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

Current as of September 25, 2023

Domains updated September 2023:

- **Modified societal perspective**: When direct data on patient and caregiver productivity are lacking, analyses will be performed using an "indirect approach" based on QALY gains so that parameter inputs will be "non-zero."
- **Quantifying unmet need**: ICER will provide empirical results for the absolute shortfall and proportional shortfall to inform deliberation and voting on unmet need as a contextual consideration during public meetings.
- **Enhanced clarity on methods:** drug pricing, inflation, subgroup analyses, and affordability and access alert domains.

Table of Contents

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, analyses of health shortfalls, and potential budget impact analyses. The reference case is defined by the components, methods, and reporting elements to be used in these analyses. ICER's cost-effectiveness 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 for cost-effectiveness and potential budget impact analyses is provided in Table 1, with additional details below. This document also includes a description of absolute and proportional shortfall calculations that are used to inform unmet need as a benefit beyond health during committee deliberations. Details can be found in Section 2: Quantifying Unmet Need (Proportional and Absolute Quality-Adjusted Life Year [QALY] and Equal-Value Life Year [evLY] shortfalls).

Table 1. Overview of ICER's Reference Case Elements

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 the 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 intervention(s) 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 system perspective (default) • Societal perspective as scenario analysis

	○ Estimate net productivity impacts ○ Include all relevant societal impacts to the extent possible ○ Consider including impact on caregiver quality of life when compelling and appropriate data are available ○ Apply the "non-zero" approach to missing data elements for patient and caregiver productivity time • Present health system perspective in tandem with modified societal perspective as "co-base case" when: ○ Impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial, and ○ When not using the "non-zero" approach ○ These costs are large in relation to health care costs ○ Examples include when incremental cost-effectiveness ratio changes by greater than 20% or by greater than $200,000 per evLYG or QALY, and/or when result crosses thresholds of $100,000-$150,000 per evLYG or 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 (evLY gained, undiscounted and discounted) • Other natural outcomes (e.g., hospitalizations avoided), when feasible • Cost per evLY gained • Cost per QALY gained • Cost per life year, if mortality effects • Cost per consequence (e.g., cost per hospitalization avoided), when appropriate and feasible

Element	Specific Details
	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 (health care system 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

Element	Specific Details
	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 Comparative Clinical Effectiveness 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
	  o Generic preference-based measure is recommended; no specific generic preference-based measure is required, but EQ-5D-5L is preferred if available
	  o 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 evLYGs and QALYs, conduct a search for "mapping" studies that allow translation of surrogate outcomes into quality-of-life measures
	  o Discuss validity of mapping studies and translation into evLYGs and QALYs, as well as rationale for choosing
	• If using URD framework, acknowledge and highlight additional uncertainty in translating patient outcomes into evLYG and QALY measures

Resource Use and Costs	• Include all relevant resources and costs based on the health care system perspective
	  o Include costs paid by third-party payers
	  o Note if costs paid out of pocket by patients are included (or cannot be determined if excluded)
	  o Identify any excluded costs, and rationale
	• Describe source of cost data and resource utilization, and the methods for how we seek and evaluate those inputs.
	  o For treatment acquisition costs, the value used in the analysis should consider three factors: 1) whether the treatment is branded or generic; 2) whether the price is known; and 3) whether the treatment is required to be administered by a provider
	• 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
	Converting to Current Year US Dollars
	• Convert all health-related costs to the same year of the model analysis plan in US dollars, using the Personal Consumption Expenditures – Health care services (PCE-H) price index (Table 2.3.4; Line 16) from the Bureau of Economic Analysis (BEA).
	• When current year costs are not available for non-health care costs, convert costs to current-year US dollars, using the Personal Consumption Expenditures – General (PCE) price index (Table 2.3.4; Line 1) from the Bureau of Economic Analysis (BEA). Inflation of non-health care costs is likely to be a rare occurrence but may occur in the context of conducting an analysis from the societal perspective.

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

	○ 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) ○ Concordance 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?) • 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) • Check face validity through extensive conversations within ICER's research team and external 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: ○ 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	• For each intervention and comparator, present the following results in tables: ○ Costs, including treatment costs, other health care costs and total costs (undiscounted and discounted) ○ Treatment costs only to include treatment acquisition costs (not administration or mark-ups) ○ Costs, including treatment 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 evLYG (discounted) ○ Incremental cost per QALY (discounted) ○ Incremental cost per other effectiveness measure ▪ If the analysis finds a major difference between cost per evLYG and cost per QALY, 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 evLYG and per QALY ○ Health benefit price benchmarks (HBPBs) will be reported using standard range from $100,000 to $150,000 per evLYG and QALY ○ 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). ○ Report % achieving $50,000, $100,000, $150,000, and $200,000 per evLYG thresholds, and graph using scatter plots or cost-effectiveness acceptability curves (CEAC) • Conduct scenario analyses ○ Where evidence on distinct subgroups is available, conduct a stratified analysis and present results for each subgroup ○ Conduct analysis 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 ○ Conduct two 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), generally 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 evLYG or QALY o In cases where an intervention that increases evLYGs or QALYs is not found to be cost effective even with a zero-dollar price, a separate scenario analysis excluding non-intervention 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. Subgroup analyses conducted for racial/ ethnic or socioeconomic status alone should not be conducted 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 or placeholder price, and threshold prices to achieve cost effectiveness at $50,000, $100,000, and $150,000 per evLYG) • 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 two 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

	○ 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
Affordability and Access Alert	• Include an affordability and access alert in the final report: 1. When the price in the base-case cost-effectiveness analysis is not a placeholder and that price crosses the potential budget impact threshold in the potential BIM at the optimal utilization 2. When the price in the base-case cost-effectiveness analysis is a placeholder and the threshold price at $150,000 per evLYG gained crosses the potential budget impact threshold in the potential BIM at the optimal utilization When one of these scenarios is not met, an affordability and access alert is not issued and the report explains why an alert was not issued (e.g., potential threshold is not crossed at the level of optimal utilization or price is a placeholder and the price at $150,000 per evLYG doesn't cross the potential threshold at the level of optimal utilization)

BIM: budget impact model, evLY: equal value of life years, evLYG: equal value of life years gained, SST: single and short-term therapies, QALY: quality-adjusted life year, US: United States

Adapted from CADTH Methods and Guidelines, 4th Edition;[1] Neumann et al. CE in Health and Medicine, 2nd Edition. [2]

1. Explanations

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.

Consistent with our consideration of subgroup analysis in ICER's white paper on health equity, when subpopulations are clearly defined *a priori* by clinical characteristics, it is often an important goal to examine relative cost-effectiveness of treatment in these subpopulations. However, analyses focused on subpopulations based solely by race/ethnicity or socioeconomic status are vulnerable to confounding clinical variables, raising the risk of misinterpretation of results.[3] Therefore, in each report we will provide the rationale for why we preformed or avoided cost-effectiveness analyses of subpopulations defined by characteristics other than appropriate clinical markers of risk or outcome.

Data permitting, subgroup analyses of appropriate clinical markers of risk or outcome will be considered for patient groups that could be of interest either clinically or economically. Such subgroup analyses have been and will continue to be undertaken when ICER believes that health technologies are likely to be approved or have been used extensively within these subgroups of interest, and as mentioned earlier, pending data availability.

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 US population likely to be treated with the interventions.

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 conventional base case will take a health care system 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 an analysis using a modified societal perspective, which will include costs and outcomes beyond direct health care impacts. Potential domains to include in this modified societal perspective are listed in an impact inventory in Appendix A (adapted from the Second Panel on Cost-Effectiveness in Health and Medicine.[4] This inventory should be used to document the specific impacts that are and are not included in both the health care system 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 patient and transportation costs related to treatment, productivity for the patient and caregiver, and disutility for the caregiver. Other indirect costs, such as 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.

When direct data are lacking for the impact of an intervention on patient productivity (formal and informal labor, household production, and time seeking care) and caregiver productivity time, an

indirect approach to valuing these domains will be used. To inform estimates for the indirect approach, ICER will use the published relationship between patient utility scores and US-based patient time use data[5] to derive the anticipated impacts of the treatment on time spent in each activity due to the disease and its management for the patient. Since no parallel relationship between patient utility scores and caregiver time use data exists for the US setting, ICER will assume that caregiver time spent is proportional to 75% of patient formal labor time lost. This estimate is based on the modeled relationship between caregiver time required[6] and patient time lost[7] according to patient utility scores in the United Kingdom setting.

In conducting an analysis using the published relationship between patient utility scores and time use, there is an opportunity to continue to capture productivity time lost during periods of non-life extension (which is most consistent with the conventional approach to estimating productivity impacts in cost-effectiveness analysis) while also estimating productivity time gained during periods of life extension. In these circumstances, and in line with the published literature,[5] the analysis will include patient productivity time lost during non-life extension while estimating patient productivity time gained and patient consumption costs during periods of life extension. Patient consumption costs are not applicable during non-life extension time because they are assumed to apply equally to both the intervention and comparator, and thus, are cancelled out in the incremental analysis. The coefficients for each time use activity are reported in Table 2 of Jiao and Basu 2023,[5] and a detailed example of the application of the approach is provided in the supplementary materials of the same publication (Table S1.3). For application in an ICER review, hours per day spent on each time use category can be calculated using review-specific age, utility, and disability status (as a percentage of patients who are experiencing a disability) estimates.

In situations where direct data are available for at least one indirect societal cost domain, the modified societal perspective should be undertaken with the available data. A scenario analysis using the indirect "non-zero" approach may be considered in circumstances where the impact of the treatment on indirect societal costs are expected to be substantial and anticipated to be of interest to stakeholders.

We will use the human capital approach[8] to value all time gained according to the marginal pre-tax wage rate plus fringe benefits[9] for formal and informal labor time and household production ($43.07/hour [$29.71/hour + $13.36/hour]) and the post-tax (13.6%) wage rate plus fringe benefits for time seeking care ($43.07/hour x (1-0.136) = $37.21 [$25.67/hour + $11.54/hour]).[10] Time seeking care is assumed to replace leisure time at the margin. Details are provided in Table 2 below. Patient and caregiver productivity time will be estimated assuming 365.25 days per year, and the same wage rates will be assumed for all patients and informal caregivers regardless of age, sex, and condition. Consumption costs will be calculated in line with the published literature as the annual non-medical consumption per consumer unit divided by the average size of consumer units[5] (2.4) from the US Bureau of Labor Statistics.[11] For 2021, the annual consumption cost is calculated

as $25,615 - i.e., (total average annual expenditures [$66,928] – health care related expenditures [$5,452])/2.4 consumer units).

Table 2. Valuation of Productivity Time for Patient and Caregiver

Patient and Caregiver Productivity Time	**Regression Coefficients (Jiao & Basu 2023)** (rc1, rc2, rc3, rc4, rc5, intercept) *	**Wage Rate**	**Fringe Benefits**	**Tax Rate**	**References and Notes**
Patient Formal Labor Time	Labor coefficients (1.71355, 0.15615, -0.00188, -1.19989, 0.62020, -5.74987)	$29.71**	$13.36	NA	BLS data as of July 18, 2023; March 2023 (Released June 16, 2023)[9]
Patient Informal Labor Time	Caring for non-household members coefficients (-0.20152, 0.03556, -0.00035, -0.03619, 0.04725, -5.10490) and volunteer activity coefficients (2.48602, 0.00250, 0.00010, -0.38779, 0.09061, -6.73669)				
Patient Household Production	Caring for household members or household services coefficients (0.31294, 0.03769, -0.00037, -0.24830, 0.04762, -3.02665)				
Patient Time Seeking Care	Medical care coefficients (-3.19543, -0.01309, 0.00031, 0.07307, 0.42488, -3.64569)	$25.67†	$11.54	13.6%	2020 Federal income tax (accessed July 2023)[10]
Caregiver Productivity Time (Formal Labor)	Proportional to 75% of patient formal labor time lost.	$29.71**	$13.36	NA	BLS data as of July 18, 2023; March 2023 (Released June 16, 2023)[9]

*Applied using the following algorithm as reported in Jiao and Basu 2023[5] (hours spent per day): [exp(rc1 x utility + rc2 x Age + rc3 x Age^2 + rc4 x disability status + rc5 x disability status x utility + intercept)/(1+ exp(rc1 x utility + rc2 x Age + rc3 x Age^2 + rc4 x Disability status + rc5 x disability status x utility + intercept))]x24. This equation is multiplied by 365.25 productivity days/year to get to an annual number of hours spent within each time domain.
**Pre-tax wage rate
†Post-tax wage rate

What follows is a simplified illustration of the implementation of the indirect "non-zero" approach. Let's assume that an intervention improves utility in the population by 0.05 over the course of 20 discounted life years. We will assume that the baseline utility of the population is 0.70 and remains as such for 20 years. There is no difference in survival across the two treatment strategies, the starting age of the population is 60 years, and the disability status is set to 100% of the cohort. If no direct evidence is available on the intervention's impacts on patient productivity time or on caregiver time, then applying the indirect approach would yield $54,900 in cost offsets related to patient productivity time and $20,100 in cost offsets related to caregiver productivity time for the intervention versus the comparator across the 20 discounted life years. Consumption costs would be $0 because there is no difference in survival. If an intervention added one year of discounted survival versus the comparator (assuming the prior conditions remain), there would be $93,700 in

cost offsets related to patient productivity time and $22,000 cost offsets related to caregiver productivity time. These cost offsets would be reduced by $24,300 in consumption costs due to the additional year of discounted survival for the intervention versus comparator arm.

Conditions to be met to consider the modified societal perspective as a co-base case

For all interventions, results from the health care system and modified societal perspectives should be presented together as a "co-base case" when three conditions are satisfied: 1) the impact of treatment on indirect costs is judged to be substantial, 2) direct data are available for the impact of treatment on at least one of the indirect cost domains, and 3) 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 evLYG or QALY, and/or when the result crosses thresholds of $100,000-$150,000 per evLYG or 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, equal value life-years gained (evLYG),[12] and quality-adjusted life-years (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 evLYG and cost per QALY reported as the primary outcomes will be the default choice for ICER's reference case. Analysts should also present results in terms of cost per life year gained and 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).[13] 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., health care system or modified 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 modified 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 health care 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 will be 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.

Analysts 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-5L preference-based 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 evLYGs or 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 evLYGs and QALYs, as well as the rationale for choosing specific mapping algorithms. If an analysis is using the ultra-rare disease (URD) framework, the model report should acknowledge and highlight additional uncertainty in translating patient outcomes into evLYs and QALYs, if relevant.

Resource Use and Costs

The reference case model should include all relevant resources and costs based on the health system 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 treatment acquisition costs, the cost included in the economic evaluation is dependent on three factors, including: 1) whether the treatment is generic or branded; 2) whether the treatment is required to be administered by a provider; and 3) whether the price is known yet.

For generic treatments that do not require provider administration and a price is known, the acquisition price is based on the lowest wholesale acquisition cost (WAC) across all generic versions in the model unless a specific branded or generic formulation is being analyzed, for which the lower price for that specific branded or generic formulation would be used. RED BOOK is the primary source for identifying these acquisition costs. No separate net price is estimated given the generic nature of the treatment. The WAC is used as the acquisition cost throughout all analyses and throughout the report.

For generic treatments that require provider administration, and a price is known, the acquisition price is based on the price from the average sales price (ASP) drug pricing file that is updated quarterly. The price from this file is inclusive of the ASP and the associated mark-up. When modeling the price, remove the mark-up (typically calculated as the ASP+6%) and program the mark-up in a separate input. Then the model will track a drug price that is reflective of the ASP in one input and a separate input that is reflective of the mark-up. The two inputs when summed, equate to the value found in the ASP Drug Pricing File. For biosimilars, the mark-up is calculated at 6% of the original biologic and thus the price of the original biologic should be used when estimating the amount of the relative mark-up. No separate net price is estimated given the generic nature of the treatment. The ASP is used as the acquisition cost throughout all analyses and throughout the report. The treatment prices used throughout the report (e.g., unit cost, annual cost, lifetime treatment costs in the results, undiscounted treatment costs used in BIM, price on which percent discounts to reach health benefit price benchmarks [HBPBs] are needed) should not be inclusive of the mark-up. A footnote should be added to tables and clarifying text should be added to the report to clearly detail that the total costs include the mark-up but when the treatment cost is presented it is specific to the acquisition cost alone.

For branded treatments that do not require provider administration and a price is known, the treatment acquisition list price should be equivalent to the average WAC across all applicable formulations. RED BOOK is the primary source for identifying these acquisition costs. A separate treatment acquisition net price should also be estimated. To calculate the net price:

(1) Apply the average discount (over four quarters; obtained from SSR Health, LLC) to the list price to calculate the net price, or
(2) If SSR Health net prices are not available or not considered reliable, review the Federal Supply Schedule (FSS) and calculate a discount of the FSS price from the WAC price, or
(3) If neither SSR Health nor FSS have the treatment in their data, ask the manufacturer to provide the average discount or net price; if the discount or net price provided is a range, use the conservative end of the range, or

(4) If neither SSR Health nor the FSS have the treatment in their data, and the manufacturer does not provide a discount or net price, review SSR Health for a net price for treatments in the same class or treatments that are considered analogs, or
(5) If no estimate from manufacturers and no treatments in the same class or treatments are considered analogs, use the average discount for brand drugs from IMS cost trends reports.

In the report, use the net price in the conventional base-case and sensitivity analyses. Use the list price when calculating the percent discount needed to reach each HBPB. Provide BIM inputs separately for the list and net price, as well as the three thresholds.

For branded treatments that require provider administration, estimate the acquisition price by retrieving the price from the ASP drug pricing file. This price is inclusive of the ASP and the associated mark-up. When modeling the price, remove the mark-up (typically calculated as the ASP+6%) and program the mark-up in a separate input. Then the model will track a drug price that is reflective of the ASP in one input and a separate input that is reflective of the mark-up. The two inputs when summed, equate to the value found in the ASP Drug Pricing File. The ASP is used as the acquisition cost throughout all analyses and throughout the report and a separate net price is not identified for treatments that require provider administration. The treatment prices used throughout the report (e.g., unit cost, annual cost, lifetime treatment costs in the results, undiscounted treatment costs used in BIM, price on which percent discounts to reach HBPBs are needed) should not be inclusive of the mark-up. A footnote should be added to tables and clarifying text should be added to the report to clearly detail that the total costs include the mark-up but when the treatment cost is presented it is specific to the acquisition cost.

For branded treatments that do not require provider administration but do not have a price that is publicly available:

1) Ask the manufacturer to provide the expected price;
2) If they do not, search for investor analysts' opinions or earnings calls transcripts on launch price;
3) If still not available and there are other similar drugs in the class, calculate the average net price across these drugs (using net pricing steps described in the section for branded treatments with a price available that do not require provider administration) and use that average as the placeholder price for the treatment;
4) If no analysts' price and no similar drugs in the class, calculate prices to reach thresholds of $50,000/evLYG, $100,000/evLYG, $150,000/evLYG, and $200,000/evLYG.

If selecting option 4, use the price to achieve $100,000 per evLYG in all sensitivity and scenario analyses. Regardless of specific approach, the price selected will be a placeholder price and should be identified as such throughout the review with clarifying text and footnotes to respective result displays. The placeholder price is assumed to be inclusive of any discount and thus no separate net price is identified. The placeholder price is used in the conventional base-case and sensitivity

analyses. If using a placeholder, HBPBs will still be calculated, but the percent discount needed to reach each HBPB will not be calculated. Provide BIM inputs for the placeholder price.

For branded treatments that do require provider administration but do not have a price that is publicly available, follow the steps under the section for branded treatments without a price available that do not require provider administration but then add a 6% mark-up. Program the mark-up in a separate input in the inputs tab. Then the model will track a placeholder price in one input and a separate input that is reflective of the mark-up. The placeholder price estimated is assumed to be inclusive of any discount. No separate net price will be identified. The placeholder price is used in the conventional base-case and sensitivity analyses. If using a placeholder, HBPBs will still be calculated, but the percent discount needed to reach each HBPB will not be calculated. Provide BIM inputs for the placeholder price. The treatment prices used throughout the report (e.g., unit cost, annual cost, lifetime treatment costs in the results, undiscounted treatment costs used in BIM, price on which percent discounts to reach HBPBs are needed) should not be inclusive of the mark-up. A footnote should be added to tables and clarifying text should be added to the report to clearly detail that the total costs include the mark-up but when the treatment cost is presented it is specific to the acquisition cost.

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.

Converting to Current Year US Dollars

All costs should be converted to current-year US dollars, using foreign exchange rates.[14]

Convert all health-related costs to the same year of the model analysis plan in US dollars, using the Personal Consumption Expenditures – Health care services (PCE-H) price index (Table 2.3.4) from the Bureau of Economic Analysis (BEA).

To convert costs to current-year dollars, identify a price index for the starting year and then ending (or current) year. For the starting year, click modify in the top, right corner of the webpage for Table 2.3.4 and select "Annual" for your starting year. The starting year reflects what year the cost data are in the source identified. Scroll down to row 16 of the table for health care services to obtain the price index for that year. Similarly, to select the price index for the ending year, scroll down to row 16 of the table for health care services to obtain the price index for the most recent year that data are available. The end year reflects the present value (or as near as possible). Divide the price index from the ending year by the price index for the starting year. That value will be what you multiply by the cost input from the source to inflate the cost input to present value.

Example: At the time the model analysis plan is published, there is a source from 2008 for the cost ($2,000) of managing post-surgical complications in the US that aligns with the population of interest. To convert this value to current year, for example, January 3, 2022, US dollars, use the most recent annual price index available (which in this case was a 2020 price index). The cost estimates would be inflated to 2020 US Dollars as follows:

$$= \$2{,}000 \text{ x } \left(\frac{\text{Annual Price index for 2020}}{\text{Annual Price index for 2008}}\right)$$

$$= \$2{,}000 \text{ x } \left(\frac{112.513}{91.606}\right)$$

$$= \$2{,}456.45$$

When current year costs are not available for non-health care costs, convert costs to current-year US dollars, using the Personal Consumption Expenditures – General (PCE) price index (Table 2.3.4; Line 1) from the BEA. The same methods that were used for health care costs apply. Inflation of non-health care costs is likely to be a rare occurrence but may occur in the context of conducting an analysis from the modified societal perspective. Please see Appendix B for an illustrative summary of guidance for converting to current year US dollars.

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. [4]

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 model validation (e.g., model debugging, checking extreme scenarios) is conducted. 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 experts. In addition, ICER reviews 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, evLYGs, 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 life-year, 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, one-way sensitivity analyses should be conducted, and results should be presented 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 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, analysts should conduct a stratified analysis and present results for each

subgroup. In line with ICER's white paper on health equity, analyses focused on subpopulations based solely by race/ethnicity or socioeconomic status alone should not be conducted. 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.

Economic evaluations will include two analyses 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 may include threshold-based price analyses based on the following:

- 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 evLYG and QALY.

In cases where an intervention that increases evLYs and/or QALYs is not found to be cost effective, even with a zero-dollar price, a separate scenario analysis excluding non-intervention health care costs will be presented. By non-intervention health care costs, ICER means all costs except those directly tied to administering the intervention or other modeled treatment options (i.e., comparator costs). 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 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 annual, non-cumulative net or placeholder (usually equal to net of another agent or average or weighted average of a therapeutic class) interventional cost per patient, non-interventional 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 (e.g., market share data) to estimate the size of the potential candidate population for each new treatment. For generally prevalent models, the model will assume that an equal proportion of prevalent patients (20%) would be treated with the new treatment each year over five years, arriving at a cumulative 100% uptake at five years; for generally incident models, the model will assume that one incident cohort would be treated in each of the five years, for a total of five incident cohorts treated over the potential budget impact analysis time horizon. When analyzing the budget impact of multiple new interventions, the eligible patient population is split equally across all new interventions. See the *Methods* section below for additional information on allocation of eligible patients.

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 (with regard to time horizon) net or placeholder 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.

Perspective

Potential budget impact analysis takes the health system perspective and thus includes all direct medical health care expenditures covered and reimbursed by third-party payers or others furnishing care (e.g., integrated health care delivery networks). Patient out-of-pocket costs should not be removed as part of the base-case analysis, and similarly, should not be removed from the cost-effectiveness annual cost outputs that feed into the budget impact model. Should stakeholders take interest in removing patient cost share from estimates of the payer's budget impact, they can do so via the ICER Analytics Interactive Modeler platform. If a modified societal co-base case is included in the cost-effectiveness analysis, these costs should not be included in ICER Reports as they represent costs exterior to the health care sector or health system perspective.

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 placeholder or actual net price, and if available, list price, and the three threshold prices to achieve cost effectiveness at $50,000, $100,000, and $150,000 per evLYG. 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.

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 standard care), we will calculate potential budget impact for 100% of the eligible population at the end of five years (20% incremental new uptake per year).
- Existing treatments launched within prior two 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 all 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 all existing treatments. Initial market shares for existing treatments must be applied.
    - 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.
- Mix of existing treatments launched within two years and >2 years:
    - See "*existing treatments launched within prior two years"* bullet above
- 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 average annual per-patient potential budget impact data presented in tabular format in an appendix of the report.

Potential Budget Impact Threshold

The goal of ICER's potential budget impact analysis is to estimate the net budget impact 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 policymakers 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 five 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 potential budget impact 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 here.

Affordability and Access Alert

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. The potential budget impact analysis section of each final report will include an affordability and access alert if 1) the intervention price is not a placeholder price and the potential budget impact analysis findings at that price cross the potential budget impact threshold at the level of optimal clinical utilization or 2) the intervention price is a placeholder price but the potential budget impact analysis findings at the threshold price that achieve a $150,000 per evLY incremental cost-effectiveness ratio cross the potential budget impact threshold at the level of optimal clinical utilization. When one of these two scenarios is not met, an affordability and access alert is not issued, and the report explains why the alert was not issued.

2. Quantifying Unmet Need (QALY and evLY Shortfalls)

As stated in ICER's Value Assessment Framework, giving priority to treatments according to "lifetime burden of illness" or "need" best represents the ethical instincts of a society or other decision-makers.[15,16] To inform unmet need as a benefit beyond health, ICER provides empirical results for the absolute shortfall and proportional shortfall. Shortfalls are commonly measured using the QALY but can also be measured using the evLY (or evLYG). As described in ICER's Value Assessment Framework, concerns regarding the valuation of life extension by the QALY lead ICER to emphasize the evLYG as the metric in health benefit price benchmarks and other elements of determining the overall value of treatments. For shortfall considerations, ICER will emphasize the results of shortfalls based on the evLYG but will retain information on QALY results for benchmarking with academic and international efforts.

The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[17] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall.

The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[18,19] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment.

To calculate the absolute QALY shortfall for a condition, subtract the lifetime undiscounted quality-adjusted life expectancy for the current standard of care for that condition from the lifetime undiscounted quality-adjusted life expectancy for the general population (calculated using age- and sex-adjusted estimates for mortality and age-adjusted estimates for quality of life). The quality-adjusted life expectancy for the general population is calculated using the same baseline age and sex distribution as what was modeled for the condition's standard of care. To calculate the proportional QALY shortfall for each condition, divide the absolute QALY shortfall by the quality-adjusted life expectancy for the general population with the same age and sex distribution at baseline.

The calculations for the absolute evLY shortfall and proportional evLY shortfall are equivalent to the calculations for the QALY shortfalls except the quality-adjusted component of the life expectancy calculation does not vary by age, but is rather fixed at 0.851 for all ages. Therefore, to calculate the absolute evLY shortfall for each condition, subtract the lifetime undiscounted equal-value life expectancy for the current standard of care for that condition from the lifetime undiscounted equal-value life expectancy for the general population (calculated using age- and sex-adjusted estimates for mortality and a constant 0.851 for quality of life). The life expectancy for the general population is calculated using the same baseline age and sex distribution as the condition's standard of care. To calculate the proportional evLY shortfall for each condition, divide the absolute evLY shortfall by the equal-value (using a constant 0.851 for all ages) life expectancy for the general population with the same age and sex distribution at baseline.

For each ICER assessment the shortfall estimates will be displayed and compared to a league table of past ICER assessment shortfalls. Table 3 shows the absolute and proportional QALY and evLY shortfalls for conditions assessed in prior ICER reviews.

Table 3. Absolute and Proportional QALY and evLY Shortfalls for Conditions Assessed in Prior ICER Reviews

Condition	Absolute QALY Shortfall	Absolute evLY Shortfall	Proportional QALY Shortfall	Proportional evLY Shortfall
Amyotrophic Lateral Sclerosis	18.60	19.42	95.2%	95.4%
Alzheimer's Disease	8.82	9.37	70.1%	71.3%
Chronic Kidney Disease	17.15	18.08	77.8%	78.7%
Atopic Dermatitis	8.64	9.92	25.1%	27.7%
Beta Thalassemia	25.04	25.53	52.0%	52.5%
Bladder Cancer	6.08	6.58	55.6%	57.5%
Cardiovascular Disease	2.87	3.52	18.2%	21.4%
COVID-19 Outpatient	1.01	2.12	3.8%	7.7%
COVID-19 Inpatient	1.82	2.65	9.2%	12.9%
Depression	8.42	9.65	29.1%	32.0%
Diffuse Large B-Cell Lymphoma	16.11	16.93	82.2%	82.9%
Duchenne Muscular Dystrophy	52.68	51.93	85.8%	85.6%

Hemophilia	10.78	10.92	21.7%	21.9%
Hereditary Angioedema	1.75	3.01	5.3%	8.8%
High Cholesterol	1.08	1.70	7.2%	10.9%
Hypertrophic Cardiomyopathy	0.00	0.00	0%	0%
Lupus Nephritis	20.73	22.10	54.2%	55.8%
Menopause	0.00	0.00	0%	0%
Multiple Myeloma	17.91	18.69	95.6%	95.7%
Relapsing Remitting Multiple Sclerosis	17.54	18.86	49.9%	51.7%
Secondary Progressive Multiple Sclerosis	24.28	25.44	89.0%	89.4%
Nonalcoholic Steatohepatitis	8.92	9.87	40.1%	42.5%
Obesity	3.22	4.50	10.7%	14.3%
Osteoporosis	2.01	2.61	15.0%	18.7%
Pediatric B-Cell Acute Lymphoblastic Leukemia	54.20	53.94	93.9%	93.9%
Peanut Allergy	0.00	0.00	0%	0%
Prostate Cancer	3.11	3.57	32.5%	35.6%
Retinal Disease	22.35	21.56	34.1%	33.3%
Severe Asthma	3.15	4.19	12.8%	16.4%
Spinal Muscular Atrophy	55.75	54.75	82.0%	81.7%
Tardive Dyskinesia	10.31	11.61	29.7%	32.3%
Ulcerative Colitis	5.31	6.57	16.2%	19.3%

evLY: equal-value life year, QALY: quality-adjusted life year

References

1. Guidelines for the economic evaluation of health technologies: Canada. In: 4th ed. Ottawa: CADTH; 2017: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.
2. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. *Cost-effectiveness in health and medicine.* New York: Oxford University Press; 2016.
3. ICER. Advancing Health Technology Assessment Methods that Support Health Equity. In:2023.
4. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
5. Jiao B, Basu A. Associating Health-Related Quality-of-Life Score with Time Uses to Inform Productivity Measures in Cost-Effectiveness Analysis. *PharmacoEconomics.* 2023:1-13.
6. Rowen D, Dixon S, Hernández-Alava M, Mukuria C. Estimating informal care inputs associated with EQ-5D for use in economic evaluation. *The European Journal of Health Economics.* 2016;17:733-744.
7. Mukuria C, Rowen D, Hernández-Alava M, Dixon S, Ara R. Predicting productivity losses from health-related quality of life using patient data. *Applied Health Economics and Health Policy.* 2017;15:597-614.
8. Basu A. *Estimating costs and valuations of non-health benefits in cost-effectiveness analysis.* Vol 2017: Oxford University Press New York; 2016.
9. Employer Costs for Employee Compensation - December 2022 [press release]. March 17, 2023 2023.
10. York E. Summary of the Latest Federal Income Tax Data, 2023 Update. *Tax Foundation.* 2023. https://taxfoundation.org/publications/latest-federal-income-tax-data/. Accessed May 2023.
11. U.S. Bureau of Labour Statistics. Consumer Expenditures in 2021. https://www.bls.gov/opub/reports/consumer-expenditures/2021/home.htm. Published 2023. Accessed.
12. Campbell JD, Whittington MD, Pearson SD. An Alternative Measure of Health for Value Assessment: The Equal Value Life-Year. *Pharmacoeconomics.* 2023.
13. Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value Health.* 2012;15(6):812-820.
14. Internal Revenue Service. Yearly Average Currency Exchange Rates.
15. Reckers-Droog VT, van Exel NJA, Brouwer WBF. Looking back and moving forward: On the application of proportional shortfall in healthcare priority setting in the Netherlands. *Health Policy.* 2018;122(6):621-629.
16. Versteegh MM, Ramos IC, Buyukkaramikli NC, Ansaripour A, Reckers-Droog VT, Brouwer WBF. Severity-Adjusted Probability of Being Cost Effective. *Pharmacoeconomics.* 2019;37(9):1155-1163.
17. Ottersen T, Førde R, Kakad M, et al. A new proposal for priority setting in Norway: Open and fair. *Health Policy.* 2016;120(3):246-251.
18. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *Pharmacoeconomics.* 2004;22(17):1097-1107.

19. van de Wetering EJ, Stolk EA, van Exel NJ, Brouwer WB. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *Eur J Health Econ.* 2013;14(1):107-115.

Appendix A. Impact Inventory (adapted from Neumann, Sanders et al.[4]

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 health care sector, while other interventions may have substantial impacts beyond the formal health care 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

Appendix B. Converting to Current Year US Dollars