Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions

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Introduction

This paper presents a set of proposed adaptations to the ICER value assessment framework when the topic under review is a treatment for an "ultra-rare" condition. Once posted, these proposals will be open for a 60-day public comment period, following which ICER will reflect on comments received, pursue additional feedback from stakeholders, and post a final version of adapted methods in the early fall 2017. In the future, the formal update to these methods will be performed simultaneously with the updates to the overall value assessment framework every two years.

The proposed adaptations are meant to complement and build upon the recent update to the ICER value assessment framework that will guide ICER's methods of evidence analysis and stakeholder engagement during the coming 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.

ICER acknowledges the important insights gained from discussions with patient groups and many other stakeholders before, during, and following that public meeting. Stakeholders recognize that in any health system there is no perfect, universally accepted solution to the distinctive tensions that can arise between 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 rare conditions. The adaptations to value assessment methods presented below do not seek to address the challenges by establishing an entirely separate structure for the assessment of treatments for rare conditions. 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 treatments for rare conditions.

Ultimately, the purpose of these proposed adaptations 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 address these tensions through an open, collaborative process. We look forward to receiving and considering public comment from a broad range of perspectives.

Proposed Adaptations

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 potentially 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.

Discussion

As noted in the ICER white paper, definitions of "orphan" or "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, given a current estimate of US population size of 326 million, would represent approximately 61 cases per 100,000. The European Union's definition, which affects joint public health actions and regulatory submissions to the European Medicines Agency (EMA), is somewhat lower (50 per 100,000).[1] Finally, Japan considers diseases to be rare if they affect fewer than 50,000 patients, or <40 per 100,000 given current population estimates.

Further, neither in the US nor in other countries is there an explicit definition used by regulatory processes to identify a boundary between rare and "ultra-rare" conditions, but many countries have established separate procedures for consideration of funding treatments for patient populations that are much smaller than the lower bounds of the standard orphan population size.[2] For example, the health technology assessment (HTA) 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 named the Highly Specialized Technologies (HST) program to diseases with a prevalence of two per 100,000 or less.[3,4]

ICER believes that application of adapted methods of value assessment are not needed for the majority of "orphan" drugs as defined by the Orphan Drug Act, as sufficient patient numbers are usually available for "routine" clinical trials, and outcome measures are likely to be relatively standardized and well-documented. Only when patient populations near a smaller size of

approximately 10,000 individuals does it seem that assessment methods might need to change in some way to recognize the distinctive practical challenges to evidence generation, and to give special consideration to value in the context of the price X volume needed to provide adequate rewards for risk and innovation. A patient population of 10,000 equates to approximately three patients per 100,000 overall population in the United States.

Ethicists and others have argued, however, that rarity alone does not justify an alternative approach to value assessment. Discussion at the Orphan Drug stakeholder meeting suggested that a combination of complementary factors, specifically high severity and the potential for a substantial gain in quality and/or length of life, would create a situation in which special attention to broader ethical and contextual issues should accompany any traditional analysis of cost-effectiveness and potential budget impact. ICER is not proposing to include as a criterion that the condition affect primarily children. Although pediatric conditions do often engender questions about the priority that society would place on potential treatments, ICER does not believe that it should be a pre-requisite for application of the adapted value assessment methods proposed below.

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.

Discussion

Following stakeholder input, ICER believes that decision-makers will be better served by retaining consistency in the application of ICER's EBM matrix and its approach to judgments on the magnitude of health benefit and level of certainty. Establishing artificial criteria for number or type of studies, or trying to specify a different threshold of uncertainty for treatments of ultra-rare conditions would be more likely to obscure important distinctions related to these treatments than to aid in consistency and transparency of decision-making.

However, informed by input from stakeholders, ICER will consider in its own judgments, and will highlight in the report, specific context regarding the acknowledged challenges that often arise in evidence generation for these treatments. Decision-makers should be given context to allow them to understand what might be viewed as feasibility constraints on manufacturers in generating robust evidence packages, and should know the historical context of the evidence produced for regulators and payers for similar treatments in the past.

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.

Discussion

Even though some countries do not include cost-effectiveness analysis as a core element in the assessment of treatments for ultra-rare conditions, stakeholder input has confirmed 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 decisions regarding these treatments. Other methodological changes will be made when special circumstances make it extremely difficult to estimate the impact of treatment on quality-adjusted life years, such as when diseases affect very young children or are associated with pronounced mental and/or physical disability in patients of any age.

ICER considered enlarging the cost-effectiveness range used for its value-based price benchmark but stakeholder input suggested that it would be preferable to remain consistent in the use of $100,000 to $150,000 per QALY. Doing so 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. ICER will add language to all its report formats to highlight this point as well.

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.

Discussion

ICER's standard value assessment framework includes important domains labeled as "other benefits and disadvantages" and "contextual considerations." Discussion with patient groups and stakeholders affirms the importance of these domains in the assessment of treatments for ultra-rare conditions, and has suggested that information should be included in the report on the potential of these treatments to have distinctive, and in some cases, broader effects. In particular, ICER will seek input (and evidence wherever possible) on the potential impact of these treatments on families, and even on 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.

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.

Discussion

Comment from patient groups, policy makers, and some life science companies has made it clear that to many observers it is relevant to their judgment of fair pricing and of value to know the costs expended during the innovation pathway, and to try to understand the future profits likely to be made by the company bringing the treatment to market.

There are, understandably, many different points of view on this issue, and it is not clear what the scope of information would need to be, how this information would be obtained, and how it should be interpreted. There is a significant risk of false assumptions and unintended consequences.

Nevertheless, arguments to justify the high price of many treatments for ultra-rare conditions are often based on the costs of production and the small patient populations which must be the source of adequate rewards for risk and innovation to maintain incentives for companies to develop the next generation of treatments.

ICER proposes to launch a discussion with pharmaceutical companies and other stakeholders to determine what kind of template of information related to the costs of development might be feasible as part of future reports. In one way or another, ICER hopes to include some kind of information on this topic in reports launching in mid-2018. Until that time, ICER will engage in dialogue with individual companies whose treatments are the subject of ICER reviews to see whether some information on development costs can be discussed as part of the public meetings during which ICER reports are deliberated.

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.

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. ICER proposes that there be no change to the range of cost-effectiveness within which the independent appraisal committees will take votes on long-term value of treatments for ultra-rare conditions. However, given the broader considerations and possible distinctive weightings for other benefits and for contextual considerations related to treatments for serious ultra-rare conditions, ICER proposes that it will not assign any value rating to ultra-rare treatments if the base-case cost-effectiveness ratio exceeds $175,000 per QALY. In this situation, we believe that it will be more informative to capture the votes on other benefits and contextual considerations, highlight how these factors often play an augmented role in determinations of value for treatments of ultra-rare conditions, and allow decision-makers to consider this information without an ICER-designated value rating.

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. This ethical tension is captured well in a paper by Hughes and colleagues:

> *"A key issue around whether…funding should support the provision of ultra-orphan drugs is whether the rarity and gravity of the condition represents a rational basis for applying a different value to health gain obtained by people with that condition. That ultra-orphan drugs are reimbursed at all, illustrates the fact that budget impact, clinical effectiveness and/or equity issues are given precedence over cost-effectiveness in decisions on resource allocation in some countries. The consequence, however, is that the opportunity cost of supporting the use of ultra-orphan drugs necessitates that patients with a more common disease, for which a cost-effective treatment is available, are denied treatment."*[5]

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.

The proposed adaptations to the ICER value assessment framework presented above represent 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 look forward to the chance to reflect further on additional public comment and to continuing our efforts to listen and learn as we take concrete steps to achieve sustainable access to high-value care for all patients in the United States.

References

1. European Medicines Agency. Orphan Designation. 2017. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac0580b18a41. Accessed May 5, 2017.
2. Kanavos P, Nicod E. What is wrong with orphan drug policies? Suggestions for ways forward. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2012;15(8):1182-1184.
3. Richter T, Nestler-Parr S, Babela R, et al. Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2015;18(6):906-914.
4. *NICE and NHS England consultation on changes to the arrangements for evaluating and funding drugs and other health technologies assessed through NICE's technology appraisal and highly specialised technologies programmes.*: National Institute for Health and Care Excellence; March 15 2017 2017.
5. Hughes DA, Tunnage B, Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? *QJM : monthly journal of the Association of Physicians.* 2005;98(11):829-836.