A Guide to ICER's Methods for Health Technology Assessment

October 27, 2020

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and life science companies. For a complete list of funders, visit http://www.icer-review.org/about/support/. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

About ICER's Public Deliberative Programs

The New England Comparative Effectiveness Public Advisory Council (New England CEPAC), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC), and the California Technology Assessment Forum (CTAF) – core programs of ICER – provide a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. These programs seek to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The New England CEPAC, Midwest CEPAC, and CTAF are independent committees of medical evidence experts, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All committee members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions.

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1. Introduction

ICER conducts evidence-based reviews and economic evaluations of healthcare interventions such as drugs, devices, and diagnostic tests. ICER's reports assist patients, clinicians, payers, life science companies, and other stakeholders gain a fuller understanding of the potential benefits and harms of health care innovations, as well as their long-term cost-effectiveness and potential health-system budgetary impact. ICER's reports also incorporate contextual considerations germane to the specified topic area.

ICER's commitment to multi-stakeholder engagement and transparency helps to ensure that it conducts work of high quality, using well-documented and methodologically rigorous approaches. This document provides a technical overview of the health technology assessment (HTA) principles and methods that guide ICER's work (for a plain language summary of the HTA process, refer to this guide). *Health technology* refers to any healthcare intervention (e.g., pharmaceuticals, diagnostic and screening tests, delivery system interventions) that can be used to improve health or prevent disease. The assessment of these health technologies involves the systematic evaluation of existing evidence using rigorous methods while taking uncertainty into account.

Eight key operating principles guide ICER's HTA process, including ICER's commitment to using well-documented and methodologically rigorous approaches, involvement of all interested stakeholders, transparency, independence, impartiality, solicitation of public comment and peer review, routine updates to analyses as significant new evidence becomes available, and publication of timely reports. These principles are described in detail in Section 2.

ICER's HTA process is also guided by the ICER Value Assessment Framework. The framework was developed with input from patients and patient advocates, clinical societies, life science companies, pharmaceutical benefit managers, and insurers, identifies the key domains that factor into considerations of value. ICER's Value Assessment Framework, along with modifications for ultra-rare conditions, is described in Section 3.
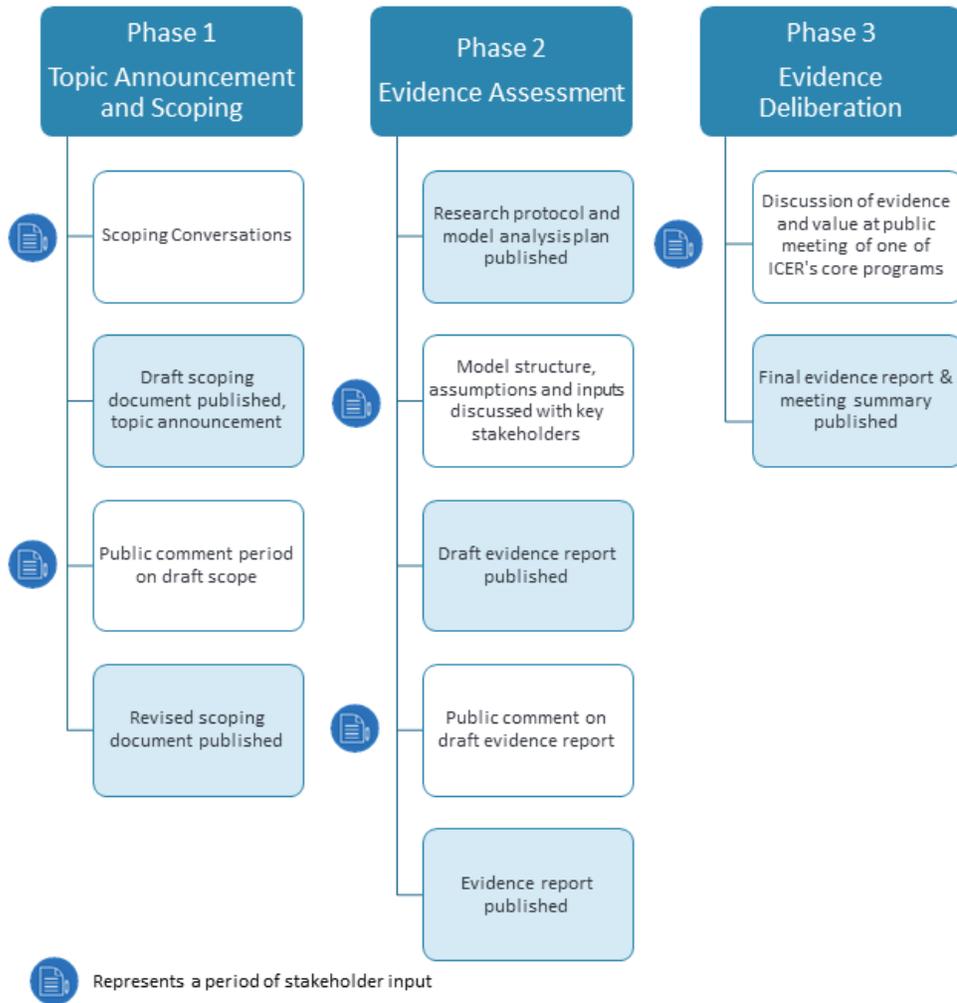
Figure 1 presents ICER's HTA process, which can be broadly grouped into three phases: topic selection and scoping, evidence assessment, and evidence deliberation. Each phase is described briefly below and in more detail in later sections of this document. Throughout each phase, ICER seeks to engage multiple stakeholders and the general public. Public comments allow ICER to address the concerns of patients, clinicians, policymakers, life science companies, and other health care decision makers to ensure that the HTA has the broadest possible relevance. Section 4 details the stakeholder engagement process, opportunities for public input, and how input is incorporated into the HTA.

During the topic selection and scoping phase, ICER determines the specific research questions to be addressed. ICER conducts its own research and engages with stakeholders to write a report scope that is defined in terms of the population, interventions, and outcomes of interest, and is based on current understanding of the topic. The scope is further revised after receipt of public comments. Importantly, ICER conducts explicit outreach to patient groups, clinical experts, payers, and life science companies during all phases of the scoping process to inform its work. Topic selection and scoping are described in further detail in Section 5 and Section 6, respectively.

Next, the evidence assessment phase begins. This phase has two components: an evidence review and an economic model to assess one or more interventions versus a relevant comparator(s). The evidence review identifies and summarizes the relevant evidence as defined by the project scope. The economic model contextualizes the evidence from a US health system perspective (for exceptions, see Section 8), which includes estimates of the costs and outcomes associated with each intervention. The results of both components are posted for public comment in a Draft Evidence Report, and feedback is incorporated into a revised Evidence Report. Details regarding the evidence review component are described in Section 7 and the economic modeling component is described in Section 8.

The evidence review and economic evaluation provide the backbone for public discussion on the value of interventions during the evidence deliberation phase. Each ICER Evidence Report is presented at a public meeting of one of its three core public programs: the New England Comparative Effectiveness Public Advisory Council (New England CEPAC), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC), and the California Technology Assessment Forum (CTAF). Each program convenes independent voting panels comprised of practicing clinicians, researchers, health economists, medical ethicists, and experts in patient advocacy and engagement to publicly discuss evidence related to the clinical effectiveness and value of the intervention(s) under review, and how the evidence should be translated into practice and policy. Each public meeting also includes time for life science companies and other stakeholders to deliver three- to five-minute oral remarks before the vote occurs, and time is set aside for follow-up discussion with the voting panel. After deliberation of the evidence, a policy roundtable convenes for a moderated discussion on how to move the evidence into practice and policy. The Final Evidence Report, including a summary of votes taken at the public meeting and subsequent policy recommendations, is available on ICER's website for public access. Details about the public meeting, panels, and Final Evidence Report are provided in Section 9.

Figure 1. Overview of ICER's HTA Process

Phase 1
Topic Announcement and Scoping
- Scoping Conversations
- Draft scoping document published, topic announcement
- Public comment period on draft scope
- Revised scoping document published

Phase 2
Evidence Assessment
- Research protocol and model analysis plan published
- Model structure, assumptions and inputs discussed with key stakeholders
- Draft evidence report published
- Public comment on draft evidence report
- Evidence report published

Phase 3
Evidence Deliberation
- Discussion of evidence and value at public meeting of one of ICER's core programs
- Final evidence report & meeting summary published

Represents a period of stakeholder input

2. Fundamental Operating Principles

Eight key operating principles guide ICER's work. ICER's approach to public HTA is in concert with principles of other health technology assessment agencies worldwide.[1] Although each topic involves many considerations, these eight principles are applied consistently to all of our projects.

Rigorous methodology

To provide decision-makers with useful and reliable information, ICER strives to produce work of the highest caliber, using well-documented and methodologically rigorous approaches. To achieve scientific and analytic rigor in its assessments, ICER follows established best methods for systematic literature reviews and economic evaluations.[2-5]

Inclusiveness

ICER believes that all stakeholders who have an interest in an HTA topic should be included in the review and deliberation process. Each HTA includes several opportunities for interested stakeholders to provide formal feedback on ICER's research: during an Open Input Period, in response to a draft scope, in response to a Draft Evidence Report, and during the public meeting. In addition, ICER conducts explicit outreach to key stakeholders for informal conversations throughout the project.

Transparency

ICER is committed to open and transparent engagement with all stakeholders that have an interest in each of its HTAs. To this end, ICER publishes its scoping document (Section 6), research protocol (Section 7), model analysis plan (Section 8), and report (Sections 7, 8, and 9). Each report includes a detailed technical appendix intended to provide full information on the structure, data elements, and key parameters for the economic evaluation as well as additional details pertaining to the evidence review methods and results.

ICER also publishes the comments it receives on the draft scoping document and Draft Evidence Report, as well as a response to comments on the report that outlines how received feedback is incorporated into the revised Evidence Report.

In addition, ICER shares a limited-release of economic model files and code to stakeholders willing to agree to confidentiality and privacy restrictions. This policy allows participating stakeholders to include detailed critique of the model in public comments submitted on the Draft Evidence Report. ICER's statement on model transparency can be found here.

Independence

ICER strives to maintain integrity in the HTA process by requiring that all individuals involved in the report development and deliberation processes conform to strict conflict of interest policies. These standards apply to employees, collaborators, members of independent voting bodies, and individuals who participate in our public meetings.

- **Voting Bodies:** All members of the independent voting bodies must meet established criteria to avoid any potential conflicts of interest when voting.

- **Meeting participants:** Participants in public meetings, including members of the policy roundtable and individuals delivering oral comments, must disclose any potential conflicts of interest.

- **ICER Employees and Collaborators**: All ICER employees and collaborators must adhere to the Code of Business Conduct and Ethics.

ICER also believes in maintaining organizational funding streams that do not compromise the independence or objectivity of its work. Approximately 80% of ICER's funding comes from non-profit organizations, which is directed to support ICER's public programs. The remainder of funding is provided by health insurers and life science companies and is directed exclusively toward support of an ICER Policy Summit intended for these stakeholders. Detailed information about sources of ICER funding are available here.

Impartiality

ICER seeks to independently analyze evidence on effectiveness and value while supporting a broader dialogue on value in which all stakeholders can participate. ICER does not represent the interests of any single stakeholder.

Review

ICER believes informal and formal adjudication processes can improve the quality, transparency, and methodological rigor of its work. To that end, ICER invites experts specializing in the clinical area of focus, economic evaluation, or the patient experience to independently review the Draft Evidence Report for accuracy. In addition, ICER solicits public comment on draft documents, presents analyses to ICER's independent public deliberative bodies, and disseminates findings at conferences or in peer-reviewed journals.

Timeliness

ICER strives to align the publication of its evidence reviews with the time period most relevant for decision-making. As an example, when evaluating a new pharmaceutical or medical device, ICER endeavors to publish its findings and convene a public meeting around the time of that intervention's likely FDA approval date, so that a relevant discussion around evidentiary gaps, pricing, and other concerns can be held at this critical juncture. ICER recognizes that important evidence may still be emerging on an intervention during the time of FDA approval and has therefore committed to updating its reviews when significant new information becomes available (See Update below).

Update

ICER recognizes that relevant new data may become available after completion of an initial evidence report that might substantially change our original conclusions and lead to major shifts in clinical practice guidelines or payer coverage policies. In such instances, ICER is committed to publishing updated analyses and reports.

3. ICER's Value Assessment Framework

ICER's HTA process is guided by the ICER value framework. The framework is intended to make transparent how value is conceived of and evaluated in ICER reports with the goal of helping the United States health care system provide sustainable access to high-value care for all patients.

The framework is built on two major constructs: "long-term value for money" and "short-term affordability" (see Figure 2). These components are described briefly in the subsections that follow and in greater detail on ICER's website.[6]

Figure 2. ICER's Value Assessment Framework
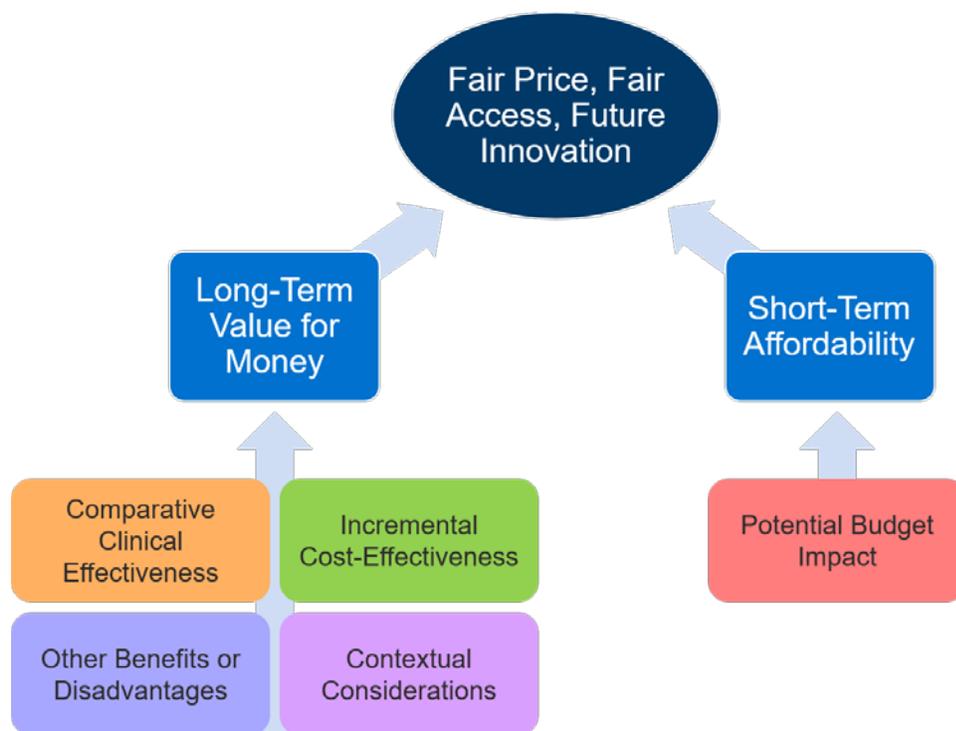
Long-term Value for Money

Four domains comprise the long-term value for money component of ICER's value framework: 1) comparative clinical effectiveness; 2) incremental cost-effectiveness; 3) other potential benefits or disadvantages; and 4) contextual considerations. These domains are described in further detail below.

1. ***Comparative clinical effectiveness*** is a judgment of the overall difference in clinical outcomes (both benefits and potential harms) between two interventions (or between an intervention and placebo), tempered by the level of certainty in observed differences given the strengths and weaknesses of the body of evidence. The ICER Evidence Rating Matrix

(see Section 7) serves as a conceptual tool for considering comparative clinical effectiveness.

2. ***Incremental cost-effectiveness*** is an estimate of the average incremental cost per patient of one intervention compared to another that would achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. As with comparative clinical effectiveness, relative certainty in the cost and outcome estimates is also a consideration. As a measure of cost-effectiveness, ICER's voting panels follow common academic and health technology assessment standards by using the cost per quality-adjusted life year (QALY) gained as the primary measure of cost-effectiveness as well as the equal value life years gained (evLYG), with formal voting on "long-term value for money". Section 8 describes ICER's methods for cost-effectiveness modeling in greater detail.

3. ***Potential other benefits or disadvantages*** refer to any potential advantages or drawbacks offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that lie outside the available evidence on clinical effectiveness and/or may be difficult to quantify in analyses of cost-effectiveness. Examples of other benefits include modes of treatment delivery that are likely to result in higher real-world adherence and treatments that differentially benefit underserved communities, and new potential mechanisms of action for treating clinical conditions that currently have low rates of response to existing therapies. A disadvantage could include an increased burden of treatment on patients or their caregivers. During evidence deliberation, panel members from ICER's core programs discuss and vote on whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money for the interventions being evaluated.

4. ***Contextual considerations*** include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include the severity of the condition, whether other treatments are available or soon will be, and other societal priorities that are important to acknowledge as part of any discussion on value. As with potential other benefits and disadvantages, panel members discuss and vote on whether these considerations should factor into the overall judgment of long-term value for money for the interventions of interest.

Short-term Affordability

ICER analyzes the short-term potential budget impact of changes in health expenditures with the introduction of a new test, treatment, or delivery system process. It remains a core principle of

ICER's value framework that it should evaluate both short and long-term costs across the entire health care system, so that care options that might increase spending for one type of service (e.g., drugs) while reducing other spending (e.g., hospital costs) receive full credit for cost offsets. ICER uses a five-year timeframe for its potential budget impact analysis in an attempt to capture some of the important potential clinical benefits and cost offsets provided by newer care options.

The results of the potential budget impact analysis are compared to a national threshold, calculated by ICER, that is tied to growth in the overall US economy. This threshold is intended to signal to stakeholders and policy makers when the amount of added health care costs associated with a new service may be difficult for the health care system to absorb over the short term without displacing other needed services or contributing to rapid growth in insurance costs that threaten sustainable access to high-value care for patients, and to trigger discussions of possible policy steps to manage the introduction of high-value services that nonetheless have significant potential budget impact. The threshold is updated annually to reflect changes in US medical and pharmaceutical spending as well as gross domestic product. Section 8 describes ICER's methods for budget impact analysis in further detail.

Modifications for Treatments of Ultra-Rare Conditions

ICER modifies its approach to value assessment when certain conditions qualify as ultra-rare, i.e., in cases in which the intervention(s) under review will be used for fewer than 10,000 individuals in the United States, and future indications are not expected to significantly increase this number. In such situations, ICER does not change its standards for rating the evidence of comparative clinical effectiveness, but highlights the potential challenges of generating high quality evidence for the interventions being evaluated. In addition, the modified framework gives greater weight to the intervention's impact on patient and caregiver productivity, education, disability, and other societal considerations. See here for a full description of modifications to ICER's value framework for ultra-rare conditions.

Modifications for High-Impact "Single and Short-Term Therapies" (SSTs)

ICER also uses an adapted approach to value assessment for high-impact single or short-term therapies (SSTs). SSTs are defined as "therapies that are delivered through a single intervention or a short-term course (less than one year) of treatment that offer a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes." SSTs include potential cures that can eradicate a disease or condition and high-impact therapies that can produce sustained major health gains or halt the progression of significant illnesses. Adaptations to ICER's approach to value assessment for SSTs include making cure proportion modeling the standard reference case whenever relevant, developing scenario analyses to reflect optimistic and conservative assumptions about the benefits of the SSTs under review, threshold analyses to determine the duration of benefit required to achieve standard cost-effectiveness thresholds (e.g.,

$150,000/QALY), and hypothetical shared savings scenarios. ICER's methods for assessing SSTs are described in greater detail [here](#).

4. Stakeholder Engagement

Throughout the HTA process, ICER seeks input from healthcare stakeholders including patients, advocacy organizations, clinicians, clinical societies, life science companies, insurers, and others. Each HTA includes several opportunities for all stakeholders to provide formal feedback on ICER's research: during an Open Input Period, in response to a draft scope, in response to a Draft Evidence Report, and during the public meeting.

Additional input opportunities are available by invitation to a subset of key stakeholders, including through attendance to a preliminary methods presentation, peer review prior to the publication of a Draft Evidence Report, and participation on a policy roundtable during the public meeting.

Throughout each HTA, ICER seeks stakeholder input on the following:

- Important patient-relevant and patient-centered outcomes, especially those not adequately captured in the clinical trial data
- Testimony from patients on the daily experience of managing their condition and its treatment as well as its impact on their lives and the lives of their families and caregivers
- Key publications related to the clinical trial program
- The appropriate population, interventions, comparators, outcomes, timeframe, and setting(s) of care (PICOTS) to be considered in the evidence review
- Other potential benefits or disadvantages of new and existing treatments
- Other important context about the condition or its treatment
- Key research needs
- Recommendations on key stakeholder groups ICER should seek input from, including:
    - National or regional clinical experts and researchers
    - Patient advocacy organizations
    - Individual patients and caregivers
- Any other input deemed relevant and critical to a comprehensive understanding of the evidence base
- Information about low-value services that could be reduced or eliminated from the current care paradigm in order to make headroom in health care budgets to pay for new innovations

There are certain milestones in the HTA process during which stakeholders may see the results of their feedback. As an example, recommendations related to the population, comparators, and outcomes to be considered in the evidence review may be reflected in the draft or revised scoping documents ICER publishes at the beginning of the HTA process (see Section 6). Information related

to the benefits, disadvantages, and context surrounding new and existing therapies may appear in ICER's Evidence Report or represent a prominent topic of discussion at the public meeting on the topic (see Section 9).

The following chapters include details about specific engagement opportunities. In addition, in-depth guides for patients and life science companies who wish to provide input can be found here.

5. Topic Selection

The HTA process begins with topic selection. ICER reviews a variety of topics including drug therapies, specific clinical interventions, procedures, and broader health system topics. When choosing a topic, ICER considers a list of key criteria to ensure that the topics being reviewed will have a meaningful impact.

The following criteria are used to guide the topic selection process:

- Projected timing of FDA approval within one year
- Predicted likelihood of FDA approval
- Projected significant budget impact
- Timely, by virtue of health policy landscape and stakeholder priorities
- Substantial opportunity to improve health outcomes by applying best evidence or potential for significant public health/health system impact
- Increasing significance to the public by virtue of prevalence, severity, disparities, and cost
- Emerging treatments with potentially large eligible patient populations, especially when less expensive alternatives are available
- Topics for which a review of evidence suggests specific actions for payers, physicians, patients, and policymakers and is likely to improve clinical practice or policy
- Topics addressing potentially overused or underused tests with substantial uncertainty over appropriate use
- Topics for which there is wide variation in approaches to delivery system design or financing, with substantial uncertainty over standards and best practices
- Topics involving vulnerable populations with the potential to reduce health disparities
- Topics that may leverage current health reform initiatives

Topic Updates

Relevant new data may become available after ICER completes an initial evidence report. When such information has the potential to substantially change the conclusions of the initial report or lead to major shifts in clinical practice guidelines or payer coverage policies, ICER conducts a topic update. ICER's criteria for new evidence and condition updates are described here.

Stakeholder Involvement

To identify potential review topics, ICER conducts horizon scans of new and emerging therapies and consults each program's advisory board (CTAF, Midwest CEPAC, and New England CEPAC). In addition, stakeholders may also submit suggestions for review topics that meet the criteria listed above.

6. Scoping

Overview

After a topic has been selected for appraisal, ICER begins its scoping process. Throughout this phase of the HTA, ICER solicits guidance from a variety of stakeholders to clearly define what the review will and will not examine.

Scoping begins with a five-week, non-public period during which ICER seeks input from targeted patients organization, clinicians, life science companies, and payers. ICER schedules conference calls with these stakeholders to gather their perspectives, and they may also submit written commentary on the topic (see Early Written Input below). ICER considers this commentary, as well as the suggestions and feedback received during calls with stakeholders (see Stakeholder Calls below), when developing the draft scoping document. Included in the draft scoping document is a proposed framework for reviewing the clinical evidence, other potential outcomes of interest (e.g., resource utilization, productivity gains), and economic analyses. The document outlines decisions related to the following:

- The clinical area and the population(s) for whom the intervention is intended; key subpopulations for whom the relative effectiveness of the intervention may vary are also identified
- The intervention
- The relevant comparator interventions
- The health outcome measures the analysis will consider
- The settings and time horizon over which health outcomes will be assessed
- Other special considerations, for example, whether the intervention and population of focus meet ICER's criteria for ultra-rare conditions and will therefore be appraised using an adapted approach to value assessment.

The draft scoping document is posted to the ICER website and open for public comment for a period of approximately 15 business days. ICER takes the commentary received during this period under advisement and finalizes decisions around its appraisal. The scoping process culminates with the publication of a final scoping document within approximately 10 business days of receipt of public comments.

Components of the Scoping Document

Background

The background section of the scoping document introduces the disease or clinical area relevant to the intervention under review. Important contextual information, which may include epidemiology, prognosis and natural history, current standards of care, and the rationale for selecting an intervention for appraisal, is briefly described. A more detailed overview of the topic's contextual landscape is described in the Evidence Report.

Report Aim

The report aim articulates what the review will address and the overall purpose of the appraisal. Detailed scoping decisions are outlined individually using the PICOTS (population, intervention, comparators, outcomes, timing, setting and study designs) framework (see below).[7]

Population

The scoping document defines the population that is eligible to use the intervention under review. For certain topics, such as drug therapies, the population may be defined to align with current or anticipated FDA indications for that therapy. The scoping document also identifies key subpopulations for whom the relative effectiveness of the intervention may vary.

Intervention

The scoping document lists the intervention(s) of focus for the review. Interventions may include drug therapies, medical tests, devices, and delivery system innovations. When relevant, the scoping document will define specific attributes of the intervention(s) of focus (e.g., mode of administration, line of therapy, etc.).

Comparator Interventions

Relevant comparators are selected through a survey of clinical guidelines from professional societies, consultation with clinical experts, and review of clinical trial designs. Appropriate comparators represent alternative therapies used among the populations and settings of focus. Active comparators (i.e., non-placebo interventions) are prioritized when feasible.

Outcomes

The scoping document identifies the measures of potential benefit and harm that are critical to the evaluation of net health benefit for the intervention. Health outcomes, i.e., changes in symptoms or conditions that people feel and that affect the quantity or quality of life (e.g., change in pain, quality of life, death) are prioritized.[8] Relevant intermediate outcomes are also specified.

Intermediate outcomes reflect changes in pathologic, physiologic, or behavior measures that may or may not be predictive of health outcomes; examples of intermediate outcomes include change in cholesterol, asymptomatic vertebral fractures, and blood pressure.[8] When appropriate, the scoping document lists other, non-clinical outcomes that the review may seek to evaluate such as resource utilization or other measures of societal benefit.

Timing

The scoping document specifies the time horizon over which outcomes will be assessed, as well as the minimum duration of study follow-up adequate to capture these outcomes.

Setting

Considerations relevant to the setting of use for the intervention (e.g., inpatient, clinic, outpatient) are specified in the scoping document.

Study Design

The scoping document lists the types of study designs that will inform a project. ICER includes peer-reviewed publications of randomized controlled trials, observational studies, and high-quality systematic reviews. Detailed specifications related to study design (e.g., minimum sample size) are developed following the posting of the final scoping document and are described in the research protocol (see Section 7).

Sources of Evidence

The scoping document proposes the sources of evidence that will inform the HTA. Every evidence review draws upon peer-reviewed publications related to the topic of interest.

In addition, ICER considers input from patients and patient advocacy organizations, as well as emerging evidence available in conference proceedings, regulatory documents, information submitted by life science companies, and other grey literature when such evidence meets ICER standards (for more information, see ICER's policies on the inclusion of grey literature and in-confidence data).

Economic Evaluation

The scoping document outlines the proposed modeling framework, including the specific question to be addressed from the analysis (i.e., the decision problem). The decision problem should be consistent with the aims of the evidence evaluation, and any differences should be justified. The scoping document proposes the type of model (e.g., decision tree, microsimulation, Markov cohort model), as well as the relevant health states under consideration. Additional details regarding the

model are developed after the posting of the final scoping document and are detailed in the model analysis plan (see Section 8 and Reference Case).

Stakeholder Involvement

Early Written Input

Once a topic has been selected, ICER accepts non-public, written input from invited stakeholders. During this period, which spans approximately three weeks, targeted stakeholders, including patient groups, clinicians, and life science companies, are invited to submit commentary on a broad range of issues related to the topic (see Section 4 for a general list of considerations on which ICER seeks external input).

ICER uses this information to inform the development of draft and final scoping documents, and as a source of information throughout the HTA process.

Stakeholder Calls

During the scoping phase of each HTA, ICER holds conference calls with key stakeholders to inform its research direction. During the first five weeks of the assessment, ICER will contact key stakeholders from the patient, clinician, manufacturer, and payer community to learn their perspectives on how ICER should approach its review.

Public Comment

At the end of the initial five-week period, ICER publicly announces the topic and posts a draft scoping document for a three-week public comment period, which provides all stakeholders, including those who we have already spoken to, another opportunity to provide feedback on ICER's research approach.

7. Evidence Review and Synthesis

Overview

Following publication of a final scoping document, ICER develops a research protocol. The protocol is akin to a workplan and outlines the research methods the evidence review team intends to employ in its review and synthesis of the evidence. This document typically describes how ICER will identify relevant literature (see Systematic Review Methods), evaluate evidence for risk of bias (see Assessment of Bias and Study Quality), synthesize data (see Evidence Synthesis), and assess the strength of the entire body of evidence pertaining to an intervention (see ICER Evidence Rating). Along with other documents pertaining to a given project, the research protocol is published for public consumption on the Open Science Framework and registered with the PROSPERO database.

Upon registration of the research protocol, ICER begins its evidence review. Prior to publication of the Draft Evidence Report, ICER invites peer review from clinical experts and individuals familiar with systematic review methods. When possible, experts in economic modeling and individuals familiar with the patient experience may also review the draft. The draft report is then published and available for public comment by any stakeholder who wishes to provide input (See Stakeholder Involvement). In preparation for evidence deliberation at the public meeting, ICER integrates stakeholder comments into a revised Evidence Report which is made publicly available approximately two weeks before the public meeting. A Final Evidence Report, which includes a summary of the evidence deliberation at the public meeting, is published approximately two weeks after the public meeting (see Section 9).

Systematic Review Methods

A systematic review identifies all relevant existing evidence using explicit, replicable methods in a way that minimizes the risk of biased selection of studies. ICER documents its decision to conduct a full systematic review or use existing systematic reviews in the research protocol.

When ICER conducts a full systematic review, established best methods of systematic literature reviews are followed in order to foster transparency and facilitate reproduction of results.[3,4] Reviews are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[2] The completed checklist is provided in the appendix of all reports.

Literature Search Methods

ICER develops individual search strategies to systematically search electronic databases such as MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for studies relevant to the

appraisal. When appropriate, ICER also searches discipline-specific databases, such as PsycINFO for behavioral interventions, CINAHL for nursing-relevant studies, and others. The search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms. Searches are generally limited to English-language studies of human subjects and exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. ICER provides the search strategy in the published protocols and in the appendix of all reports.

To supplement the database searches, investigators perform a manual check of the bibliographies of recent systematic reviews and invite key stakeholders to share references germane to the scope of an appraisal. Investigators also search for data contained in grey literature sources, such as regulatory documents, conference proceedings, data shared by life science companies, and open-input submissions from stakeholders that may be relevant to the topic. ICER's website contains more information on ICER's policies for inclusion of grey literature and data in confidence.

Eligibility Criteria

Study inclusion and exclusion criteria are developed based on the PICOTS framework (described in Section 6).[7] Specific eligibility criteria pertinent to the topic area are listed (e.g., disease- or intervention-specific characteristics) as well as the types of studies (e.g., randomized trials or observational studies, criteria related to sample size or study duration).

Study Selection

Study selection occurs through two levels of screening: at the title/abstract and full-text levels. Initially, each title and abstract identified through electronic searches is independently screened by two investigators. A third reviewer works with the initial two reviewers to resolve any issues of disagreement through consensus. Reasons for exclusion are categorized according to the PICOTS elements during both title/abstract and full-text review. A flow diagram illustrating the selection of studies is presented in the appendix of each report.

Data Extraction

Data extraction is performed by investigators on the evidence review team. Data related to study design, sample size, intervention (e.g., dosage, frequency, mode of administration), study inclusion criteria, population characteristics at baseline, and outcomes are extracted into standardized forms. When more than three studies are included in a review, the extraction forms are developed *a priori* and pilot tested on a small subsample of studies. The revised, finalized form is then used for all included studies.

Extracted data are peer-reviewed by the evidence review team for logic and accuracy; a random proportion of data may be validated by a third investigator for additional quality assurance. All

(non-confidential) data are presented in the report or otherwise made publicly available (e.g., through a publicly available data repository website).

Assessment of Publication Bias

ICER also evaluates the evidence base for the presence of potential publication bias by searching the clinicaltrials.gov database of trials. The site is scanned to identify studies completed more than two years ago that would have met an appraisal's inclusion criteria and for which no findings have been published. Any such studies may provide qualitative evidence for use in ascertaining whether there was a biased representation of study results in the published literature.

Assessment of Bias and Study Quality

The methodological quality of included studies is evaluated using appropriate tools for the evidence base under review. Many tools exist, including some design-specific tools as well as others that can be used broadly. Examples of tools include those employed by the US Preventive Services Task Force (USPSTF),[9] Cochrane Collaboration,[10] and others. Nevertheless, no single tool exists that can evaluate all possible studies included across all reviews.

For each review, ICER will select or adapt a quality rating tool that is relevant to the topic and document the choice in the protocol. For example, some rating schemes are disease-specific (e.g., Cochrane Back & Neck for low back and neck pain interventions). Regardless of the tool used, the general principles of assessing the methodological quality stipulate that the risk of biased results in a study will be the focus, not the quality of reporting or other aspects pertaining to study development. Furthermore, some aspects of study conduct (e.g., obtaining ethical approval or calculating sample size) have no bearing on the risk of bias, whereas some "best possible" methods may yield biased estimates. For example, blinding may not always be feasible or ethical, but if an outcome is influenced by knowledge of treatment assignment, the results may still be considered at high risk of bias.

Of note, the risk of bias assessment focuses on the internal validity of the study, i.e., how well the study is able to estimate what it set out to do. Aspects of generalizability or precision are not incorporated. Generalizability deals with the applicability of results beyond the given study, and it is not a relevant consideration if conditions for internal validity are not met. Precision is related to sample size and variance. For example, a small study may have imprecise results (i.e., wide confidence intervals) and be at low risk of bias, whereas a large study may have precise results (i.e., narrow confidence intervals) and still be at high risk of bias.

The assessment of risk of bias requires judgment about how particular aspects of a study may lead to biased results. The rationale for the assessments is explicitly determined *a priori* in the protocol for the evidence review, and the judgment itself is provided in the appendix of each report.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the comparative effectiveness of the interventions of interest. The analysis is based on data from all relevant studies identified from the systematic review and contains two components: 1) a summary of the evidence base; and 2) a synthesis of key outcomes.

Summary of the Evidence Base

For all HTAs, the identified studies are summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the existing evidence base pertaining to the HTA topic. Relevant data include those specified in the data extraction section. Any key differences between the studies in terms of study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), patient subgroups, and study quality are described.

Synthesis of Results

For each outcome, all studies reporting results are assessed for similarity in terms of the specified key characteristics from the protocol. The reported results from the studies that are sufficiently similar are then checked to determine if the data are appropriate for analysis (e.g., sample sizes, number of patients experiencing the outcome, and point estimates with uncertainty estimates, are reported as appropriate). When there are no sufficiently-similar studies or inadequate data, analyses in the Evidence Report are descriptive only. Key considerations for interpreting the results within the context of the evidence base are specified in the Evidence Report.

A quantitative synthesis of the outcome results is conducted when studies are sufficiently similar and reported data are appropriate for analysis. The quantitative synthesis may be a pairwise meta-analysis or a network meta-analysis. Each of these analyses are described briefly below.

A pairwise meta-analysis may be conducted to quantitatively synthesize results from multiple studies assessing the same intervention and comparator.[11] Details regarding the specific methods, including the chosen metric for analysis (e.g., mean difference, odds ratio, rate ratio), are proposed in the research protocol and detailed in the reports. All data used in the analyses are also provided in each report.

A network meta-analysis (NMA) extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]).[12,13] NMAs confer many advantages over pairwise meta-analyses when multiple treatment options are being considered. For example, the results from an NMA provide estimates for all treatment comparisons, including those that have not been directly evaluated in head-to-head studies.

For any network where there are "loops" in evidence, the direct and indirect estimates are empirically compared, for example using a node-splitting approach, to assess inconsistency.[14] If there is evidence of inconsistency, the evidence review team attempts to explain and resolve the inconsistencies through further examination of the studies and characteristics. Analysis results are presented for the direct and indirect evidence separately. If there is no evidence of inconsistency, the pooled results are also presented. The specific approaches for analysis, including inconsistency models and assessments, are proposed in the research protocol.

Heterogeneity Assessment

Prior to conducting any NMA, the evidence review team examines the distribution of study and patient characteristics within each pairwise comparison to assess heterogeneity and across comparisons to assess transitivity. The evidence review team explores the reasons for study differences (e.g., patient characteristics, treatment setting) and conducts subgroup or meta-regression analyses (i.e., controlling for key study/patient characteristics) where feasible.

When a pairwise meta-analysis or NMA is feasible, the analysis models include random effects on the treatment parameters. Random effects allow each study's treatment effect to be different but related. The amount of between-study variance is called statistical heterogeneity. Scenario analyses pertaining to the heterogeneity parameter are described and justified (e.g., using informative prior distributions).

Presentation of Quantitative Results

The results from all analyses are presented tabularly in terms of point estimates and 95% confidence intervals (or 95% credible intervals when using a Bayesian approach). Forest plots, which include the data from each individual study as well as a pooled effect estimate, are also presented in the Evidence Report. In addition, for all NMAs, diagrams illustrating the network of evidence, league tables providing all pairwise estimates, or any additional output (e.g., rankograms or surface under the cumulative ranking curve) are provided in the Appendix of each report.

ICER Evidence Rating

Following synthesis of the evidence, ICER assigns an evidence rating to each of the interventions evaluated in its appraisal. These ratings reflect a judgment made at a moment in time and may be updated as new or additional evidence becomes available.
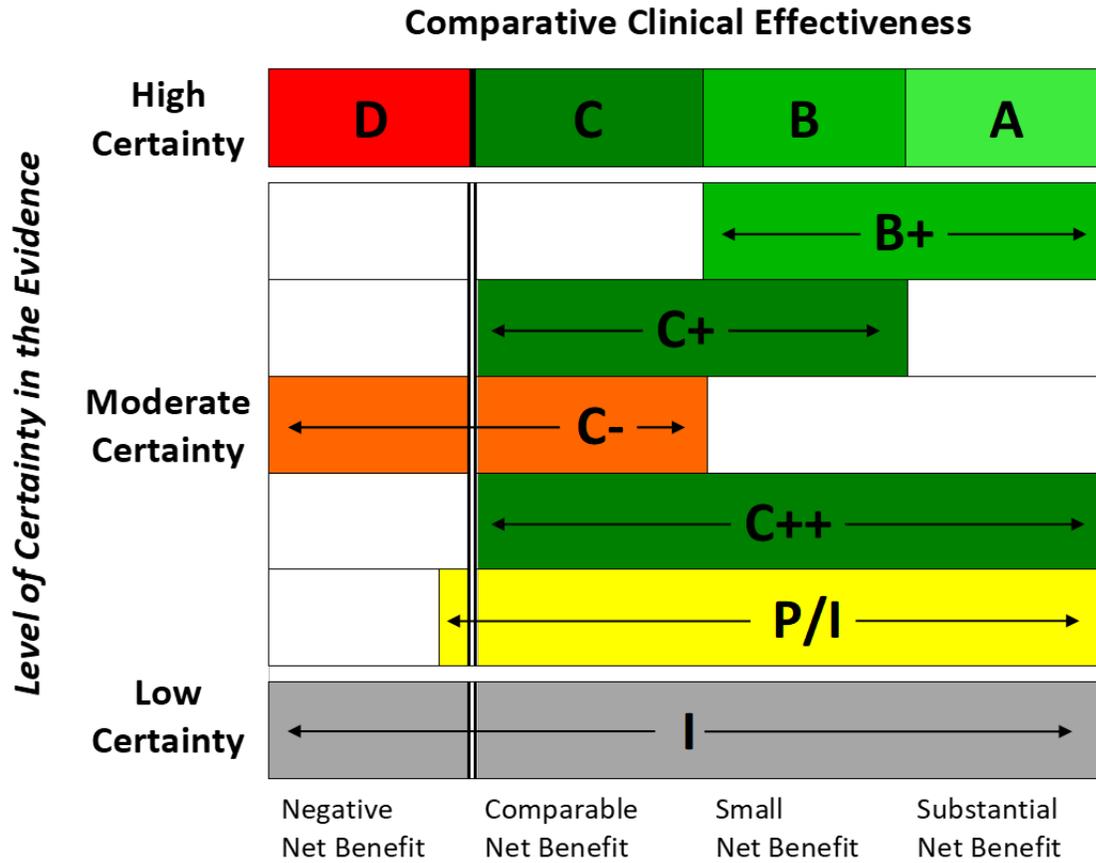
ICER developed the ICER Evidence Rating Matrix (see Figure 4) to evaluate evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

   a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between benefits and risks and/or adverse effects AND

b) The level of **certainty** in the best point estimate of net health benefit.[15]

The design of ICER'S Evidence Rating Matrix was informed by the approaches developed by the United States Preventive Services Task Force (USPSTF); the international Grading of Recommendations Assessment, Development and Evaluation (GRADE) group;[16] and the Effective Healthcare Program of the Agency for Healthcare Research and Quality (AHRQ).[15] While each organization has developed unique criteria to rate the strength of evidence, each approach evaluates the entire body of evidence along a series of domains. The most important domains common to the four approaches include risk of bias, generalizability to "real-world" populations, consistency of findings across studies, directness (i.e., how closely the evidence measures the populations, interventions, and outcomes of interest), and precision.

Figure 4. ICER Evidence Rating Matrix

Comparative Clinical Effectiveness

Level of Certainty in the Evidence

High Certainty	**D**	**C**	**B**	**A**

B+ →

C+ →

C- →

Moderate Certainty

C++ →

P/I →

Low Certainty · **I** →

Negative Net Benefit	Comparable Net Benefit	Small Net Benefit	Substantial Net Benefit

Comparative Net Health Benefit

A = *"Superior"* - *High certainty of a substantial (moderate-large) net health benefit*
B = *"Incremental"* - *High certainty of a small net health benefit*
C = *"Comparable"*- *High certainty of a comparable net health benefit*
D= *"Negative"*- *High certainty of an inferior net health benefit*
B+= *"Incremental or Better"* – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = *"Comparable or Incremental"* - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = *"Comparable or Inferior"* – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = *"Comparable or Better"* - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = *"Promising but Inconclusive"* - *Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = *"Insufficient"* – *Any situation in which the level of certainty in the evidence is low*

Stakeholder Involvement

ICER solicits stakeholder input during various timepoints of the evidence assessment. When quantitative synthesis of the evidence (via pairwise or network meta-analysis) is feasible, a subset of key stakeholders may be invited to attend a presentation of model structure, assumptions, and Inputs and submit feedback. Similarly, prior to the publication of ICER's Draft Evidence Report, experts specializing in the topic area of focus, economic evaluation, or the patient experience are invited to independently review the draft document for accuracy.

Following expert review, the Draft Evidence Report is posted to ICER's website for a period of 20 business days, during which any member of the public may submit comments on the report (details on how to submit public comment are described here). ICER reviews all feedback received through public comment and incorporates required revisions into an updated Evidence Report. Both the revised Evidence Report and a document detailing ICER's response to public comments are published before the public meeting. In addition, stakeholders may deliver oral comment at the public meeting for consideration by the voting panel.

8. Economic Modeling

Overview

Economic modeling provides a formal framework for contextualizing the available evidence. For example, an economic model may extrapolate clinical trial data to assess the potential clinical and economic effects over the longer term. In order for the model to be a useful component in the evidence appraisal, the model should be detailed enough to capture the key features of the decision problem. The required level of detail typically adds complexity to models, which may present challenges for understanding the model or interpreting its results. ICER's commitment to open and transparent engagement with all stakeholders extends to the development and modification of economic models found here. To fulfill this commitment and explain the model approach in detail, ICER develops a model analysis plan following the publication of a final scoping document. The model analysis plan outlines the methods the economic modeling team intends to employ, including information on the model structure and processes, all major inputs and sources of data, and key assumptions. In addition, the plan specifies whether the model is an adaptation of an existing model (with references as appropriate) or is being newly developed for this HTA. As with the research protocol, the model analysis plan is published on the Open Science Framework.

Following discussions with stakeholders, review of additional data sources, and other activities, the model analysis plan may be updated. The final version of the model used in conducting analyses is described in detail in the Evidence Report to allow an experienced researcher to be able to replicate the economic model and analyses. In addition, ICER shares a limited-release of economic model files and code to stakeholders willing to agree to confidentiality and privacy restrictions. This policy allows participating stakeholders to include detailed critique of the model in public comments submitted on the Draft Evidence Report.

When developing an economic model, ICER aims to follow an established "reference case." The reference case is the framework of methods that ICER and its modeling collaborators follow when conducting the base-case cost-effectiveness analysis; this framework generally follows the Second Panel on Cost-Effectiveness in Health and Medicine's recommendations for the health care perspective reference case,[5] and is also generally consistent with published guidance from international HTA organizations. Following the reference case enables consistency in analytical approaches, but reasons may exist for deviating from the reference case to reflect particular circumstances. If reasons exist for not fully applying the reference case methods, they are clearly specified and justified. Any modifications to the model or analyses are explicitly detailed in the model analysis plan and Evidence Report.

A summary of the main components of any economic model and analysis is provided below.

Elements of an Economic Model

Decision Problem

The decision problem (i.e., the specific question to be addressed from the analysis) is specified in terms of the overall objective, the interventions of interest and their key comparators, the relevant population groups and subgroups being considered, and the outcomes. Any differences in the population, intervention, or outcomes from the aims and structure of the clinical evidence review are documented with justifications. The analytic perspective (typically health care system) and time horizon (typically lifetime) used in primary analyses are also specified.

Model Structure

The type of model is described, including a textual and/or graphic depiction of the model structure, process, and outputs. The links between each intervention and its short-term effects, long-term effects, and final outcomes are described, including the health states and sequence of possible transitions between them. Typical choices for model structure include decision trees, Markov cohort, or microsimulation models. Key assumptions regarding the model structure are articulated with their corresponding rationale. The economic modeling team identifies the software used to create the model and run analyses, which may include statistical programming software (e.g., R), decision analysis software (e.g., TreeAge), or Microsoft Excel.

Model Parameters and Data Sources

Model parameters include those pertaining to intervention effectiveness, transition rates between health states, measurement and valuation of health states, resource use, and costs. All model parameters are described, including risk equations as appropriate.

Data informing all model parameters are provided in tables or text. ICER aims to use data from published or publicly available sources, including peer-reviewed journals, supplementary appendices, briefing documents used by regulatory authorities, and conference proceedings. In addition, because life science companies may have relevant information that is currently held in confidence, ICER has structured a process to accept and use such data. Results from the evidence review, including the results from any meta-analysis, are used to inform input parameters when possible. Data informing the cost input parameters are inflated to the current year as needed (e.g., 2019 US dollars). Discount rates for costs and outcomes (typically 3% per year) are specified.

Deficiencies in the evidence base are common for any HTA and often present challenges with informing some parameters in the economic model. For example, some data may only be available from a setting outside the US or from a population that differs from the one being considered. Furthermore, although the time horizon of the economic analysis is typically lifetime, clinical effectiveness data come from clinical trials which are often of a shorter duration. Therefore, the

economic modeling team explicitly describes the limitations of the evidence and any assumptions used for extrapolation. Data limitations are explored through discussion of uncertainty and sensitivity and scenario analyses (see Economic Model Analyses and Results).

Summary Measures

Health effects are expressed in terms of total and incremental quality-adjusted life-years (QALYs), equal value life years gained (evLYG), life-years, and a specific outcome achieved (e.g., treatment response, event avoided). Costs are reported in terms of total and incremental costs. Health benefits and costs are summarized as an incremental cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per outcome achieved.

Validation and Calibration

All models are validated prior to conducting analyses. Validation entails assessing whether a model has been implemented correctly (internal validation) and if its assumptions and results are in line with the current evidence and expectations ("face validity", external validation). All models are internally validated by an independent modeler. The specific approach to internally validate the model during development is detailed in the model analysis plan and follows ICER's validation checklist (publication forthcoming). After the presentation of model structure, assumptions, and inputs, key stakeholders also provide feedback on the model assumptions, parameters, structure, and overall face validity. In addition, we review and compare published models that included the same interventions or comparators of interest, were developed in the last 10 years, and were similar to our model from a setting and population perspective.

Calibration entails assessing if the model inputs and outputs are consistent with known scenarios. Any calibration procedures used during model development are proposed in the model analysis plan, including the calibration target (and source), the goodness-of-fit metric, and criteria for judging fit. Results from the calibration procedure are presented in the Evidence Report.

# Economic Model Analyses and Results

Base-Case Analysis

The base-case analysis represents the primary modeling approach employed, using the input parameter values specified in the Model Inputs and Data section of the Evidence Report. Results are reported in terms of discounted and undiscounted total health benefits and costs for each intervention. The results for the incremental health benefits (e.g., life-years and QALYs), costs, and cost per health benefit are presented for each intervention versus its relevant comparator(s).

Sensitivity and Uncertainty Analyses

The economic modeling team also conducts one-way sensitivity analyses and presents the results in "tornado diagrams" that display the findings across a feasible range for each input parameter estimate (See Figure 5). A table contains the distributional assumptions about the input parameters varied. Expected values of costs and outcomes for each intervention are also estimated through "probabilistic sensitivity analysis", which captures some of the uncertainty in the input parameter estimates. This type of analysis takes repeated samples, typically 1,000 or more, from the (joint) distribution of all key model input parameters simultaneously; results are presented tabularly in terms of the percentage of simulations that achieve $50,000, $100,000, $150,000, and $200,000 per QALY thresholds, and graphically using scatter plots and cost-effectiveness acceptability curves (CEAC), which reflect the percentage of simulations that result in incremental cost-effectiveness ratios that fall at or under different cost-effectiveness thresholds.

Figure 5. Example of Tornado Diagram for One-Way Sensitivity Analyses (Niraparib versus Placebo in Maintenance Therapy for Platinum-Sensitive Ovarian Cancer)[17]
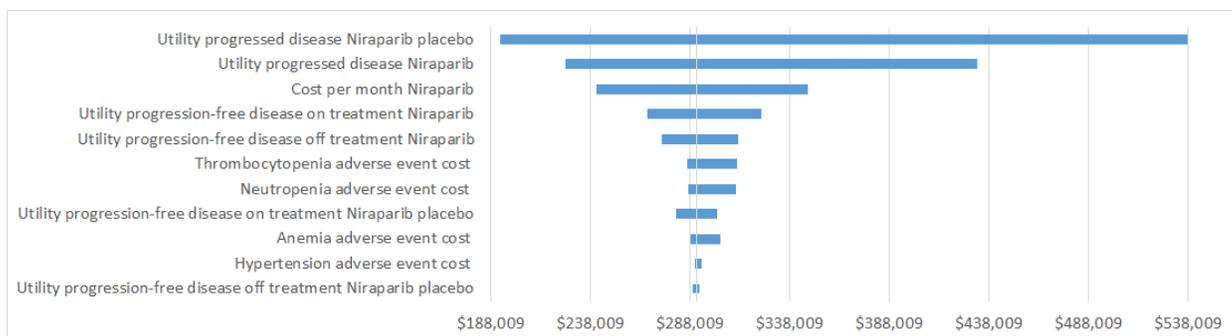
Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Utility Progressed Disease Niraparib Placebo	$193,009	$538,196	0.55	0.80
Utility Progressed Disease Niraparib	$225,429	$432,333	0.55	0.80
Cost per Month Niraparib	$240,956	$347,083	$10,958	$16,232
Utility Progression-Free Disease on Treatment Niraparib	$266,565	$323,928	0.72	0.82
Utility Progression-Free Disease off Treatment Niraparib	$274,188	$312,063	0.66	0.76
Thrombocytopenia Adverse Event Cost	$286,786	$311,963	$3.39	$57,182
Neutropenia Adverse Event Cost	$287,316	$310,968	$1.48	$77,892
Utility Progression-Free Disease on Treatment Niraparib Placebo	$281,412	$301,723	0.66	0.76
Anemia Adverse Event Cost	$288,597	$303,335	$5.02	$38,830
Hypertension Adverse Event Cost	$290,529	$294,145	$125	$26,587
Utility Progression-Free Disease off Treatment Niraparib Placebo	$289,755	$293,095	0.66	0.76

Other Analyses

Specific scenario analyses (e.g., using a modified societal perspective that incorporates estimates such as productivity losses, caregiver burden, and other indirect costs) and subgroup analyses are conducted when appropriate.

In addition, the economic modeling team reports results from long-term cost-effectiveness threshold analyses, which estimate the intervention costs or prices that correspond to commonly-cited thresholds extending from $50,000 per QALY and evLYG to $200,000 per QALY and evLYG.

Potential Budget Impact Analysis

The potential short-term monetary impacts of a new intervention are understood through ICER's potential budget impact analysis. Potential budget impact is defined as the total cost of using each new therapy in place of the relevant existing therapies for the treated population, calculated as the difference in health care costs (including drug and non-drug costs) minus any offsets from averted health care events or other aspects of treatment (e.g., reduced infusion duration or frequency). The potential health system budgetary impact of the intervention is explored over a five-year time horizon. With a five-year timeframe, some of the potential cost-offsets provided by new interventions are captured.

ICER's potential budget impact analyses depend on assumptions related to price.[6] Prices modeled in the potential budget impact analysis will typically include: wholesale acquisition cost (WAC), estimated net price from various sources, and prices to achieve cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained. As part of the analysis for new drugs, ICER presents information on a national level that allows stakeholders to know, at multiple given price points, the percentage of candidate patients who could be treated each year without exceeding a calculated budget impact threshold. This threshold is based on an underlying assumption that increases in health care costs should not significantly outpace growth in the overall US economy.[6]

Within the potential budget impact analysis section of each final report, ICER will include an "affordability and access alert" if discussion among stakeholders at the public meeting suggests that utilization driven by clinical need at estimated net pricing would exceed the budget impact threshold without active intervention by insurers and others to manage access to the treatment. The affordability and access alert signals that the additional health care costs with a new intervention may be difficult for the health care system to absorb over the short term. In this situation, other needed services may be displaced or health care insurance costs may rapidly rise, which would threaten sustainable access to high-value care for all patients.

Health Benefit Price Benchmarks

Finally, a "health benefit price benchmark" is developed for the new intervention, which reflects prices aligned with long-term cost-effectiveness thresholds ranging from $100,000 to $150,000 per QALY gained and from $100,000 to $150,000 per evLYG. The prices represent discounts or price premiums from wholesale costs that would be required to reach these cost-effectiveness thresholds.

Stakeholder Involvement

As noted in Section 7, ICER solicits stakeholder input during various timepoints of the evidence assessment. ICER engages key stakeholders in the development of its model analysis plan and data inputs. Prior to the publication of the Draft Evidence Report, ICER may invite a subset of stakeholders to attend a presentation of model structure, assumptions, and inputs from the economic model and submit feedback. Similarly, experts specializing in economic evaluation, the topic area of focus, and/or the patient experience may be invited to independently review the Draft Evidence Report for accuracy.

Following expert review, the Draft Evidence Report is posted to ICER's website for a period of 20 business days, when any member of the public may submit comments on the report (details on how to submit public comment can be found here). ICER reviews all feedback received through public comment and incorporates required revisions into an updated Evidence Report that is published along with a response to comments prior to the public meeting.

9. Public Meeting, Dissemination, and Implementation of HTA Findings

ICER's Core Programs

Findings from ICER's HTAs are presented at a public meeting of one of its three core public programs: the New England Comparative Effectiveness Public Advisory Council (New England CEPAC), the Midwest CEPAC, and the California Technology Assessment Forum (CTAF). Each public program is composed of two groups: an advisory board and a voting panel. The Advisory Board includes representatives from regional provider groups, patient and consumer advocacy organizations, and public and private insurers who provide guidance to ICER on topic selection and aid in the dissemination and implementation of HTA findings. The voting panels, in contrast, are composed solely of practicing clinicians, researchers, medical ethicists, and experts in patient advocacy and engagement; payer representatives occasionally serve on the panels as well, but only in an ex officio (i.e., non-voting) capacity. Panel members are recruited as individuals, not as representatives of their organization, specialty society, or other interest, and are subject to strict conflict of interest requirements. Members of the voting panel are selected for their expertise in the critical evaluation of medical and economic evidence.

Public Meeting

Approximately two weeks prior to each meeting, ICER publicly releases a revised Evidence Report that reflects changes made in response to public comment and distributes it to the relevant voting panel. This version of the report includes background and contextual information regarding the disease and its treatment, as well as the results of the comparative effectiveness, cost-effectiveness, and potential budget impact analyses. The voting panel also reviews public comments received on the Draft Evidence Report as well as ICER's response to those comments. These documents inform the deliberation, vote, and policy discussions that take place during the public meeting.

Each meeting follows an agenda similar to the one listed in Table 1, and can broadly be divided into three portions: the presentation and deliberation on the evidence (items 1-3), the panel vote (item 4), and a discussion of policy considerations (items 5-7).

Table 1. Example Public Meeting Agenda

Agenda Item	Primary Participants
1. Presentation of the Evidence and Economic Modeling, Q&A/Discussion	ICER staff and consultants, voting panel, patient and clinician members of the policy roundtable, life science companies (as needed), patient advocacy organizations (dependent on topic)
2. Public Comments and Discussion with Life Science Companies	Life science companies
3. Public Comments and Discussion with Patients, Clinicians, and Public	Patients, Clinicians, Payers, Researchers, and other interested individuals
4. Voting on comparative effectiveness and value questions; additional discussion	Moderator; voting panel; clinical, patient, and subject-matter experts from the policy roundtable; life science companies (as needed)
5. Policy roundtable discussion	Moderator, voting panel, policy roundtable
6. Reflections from voting panel	Moderator, voting panel
7. Summary and closing remarks	Moderator

During the evidence presentation, ICER staff and consultants present the evidence contained in the report to the voting panel. Each public meeting also includes time for life science companies and other stakeholders to deliver three- to five-minute oral remarks before the vote occurs, and time is set aside for follow-up discussion with the voting panel. ICER recruits topic experts (i.e., patients and clinicians) to provide input to the voting panel throughout the meeting when questions arise.

Following the evidence presentation, the voting panel considers a series of questions that are framed to determine 1) whether there is adequate evidence to demonstrate that an intervention provides a greater net health benefit than its comparator, and 2) whether the long-term value for money of a treatment versus its comparator is low, intermediate, or high. In addition, the panel may vote on whether an intervention offers specific benefits and/or disadvantages that have not been captured in the evidence (e.g., reduction in impact on caregivers or family, better adherence) and deliberate on which contextual considerations (e.g., the severity of the condition) are important in assessing an intervention's long-term value for money. Report authors, clinical experts, and patients are available to serve as a resource for the voting panel during this portion of the meeting.

After the voting has concluded, a policy roundtable convenes for a moderated discussion on how to move the evidence into practice and policy. Roundtable participants represent a range of perspectives, including patients, payers, providers, and life science companies. Frequent topics of discussion include the development of evidence-based insurance coverage and reimbursement policies, a research agenda to address inadequacies in the evidence base, and how to educate patients and clinicians about the appropriate use of an intervention, among others. These discussions, as well as the vote tallies, are summarized and published in the Final Evidence Report, which is typically released approximately two weeks after each meeting.

Dissemination and Implementation of HTA Findings

Following the public meeting, ICER's Final Evidence Report remains in the public domain. Stakeholders may use the report findings and recommendations from policy roundtable discussions in several ways, which include the following:

- To facilitate evidence-based practice.
- To help patients and clinicians have informed discussions about care and support shared decision making.
- To assist life science companies in developing value-based prices at the launch of a new product.
- To guide pricing and contracting negotiations between payers and life science companies.
- To assist payers in making formulary decisions and developing evidence-based coverage criteria.
- To identify existing gaps in the literature and prioritize the most pressing research needs.
- To inform federal and state policy solutions aimed at improving access and affordability within the healthcare system.

10. Glossary

Adverse event – A harmful, unintended occurrence during or after the administration of a health technology, which may or may not be caused by the use of that technology.

Analytic framework – A graphical representation of the key assumptions the systematic review seeks to evaluate in order to determine the net health benefit of the intervention(s) under appraisal. The framework diagrams linkages between an intervention and its possible benefits and harms in a given population.

Base-case analysis – the analysis using the initial set of assumptions and input parameter values.

Budget impact – an estimate of the projected cumulative resource expenditure for a particular intervention in a specific population over a period of time.

Cost-Effectiveness Acceptability Curve – A graph that plots the percentage of simulations that result in ICERs that fall at or under different cost-effectiveness thresholds.

CEPAC – Comparative Effectiveness Public Advisory Council; ICER convenes public meetings of two regionally-focused CEPACs based in New England and the Midwest to review objective evidence reports and develop recommendations for how stakeholders can apply evidence to improve the quality and value of health care. The mission, processes, and role of the CEPAC programs are the same as that of CTAF, despite a different naming convention.

Clinical effectiveness – The degree of health benefit produced by an intervention.

Comparator – an alternative health technology against which an intervention is evaluated.

Cost-effectiveness analysis – a type of economic evaluation in which an outcome is measured in incremental costs per incremental health unit, such as life years gained or clinical event avoided.

Cost-effectiveness threshold – the maximum amount of money a decision-maker could pay to ensure that the health benefits gained by patients using new treatments are not outweighed by health losses due to long-term cost pressures.

CTAF – California Technology Assessment Forum; CTAF represents one of ICER's core programs that convene three times a year to review objective evidence reports and develop recommendations for how stakeholders can apply evidence to improve the quality and value of health care. The mission, processes, and role of CTAF are the same as the CEPAC programs, despite different naming conventions.

Direct comparison – An evaluation of two interventions that have been assessed head-to-head.

Dominance – In cost-effectiveness analysis, when one intervention is more effective and less costly than its comparator, the comparator is considered to be 'dominated.'

evLYG analysis – An analysis that accounts for improvements in patients' quality of life while counting any gains in length of life equally regardless of quality of life. For all additional years of life gained, this analysis awards the quality of life of the general population, irrespective of the health state patients are in during these additional years of life gained.

Forest plot – A graphical depiction of the results of a meta-analysis, which includes the data from each individual study as well as a pooled effect estimate.

Health benefit price benchmarks – The estimated prices that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY or evLYG.

Health technology assessment (HTA) – The systematic evaluation of evidence related to any healthcare intervention that can be used to improve health and prevent and treat disease; HTAs inform policy- and decision-making surrounding the use of such interventions.

Inconsistency – Disagreement between direct and indirect evidence.

Incremental cost-effectiveness ratio (ICER) – The ratio of the difference in costs between two possible interventions, divided by the differences in their effectiveness.

Indirect comparison – An evaluation of two interventions via one or more common comparators.

Meta-analysis – A type of statistical analysis that combines data from multiple studies assessing the same two interventions and generates a pooled, summary estimate of the relative effect of one treatment versus a comparator.

Net health benefit – the balance between benefits and risks and/or adverse effects.

Network meta-analysis – An extension of pairwise meta-analyses to include many interventions and generate a series of pooled, summary estimates of the relative effect of each treatment versus each comparator.

Observational study – a non-experimental study in which investigators draw inferences about what is observed without trying to influence the outcome of the study; types of observational studies include cohort, cross-sectional, case-control and ecological studies.

One-way sensitivity analysis – a method of analysis in which the value of one model input parameter is varied at a time to assess the effect of the parameter on results.

Opportunity cost – the value of something that must be foregone in order to acquire something else.

Parameter – a characteristic that influences the output of a model.

PICOTS – Population, intervention, comparator, outcomes, timing, and setting; ICER uses these items as a framework for defining the scope of its appraisals.

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA is a set of criteria that guide the conduct and reporting and systematic reviews and meta-analyses.

Probabilistic sensitivity analysis – a method of analysis used to account for parameter uncertainty in which values for input parameters are sampled based on pre-specified probability distributions.

Quality-adjusted life-year (QALY) – A measure of health benefit that accounts for changes in both quantity (e.g., mortality) and quality of life.

Randomized controlled trial – a type of study design in which participants are allocated at random into intervention and control groups.

Reference case – the framework of methods that ICER follows when conducting the base-case cost-effectiveness analysis.

Scenario analysis – A type of analysis that estimates results using alternative model assumptions.

Sensitivity analysis – a method of analysis in which model inputs are varied in order to determine how such changes affect the results.

Statistical heterogeneity – variation in the magnitude or direction of results between studies.

Subpopulation – A subset of a larger population.

Systematic review – a literature review that identifies and summarizes the results of all empirical studies meeting pre-defined eligibility criteria.

Threshold analysis – a type of sensitivity analysis in which the values of model input parameters are varied in order to determine the value that produces a specific result (e.g., a given cost-effectiveness value.

Time horizon – the period of time over which outcomes are evaluated.

Tornado diagram – a graphical depiction of the results of one-way sensitivity analyses in which the analyses with the greatest impact on model results are displayed with the largest bars and are stacked at the top of the chart.

Transitivity assumption – A key property in a network meta-analysis that preserves the ranking order relations of interventions with respect to a given outcome.

Utility – a measure of preference for a health outcome.

Validity – the assessment of whether a model has been implemented correctly (internal validity) and if its assumptions and results are in line with the current evidence and expectations (face validity).

Value assessment framework – a decision support tool intended to guide stakeholders in making decisions that will promote sustainable access to high-value care for all patients.

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