**A comparative analysis of anticancer drug appraisals including managed entry agreements in South Korea and England**

Running heading: Comparative analysis of anticancer drugs in South Korea and England

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**Abstract**

**Objectives:** This study aimed to compare appraisal decisions about anticancer drugs between the health technology assessment (HTA) agencies in Korea and England, and investigate whether the decisions and supporting evidence are comparable.

**Methods:**

This study identified 49 anticancer drugs listed by the Korean Ministry of Health & Welfare between January 2014 and December 2019. Of those, 46 anticancer drugs for 58 indications were included for analysis. Official appraisal documents from both countries for 58 drug-indication pairs were compared and assessed in terms of clinical and economic evidence. Evidence items and their groups for analysis were pre-defined.

**Results:** Three-quarters of cases were recommended with managed entry agreements (MEAs) in England and three-fifths in Korea. Finance-based MEA types were most common in both countries. Korean and English authorities made consistent decisions in forty-eight cases (83%) when classifying decisions as ‘recommended’ and ‘not recommended’, while the degree of agreement lowered to sixteen cases (28%) when subdividing decisions according to MEA types. When the evidence base was identical, their decisions were more likely to be consistent. Regarding clinical evidence, while the majority of cases referred to the same pivotal studies, differences between the committees’ recognized comparators and the appraisal date caused discrepancies in decisions. Economic evidence, including ICER estimates, was identical only in 12 cases (21%), which contributed to discrepancies.

**Conclusion:** England relies on economic evaluation, with increasing use of data collection agreements, in contrast with Korea’s new procedure exempting companies from providing economic evaluation. Whilst there is possibility for international cooperation in assessment of clinical evidence, transferability issues exist, particularly with regard to economic evidence.

**Key Points for Decision Makers**

**1.** The majority of appraisals depended on common pivotal studies, implying that each country can refer to other countries’ assessment of the clinical evidence to a considerable degree.

**2.** Economic evidence requested, however, was quite different between the countries under comparison because each country tries to develop its own solution dealing with the uncertainties at the time of decision.

**3.** More international comparisons in this issue should be made to find ways for information sharing regarding the technology appraisal for managed entry agreements.

**Statements and Declarations**

**Funding** None.

**Conflict of interest** The authors declare no conflict of interest.

**Data transparency** All data generated during this study are included in this published article and its supplementary information files.

**Ethics approval** Not applicable.

**Author contributions** All authors contributed to the study conception and design. Iyn-Hyang Lee and Eun-Young Bae conducted material preparation, data collection and analysis, and wrote the first draft of the manuscript. Karen Bloor critically reviewed and edited the first draft. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Consent to participate** Not applicable

**Consent for publications** Not applicable

**Code availability** Not applicable

**1 Introduction**

Countries with publicly funded healthcare systems find it increasingly difficult to balance the budget pressures of the healthcare sector with patient access to innovative high-cost technologies such as anticancer drugs [[1](#_ENREF_1)]. Anticancer drugs are being developed using expensive new technologies such as biologics and targeted therapies, and patients who lack alternatives have a high demand for these new technologies. According to a recent OECD health report, cancer was the second highest cause of death, attributed to about 24% of all deaths in 2019 across OECD countries [[2](#_ENREF_2)]. In public health care systems, cost of cancer drugs becomes a significant financial burden. Nevertheless, data to prove their value are often insufficient. Clinical trials conducted for a limited period on a limited number of subjects increase uncertainty in the internal and external validity of the clinical effect of a new drug [[3](#_ENREF_3)].

Reimbursement decisions for these new technologies, which inherently involve significant uncertainty regarding clinical evidence, cost-effectiveness and budget implications, are not straightforward [[4-6](#_ENREF_4)]. Mistaken decisions for high-cost technologies with uncertain benefits can lead public payers to face substantial consequences. Paying for products without sufficient benefits wastes limited medical resources and consequently deteriorates the overall health of the population. On the other hand, rejection of cost-effective products can delay patient access to the benefits of useful treatments and innovations.

In response to such uncertainty, over the past decade many countries have employed managed entry agreements (MEAs) [[7-9](#_ENREF_7)]. MEAs were introduced as agreements between healthcare payers and pharmaceutical companies, which conditionally reimburse pharmaceuticals based on the limited information about their budget impact or performance that is available at the time of market launch. MEAs may benefit payers by reducing the risk of both over-paying for products that turn out to be less effective than expected, and delaying access to effective care. Companies may benefit by gaining early market access for new high-cost products, even when their cost-effectiveness is unclear.

MEAs are classified into finance-based or performance-based agreements. Finance-based agreements focus on controlling total expenditure by reimbursing a discounted net cost compared to the list price, and consequently reducing the budget impact of a product, without considering its performance. Examples include discounts or rebates, volume caps, expenditure caps, free initial treatments and price-volume agreements. Performance-based agreements make reimbursement a condition of evidence development or patient response, in order to reduce uncertainty or to increase the cost-effectiveness of new pharmaceuticals. Examples include coverage with evidence development, payment-by-results and conditional treatment continuation [[9](#_ENREF_9)].

Amid this situation, there have been proposals to encourage cooperation between countries, which could ameliorate the problems of confidentiality agreements on pharmaceutical prices [[10](#_ENREF_10), [11](#_ENREF_11)]. A recent OECD report suggested the need for international sharing of information relating to MEAs, aiming to reduce duplicated workload, increase the chances of payers learning from overseas experience, and increase transparency of relevant information [[9](#_ENREF_9)]. In order to share data, the comparability of country-specific evaluations must be premised, but there have been few studies on this.

This study compares appraisal decisions regarding anticancer drugs made by the Korean authority, the Health Insurance Review and Assessment Service (HIRA), with those made by the National Institute for Health and Care Excellence (NICE), which guides reimbursement decisions in the English NHS. These two countries were chosen because they have established a relevant system with interesting comparative issues. England is a country that many countries refer to and transparently disclose their evaluation results. Comparatively, Korea introduced a health technology assessment (HTA) system recently in a relative term, and the Korean authority has requested an economic evaluation within a limited range. Therefore, we expected that Korea would be able to represent the situation of several countries that have introduced an HTA in limited operations. We review existing appraisal documents, and analyze similarities and differences in evidence used for appraisal discussions in these two health care systems, including the source data and levels of uncertainty. Exploring data from both countries, we investigate similarities and differences between their decisions for the same product. We hypothesize: First, that there are few differences in the clinical data used by the two study countries because most anticancer drugs are marketed by global pharmaceutical companies; second, even for the same product, economic evidence has lower transferability; and third, that decisions are similar across the two countries if the clinical and economic evidence evaluated for the drug are similar.

**2 Country Background**

**2.1 MEAs in South Korea**

Since 2007 when a positive list system was implemented, the Health Insurance Review & Assessment Service (HIRA) has assessed companies’ applications for reimbursement, considering clinical effectiveness and cost-effectiveness and making a final determination about whether the candidate product deserves to be on the benefit list. Implicitly, if the incremental cost-effectiveness ratio (ICER) of the intervention exceeds approximately 25 million KRW (around US$20,800) per QALY, it is considered not cost-effective. Exceptionally high thresholds may apply to cases such as life-threatening diseases or rare illnesses [[12](#_ENREF_12)]. Having said that, formal cost-effectiveness analysis is not always requested. Cost-effectiveness analysis is submitted only when the new drug is judged as having superior effectiveness to its comparator(s). Otherwise, instead of formal cost-effectiveness analysis, the Korean authority can conduct internal cost comparisons. In an internal cost comparison, the authority compares the cost per day or treatment cycle between the submitted drug product and its committee-recognized comparator(s). If a new drug is judged non-inferior to comparator(s) in clinical effectiveness, the drug is recommended only when its price is lower than those of existing alternatives.

If the product is recommended for listing, the National Health Insurance Service (NHIS) starts to negotiate a price for each product. When an agreement reached between the NHIS and the company, the Ministry of Health and Welfare publicly announces the results and dates of determination in effect.

In response to criticisms that the positive list system reduced patient access to new, high-cost pharmaceuticals, the Korean authority implemented risk-sharing agreements (RSAs), a type of MEA. The government clearly stated that the RSA procedure would be utilized only for exceptional cases. About a year later, the Korean authority introduced another new scheme named the economic evaluation exemption procedure (EEEP). This study analyzed RSAs and EEEP as the Korean MEA system.

Risk-sharing agreements. RSAs were introduced in Korea in December 2013 for four conditions (cancer, cardiovascular diseases, brain diseases and rare diseases) [[13](#_ENREF_13)]. In principle, this provides a way to improve the cost-effectiveness of products that are not demonstrably cost-effective at the list price, facilitating patient access to high-cost drugs such as anticancer therapies [[13](#_ENREF_13)]. If requested by a company, the Drug Reimbursement Evaluation Committee (DREC), an advisory group of the HIRA, reviews cases based on evidence submitted by the companies. The DREC provides advice to the CEO of HIRA. HIRA is responsible for the final recommendation, but, it always respects the DREC’s decision. There are several subtypes of RSA, including refunds, expenditure caps, and utilization caps (or fixed costs per patient), all of which are considered as finance-based agreements; and conditional treatment continuation and money back guarantee (CTC), and coverage with evidence development (CED), both considered as performance-based agreements.

Economic evaluation exemption procedure. On occasion, there could be a pharmaceutical product in an area of high clinical need, where cost-effectiveness analysis is impractical because of the shortage of research evidence. For such products, the EEEP was introduced in February 2015 [[12](#_ENREF_12)]. Products targeting all cancers or rare, life-threatening conditions are eligible for this exemption if they have no therapeutic alternatives, have limited or poor quality evidence available for economic evaluation (e.g., single-arm trial evidence), and are listed in three or more of seven reference countries (France, Germany, Italy, Japan, Switzerland, UK and US). For a product eligible for EEEP, HIRA waives the submission of conventional economic evaluation, determines its price based on the minimum prices of the seven reference countries, and regulates costs by means of an expenditure cap.

**2.2 MEAs in the English NHS**

NICE provides evidence-based recommendations based on an assessment of the clinical and cost-effectiveness of new technologies. While the HIRA reviews all new medicines submitted for listing, NICE evaluates technologies that are formally referred from a Minister to produce guidance through the topic selection and scoping process. However, all new significant drugs and indications are expected to be selected. NICE judges cost-effectiveness against an explicit threshold; Typically, if the ICER of the intervention exceeds £30,000 (around US$39,000) per QALY, it is considered not cost-effective, but exceptionally high thresholds are applied for end-of-life treatment or treatments for rare diseases [[14](#_ENREF_14), [15](#_ENREF_15)]. The technology appraisal committee deliberates each case based on the submitted evidence and assessment reports produced by independent evidence review groups [[16](#_ENREF_16)]. The committee’s decision ranges from “routine commissioning” to “not recommended”, and sometimes the case is recommended on the condition of complying with a suggested managed entry agreement [[17](#_ENREF_17)].

In England, the first MEA was the 2002 risk-sharing agreement enabling access to beta-interferon and glatiramer acetate for patients with multiple sclerosis, after NICE recommended against their use, but recommended negotiation between the manufacturers and the Department of Health to lower the price. A few more agreements were made after that under the title of patient access scheme [[21](#_ENREF_21)]. Despite criticisms that the agreement for beta-interferon was a costly failure [[22](#_ENREF_22)] the risk sharing approach has since been institutionalized as Patient Access Schemes (PAS). A commercial framework that further strengthens the flexibility of commercial arrangements between pharmaceutical companies and NHS England now presents a variety of MEA options including PAS, confidential commercial arrangements, and managed access schemes [[19](#_ENREF_19)].

Patient Access Scheme. The Patient Access Scheme (PAS) is a representative managed entry arrangement in England, introduced by the 2009 Pharmaceutical Price Regulation Scheme (PPRS) as a mechanism to improve cost-effectiveness for drugs which were judged not to be cost-effective at their list price [[23](#_ENREF_23)]. PAS has two types; a simple confidential PAS and a published complex PAS. If a pharmaceutical company applies a simple PAS, it should provide a rebate or simple discount on the list price; the contract remains confidential. A complex PAS includes outcome-based risk sharing schemes, dose caps, single indication discounts and free upfront stock. Details of such schemes are published.

Confidential commercial arrangements. The 2019 Voluntary Scheme for Branded Medicines Pricing and Access (Voluntary Scheme), which replaced the 2014 PPRS, states that more flexibility will be permitted than existing commercial options, and detailed plans were published in the commercial framework [[19](#_ENREF_19), [24](#_ENREF_24), [25](#_ENREF_25)]. In addition to PAS, other types of commercial arrangements are included in the framework, which differ from a complex PAS in that the details of agreements are confidential. Examples of commercial arrangements include (but are not limited to) budget caps, price/volume agreements, cost-sharing, stop/start criteria, and outcomes-based agreements/payment by results [[19](#_ENREF_19)].

Managed Access Program. A data collection scheme is agreed upon by NHS England and the relevant company when substantial uncertainties exist in the clinical outcome or cost-effectiveness of a considered technology. However, the potential exists to provide substantial clinical benefit and be cost-effective, and the uncertainty might be addressed by collecting data in the near future [[19](#_ENREF_19)]. Both parties agree on which data will be collected and when the committee will reconsider the case [[19](#_ENREF_19)]. Additionally, the company and NHS England agree on the reimbursement level, which is paid by the Cancer Drug Fund (CDF) during the data collection period. Until now data collection agreements (DCAs) have only been applied to cancer or highly specialized drugs, but they can, in principle, be extended to other disease areas [[19](#_ENREF_19)].

The CDF was created in England to pay for cancer drugs that were not appraised by the NICE or were appraised but not recommended for routine commissioning. In 2016, this fund became part of the NICE, implementing a “managed access” process whereby payments are made during the additional data collection period for promising new drugs. Since then, all new cancer drug-indication pairs have been appraised by NICE [[18](#_ENREF_18), [19](#_ENREF_19)] and similar fund has been created for other conditions to reimburse innovative drugs [[20](#_ENREF_20)].

Moreover, NHS organizations have a legal obligation to reimburse the technologies recommended by the NICE within three months of the decision, which raises concerns about the affordability of implementing NICE recommendations. The English NHS’s role has expanded since 2016, actively engaging in negotiations with companies to increase the likelihood of submitted drugs being cost-effective and affordable [[19](#_ENREF_19)]. Suppose that the budget impact for a new therapy exceeds £20 million in any year, over the first three years after its first use in the NHS, In that case, NHS England engages in commercial discussions to manage affordability [[21](#_ENREF_21)].

**2.3 Major administrative differences between the two countries**

The first difference is the scope of application. In Korea, the scope of application of RSAs is limited to cancer and rare disease treatments addressing unmet needs and having potentially significant effects such as prolonging survival. Other drugs can be applied according to the committee's consideration, although this is an exceptional situation. English PAS schemes also prioritize unmet needs, but are not explicitly limited to the treatments of cancer or rare diseases.

In Korea, the company applies for the MEA scheme, and the HIRA evaluates the drug’s eligibility and the suggested scheme’s applicability. If the drug is cost-effective after applying the MEA condition, a final contract is signed between the NHIS and the company following negotiation on the detailed condition. The recommended drugs are listed only when the price negotiations are successful. In England, the NHS engages in a commercial access agreement, similar to the role of Korea’s NHIS. However, in practice, NHS clinicians and organizations retain the discretion to decide whether to use specific technologies for patients, although legally, they are expected to reimburse the recommended drugs.

Another important difference is how to establish the economic rationale for each product. NICE in England, almost without exception, reviews the economic evaluation evidence of each product to assess cost-effectiveness, which is within NICE’s remit. In Korea, as mentioned above, cost-effectiveness analysis is submitted only when the new drug is judged of superior effectiveness to its comparator(s). Otherwise, instead of formal cost-effectiveness analysis, the Korean authority can conduct internal or external cost comparisons. The EEEP includes an external comparison process regarding listing and pricing (External Reference Pricing, ERP).

There is also a difference in the management unit. NICE in England reviews technology appraisals based on each indication of a drug, and sometimes on meaningful sub-populations. The Korean authority publishes one Health Technology Assessment (HTA) report including all the possible indications at the time of review. While evaluating, it is allowed to make different decisions depending on each indication and/or sub-population of a drug.

Although England and Korea have different health care systems and different HTA systems, both use HTA in formal reimbursement decision-making. This makes it possible to compare evidence bases used by each country for the same drug-indication pairs and assess their transferability, further exploring the possibility of international collaboration.

**3 Methods**

**3.1 Creating a cohort of anticancer drugs**

This study considered anticancer drugs listed for reimbursement by the Korean Ministry of Health and Welfare from January 2014 to December 2019. The study timeframe was chosen based on the start date of the Korean MEA (end of 2013) and data availability at the time of research planning (spring 2020).

The potential cohort comprised 49 anticancer drugs, the list of which was obtained from the Korean HIRA. These were appraised between 2013 and 2019 in South Korea and between 2008 and 2019 by the NICE. The paring process was carried out between the Korean and English HTAs. Since the Korean authority publishes one HTA report including all possible indications at the time of review, as mentioned in the country background section, a single HTA from Korea could match multiple English HTAs. If multiple drug-indication pairs existed, the drug name was followed by a number to distinguish it. For example, two pairs of lenvatinib were denoted as lenvatinib*1* and lenvatinib*2*. Figure 1 displays the selection process of the study drugs, resulting in 58 drug-indication pairs. If the committee's decision differed for the sub-populations, it was separated as a particular case for analysis.

**Fig. 1 Selection process of study cohort of anticancer drugs**

**3.2 Data sources**

This study considers information officially announced by the two countries’ authorities (HIRA and NICE). Electronic searches were performed using the HIRA and NICE websites to identify appraisal documents [[17](#_ENREF_17), [26](#_ENREF_26)]. Appraisal documents in both countries are official publications which include the deliberations of the relevant committee and the information on which discussions are based. In parallel, clinical information in the appraisal document, if necessary, was supplemented by trial publications from PubMed and ClinicalTrials.gov.

**3.3 Data extraction**

The list of items extracted was defined a priori; this included the target cancer site, date of appraisal, appraisal committee’s recommendation, study designs of pivotal clinical evidence considered in the deliberations of the committee, information about overall survival (OS) as a clinical outcome, information regarding generalizability to each country’s context, comparator(s) used in clinical evidence and those the committee recognized, information regarding economic evidence, and any social considerations. Social considerations included whether or not to meet NICE end of life criteria or whether or not to have substitutable treatment(s) in either market. The full text of each appraisal document was assessed and relevant data were extracted by two researchers independently. At any stage, uncertainty or discrepancies were discussed until consensus was reached. The extracted data were tabulated in Microsoft Excel.

**3.4 Data analysis**

To assess *clinical evidence*, information regarding the pivotal study design(s), overall survival (OS) extension and the comparator was considered. Study design was categorized into randomized controlled trials (RCTs) or single arm trials. When both RCTs and single arm trials were deliberated in the committee, information was categorized as in the RCTs group. Information for OS extension as a clinical outcome was categorized into three groups: provided, not provided, and immature. Cases with OS extension were subdivided as ≥3 years, <3 years, or not significant (NS). Types of comparison were categorized into head-to-head (H2H) or indirect comparison. We considered a H2H comparison as a clinical study which included comparator(s) recognized by the appraisal committee. If available, we collected information from the appraisal reports regarding whether an indirect comparison was acceptable or not. Assessment information on the generalizability to each country’s context was collected. Generalizability was generally considered for study population(s) and comparator(s), but sometimes it was evaluated considering the practice environment as a whole.

*Economic evidence* was categorized into ICER estimates and other information. ICER estimates were further classified into within or above the cost-effective range for usual or special conditions. ICER estimate(s) which each committee acknowledged in the final appraisal determination documents were utilized for analysis. Other information includes cost comparisons and external reference prices, which are applicable only to South Korea.

We compared recommendations of 58 product/indication pairs according to the type of decision: routine use, simple/other finance-based agreements, performance-based agreements, and not recommended. We considered Korean refunds and English PAS simple discounts as equivalent, i.e., *simple financial agreements.* Remaining financial agreements: Korean expenditure caps and British commercial arrangements were classed as *other financial agreements*. If both refunds and expenditure caps are applied, they are classified as *other financial agreements* in the Korean cases. If both PAS and commercial arrangements are applied, they are classified as *other finance-based agreements* in English cases. English managed access agreements are classified as performance-based agreements. In Korea, there were no cases of performance-based agreements such as CTC or CED in this analysis.

We classed the recommendations as positive (routine use and all types of MEA agreement) and negative (not recommended) to compare the appraisal recommendations of two countries according to the evidence used. We simplified the similarity of the evidence in a binary form, i.e., identical and not identical. If evidence belonged to the same group according to the classification criteria above, they were evaluated as identical. Cases were classified as partially identical if they utilized evidence from partially matched 'pivotal studies' or 'comparators' between the two countries. We further configured each evidence item into 3 or more categories, if applicable. Results were summarized as counts and percentages.

**4 Results**

**4.1 Descriptive summary of study drugs**

The appraisal decisions by year for 58 drug-indication pairs are presented in Table 1. The details of the drugs included are reported in supplementary material (Online Resource 1).

Table 1.

The highest number of appraisals was in 2016/2017, immediately after the reform of the Cancer Drugs Fund in England. For seven products, DCAs were created, all after 2016. In England, more than half of the cases were determined by a simple discount. In Korea, expenditure caps were the most frequently determined decision and about half of them were EEEP cases. 16 products were recommended for routine use in South Korea, and only four cases in England. Seven (12%) and 11 (19%) cases were not recommended in South Korea and England, respectively.

**4.2 Characteristics of evidence used for committee appraisal**

Table 2 summarizes the characteristics of evidence appraised and the appraisal committees’ recommendation for 58 pairs by country. In both Korea and England, the majority of cases used RCTs as the main source of clinical evidence. Of those, 66% (33/50) of Korean cases and 81% (42/52) in England were classed as head-to-head comparisons. 43% (25/58) of decisions in Korea and 28% (16/58) in England were based on indirect comparisons. In a third of these cases in England, evidence in indirect comparisons was judged as unacceptable, while no such information was given in Korean appraisal documents.

In 52% of cases in Korea and 59% of cases in England, data included overall survival (OS) information. Significantly prolonged survival was reported for 24 (41%) and 28 (48%) of the 58 decisions in South Korea and England, respectively. In 17 cases the OS gain was longer than 3 months, accounting for about 30% of the total included pairs.

59% of the cases provided information that the clinical evidence was assessed as generalizable to English practice. But, 57 cases (out of 58) in Korea did not provide meaningful information about generalizability. Of those 57 cases, the Korean committee positively recommended 50 cases (88%) (Table S1 in Online Resource 2).

All but two decisions were made based on ICER values in England, whereas in Korea this applied to less than half (25/58, 43%). Two cases were afatinib and lenvatinib*2*, reported in the Technical Appraisal reports TA310 and TA535 respectively, which stated no ICER estimates.

In both countries, numerous appraisals 18/25 (72%) in Korea and 26/56 (45%) in England accepted cost-effectiveness levels above the usual threshold range, with consideration of special conditions such as end of life or substitutability criteria. In England, 14 cases had ICERs higher than the cost-effective range (either＞£30,000 for usual cases or＞£50,000 for special cases), of which ten were not recommended, two were recommended with simple financial agreements, and two with performance-based agreements (Table S2 in Online Resource 2). The Korean committee decided 20 cases (34%) with straightforward cost comparisons between study drugs and their comparators, of which five were not recommended. Twelve cases (21%) utilizing external reference pricing were positively recommended with expenditure caps under the EEEP (Table S2 in Online Resource 2).

Table 2.

**4.3 Degree of agreement in recommendations**

Considering the degree of agreement between Korea and England, classifying decisions between routine use, three types of MEA, and not recommended, the decisions were entirely consistent in 16 (28%) out of 58 pairs (Table 3). The two countries made entirely conflicting decisions (recommended as routine use in one country but not recommended in the other) in 5 cases: aflibercept, bevacizumab*1*, denosumab*1*, fulvestrant*1* and nivolumab*3*.

Table 3.

Table 4.

Combining MEAs and routine use as positive recommendations, the degree of agreement between the two countries’ decisions increases to 83% (48/58). Table 4 shows the consistency of decisions in the two countries based on whether or not the underpinning clinical studies, committee-recognized comparators, comparison methods, overall survival improvement, or the evaluation opinions on economic evidence were identical.

The biggest difference in evidence used by the two countries was in economic evidence, which was identical in 12 cases (21%) but not in 46 (79%).Overall survival was different in 22 cases (38%). Eleven (92%) out of twelve cases which were identical in economic evidence, i.e., appraised as cost-effective, were positively recommended in both countries. The cases where the assessment of OS was the same were more likely to make identical decisions (32/36, 89%) than the cases where the assessment of OS was different (16/22, 73%). In particular, the probability of making a positive decision was higher in cases with OS improvement (14/15, 93%). In addition, the cases where the committee-recognized comparators were the same (including partial matches) were also more likely result in the same decision (35/40, 88%) than cases where they were not. There were few differences in the consistency of committee decisions according to the mode of comparison.

**5 Discussion**

Comparing the decisions of Korea and England for 58 anticancer drug-indication pairs, MEAs were used more frequently in England than in Korea. Three-quarters of study drugs were recommended with MEAs in England and three-fifths in Korea. This may be because the scope of MEAs are narrower in Korea than in England; In Korea, the drugs should meet several conditions to apply for an MEA. Additionally, the fact that MEAs started in England even before they were institutionalized in Korea also explains why MEA is more common in England. In both countries, finance-based MEAs were most common, as seems to be the same for other OECD countries - performance-based agreements remain relatively rare [[9](#_ENREF_9), [11](#_ENREF_11), [27](#_ENREF_27)]. Considering the degree of agreement between Korea and England by classifying decisions as ‘recommended’ and ‘not recommended,’ 48 cases (83%) showed consistent decisions, while the degree of agreement lowered to 16 (28%) when the MEA type was subdivided. The difference in MEA type might reflect the different market strategies of the company and the different preferences of each authority on the type of MEA [[28](#_ENREF_28)].

In both countries, RCTs were the primary source of clinical evidence, but only 17 out of 58 pairs (29%) made decisions based on the same data sources; the concordance rate increases significantly if cases using partially identical evidence are included. Two main reasons for such discrepancies were the different comparators recognized by each national committee and the date of the evaluation. The country appraising a drug later could in some cases use follow-up data, creating a sometimes notable difference in overall survival.

When the evidence base was identical, the two countries were more likely to make consistent decisions; both tended to make the same decisions when the comparators were the same or their overall survival judgment was consistent. As the comparators should reflect current practice [[16](#_ENREF_16), [29](#_ENREF_29)], the selected comparators can be different between countries, and thereby different pivotal studies can be used. However, in this study, the two countries used identical or partially identical comparators in many cases, and the evidence base was also very similar. This means each country can refer to the other country’s appraisals on clinical evidence.

The most notable difference between countries was the difference in economic evidence types. Korea requires cost-effectiveness analysis only when the submitted drug proves its superiority to comparators and internal or external reference pricing is applied for other drugs. In contrast, the ICER is routinely used in English decision-making. Although Korea makes a decision based on cost comparisons for some cases where an ICER is used in England, it does not necessarily mean that it is inappropriate or worse than extensive cost-effectiveness analysis. This might be the best option for countries with limited HTA capacity when they have to judge the cost-effectiveness of all new submissions within a fixed timeline.

When an ICER was considered in each country, this value acted as a critical criterion for decision-making. Both countries made positive recommendations if they were within the ICER thresholds, and both have accepted relatively high ICERs for drugs that meet particular conditions, such as treating life-threatening diseases.

Another evident difference between the two countries was in their responses to uncertainty. England has signed DCAs in seven cases, but Korea did not operate any DCA-type agreement. Instead, Korea implemented the EEEP, a policy that exempts the submission of economic evaluation data [[30](#_ENREF_30)]. These two countries have introduced DCAs and EEEP as a counterbalance to the uncertain performance of new drugs. While a DCA makes a condition of resolving uncertainty through data collection, the EEEP pursues administrative simplicity while responding to fiscal impacts rather than actively resolving uncertainties. The DCA is a very active method of resolving data uncertainty, but as data collection itself is very expensive, it applies to only a few drugs where the value of information (the benefit of resolving uncertainty) is high. On the other hand, there is no incentive for pharmaceutical companies to gather additional evidence when they can apply for EEEP [[27](#_ENREF_27)]. Moreover, it becomes increasingly challenging to obtain transparent information about overseas prices, when referenced in EEEP instead of cost-effectiveness data.

International collaboration is a way to increase data value by sharing between countries [[9](#_ENREF_9)] and reducing the cost of data production in individual countries, which is more critical for less-resourced countries. Additionally, increasing negotiating power encourages pharmaceutical companies to generate further evidence. However, this study suggests many aspects that must be aligned before international collaboration can become widespread. The reimbursement decision and the evidence base used can differ among countries, limiting the transferability of evidence between countries. Economic evidence is even less transferrable than clinical evidence because price, resource use, and utility estimates vary with institutional and socio-economic environments [[31](#_ENREF_31)]. In many cases, however, the local branches of multinational companies adapt the model developed at their headquarters [[32](#_ENREF_32)], so countries could share assessments of a model’s validity, if not the ICER itself. In line with this, Eichler and colleagues, who explored opportunities for regulatory alignment focusing on performance-based MEA(s), suggested establishing a conceptual framework for the scheme and working together on setting the evidence-generation strategy [[33](#_ENREF_33)].

Undoubtedly, the eventual interest of stakeholders, such as policy-makers and researchers, is the impact of MEA(s) on society. Some evidence suggests that MEAs might improve patient access, but other policy outcomes have not been evaluated adequately [[9](#_ENREF_9)]. Evidence is generally lacking regarding the impact of MEAs on public health and healthcare resources [[7](#_ENREF_7), [9](#_ENREF_9), [11](#_ENREF_11), [34](#_ENREF_34), [35](#_ENREF_35)]. The effect of MEAs on the cost-effectiveness of target drugs or healthcare finances remains unclear [[9](#_ENREF_9), [36](#_ENREF_36), [37](#_ENREF_37)], but a recent analysis suggests that MEAs may lead to a higher list price [[38](#_ENREF_38)]. Evaluating MEAs is challenging because data are not disclosed transparently for confidentiality [[7-10](#_ENREF_7)], which brings us back to the issue of international collaboration.

This study had several limitations. The drugs included were those listed between 2014 and 2019 in Korea, excluding those which listing was not applied for or evaluated, but not listed in Korea. This is why the “no recommendation” cases are so low in Korea.However, the results of the analysis included a couple of cases that were turned down in Korea. This was because the comparison was conducted on a drug-indication basis; there are drugs for which only a part of the indications is accepted. If all indications for these drugs were rejected, they were excluded from our analysis. In addition, as the unit of analysis in this study is the committee's appraisal, it reflects the committee's perspective and decisions. Thus, the final listing may differ from the appraisal results.

We only analyzed the final recommendation when there were multiple appraisal documents for the same drug-indication pair. In the previous analysis, which explored the impact of relevant factors on coverage decision-making, submission history did not significantly impact recommendation [[39](#_ENREF_39)]. Only two countries-Korea and England-were compared. Therefore, it may be difficult to generalize our results more widely as HTA systems vary from country to country.

**6 Conclusion**

This study compared reimbursement decisions and supporting evidence for 58 anticancer product-indication pairs in Korea and England. England applied MEAs more frequently than Korea, and both countries most frequently used finance-based agreements. There were few cases where the clinical evidence was completely identical, but the majority depended on common pivotal clinical studies. This implies that each country can refer to other countries’ assessments of the supporting clinical evidence. Economic evidence, however, was quite different because cost-effectiveness analysis is required only for a limited number of drugs in Korea, while an ICER is presented in most appraisals in England. There are many restrictions on referencing economic evaluation results of other countries, even in the presence of ICER estimates, as the method guidance, price, utility, practice pattern, and other contextual factors differ. However, the need for international cooperation still exists. In particular, there are advantages of lowering the cost of obtaining further evidence through collaboration between countries.

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