



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
<i>Decision Problem</i>	
Objectives	<ul style="list-style-type: none"> State the goals of the analysis, specific to the topic area
Target Population	<ul style="list-style-type: none"> Describe the population(s) and setting(s) in which the interventions are to be used Specify and define any subpopulation(s) (e.g., defined by demographic or disease characteristics)
Intervention	<ul style="list-style-type: none"> Clearly describe the health care intervention(s) being evaluated, including components, dose, duration, etc., as appropriate
Comparators	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Health care sector perspective (default) Societal perspective as scenario analysis <ul style="list-style-type: none"> Estimate net productivity impacts Include all relevant societal impacts to the extent possible If under ICER’s ultra-rare disease (URD) framework, present health system payer perspective in tandem with modified societal perspective as “co-base case” when: <ul style="list-style-type: none"> Impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial, and These costs are large in relation to health care costs

	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Costs (undiscounted and discounted) Life-years (undiscounted and discounted) Quality-adjusted life years (QALYs, undiscounted and discounted) Other natural outcomes (e.g., hospitalizations avoided), when feasible Cost per quality-adjusted life year (QALY) Cost per life year, if mortality effects Cost per consequence (e.g., cost per hospitalization avoided), when appropriate and feasible
<i>Model Structure</i>	
Type of Model	<ul style="list-style-type: none"> Describe the model type (e.g., decision tree, state transition, microsimulation, dynamic transition, dynamic simulation) Specify the following: <ul style="list-style-type: none"> How events over time are handled (e.g., health states that include event history or number of years in a state, as appropriate) Unit of analysis (e.g., individual, cohort, population) Whether and how individuals can interact with others in the model State if the model is an existing model or if it was developed <i>de novo</i>
Intervention Effects	<ul style="list-style-type: none"> Identify all downstream effects of the intervention(s) as they relate to health, resource use, and other economic impacts (healthcare sector and societal) <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> Specify the effects of the interventions included in each of the analytic perspectives Justify the rationale for not including any intervention effect in the analysis, if applicable
Event Pathways	<ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> Events and health states should capture elements of the disease process, not utilization alone Include conceptual schematic of model
Software	<ul style="list-style-type: none"> State the software (including version number) used to develop the model
<i>Model Parameters and Data Inputs</i>	
Quantifying Effects of Interventions	<ul style="list-style-type: none"> For each effect captured in the model, state the method for identifying the treatment effect estimates

	<ul style="list-style-type: none"> ○ Systematic literature reviews with meta-analyses should be conducted or referenced (e.g., from the Clinical Review section of the Evidence Report) ○ When infeasible or impractical to conduct a systematic review, justify data sources used ● State and justify any corrections for biases or adjustments for transferability in the estimates used in the model
Measurement and Valuation of Health	<ul style="list-style-type: none"> ● 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) ● 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 <ul style="list-style-type: none"> ○ 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	<ul style="list-style-type: none"> ● Include all relevant resources and costs based on the health system payer perspective <ul style="list-style-type: none"> ○ 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 <ul style="list-style-type: none"> ○ Use Red Book for WAC and data from SSR Health, LLC for net drug prices, when available <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ Ask manufacturer(s) for expected discount, and use for net price <ul style="list-style-type: none"> ● 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 reports⁹ (currently 27%) ○ If WAC and FSS or SSR net prices not available: <ul style="list-style-type: none"> ▪ Search for investor analysts' opinions on launch price, if available

	<ul style="list-style-type: none"> ▪ 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) • Apply estimate of provider mark-up for hospital- or clinic-administered drugs from literature or other sources (including expert opinion where needed) <ul style="list-style-type: none"> ○ Use Magellan Rx Management’s Medical Pharmacy Trend Report¹ for commercial or mixed populations in non-hospital settings ○ Use ASP+6% for Medicare populations receiving Part B drugs ○ Use Newcomer 2016² 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 <ul style="list-style-type: none"> ○ 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 year⁴
Discounting	<ul style="list-style-type: none"> • 3% per year for both costs and outcomes
Data Assumptions and Limitations	<ul style="list-style-type: none"> • List key data and structural assumptions in a table along with rationale for each, including assumptions related to: <ul style="list-style-type: none"> ○ The natural history of disease ○ Whether there is an associated change in health or additional cost associated with each consequence ○ Extrapolation of short-term data (e.g., from clinical trials) to longer time horizons (e.g., life-time) <ul style="list-style-type: none"> ▪ For major clinical effects, consider extrapolation scenarios for: <ul style="list-style-type: none"> • No continued effect • Same effect as observed in trial • Diminished effect over time ○ 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)

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

	<ul style="list-style-type: none"> ○ Adherence and treatment discontinuation ○ 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?) ○ 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?) <ul style="list-style-type: none"> ● Describe the limitations of the evidence and analysis
<i>Analyses and Results</i>	
Validation	<ul style="list-style-type: none"> ● 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	<ul style="list-style-type: none"> ● Calibration may be used to estimate model parameters for which little or no data exist ● Detail calibration procedures used, if applicable, including: <ul style="list-style-type: none"> ○ Data sources for calibration targets ○ Goodness-of-fit metrics ○ Search criteria used to obtain calibration estimates ○ Stopping criteria to determine when calibration is complete
Presentation of Results	<ul style="list-style-type: none"> ● For each intervention and comparator, present the following results in tables: <ul style="list-style-type: none"> ○ Costs, including intervention/comparator costs, other health care costs and total costs (discounted) ○ Costs, including intervention/comparator costs, other health care costs and total costs (undiscounted, by year for years 1-5) ○ Life-years (discounted) ○ QALYs (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: <ul style="list-style-type: none"> ○ Incremental cost per LY ○ Incremental cost per QALY ○ Incremental cost per other effectiveness measure
Uncertainty and Sensitivity Analyses	<ul style="list-style-type: none"> ● Conduct one-way sensitivity analyses, and present results in tornado diagrams ● Conduct threshold analyses for intervention prices to achieve \$50,000, \$100,000, and \$150,000 per QALY <ul style="list-style-type: none"> ○ If using URD framework, provide willingness-to-pay threshold results for \$50,000, \$100,000, \$150,000, \$250,000, and \$500,000 per QALY; value-based price benchmarks will be reported using standard range from \$100,000 to \$150,000 per QALY, but include text indicating that decision-makers in US and international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding

	<p>decisions at higher prices, and thus higher ICERs, than applied to decisions about other treatments</p> <ul style="list-style-type: none"> ○ Value-base price benchmarks (VBPB) using willingness-to-pay thresholds linked to the modified societal perspective will be presented alongside the standard VBPB ● Derive expected values of costs and outcomes for each intervention through probabilistic analysis, using sufficient sampling to reflect distributional uncertainty (e.g., 5,000 simulations). <ul style="list-style-type: none"> ○ Report % achieving \$50,000, \$100,000 and \$150,000 per QALY thresholds ● Conduct scenario analyses <ul style="list-style-type: none"> ○ Where evidence on distinct subgroups is available, conduct a stratified analysis and present results for each subgroup ○ Conduct scenario using (modified) societal perspective, including productivity, etc.; identify factors included using impact inventory <ul style="list-style-type: none"> ▪ Use Notes column to describe elements deemed to be appropriate for a given model but for which no data are currently available ○ When major impact of intervention is to extend life with a chronic and severe condition, compare \$/LY with \$/QALY, and include discussion of the influence of lower utilities for individuals with chronic severe conditions on \$/QALY. (When the impact of lower utilities for baseline chronic conditions makes a substantive difference in the calculated incremental cost-effectiveness ratios, ICER will seek public comment on which outcome should serve as the base case within the report.) ○ Conduct other scenarios as appropriate (e.g., different age cohorts, risk levels, long-term effectiveness, time horizons, utility scales/functions, survival functions, payment strategies)
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Adapted from CADTH Methods and Guidelines, 4th Edition;⁵ Neumann et al. CE in Health and Medicine, 2nd Edition.⁶

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.

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. Stratified analyses should be conducted where distinct subgroup data are available; in general, modeled subgroups should match those of focus in the Clinical Effectiveness Review.

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 Medicine⁶). 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.

If the analysis is using the [ultra-rare disease \(URD\) framework](#), 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.

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, 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 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.

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.

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.

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.

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.

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, **Error! Bookmark not defined.** 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 there 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%.⁹

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.

⁸ RED BOOK Online. Greenwood Village (CO): Truven Health Analytics; 2018. Available from: www.micromedexsolutions.com.

⁹ 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.

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). 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 Report¹ for commercial or mixed populations in non-hospital settings, and Newcomer 2016² for patients treated in hospital-owned cancer clinics.

All costs should be converted to current-year US dollars, using foreign exchange rates,¹⁰ the Personal Health Care (PHC) Expenditure deflator developed by the Centers for Medicare and Medicaid Services (CMS) for healthcare expenditures¹¹, 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 to update to the current year.¹³

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., life-time). 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

¹⁰ Internal Revenue Service. Yearly Average Currency Exchange Rates. Available at:

<https://www.irs.gov/individuals/international-taxpayers/yearly-average-currency-exchange-rates>

¹¹ Grosse SD, Zuvekas.SH. The price is right: on adjusting health expenditures for inflation. Centers for Disease Control and Prevention Mimeo 2015 [unpublished].

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

¹³ 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

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 discounted life-years and discounted 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 incremental cost per LY, incremental cost per QALY, and (if appropriate) incremental cost per other effectiveness measure should 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.

Uncertainty and Sensitivity Analyses

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, and \$150,000 per QALY. 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 and \$150,000 per QALY thresholds. 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. 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.

If using the [URD framework](#), the analysis should provide willingness-to-pay threshold results for \$50,000, \$100,000, \$150,000, \$250,000, and \$500,000 per QALY. The value-based price benchmarks will continue to be reported using the standard range from \$100,000 to \$150,000 per QALY, but will include text indicating that decision-makers in US and international settings often give special weighting to other benefits and to contextual considerations that may lead to coverage and funding decisions at higher prices, and thus higher ICERs, than applied to decisions about other treatments.

To ensure equity, Reference Case models should generally weight all outcomes equally regardless of the characteristics of the people receiving or affected by the interventions in question. However, when the major impact of an intervention is to extend life with a chronic and severe condition, the Reference Case will compare costs per LY with costs per QALY, and include discussion of the influence of lower utilities for individuals with chronic severe conditions on the incremental cost-effectiveness ratios. (When the impact of lower utilities for baseline chronic conditions makes a substantive difference in the calculated incremental cost-effectiveness ratios, ICER may seek public comment on which outcome should serve as the base case within the report.)

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	<input type="checkbox"/>	<input type="checkbox"/>	
	Health-related quality of life effects	<input type="checkbox"/>	<input type="checkbox"/>	

	Adverse events	<input type="checkbox"/>	<input type="checkbox"/>	
Medical costs	Paid by third-party payers	<input type="checkbox"/>	<input type="checkbox"/>	
	Paid by patients out-of-pocket	<input type="checkbox"/>	<input type="checkbox"/>	
	Future related medical costs	<input type="checkbox"/>	<input type="checkbox"/>	
	Future unrelated medical costs	<input type="checkbox"/>	<input type="checkbox"/>	
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	<input type="checkbox"/>	
	Unpaid caregiver-time costs	NA	<input type="checkbox"/>	
	Transportation costs	NA	<input type="checkbox"/>	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	<input type="checkbox"/>	
	Cost of unpaid lost productivity due to illness	NA	<input type="checkbox"/>	
	Cost of uncompensated household production	NA	<input type="checkbox"/>	
Consumption	Future consumption unrelated to health	NA	<input type="checkbox"/>	
Social services	Cost of social services as part of intervention	NA	<input type="checkbox"/>	
Legal/Criminal justice	Number of crimes related to intervention	NA	<input type="checkbox"/>	
	Cost of crimes related to intervention	NA	<input type="checkbox"/>	
Education	Impact of intervention on educational achievement of population	NA	<input type="checkbox"/>	
Housing	Cost of home improvements, remediation	NA	<input type="checkbox"/>	
Environment	Production of toxic waste pollution by intervention	NA	<input type="checkbox"/>	
Other	Other impacts (if relevant)	NA	<input type="checkbox"/>	

NA: not applicable