1 Objectives

This guideline presents methods of analysis to prepare for cost-effectiveness evaluations to the Central Social Insurance Medical Council.

2 Perspective of analysis

2.1 The perspective of analysis should be specified, and the range of costs corresponding to this perspective should be determined.

2.2 "Public healthcare payer's perspective" is a standard perspective that pertains to factors such as costs, comparators, and target populations within the range of the public healthcare insurance system in Japan.

> **2.2.1** Regarding healthcare technologies that are not covered by the public health insurance system, such as some prophylactic procedures (e.g., health checkup, vaccinations), it is acceptable to present analyses that include these technologies in addition to an analysis from the "public healthcare payer's perspective."

2.3 If the effect on long-term care costs is important with regard to the healthcare technology, it is acceptable to perform an analysis from the "public healthcare and long term care payer's perspective."

2.4 If the introduction of a technology has a direct influence on productivity, it is acceptable to perform an analysis that considers broader costs and counts productivity loss as a cost.

2.5 Even when an analysis is conducted from a perspective other than the "public healthcare payer's perspective," an analysis from the "public healthcare payer's perspective" should also be submitted.

3 Target population

3.1 Patients who meet the indication of the technology at the time of analysis will be used as the target population.

3.2 If the technology is applicable to multiple major populations or involves multiple application methods, an analysis should be conducted for each population or method.

> **3.2.1** However, if item 3.2 is difficult to achieve, it is acceptable to perform an analysis of the selected population(s) or method(s) on the basis of factors such as the number of patients or features of the illness. The appropriateness of such an analysis should be discussed through preliminary consultation.

4 Comparator(s)

4.1 The comparator(s) should be those which are widely used in clinical practice and are expected to be replaced to a large extent by the target technology at the time when the technology was introduced to treat the target population.

4.1.1 Non-treatment or watchful waiting can also be used as a comparator.

4.1.2 Except for the cases described in item 4.1.1, as a rule, comparator(s) should be those that are reimbursed from public health insurance.

4.1.3 If multiple healthcare technologies fall under item 4.1 and are similar to each other, the comparator(s) should be selected while considering the extent of replacement, as well as similar technology when determining the official price, cost-effectiveness, and other factors.

4.1.4 However, if the results are expected to vary greatly depending on the selected comparator, cost-effectiveness should be evaluated in comparison with multiple healthcare technologies.

4.2 If the comparator cannot be definitively determined according to the principles of 4.1 or if the analysis based on the principles has some problems, comparator(s) should be selected through preliminary consultation.

4.3 Sufficient explanation of the reasons underlying the selection of the comparator(s) is needed.

5 Additional benefit in effectiveness/safety

5.1 When a cost-effectiveness evaluation is conducted, the additional benefit in effectiveness, safety, and/or other factors of the technology should be evaluated.

5.2 Evaluations of the additional benefit in effectiveness, safety, and/or other factors should be conducted on the basis of a systematic review of comparative studies [randomized controlled trials (RCTs), as a rule]. The studies should be compared with the healthcare technology selected in section "4. Comparators." The results of unpublished clinical studies/trials may also be included in the systematic review if they are deemed appropriate.

5.2.1 When a systematic review is conducted, clinical questions (CQs) should be clearly presented. For example, a definition of structured CQs according to PICO (P: patient, I: intervention, C: comparator, O: outcome) may be provided.

5.2.2 When setting the endpoint of additional effectiveness, safety, and/or other factors, the endpoint does not always need to match the outcome used in the cost-effectiveness analysis. However, the above-mentioned evaluation should use a clinically significant endpoint for the technology (if possible, a "true endpoint" or inclusion of its analogs).

5.2.3 It is acceptable to utilize any existing reliable systematic review. In such cases, the existing review will be used directly or in combination with a new additional study. In this case, it should confirm the consistency of the existing review by considering the CQs and coverage of the most recent literature.

5.2.4 If deemed appropriate, meta-analysis results should be presented. In such cases, the required reporting factors include the employed statistical method, assessment of heterogeneity, forest plot, integrated results, and confidence interval, among others.

5.2.5 When a systematic review is performed as described in item 5.2, a description of the inclusion/exclusion criteria, databases used, search algorithm, and research selection process is required in accordance with the PRISMA statement.

5.3 If no studies or only insufficient studies involving comparisons with the healthcare technology selected in section "4. Comparators" are available but other comparative studies are present, a systematic review should be performed using a process similar to that described in item 5.2, and the results should be presented.

5.3.1 It is acceptable to add results obtained through an indirect comparison based on a systematic review conducted in accordance with item 5.3.

5.3.2 If an indirect comparison is conducted, sufficient discussion of the prerequisites for the indirect comparison (e.g., illness, severity, patient background) is also needed, and anticipated biases should also be considered.

5.4 If there is no available comparative study of the technology, the results of single-arm studies of the target technology and comparator(s) must be presented in a systematic review.

6 Methods of analysis

6.1 A cost-effectiveness analysis that calculates cost and effectiveness separately without converting effectiveness into monetary units should be used.

6.2 If the analysis described in section "5. Additional effectiveness/safety" allows a judgment that reveals additional benefit in effectiveness and/or safety, the incremental cost-effectiveness ratio (ICER) should be calculated from the expected cost and effectiveness in each group.

6.3 In the following cases, only the expected cost and effectiveness in each group need to be presented, and the ICER calculation should be omitted.

6.3.1 If the technology is equivalent or superior in terms of effectiveness (non-negative incremental effectiveness) and lower in terms of cost, relative to the comparator. In this case, the technology is deemed "dominant" without a calculation of ICER.

6.3.2 If the technology is equivalent or inferior in terms of effectiveness (non-positive incremental effectiveness) and higher in terms of cost, relative to the comparator. In this case, the technology is deemed "dominated" without a calculation of ICER.

6.3.3 If the technology is deemed "dominated" by means of extended dominance through a simultaneous evaluation of multiple technologies. In this case, the judgment of "extended dominance" is passed without a calculation of ICER.

6.3.4 A cost comparison with the comparator (so-called "cost minimization analysis") should be performed if the analysis described in section "5. Additional effectiveness/safety" fails to demonstrate additional benefit in effectiveness or safety relative to the comparator, but the outcome of the technology appears

equivalent to that of the comparator.

6.4 If the cost and/or effectiveness in a target population or with a method of use are highly heterogeneous, a subgroup analysis should be performed.

6.5 If a cost-effectiveness analysis published in an academic journal or the results of an evaluation at a major overseas health technology assessment (HTA) organization are available, these results should also be presented.

7 Time horizon

7.1 The time horizon should be sufficiently long to evaluate the influence of the technology on cost and effectiveness.

7.2 The same time horizon should be applied for both cost and effectiveness.

7.3 The reason for setting this time horizon should be specified.

8 Choice of outcome measure

8.1 The quality-adjusted life year (QALY) should be used as a basic outcome. Other outcome can be used depending on the characteristics of the illnesses, drugs, and/or medical devices.

8.1.1 When QALY is used, life year (LY) should also be presented, if the healthcare technology has effects on survival.

8.1.2 As a rule, if QALY is not selected as an outcome unit, appropriateness must be discussed through a preliminary consultation that considers the characteristics of the drugs, medical devices, or other factors.

8.2 When QALY is calculated, the QOL score should be reflective of the value for a general population using questionnaires (EQ-5D, SF-6D, HUI, etc.), the standard gamble (SG) method, and the time trade-off (TTO) method.

8.2.1 If Japanese QOL scores are newly collected for a cost-effectiveness analysis, the use of an instrument with a scoring algorithm developed in Japan is recommended.

8.2.2 If data corresponding to item 8.2 are unavailable, it is acceptable to use mapping of other appropriate patient-reported outcomes (PROs). When using a QOL score obtained from mapping, the conversion into a QOL score via an appropriate method should be explained.

8.3 When the QOL score is assessed, the subjects' own QOL responses should be used.

8.3.1 Answers from a proxy (e.g., family member, caregiver) may be used only when responses cannot be obtained from the subjects.

8.3.2 Proxy responses from a healthcare professional should be considered in light of possible discrepancies from subjects' own responses.

8.4 As long as a QOL score that satisfies item 8.2 and 8.3 is available, the use of Japanese results is preferentially recommended.

8.4.1 If Japanese research is absent or insufficient but high quality research is available overseas, it is acceptable to use the data collected overseas.

9 Sources of clinical data

9.1 Calculations of the ICER and other factors should preferentially use effectiveness, safety, and QOL data derived from high quality research, with a high evidence level reflective of practical clinical results.

9.1.1 The selection of effectiveness, safety, and QOL data on the basis of a systematic review of Japanese and overseas clinical research is recommended. This review may also include unpublished clinical study/trial data if deemed appropriate.

9.1.2 Data with a high evidence level should be used preferentially. The use of data deemed appropriate from the viewpoints of research quality, target population, and generalization is recommended (for example, it is possible that the results of a randomized controlled trial may differ markedly from practical clinical results).

9.2 Japanese data should be used preferentially if there is evident heterogeneity in effectiveness and safety between Japanese and overseas data with similar levels of research quality and evidence.

9.3 If the results of a single study are used although a systematic review has revealed the presence of multiple clinical studies, an explanation is needed regarding the reason for the selection of the single study.

9.4 If direct comparison data are unavailable or the available data are deemed unsatisfactory in terms of research quality or evidence level, it is acceptable to conduct an analysis through indirect comparison.

9.4.1 If an indirect comparison is conducted, refer to item 5.3.2.

10 Calculation of costs

10.1 The analysis should cover the following range of costs, depending on the perspective of the analysis.

	"Public healthcare payer"	"Public healthcare and long-term care payer"	Consideration of broader costs
Public healthcare costs	•	•	•
Long-term care costs		•	(•)
Productivity loss			•

10.2 The estimation should include not only the costs of the target technology and the comparator, but also the costs of factors such as adverse events and related future events.

10.3 Regarding costs such as those of the target technology and the comparator, the medical resource consumption and unit costs should be reported separately.

> **10.3.1** However, this provision does not necessarily apply to cases wherein the costs of adverse events and related future events are analyzed using the results of a claim analysis, existing cost-of-illness studies, or similar research.

10.4 An analysis of public healthcare costs should include not only the portion of costs paid by the insurer, but also those paid by the government and patients as copayment (i.e., total public healthcare expenses).

> **10.4.1** Depending on the situation, it may be acceptable to present an additional analysis that includes the costs of health checkups, vaccinations, or similar procedures that are funded publicly and not reimbursed by Japan's national healthcare insurance system.

10.5 Unit costs should be derived to the extent possible from the latest medical fee schedule, drug price list, or similar resources. It is particularly essential to use the latest unit costs

for the target technology or the comparator.

10.5.1 Unit costs at the time of analysis, rather than at the time of actual medical resource consumption, should be used.

10.5.2 If the use of unit costs at the same time point is difficult (e.g., analyses using data from past cost-of-illness studies, analyses of claims data), it is acceptable to make adjustments such as multiplication by the medical payment system revision rate. Such adjustments may be omitted if a sensitivity analysis has shown the influence on results to be minimal.

10.5.3 A scenario analysis using the prices of generic drugs should also be conducted if an influence on the results cannot be ruled out.

10.6 Unit costs of the targeted technology should be subjected to sensitivity analysis.

10.7 To enable a more appropriate evaluation of the influence of target technology introduction on other medical resource consumption, the estimation should be based on fee-for-service costs rather than diagnosis procedure combination (DPC)-based costs.

10.7.1 However, DPC-based costs may be used if a precise estimation of the costs is difficult (e.g., adverse events, related future events, and other factors) and the use of such expenses is unlikely to markedly affect the results.

10.8 Future costs should also be estimated on the basis of current medical resource consumption and unit costs.

10.9 Medical resource consumption should reflect the average quantity used (e.g., dose, body weight, height) and standard healthcare practices in Japan. If an appropriate reflection cannot be expected (e.g., overseas clinical study data, data from limited institutions), appropriate adjustment will be needed.

10.10 Costs include only related medical costs that are directly affected by the target technology, and do not include unrelated medical costs.

10.11 Calculations of medical resource consumption based on overseas data will require attention regarding possible differences in healthcare technology use between Japan and overseas countries. The unit costs in Japan should be reflected in the analysis.

11 Long-term care costs and productivity loss

11.1 Long-term care costs and productivity losses arising from an inability to perform work should not be included in the base-case analysis.

> **11.1.1** It is acceptable to include long-term care costs and productivity losses in additional analyses. However, judgments regarding the appropriateness of including productivity losses should take into account the possibility of working in the context of the illness characteristics, among other factors.

11.2 When long-term care costs are included in the analysis, these costs should be calculated based on the care level.

11.3 The amount utilized under public long-term care insurance should be based on the actual quantity of resources consumed. If this quantity is difficult to determine, it is acceptable to use the average amount utilized per beneficiary or similar data.

11.4 Decreases in productivity losses may be classified as follows:

(A) Decreases arising directly from healthcare technology (e.g., treatment-related shortening of hospital stay period);

(B) Decreases arising indirectly from outcome improvements (e.g., alleviation of illness, survival period extension).

When productivity loss is included in an analysis, only (A) should be included in the calculation of costs.

11.5 Productivity losses should be estimated using the human capital method. This method was designed to generate estimations based on the expected earned wage in the absence of illness.

> **11.5.1** The unit wage used for estimations of productivity loss should be the average wage across all industries, all ages, and both genders or the average wage

for each age group in all industries and both genders derived from the latest "Basic Survey on Wage Structure" (Wage Census), not to discriminate by income.

11.5.2 Estimations of productivity loss require an actual investigation of the employment status in the target population (i.e., a measure of the days or hours of work missed). The actual measured number of days or hours should then be multiplied by the average wage across all industries, all ages, and both genders to estimate productivity loss.

11.5.3 If the item described in 11.5.2 is difficult to perform, productivity loss should be calculated by multiplying the expected number of days (excluding holidays) or hours of work missed in the target population by the average wage across all industries, all ages, and both genders. A 100% employment rate should be assumed for those aged 18 years and older.

11.6 If other individuals (e.g., family members) experience productivity losses because of the provision of nursing or informal patient care, it is acceptable to count these productivity losses as costs under the same conditions and using the same methods as those used to calculate the patient's productivity loss.

11.7 Time costs that are unrelated to a decrease in work should not be included in the cost estimations.

12 Discounting

12.1 Future costs and effectiveness should be discounted and converted into current values.

> **12.1.1** Discounting is not needed if the time horizon is 1 year or less or is otherwise sufficiently short to ignore the influence of discounting.

12.2 Both cost and effectiveness should be discounted at a rate of 2% per year.

12.3 The discount rate should be subjected to a sensitivity analysis and should be changed at a rate of 0–4% per year.

13 Modeling

13.1 To predict prognosis and future expenses, it is acceptable to conduct a model analysis using a decision model, Markov model, and/or other models in accordance with the principle described in section 7.

13.2 When a model analysis is conducted, the validity of the model should be presented. For example:

(A) Internal validity: This addresses why a model with a given structure has been created, whether or not the natural course of illness has been sufficiently evaluated, whether or not the parameters used are appropriate, and other factors.

(B) External validity: This addresses whether or not the estimation yielded from the model is appropriate in comparison to other clinical data, and other factors.

13.3 The assumption used to create the model should be described clearly.

13.4 All parameters and data sources used for model creation should be described.

13.5 The model used and the calculation processes should be expressed in the form of electronic files and in a manner that can be understood by third-party experts and can change parameters.

14 Uncertainty

14.1 If the patterns of clinical practice or other factors are not uniform and this discrepancy could affect the results, analyses based on multiple scenarios should be conducted.

14.2 For situations wherein the uncertainty is large because of a long time-horizon, it is also necessary to perform a shorter-term analysis, such as an analysis of the period for which clinical study data are available.

14.3 If no available studies involve a comparison with the comparator according to the section section 5, particularly when a comparison has been made concerning results between single-arm studies, a sensitivity analysis with a sufficiently wide range is required because of the large uncertainty.

14.4 Sensitivity analyses are needed for parameters with large variances, those based on assumptions rather than actual data, those with possible heterogeneity between overseas and domestic data, and others.

14.5 A probabilistic sensitivity analysis is also desirable. In such a case, it is necessary to present the distribution used for analysis, scatter plots on the cost-effectiveness plane, and cost-effectiveness acceptability curves.