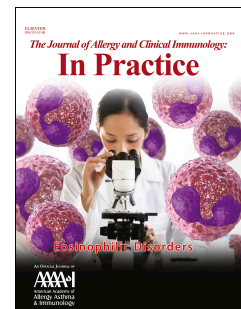


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Review: A Practical Guide to Understanding Cost-Effectiveness Analyses

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Review: A Practical Guide to Understanding Cost-Effectiveness Analyses

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Abbreviations: incremental cost-effectiveness ratio (ICER), Consolidated Health Economic Evaluation Reporting Standards (CHEER), quality adjusted life year (QALY), willingness to pay (WTP), National Institute for Health and Care Excellence (NICE), net monetary benefit (NMB)

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MG: is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Sanofi/Regeneron, Genentech, Nutricia, Novartis, Acquestive, Allergy Therapeutics, Pfizer, US World Meds, Allergenics, Aravax, and Prota, all unrelated to vaccines/vaccine development; is a member of the scientific advisory council for the National Peanut Board; is an associate editor for the Annals of Allergy, Asthma, and Immunology, and is member of the Joint Taskforce on Allergy Practice Parameters. He has received honorarium for lectures from ImSci and MedLearningGroup. **JO:** Research/Adjudication: AstraZeneca (unrelated to vaccines/vaccine development), GSK, Sanofi, Novartis; Consultant: GSK, AstraZeneca (unrelated to vaccines/vaccine development), Sanofi; Associate Editor: Annals of Allergy Asthma Immunology, AllergyWatch; Section Editor: Current Opinion of Allergy; Royalties: Up to Date; Board Liaison American Board of Internal Medicine for the American Board of Allergy and Immunology. **CC.** No conflicts to declare.

Unstructured Abstract:

Cost-effectiveness analysis is a way to understand the value of a healthcare intervention, in terms of assessing the money spent to produce beneficial outcomes. Cost-effectiveness analyses are used by various stakeholders for such purposes, given healthcare resources and financing may be scarce, depending on the economy, and certain interventions may be very costly to produce such outcomes, compared to other options. These analyses are built upon well-researched and robust inputs for costs and outcomes, and may be modeled using a technique called markov chain models, which allow transitions among the various health states (e.g., alive, dead, outgrow allergy, allergy relapses, etc.) relative to the condition of interest to reflect a base-case scenario, then the margins of the inputs explored for sensitivity analysis of the potential findings. These analyses should be investigated from multiple perspectives (e.g., society, healthcare payer, etc.). Limitations of the analysis should be very clearly stated. While such models are an informative way to explore a situation and can be performed without additional direct patient intervention, a weakness of the approach is that this may overlook individual patient nuances. Cost-effectiveness analyses are important policy tools to show, on average, an optimal way to improve value in population health.

Introduction:

Clinicians are faced with a multitude of choices in managing our patients' allergic conditions. Our field has rapidly advanced the understanding of the immune response, which has led to an evolution of choices we have with which to treat allergic diseases. As is common in any industry, while there are choices, these choices come with differing costs, differing outcomes/effectiveness, and based on these two attributes, different value. The unfortunate reality of most healthcare systems is that a third party beside patient and clinician often makes the decision of what therapies we can offer our patients, based on a determination of which hold greater or lesser perceived value.¹ Most of us can relate to the frustration of what the end result of that valuation may be when the therapy we want to offer our patient is denied. However, the best way to advocate for our patients is to understand how these valuation models are built, so that we have insight into how clinical outcomes and cost influence these decisions.^{2,3} This primer on understanding cost-effectiveness analyses aims to use a case-based narrative to give the clinician a practical understanding of this tool, so that the we as clinicians can better advocate for our patients. A glossary of highlighted terms is included in Table 1 for reference.

Case Presentation

You are evaluating a patient in your office for their asthma, which has previously been well-controlled, but in the past year, has become more difficult to control. Two years ago, the patient had previously presented to the emergency department at least 3 times in 6 months, requiring oral steroids on each of these occasions, including an admission to the ICU for status asthmaticus. These acute issues developed despite previously being stable for at least 6 months on a high-dose inhaled corticosteroid regimen combined with a long-acting beta-agonist. After discussion of the options, risks, and benefits, you and the patient mutually decided to try a biologic agent as the next step, which was supported by current asthma guidelines. The agent you choose must be pre-authorized by the patient's insurance plan. For the past 18 months, the patient has been well-controlled on your choice of biologic. Last week, this patient informed you that their insurance sent a notice to them, mandating they change to a different biologic that the insurer has deemed more cost-effective than the agent currently being used.

What is a Cost-effectiveness Analysis?

Cost-effectiveness analysis is a valuation model which compares the health outcomes (e.g. medical outcomes, both good and bad) and economic outcomes (e.g., costs) associated with one therapy against those associated with one or multiple other therapies. The health outcomes are referred to as effectiveness, and account for the net sum of any beneficial and detrimental outcome of the therapy. Costs represent the monetary worth of the service and/or outcome in question.^{4,5} These analyses are always conducted over a pre-specified time horizon. These models typically have a few common parts: a) The therapies being compared and the base-case scenario; b) the economy in which the comparison is being made (e.g., US, UK, etc.); c) the **perspective(s)** under which the model is evaluated (e.g. the payer or society); d) the time horizon; e) the evaluation cycle length; f) the decision model comparing strategies and consequences; g) the table of inputs for the decisions and outcomes, h) an output table of the costs/effectiveness and cost-effectiveness ratio; and i) multiple sensitivity analyses to show the effect of changes in a particular input.^{2,3,6} A guideline for how cost-effectiveness analyses

should be performed and reported have been established by a task force from the Professional Society for Health Economics and Outcomes Research, titled the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.⁷ This reporting checklist helps ensure standardization and quality of such analyses, though some have advocated that it is more of a “reference than a rule book”.⁸

How Do We Define Effectiveness?

Cost-effectiveness can be measured in several ways, but in health economic evaluations is most commonly measured as a cost per unit of a measure that assesses the value of both the quantity and quality of life relative to a disease, referred to as a **quality adjusted life year (QALY)**.⁹ The concept of a QALY is based on the realization that not all years of life are lived and valued equally, where patients generally prefer (and place more value upon) healthy years of life compared to sick ones. A QALY represents a perfect year of health relative to the patient’s disease state and is measured as a fraction or percentage, with the value of the year of life falling somewhere between 1 (representing a perfect year of health) and 0 (which represents death). A QALY of 1 means that the individual lived the year with “full value” for that year. QALYs are determined through indices which directly elicit health state utility, a metric that quantifies preference for a particular health state under a condition of risk (e.g., the disease of interest).⁹ **Health state utility** is calculated through exercises that determine how much time someone would trade (or how much risk they would gamble) to gain a perfect year of health with their condition, or through a set of questions that can determine how well someone is functioning in terms of mental and physical health relative to others unaffected by disease (Figure 1).¹⁰ The value of health state utilities has been shown to be stable over time, when sampled in appropriate representative populations for the given disease state, but the one limitation of health state utilities is that these have not been measured for every disease. Published reference standards for the health state utilities of various diseases (by age, sex, and region of the world) are available.¹¹⁻¹⁴ Health state utility is a commonly measured secondary outcome in studies, as it can directly translate into gain/loss from an intervention which can be assessed as an overall health benefit.

How Do We Define Cost-Effectiveness:

Cost-effectiveness is formulated by determining the net costs of the therapy divided by the net benefits of the therapy. However, this is usually expressed as a comparison between two therapies as follows:

$$(\text{Cost of therapy A} - \text{Cost of therapy B}) / (\text{Effectiveness of therapy A} - \text{Effectiveness of therapy B})$$

This calculation produces an **incremental cost-effectiveness ratio (ICER)** of cost per unit of effectiveness in comparing one therapy to another, representing the cost to gain a single year of healthy life (e.g., QALY) relative to the particular disease. Therapies with lower costs producing more QALY, relative to a comparator, are considered more cost-effective. A therapy is considered dominant when, relative to the other option(s), it has both the lowest cost and the largest QALY gain. Conversely, a therapy is considered dominated when it has the highest cost and lowest QALY gain. Analyses with a **dominant or dominated** therapy are reported as such, usually without an actual ratio. However, sometimes the more expensive therapy has the higher QALY gain, or the cheaper therapy has a lower QALY gain. In these situations, no therapy is

dominant or dominated, and the analysis is reported as an incremental cost-effectiveness ratio (ICER).^{2,4,5,15} (Figure 2)

The cost-effectiveness ratio has a far more nuanced interpretation to determine cost-effectiveness. Each economy (e.g. society, region, country, etc.), health authority or government may have their own pre-determined threshold for what costs per QALY will be considered cost-effective and these may vary considerably. For example, in the US, while there is no national standard, most consider an ICER of \$50,000-\$150,000 as cost-effective (based on 1970's end stage renal failure data).¹⁶ Elsewhere, in nationalized single-payer systems such as the UK, regulatory agencies such as the National Institute for Health and Care Excellence (NICE) has very firm standards that range between 30,000 to 50,000 pounds (\$41,000 to \$68,700) per QALY. Thresholds must adjust for inflation within any economy.^{17,18} An alternative way beyond a fixed-ceiling approach would be to determine a societal **willingness to pay (WTP)** that accommodates societal healthcare spending and the specific interests of a society or population of interest for a particular therapy. WTP could also be defined as the maximal amount someone would pay, out of pocket, for a therapy

After discussion with the insurance company, you learn that the biologic agent you wish to continue has an annual cost nearly \$25,000 greater than the one required by the patient's insurance carrier, but is associated with better QALY gains. However, you determine that the insurance company has only considered their costs, and not the indirect costs to the patient and society in their valuation model.

How To Use A Decision Model to Determine Cost-Effectiveness

The most common method for creating cost-effectiveness models uses **Markov-chain models** to allow for transitions between different potential health states, which allows for evaluation of a disease under various conditions of recurrence, exacerbation, control, and remission.¹⁵ It is this transition that allows the model to more closely approximate real-life, where over the course of treating a patient, you may see them move through these various states. Transitions may occur after each cycle (typically a year, but this can be other intervals) along a simulated time horizon. A state transition diagram must be configured, establishing the potential health states and transition probabilities between each realized health state condition.^{3,15,19} These probabilities generally include (but may not be limited to) being alive with disease, getting ill from disease, dying from disease, dying from natural or other causes, or having the disease resolve. With the exception of death, the model allows for someone to contextually transition in and out of various health states over the time horizon being investigated. This allows for inclusion of events both related and unrelated to the disease under evaluation, which may affect health status and may result in potential fatality. An example of a state-transition diagram is provided in Figure 2. Once the state transitions are established, a decision-tree evaluating the potential strategies and outcomes associated with each strategy (direct and indirect) must be developed, and probabilities and costs for real-life modeled events on each branch must be specified. Generally, these key inputs are described in a "table 1", which includes the specific probability (and confidence interval) around each individual outcome (or cost), a discount (e.g. inflation) rate, and associated health utility/disutility descriptions for each health state.^{3,15} Depending on the perspective of the analysis, indirect costs and outcomes are included that provide a comprehensive picture regarding the condition's direct and indirect effect on life in modeled disease states. To help

inform these probabilities, robust sources for inputs, such as a meta-analysis or other systematic review, clinical trial, or governmental source are preferred.²⁰⁻²⁵ Certain inputs may have to be estimated if published sources are not available. Inputs can have directly presumed confidence intervals to allow for uncertainty, or uncertainty can be derived through use of a probability distribution. Wide confidence intervals are preferred and can be pooled from multiple existing sources for the estimate.

Once the probabilities and distributions are established, these can be programmed into each step of the branching decision model, and the tree analyzed by cycle over a time horizon, according to a set of pre-determined assumptions that represent a “base-case” of assumptions for a scenario. Computer programs such as Microsoft excel (Redmond, WA), or specialized dedicated decision tree software (e.g., TreeAge, Williamstown, MA) can be programed to summate the probabilities, outcomes and costs. The decision tree can be modeled in two ways—as a microsimulation which may use distributed probabilities or point estimates, or as a theoretical patient cohort following the probabilities. One commonly used method is a Monte Carlo simulation, which may use a distribution around an event probability in a virtual randomized trial to determine the most probable outcome (and confidence interval). Often both the cohort and simulation approaches are used to produce more robust estimates.^{7,15} In our hypothetical case, the base-case would be a patient with severe asthma and a history of a recent ICU admission (acknowledging comorbidities) who has been well-maintained on an asthma biologic in addition to high dose combination inhaled corticosteroids/long-acting beta agonist therapy, being changed to a different biologic.

You ask the insurer for some more information about how the cost determination was made, and you are told that the two agents in question were compared from a payer perspective, and based on a recently published meta-analysis of clinical trial outcomes. You read the study, and note that some outcomes were narrowly defined, as well as may be sensitive to certain subgroup assumptions which are likely not applicable to your patient’s phenotype, and appreciate that a more critical view of cost-effectiveness in this circumstance could result in different outcomes and conclusions.

Finding Good Model Inputs and Appropriate Perspectives

George Box has famously stated that “all models are wrong...some are useful.”¹⁵ This emphasizes that models only approximate reality, and a model is only as good as its assumptions and inputs. Moreover, differing models for the same scenario can exist even leading to different conclusions.^{26,27} Assumptions and inputs must be defensible, and the degree to which others accept the findings depend on this. This is why stringent literature searches on the outcomes of interest that will provide the most objective and comprehensive point estimates is recommended. Where possible, if there are several studies for an estimate, these can help inform the presumed confidence interval around the estimate. Costs can generally be obtained online from medical databases, such as Medicare costs and reimbursements or other claims data from commercial sources.²³⁻²⁵ Governmental databases have published values for life expectancy, inflation rates, cost of living, and rates all-cause mortality, for example.²⁰⁻²² These rates may vary between economies if doing an international comparison.

Understanding the model perspective is also something to consider. Robust analyses should consider multiple perspectives. It is common to model from the payer perspective, where only direct cost associated with healthcare expenditures are considered. However, this is somewhat narrow, and does not account for the costs of illness as someone living with disease will also have an effect on society. This can be captured by assessing indirect costs (e.g., opportunity cost lost by the condition, costs of childcare, cost of alternative diets, cost of non-disease related expenditures, etc.).²⁸ Thus, one can see that it is possible for something to be cost-effective in one perspective but not in another. The CHEERS guidance recommends that when possible, multiple perspectives should be analyzed and reported for a question.⁷ These criteria were formulated by expert consensus to help improve the quality and comparability of cost-effectiveness analyses, as a comprehensive “checklist” to help standardize how such analyses are reported.⁷

How To Report Cost-Effectiveness

Once the model inputs for each strategy being evaluated are calculated, simulation will result in a reporting of total costs and effectiveness measure for each strategy specified (with 95% confidence intervals), and for each perspective analyzed. These are generally shown in tabular form showing the cost, the benefit, and the ICER for each strategy under each perspective.^{3,6,15} Additional outcomes (e.g., asthma exacerbations, hospitalizations, asthma associated fatalities) can also be evaluated in microsimulation. Costs are straightforward estimates to comprehend. Higher costs are less preferred than lower costs, given there is a finite amount of financial resources. No one wants to spend more money on a strategy to gain a particular benefit when that same benefit could be achieved for less. Understanding gains and losses in QALY is a bit more esoteric, but gains in QALY are beneficial, as they represent an association with increasing the number of years of better health relative to the condition of interest, which helps quantify the value of the therapy. Loss of QALY therefore represents a health detriment. Achieving a low cost per QALY defines better cost-effectiveness, but the degree to which this is appreciated is dependent on the threshold of the system under which the therapy is evaluated. While for health-utility analyses the QALY (gained/lost) is the main outcome measure, additional measures are available.^{3,6,15}

Cost-effectiveness can also be reported as a net benefit that incorporated both costs and QALY in the same metric. One such measure is the **net monetary benefit (NMB)**, in which QALY are converted to dollars at a WTP threshold. This is useful when a cost per QALY becomes difficult to conceptualize (or display) as a ratio. The net monetary benefit is a composite singular measure for both cost and effectiveness, and is derived by using the cost-effectiveness limit (i.e., WTP threshold) for the scenario. The NMB converts the QALY unit to the monetary unit of analysis at this threshold (e.g. 1 QALY=\$150,000 US) and subtracts the cost of the strategy from the total converted QALY worth. The formula is as follows: (incremental benefit x threshold)-incremental cost. Using NMB, the difference of two strategies can be calculated. A cost-effective strategy would always be associated with a positive incremental NMB.^{3,29}

You schedule a peer-to-peer call with the medical director of the patient’s plan to share your concerns with the switch. You are worried that their model did not account for lost productivity from your patient being frequently ill, that the study used to show better outcomes with the new biologic did not account for a critical interaction, and that you think the effectiveness of the

payer's preferred biologic may be overestimated because a single variable change may result in worse patient outcomes, which was not accounted for. You advocate for your patient in suggesting that the model (and policy) be re-evaluated.

How Are Models Explored for Sensitivity of the Assumptions?

There are very few instances when the inputs for a model can be very definitively specified. More often, it is of greater importance to see the ranges over which something could be cost-effective, and how small changes could alter results, than to show an “exact” estimate. This can be achieved through exploring the base-case analysis, using robust and wide ranges around any single assumption, data driven when possible and defensible as plausible when published sources are not available. Thus, **sensitivity analysis** allows for the model to be re-analyzed after making select changes to variables, to see how varying assumptions can change outcomes.^{7,15} There are two types of sensitivity analyses available: deterministic and probabilistic sensitivity.^{15,30} Deterministic sensitivity is a way to look at the influence of a fixed range of change for a single variable at a time. Here, the high and low estimate range of an input are entered into the model, to see if the direction of the change above or below the base case moves the result toward or away from the cost-effectiveness threshold. The result of multiple single-variable sensitivity analyses is often displayed as horizontal bars in a “**tornado diagram**”, stacked with the variable with the biggest degree of change on top, with the bars color coded for ranges above or below the base case to show if the shift in that parameter meets the cost-effectiveness threshold. Because the widest bars are at the top and the smallest ones at the bottom the appearance resembles a “funnel cloud”.(figure 3a).³¹ A graphical plot is another way to represent **deterministic sensitivity analysis**, with the intersection showing the threshold below which the analysis is cost-effective. (Figure 3b) The other type of sensitivity analysis is a probabilistic sensitivity analysis.³¹ These account for multiple simultaneous and stochastic changes in variables, and involve using a specific distribution to better simulate the output ranges. Probabilistic sensitivity analysis uses microsimulation to explore variable interactions, using distributions of the cost and probability inputs to show a range of benefits and costs, including multivariate interactions that may cause a strategy to be more (or less) cost-effective. These can be represented in multiple ways – two common examples are a simple scatter plot and a cost-effectiveness acceptability curve (Figure 3c and 3d).^{15,30, 31,32}

Knowledge Translation and the Limits of Cost-Effectiveness Data

Models are a fantastic way to explore a situation, which can be done without additional patient intervention, and incorporate uncertainty that can robustly examine the boundaries of how a therapy or strategy can provide benefit. These are important policy tools, and cost-effectiveness analyses can be performed using inputs from large populations to show, on average, an optimal way to improve value in population health.³⁰ A weakness of the approach is that this may overlook individual patient nuances. For example, a recently published cost-effectiveness analysis in this Journal explored if peanut allergic patients should carry one vs. two epinephrine devices with them. This analysis noted that in the base case, having all patients universally carry two devices on them was not cost-effective. However, there were situations where carrying two devices could be more cost effective compared to a contextualized approach for patients with a history of prior anaphylaxis, or who had a prior episode of anaphylaxis requiring administration of multiple epinephrine doses.³² Another potential limitation is risk of bias. It has been noted

that many industry-sponsored analyses support cost-effectiveness of the particular therapy, whereas ones without industry sponsorship may reach different conclusions.

So, how should a clinician apply a finding like that? Therein lies the rub. The model shows, on average, in a cohort of patients that behave within the range of probabilities expected for the events, there is a very clear hierarchy of cost-effective policies. However, you may have known of a patient of yours in the past, who had a history of only a mild index reaction, who upon their next allergic reaction needed to use both of their autoinjector units they were carrying, and needed a third dose administered by EMS. So, does that make the cost-effectiveness findings wrong? No. However, the model is built on a large number of patients, and their expected outcomes, and not just applied to the anecdotal experience of one's last case bias. Importantly, no scenario is ever going to be perfectly explained in a model (because a model is just an approximation of a reality). But, in models that use well-established inputs and a large enough cohort or sample for the simulation with broad sensitivity analysis, these can advise high-level strategies that are associated with more (or less) cost-effectiveness. Such models work best at a broad level for informing policy.^{6,7,30} In this example model, for the majority of patients who were analyzed in both cohort and Monte Carlo simulation in this similar situation, they did fine with a single dose and the additional epinephrine unit was of no value to them. Thus, on average, the model determined the correct utilization of resources. If there are robust sensitivity analyses, these will account for larger scale deviations from the expected outputs, and the decision-maker will have good boundaries of an outcome to decide how to use such data. Payers will use these models to inform their optimal practices, given the millions of lives they cover, and a desire to curb costs. Good analysts will revisit their models and assumptions, to constantly update inputs and refine outputs and sensitivity to optimize cost effectiveness over time.³

Your advocacy and diligence has paid off! Your peer-to-peer consultation prompted this to be discussed with the Health Economics Outcomes Research group at your patient's insurer, who, in reviewing the issues about both the perspective and the variable interaction, re-analyzed the model and discovered that they had overlooked an assumption. As a result, they have not recommended a switch in agents for particular asthma subgroups (which includes your patient), given they had wrongly estimated the benefit in that group. Your patient thanks you for your help, and has no exacerbations in the next 18 months after starting this therapy.

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Figures and Legends

Figure 1: Measuring Health State Utility Through Time-Trade Off and Standard Gamble

Legend: Examples of how questions are posed to determine the trade-off of a unit of time or expected chance of death. Scenarios shift to different ratios of time or probability of death until the respondent becomes indifferent and can no longer choose. This produces a ratio that is translated to a utility value (e.g. 18 of 20 years=0.9)

Figure 2: Quadrant Diagram of the Outcomes of a Cost-Effectiveness Analysis

Legend: This diagram outlines the 4 probabilities of a cost-effectiveness analysis, plotting effectiveness on the X axis and cost on the Y. The outcomes are higher cost/higher effectiveness, higher cost/lower effectiveness (e.g. dominated), lower cost/higher effectiveness (e.g. dominant), and lower cost/lower effectiveness.

Figure 3: Examples of Graphical Representation of Sensitivity Analysis

Legend: Figure 3a shows a deterministic sensitivity tornado plot, representing the a series of one-way sensitivity analyses, each detailing the maximal or minimal variable input to show the range of the potential outcomes. These are presented in stacked form, top down from the variable with the largest impact on top. Figure 3b shows a one-way sensitivity analysis of a single variable against net monetary benefit of two competing strategies, with the intersection showing the threshold cost-effectiveness. Figure 3c shows a probabilistic sensitivity analysis in a cost-effectiveness acceptability curve, demonstrating the simulated iterations in which the strategy would be cost effective. Figure 3d is an alternative demonstration of probabilistic sensitivity, showing a color-coded scatterplot of the iterations per each strategy denoting their cost and effectiveness.

Table 1: Glossary of Terms Used in Cost-Effectiveness Analyses

Terms Commonly Used in Cost-Effectiveness Analyses
Incremental Cost-Effectiveness Ratio: a ratio comparing the costs and benefits of strategy A with the costs and benefits of strategy B to determine the relative value of each strategy
Societal perspective: a modeling perspective which considers everyone who may be affected by a specific intervention, including patients, employers, payers, and society, where it does not matter who pays the cost and who receives the benefit
Payer perspective: a modeling perspective that considers only the direct medical costs to payers and the direct out of pocket costs that patients may pay.
Markov models: specific simulations widely used in healthcare that allow transitions between health states (e.g., sick, well, dead) to replicate clinical events that may happen over the course of experiencing a disease in a lifetime. Exploring models through probabilistic sensitivity Markov microsimulation allows use of distributions of probabilities, costs, and other events to introduce additional variation, including interactions of multiple variables and probabilities
Health state utility: a patient preference for a particular health state under conditions of risk, on a probability scale from 0 (death) to 1 (perfect health). Health utility can be directly by asking patients to rate their health along a visual analog scale in relation to either a time trade off or standard gamble scenario asking the patient to consider how much time they would trade to have perfect health, or through scenarios assessing a willingness to gamble varying degrees of health to obtain a cure or treatment for a disease.
Quality Adjusted Life Year (QALY): a value of a health state incorporating health utility to measure an intervention's effectiveness of improving both quality of life and quantity of life in a time period, relative to a particular disease. QALY combines morbidity and mortality in a single standardized measure that can be compared across varied health and disease states. Determining QALY is also referred to as cost-utility (or health utility) analysis, because QALY measures are derived from health state utilities that represent patient preferences for one particular health state over another, under conditions of risk.
Sensitivity analyses: evaluations within a cost-effectiveness analysis that re-evaluate analyze specific questions to explore the stability of findings, over a range of plausible assumptions and thresholds at which outcomes and conclusions could change.
Dominance: dominant therapies refers to a particular therapy which, in comparison to one or more alternative therapies, produces lower costs and greater benefits when compared to another. Dominated therapies, alternatively, produce higher costs and lower benefits.
Net monetary benefit: a summary statistic that quantifies the value of an intervention in monetary terms when a willingness-to-pay threshold for a unit of benefit per QALY is known. This takes these variables and combines them into one linear measure of cost and effectiveness without a ratio. NMB is calculated as (incremental benefit x threshold) – incremental cost. Incremental NMB measures the difference in NMB between alternative interventions, where positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.
Willingness to pay: this represents the threshold that a person or a payer is willing to pay for a given therapy. At the patient level, this represents the direct out of pocket costs a patient will pay for a therapy. At a payer level, this represents the currency amount per QALY that a therapy must meet.
Deterministic sensitivity analysis: A sensitivity analysis in which one or more parameters are discretely changed based on a pre-determined range (e.g. like across a 95% CI) to see how the change affects the outcomes, as a way to model uncertainty. The results of deterministic sensitivity analysis are usually expressed as line graphs or bar charts, such as a tornado diagram or bar graphs representing univariate sensitivity analyses for a wide range of input

values, ordered according to the extent (spread) or variation of the resulting model output value (with the widest variation on top).

Tornado diagram: tornado diagrams are used to present the result of multiple univariate sensitivity analyses on a single graph. Each analysis is summarized using a horizontal bar which represents the variation in the model output (usually an ICER) around a central value (corresponding to the base case analysis) as the relevant parameter is varied between two plausible but extreme values. The horizontal bars are ordered so that with those with the greatest spread (i.e. parameters to which the model output is most sensitive) come at the top of the diagram, and those with the lowest spread at the bottom. The resulting diagram of stacked horizontal bars has a distinctive tornado shape. Tornado diagrams are used to help the reviewer assess which of the model's parameters have the greatest influence on its results.

Table 2: Components of a Cost-Effectiveness Analysis

Component	Importance
Base Comparison	This identifies the therapies or objects being compared
Base Case	This identifies the particular context and assumptions under which the model is run, which then allows for things to be changed to investigate any sensitivity analyses
Economy of analysis	This identifies in which economic system the analysis will be run. Different countries will have different values of inputs and different currency values. When comparing different economies (e.g., US vs. UK) a standard reference currency must be specified as the cost basis.
Perspective	This identifies if the analysis is being conducted from the payer (e.g., includes only direct healthcare costs) or the patient (e.g. would include both direct and indirect costs). CHEERS guidance recommends at least 2 perspectives be evaluated.
Time Horizon	This identifies over how long the problem will be investigated. Some issues have short term horizons (e.g., effect of deferring COVID-19 vaccination because of an allergic reaction) or very long ones (e.g., a child developing peanut allergy in their first year of life, with a life expectancy of 80 years and a minimal likelihood of naturally regaining tolerance). Longer time horizons are appropriate for investigating the impact of therapies on chronic diseases.
Cycle length	This identifies how long will each iteration of the model be run over—is this something that is a few days, a few weeks/months, or a year to years? Chronic conditions are often modeled on a year cycle.
Model Inputs	Typically, 'Table 1' details all the model inputs (probabilities, costs, considerations, etc.), their sensitivity ranges (e.g. confidence intervals), and the sources these inputs are obtained from that are calculated in the analysis. This allows verification, validation, and potentially replication.
Analysis Table	Typically, this is 'Table 2', which shows the actual calculations. This should include the costs, the outcomes, and any other key facets that need to be displayed to understand the cost to outcome analysis, such as the costs, QALY, cost per QALY, and a determination of the incremental cost effectiveness (either the ratio, or if the analysis was

	dominated or dominant). This should include confidence intervals of every estimate.
Deterministic and Probabilistic Sensitivity Analysis	These are types of analysis that can build off the base case, and start to explore how robust the analysis and findings are by changing key values or their ranges. Most sensitivity analyses model assumptions across plausible ranges of their expected values, and help to show the degree to which these changes shift the findings towards or away from cost-effectiveness.
Limitations	This is to acknowledge that all models are imperfect, or at least have a fragile existence within a particular context. A well written limitations section will, deliberately and honestly, explain the issues and assumptions in the model that could limit the adaptation of the results.
Decision Tree and Transition Diagram	This is an important figure, which should be mentioned in the methods, which outlines a general model structure of the health states, the transition probabilities, and the decision tree showing a general model of the outcomes in the cycle for each therapy

Figure 1:

The Health Scenario

A vignette of a health condition, and a typical life with that condition is presented, including all the positives and negatives. The respondent is then offered two ways to consider future life relative to this condition. The first is to gamble immediate cure vs. chance of death. The second is by trading total years of life with this condition for a reduced amount of healthy years of life without the condition

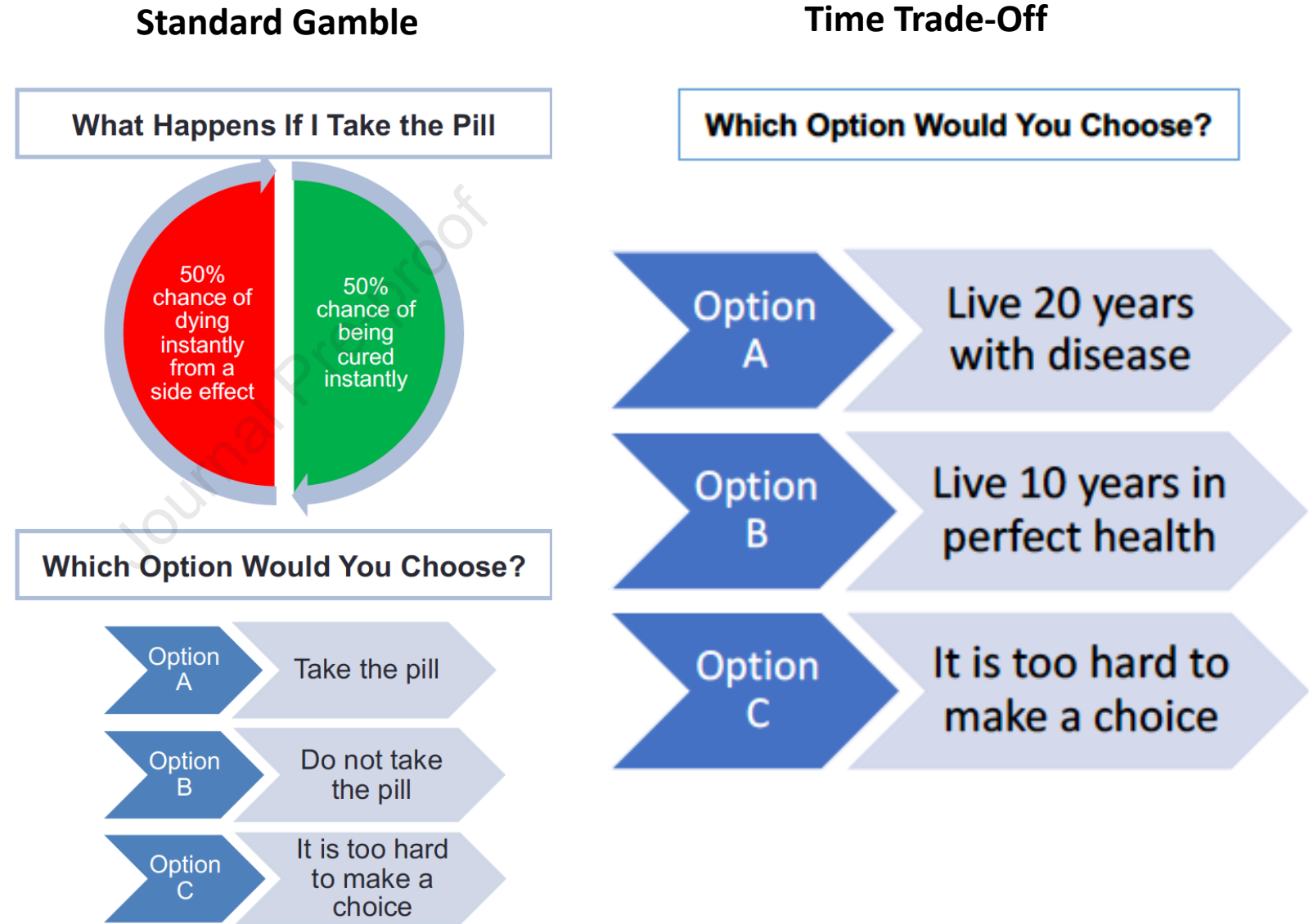


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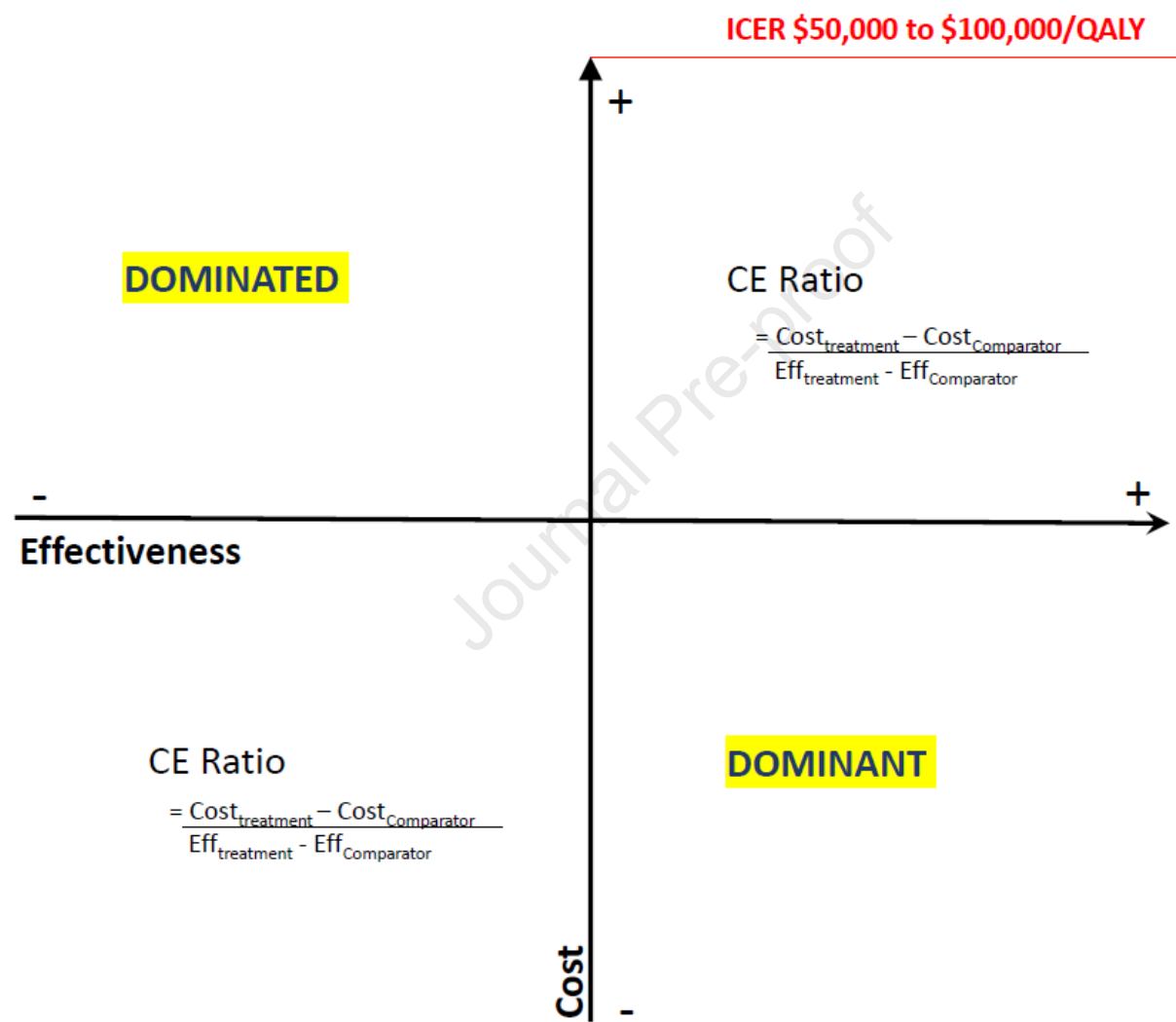
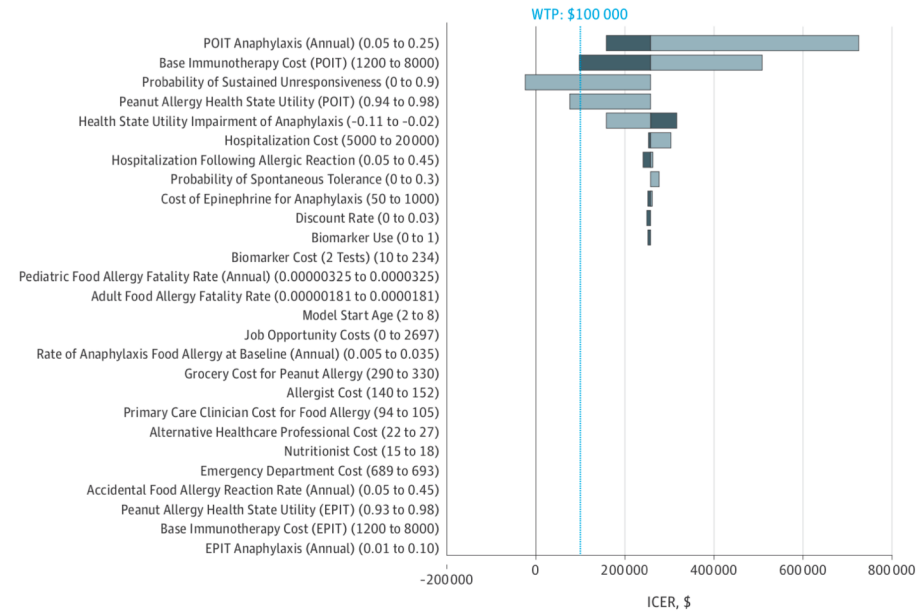
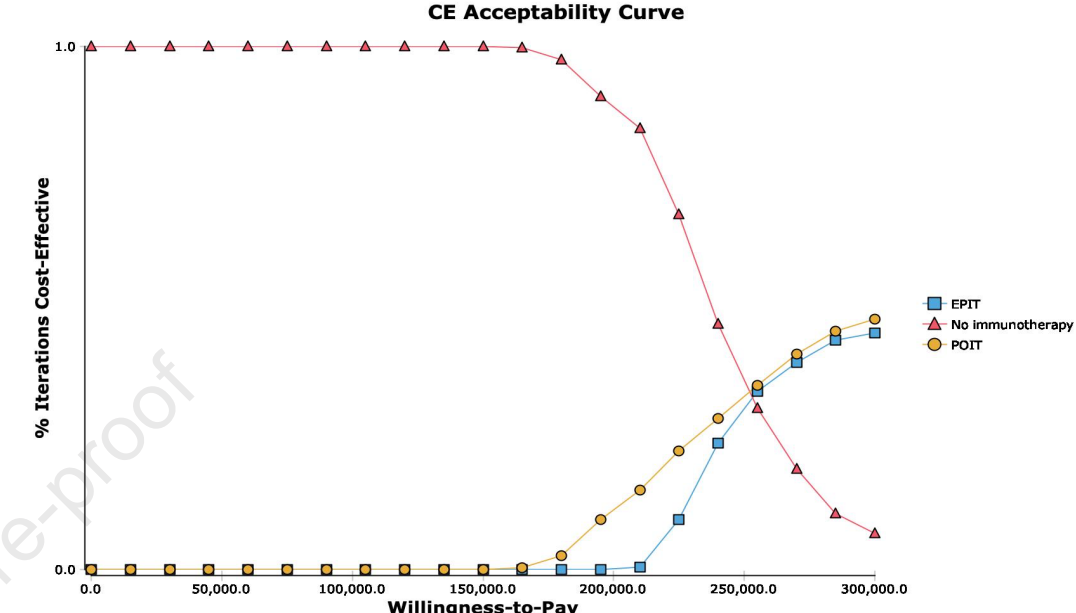


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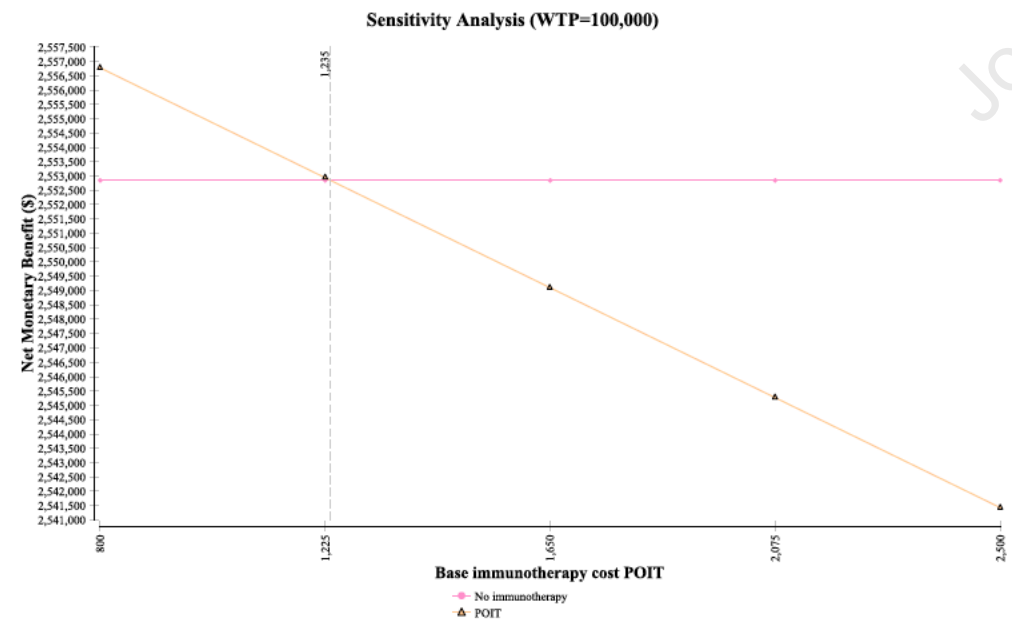
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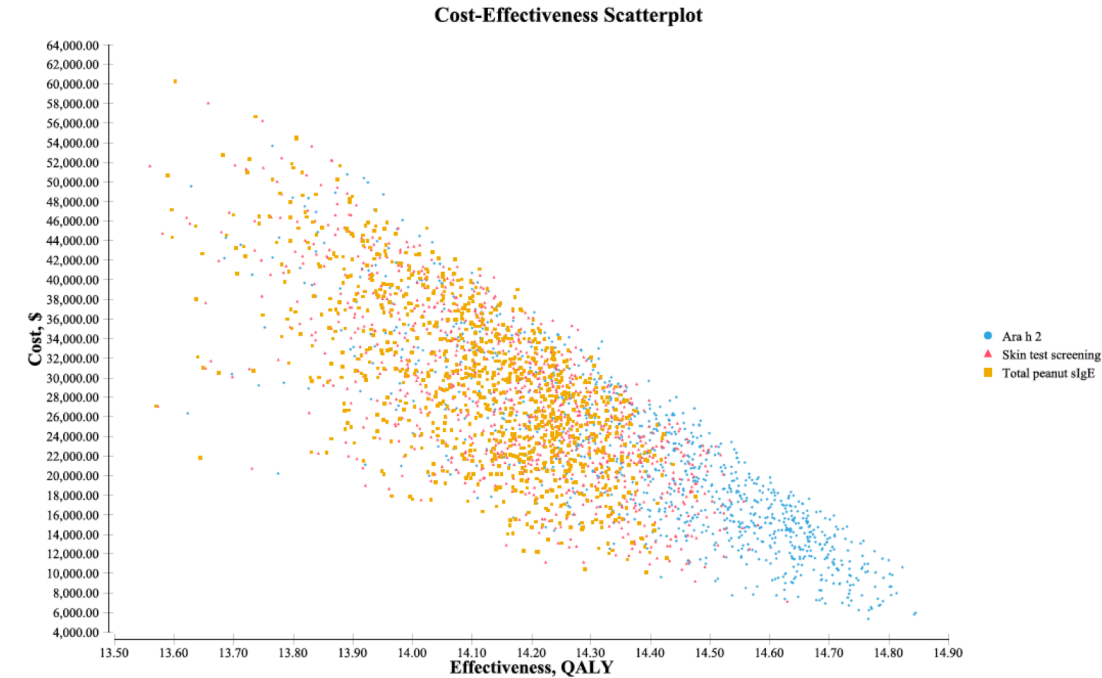
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D



CME EXAM

MS# & Article title: 21-01152, A Practical Guide to Understanding Cost-Effectiveness Analyses

Author(s): Matthew Greenhawt, John Oppenheimer, Christopher Codispodi

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Learning objectives:

1. To describe the components of a cost-effectiveness analysis.
2. To identify the key outcome measures that are used in a cost-effectiveness analysis.
3. To understand how to interpret a cost-effectiveness analysis.

Questions:

1. A Quality Adjusted Life Year (QALY) measures which of the following?
 - a. Quality (but not quantity) of life relative to a disease
 - b. Quantity (but not quality) of life relative to a disease
 - c. Both quality of life and quantity of life in a time period, relative to a particular disease
 - d. Harm caused by an intervention

Answer: c

Explanation: A QALY is value of a health state incorporating health utility to measure an intervention's effectiveness in improving both quality of life and quantity of life in a time period, relative to a particular disease. QALY combines morbidity and mortality in a single standardized measure that can be compared across varied health and disease states. Determining QALY is also referred to as cost-utility (or health utility) analysis, because QALY measures are derived from health state utilities that represent patient preferences for one particular health state over another, under conditions of risk.

2. Cost-effectiveness analyses that account only for the direct medical costs of an illness to both the payer and the patient represent which of the following perspectives?
 - a. Societal perspective
 - b. Payer perspective
 - c. International perspective
 - d. Universal Perspective

Answer: B

Explanation: The payer perspective considers only the direct medical costs to payers and the direct out of pocket costs that patients may pay. The societal perspective considers everyone who may be affected by a specific intervention, including patients, employers,

payers, and society, where it does not matter who pays the cost and who receives the benefit.

3. In your cost-effectiveness analysis, if your intervention has the lowest cost and the highest benefit compared to the other interventions that were analyzed, it would be called which of the following?

- a. The dominant intervention
- b. The dominated intervention
- c. The neutral intervention
- d. The pragmatic intervention

Answer: A

Explanation: Dominant therapies refers to a particular therapy which, in comparison to one or more alternative therapies, produces lower costs and greater benefits when compared to another. Dominated therapies, alternatively, produce higher costs and lower benefits.

4. Dividing the net cost of two therapies by the net benefit of two therapies produces which of the following?

- a. The net monetary benefit
- b. The financial windfall
- c. The incremental benefit
- d. The incremental cost-effectiveness ratio

Answer: D

Explanation: The difference in the cost divided by the difference in the benefit will produce the incremental cost-effectiveness ratio, which can then be compared to the willingness to pay threshold to determine if this value exceeds this threshold and would not be considered cost-effective.

5. Which of the following is a way to determine health state utility?

- a. Martingale method
- b. Time trade off method
- c. Clinical Impact method
- d. Confirmatory factor analysis method

Answer: B

Explanation: Option b, time trade off method, is an accepted method for determining health state utility. The martingale method is a debunked gambling system where the bettor doubles their last wager if they lose, hoping to recoup their cumulative losses with the next win. Clinical Impact method is a way of rating responses. Confirmatory

factor analysis is a data reduction method related to establishing domains in a quality of life analysis.