the chance to learn together with the broad stakeholder community from the experience of using this modified assessment framework. And we look forward to further opportunities to listen and learn as we take concrete steps together to achieve sustainable access to high-value care for all patients in the United States.

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