Development of an Official Guideline for the Economic Evaluation of Drugs/Medical Devices in Japan

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ABSTRACT

Objectives: In Japan, cost-effectiveness evaluation was implemented on a trial basis from fiscal year 2016. The results will be applied to the future repricing of drugs and medical devices. On the basis of a request from the Central Social Insurance Medical Council (Chuikyo), our research team drafted the official methodological guideline for trial implementation. Here, we report the process of developing and the contents of the official guideline for cost-effectiveness evaluation.

Methods: The guideline reflects discussions at the Chuikyo subcommittee (e.g., the role of quality-adjusted life-year) and incorporates our academic perspective. Team members generated research questions for each section of the guideline and discussions on these questions were carried out. A draft guideline was prepared and submitted to the Ministry of Health, Labour and Welfare (MHLW), and then to the subcommittee. The draft guideline was revised on the basis of the discussions at the subcommittee, if appropriate.

Results: Although the "public health care payer’s perspective" is standard in this guideline, other perspectives can be applied as necessary depending on the objective of analysis. On the basis of the discussions at the subcommittee, quality-adjusted life-year will be used as the basic outcome. A discount rate of 2% per annum for costs and outcomes is recommended. The final guideline was officially approved by the Chuikyo general assembly in February 2016.

Conclusions: This is the first officially approved guideline for the economic evaluation of drugs and medical devices in Japan. The guideline is expected to improve the quality and comparability of submitted cost-effectiveness data for decision making.

Keywords: cost-effectiveness analysis, discount, guideline, productivity loss, QALY.

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Introduction

Economic evaluation previously was largely unused in decision making as applied to the reimbursement or pricing of health care technologies (e.g., drugs, medical devices, and interventions) in Japan. Ever since 1992, when new medicines are added to the reimbursement list for public health care insurance, economic evaluation data can be submitted to the Ministry of Health, Labour and Welfare (MHLW; Ministry of Health and Welfare at the time). However, in Japan, almost all approved drugs are automatically reimbursed without referring to cost-effectiveness data. In addition, there is a lack of clear rules regarding how to use the submitted data for pricing. Therefore, even if economic data are submitted, many pharmaceutical companies do not believe that such data are reflected in the decision making on their products. As a result, economic data for only 8 new drugs were submitted to the MHLW from fiscal year (FY) 2006 to 2011, although reimbursement for 256 drugs was provided during the same period. With respect to medical devices and interventions (e.g., diagnosis and surgery), the MHLW requests economic data for reimbursement, but for the most part, these analyses merely compare costs (cost analysis) or are used for cost minimization (Table 1) [1].

In Japan, the official price of drugs and medical devices is determined by two methods: the cost calculation method and the similar efficacy comparison method. If a new product is rated as innovative, a premium can be applied to the daily price of a comparator (similar efficacy comparison method) or profit rate of a product (cost calculation method). The official price is revised every 2 years on the basis of results of the market price survey. Such prices and pricing systems for medicines, and devices are determined (strictly speaking, advised to the minister of MHLW) by a council established by the MHLW called the Central Social Insurance Medical Council (Chuikyo). From FY2012, discussions on
economic evaluation began within a subcommittee of the Chuikyo, that is, the Special Committee on Cost-Effectiveness Evaluation, which consists of 16 individuals (6 representatives of health care payers, 6 health care professionals, and 4 public interest [e.g., academics]), in addition to 4 industries and 3 health economists (coauthors: T. Fukuda, S. Ikeda, and T. Takura) as nonvoting members. Japan is one of the fastest aging countries in the world, and consequently suffers from a rapid rise of health care expenditures. This situation is exacerbated by newly developed and high-priced health care technologies such as anticancer and ant-hepatitis drugs. Despite this, cost-effectiveness has not been extensively used for health care policy decision making. Over the course of 4 years of discussions, the Chuikyo subcommittee members reached a consensus that cost-effectiveness evaluation (MHLW refers to economic evaluation as such) should be implemented on a trial basis from FY2016. The results will be applied to the future repricing of drugs and medical devices. According to their discussions, demonstrating the validity of official prices determined by the government from the perspective of cost-effectiveness is important. They also requested the consideration of a full-scale implementation and to expand the target technology to interventions using expensive devices by FY2018, that is, the year in which the pricing system is scheduled to be revised next. These activities are supported by the Basic Policy on Economic and Fiscal Management and Reform 2015 [2] as part of the Japanese government’s policy.

In the trial implementation of cost-effectiveness evaluation, manufacturers are requested to submit economic data to the MHLW. This evaluation, however, does not target all drugs and devices. Target products are determined by the Chuikyo, and selection criteria have already been set. First, regarding listed technologies for which reimbursement decisions were made between FY2012 and FY2015, four categories were set as target criteria for the recalculation of prices: 1) the highest premium rate, 2) 10% or more premium and the highest sales, in both of which cases the cost calculation method and the similar efficacy comparison method, excluding rare intractable diseases. The results of this evaluation are to be reflected in official prices with the next revision (in FY2018). Nevertheless, how to reflect the results has not yet been determined. This issue will be discussed by the Chuikyo and a consensus will be reached by the end of FY2017. Second, evaluations will be submitted for newly reimbursed technologies from FY2016 with the expectation of large sales to serve as reference material, and will not be reflected in official prices.

To apply the results of economic evaluation to health care decision making, there is a need to standardize the methods of cost-effectiveness evaluation. In the absence of guidelines, the methodology and quality of economic evaluation may vary widely. This leads to low comparability across different analyses, as well as low-quality analyses. An official guideline for economic evaluation has yet to be established in Japan, although our research team previously developed a guideline for academic researchers [3]. Many regions in Asia, such as Korea [4,5], Taiwan [6], and Thailand [7], as well as European countries have official guidelines. For this reason, our research team was asked to develop a methodological guideline for cost-effectiveness evaluation by the Chuikyo for trial implementation. Our submitted draft guideline was approved by the Chuikyo, and as a rule manufacturers must carry out the analysis stipulated by the guideline. When difficulties arise with following the guideline, manufacturers are asked to have a preliminary consultation with authorities to discuss the analysis method. Here, we report the process of developing and the contents of the official guideline for cost-effectiveness evaluation.

### Table 1 – Present state of economic evaluation submitted to the MHLW [1].

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Medicines</th>
<th>Medical devices</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA with QALY</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CEA with other outcomes</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cost-benefit analysis</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Others (e.g., cost analysis, cost minimization)</td>
<td>1</td>
<td>20</td>
<td>125</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>23</td>
<td>125</td>
</tr>
</tbody>
</table>

CEA, cost-effectiveness analysis; FY, fiscal year; MHLW, Ministry of Health, Labour and Welfare; QALY, quality-adjusted life-year.

† Data only for 8 new drugs, reimbursed from FY2006 to FY2011.

‡ There were 23 new devices with new functions, reimbursed in FY2011.

§ There were 125 interventions for which requests were sent for inclusion in the reimbursement list by academic societies in FY2011.

### Process and Methods

Main methodological issues were continually discussed at meetings of the Special Committee on Cost-Effectiveness Evaluation of the Chuikyo (hereafter, “subcommittee”) from FY2012. Most of the subcommittee members were not experts in economic evaluation, and some members had competing interests with each other. Three coauthors explained the concept of economic evaluation and technical terms, answered questions, and provided comments from the perspective of experts. These discussions led to the official publication of two interim reports from the subcommittee in September 2013 and August 2015. By August 2015, members of the subcommittee had reached a consensus on the following four points: 1) choice of outcomes, 2) range of costs, 3) comparators, and 4) data sources. The choice of outcomes was one of the most controversial issues within the subcommittee. On one hand, some members such as from medical associations and the industry strongly opposed the mandatory use of quality-adjusted life-year (QALY), as required by the National Institute for Health and Care Excellence (NICE) in England/Wales. On the other hand, some members, including insurers and health economists, supported the use of QALY. After long deliberations, a consensus was reached on the function of QALY, that is, QALY should be used as a basic outcome, but other outcomes are allowed to be used depending on the characteristics of the technology.

The second point was addressed as follows: Productivity loss should not be included in the costs in base-case analysis. According to subcommittee discussions, the estimation of productivity loss is less reliable because such loss largely varies depending on the estimation method. In addition, if productivity loss is much greater than the health care costs, the productivity loss would account for the major part of the cost. This makes it difficult to evaluate public health care expenses. The consensus regarding the third point was that the health care technology that is replaced by a new one and is used widely in clinical practice...
should be selected as the comparator. With respect to the final
point, data used in the evaluation should be based on a
systematic review, the importance of which was emphasized in sub-
committee discussions.

In the interim report published in August 2015, the subcom-
mittee also agreed that the guideline for cost-effectiveness
evaluation would be drafted by our research team, with funding
from the MHLW. This guideline must reflect the aforementioned
key discussions of the subcommittee, although many of the
technical details had not been worked out yet. Our research team
considered the remaining issues from an academic perspective.

Our suggested guideline [3] for academic researchers was
already presented to the subcommittee as reference material in
December 2013. Therefore, we revised that guideline to reflect the
contents of the subcommittee discussions and considered the
requirements for trial implementation (e.g., to evaluate both new
and already-listed technologies). Team members generated research questions for each section of the guideline. Some
questions were related to methodological issues. Discussions on
these questions were carried out by referring to various docu-
ments (such as the guidelines of other countries), technical
documents generated by health technology assessment (HTA)
agencies, published articles, and original systematic reviews, as
appropriate. Guidelines from other countries were available from
the respective HTA agency Web sites. Our team members searched PubMed and a Japanese medical database (Ichushi) for
published articles. After internal discussions, a draft guideline
was prepared and submitted to the MHLW, and then to the
subcommittee. The draft guideline was also reviewed by manu-
facturers of drugs and medical devices, and their comments were
reflected in the draft guideline, when appropriate. An updated
version of the guideline was submitted to the subcommittee in
November 2015, and a version with further minor revisions was
submitted in January 2016. In February 2016, our guideline
was officially approved by the Chukyo general assembly. Although
the original version of the guideline is in Japanese, we translated
it into English.

Results
Referring to the guidelines of other countries [5–22] and previ-
ously proposed guidelines for academic researchers in Japan
[3,23], we decided to include the following 15 sections in the
guideline: 1) objectives, 2) perspective of analysis, 3) target
population, 4) comparator(s), 5) additional benefit in effective-
ness/safety, 6) method of analysis, 7) time horizon, 8) choice of
outcome, 9) sources of clinical data, 10) calculation of costs, 11)
long-term care costs and productivity loss, 12) discounting, 13)
modeling, 14) uncertainty, and 15) reporting/publication. The full
text of the developed guideline is provided as an Appendix. A
summary of the guideline is presented in Table 2.

Perspective of Analysis
The range of costs for economic evaluation is determined by the
perspective of analysis. Analysis from the “public health care
carer’s perspective” should include only public medical costs,
which are generally covered by public health care insurance in
Japan. In this guideline, the “public health care payer’s perspec-
tive” is a perspective for base-case analysis on the basis of the
subcommittee discussions and must be included even when other
perspectives are applied. In Japan, costs of health care
technologies for prophylaxis (e.g., vaccinations) are not included
in public medical costs. Nevertheless, if these costs are paid for
using public funding, they can be included in costs in addition to
an analysis from the “public health care payer’s perspective.”

| Table 2 – Summary of Japanese guideline for cost-
effectiveness evaluation. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Perspective</td>
<td>“Public health care payer’s perspective” is considered standard. Other perspectives can be applied, as necessary.</td>
</tr>
<tr>
<td>Target population</td>
<td>Patients who meet the indication of the technology at the time of analysis</td>
</tr>
<tr>
<td>Comparator</td>
<td>Technology, reimbursed by public health insurance, widely used in clinical practice and expected to be to a large extent</td>
</tr>
<tr>
<td>Additional benefit</td>
<td>The additional benefit in terms of effectiveness, safety, and/or other factors of the technology should be evaluated on the basis of a systematic review.</td>
</tr>
<tr>
<td>Method of analysis</td>
<td>CEA (basically, CUA should be used)</td>
</tr>
<tr>
<td>Results of analysis</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td>Should be performed if needed</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Long enough to evaluate the value of health care technologies</td>
</tr>
<tr>
<td>Outcome measure</td>
<td>QALY should be used as a basic outcome.</td>
</tr>
<tr>
<td>Methods to derive QOL score</td>
<td>Preference-based instruments with scoring algorithms developed in Japan</td>
</tr>
<tr>
<td>Mapping</td>
<td>Systematic review</td>
</tr>
<tr>
<td>Sources of clinical data</td>
<td>Yes</td>
</tr>
<tr>
<td>Indirect comparison</td>
<td>All costs paid by public insurers, central and local governments, and patients; productivity loss, depending on choice of perspective</td>
</tr>
<tr>
<td>Costs to be included</td>
<td>Medical fee schedule and drug price list set by the MHLW</td>
</tr>
<tr>
<td>Estimation of productivity loss</td>
<td>Human capital method</td>
</tr>
<tr>
<td>Discount rate</td>
<td>2% (sensitivity analysis 0–4%)</td>
</tr>
<tr>
<td>Modeling</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Deterministic and probabilistic sensitivity analyses</td>
</tr>
<tr>
<td>Reporting</td>
<td>The style set should be used. The analysis/review results should be made public.</td>
</tr>
</tbody>
</table>

Costs of long-term care for the elderly in Japan are reimbursed
by public long-term care insurance. When considering this social
security system, the “public health care and long-term care
payer’s perspective” can be used to add the costs of public
long-term care to public medical costs.

If the introduction of a health care technology directly
influences the productivity of patients, it is acceptable to perform
an analysis that considers broader costs and counts productivity
loss as a cost. Analyses that include productivity loss are some-
native to an analysis that considers broader costs and counts productivity
loss as a cost. Analyses that include productivity loss are some-

| CEA, cost-effectiveness analysis; CUA, cost-utility analysis; MHLW, Ministry of Health, Labour and Welfare; QALY, quality-adjusted life-year; QOL, quality of life. |
with the corresponding South Korean guideline [5], which recommends the “limited societal perspective.”

The names of perspectives are not globally consistent. The French guideline [16] recommends use of the “collective perspective,” which considers only direct medical costs. The Belgian guideline [17] uses the term “perspective of health care payer,” and the guideline in New Zealand uses “perspective of funder” [19]. Although the names of these perspectives differ, our perspective of base-case analysis is identical with these guidelines. It is noteworthy that the Canadian guideline [10] applies the perspective of the publicly funded health care system and recommends the inclusion of time costs to patients and their families, which differs from the Japanese guideline.

The guidelines of England/Wales [20], Scotland [11], and Ireland [14] state that social care costs should be included in the base-case analysis. Other countries (e.g., the Netherlands [22], Sweden [9], Norway [18], Finland [21], Portugal [8], and Taiwan [6]) apply the “societal perspective.” Inclusion of these “additional” perspectives is permitted in the Japanese guideline, although the “public health care payer perspective” is a perspective for the base-case analysis.

Target Population and Comparators

Patients who meet the indication of the technology should be considered as the target population. As with other guidelines, the replaced and widely used technology in clinical practice should be used as a comparator(s). Considering the evaluation of already-listed technologies, the comparator is limited to technologies that exist when the new technology is introduced. If multiple technologies are potential candidates to be a comparator, the technology should be selected on the basis of the extent of replacement, similarities in technology when determining the official price, cost-effectiveness, and other factors.

If different major populations and/or comparators can be selected, and cost-effectiveness varies depending on them, an analysis should be conducted for each population and comparator. Nevertheless, as multiple analyses are often difficult, such situations should be discussed at preliminary consultations.

Additional Benefit in Effectiveness/Safety

Before cost-effectiveness is calculated, the additional benefit of the technology in terms of effectiveness/safety must be evaluated on the basis of a systematic review. The guideline recommends that a PICO-style (P: patient; I: intervention; C: comparator; O: outcome) research question be provided. If a head-to-head comparison does not exist, an indirect comparison is allowed. If there is no clear additional benefit (i.e., if incremental effectiveness is 0), a cost comparison with the comparator must be performed.

Method of Analysis

In general, economic evaluation is classified into four types of analyses [26]: 1) cost minimization analysis (CMA; costs are calculated only when an equivalence of outcome is shown), 2) cost-effectiveness analysis (CEA; outcomes are measured by a natural unit such as life-years gained or event avoided), 3) cost-utility analysis (CUA; QALY is used as the outcome unit), and 4) cost-benefit analysis (CBA; outcomes are valued in monetary units). CMA is treated as a part of CEA by Drummond et al. [27].

CMA, CEA, and CUA are occasionally regarded as the same type of analyses because outcomes and costs are calculated separately with different units. In this guideline, they are treated as the same CEA, and CEA is recommended in this sense. This usage of CEA conforms to subcommittee discussions. In addition, incremental cost-effectiveness ratio should be used for the results of CEA without a dominant or dominated case.

Choice of Outcome Measure

QALY should be used as a basic outcome in this guideline on the basis of the subcommittee discussions. Other outcomes can be used depending on the characteristics of the disease, drugs, and/or medical devices. If QALY is not selected as an outcome, appropriateness must be discussed through a preliminary consultation that considers the characteristics of the drugs, medical devices, or other factors.

QALY is the most preferred outcome measure in the guidelines of many countries (e.g., England/Wales [20], Scotland [11], the Netherlands [22], Sweden [9], Finland [21], Norway [18], Ireland [14], and New Zealand [19]), and is one of the preferred outcome measures in other countries (e.g., France [16], Belgium [17], Canada [10], Australia [12], and Poland [13]). It is noteworthy that French and Belgian guidelines recommend the use of only life-year (LY) or QALY. The Japanese guideline prefers QALY and is in line with the former countries in this regard, but it also recommends that an LY-based analysis be submitted if the evaluated technology impacts LYS.

When new quality-of-life (QOL) data for economic evaluation are collected, preference-based measures with scoring algorithms developed in Japan should be used. For example, the EuroQoL five-dimensional questionnaire (EQ-5D [28–30]) meets this requirement. Direct methods such as standard gamble and time trade-off are less preferred. Nevertheless, in this guideline, because only a few domestic surveys on QOL scores are available, this rule cannot be applied to all existing QOL scores used for economic evaluation. If QOL data are not available, QOL scores converted from other patient-reported outcome data by mapping are also allowed.

In the guidelines of England/Wales [20], the Netherlands [22], and New Zealand [19], only the use of the EQ-5D is recommended. The French guideline [16] allows the use of the Health Utilities Index 3 in addition to the EQ-5D. The guidelines of some countries (e.g., Belgium [17], Norway [18], and Ireland [14]) do not refer to any specific instrument, although they recommend the use of generic preference-based measures rather than direct methods. The guidelines of the other countries do not have a preference between direct and indirect methods.

Costs

Costs are calculated from the sum of each item’s subtotal costs, which can be obtained by multiplying unit costs by medical resource consumption. The latest (not at the time of consumption) medical fee schedules and drug price list set by the MHLW should be referred to for unit costs. In some cases such as claims data analysis (of public health care insurance in Japan), it may be difficult to adjust unit costs by the latest fees or prices. If sensitivity analysis confirms that the results of CEA are not influenced by differences in unit costs, costs can be calculated without adjustment.

In Japan, some hospital costs are reimbursed by a fee-for-service system and others by a diagnosis procedure combination/per-diem payment system, similar to the diagnosis-related group/prospective payment system in terms of inclusive payment. The fee-for-service system is recommended for calculation of hospital costs. When costs such as adverse events and future events are difficult to calculate on a fee-for-service basis, average prospective payment may be applied, but not for the target technology.

There is some controversy regarding how to treat unrelated medical costs in economic evaluation [31–37]. Treatment of high
blood pressure reduces mortality from cardiovascular events and stroke and leads to prolonged life and increased unrelated medical costs (e.g., dementia, diabetes, and dialysis). The present guideline recommends the exclusion of unrelated medical costs given the difficulty of rigid estimations. The guidelines of many countries also recommend not including unrelated medical costs. Interestingly, however, the Swedish guideline [9] states that all unrelated costs (including all costs relating to social security etc.) should be included as “consumption minus production.”

Productivity Loss
Productivity loss, caused by missing work or being less productive because of disease, can be included in costs depending on the selected perspective. When included in the analysis, analysis without productivity loss should also be conducted simultaneously.

The range of productivity loss included in the analysis can include family members or friends rather than patients alone. According to this guideline, only a productivity loss directly attributable to the health care technology (e.g., shortened hospital stay) is permitted for inclusion. An indirect productivity loss resulting from an improvement in the patient’s health status (e.g., survival period extension) should not be included in productivity loss to avoid double counting (i.e., counting a factor for both effectiveness and costs) and overestimation.

Productivity loss estimation based on lost wages is referred to as the “human capital method.” If full employment is not achieved, however, the work is often performed by other people and long-term productivity may not be lost. There is some insistence that only friction costs [38,39] should be included on the basis of the period needed to restore the initial production level. Indeed, economic evaluation guidelines of some countries (e.g., the Netherlands) recommend the friction costs method [40]. In the Belgian guideline [17], friction costs are used for long-term absence on the basis of the notion that “vacant workplaces can be filled again within a certain period of time,” although the human capital method should be used for short-term absence. In the Japanese guideline, the human capital method is recommended for ease of calculation; nevertheless, productivity loss arising from outcome improvements (i.e., one of long-term productivity losses) cannot be included.

The human capital method is also recommended in many countries (e.g., France [16], Belgium [in case of short-term absence] [17], and Poland [13]). Some economic evaluations include time costs for hospital visits or hospitalization (e.g., Canadian guideline [10]), even if they are unrelated to a reduction in work. For a more conservative estimation, however, time costs should not be included in this guideline.

Discounting
A discount rate of 2% per annum for costs and outcomes is recommended. We further recommend that the discount rate be changed from 0% to 4% per annum for sensitivity analysis.

A discount rate of 3% per annum is often used, for example, as suggested by a Washington panel [41], but there is no clear rationale for using this rate in Japan. Recommended discount rates vary by country. For example, a discount rate of 3% is used in Sweden [9] and Finland [21]; 3.5% in England/Wales [20], Scotland [11], Ireland [14], and New Zealand [19]; 4% in France [16] and Norway [18]; and 5% in Canada [10], Australia [12], Portugal [8], South Korea [5], and Taiwan [6]. There are different methods and views regarding the determination of discount rates [42–47]. One is based on the real interest rate of low-risk bonds (e.g., long-term government bonds) [47]. The nominal interest rate of 10-year Japanese government bonds over the past decade ranged from 0% to 1.5%, deflation has continued, and the consumer price index has increased by an average of 1% to –1% per annum. Considering these factors, a discount rate of 3% per annum may be too high. The present guideline thus uses a discount rate of 2% per annum. This rate, however, should be reconsidered if economic conditions in Japan change substantially.

In some countries, different discount rates for costs and outcomes are applied with the assumption that the value of health will increase [42]. For example, discount rates in the Netherlands [22] and Belgium [17] are 4% and 3%, respectively, for costs, and 1.5% for outcomes in both countries. In Poland [13], discount rates of 5% for costs and 3.5% for outcomes are recommended. In the present guideline, the same discount rate is used because the growth rate of the value of health is unclear.

Uncertainty
There are numerous uncertainties associated with the results of economic evaluation. Thus, it is important to quantify and present the degree of uncertainty in a clear manner. Heterogeneity is a part of uncertainty in the broad sense. It means that factors such as comparators, patterns of clinical practice, and patient populations vary. If these factors vary to an extent that influences results, sensitivity analysis should be performed on the basis of various scenarios.

We classified uncertainty narrowly as 1) model uncertainty and 2) parameter uncertainty. Model uncertainty results from methodological uncertainty and the structure and assumption of models. Methodological uncertainty arises from issues such as discount rates and methods to estimate QOL scores that cannot be theoretically decided in one way. Uncertainty due to the structure and assumption of models arises from factors such as modeling of health states and treatment process, selection of parameters, and assumptions that extrapolate observed data for prognosis predictions. These types of uncertainties should be evaluated in a sensitivity analysis of parameters. In addition, if analyses have a high degree of uncertainty because of a long time horizon, analyses with a shorter time horizon should also be performed.

Parameter uncertainty results from uncertainty in parameter estimations. To deal with uncertainty caused by statistical inference, probabilistic and deterministic sensitivity analyses should be performed [48,49]. In the present guideline, probabilistic sensitivity analysis is also recommended, when possible.

Reporting/Publication
The model and other parameters for the CEA should be submitted in the form of an electronic file by manufacturers. The file must be understandable to third-party experts and the parameters must be editable. The analysis/revie results should also be made public. If, however, some incorporated data are difficult to publish because of intellectual property considerations, these data may be specified in advance.

Discussion
This is the first officially established guideline for economic evaluation in Japan. The guideline was drafted on the basis of discussions with the Chuikyo subcommittee. Most of the subcommittee members were not experts in economic evaluation, and some members had competing interests with each other. This is the main reason for the delay in obtaining a consensus. By the end of the discussions, many members readily understood the concept of economic evaluation, even from a technical perspective. Although the consensus reached on methodological issues appeared reasonable to us, further discussions may contribute to consensus building among various stakeholders.
The process and timeline from trial implementation to full implementation is unclear, because this depends on future discussions within the Chuikyo. Our guideline is intended for the trial implementation phase. If the policy of economic evaluation largely changes by the time of full implementation, the guideline may need to be revisited and revised.

We established a methodological guideline for cost-effectiveness evaluations, although positive issues need to be addressed for full implementation. For example, in Japan, there is a shortage of experts in economic evaluation. Experience of performing such evaluations is also limited in industries, because economic data have not been requested from authorities for a long period. Capacity building for cost-effectiveness evaluation is important for full implementation. Moreover, Japanese data on costs and QOL for economic analysis are at present insufficient. Thus, we as health economists must promote the collection of data, in particular those pertaining to QOL and costs.

This guideline requires that results of economic evaluation be reported in a particular style, which we modeled after the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement developed by the ISPOR task force [50] and the style used by other HTA agencies. A common style is important for standardizing and improving the quality of reports, and the present style requires the following eight items: 1) characteristics of drugs or medical devices, 2) setting of CEA, 3) additional benefit in effectiveness/safety, 4) detailed analysis method, 5) results of analysis, 6) data for review, 7) members involved in the analysis, and 8) references. Some subitems also exist under the eight items. This style was reviewed by the manufacturers of drugs and medical devices.

We did not include the controversial issue of equity considerations for QALYs. The controversy relates to whether all QALYs should be equally treated or should be weighted on the basis of the situation [51–53]. For example, NICE considers QALYs gained at the end of life, although they insist “in the reference case, an additional QALY should receive the same weight regardless of any other characteristics of the people receiving the health benefit” [20]. We believe that equity considerations are important, and the Chuikyo subcommittee expressed an interest in ethical considerations in cost-effectiveness evaluation. Ethical and social issues should be discussed in the future in the presence of an expert organization on cost-effectiveness evaluation, which was newly established for the “appraisal” phase. Unlike the NICE guideline [20], the present guideline focuses only on the “assessment” phase.

In the trial implementation phase, the cost per QALY threshold is not determined. Some Chuikyo subcommittee members supported the role of a threshold and the MHLW also suggested the introduction of a threshold. This was, however, opposed by some members. Therefore, unlike the NICE guideline, the present guideline does not provide a cost per QALY threshold value. Our research team suggested to the Chuikyo three methods to calculate the threshold: 1) comparison with the efficiency of technologies already being reimbursed (i.e., opportunity costs), 2) willingness to pay, and 3) gross domestic product per capita. Referring to values determined by these, discussions on threshold will continue among members of the subcommittee during the trial implementation phase.

We believe that our newly developed guideline will contribute to the improved quality and comparability of submitted cost-effectiveness data by manufacturers. It may also facilitate discussions at the Chuikyo and contribute to the definitive introduction and expansion of target technologies.

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Supplementary Materials

Supplementary material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2016.08.726. or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

R E F E R E N C E S


