Scope of vignette:
- authorised products (with marketing authorisation)
- decision process about routine use (and not named-patient individual requests for reimbursement)
- submissions for P&R made by manufacturers

Green = related to/any special considerations for rare disease and ultra-rare disease treatments

United States (ICER)	**Standard HTA process (non-orphan drugs)[1]**	**Special process (ultra-orphan drugs)**
Overview of health system and P&R/HTA process	Multi-payer health care system: mix of public and private, for-profit and non-profit insurers and health care providers. [1] Each private and public health insurer performs their own internal assessments to decide how much to pay for new drugs, and in some cases, whether to pay for new drugs. [2] The **Institute for Clinical and Economic Review (ICER)** is an independent and non-partisan research organization that objectively evaluates the clinical and economic value of prescription drugs, medical tests, and other health care and health care delivery innovations. [3] ICER has three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC), and the New England CEPAC. Each program has an independent voting council that convenes at public meetings to review the ICER report, deliberate on key questions, and host a policy roundtable discussion with stakeholders to discuss how to apply the evidence to practice and policy.[4] The HTA reports produced by ICER are used by health insurers in pricing negotiations with pharmaceutical companies and to inform their clinical utilization management policies.[2] The Department of Health and Human Services (HHS), at the federal level, is the primary agency responsible for regulating the health care system in the US. Each state also has its own Department of Health (DoH) to implement state-level health policies. Health care provision and financing for those serving or formerly serving in the military are independently managed by either the Department of Defense (DoD) or the Department of Veterans' Affairs (VA). The HHS, along with its sub-agencies – Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA – regulates approval and registration of drugs and medical devices), National Institutes for Health (NIH) and the Agency for Healthcare Research and Quality (AHRQ) is responsible for developing and supervising implementation of health policies, and managing a large part of healthcare expenditure via the Centers for Medicare & Medicaid Services (CMS), which is the largest public health insurer. CMS operates health insurance schemes, and sets reimbursement rates for health care services. Reimbursement rates from private insurance companies are often based on CMS rates. The	

[1] ICER recently implemented an extended process for large reviews (of entire classes of medications). The process is 9 weeks longer than the standard process. This process is not discussed in this vignette. Further information can be found at: https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_2023_VAF_013120-4.pdf

United States (ICER)	Standard HTA process (non-orphan drugs)[1]	Special process (ultra-orphan drugs)
	Medicare program is barred from negotiating drug prices, and the Medicaid program must cover all approved drugs in exchange for a standard discount from the drug's manufacturer. The Pharmacy and Therapeutics (P&T) Committee develops and manages formulary systems used in different settings, including hospitals, long-term care, insurance companies, managed care organisations. For hospitals, they must decide which drugs (for use during inpatient or outpatient procedures or hospitalization) will be on their formulary to be used for a covered procedure. Hence, it is important for hospitals to maintain their own formularies. There is no federal HTA requirement, but Medicare sometimes requests that the Agency for Health Care Quality (AHRQ) review new treatments or procedures for efficacy, safety, and comparative effectiveness. [5]	
Differentiation of rare disease treatments in the P&R system	ICER defines a treatment for an ultra-rare condition as one with an intended patient population of fewer than 10,000 people	
Eligible medicines	Any drugs that are approved by the FDA or are expected to be approved in the near future. [2]	Treatments with an eligible US patient population of fewer than approximately 10,000 individuals No ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals [6]
Process	1. Topic selection - Horizon scanning is performed to identify potential topics - Key criteria (e.g. projected timing of FDA approval, substantial opportunity to improve health outcomes) are used to guide topic selection - ICER selects topics based on its own independent research, a review of publicly-available information about the emerging drug pipeline, and discussions with stakeholders including ICER advisory boards[2].	

[2] Each program (CTAF, New England and Midwest CEPACS) is comprised of two bodies:

- Advisory board: Non-voting, not subject to COI requirements. Provides some advice to ICER on topic selection but does not have decision-making authority; may advise on implementation opportunities; may serve as an invited expert

United States (ICER)	Standard HTA process (non-orphan drugs)[1]	Special process (ultra-orphan drugs)
	2. Scoping - Preliminary internal review of available evidence - Expert input (doctors, patients, payers, manufacturers, and policy experts) provide more thorough knowledge and context - A scoping document is then created to define population, intervention, comparators, outcomes, timing, setting, study design, and broad details of the economic modeling effort to ensure scope is manageable and useful - Draft scoping documents are subject to a three-week public comment period and may be revised based on stakeholder input 3. Clinical evidence review, economic modelling, and report generation - Clinical and health economics teams create a protocol for the clinical evidence review and a model analysis plan to explain how the research will be performed, including details of planned qualitative and quantitative analyses. - The protocol and model analysis plan are posted to a public website, the 'Open Science Framework' - Based on the published evidence, other publicly-available data, confidential data [8] (in some cases) and stakeholder input, a draft HTA report is posted on the ICER website and open to the public for comments for four weeks - All comments received within the four weeks are reviewed internally, and ICER will provide written responses and revise analyses as necessary - The revised report is made available to the	

speaker (non-voting) at public meetings. Advisory board members are representatives from provider groups, payers, and patient/consumer organizations.

- Voting council: convenes at public meeting, has voting ability (except for ex-officio members), and is subject to strict COI requirements (https://icer-review.org/methodology/rules-that-apply-to-icer/coi-voting-bodies/). Voting council members are practicing clinical experts, health economists, pharmacists, health services researchers, health policy experts, and patient experts, all of whom are recruited based on their expertise in evaluating clinical and economic evidence.

United States (ICER)	Standard HTA process (non-orphan drugs)[1]	Special process (ultra-orphan drugs)
	public two weeks prior to the public meeting 5. Public meeting - Each HTA report is discussed in a public meeting through one of ICER's three independent programs: CTAF, Midwest CEPAC or New England CEPAC. The Council members come from a broad range of institutions and their votes represent their own perspectives (not that of their employer) - During the meeting, council members from one of the public programs hear a presentation of the clinical and economic evidence from the authors of the ICER report, and are asked to vote on questions regarding the comparative clinical effectiveness, broader "potential other benefits or disadvantages" or "contextual considerations" surrounding the treatment and disease, and the long-term value of a treatment at its current prices.[3] Members of the public can pre-register to deliver 5-minute public comments during the meeting. - At the end of the meeting a moderated discussion occurs with patients, clinical experts, manufacturers and payers regarding how to move evidence into insurance policy, pricing decisions, and clinical practice 6. Finalization of materials - Comments from the public meeting are incorporated into the final report, as well as a 'Report at a Glance', that includes the panel votes and policy recommendations. The final documents are put on ICER's website [2]	

[3] Specifically for each topic, the following votes are taken:

- Comparative clinical effectiveness: whether the evidence is adequate to demonstrate a net health benefit to patients for a comparison of treatment A vs. treatment B. A "yes" vote means the evidence demonstrates a net health benefit. A "no" vote means that currently-available evidence is inadequate to do so.
- Potential other benefits and contextual considerations: Councils also vote on whether any broader considerations that were not, or could not, be studied may lead to a judgment of higher/lower value [p. 32-38, reference 7]
- Long-term value for money at current prices: this concept includes comparative clinical effectiveness, potential other benefits, contextual considerations, and the results of the cost-effectiveness analyses. It is meant to represent a judgment of whether current price of the treatment is "fair" given the demonstrated benefits to patient populations.

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Disease specific expert input (e.g. clinicians or patients in any stage of the process)	Stakeholder input is sought from: - Patients advocacy groups – ICER has a patient engagement guide to help patient organizations, patients, and families participate. - Disease-specific expert physicians - Companies – to engage in open dialogue throughout the process – a manufacturer engagement guide is available for companies who wish to use this opportunity - Payers [2], [7] Stakeholder input is invited in the beginning and throughout review the process, including: - Scoping (early input to inform initial research plan and condition via written submissions and discussions written public comment on draft scope, key informant interviews) - Draft evidence report (written and verbal feedback on preliminary model with invited stakeholders, written public comment on draft report, pre-posting review of the draft report by clinical experts and patient organizations, sometimes a formal patient survey) - Public meeting (oral public comments, written summary of oral public comments, participation in policy roundtable by invited stakeholders) - Final evidence report (includes policy recommendations discussed during the policy roundtable conversation and written summaries of oral public comments) [6] Additionally, ICER has a Patient Engagement Program, which allow patients and patient organizations to contribute in many different ways depending on their resources and focus. Contributions can be in the form of ICER's patient input questionnaire, phone conversations, written comments, in some cases a formal survey that informs qualitative and/or quantitative analyses, participation at a public meeting. ICER further requests input from stakeholders on whether there are examples of low-value care that could be reduced/eliminated to create more "headroom" to pay for newer treatments. For the ultra-rare diseases, ICER invites manufacturers to submit information on the research and development costs associated with their intervention, if they believe that these costs are important elements of their justification for the treatment's price. Manufacturers may also participate in an economic model transparency program during the public comment period on the draft report, during which they receive a working version of the economic model for review. [6]	
Key domains in assessment	Long-Term Value for Money, a concept that encompasses [7]: • Comparative clinical effectiveness • "Potential other benefits or disadvantages" and "contextual considerations" • Long-term cost effectiveness Short-Term Affordability, which represents: • Potential budget impact [2]	

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Evidentiary requirements	Flexible and inclusive approach to sources of evidence, with emphasis on trial rigor. Preference for RCTs when available, which can be complemented by real world evidence and grey literature. [7]	Same standards of evidence as standard process, but for ultra-RDTs, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges conducting RCTs, validating surrogate outcome measures, and obtaining long-term data on safety and on clinical benefit. [6]
PROMs	PROMs considered if available. As with all forms of evidence, ICER will assess internal and external validity. [7]	- When there are challenges translating clinical trial outcome measures 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. [6]
Appraisal framework	ICER's framework uses two concepts: "Long-Term Value for Money" and "Short-Term Affordability," which are considered separately. Both concepts are intended to achieve sustainable access for high-value care for all patients **"Long-Term Value for Money"** is the primary anchor of the ICER Value Assessment Framework and is composed of: *Comparative Clinical Effectiveness* - ICER uses the ICER Evidence Rating Matrix [9] to provide a combined rating of 1) the magnitude of the difference between a therapeutic agent and its comparator in net health benefit, and 2) the level of certainty surrounding the best point estimate of net health benefit *"Potential Other Benefits or Disadvantages" and "Contextual Considerations"* - These domains are meant to capture aspects of the treatment or disease that are	Assessment is made within the context of ultra-RDTs: - ICER does not change its approach to using the Evidence Rating Matrix [9] for treatments for ultra-rare diseases. 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. - ICER includes an additional "potential other benefit" to capture evidence and perspective on the potential for these treatments to affect the infrastructure for screening and care of the affected individuals, via a specific template that patients and others can complete [6]

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	often poorly-captured by clinical trial data and other broader contextual issues regarding the condition itself and ethical, legal, and social priorities that are important to acknowledge as part of any discussion of value [7]. These domains are discussed in the report and subject to a vote at public meetings, but are not quantitatively incorporated into the analyses. *Long-term cost effectiveness* - The base case cost-effectiveness analysis uses a lifetime time horizon and takes the health system perspective. ICER promotes the societal perspective analysis, which is usually included as a scenario, to a co-base case if one or more of the following are true: Incremental cost effectiveness ratios change by more than 20%, and/or by more than $200,000 per QALY, and/or cross the threshold of $100,000-$150,000 per QALY. This would entail consideration of the impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs. A health benefit price benchmark linked to the societal perspective may be also be presented - For all treatments, including those for ultra-rare diseases, ICER will provide willingness-to-pay threshold results from $50,000 per QALY/evLYG to $200,000 per QALY/evLYG. No special quantitative weighting system will be applied to different magnitudes of QALY gains or to baseline severity of the condition [6]. - ICER "Health-Benefit Price Benchmarks" represent the price to meet the thresholds of $100,000 per QALY/evLYG to $150,000 per QALY/evLYG **"Short-Term Affordability"** is a complementary perspective that is assessed through potential budget impact analysis. - ICER conducts a potential budget impact analysis with a five-year time horizon to explore what proportion of the patient population could be treated	- Cost-effectiveness model will include context by acknowledging and highlighting additional uncertainty for ultra-RDTs in translating patient outcomes into quality-adjusted life year (QALY) or equal value of life year gained (evLYG) measures - ICER will calculate a health-benefit price benchmark for these treatments using the standard range from $100,000 to $150,000 per QALY/evLYG, 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

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	without exceeding an annual potential budget impact threshold at list price, negotiated price, and the prices to achieve cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained. - The potential budget impact threshold is double the average net budget impact for new drugs that would contribute to overall health care cost growth beyond the anticipated growth in national GDP plus an additional 1%.	
Reimbursement decision	Each private and public health insurer performs their own internal assessments to decide how much to pay for new drugs, and in some cases, whether to pay for new drugs. [2] Evidence dossiers summarising the key clinical and economic evidence for a drug are often used as a reference document by P&T committee's for their formulary decision making, along with other key considerations such as drug acquisition costs and potential budget impact. For prescription drug coverage in the public sector, Medicare offers a prescription drug plan (Part D), which is offered through health plans. Similarly, Medicare Advantage Plans typically offer the same prescription coverage. These plans have their P&T committees make decisions on what drugs to include in the formulary, using the information from evidence dossiers and accounting for drug acquisition costs and potential budget impact. Typically, CMS is required to approve the formulary of these health plans. [5]	
Pricing process	Payers (both CMS and private insurance companies) do not regulate the price of drugs, which allows manufacturers to set prices freely. Payers are allowed, however, to set the reimbursement price/rate. The reimbursement process differs between the public sector (CMS) and the private sector. [5]	
Managed entry agreements	Not applicable	
Key challenges	x Lack of good quality clinical data X Lack of real world data X Introducing value for money (often not cost-effective) X Monitoring treatment efficacy X Managing budget impact X Lack of criteria/transparency of OMP P&R processes X Making arrangements to work for all stakeholders X Lack of long-term meaningful outcomes	

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Impact of special processes	There have been several cases where considerations specific to ultra-rare diseases have led Councils to judgments of higher value (e.g. the availability of effective SMA treatments now makes the case for widespread screening in infants. Before, there was no need to do so because there were no disease-modifying treatments). Even in cases where the evidence base has been inconclusive, most commonly due to the use of poor surrogate measures, those shortfalls have helped to develop targeted recommendations for future therapies. A good example is for the DMD review – the evidence base relied on the 6 minute walk test and patient input indicated that novel video outcomes focused on functional ability would be a better method. This was included as a recommendation in the Final Report	
Proposed policy change	None. The current value assessment framework, including the adaptations for ultra-rare diseases, is intended for use through 2023.	
Joint initiatives	None.	
SOURCES		
1	https://www.commonwealthfund.org/international-health-policy-center/countries/united-states	
2	http://icer-review.org/wp-content/uploads/2018/08/ICER-Guide-to-Understanding-Health-Technology-Assessment-6.19.18.pdf	
3	https://icer-review.org/about/	
4	https://icer-review.org/advisory-and-governance-boards/#ctaf	
5	https://tools.ispor.org/htaroadmaps/USPh.asp	
6	https://icer-review.org/wp-content/uploads/2020/01/ICER_URD_Framework_Adapt_013120.pdf	
7	https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_2023_VAF_013120-4.pdf	
8	https://icer-review.org/use-of-in-confidence-data/	
9	https://icer-review.org/wp-content/uploads/2020/01/ICER_EBM_Matrix_User_Guide_013120.pdf	

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This vignette was compiled based on information provided by country experts and desk research. The information provided may be incomplete or contain inaccuracies. If you have any comments or updates, please email us at the following email addresses:

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