HGPI Expert Policy Advocacy Platform Project

Better Use of "Cost-effectiveness Evaluation for Pharmaceuticals" in Japan
Policy Proposal

Ataru Igarashi

Fellow, Health and Global Policy Institute

Project Associate Professor, Graduate School of Pharmaceutical Sciences,
The University of Tokyo
Visiting Associate Professor, Graduate School of Data Science,
Yokohama City University

Specified Nonprofit Corporation, Health and Global Policy Institute

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Executive Summary

Better Use of Cost-Effectiveness Evaluation for Pharmaceuticals in Japan

In FY2022, Health and Global Policy Institute (HGPI) launched the "HGPI Expert Policy Advocacy Platform" to facilitate the creation and promotion of policy recommendations presented by individual HGPI Fellows and others associated with the Institute. These recommendations address urgent topics recognized by our Fellows and undergo careful examination from HGPI's internal review committee. After approval, they are presented as policy recommendations from HGPI to provide options to citizens interested in policy. In doing so, we hope to produce a wide variety of both feasible and creative solutions to pressing health policy issues.

As the second item in this project, HGPI Fellow Dr. Ataru Igarashi has presented the following policy recommendations, titled "Better Use of Cost-Effectiveness Evaluation for Pharmaceuticals in Japan." In discussions on the topic of cost-effectiveness evaluation (CEE) of pharmaceuticals, an increasing number of opinions on expanding Japan's evaluation system have been expressed in recent years. These recommendations offer suggestions regarding the ideal form of accountability for better use of CEE and methods of achieving effective use of CEE in Japan. Please note that this proposal represents the personal views of Dr. Igarashi and does not represent the views of HGPI.

Background

- Since CEE was institutionalized in Japan in April 2019, it has been positioned as a complement to the National Health Insurance drug pricing system rather than as a decision-making tool for reimbursement eligibility, and has been used to reduce prices after pharmaceuticals are listed. These price reductions have mainly targeted premiums applied to listed prices.
- Meanwhile, discussions have also been held on expanding CEE, with some expressing the view that CEE results should be used to significantly reduce prices or to determine eligibility for reimbursement.
- However, there have yet to be sufficient discussions on if CEE results or their significance are currently being adequately explained to citizens, or if expanding CEE will contribute to public access to pharmaceuticals.
- These recommendations will share methods for making more effective use of CEE in Japan.

① Current circumstances surrounding CEE and decisions on reimbursement eligibility in Europe and Japan

- England, Germany, and France (which are commonly-referenced examples from Europe) have different circumstances from Japan in terms of how CEE is related to decisions about reimbursement eligibility**,** drug pricing, or pharmaceutical access.
- In England, the result of CEE is one factor that is considered when determining reimbursement eligibility.
- There are no examples of the use of CEE from Germany.
- When certain conditions are met, France requires pharmaceutical companies to submit cost-effectiveness data, but CEE results do not influence decisions on reimbursement eligibility. Rather, CEE results only have indirect impacts on pricing negotiations.

② The impact of expanded CEE on access and responding to that impact

- Below, we will consider potential impacts and necessary measures if Japan were to use CEE results to determine reimbursement eligibility.
- If a pharmaceutical's eligibility for reimbursement was revoked based on the results of CEE that was conducted after it had already been granted regulatory approval and was listed, it would result in an ex post facto restriction of access and would likely result in extremely strong opposition from citizens and those serving in clinical settings. Given this potential impact, CEE results must be explained carefully, and a system must be designed in a manner that takes the need to ensure access to medicines into account.
- Granting reimbursement eligibility based on CEE results after regulatory approval but before listing will inevitably extend the period between approval and reimbursement. For citizens, this will limit access to new pharmaceuticals. It will be necessary to obtain sufficient public understanding of the need to revise the approval and listing processes.
- The expansion of CEE must not exacerbate drug lag or drug loss. It will be necessary to clarify which pharmaceuticals are to be excluded from evaluation (rare disease therapeutics, infectious disease therapeutics, pediatric medicines,

etc.) and to allow for flexibility in applying criteria for determining cost-effectiveness (such as incremental cost-effectiveness ratio (ICER) values).

Recommendations: Three key points to better utilize cost-effectiveness evaluation of pharmaceuticals

A. Ensure CEE results are communicated to the public in an accurate and easy-to-understand manner

The results of CEEs and the basis for those results—including the rationality for determining additional benefit and the content of discussions on appraisals—should be presented to the public and made available for third-party confirmation in a timely manner. At the same time, it will also be necessary to accurately communicate the content of CEEs to the public in terms that are easily understood.

B. Determine CEE results (i.e. conduct appraisals) with multi-stakeholder engagement

It will be necessary to consider if it is best to fully entrust CEE appraisals to expert committees that consist solely of specialists. CEE results should be a significant presence that contribute to achieving patient-led treatment by taking economic efficiency and patient benefits into account and by having participation from multi-stakeholders (including patients and long-term care providers) in addition to experts.

C. Develop human resources who can shoulder accountability for CEE results

Expanding CEE is highly likely to drastically change the nature of the public health insurance system in Japan and to directly impact pharmaceutical access for citizens. Given their great responsibility, the people involved in CEE must be professionally competent and have considerable insight to be accountable to the public.

Background

Of the 64 pharmaceuticals and medical devices designated eligible for evaluation since the April 2019 introduction of the CEE system, 34 pharmaceuticals and medical devices have completed evaluation (as of April 21, 2025).[1)] In Japan, this system is "a supplement to the drug pricing system" and is not used to determine health insurance reimbursement eligibility. Instead, it is a system for increasing or decreasing prices for items that have already been listed, mainly targeting the portions of listed prices that are premiums.

However, in discussions on promoting the further utilization of CEE, it has been expressed repeatedly at Central Social Insurance Medical Council meetings or at the Fiscal Council[2)] that CEE results should not only be used to determine drug price reductions that only target premiums, but should also be used to lower drug prices to those of comparative drugs or to determine reimbursement eligibility. Yet, these opinions on expanding CEE are limited to the extent to which the use of evaluation results should be expanded when considering the scope of insurance reimbursement. There are insufficient discussions on whether adequate explanations on the current situation surrounding the use of CEE results in Japan or the significance of that use are being provided to the public, or if those results are contributing to citizens' access to pharmaceuticals and medical devices as part of ongoing efforts to eliminate drug lag and drug loss.

Based on the premise that CEE will be further leveraged in the future and while reflecting on the current circumstances surrounding the use of CEE in Europe, these recommendations were created in recognition of the need to illustrate measures for the better utilization of CEE in Japan from the perspectives of ensuring public access to pharmaceuticals and upholding accountability to citizens. We hope these recommendations will contribute to discussions on enhancing the use of CEE to further benefit citizens.

① Current status of CEE and decision-making regarding reimbursement eligibility in Europe and Japan

The topics of ensuring the sustainability of public health insurance and improving access to pharmaceuticals have continuously been at the center of discussions in Japan and throughout Europe. Figure 1 below briefly introduces the relationships between CEE and insurance reimbursement eligibility, drug pricing, and pharmaceutical access in England, Germany, and France (which are commonly used as examples from Europe) and attempts to compare their circumstances with those in Japan.

Figure 1
Use of CEE for pricing and reimbursement eligibility decisions for pharmaceuticals in each country

	England	Germany	France	Japan
Determining reimbursement eligibility	• Performing appraisals ・Clinical usefulness ・**Cost-effectiveness** ・Other factors	• Based on **additional benefit** (using six-point scale)	• Based on medical benefit (SMR, four-point scale)	• In principle, receiving regulatory approval (when effectiveness and safety are confirmed) gives eligibility for reimbursement
Pricing (Pricing negotiation with manufacturer)	• When **CEE results** do not meet standards for reimbursement eligibility, confidential negotiations are sometimes held with manufacturers	• Confidential negotiations are held with manufacturers based on results of **additional benefits evaluation** (on six-point scale)	• Confidential negotiations are held with manufacturers based on results of **additional benefits evaluation** (ASMR, five-point scale)	• Determined by MHLW based on drug pricing rules • No negotiations with manufacturers are held

When reimbursement eligibility is determined in England, CEE results are one factor considered in appraisal. There are no examples of CEE results being used in Germany. In France, CEE results do not influence decisions on reimbursement eligibility. All three countries differ from Japan in that they negotiate with manufacturers on pricing

There are a number of agencies responsible for Health Technology Assessment (HTA)[1] in Europe. These include the National Institute for Health and Clinical Excellence (NICE) in England, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesunditswesen, or IQWiG) in Germany, and the National Authority for Health (Haute Autorité de santé, or HAS) in France. In England, NICE makes substantive decisions on reimbursement eligibility, while IQWiG in Germany and HAS in France are involved in pricing. In Japan, the roles of these HTA agencies are often misunderstood, with people mistakenly believing they only evaluate cost-effectiveness. This leads to the misinterpretation that cost-effectiveness is what determines reimbursement eligibility in England and pricing in France and Germany. As we will see below, these HTA agencies do not only handle cost-effectiveness. The functions of HTA agencies in each European country must be considered separately from the role of cost-effectiveness in their respective systems.

1. England

In England, new health technologies (including both pharmaceuticals and medical devices) that are recommended for use in the public health service are determined by NICE.[3)] The pharmaceuticals that are selected are analyzed by industry or academic groups, and final decisions regarding recommendations are made by multi-stakeholder committees after interpreting the results of those analyses while taking into account factors like clinical usefulness and cost-effectiveness compared to existing treatments. Even in cases where it is determined that analysis results do not meet the drug pricing criteria set by NICE, there are systems in place that enable companies to lower prices or take similar measures to ensure patients can access medicines, such as through confidential pricing agreements like Patient Access Schemes (PAS) or Commercial Access Agreements (CAAs).

There are also efforts underway at NICE to reduce the time between approval and reimbursement decisions. For pharmaceuticals that meet certain criteria, NICE aims to publish guidance (that includes content of recommendations on eligibility based on cost-effectiveness) within 90 days of receiving market authorization from the Medicines and Healthcare products Regulatory Agency (MHRA). While advancing efforts to reform the actual evaluation process, they aim to shorten the time required to provide guidance and improve patient access to medicines.

2. Germany

In Germany, the median time from approval to reimbursement is almost the same as Japan (1.6 months in Germany vs. 2.0 months in Japan) and is the shortest among European countries.[4)] This is because the 2011 Pharmaceuticals Market Reorganisation Act (Arzneimittelmarkt-Neuordnungsgesetz, or AMNOG) introduced a rule that allows for reimbursements at the desired prices of pharmaceutical companies who submit materials needed for evaluation (described below) to the German Federal Joint Committee (Gemeinsame Bundesausschuss, or G-BA). IQWiG[5)] evaluates the "extent of additional benefit" (Ausmaß des Zusatznutzens) within three months of launch and, using the results of that evaluation, the G-BA makes a decision within the following three months. For standard therapies, prices are negotiated with pharmaceutical companies after additional benefit is evaluated using a six-point scale, which includes: (1) major additional benefit, (2) considerable additional benefit, (3) minor additional benefit, (4) additional benefit not quantifiable, (5) no evidence of additional benefit, and (6) less benefit than comparator.

The function of IQWiG is limited to evaluating additional benefits, so while it corresponds to HTA for its broader definition, IQWiG is not conducting what could be referred to as CEE. When negotiations on how additional benefits are interpreted between pharmaceutical companies and IQWiG are unsuccessful and mediation has failed, AMNOG rules allow CEE as a last resort. However, there are no examples of CEE actually being conducted in Germany from 2011 to the present.

3. France

In France, the median time from authorization to reimbursement is 16.1 months.[4)] After evaluating materials submitted

[1] Broadly defined, HTA is "a multidisciplinary area of policy analysis that examines the medical, social, ethical, and economic impacts of the development, proliferation, and use of health technology," and it is not necessarily limited to health economic evaluation or CEE. However, when CEE is referred to as "HTA," a more narrow definition applies: "a research area that aims to streamline healthcare by determining the benefits of health technology or its pricing based on cost-effectiveness evaluation." Assessments of additional benefit conducted by IQWiG in Germany or HAS in France are included in the broader definition of HTA, but differ entirely from the more narrow definition that equates to CEE.

by pharmaceutical companies and holding discussions that involve clinical specialists and patients, HAS[6] provides notifications detailing "medical benefit" (Service médical rendu, or SMR) and "medical benefit compared to the standard of care" (Amélioration du service médical rendu, or ASMR) within 90 days. SMR is a four-point scale that indicates the need for reimbursement itself (major, considerable, minor, insufficient) and is used to determine eligibility for and rate of reimbursement. ASMR is a five-point scale for the additional benefits of existing therapies (Level I: major improvement, Level II: important improvement, Level III: moderate improvement, Level IV: minor improvement, and Level V: no improvement) and it serves as the basis for pricing negotiations with pharmaceutical companies. Reimbursement is determined after the completion of pricing negotiations with pharmaceutical companies, which is a factor for the extended period from authorization to reimbursement, but HAS introduced an accelerated certification system for innovative drugs in 2021.

Similar to IQWiG in Germany, the main function of HAS is to evaluate clinical usefulness (in terms of SMR and ASMR). For pharmaceuticals with ASMR ratings of Level III (moderate improvement) or above, negotiations proceed quickly and with favorable conditions for pharmaceutical companies (and result in prices that generally exceed European averages). Pharmaceutical companies wishing to receive ASMR ratings of Level III or above but whose products are likely to have a certain degree of financial impact have been required to supply data on cost-effectiveness since 2012. This is why comments to the effect of, "Cost-effectiveness is used for price adjustments in France, so they have a similar system to Japan" can sometimes be heard in Japan. However, whether the cost-effectiveness of an item is good or bad—in other words, its ICER value—is not directly linked to pricing in France. Instead, pricing is determined through negotiations with pharmaceutical companies. Rather than ICER value, problems related to cost-effectiveness data are assessed in terms of the methodology of evaluation methods using a three-point scale. If it is determined that a pharmaceutical has "major problems," the manufacturer loses the preferential negotiating rights granted at ASMR Level III or above. This is the extent of the use of CEE in France.

4. Japan

In Japan, the median time from approval to reimbursement is 2.0 months.[4] This is comparable to Germany, which has the shortest turnaround time in Europe. One could say this reflects the characteristics of Japan's drug pricing system, in which pharmaceuticals that have been granted regulatory approval are generally listed within 60 days in principle, or within 90 days at most.

However, in Japan's current CEE system, completing an evaluation based on appraisal and presenting results requires 15 to 18 months. This includes 270 days for pharmaceutical companies to conduct the industry analysis to meet the designated timing the item will be listed, which is followed by the public analysis which takes 90 days (for verification) or 180 days (for reanalysis). Public analyses are performed by the Center for Outcomes Research and Economic Evaluation for Health, or C2H,[7] then tentative evaluations are provided after the results are discussed by the Central Social Insurance Medical Council CEE Expert Committee. Final decisions are made at the Central Social Insurance Medical Council General Assembly.

Furthermore, while additional benefits are the first item evaluated in CEE in Japan, these evaluations go no further than to determine the presence or absence of additional benefits, and do not indicate degree of uncertainty. Outcome indicators used to assess additional benefits are also limited. ICER is calculated when findings indicate that there are additional benefits, and when they do not, one of two results is provided: "cost decrease" or "cost increase." However, these results do not impact reimbursement eligibility or rate of reimbursement. There are also no price negotiations with pharmaceutical companies based on CEE results, or similar discussions.

Perhaps owing to the fact that their systems are referred to as "cost-effectiveness evaluation," there are sometimes arguments that European countries only evaluate cost-effectiveness to determine reimbursement eligibility. However, as previously discussed, this understanding is not accurate. In England, both clinical benefit and cost-effectiveness are evaluated, and pricing is determined while also taking other factors like end of life, equity issues, and caregiver burden into consideration. Evaluation in Germany takes "extent of additional benefit" (Ausmaß des Zusatznutzens) into account, while

France examines "medical benefit compared to the standard of care" (Amélioration du service médical rendu). We must note that, as their names suggest, these evaluations determine if a pharmaceutical provides a positive effect relative to existing treatments (the standard of care), and to what extent. This means that a key point of note to keep in mind when advancing discussions is the fact that cost-effectiveness is only a single element in evaluating pharmaceuticals or determining eligibility for reimbursement (Figure 2).

Figure 2
Use of additional benefit and cost-effectiveness evaluations in each country

	England	Germany	France	Japan
Additional benefit evaluation	• Considered as one element for determining reimbursement eligibility	• Used in determining reimbursement eligibility based on **six-point scale evaluation** • Used in negotiations with manufacturers	• Used in negotiations with manufacturers based on **five-point scale evaluation**	• Used to adjust listed prices for some items **based on presence/absence** (part of CEE)
Cost-effectiveness evaluation	• Considered as one element for determining reimbursement eligibility • Used in negotiations with manufacturers	• No substantive use	• Used in negotiations with manufacturers	• Used to adjust listed prices for some items

Although they are not sufficiently distinguished from each other, additional clinical benefit and costeffectiveness are treated as different concepts in Japan's system. Also, methods of utilizing evaluations vary among England, Germany, and France, and are not uniform.

② **The impact of expanded CEE on access and responding to that impact**

There are three main approaches being examined in discussions on expanding the CEE system in Japan: (1) expand selection criteria for CEE and increasing the number of products eligible for CEE; (2) expand the scope of pricing adjustment based on CEE results to significantly reduce drug prices; or (3) expand the use of CEE results from pricing adjustments to also include insurance reimbursement eligibility, creating a place in the market for pharmaceuticals that have been granted regulatory approval but are not covered by insurance.

In these recommendations, we would like to delve into the third option, which is based on the systems used in Europe and in which Japan would use CEE results to determine reimbursement eligibility as well as in calculating drug prices. In general, there are two potential scenarios based on the timing CEE is performed, discussed below. We would like to examine situations that are likely to occur in each scenario as well as necessary measures centered on access to pharmaceuticals, consistency with existing systems, and providing explanations to the public.

Scenario A
Pharmaceuticals would undergo CEE after receiving regulatory approval and being listed, and CEE results would be used to determine insurance eligibility and to recalculate listed prices.

Scenario B
Pharmaceuticals would undergo CEE after receiving regulatory approval but before being listed, and CEE results would be used to determine insurance eligibility and listed prices.

The timing of CEE in Scenario A would allow the system to maintain its current design, in which CEE was introduced to supplement the pricing system. However, if CEE results were used to determine an item was ineligible for reimbursement after reimbursements were already being provided, for citizens, this would result in an ex post facto restriction of access, which is when health services that were once available with insurance coverage become unavailable after a certain amount of time. Seeing access restricted for items that were once available would likely result in a great amount of

confusion for citizens as well as for people serving in clinical settings.

There are no examples of other countries using such systems. The negative impacts of cancelling eligibility for reimbursement would be significant, so in practice, it would probably be difficult to do so. At a minimum, to remain accountable to the public, it would be necessary to clarify that eligibility could be cancelled as a result of CEE at the time of the item's listing. In the event eligibility was actually cancelled, it would also be necessary to carefully explain how the evaluation gauged additional benefits and cost-effectiveness, which are the basis of CEE results. Instead of uniformly revoking eligibility for reimbursement based on CEE results, it will be necessary to design systems that take into account methods of ensuring access to pharmaceuticals. These might include, for example, continuing to provide reimbursements for patients who meet certain conditions, even when evidence of additional benefit is still insufficient.

Furthermore, when CEE results are used to recalculate a listed price and the adjustment exceeds the scope in which pricing can currently be adjusted, discussion points begin to emerge regarding how to recalculate prices based on CEE results in a manner that aligns with existing pricing rules, such as the similar drug efficacy comparison method used for drugs that have similar effects (when such drugs exist), the cost accounting method when similar drugs do not exist, and the usefulness evaluation method which gauges the benefits provided by pharmaceuticals.

Scenario B would allow items to be listed immediately after regulatory approval and would require drastic changes to characteristic features of Japan's health insurance system. Since it would add a step for CEE to be performed between approval and listing, it would lead to unavoidable delays for reimbursements, which could in turn delay access for the public and create a new form of drug lag.

Scenario B is similar to Scenario A in terms of accountability to the public, but it would be necessary to provide easy-to-understand explanations on the advantages and disadvantages of introducing the system and to help the public fully understand why the existing approval and pricing processes need to be changed. Determining how to ensure CEE results-based pricing would stay consistent with existing rules for pricing new medicines is likely to be more important in Scenario B. Despite the direct impact of pricing on treatment options and out-of-pocket costs for patients, how official medicine prices shape pricing itself has not been the topic of much discussion in the past, so this may create a stir.

From the perspective of the public's access to medicines, both scenarios will require designing systems that aim to avoid creating any effects that lead to drug lag or drug loss, which the national Government is currently advancing measures to eliminate. In the current CEE system, "items used only for the treatment of designated intractable diseases, items for hemophilia or HIV infection," and "items used only for children" are excluded from the scope of evaluation.[8)] To ensure that expanding the scope of CEE use does not disrupt incentives that encourage pharmaceutical companies to develop drugs in Japan, items that will be excluded from CEE that are particularly impacted by drug lag or drug loss (such as items for treating rare or infectious diseases or items used in children) must be further clarified. Another option may be to take steps to ensure flexibility in ICER criteria used to determine cost-effectiveness in the event such items are considered eligible for CEE. It will be necessary to avoid simple conclusions like, "Expanding the CEE system will be okay as long as it lowers drug prices."

Recommendations

Three key points to better utilize cost-effectiveness evaluation of pharmaceuticals

As discussed above, if Japan's CEE system is expanded and the results of such evaluations begin to be used to determine reimbursement eligibility, CEE results themselves will begin to have a major impact on public access to pharmaceuticals and medical devices. This will attract far greater interest toward CEE results than at present and will increase demand for accountability. Efforts to enhance accountability should not be limited to explaining the results of individual evaluations; it will also become necessary to discuss the process leading up to CEE results. Below, we would like to discuss three key points on defining the ideal form of accountability and methods of achieving it, even when information of a specialist nature must be communicated (Figure 3).

Figure 3
Summary of recommendations

Three key points to better utilize cost-effectiveness evaluation of pharmaceuticals

A. **Ensure CEE results are communicated to the public in an accurate and easy-to-understand manner**

B. **Determine CEE results (i.e. conduct appraisals) with multi-stakeholder engagement**

C. **Develop human resources who can shoulder accountability for CEE results**

A. Ensure CEE results are communicated to the public in an accurate and easy-to-understand manner

In Japan, CEEs that generate the result "additional benefits present" are included in the category for which ICER is calculated; otherwise, they are assigned "no additional benefits" and are categorized as "cost increase" or "cost decrease." CEEs that result in "no additional benefit" include those for which "the presence of additional benefits cannot be determined." Originally, there should have been a method to clearly distinguish the cases in which "no additional benefits" can be taken literally from the cases in which it means "the presence of additional benefits cannot be determined" as soon as CEE is complete. There are also some products assigned "analysis suspended" due to insufficient data or the need to collect additional data, and the criteria for this outcome are also unclear.

In practice, items that receive "no additional benefit" or "cost increase" results are interpreted, in a blanket manner, as having the same effects as comparable drugs but at increased cost. Some claim[9] that these results mean it is necessary for those serving in real-world clinical settings to determine medicine selection based on these results of this evaluation, but there is room for debate as to whether this interpretation is accurate.

In other words, additional benefits must be evaluated through the systematic review of randomized controlled trials in accordance with the CEE analysis guidelines.[10] CEE results of "no additional benefit" do not reflect points that become important when making decisions in real-world clinical settings, such as if sufficient consideration had been given to items like the patient population that underwent analysis, the selection of comparator drugs, if the indicators used for evaluation were clinically appropriate, or if the data used in the evaluation was up-to-date and scientifically relevant. CEE reports submitted to Central Social Insurance Medical Council General Assembly include the heading "Key Items for Consideration in Formulating the CEE Recommendation" in "Comprehensive CEE Appraisals," and in the past, these sections have only mentioned the differences in views between the industry analysis and the public analysis regarding "no additional benefit" outcomes a few times, in excerpts. (For more details, please see the column below titled, **"**Examining 'No Additional Benefits' Results for COVID-19 Therapeutics.")

In Japan, pharmaceuticals are listed after pricing is conducted based on the content of regulatory approval. In other words, approved pharmaceuticals have been recognized as safe and effective by a pharmaceutical affairs body of the Government. If one such product were to later receive a negative CEE result, some might perceive that as the Government sending

mixed messages. Currently, not only do members of the general public and patients lack an accurate understanding of CEE results, it is also difficult to say that these results are fully understood among people serving in clinical settings. In part, this may be due to the fact that discussions at the CEE Expert Committee are closed, and there are many pharmaceuticals for which minutes of the relevant meetings have not been disclosed even one year after evaluation.[11] Those minutes should be presented in a timely manner so third parties can confirm details regarding the content of CEEs, including various aspects of the discussions, such as their validity.

The term "cost increase" denotes that an item is as effective as the comparator technology, but at a higher cost, and this is easily misunderstood. When expanding CEE as a system, this result should be renamed to more clearly convey its intended meaning. It may be necessary to adopt more descriptive wordings that take the degree of additional benefit or uncertainty into account, like those used in Germany or France.

It will also be important for the decisions made after regulatory approval, listing, and CEE and the basis for those decisions to be organized and presented in an easy-to-understand manner. Regarding the differences in decisions for these items, if CEE results are used only to adjust the premium portions of listed prices (where the maximum possible reduction is 15% of the original listed price), CEE results would not attract interest from the public or people serving in real-world clinical settings, but if CEE results were used to determine reimbursement eligibility or were reflected in clinical guidelines and other guidance from academic societies, they would be an item that would demand attention in efforts to ensure that healthcare takes economic efficiency into account.

B. Determine CEE results (i.e. conduct appraisals) with multi-stakeholder engagement

Efforts to consider CEE from the perspectives of healthcare professionals or insurers are currently meant to take place at the Central Social Insurance Medical Council General Assembly. However, as previously discussed, neutral discussions on CEE from a specialist perspective are held at the CEE Expert Committee (hereinafter, "the Expert Committee"). In addition to reviewing the content of industry analyses and public analyses, specialist reviews at that committee also include the formulation of comprehensive proposals on CEE results called "appraisals." Deliberations on the recommended CEE results formulated in accordance with appraisals take place at the Central Social Insurance Medical Council General Assembly, which makes final decisions on CEE results.

In the future, if CEE results begin to directly impact public access to medicines (such as by determining eligibility for reimbursement), there will be room to consider if it will be appropriate to continue to fully entrust CEE appraisal to committees consisting solely of experts (namely, four specialists in health economics, two in clinical practice, three in medical statistics, and two in medical ethics).[12]

For example, involving people who could represent the perspectives of people living with the targeted disease or their caregivers alongside experts during the appraisal stage of CEE could make it possible for discussions to delve deeper into factors like the nature of the disease. Unfortunately, this is a subject that has received almost no discussion in Japan, and a committee member has pointed out the need to involve those most affected in the Expert Committee so it can serve as a system to collect a broad range of opinions of affected parties and attain consistency with similar systems overseas.[13] Patient involvement is one method being used at NICE in England, where it serves to help identify which elements of the drug being evaluated are deemed important by patients and to ensure there is sufficient discussion before reaching a decision. This decision-making method is highly significant for achieving patient-centered treatment, giving ample consideration to economic efficiency and patient benefits, and ensuring that CEE results do not impede access to medicines.

Performing appraisals with committees comprising a limited number of experts is unlikely to become a major issue if CEE results that indicate "additional benefit" or "cost-effective" continue to only be used for partial pricing adjustments. However, if CEE results are to also be used to determine reimbursement eligibility, it will be necessary to actively consider the need to involve a wider variety of stakeholders in performing appraisals and to deepen discussions.

C. Develop human resources who can shoulder accountability for CEE results

Strengthening the CEE system by securing and training human resources has been brought up repeatedly in discussions on the CEE system. As mentioned several times in these recommendations, expanding CEE is highly likely to transform the current state of public health insurance in Japan and directly impact the public's ability to access new pharmaceuticals and medical devices. In the future, the people involved in Japan's CEE system will shoulder even greater responsibilities than before. There are many issues that must be addressed, such as ensuring sustainability of the health insurance system while maintaining access to pharmaceuticals for citizens, or providing accountability by explaining CEE results to citizens in a manner that is easy to understand. This means that in addition to scientific and academic expertise, people involved in CEE must have broader perspectives than ever before.

Conclusion

Considering the sustainability of Japan's public health insurance system, there is a growing need to make effective use of CEE. However, as mentioned above, CEE is not a "silver bullet" that can instantly make healthcare economically sound by conducting analyses and generating results that can be used to lower drug prices or determine eligibility for reimbursement from insurance. When expanding the use of CEE, it will be necessary to hold discussions that reexamine the ideal structure of the system from the perspectives of maintaining and improving access to medicines in Japan while remaining consistent with Japan's existing pricing system (which differs from systems in Europe) and enhancing public accountability. After long discussions in Europe, which has been a leader in this area, processes[14)] for evaluating pharmaceuticals on the EU level are set to be introduced in January 2025, with the aim of reforming access to medicines for patients by accelerating decision-making for reimbursement eligibility and pricing. It is our hope that CEE in Japan does not become only a tool for reducing listed prices, but that future discussions will be held on obtaining ample understanding from citizens so CEE can be utilized in a manner that contributes to better healthcare access.

Column: Examining "No Additional Benefits" Results for COVID-19 Therapeutics

After undergoing Cost-Effectiveness Evaluation (CEE), some items are rated "no additional benefit" or "cost increase: item is as effective as the comparator technology, but at a higher cost." For example, Coronavirus Disease 19 (COVID-19) therapeutics Lagevrio and Xocova were rated "no additional benefits" or "poor cost-effectiveness," and these results even received newspaper coverage. During a discussion on Xocova at a General Assembly of the Central Social Insurance Medical Council,[1)] a medical specialist said, "We must avoid causing confusion in clinical settings," while an insurer said, "Therapeutic selection should be determined with a firm basis in evaluation results."

As mentioned in the body of these recommendations, in Japan, CEE results only describe the presence or absence of additional benefits, and do not indicate the degree of benefit. Given that context, what sorts of discussions took place for pharmaceuticals that were deemed to provide "no additional benefit"? In this column, we will briefly examine Expert Committee discussions on "additional benefits" using Lagevrio and Xocova as examples.

The first steps in Japan's CEE system are an industry analysis, followed by a public analysis. Based on the "Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council," these analyses "determine if the data demonstrates an additional benefit or not." These analyses are followed by an appraisal from the Expert Committee, which is basically a discussion on which is more appropriate between the industry analysis and the public analysis. As for the order of discussions at the Expert Committee, (1) first, the manufacturer or distributor shares opinions on the public analysis; then (2) the Expert Committee makes a judgment and decision in response to those opinions. The manufacturer/distributor can submit a written objection to the decision. If the content of that objection is accepted, the appraisal then indicates (3) the objection of the industry representative and (4) the Expert Committee's opinion on that objection. However, outside of what is shared in an excerpt from the "Key Items for Consideration in Formulating the CEE Recommendation" reported at the Central Social Insurance Medical Council General Assembly and in meeting minutes published on the MHLW's website, the content of these discussions is confidential. At the time of writing, minutes have not been published for the Expert Committee's meetings on Lagevrio or Xocova. Please bear in mind that the following is based on the limited information that has been made public.

Lagevrio was designated for CEE on August 10, 2022 and results were published on March 13, 2024.[2)] According to "Key Items for Consideration," the public analysis included an evaluation of results for a sample from the PANORAMIC trial in the UK and a retrospective observational study using a large database from overseas. It includes the statements, "The post-hoc analysis of the PANORAMIC trial showed a tendency of improved odds ratios for hospitalization or death in the subgroup age 80 years and older than in the overall population," and "Clinical experts suggest Lagevrio may have additional benefits for older adults, but further data and consideration are required." However, as age subgroups were not established and additional benefits were not evaluated in older adults (the population with the most important risk factors), it concluded that Lagevrio had "no additional benefit (the group could not determine that additional benefits were provided)." Further rationale for this decision included that "available evidence on treatment effectiveness was limited, so no subgroup difference for effect on incidence of hospitalization or death could be established."

In its response, the company argued that reduced incidence of hospitalization or death with Lagevrio was supported by real-world evidence as a whole. Its objection went further to question the validity of evaluating additional benefit solely on the PANORAMIC trial and reiterated its claim that Lagevrio provided additional benefit with new QOL data from that same trial.

The Expert Committee's conclusion favored the results of the PANORAMIC trial endpoint on severe COVID-19 outcomes, which had insufficient power, over real-world evidence including bias. Stating that the data was "of greater relevance to circumstances in Japan," it accepted the results of the public analysis and maintained the conclusion that Legevrio provided "no additional benefit."

As for Xocova, it was designated for CEE on March 8, 2023 and results were published on October 9, 2024.[3)] According to

"Key Items for Consideration," the public analysis found that randomized controlled trials "did not show data to support the efficacy of Xocova in preventing severe outcomes, improving symptoms, or suppressing post-COVID19 conditions" and that Xocova provided "no additional benefit (the group could not determine that additional benefits were provided)." The manufacturer stated that Xecovoa accelerates recovery of symptoms through early administration, thus demonstrating additional benefit by providing earlier recovery from the viral infection itself as well as earlier suppression of the inflammatory response. However, the Expert Committee concluded that while Xocova "could not be said to be completely ineffective" in reducing symptoms, it had "extremely poor cost-effectiveness, even after sensitivity analysis," and that it provided "no additional benefit."

In response to that outcome, the manufacturer submitted an objection that included new real-world evidence on Xocova's efficacy in preventing severe outcomes from data on Japanese subjects to argue that it provided additional benefits.

In its conclusion, the Expert Committee said the real-world evidence "is commendable in that it has been adjusted using currently available data on Japanese subjects, but it is insufficient as a scientific basis for additional benefit," and ultimately upheld the findings of the public analysis. Like Legevrio, the conclusion of "no additional benefit" for Xocova remained unchanged.

Among therapeutics for COVID-19, Paxlovid was also designated for CEE on March 8, 2022, but on September 11, 2024, the decision was made that it would be appropriate to conduct CEE on its additional benefit using data from the UK PANORAMIC trial, so analysis was suspended until the results of that trial were released.[4)]

Even though Lagevrio and Xocova treat the same condition, COVID-19, their evaluations had different content. However, even just by checking "Key Items for Consideration," we can see that discussions examined how to evaluate real-world evidence from Japan and overseas or issues related to uncertainty (as demonstrated by statements like "the evidence is limited" and "could not be said to be completely ineffective") before arriving at the conclusion of "no additional benefit." In particular, given changes in prevalent strains and vaccination coverage, real-world evidence and uncertainty should have been key discussion points for therapeutics for COVID-19. As mentioned in the main body of these recommendations, it will be necessary for the minutes of these meetings on CEE to be presented in a timely manner so third parties can confirm the content of the evaluations themselves as well as the validity of the discussions.

If CEE results indicate "no additional benefit," this result is simply stated as, "Cost increase: item is as effective as the comparator technology" in the final evaluation. However, minutes for Expert Committee appraisal meetings that include specific details regarding how these discussions proceed are not made public, and it is difficult for third parties to grasp their content only with the materials that are released. There may be room for discussion on whether it is appropriate to make decisions regarding drug selection in clinical settings based on CEE results of "no additional benefit."

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Expert Policy Advocacy Platform of the Health and Global Policy Institute (HGPI)

As a non-profit, independent health policy think tank, the Health and Global Policy Institute (HGPI) has been working to realize public- and party-driven healthcare policies by making a wide variety of policy proposals since its establishment in 2004. In many cases, HGPI's policy proposals have helped promote discussion and policy progress in areas such as oncology measures, women's health, dementia, drug-resistant bacteria, and health technology assessment.

When formulating policy proposals, HGPI places importance on the process of identifying issues through discussions among multi-stakeholder and global experts. While being closed to the public, flat discussions are held between multi-stakeholders of industrial, governmental, academic, and private sectors, to clarify policy issues, identify the points to discuss, and offer directions for solutions. In addition, we hold expert meetings and public symposiums, inviting global experts, to share policy issues internationally and disseminate them to society at large.

This process of formulating policy proposals is meaningful in Japan, where opportunities for flat discussions among multi-stakeholder groups are limited, and we believe that it has attracted interest from many stakeholders, including government officials, and led to the formulation of feasible policy proposals. On the other hand, the formulation of policy proposals through multi-stakeholder discussions requires multiple processes, including the setting up of repeated discussion forums, and takes a lot of time. In some policy areas, urgent themes and specific proposals that do not necessarily require multi-stakeholder consensus are valuable, and there is a need for a different process for formulating policy proposals than those used in the past.

Therefore, HGPI has launched the "HGPI Expert Policy Advocacy Platform" project, in which fellows and other concerned parties affiliated with HGPI can individually present and promote their policy recommendations. The content of policy recommendations that the fellows identify as pressing issues will be scrutinized and approved by a committee established within HGPI, and will be included as part of the policy proposals issued by HGPI, thereby presenting options to address the issues with the aim of providing creative and feasible solutions to persons interested in policy. Please note that the content of the presentation is the personal opinion of the presenter and does not represent the organization.

Health and Global Policy Institute (HGPI)
Grand Cube 3F, Otemachi Financial City,
Global Business Hub Tokyo
1-9-2, Otemachi, Chiyoda-ku, Tokyo
100-0004 JAPAN
TEL: +81-3-4243-7156 FAX: +81-3-4243-7378
Info: info@hgpi.org