INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

ICER's Reference Case for Economic Evaluations: Principles and Rationale

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Overview

To encourage consistency in analytic approaches when modelling, ICER has defined a "reference case" specifying the approach that ICER and its collaborators follow for cost-effectiveness analyses. The reference case is defined by the components, methods, and reporting elements to be used in a cost-effectiveness analysis. ICER's reference case generally aligns with the Second Panel on Cost-Effectiveness in Health and Medicine's recommendations for a health care perspective reference case. Note that following the reference case does not preclude additional analyses being conducted, and reasons may exist for deviating from the reference case to reflect particular circumstances. In these cases, any deviations from the reference case will be clearly specified and justified in the model analysis plan and Evidence Report. A summary of ICER's reference case is provided in Table 1, with additional details below.

Table 1. Reference Case Principles

Element	Specific Details
Decision Problem	
Objectives	• State the goals of the analysis, specific to the topic area
Target Population	• Describe the population(s) and setting(s) in which the interventions are to be used o Point out any discrepancy between the indicated population and modeled populations and discuss relevance of model results to indicated population. • To the extent possible, conduct subgroup analyses for patient groups that are of clinical or economic interest o Specify and define any subpopulation(s) (e.g., defined by demographic or disease characteristics) o Discuss population heterogeneity and subgroups, and likely implications for cost-effectiveness
Intervention	• Clearly describe the health care intervention(s) being evaluated, including components, dose, duration, etc., as appropriate
Comparators	• Compare to available and feasible relevant alternative treatments, including specific active comparators, "usual care" (i.e., the treatments currently generally used), or a "do-nothing" option, as appropriate

Perspective	• Health care sector perspective (default)
	• Societal perspective as scenario analysis
	  o Estimate net productivity impacts
	  o Include all relevant societal impacts to the extent possible
	• Present health system payer perspective in tandem with modified societal perspective as "co-base case" when:
	  o Impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial, and
	  o These costs are large in relation to health care costs
	  o Examples include when incremental cost-effectiveness ratio changes by greater than 20% or by greater than $200,000 per QALY, and/or when result crosses thresholds of $100,000-$150,000 per QALY.
	• Use Second Panel's impact inventory (see Appendix A) to document specific health care and societal impacts included, including whether patient out-of-pocket costs are captured

Time Horizon	• Lifetime (default) • If shorter, should be long enough to capture all relevant differences in future costs and outcomes associated with treatments being compared, and rationale for shorter duration (e.g., assessment of treatment for acute condition with no long-term sequelae) should be stated
Outcomes	• Costs (undiscounted and discounted) • Life-years (undiscounted and discounted) • Quality-adjusted life years (QALYs, undiscounted and discounted) • Equal value life-years gained (evLYG, undiscounted and discounted) • Other natural outcomes (e.g., hospitalizations avoided), when feasible • Cost per QALY • Cost per evLYG, if mortality effects • Cost per life year, if mortality effects • Cost per consequence (e.g., cost per hospitalization avoided), when appropriate and feasible
Model Structure	

Type of Model	• Describe the model type (e.g., decision tree, state transition, microsimulation, dynamic transition, dynamic simulation)
	• Specify the following:
	  o How events over time are handled (e.g., health states that include event history or number of years in a state, as appropriate)
	  o Unit of analysis (e.g., individual, cohort, population)
	  o Whether and how individuals can interact with others in the model
	• State if the model is an existing model or if it was developed *de novo*

Intervention Effects	• Identify all downstream effects of the intervention(s) as they relate to health, resource use, and other economic impacts (healthcare sector and societal)
	  o Effects of interventions include those that are intended and unintended, both positive (e.g., health improvement) and negative (e.g., serious adverse events)
	• List all effects of interventions in the Impact Inventory
	  o Specify the effects of the interventions included in each of the analytic perspectives
	  o Justify the rationale for not including any intervention effect in the analysis, if applicable

Event Pathways	• Define the pathway of events that stem from how the use of the intervention(s) or comparator(s) relates to each effect included in the analysis o Events and health states should capture elements of the disease process, not utilization alone • Include conceptual schematic of model
Software	• State the software (including version number) used to develop the model
Model Parameters and Data Inputs	

Quantifying Effects of Interventions	• For each effect captured in the model, state the method for identifying the treatment effect estimates
	  o Systematic literature reviews with meta-analyses should be conducted or referenced (e.g., from the Clinical Review section of the Evidence Report)
	  o When infeasible or impractical to a conduct systematic review, justify data sources used
	• State and justify assumptions regarding long-term impacts beyond available data, including durability of effect and survival analytic techniques
	  o For high-impact SSTs, use cure proportion modeling whenever relevant, but also provide survival analysis based on other modeling approaches when feasible.
	• State and justify any corrections for biases or adjustments for transferability in the estimates used in the model

Measurement and Valuation of Health	• Health preferences should reflect those of the general US population (preferably); provide rationale if patients with the condition, individuals at heightened disease risk, or a different population is used. • Describe health preferences source/measurement (usually from an indirect method of measurement based on a generic classification system, e.g., EQ-5D-5L), including population, and the methods for seeking and evaluating these inputs, including comprehensive literature review

	○ Generic preference-based measure is recommended; no specific generic, preference-based measure is required, but EQ-5D is preferred if available ○ Use disease-specific preference-based data if generic measures considered non-responsive for relevant health states, or if appropriate generic preference-based data are not available • When there are challenges translating outcome measures used in clinical trials and available patient-reported data into QALYs, conduct a search for "mapping" studies that allow translation of surrogate outcomes into quality of life measures ○ Discuss validity of mapping studies and translation into QALYs, as well as rationale for choosing • If using URD framework, acknowledge and highlight additional uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures
Resource Use and Costs	• Include all relevant resources and costs based on the health system payer perspective ○ Include costs paid by third-party payers ○ Note if costs paid out of pocket by patients are included (or cannot be determined as excluded) ○ Identify any excluded costs, and rationale • Describe source of resource utilization and cost data, and the methods for how we seek and evaluate those inputs, including comprehensive literature review ○ For drugs with generic versions available, use the average WAC across the generic versions (unless analyzing a specific branded or generic formulation). ○ For branded drugs, use Red Book for WAC and data from SSR Health, LLC for net drug prices, when available ▪ Use Federal Supply Schedule (FSS) prices if SSR net prices not available ▪ Use payer-specific discounts if payer mix is known (e.g., 23.1% for Medicaid populations) ○ If WAC available but not FSS or SSR net prices, show ICER for WAC and: ▪ Ask manufacturer(s) for expected discount, and use for net price • If potential discount range is provided, use conservative end of the range for discount price (i.e., the higher end of the price range as a substitute for the SSR net price) ▪ If no estimate from manufacturers, use average discount for SSR net prices of drugs in same class or considered analogs ▪ If no estimate from manufacturers and no analogs, use average discount for brand drugs from IMS cost trends reports[10] (currently 27%)

	○ If WAC and FSS or SSR net prices not available: ▪ Search for investor analysts' opinions on launch price, if available ▪ If not available and other, similar drugs in class, set price to average for class ▪ If not available and new class, conduct analysis for threshold prices only, with no base case • Use publicly available data for other health care costs (e.g., Medicare fee schedules, HCUPnet DRG reimbursement rates, or publications using commercial claims data), using consistent sources to the extent possible • Apply estimate of provider mark-up for hospital- or clinic-administered drugs from literature or other sources (including expert opinion where needed) ○ Use Magellan Rx Management's Medical Pharmacy Trend Report[1] for commercial or mixed populations in non-hospital settings ○ Use ASP+6% for Medicare populations receiving Part B drugs ○ Use Newcomer 2016[2] for patients treated in hospital-owned cancer clinics • Convert all costs to current-year US dollars, using the Personal Health Care (PHC) Expenditure deflator developed by the Centers for Medicare and Medicaid Services (CMS)[3] for healthcare expenditures and general CPI for non-healthcare costs ○ As the PHC Expenditure indices are generally only available with a lag-time of two years, use the PHC deflator up to the most recent year available, and then apply the personal consumption expenditure (PCE) price index to update to the current year[4] ○ When the PCE inflation lag is more than one year, inflate directly using the BEA National Data that has more recent (with only one quarter-year lag) health care-specific inflation index. ○ When inflating, use the most recent annual (not bi-annual or quarterly) index. Follow the steps below: 1. In the BEA National Data site, choose section 2 (personal income and outlays); 2. Choose table 2.3.4 (price indexes for personal consumption expenditures by major type of product); 3. Use the "modify" option in the top right corner of the page (the first option in the row presented); 4. Set Series to "Annual" and pick years required, with last year as current year, so that table generated will show most recent annual index; 5. From the table, choose line item 16, noting that 2012 is the index year (value=100, as in the PCE data);

	6. Calculate the ratio of the most recent year to the baseline year and apply this multiple to the baseline year to inflate to the most recent year.
Discounting	• 3% per year for both costs and outcomes
Data Assumptions and Limitations	• List key data and structural assumptions in a table along with rationale for each, including assumptions related to: o The natural history of disease o Whether there is an associated change in health or additional cost associated with each consequence o Extrapolation of short-term data (e.g., from clinical trials) to longer time horizons (e.g., lifetime) ▪ For major clinical effects, consider extrapolation scenarios for: • No continued effect • Same effect as observed in trial • Diminished effect over time o Linking intermediate outcomes (e.g., improvements in disease activity) to long-term outcomes (e.g., reduced mortality) o Extrapolation to other populations (e.g., specific age groups that were not studied in clinical trials) o Adherence and treatment discontinuation o Calculations of treatment costs, as appropriate (e.g., if the treatment is dosed according to weight, what weight was used? What discount was applied to new treatments?) o Which transitions each intervention is assumed to affect (e.g., does treatment directly affect mortality, or does it only affect short-term or long-term clinical outcomes that have their own association with mortality?) • Describe the limitations of the evidence and analysis
Analyses and Results	
Validation	• Conduct and describe internal validation checks (e.g., model debugging, checking extreme scenarios) using validation checklist • Check face validity through extensive conversations within ICER's research team and external clinical experts • Review feedback from external stakeholders to assess model validity • Compare base case results to those from other published analyses
Calibration	• Calibration may be used to estimate model parameters for which little or no data exist • Detail calibration procedures used, if applicable, including: o Data sources for calibration targets o Goodness-of-fit metrics o Search criteria used to obtain calibration estimates

	○ Stopping criteria to determine when calibration is complete
Presentation of Results	• For each intervention and comparator, present the following results in tables: ○ Costs, including intervention/comparator costs, other health care costs and total costs (undiscounted and discounted) ○ Costs, including intervention/comparator costs, other health care costs and total costs (undiscounted, by year for years 1-5) ○ Life-years (undiscounted and discounted) ○ QALYs (undiscounted and discounted) ○ Equal value life-years gained (evLYG, undiscounted and discounted) ○ Additional clinical effectiveness measure(s) as appropriate (e.g., hospitalizations avoided) • For each intervention relative to its comparator(s), present the following point estimate results in tables: ○ Incremental cost per LY (discounted) ○ Incremental cost per QALY (discounted) ○ Incremental cost per evLYG (discounted) ○ Incremental cost per other effectiveness measure ▪ If the analysis finds a major difference between cost per QALY and cost per evLYG, include specific language describing the underlying characteristics of the treatment and the condition that lead to the difference.
Uncertainty and Sensitivity Analyses	• Include discussion of "Uncertainty and Controversies" including important alternative model structures and assumptions suggested by stakeholders, and exploration of different conservative or optimistic model variations ○ Compare base case results to those from other published analyses • Conduct one-way sensitivity analyses, and present results in tornado diagrams • Conduct threshold analyses for intervention prices to achieve $50,000, $100,000, $150,000, and $200,000 per QALY and per evLYG ○ Health benefit price benchmarks will be reported using standard range from $100,000 to $150,000 per QALY and evLYG ○ Health benefit price benchmarks using thresholds linked to the modified societal perspective will also be presented for assessments using a co-base case • Derive expected values of costs and outcomes for each intervention through probabilistic analysis, using sufficient sampling to reflect distributional uncertainty (e.g., 1,000 simulations).

	o Report % achieving $50,000, $100,000, $150,000, and $200,000 per QALY thresholds, and graph using scatter plots or cost-effectiveness acceptability curves (CEAC) • Conduct scenario analyses o Where evidence on distinct subgroups is available, conduct a stratified analysis and present results for each subgroup o Conduct scenario using (modified) societal perspective, including productivity, etc.; identify factors included using impact inventory ▪ Use Notes column to describe elements deemed to be appropriate for a given model but for which no data are currently available o Conduct two hypothetical scenarios for all high-impact SSTs under review, as well as other, non-SST treatments with relevant and substantial potential cost-offsets (e.g., potential cost offsets > $1 million over lifetime), including threshold analyses for treatment price: ▪ 50/50 shared savings model in which 50% of the lifetime health system cost offsets from a new treatment are assigned to the health system instead of being assigned entirely to the new treatment ▪ Cost-offset cap model in which the health system cost offsets generated by a new treatment are capped at $150,000 per year but otherwise assigned entirely to the new treatment o When relevant, conduct scenario analysis including limited number of outcome-based payment arrangements ▪ In cases where price is known but there is no guidance from stakeholders, exploratory scenario analysis using outcomes and levels of financial risk-sharing that meet specific thresholds may be performed o For high-impact SSTs, conduct two scenario analyses to reflect optimistic and conservative assumptions regarding the benefit of SSTs under review, to be presented in conjunction with the base case ▪ Inputs for modeling the optimistic and conservative scenarios will be sought beginning with the scoping phase. o For high-impact SSTs, if treatment price is known or can be estimated, include a threshold analysis scenario determining duration of beneficial effect for those patients receiving short-term benefit that would be needed to achieve thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY. o In cases where an intervention that increases QALYs is not found to be cost effective even with a zero-dollar price, a

	separate scenario analysis excluding unrelated (non-drug) health care costs should be presented. o Exploratory scenario analyses to capture impacts of new technologies on disparities in life expectancy across different subpopulations in the US health care system should be conducted when feasible and relevant. o Conduct other scenarios as appropriate (e.g., different age cohorts, risk levels, long-term effectiveness, time horizons, utility scales/functions, survival functions, payment strategies)
Potential Budget Impact Analysis	
Eligible Population	• Use epidemiologic and other data to estimate size of potential candidate population in the US for each new treatment • Assume an equal proportion of patients (20%) are treated each year over five years, arriving at cumulative 100% at five years.
Time Horizon	• Use an undiscounted five-year timeframe
Potential Budget Impact Threshold	• Results are compared to a national annual threshold for each new pharmaceutical intervention, updated each calendar year using the most recent inputs available. Current potential budget impact threshold calculations are detailed at https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/.
Methods	• The cost-effectiveness model is used to estimate total costs of each new treatment and comparator, assuming different prices (treatment's list and net prices, and threshold prices to achieve cost effectiveness at $50,000, $100,000, and $150,000 per QALY). • Potential budget impact is defined as total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in costs from averted health care events or other aspects of treatment. • Evaluate whether a new drug would be likely to take market share from one or more drugs, using clinical expert opinion regarding treatments likely to be displaced by use of a new treatment within the eligible population. • Determine whether potential budget impact threshold is reached at each combination of price and percent uptake among eligible patients at five years, following one of the procedures listed below, dependent on whether existing treatments are being displaced. o No existing active treatment: If intervention is for a condition which has no existing active treatment in the market (other than best supportive care), calculate potential budget impact for 100% of the eligible population at the end of five years (20% marginal new uptake per year). o Existing treatments launched within prior 2 years: If intervention is for a condition with existing active treatment(s), one or more of which was launched within the last two years, equal proportions of the eligible population

	will be split among the intervention and the recently launched treatment(s), with 100% displacement of relevant treatments launched more than two years ago. o Existing treatments all on market >2 years: If intervention is for a condition with existing active treatment(s) all launched more than two years ago, calculate potential budget impact for 100% of eligible population at end of five years, with displacement of existing treatments. o Multiple existing treatments: When there are multiple existing treatments on the market, use clinical expert opinion to estimate the percentage of patients converted from each existing treatment to the new treatment. o Untreated patients: For all cases, include the untreated portion of the eligible population, as long as considered eligible for the new treatment. • The analysis will present a cumulative per-patient potential budget impact for each year over the five-year time horizon, with results presented graphically for each intervention assessed, and numerical data presented in tabular format in an appendix.
Access and Affordability Alert	• Include an "affordability and access alert" in the final report if discussion among stakeholders at the public meeting suggests utilization would exceed the budget impact threshold without active intervention

Adapted from CADTH Methods and Guidelines, 4th Edition;[5] Neumann et al. CE in Health and Medicine, 2nd Edition.[6]

Explanation

Decision Problem

Objectives

Each reference case analysis should begin with a clear statement of the goals of the analysis (i.e., the research question(s) to be answered). A Model Analysis Plan should be developed for each project using ICER's template, which defines the decision problem to be considered in the economic model. In general, the analysis plan should follow the outline specified in the final scoping document for the project (as published by ICER) or should provide reasons for any deviation from that scope. The Model Analysis Plan will specify the objectives of the economic analysis and the model type (e.g., decision tree, Markov, semi-Markov, microsimulation, discrete event simulation, etc.) to be used for the analysis. In addition, the plan should specify whether the model is an adaptation of an existing model (with references as appropriate) or is being developed *de novo* for this analysis.

Target Population

The Reference Case should include a detailed description of the populations and settings in which the interventions are to be used. This will generally match the population included in the pivotal trials or indicated in the published or anticipated FDA label, as well as the evaluation's Clinical Effectiveness Review. Justification should be provided when the modeled population differs appreciably from any of these. In addition, any discrepancy between the indicated population and modeled populations, and relevance of model results to the indicated population, will be discussed.

Stratified analyses should be conducted where distinct subgroup data for patient groups that are of clinical or economic interest are available; in general, modeled subgroups should match those of focus in the Clinical Effectiveness Review. A sub-section on "Heterogeneity and Subgroups" includes a discussion of heterogeneity and subgroups within the patient population and any likely implications for cost-effectiveness. Economic evaluations will include analysis of patient subgroups when robust data and relevant inputs from clinical trials and/or real-world evidence are available to do so.

For analyses using cohort or simulation models, the number of patients being modeled, and their key characteristics should be specified. Potential budget impact analyses will use estimates of the eligible U.S. population likely to be treated with the interventions.

If using the ultra-rare disease (URD) framework, acknowledge and highlight any additional uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures.

Intervention

The health care intervention(s) being evaluated should be clearly described, including components such as mode of administration, dosing, duration of treatment, auxiliary treatments, settings of treatment, etc., as appropriate.

Comparators

The intervention should be compared to the available and feasible relevant treatments that would most likely be used for the target population in the absence of the intervention. This will often represent specific alternative treatments currently available for the target population, some of which may have been active comparators to the intervention in clinical trials; a generally defined "usual care" approach (i.e., a mix of active and supportive care options); or a "do-nothing" option (typically used for placebo comparisons in clinical trials), as appropriate.

Perspective

ICER's base case will take a health care sector perspective as its general standard, including all direct health care-related costs and effects. These are expected to include all relevant costs borne by third-party payers or integrated health systems. Cost sources may also include patient out-of-pocket costs; if so, this should be noted. Decisions to present the patient out-of-pocket component separately should be made based on availability of such data.

In addition, each analysis should include a scenario analysis using a (modified) societal perspective, which will include costs and outcomes beyond direct health care impacts, to the extent possible given available data. Potential domains to include in this modified societal perspective are listed in an impact inventory in Appendix A (adapted from the 2nd US Panel on Cost-Effectiveness in Health and Medicine[6]). This inventory should be used to document the specific impacts that are and are not included in both the health care sector and modified societal perspectives, as well as the rationale for their inclusion or exclusion.

It is anticipated that, for most analyses, the modified societal perspective will minimally include productivity effects. Other indirect costs, such as caregiver time, criminal justice costs, nursing home or assisted living arrangements, and impacts on education, may be included based on relevance to the topic and population of focus.

For all interventions, results from the health care sector and modified societal perspectives should be presented together as a "co-base case" when two additional conditions are satisfied: 1) the impact of treatment on indirect costs such as patient and caregiver productivity, education, disability, or nursing home costs is judged to be substantial, and 2) these costs are considered large in relation to health care costs associated with treatment of the condition. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses thresholds of $100,000-$150,000 per QALY.

Time Horizon

To attempt to ensure that all downstream costs and effects are accounted for, the default time horizon for ICER's Reference Case will be lifetime. In some cases, the nature of the condition or intervention being studied, or the lack of long-term data may necessitate the use of a shorter horizon. However, in such cases, the shorter time horizon should still be long enough to capture all

relevant differences in future costs and outcomes associated with the treatments being compared. Time horizon may also be considered as a parameter of interest in sensitivity analyses.

Outcomes

The specific model outcomes should be specified. Costs, life-years, evLYG, and QALYs, both undiscounted and discounted, should be tabulated. Analysts should also present results for other outcomes as natural units (e.g., cost per treatment response, cost per event averted), when feasible. Cost-utility analysis (CUA) with incremental cost per QALYs as the primary outcome will be the default choice for ICER's Reference Case. In all cases where effects on length of life are relevant, cost per evLYG and cost per life-year should also be reported. Analysts should also present results in terms of incremental costs for clinical outcome achieved (e.g., cost per treatment response, cost per event averted), when appropriate and feasible.

Model Structure

Type of Model

The type of model relates to the specified decision problem. Broadly, types of models include decision trees, state-transition cohort models, microsimulation models, dynamic transmission models, or dynamic simulation models. Models can also include components with different model types; for example, a model may include a decision tree for an initial (shorter) period, followed by a state-transition model for longer-term extrapolations. Decision trees are suitable when there are no recurrent events and when the time horizon is short. State-transition models of cohorts (also called Markov cohort models) capture changing health states over time. Microsimulation models simulate individuals, which can be advantageous when modeling complex disease or care processes; microsimulations should model a sufficient number of individuals to achieve stable results (assessed by calculating variance over multiple runs).[7] Dynamic transmission models capture the interactions between individuals, which is suited for decision problems where the transmission of disease is important (e.g., infectious diseases). Dynamic simulation models (e.g., discrete event simulations, agent-based models) are best suited for decision problems evaluating systems with competing demands for resources (such as settings of care) or interactions between individuals (such as transmission of disease).

The type of model will relate to the following factors: (a) how time is handled; (b) the unit of analysis; and (c) the interactions of individuals in the model. Time can be fixed (e.g., decision tree), treated as discrete (e.g., state-transition models), or continuous (e.g., discrete event simulations). In addition, events over time may be allowed to vary, which must be handled appropriately (e.g., health states defined by prior event history or duration of time). The unit of analysis can be an individual or cohort; if an individual unit of analysis is considered, the total number of individuals will be specified and justified. If individuals are allowed to interact with others or with a system, the dynamic components of the model should be described.

The Model Analysis Plan and Evidence Report will also specify if the model was used or modified from existing sources or was developed *de novo*. If modified from existing sources, the appropriate references will be provided.

Intervention Effects

All effects of the intervention(s) as they relate to health, resource use, and other economic impacts will be identified through the scoping process. The effects of the intervention include those which are intended and unintended, with positive or negative impacts. The effects included in an analysis will depend on the perspective (e.g., healthcare or societal), and will be guided by practical considerations (e.g., data availability). To clarify the effects included in a model and analysis, the Impact Inventory will be completed (see Appendix A). The Impact Inventory is a formal framework for considering and specifying the effects included in the analyses using the health system payer and societal perspectives. If an identified effect is not included in an analysis, the rationale will be provided with justifications.

Wherever feasible, inputs on clinical effectiveness should match those reported in the Clinical Effectiveness Review, including estimates derived by any quantitative synthesis of the data (e.g., network meta-analysis on relative risk of hospitalization).

Event Pathways

The method by which the intervention(s) and comparator(s) relate to the included effects will be detailed. The sequence or pathway of events stemming from first use of the intervention(s) should capture not only healthcare utilization, but also the key elements of the disease process. A conceptual diagram or model schematic will be provided, which visually represents the event pathway and health states built into the model structure.

Software

The software, including version and any analysis packages, used to develop the model is specified in the model analysis plan and Evidence Report.

Model Parameters and Data Inputs

Quantifying Effects of Interventions

A systematic literature review is the preferred method for identifying relevant literature pertaining to the estimates of treatment effect, and in some cases, adverse events. For each effect captured in the model, the systematic review will be referenced (e.g., from the clinical review section of the Evidence Report). When it is infeasible or impractical to conduct a systematic review for a particular effect estimate, the data source used will be justified.

Modelers should state and justify assumptions regarding long-term impacts beyond the available data, including those around durability or maintenance of effect and which survival analytic techniques were considered and used. For high-impact SSTs, models should use cure proportion modeling whenever relevant, but also provide survival analyses based on other modeling approaches when relevant and feasible.

If there is evidence to suggest the identified treatment effect estimates from the existing literature are biased or otherwise not transferable to the context of the model, any adjustments or corrections used will be detailed and specified.

Measurement and Valuation of Health

Reference Case models should include all relevant health outcomes, including serious adverse events that impact costs or quality of life. In general, measures of health state preferences (utility) should reflect those of the general US population, as ICER models primarily inform decisions at the population level (e.g., payer or health system formulary decisions) that involve individuals both with and without the condition of focus.

Where general population estimates are not available or appropriate, different populations may be used, such as patients with the specific condition under study, those affected by similar symptoms, proxy respondents, or mixed samples, with appropriate rationale provided. In all cases, a description of the sources and methods used for health preferences measurement should be provided. This will often involve a method of measuring health states in patients that are then mapped into a generic classification system with associated utility weights, such as the EQ-5D-5L.

In general, the use of generic, preference-based measures for utility values is recommended. While no specific generic, preference-based measure is required, EQ-5D values are preferred if available. As the most widely used generic measure, this helps ensure comparability across studies. Models should use disease-specific preference-based data if generic measures are considered not to be responsive enough to distinguish relevant health states or treatment attributes, or if appropriate generic preference-based data are not available.

When there are challenges in translating the outcome measures used in clinical trials or available patient-reported data into QALYs, analysts should conduct a search for "mapping" studies that allow translation of surrogate outcomes into quality of life measures. If used, the report should discuss the validity of the mapping studies and their translation into QALYs, as well as the rationale for choosing specific mapping algorithms. If an analysis is using the URD framework, the model report should acknowledge and highlight additional uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures, if relevant.

Resource Use and Costs

The Reference Case model should include all relevant resources and costs based on the health system payer perspective including costs paid by third-party payers, noting whether out of pocket expenses for patients are included. Any excluded costs should be identified, with the rationale for exclusion provided. The sources for resource utilization and cost data should be provided, along with the methods for how we seek and evaluate those inputs, including details of the comprehensive literature review.

For drugs with generic versions available, economic evaluations will use the average WAC across the different generic versions, unless analyzing a specific branded or generic formulation. For branded drugs, wholesale acquisition costs (WAC) should be obtained from the Red Book online.[8]

Where available (generally for branded drugs from publicly-traded companies for which publicly-disclosed net sales figures are available), obtain net discount estimates from the SSR Health LLC database,[9] which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price. Estimated net prices will be calculated by comparing the four-quarter rolling averages of both net prices and WAC per unit to arrive at a mean discount from WAC for the drug. This average discount is then applied to the most recent available wholesale acquisition cost (WAC) to arrive at an estimated net price per unit. If SSR net prices are not available, use most recent Federal Supply Schedule (FSS) prices. Analyses should use payer-specific discounts if and when the payer mix is known (e.g., 23.1% for treatments for predominantly Medicaid populations).

If WAC is available but not FSS or SSR net prices, analysts will report the ICER for WAC and attempt to estimate the expected net price using the following steps. First, ask the manufacturer(s) for the expected discount, and use that to estimate net price. If a potential discount range is provided, use the conservative end of the range to estimate the discount price (i.e., the higher end of the price range as a substitute for the SSR net price). If no estimate is provided from the manufacturers, use the average discount for SSR net prices of drugs in the same class or that could be considered analogs. If no estimates are provided from manufacturers and the are no analogs identified, use the average discount for all branded drugs. According to IQVIA, a large data aggregation and consulting firm, the most recent industry-wide estimated discount was 27%.[10]

In cases where the WAC and FSS or SSR net prices are not available, search for and use an average of investor analysts' opinions on launch price, if available. If no estimates of launch price are available and there are other drugs in the same class with similar characteristics, use the average price for the class as a placeholder for launch price. If no similar interventions or a novel class of drugs, conduct the analysis using threshold prices only, with no base case price.

To the extent possible, analysts should use publicly available data for other health care costs (e.g., Medicare fee schedules, HCUPnet DRG reimbursement rates, or publications using commercial claims data). Models should include cost data from consistent sources to the extent possible. Costs for hospital- or clinic-administered drugs should include estimates of provider mark-up from the literature or other sources, including expert opinion where needed. Use ASP+6% for Medicare populations receiving Part B drugs. For other populations, relevant sources include Magellan Rx Management's Medical Pharmacy Trend Report[1] for commercial or mixed populations in non-hospital settings, and Newcomer 2016[2] for patients treated in hospital-owned cancer clinics.

All costs should be converted to current-year US dollars, using foreign exchange rates,[11] the Personal Health Care (PHC) Expenditure deflator developed by the Centers for Medicare and Medicaid Services (CMS) for healthcare expenditures[3], and the general CPI for non-healthcare costs,[12] as appropriate. As the PHC Expenditure indices are generally only available with a lag-time of two years, models should use the PHC deflator up to the most recent year available, and then apply the personal consumption expenditure (PCE) price index or BEA National Data to update to the current year.[4] Detailed steps are provided in the table above.

Discounting

To account for time value and ensure comparability across studies, all models should use constant-rate discounting of both costs and outcomes, at the rate of 3% per year, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine.[6]

Data Assumptions and Limitations

All key assumptions used in the model should be listed in a table, along with the rationale for each assumption and sources of relevant data. This should include assumptions related to the natural history of disease, whether there is an associated change in health or additional cost associated with each consequence, and the method for extrapolation of short-term data (e.g., from clinical trials) to longer time horizons (e.g., lifetime). For extrapolation of major clinical effects, analysts should consider extrapolation scenarios for no continued effect, the same effect as observed in trial data, and diminished effect over time. Additional assumptions to list include: the process for linking intermediate outcomes (e.g., improvements in disease activity) to long-term outcomes (e.g., reduced mortality), extrapolation to other populations (e.g., specific age groups that were not studied in clinical trials), and the handling of adherence and treatment discontinuation. Any assumptions or inputs used in the calculation of treatment costs should be described, as appropriate, such as the weight assumed if the treatment is dosed according to weight. In addition, the model transitions that each intervention is assumed to affect should be described, such as whether treatment directly affects mortality or only affects other short-term or long-term clinical outcomes.

Finally, any limitations of the evidence available or of the methods or analytic techniques should be described in the report of the cost-effectiveness analysis.

Analyses and Results

Validation

Validation of an economic model occurs throughout the development process. Internal validation (e.g., model debugging, checking extreme scenarios) is checked using ICER's internal validation checklist. Face validity (e.g., the model structure and processes are appropriate for the decision problem) is checked through extensive conversations within ICER's research team and external clinical as well as modeling experts. In addition, ICER reviews critical feedback from external stakeholders in their assessment of validity. Reference case methods and results are also compared to those from other published analyses of the relevant interventions or therapy area, with rationale for any differences observed. These validation procedures and results should be described in any reporting of model methods and results.

Calibration

In some models, there may be parameters for which little or no data exist. For these parameters, calibration may be used as an estimation technique. Calibration is an iterative process that entails finding values for parameters such that the projected model outputs match (i.e., "fit") the observed data (i.e., calibration targets). If calibration is performed, the procedures will be detailed including:

(a) the data sources for the calibration targets; (b) the goodness-of-fit metric(s) used, such as a likelihood-based metric or distance measure; (c) how the parameter space was searched, for example using a grid-based search or an algorithm; and (d) the stopping criteria to determine when the calibration is complete.

Presentation of Results

The model should be used to conduct a deterministic base case analysis (if appropriate for model type), following these Reference Case guidelines to the extent possible. Outcomes from the model should be presented for each intervention and comparator and will generally include all of the following. Reported output from the model should include undiscounted and discounted costs, life-years, evLYG, and QALYs. In addition to these outcomes, if appropriate, at least one clinical effectiveness measure should be tallied, such as hospitalizations avoided by treatment or absolute rates of hospitalization for each intervention and comparator. Discounted costs, broken out into costs for the intervention and comparators, other health care costs, and total costs, should also be reported. In addition, the model output should provide undiscounted costs (including intervention/comparator costs, other health care costs, and total costs) broken out by year for years one through five, for use in potential budget impact analyses. Finally, the discounted incremental cost per LY, incremental cost per evLYG, and incremental cost per QALY should be calculated for each intervention-versus-comparator pair. If appropriate, incremental cost per other effectiveness measure should also be calculated for each intervention-versus-comparator pair. In specific cases where appropriate (e.g., mutually exclusive interventions used in the same population), incremental cost per outcome may be presented for comparisons between interventions as well. If the analysis finds a major difference between cost per QALY and cost per evLYG, specific language will be included to describe the underlying characteristics of the treatment and the condition that lead to the differences.

Uncertainty and Sensitivity Analyses

Economic evaluations will include discussion of "Uncertainty and Controversies," including important alternative model structures and assumptions suggested by manufacturers and other stakeholders, and exploration of different conservative or optimistic model variations, in particular, any alternative model structures or inputs that differ importantly from the base case. This sub-section consolidates and expands discussion of factors related to uncertainty, including lack of information on natural history, limitations of the data on patient outcomes, difficulties translating existing data into measures of quality of life, and disagreements over the plausibility of certain inputs or assumptions.

Summaries of relevant published cost-effectiveness analyses are also included in this sub-section, pointing out differences in model structure, inputs and assumptions, and the impact of these differences on model results. This section will review and compare the current model to published models that included the same interventions or comparators of interest, were developed in the last 10 years, and were similar to the current model from a setting and population perspective.

To account for uncertainty, modelers should conduct one-way sensitivity analyses, and present the results in "tornado diagrams" that display the findings across a feasible range for each parameter estimate. In addition, the model output should provide threshold analyses to determine the intervention prices that would be estimated to achieve common willingness-to-pay thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY and per evLYG. In addition to deterministic sensitivity analyses, the model should derive expected values of costs and outcomes for each intervention through probabilistic sensitivity analysis, using sufficient sampling to reflect distributional uncertainty (e.g., 5,000 simulation runs if feasible). Output from this analysis should include a table reporting the percent of simulations that achieve $50,000, $100,000, $150,000, and $200,000 per QALY and per evLYG thresholds, as well as Graph(s) using scatter plots or cost-effectiveness acceptability curves (CEAC).

Specific scenario analyses should be conducted where appropriate. Where evidence on distinct subgroups is available, modelers should conduct a stratified analysis and present results for each subgroup. As mentioned above, a scenario using a (modified) societal perspective should be modeled, with the included productivity and other impacts identified using an impact inventory table.

Using both cost per QALY and the cost per evLYG results will enable policy makers to gain a broad overview of the cost-effectiveness of treatments while ensuring that results are available to demonstrate whether there is any impact of extended life at a low quality of life. If ICER's analysis finds a major difference in these two measures, reports will include specific language describing the underlying characteristics of the treatment and condition that lead to the difference.

Economic evaluations will include two hypothetical scenarios for all high-impact SSTs under review, as well as other, non-SST treatments with relevant and substantial potential cost-offsets, such as potential cost offsets that are greater than $1 million over a lifetime, These scenarios will include threshold analyses for treatment price under two situations:

- a 50/50 shared savings model in which 50% of the lifetime health system cost offsets from a new treatment are assigned to the health system instead of being assigned entirely to the new treatment, and
- a cost-offset cap model in which the health system cost offsets generated by a new treatment are capped at $150,000 per year but otherwise assigned entirely to the new treatment.

When relevant, evaluations will include information from manufacturers and payers to model a scenario analysis including a limited number of outcome-based payment arrangements for the intervention under review. In cases where the list price of the treatment is known but there is no guidance from stakeholders, an exploratory scenario analysis using outcomes and levels of financial risk-sharing that could meet cost-effectiveness thresholds may be performed.

In addition to the base case and associated sensitivity analyses, economic evaluations will include two specific scenario analyses to reflect an optimistic and a conservative assumption regarding the benefit of SSTs under review. Input for best approaches to modeling the optimistic and conservative

scenarios will be sought beginning with the scoping phase and will be included as part of the model analysis plan. These scenario analyses will be presented in conjunction with the base case.

For high-impact SSTs, when the SST price is known or can be estimated, assessments will also include a scenario with a threshold analysis determining the duration of beneficial effect (e.g. cure) for those patients receiving short-term benefit that would be needed to achieve standard cost-effectiveness thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY

In cases where an intervention that increases QALYs is not found to be cost effective, even with a zero-dollar price, a separate scenario analysis excluding unrelated (non-drug) health care costs will be presented. In such cases, there are no positive prices for an intervention that will reach specific cost-effectiveness thresholds. This may occur in situations where a new treatment is added on to existing treatment that is already near or beyond the cost-effectiveness threshold. Another example where this may occur is when a new treatment results in more time spent in health states that have very high costs and/or a low utility value, making it impossible for the incremental cost effectiveness ratio to reach specific thresholds even at zero price. In such cases a scenario analysis excluding health state costs that are not related to the intervention *per se* may be informative.

Other scenario analyses can be considered on a topic-specific basis as appropriate, including different age cohorts, risk levels, long-term effectiveness assumptions, time horizons, utility scales or functions, survival functions, or payment and contracting strategies.

The health benefit price benchmarks will continue to be reported using the standard range from $100,000 to $150,000 per QALY and per evLYG. Health benefit price benchmarks using thresholds linked to the modified societal perspective will also be presented for assessments using a co-base case.

Potential Budget Impact Analyses

Eligible Population

Potential budget impact analyses are based on net cost per patient and estimates of the proportion of the US population eligible for treatment with the new intervention. ICER uses epidemiologic and other data to estimate the size of the potential candidate population for each new treatment. We then assume that an equal proportion of patients (20%) would be treated with the new treatment each year over five years, arriving at a cumulative 100% uptake at five years.

Time Horizon

The potential health care system budgetary impact of the intervention is explored over a five-year time horizon. Results from the cost-effectiveness model are used to provide undiscounted net costs (including intervention/comparator costs, other health care costs, and total costs) broken out by year for years one through five, for use in the potential budget impact analyses.

Potential Budget Impact Threshold

The goal of ICER's potential budget impact analysis is to estimate the net cost per patient treated with new interventions so that decision-makers can use their own assumptions about uptake and

pricing to determine their own estimate of potential budget impact. We also seek to produce calculations that will help policy makers identify situations in which the potential uptake of a new treatment, at various pricing levels, might exceed a budget impact threshold that signifies that the budget impact in the near term (over 5 years) would contribute to overall health care cost growth at a higher rate than growth in the national economy (plus 1%). Results of the analysis are compared to a national annual threshold for each new pharmaceutical intervention, updated each calendar year using the most recent inputs available. Current potential budget impact threshold calculations are detailed at https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/.

Methods

ICER uses the cost-effectiveness model in an economic evaluation to estimate the potential total budgetary impact of new treatments in the US, assuming different prices, including the treatment's list and net prices, and the three threshold prices to achieve cost effectiveness at $50,000, $100,000, and $150,000 per QALY. Potential budget impact is defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events.

To accomplish these goals, ICER's potential budget impact analyses must evaluate whether a new drug would be likely to take market share from one or more drugs. ICER will continue to use clinical expert opinion regarding the treatments likely to be displaced by use of a new treatment within the eligible population. ICER will then follow one of the procedures listed below, dependent on whether existing treatments are being displaced. These are explicitly NOT meant to represent our assumptions of the budget impact of new interventions that are most likely in the real world. Our methods are intended to provide the calculations that can underpin a graphic figure that allows decision-makers and policy makers to make their own assumptions.

- No existing active treatment: If the intervention is for a condition which has no existing active treatment in the market (other than best supportive care), we will calculate potential budget impact for 100% of the eligible population at the end of five years (20% marginal new uptake per year).
- Existing treatments launched within prior 2 years: If the intervention is for a condition with existing active treatment(s), one or more of which was launched within the last two years, equal proportions of the eligible population will be split among the intervention and the recently launched treatment(s), with 100% displacement of relevant treatments launched more than two years ago.
- Existing treatments all on market >2 years: If the intervention is for a condition with existing active treatment(s) all launched more than two years ago, we will calculate potential budget impact for 100% of the eligible population at the end of five years, with displacement of existing treatments.

- Multiple existing treatments: When there are multiple existing treatments on the market, clinical expert opinion will be used to estimate the percentage of patients converted from each existing treatment to the new treatment.
- Untreated patients: For all cases, we will include the untreated portion of the eligible population, as long as they are considered eligible for the new treatment.

The analysis will present a cumulative per-patient potential budget impact for each year over the five-year time horizon, with results presented graphically for each intervention assessed, and numerical data presented in tabular format in an appendix of the report.

Access and Affordability Alert

The potential budget impact analysis section of each final report will include an "affordability and access alert" if discussion among stakeholders at the public meeting of ICER's independent appraisal committees 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.

Appendix A. Impact Inventory (adapted from Neumann, Sanders et al.[6])

Note that the purpose of this checklist is to report whether different impacts were considered in the health system payer and modified societal perspective analyses. Not all impact types will be relevant for every intervention. For example, some interventions may have impacts limited to the formal healthcare sector, while other interventions may have substantial impacts beyond the formal healthcare sector.

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	☐	☐	
	Health-related quality of life effects	☐	☐	
	Adverse events	☐	☐	
Medical costs	Paid by third-party payers	☐	☐	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	☐	
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

[1] Magellan Rx Management. Medical Pharmacy Trend Report, 2016 Seventh Edition (available at www.MagellanRx.com).
[2] Newcomer LN. Those who pay have a say: A view on oncology drug pricing and reimbursement. Oncologist 2016; 21:779-781.
[3] Grosse SD, Zuvekas.SH. The price is right: on adjusting health expenditures for inflation. Centers for Disease Control and Prevention Mimeo 2015 [unpublished].
[4] Agency for Healthcare Research and Quality. 2015. "Medical Expenditure Panel Survey (MEPS). Using Appropriate Price Indices for Analyses of Health Care Expenditures or Income Across Multiple Years." Last Modified April 3, 2015. Accessed May 25, 2018. https://meps.ahrq.gov/about_meps/Price_Index.shtml.
[5] Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa: CADTH; 2017 Mar.
[6] Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, editors. *Cost-Effectiveness in Health and Medicine, Second Edition*. New York, NY: Oxford University Press; 2017.
[7] Siebert, U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, Kuntz KM. State-transition modeling: A report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. Med Decis Making 2012; 32(5):690–700.
[8] RED BOOK Online. Greenwood Village (CO): Truven Health Analytics; 2018. Available from: www.micromedexsolutions.com.
[9] SSR Health L. 2018; https://www.ssrhealth.com/.
[10] Aitken M, Kleinrock M, Pennente K, Lyle J, Nass D, Caskey L. *Medicines Use and Spending in the U.S.: A review of 2015 and Outlook to 2020.* Parsippany, NJ: QuintilesIMS; 2016.
[11] Internal Revenue Service. Yearly Average Currency Exchange Rates. Available at: https://www.irs.gov/individuals/international-taxpayers/yearly-average-currency-exchange-rates
[12] Bureau of Labor Statistics, United States Department of Labor. Consumer Price Index Historical Table, U.S. City Average, All items. Available at: https://www.bls.gov/regions/midwest/data/consumerpriceindexhistorical_us_table.pdf.