Supplementary Online Content

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eAppendix. Recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine

Recommendations on Perspectives for the Reference Case

Reference Cases and Reference Case Perspectives

1. We recommend that all studies report a Reference Case analysis based on a healthcare sector perspective and another Reference Case analysis based on a societal perspective. The Reference Cases are defined by recommendations for components to consider for evaluation, methods to use, and elements for reporting. We recommend that Reference Case analyses measure health effects in terms of quality-adjusted life years (QALYs). Standardizing methods and components within a perspective is intended to enhance consistency and comparability across studies.

Healthcare Sector Reference Case

2. We recommend that the results of the healthcare sector Reference Case analysis be summarized in the conventional form, as an incremental cost-effectiveness ratio (ICER). Net monetary benefit (NMB) or net health benefit (NHB) may also be reported, and a range of cost-effectiveness thresholds should be considered. We recommend that the healthcare sector perspective include formal healthcare sector (medical) costs borne by third-party payers or paid for out-of-pocket by patients. Both types of medical costs include current and future costs, related and unrelated to the condition under consideration.

Societal Reference Case: The Impact Inventory and Summary and Disaggregated Measures

3.A. *Inclusion of an Impact Inventory*. The Second Panel continues to strongly support evaluation of the broader impacts of interventions designed to improve health. We recommend that the societal Reference Case analysis include medical costs (current and future, related and unrelated) borne by third-party payers or paid for out-of-pocket by patients, time costs of patients in seeking and receiving care, time costs of informal (unpaid) caregivers, transportation costs, effects on future productivity and consumption, and other costs and effects outside the healthcare sector. To make this evaluation more explicit and transparent, we recommend inclusion of an "Impact Inventory" that lists the health and non-health impacts of an intervention that should be considered in a societal Reference Case analysis. The main purpose of the Impact Inventory is to ensure that all consequences, including those outside the formal healthcare sector, are considered regularly and comprehensively, as they have generally not been to date.

3.B. *Quantifying and valuing non-health components in the Impact Inventory*. We recommend that analysts attempt to quantify and value non-health consequences in the Impact Inventory, unless those consequences are likely to have a negligible effect on the result of the analysis.

3.C. *Summary and disaggregated measures*. The Panel agrees that it would be helpful to inform decision makers through the quantification and valuation of all health and non-health impacts of interventions, and to summarize those impacts in a single quantitative measure such as an ICER, NMB, or NHB. However, there are no widely agreed upon

methods for quantifying and valuing some of these broader impacts in cost-effectiveness analysis (CEA). We therefore recommend that analysts present the items listed in the Impact Inventory in the form of disaggregated consequences across different sectors. We also recommend that analysts use one or more summary measures, such as an ICER, NMB, or NHB, that include some or all of the items listed in the Impact Inventory. Analysts should clearly identify which items are included and how they are measured and valued, and provide a rationale for their methodological decisions.

Reporting the Reference Cases and Other Perspectives

4.A. *Stating the perspective*. We recommend that analysts clearly state the perspective of every analysis reported.

4.B. *Presenting other perspectives*. Where specific decision makers have been identified, such as a particular public or private payer, analysts may wish to present results from that decision maker's perspective in addition to the Reference Case perspectives. In such cases, we recommend that analysts clearly state the primary decision maker(s) whose deliberations are intended to be informed by the analysis.

4.C. *The importance of transparency and sensitivity analysis*. The items included in a CEA and the manner in which they are valued involve numerous choices. We recommend that analysts be transparent about how they have conducted analyses, and that they convey how results change with alternative assumptions. Sensitivity analysis should describe as clearly as possible the assumptions to which the results for different perspectives are sensitive.

Designing a Cost-Effectiveness Analysis

1. Cost-effectiveness analysis (CEA), return-on-investment analysis, cost-minimization analysis, cost-consequence analysis, and cost-benefit analysis are alternative forms of analysis. The use of one does not preclude the use of the others.

2. We recommend that all studies report a Reference Case analysis based on a healthcare sector perspective and a Reference Case analysis based on a societal perspective. The Reference Cases include recommended methods, elements for reporting, and recommendations concerning what to include in the healthcare sector and societal perspectives. Inclusion of standardized components and standardization of methods within a perspective are intended to enhance consistency and comparability across studies.

3. We recommend that the results of the healthcare sector Reference Case be summarized in the conventional form, as an incremental cost-effectiveness ratio (ICER). The net monetary benefit (NMB) or net health benefit (NHB) may also be reported, and a range of cost-effectiveness thresholds should be considered. We recommend that the healthcare sector perspective analysis include all formal healthcare (medical) costs—current and future, and related and unrelated—regardless of who bears the costs.

4. The Second Panel strongly supports evaluation of the broader impacts of health interventions. Thus, we recommend that analysts include a societal perspective Reference Case analysis. The societal perspective is essential whenever interventions are likely to have important effects on sectors of the economy outside of healthcare, and when there is a need or desire to understand all costs and effects regardless of to whom they accrue.

The societal perspective includes medical costs (current and future, related and unrelated) borne by third-party payers or paid for out-of-pocket by patients, time costs of patients in seeking and receiving care, time costs of informal caregivers, transportation costs, effects on future productivity and consumption in added years of life, and other costs and effects outside the healthcare sector. The Second Panel agrees that it would be helpful to inform decision makers through the quantification and valuation of all health and non-health consequences of interventions, and to summarize those consequences in a single quantitative measure. However, there are no widely agreed upon methods for quantifying and valuing some of these broader impacts in CEA. We therefore recommend that analysts present the items listed in the Impact Inventory in the form of disaggregated consequences across different sectors. We also recommend that analysts use one or more summary measures, such as an ICER, NMB, or NHB, that include some or all of the items listed in the Impact Inventory. Analysts should clearly identify which items are included and how they are measured, and provide a rationale for their methodological decisions.

5. To help make the evaluation more explicit and transparent, we recommend inclusion of an Impact Inventory in every societal Reference Case analysis, even if the analyst does not quantify or value effects beyond the healthcare sector. The Impact Inventory lists the health and non-health impacts of an intervention that the analyst should consider in a societal Reference Case analysis.

6. All aspects of the interventions that may affect their cost or effectiveness should be defined for the analysis. These will include the target population and features such as the specific technologies used, the type of personnel delivering the intervention, the site of delivery, whether the service is "bundled" with other services, the frequency of the intervention, and its timing.

7. The scope of a study should be defined broadly enough to encompass the full range of groups of people affected by the intervention and all important consequences. For example, if an intervention affects both mother and child, the analyst should include the health impacts and costs to each.

8. When there is heterogeneity in estimates of cost-effectiveness between different subpopulations, the analyst should present these differences as subgroup analyses. The analyst should be aware that subgroup analyses may raise ethical issues and questions of equity. The Second Panel provides a framework for consideration of ethical questions that may be important to the analyst, decision makers, and stakeholders.

9. Both Reference Case analyses should consider the full range of available and feasible options, including existing practice (the "status quo") and a do-nothing option, as appropriate.

10. Options being compared may include more than specific interventions, extending, for example, to therapeutic strategies, alternative treatment starting and/or stopping rules, joint or sequential diagnostic test strategies, alternative levels of intensity of an intervention, and public health interventions. In all cases, these should be specified as mutually exclusive options and be compared using incremental CEA.

11. Costs and outcomes that have little impact on the estimate of cost-effectiveness or the likelihood of an intervention being cost-effective, and therefore little impact on the relevant decisions, can reasonably be excluded from an analysis. Their magnitude should be indicated in the Impact Inventory, clarifying the decision to exclude them.

12. The time horizon adopted in a CEA should be long enough to capture all differences between options in relevant costs and effects.

13. We recommend that analysts develop a written protocol for the design and conduct of the CEA. The protocol should describe, at a minimum, the objectives of the study, including the research questions; the type of economic evaluation to be conducted; the perspective of the analysis; the intervention and comparators; the population under consideration; the time horizon for the study; sources of data; a list of key assumptions; and an analysis plan, including the outcomes the analysis will assess. The analysts should update the protocol as the study progresses, and note any changes from the original protocol.

Decision Models in Cost-Effectiveness Analysis

1. We recommend that the analyst perform a broad conceptualization of the decision problem with input from clinical and policy experts. The scope of the cost-effectiveness analysis (CEA) for which the model is being used should be clearly defined.

2. The initial conceptualization of the model should be independent of the data identification phase. The model should represent the decision problem and be described in a detailed and transparent manner. The model structure should accommodate relevant consequences of the alternatives under consideration. The conceptualization process should be iterative with the model development and parameterization phases.

3. Analysts should consider the following factors, ideally in consultation with the decision maker, to inform the use of a decision model: (1) need for extrapolation (e.g., beyond the time horizon of the available data, beyond intermediate study outcomes, to other populations, to other strategies) and/or (2) need to integrate multiple data sources (e.g., evaluate diagnostic tests, multiple strategies, weighing harms with benefits).

4. Use a model that is appropriate for addressing the study questions. Often more than one model type would work. Factors to consider include (1) short-term fixed time horizon or not; (2) the unit of analysis; (3) interactions between simulated individuals or other model components. Use good practices in modeling guidelines (International Society for Pharmacoeconomics and Outcomes Research [ISPOR] and Society for Medical Decision Making SMDM] Task Force).

5. Full documentation and justification of structural assumptions should be provided. When there are alternative plausible structural assumptions, appropriate uncertainty analyses to examine their effects on model outputs should be undertaken.

6. In developing a model, analysts should specify (1) the starting population(s), including all subgroups, and 2) whether they are analyzing a cohort or population. Analysts should provide their rationale for analyzing a population instead of defined cohorts.

7. Consider all available evidence for informing model parameters and use a summary of that evidence where appropriate. Identify all data sources within reason and justify the choice of evidence used.

8. The methods used to critically appraise sources of data for cost-effectiveness models should be stated.

9. Use appropriate methods to analyze or combine data from different sources.

10. Calibration is an appropriate way to estimate model parameters. When estimating parameters using a calibration approach the following components should be presented: (1) data sources used for calibration target(s); (2) the goodness-of-fit metric used to determine the degree of fit; (3) the manner in which the parameter space was searched; and (4) the criteria used to determine that the fit was reasonable.

11. The analyst should report how the model results are calculated. If an individual-level simulation is performed, specify and justify the number of iterations per model run. If a probabilistic sensitivity analysis (PSA) is performed, specify the number of simulations per parameter set.

12. Validation of the decision model should occur throughout the conduct of a CEA. The analyst should describe and justify how the model was validated. The types of validation to consider are (1) face validity, (2) internal validity (verification), and (3) external validity.

13. Model descriptions should be detailed enough to allow for reproduction. Model results should be presented in a disaggregated format for purposes of model transparency.

Identifying and Quantifying the Consequences of Interventions

1. A cost-effectiveness analysis (CEA) should identify all *types of consequences* affected by the choice of interventions being compared, relating to health (survival and/or health status), resource use in the healthcare sector, and consequences outside the healthcare sector. Both positive consequences (e.g., health benefits, improvements in non-health outcomes such as education, reductions in resource use) and negative consequences (e.g., health harms, harms in other sectors, and increases in resource use) should be identified.

2. The comprehensive identification of consequences should be summarized in an Impact Inventory, a required part of the Reference Case. The Impact Inventory should organize consequences based on the sector to which they pertain, and it should indicate, for each of the consequences that are listed, whether the consequence is included in each of the perspectives used in the analysis.

3. Decisions about which of these consequences to *measure and value* in the analysis should, first, be consistent with the specified perspective of the analysis and, second, strike a reasonable balance between expense and difficulty on the one hand, and potential importance in the analysis on the other. Consequences that are deemed likely to be insignificant in the context of the analysis can reasonably be excluded, and this exclusion should be explicitly noted in the impact inventory and justified within the supporting information.

4. Estimates of the probabilities or frequencies of health and economic consequences associated with alternative choices should be based on the best available evidence, in consideration of the full array of available information from either primary or secondary data sources, including corrections for sources of bias to the extent possible, and in recognition of time and resource constraints.

5. Estimates of the probabilities or frequencies of health and economic consequences associated with alternative choices should be specific to the individuals and groups affected by the intervention. Such estimates may have to be transferred to the target

setting from other settings, based on credible understanding of pertinent relationships, and with adequate exploration of the invoked assumptions.

Valuing Health Outcomes

1. For Reference Case analyses from both the healthcare sector and societal perspectives, the health consequences of changes in morbidity and mortality should be aggregated into a single measure using quality-adjusted life years (QALYs).

2. In general, because lives saved or extended by an intervention will not be in perfect health, a saved life year will count as less than 1 full QALY.

3. To satisfy the QALY concept, the quality weights must be preference-based, interval-scaled, and measured or transformed onto an interval scale where the reference point "dead" has a score of 0.0 and the reference point "perfect health" has a score of 1.0.

4. Community preferences for health states are the most appropriate ones for use in the Reference Case analyses. In general, we recommend the use of generic preference-based measures such as the EuroQol 5D (EQ-5D), Health Utilities Index (HUI), Short Form 6D (SF-6D), and Quality of Well-Being (QWB). But we also noted that there are situations in which using patient preferences would be preferable.

5. When community preferences are used and the program (treatment or prevention) is related to an illness or condition, a sensitivity analysis that furnishes information on preferences of persons with the condition will provide important ancillary information. Such sensitivity analyses may be based on the direct elicitation of preference scores from people with the condition and/or the development of alternative scoring functions based on preference scores from those with the condition.

6. If distinct subgroup preferences are identified that will markedly affect a cost-effectiveness ratio, the Reference Case analyses should provide this information and include separate sensitivity analyses that reflect this difference.

7. The health-related quality of life of those whose lives have been saved or extended by a health intervention may be influenced by characteristics such as the age, sex, race, or socioeconomic status of the population involved. This may affect the Reference Case analyses in ways that are ethically problematic. In these instances, we recommend that sensitivity analysis be conducted to indicate explicitly how the analysis is affected by these characteristics.

8. A cost-effectiveness analysis (CEA) should be based on a health-state classification system which reflects attributes (domains or dimensions) that are important for the particular problem under consideration. If the CEA is intended for use in a Reference Case analysis from either the healthcare sector or societal perspective, the preference measure used should be a generic one or one capable of being compared to a generic system. More fundamentally, a key criterion is empirical evidence on the validity and responsiveness of the instrument in that context.

9. In general, the effects of morbidity on productivity and leisure are probably not adequately reflected in the estimated QALYs and should therefore be estimated in pecuniary terms and included in the numerator in a CEA. This recommendation introduces some risk of double counting. Appropriate sensitivity analyses may be informative.

Estimating Costs and Valuations of Non-Health Benefits in Cost-Effectiveness Analysis

1. In cost-effectiveness analysis (CEA), all resource use should be valued in monetary terms and be included in the numerator of an incremental cost-effectiveness ratio (ICER). The denominator of an ICER should reflect only health as expressed in quality-adjusted life years (QALYs).

2. All resource use that is both germane to the analysis and non-trivial in magnitude should be included in the Reference Case analyses from both the healthcare sector and societal perspectives. Resource use should be reflected regardless of whether a monetary transaction takes place.

3. From a long-term perspective, costs in CEA should reflect the opportunity costs of the resources used, which represent the marginal or incremental costs of resources, rather than average costs. Therefore, attention should be paid to instances where constant return-to-scale for resources used may not apply when implementing an intervention in a population.

4. In principle, the full three-step approach to determining costs, entailing the identification, measurement (quantification), and valuation of resource use, is preferred. The choice between mirco-costing and gross-costing approaches should reflect the importance of precise cost estimates, feasibility, and cost.

5. To the extent that prices reflect opportunity costs, they are an appropriate basis for valuing changes in resources. If prices do not adequately reflect opportunity costs because of market distortions, they should be adjusted; when substantial bias is present and adjustment is not feasible, another proxy for opportunity cost should be used. Sometimes the opportunity costs of a resource may be different for the healthcare sector perspective than for the societal perspective.

6. All healthcare resources consumed over the lifetime of the patients as part of, or as a result of, an intervention should be valued in monetary terms and included in the numerator of an ICER.

7. All healthcare costs, related or unrelated, should be considered either when survivals under alternative interventions are not the same or when cost components cannot be readily identified as related to the target condition.

8. Fixed costs for research and development of a healthcare intervention should always be taken into account, unless these fixed costs are similar across all the comparator interventions.

9. In the United States, the Federal Supply Schedule (FSS) for drug prices should be used to reflect the social marginal costs of drugs for Reference Case analyses from both the healthcare sector and societal perspectives. In CEAs conducted from other perspectives, costs should reflect the transaction prices from the perspective of the analysis.

10. In addition to Recommendation 6 for this section, for a Reference Case analysis from a societal perspective, all non-healthcare resources consumed over the lifetime of the patients as part of, or as a result of, an intervention should be valued in monetary terms and included in the numerator of an ICER.

11. For a Reference Case analysis from a societal perspective, non-healthcare resources include patients' time costs, caregivers' time costs, productivity benefits,

consumption costs, friction/administrative costs, and relevant costs from all other sectors of the economy outside of healthcare. Costs that are transferred from one section of the population to another should not be included.

12. For a Reference Case analysis from a societal perspective, patients' time costs reflect the time spent receiving an intervention. This time resource is assumed to displace leisure time of the patients and is therefore valued at the marginal post-tax wage rate plus fringe benefits. Under compelling evidence that such time spent replaces labor time and not leisure time, it should be valued as productive time as explained in Recommendation 14 for this section.

13. For a Reference Case analysis from a societal perspective, if the time spent receiving an intervention has a significant positive or negative impact on health-related quality of life, this impact should be incorporated into the denominator of an ICER, leaving the time component in the numerator.

14. For a Reference Case analysis from a societal perspective, three types of productive time for patients should be considered: (a) time spent in formal labor markets; (b) time spent in informal labor markets; and (c) time spent in household production. Where sufficient data exist, all three types of productive time should be valued using the marginal pre-tax wage rate plus fringe benefits.

15. For a Reference Case analysis from a societal perspective, both formal (paid) and informal (unpaid) caregivers' time should be viewed as productive time and valued with the marginal pre-tax wage rate plus fringe benefits in the formal caregiver market.

16. The degree to which marginal wage rates, tax rates, and fringe benefit rates should be stratified based on age, sex, and/or disease conditions depends on the needs of the decision makers that the analysis aims to inform. If stratified estimates are used, the distributional consequences of such an approach should be discussed.

17. For a Reference Case analysis from a societal perspective, consumption costs should reflect the non-healthcare consumptions. Consumption costs should be considered only where there is differential survival across comparator interventions.

18. As with wage rates, stratification of consumption costs should meet the needs of decision makers. Distributional consequences arising as a result of stratification should be discussed.

19. For a Reference Case analysis from a societal perspective, intrinsic non-healthcare benefits, such as the psychological benefits of lower crime, should be valued in monetary terms and included in the numerator of an ICER. The methods of valuation would depend on the jurisdiction of the analysis. In the United States, willingness-to-pay to value these outcomes would be an acceptable method. Sensitivity analysis should be conducted by presenting the societal ICER with and without these benefits.

20. Cost-effectiveness analyses should be conducted in constant dollars that remove general price inflation. If the prices in question change at a rate different from general price levels, this variation should be reflected in the adjustments used. For example, in the United States, personal consumption expenditure (PCE) price index and the Personal Health Care (PHC) Expenditure deflator should be used to adjust for inflation in healthcare expenditures. For non-healthcare sector expenditures, the regular Consumer Price Index (CPI) should be used.

21. The costs used in a CEA should reflect the costs in the jurisdiction where the intervention is or will be implemented.

22. Costs should be discounted at the same rate as health effects.

Evidence Synthesis for Informing Cost-Effectiveness Analysis

1. Follow established guidance on systematic reviews and meta-analyses, modified as per Recommendations 2 through 8, for this section.

2. The cost-effectiveness analysis (CEA) team and the evidence synthesis team (if separate) should coordinate to refine the scope and goals of the evidence synthesis.

3. Identify the important model parameters. Important parameters are those that are (i) influential on model results or (ii) critical to the (perceived) validity of the model. Estimates of important parameters should be informed by an evidence synthesis.

4. Provide an analytical description and a critique of the evidence base.

5. Quantitative evidence syntheses should use methods that (i) model statistical variability of data, (ii) allow for between-study heterogeneity, and (iii) yield consistent estimates for all model parameters informed by the synthesis.

6. The evidence synthesis should be explicit about whether and how bias in each study and across studies was handled. The goal of the synthesis should be to produce bias-corrected estimates.

7. The evidence synthesis must be explicit about whether and how estimates were adjusted for transferability. The goal of the synthesis should be to produce estimates applicable to the modeled setting.

8. Enumerate scenarios for sensitivity analyses for (i) structure and (ii) parameter values based on the findings of the qualitative synthesis and assumptions made when accounting for/dealing with biases and transferability of estimates in the quantitative synthesis.

Discounting in Cost-Effectiveness Analysis

1. In cost-effectiveness analyses (CEAs) from both the societal and the healthcare sector perspectives, the costs and health effects of all interventions should be expressed in terms of their present value to society, as a prerequisite for generating cost-effectiveness ratios.

2. In the Reference Case analyses from both the societal and healthcare sector perspectives, costs and health consequences should be discounted at the same rate.

3.1. The discount rate should be subject to review, and possible revision, over time in light of significant changes in the underlying economic data. However, to retain comparability with existing analyses, we recommend that 3% continue to be used in base-case analyses from both Reference Case perspectives for at least the next 10 years.

3.2. Sensitivity analyses should be conducted on the discount rate used in a CEA.

Reflecting Uncertainty in Cost-Effectiveness Analysis

The following recommendations are based on those of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) Task Force, with some additions and changes as considered appropriate by the Second Panel.

Purpose of Uncertainty Analysis

1. Uncertainty analysis is essential to high-quality cost-effectiveness analysis (CEA). In determining the best approach to uncertainty analysis, the guiding principle should be how the analysis informs the choice between policy options.

2. There should be a clear report regarding what has been assumed about decision makers' policy options, including those relating to decision delay and further research.

Parameter Uncertainty

3. The specifications of all forms of sensitivity analysis require justification on the basis of the available evidence.

4. Deterministic sensitivity analysis can provide useful insights into model behavior and validation. Its role in quantifying decision uncertainty is limited. Probabilistic sensitivity analysis (PSA) provides an analytical basis to estimate decision uncertainty.

5. Where there is very little information on a parameter, this should be reflected in a broad range of possible values in the form of a distribution for PSA and a range for deterministic sensitivity analysis. Parameters should never be excluded from uncertainty analysis on the grounds that there is insufficient information to estimate uncertainty.

6. For PSA, continuous distributions should generally be used that characterise uncertainty realistically over the theoretical range of the parameter. The analyst should be transparent regarding the choice and specification of the distribution for each parameter.

7. Correlation among parameters should be considered. Jointly estimated parameters, such as those from a regression analysis, will have direct evidence on correlation, which should be reflected in the analysis. Independently estimated parameters will have no such evidence, but this should not necessarily lead to an assumption of independence.

Structural Uncertainty

8. Structural uncertainties should be tested in uncertainty analysis. Consideration should be given to parameterizing these uncertainties for ease of testing. Where this is not considered possible, scenario analysis should be undertaken.

Presenting Decision Uncertainty

9. Decision uncertainty should be presented using probabilities for specified cost-effectiveness thresholds. If structural uncertainties are left unparameterized, these probabilities should be presented for each scenario relating to the structural uncertainty. If cost-effectiveness acceptability curves (CEACs) are used, curves for each option should be plotted on the same graph, together with a cost-effectiveness acceptability frontier (CEAF).

Value of Information Analysis

10. Expected value of information analysis should be used to guide decision making under uncertainty. Other factors with potential relevance to decisions should be considered, including the likelihood that research will be undertaken if an intervention is generally funded compared with being funded only in the context of research; the extent of irreversible costs being incurred in delivering a new intervention; and whether other information of relevance is likely to emerge over time.

Ethical and Distributive Considerations

1. Where significant accommodation is likely to disability states being evaluated, those accommodations should be reflected in alternative values for relevant health states and examined in sensitivity analyses.

2. When comparing alternative life-extending interventions that would benefit patients of substantially different ages, a decision maker may wish to give greater weight to benefitting the patients who would have had significantly fewer life years or quality-adjusted life years (QALYs) if they do not receive treatment. Analysts should conduct sensitivity analysis to illustrate the impact.

3. Where the cost-effectiveness analysis (CEA) is of alternatives providing significant benefits to persons in very different initial states of health, the decision maker may wish to consider giving some priority to the worse off potential beneficiaries. Analysts may conduct sensitivity analysis to illustrate the impact of alternative assumptions.

4. When the CEA compares alternatives that provide large benefits to some individuals with other alternatives that provide much smaller benefits to a much larger number of individuals, decision makers may consider giving greater priority to the alternatives that concentrate benefits or disperse burdens. Analysts should highlight this issue when it is important.

5. When the CEA favors one group of beneficiaries over other potential beneficiaries based on a small difference in cost-effectiveness ratios, it is important for decision makers to consider whether mitigating factors cited in the text reduce the fair chances problem. If not, can the difference be reduced in other ways? Analysts should highlight and discuss this issue when it is important.

6. Users of CEA should assess whether the CEA significantly discriminates against disabled patients on the basis of their disabilities and how that discrimination, if present, might be avoided.

7. Whenever recommending departure from the most cost-effective alternative on ethical grounds, decision makers may wish to consider the reduced benefits or increased costs to others of doing so. Sensitivity analyses, which can then be compared with the base-case analysis, do this automatically.

Reporting Cost-effectiveness Analyses

1. Cost-effectiveness analyses (CEAs) should be documented in two parts, a journal article and a comprehensive technical appendix.

2. For the peer review, we recommend that editors request and authors submit the technical appendix together with the journal article to assist reviewers in assessing the study's methodology. The technical appendix should also be published along with the journal article, at a minimum in an online format, for the benefit of readers.

3. We recommend use of a structured abstract for the journal article.

4. The Impact Inventory should be reported in the journal article. Any additional perspectives beyond the Reference Case perspectives should be explicitly identified in the journal report.

5. Sufficient detail should be provided on the details of the study design, type of analysis, and modeling approach, inputs, and assumptions to enable replication of the analysis.

6. Analysts should include essential descriptors of the preference elicitation method used to measure preference weights: direct or indirect (multi-attribute) elicitation method; the elicitation task or measurement system employed; and if the weights reflect community-based preferences or not.

7. The following information comprises a basic set of recommended results in the journal article: total costs, total effectiveness, incremental costs, incremental effectiveness, and incremental cost-effectiveness ratios (ICERs). We also recommend reporting of intermediate health outcomes and disaggregated results. The basic set of results should also include some measure of the robustness of the results to changes in parameter inputs, model structure, or other sources of uncertainty. The societal perspective Reference Case results will also include potential impacts on non-healthcare sector consequences. A summary of these impacts should be included in the journal article.

8. The report should highlight the Reference Case results. Key sensitivity analyses should be conducted with respect to the Reference Case assumptions.

9. For undominated strategies, ICERs should be reported in increasing order of cost and effectiveness. Incremental cost-effectiveness ratios should not be reported for options ruled out because of dominance or extended dominance.

10. The ICERs for the current analysis should be compared to available ICERs for other interventions that compete for resources with the intervention being considered. These may be drawn from healthcare broadly if the decision context is broad, or from restricted categories, such as a particular condition or type of intervention. The emphasis should be on providing context for the decision maker.

11. The Discussion section of a journal article should include a description of any significant ethical implications of the CEA results.

12. Authors should disclose any potential conflicts of interest relevant to the analysis, including funding source, whether or not this is required by the publisher.