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STUDY PROTOCOL

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The national budget impact of managed entry agreement strategies match with high-cost drugs to maximise drug cost saving: a study protocol

Piyapat Owat [a], Chaoncin Sooksriwong [a], Hataiwan Ratanabunjerdkul [b] and Tuangrat Phodha [a]

[a]Faculty of Pharmacy, Drug Information and Consumer Protection Center, Center of Excellence in Pharmacy Practice and Management Research, Thammasat University, Pathum Thani, Thailand; [b]Faculty of Medicine, Medical Oncology Unit, Department of Internal Medicine, Thammasat University, Pathum Thani, Thailand

ABSTRACT

Background: Drug expenditure is an important part of health expenditure. Managed Entry Agreement (MEA) is a common strategy implemented in many countries, such as the United States, the United Kingdom, and the European countries to control drug expenditures, especially for new and high-cost drugs. This study aims to explore the appropriate MEA technique for reaching the lowest cost of drug procurement under specified uncertainty of the high-cost drug.

Methods: The cost of drug procurement varied by the MEA techniques will be investigated in the quantitative analysis based on MEA taxonomies and uncertainty in terms of price, use, and effectiveness. Then, the content analysis will be employed to the qualitative analytical part to summarise the matching of appropriate MEA technique with the characteristics of high-cost drug to lower the cost of drug procurement and increase access to high-cost drugs.

Discussion: The rationales for each MEA technique selection are similar across their objectives. MEA can help reduce drug expenditures. Therefore, the budget in health care system could be sustainable and the patient access to high-cost drug could be increased. However, it might not be suitable for some circumstances and should not be implemented to determine drug price or used as regular reimbursement.

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CONTACT Tuangrat Phodha tuangrat25@tu.ac.th Faculty of Pharmacy, Drug Information and Consumer Protection Center, Center of Excellence in Pharmacy Practice and Management Research, Thammasat University, Rangsit Campus, 99 Paholyothin Road, Khlong Nueng, Khlong Luang District, Pathum Thani 12120, Thailand

Background

Drug expenditure is an important part of health expenditure (Sakulbumrungsil et al., 2020). Thailand's drug expenditure accounts for 21.7% of Thailand's current health expenditure in 2021 (Thailand's current health expenditure is accounted for 5.2% of the gross domestic product in 2021) (International Health Policy Program Foundation. Ministry of Public Health, 2023). Trends show that Thailand's health and drug expenditures are increasing continuously. The policy of Thai government to regulate drug prices at the national level is to negotiate drug prices in the procurement of drugs for monopoly drugs being used in hospitals under the Ministry of Public Health (MOPH). However, the MOPH lacks the demand data necessary to confirm the agreement in advance. Without knowing the exact demand, it is difficult to set an exact-price before negotiating with the manufacturer or seller. This approach weakens bargaining power and relies more on requesting cooperation from the manufacturer or seller than engaging in negotiation. The price of drugs that manufacturers or sellers offer to each hospital vary greatly. Some hospitals get the price that is lower than the price under the agreed price (Limwattananon et al., 2012). These create problems in patients' access to drugs and create a burden on drug expenditure for the healthcare system. In addition, lowering drug prices alone is unlikely to be sufficient to increase financial protection for payers or reduce patients' out-of-pocket expenses (World Health Organization, 2022).

The process of introducing new drugs into the healthcare system is uncertain, posing risks for those involved: drug manufacturers or sellers, payers, patients, and the government. In the view of the introduction of new drugs in recent years, mechanisms to reduce uncertainty are therefore gaining increasing attention. One example is the managed entry agreement (MEA) (Brammli-Greenberg et al., 2021). When new and high-cost drugs come to market with immature clinical outcome data, this will create a challenge to the healthcare system because payers want to 'pay for value', that is, pricing and reimbursement conditions should be based on an actual clinical performance, and any potential drug expenditure savings should be achieved in the real-world conditions. MEA covers a variety of contracts between drug manufacturers, sellers, and payers. Its purpose is to address payer concerns about clinical performance and budget impact (Lucas, 2016). MEA is a common strategy implemented in many countries, such as the United States, the United Kingdom, and the European countries (e.g. Belgium, France, the Netherlands, and Italy), since it could control drug expenditure, especially for new and high-cost drugs.

MEAs are implemented in various countries to facilitate access to drugs. For example, pertuzumab is a highly effective drug that improves both

median overall survival and median progression-free survival (Swain et al., 2015), although it is very expensive. In the United Kingdom, the company has offered a confidential commercial discount on the price of pertuzumab. The estimated ICER is well below £30,000 per QALY gained. Therefore, adjuvant pertuzumab is recommended for patients with HER2-positive early-stage breast cancer at high risk of recurrence, particularly those with lymph node-positive disease (Squires et al., 2018). In South Korea, a time cap per patient agreement has been implemented for pertuzumab (Lee et al., 2021), and in Saudi Arabia, a risk-sharing agreement has been implemented for pertuzumab (Abu-Shraie et al., 2023). Palbociclib improves median progression-free survival, but the optimal duration of treatment is unclear (Mangini et al., 2015; Strohbehn et al., 2022). In the United Kingdom, the company has offered a confidential commercial discount on the price of palbociclib. The estimated ICER is well below £30,000 per QALY gained. Therefore, palbociclib is recommended for patients with hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (National Institute for Health and Care Excellence, 2017). In South Korea, a rebate agreement has been implemented for palbociclib (Lee et al., 2021). In China, a risk-sharing agreement has been implemented for palbociclib (Strohbehn et al., 2022). Lapatinib is used to treat HER2-positive metastatic breast cancer in patients who have not responded to pertuzumab. Lapatinib is not clear for what duration the drug is used, and it is not clear how many patients will be eligible for the treatment (Bamfi et al., 2009; Blackwell et al., 2012; Geyer et al., 2006). In Italy, MEA in the form of a pay-by-result agreement has been implemented for lapatinib, as the optimal duration of use is unclear, and there is no robust clinical evidence on its long-term efficacy (Blackwell et al., 2012; Geyer et al., 2006). Under this agreement, the company reimbursed the full drug costs for patients whose disease progressed within four cycles (Bamfi et al., 2009).

In conclusion, MEA is an effective strategy and should be applied, but where should the MEA be applied and which MEA technique should be the most suitable for each drug type, as the same drug may be subject to different MEA approaches in various countries? Further research should be conducted. To date, in Thailand, there is no clear criteria for choosing the MEA for drug price negotiation. There should be a guideline to suggest the decision made by the negotiation working group regarding to the particular high-cost drug. The study of matching MEA strategies with high-cost drugs to maximise drug cost saving in drug procurement is required. The findings from this study will be useful to guide the drug price negotiating committee at the national and hospital levels with proper MEA to sustainable budget of the health care system and increase access to high-cost drugs.

Methods

This study will employ both quantitative analysis and qualitative analysis. The cost of drug procurement varied by the MEA techniques will be investigated in the quantitative analysis to figure out which MEA technique would give the lowest cost under the context of drug uncertainty in terms of price, use, and effectiveness. Then, the content analysis will be employed to the qualitative analytical part to summarise the matching of appropriate MEA technique with the characteristics of high-cost drug to lower the cost of drug procurement and increase access to high-cost drugs. The findings will be summarised to guide policymakers and drug price negotiation committee in purchasing drugs with proper MEA to sustainable budget of the health care system. The diagram of the conceptual framework is shown in Figure 1.

Study design and scope

This study is a cross-sectional research design to explore the appropriate MEA technique for reaching the lowest cost of drug procurement under specified uncertainty of the high-cost drug. This study will focus on only three characteristics of uncertainty as follows: (1) uncertainty in pricing when the high-cost drugs with the predicted annual expenditure equal to or greater than $2,274.75 USD per patient per treatment course or $22,747.45 USD per public hospital (Department of Health. Government of South Australia, 2023) ($1 USD = 36.4876 THB on April 10, 2024 [Bank of Thailand, 2024]); (2) uncertainty in using when the exact number of target population could not be estimated but become high volume in the real-world practice or when the treatment duration and dosing are not certain in the real-world practice (Neyt et al., 2020); and (3) uncertainty in effectiveness when these

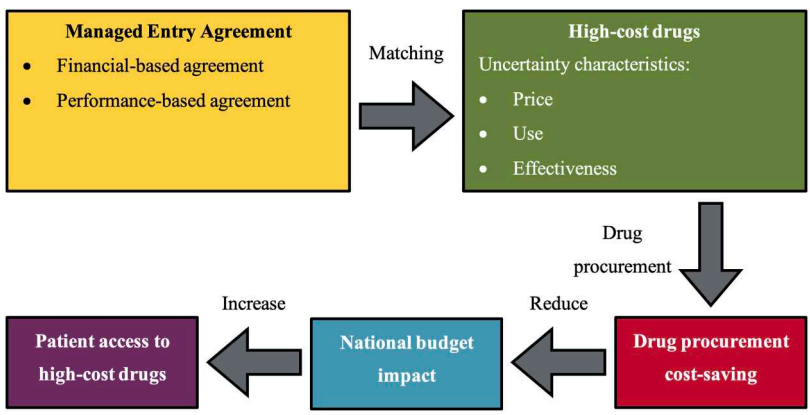

Figure 1. Conceptual framework.

criteria were missing or lack of certain evidence at least once (Neyt et al., 2020). There are 8 criteria for concerning the effective ness uncertainty as follows:

- **Efficacy:** there is no robust clinical evidence on the added therapeutic value or no robust clinical evidence on direct comparison with the appropriate alternative.
- **Safety:** there is no robust clinical evidence on safety.
- **Long-term data:** there is no robust clinical evidence on long-term effects.
- **Patient adherence and clinical practice:** there are doubts about the effect in real-world practice because of concerning about medication error in clinical practice or low adherence of the patients.
- **Quality of life:** there is no robust evidence on the quality-of-life impact.
- **Target population:** it is not clear who is likely to get most benefit from the treatment or if there are biomarkers to identify them.
- **Optimal treatment schemes:** it is not clear which duration (e.g. stopping rules), doses, or drug combinations are appropriated.

Population and sample

The population for this study is high-cost drugs available in Thailand during 2010–2023. The high-cost drugs those are available at a university hospital will be the sample of this study. According to mentioned three characteristics of uncertainty, drugs with at least one characteristic will be met the inclusion criteria. Drugs with incomplete data recorded in the hospital electronic database will be excluded from this study. Table 1 shows examples of high-cost drugs, those are potentially included in this study regarding to their uncertainty characteristics. These drugs are pertuzumab (Minckwitz et al., 2017; National Drug System Development Committee, 2023; Swain et al., 2015), palbociclib (IBRANCE (palbociclib) [package insert], 2015; Mangini et al., 2015; Strohbehn et al., 2022), and lapatinib (Bamfi et al., 2009; Blackwell et al., 2012; Geyer et al., 2006).

Table 1. Example of high-cost drug for each of uncertainty characteristic.

Uncertainty	Drug	Rationale
Price	Pertuzumab	Pertuzumab is effective for treating HER2-positive metastatic breast cancer, but it is very expensive.
Use	Palbociclib	Palbociclib is used for the treatment of postmenopausal hormone receptor-positive, HER2-negative metastatic breast cancer. It is not clear for what duration the drug is used.
Effectiveness	Lapatinib	Lapatinib is used for the treatment of HER2-positive metastatic breast cancer. It is not clear for what duration the drug is used, and it is no robust clinical evidence on long-term efficacy.

Data source

This study will gather the secondary data from 2 data sources. First, the hospital database of TUH from 1 January 2010 to 31 December 2023. Second, the website of the Drug and Medical Supply Information Center (DMSIC).

Data collection

The case record form (CRF) developed by the authors of this study will be used to collect the secondary data. The CRF has been approved by three experts those did the evaluation of Index of items Congruence (IOC). An array of variables those for estimating the number of patients using drug, the drug amount of each patient used, and the clinical outcomes including response (progressive disease by Response Evaluation Criteria in Solid Tumors criteria [RECIST criteria] [Eisenhauer et al., 2009]) and serious adverse events (grade 3 or higher [United State Department of Health and Human Services, 2017]) will be retrieved from the hospital database. The median price of each drug will be gathered from the website of DMSIC.

Data analysis

For quantitative analysis, this study will explore the appropriate MEA technique that would be the best matching with the high-cost drugs regarding to their uncertainty characteristics to get the lowest budget impact on drug procurement costs. The secondary data will be analyzed by the StataBE version 18. Data analysis in this study will follow the taxonomy of MEA as shown in Figure 2 (Dabbous et al., 2020; Ferrario & Kanavos, 2013; Gerkens et al., 2017; Klemp et al., 2011; Morel et al., 2013; Wenzl & Chapman, 2019). Various scenarios according to the taxonomy of MEA will be simulated for the change in drug procurement cost calculation. The analysis scenarios for pertuzumab, palbociclib, and lapatinib are demonstrated in Tables 2–4. These scenarios are discount (Aguiar Júnior et al., 2019; Koyuncu & Herold, 2022), free initiation treatment (National Institute for Health and Care Excellence, 2019), utilisation cap (Adamski et al., 2010; National Institute for Health and Care Excellence, 2019; Swain et al., 2015), conditional treatment continuation (Holleman et al., 2019; National Institute for Health and Care Excellence, 2012; Swain et al., 2015), pay by result (National Institute for Health and Care Excellence, 2007; Swain et al., 2015), expenditure cap (Wenzl & Chapman, 2019), and price-volume agreement (Adamski et al., 2010; Biancalani et al., 2022). Although specific types of MEAs were selected for drugs in this study, each country has different contexts, leading to varying drug uncertainty characteristics. Therefore, this study analysed various MEAs to identify the most suitable approaches for the Thai context.

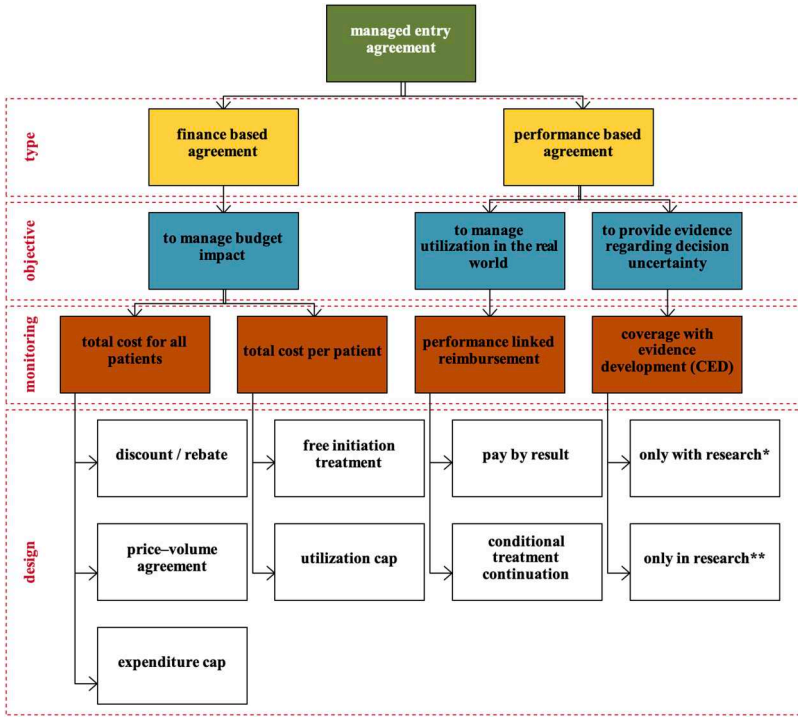

Figure 2. Taxonomy of manage entry agreement (MEA).

Flow of methodology

1. The profile of patients who received the studied drugs, pertuzumab, palbociclib, and lapatinib will be retrieved from the hospital database to analyse the pattern of drug utilisation by a decision tree.
2. Drug cost per course of treatment per patient under each MEA technique will be calculated from the formulary in Tables 2–4.

For qualitative analysis, this study compares data on the MEA technique with other drugs that have similar uncertainty characteristics. The drug cost per course of treatment per patient under each MEA technique was calculated using the formulary in Tables 2–4. The data from these calculations will be compared with data obtained from documents using content analysis method (Bengtsson, 2016), such as the NICE guidelines, aiming to improve confidence in the accuracy and validity of the MEA technique. Finally, the results will be informed to the policy decision makers such as the National Health Security Office (NHSO), the public health care insurance, the Ministry of Public Health, and the health care providers for planning the drug procurement to sustain the budget in health care system and increase patient access to high-cost drug in Thailand.

Table 2. The analysed scenarios for pertuzumab.

Drug name: pertuzumab (uncertainty: price)	Treatment: HER2-positive metastatic breast cancer	Estimated number of patients: 520 cases per year	
MEA technique	Scenario	Drug cost (per course of treatment per patient)	Budget impact (per year)
Discount	The discount strategy of 20% on drug cost.	• The drug cost is $C = (P - 20\%) \times Q$.	$C \times 520$
Free initiation treatment	The first cycle of the drug was offered for free. Thereafter, full drug price was paid.	• The drug cost is $C = (P \times Q) - (P \times 2)$. **Note:** The first cycle of pertuzumab uses two vials.	$C \times 520$
Utilisation cap	The payer paid for the drug for up to nine cycles. The drug company subsequently provided free-of-charge drugs for those patients who received more than nine cycles.	• If $Q = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10$; the drug cost is $C = (P \times Q)$. • If Q is more than ten (11, 12, 13, … , n); the drug cost is $C = (P \times 10)$. **Note:** Q is not more than ten vials because nine cycles use a total of ten vials of drug.	$C \times 520$
Conditional treatment continuation	The payer paid for the drug for up to nine cycles. Only patients who demonstrated a partial or complete response to the therapy continued with treatment. The drug company subsequently provided free-of-charge drugs for these patients.	• If patients did not show a partial or complete response within nine cycles, the drug company provided free-of-charge drugs for these patients; **the drug cost is 0 ($C = 0$)**. • If patients did show a partial or complete response within nine cycles, the drug company subsequently provided free-of-charge drugs for those patients who received more than nine cycles; **the drug cost is $C = (P \times 10)$**. **Note:** Q is not more than ten vials because nine cycles use a total of ten vials of drug.	$C \times 520$
Pay by result	Full drug costs were reimbursed by the drug company for patients who did not show a partial or complete response within nine cycles.	• If patients did not show a partial or complete response within nine cycles. Full drug costs were reimbursed by the drug company; **the drug cost is 0 ($C = 0$)**. • If patients did show a partial or complete response within nine cycles; **the drug cost is $C = (P \times Q)$**.	$C \times 520$
Expenditure cap	The payer paid for the drug for a maximum of 520 patients. Subsequently, when the number of patients exceeded 520, the drug company provided free-of-charge drugs to those additional patients.	• For patients numbered 1–520; **the drug cost is $C = P \times Q$**. • For patients numbered 521 onwards; **the drug cost is 0 ($C = 0$)**.	$C \times 520$
Price-volume agreement	If the number of patients using the drug exceeds the agreed-upon target (520 patients), the drug company must refund all the difference, which accounted for 30% of the total cost of the drug.	• If there are no more than 520 patients; **the drug cost is $C = P \times Q$**. • If there are more than 520 patients; **the drug cost is $C = (P - 30\%) \times Q$**.	• $C \times 520$ • $(C - 30\%) \times N$

C, the drug cost per course of treatment per patient; P, the drug median price for pertuzumab; Q, the number of doses each patient used; N, total number of patients using drugs.

Table 3. The analysed scenarios for palbociclib.

Drug name: palbociclib (uncertainty: use)	**Treatment:** Postmenopausal hormone receptor positive, HER2-negative metastatic breast cancer	**Estimated number of patients:** 876 cases per year	
MEA technique	Scenario	Drug cost (per course of treatment per patient)	Budget impact
Discount	The discount strategy of 20% on drug cost.	• The drug cost is $C = (P–20\%) \times Q$.	$C \times 876$
Free initiation treatment	The first cycle of the drug was offered for free. Thereafter, full drug price was paid.	• The drug cost is $C = (P \times Q)–(P \times 21)$. **Note:** The first cycle of palbociclib uses twenty-one capsules.	$C \times 876$
Utilisation cap	The payer paid for the drug for up to nine cycles. The drug company subsequently provided free-of-charge drugs for those patients who received more than nine cycles.	• If $Q = 1, 2, 3, \ldots, 187, 188, 189$; **the drug cost is $C = (P \times Q)$.** • If Q is more than 189 (190, 191, 192, … , n); **the drug cost is $C = (P \times 189)$**. **Note:** Q is not more than 189 capsules because nine cycles use a total of 189 capsules of drug.	$C \times 876$
Conditional treatment continuation	The payer paid for the drug for up to nine cycles. Only patients who demonstrated a partial or complete response to the therapy continued with treatment. The drug company subsequently provided free-of-charge drugs for these patients.	• If patients did not show a partial or complete response within nine cycles, the drug company provided free-of-charge drugs for these patients; **the drug cost is 0 ($C = 0$)**. • If patients did show a partial or complete response within nine cycles, the drug company subsequently provided free-of-charge drugs for those patients who received more than nine cycles; **the drug cost is $C = (P \times 189)$**. **Note:** Q is not more than 189 capsules because nine cycles use a total of 189 capsules of drug.	$C \times 876$
Pay by result	Full drug costs were reimbursed by the drug company for patients who did not show a partial or complete response within nine cycles.	• If patients did not show a partial or complete response within nine cycles. Full drug costs were reimbursed by the drug company; **the drug cost is 0 ($C = 0$)**. • If patients did show a partial or complete response within nine cycles; **the drug cost is $C = (P \times Q)$**.	$C \times 876$
Expenditure cap	The payer paid for the drug for a maximum of 876 patients. Subsequently, when the number of patients exceeded 876, the drug company provided free-of-charge drugs to those additional patients.	• For patients numbered 1–876; **the drug cost is $C = P \times Q$**. • For patients numbered 877 onwards; **the drug cost is 0 ($C = 0$)**.	$C \times 876$
Price-volume agreement	If the number of patients using the drug exceeds the agreed-upon target (876 patients), the drug company must refund all the difference, which accounted for 30% of the total cost of the drug.	• If there are no more than 876 patients; **the drug cost is $C = P \times Q$.** • If there are more than 876 patients; **the drug cost is $C = (P–30\%) \times Q$.**	• $C \times 876$ • $(C - 30\%) \times N$

C, the drug cost per course of treatment per patient; P, the drug median price for palbociclib; Q, the number of doses each patient used; N, total number of patients using drugs.

Table 4. The analysed scenarios for lapatinib.

Drug name: palbociclib (uncertainty: use)	**Treatment:** Postmenopausal hormone receptor positive, HER2-negative metastatic breast cancer	**Estimated number of patients:** 876 cases per year	
MEA technique	Scenario	Drug cost (per course of treatment per patient)	Budget impact
Discount	The discount strategy of 20% on drug cost.	• The drug cost is $C = (P - 20\%) \times Q$.	$C \times 876$
Free initiation treatment	The first cycle of the drug was offered for free. Thereafter, full drug price was paid.	• The drug cost is $C = (P \times Q) - (P \times 21)$. **Note:** The first cycle of palbociclib uses twenty-one capsules.	$C \times 876$
Utilisation cap	The payer paid for the drug for up to nine cycles. The drug company subsequently provided free-of-charge drugs for those patients who received more than nine cycles.	• If $Q = 1, 2, 3, \ldots, 187, 188, 189$; **the drug cost is $C = (P \times Q)$.** • If Q is more than 189 (190, 191, 192, …, n); **the drug cost is $C = (P \times 189)$.** **Note:** Q is not more than 189 capsules because nine cycles use a total of 189 capsules of drug.	$C \times 876$
Conditional treatment continuation	The payer paid for the drug for up to nine cycles. Only patients who demonstrated a partial or complete response to the therapy continued with treatment. The drug company subsequently provided free-of-charge drugs for these patients.	• If patients did not show a partial or complete response within nine cycles, the drug company provided free-of-charge drugs for these patients; **the drug cost is 0 ($C = 0$)**. • If patients did show a partial or complete response within nine cycles, the drug company subsequently provided free-of-charge drugs for those patients who received more than nine cycles; **the drug cost is $C = (P \times 189)$**. **Note:** Q is not more than 189 capsules because nine cycles use a total of 189 capsules of drug.	$C \times 876$
Pay by result	Full drug costs were reimbursed by the drug company for patients who did not show a partial or complete response within nine cycles.	• If patients did not show a partial or complete response within nine cycles. Full drug costs were reimbursed by the drug company; **the drug cost is 0 ($C = 0$)**. • If patients did show a partial or complete response within nine cycles; **the drug cost is $C = (P \times Q)$**.	$C \times 876$
Expenditure cap	The payer paid for the drug for a maximum of 876 patients. Subsequently, when the number of patients exceeded 876, the drug company provided free-of-charge drugs to those additional patients.	• For patients numbered 1–876; the drug cost is $C = P \times Q$. • For patients numbered 877 onwards; the drug cost is 0 ($C = 0$).	$C \times 876$
Price-volume agreement	If the number of patients using the drug exceeds the agreed-upon target (876 patients), the drug company must refund all the difference, which accounted for 30% of the total cost of the drug.	• If there are no more than 876 patients; **the drug cost is $C = P \times Q$**. • If there are more than 876 patients; the drug cost is $C = (P - 30\%) \times Q$.	• $C \times 876$ • $(C - 30\%) \times N$

C, the drug cost per course of treatment per patient; P, the drug median price for lapatinib; Q, the number of doses each patient used; N, total number of patients using drugs.

Discussion

The data analytical methods in this study are based on literature reviews of MEA selection. The rationales for each MEA technique selection are similar across their objectives. A performance-based agreement should reduce uncertainty and the payer's risk of taking the wrong decision. A financial-based agreement should reduce the payer's risk by making the drug more affordable, thereby reducing the cost associated with making a potentially wrong decision. However, there are slight differences that are observable and summarised in Table 5, together with examples of possible uses (Grimm et al., 2016).

In the study of Holleman (2019) (Holleman et al., 2019), it was found that various scenarios for MEA techniques were defined to serve as guidelines for calculating drug costs, as shown in Table 6.

Countries have used the MEA in various techniques with high-cost drugs for managing price, use, and effectiveness to improve the ultimate goal, which includes budget impact and cost-effectiveness (Ferrario & Kanavos, 2015).

The ten selected studies (Aguiar Júnior et al., 2019; Amdahl et al., 2017; Blommestein et al., 2016; Clopes et al., 2017; Holleman et al., 2019; Navarria et al., 2015; Ramaekers et al., 2017; Squires et al., 2018; Stevenson et al., 2018; Williamson et al., 2010). Seven studies were studied with a focus on financial-based agreements (Aguiar Júnior et al., 2019; Amdahl et al., 2017; Blommestein et al., 2016; Ramaekers et al., 2017; Squires et al., 2018; Stevenson et al., 2018; Williamson et al., 2010), and three studies were studied with a focus on performance-based agreements (Clopes et al., 2017; Holleman et al., 2019; Navarria et al., 2015). The most commonly chosen financial-based

Table 5. The rationales for MEA technique selection.

MEA technique	Rationale	Possible use
Financial-based agreement		
Discount/rebate	Bring costs down.	Treatment is simply too expensive.
Price-volume agreement	Control budget impact.	There are economies of scale.
Free initiation treatment	Bring costs down.	Treatment is too expensive, and utility gain occurs after a certain period of treatment.
Expenditure cap	Control budget impact.	Treatment is prohibitively expensive for the health system.
Utilisation cap	Bring costs down and avoid excessive treatment.	There is no further benefit after a certain length of treatment or dose.
Cost cap	Bring costs down and enable patients to benefit from treatment after reimbursement has stopped.	The length of treatment until a response is achieved is highly uncertain.
Performance-based agreement		
Conditional treatment continuation	Bring costs down and reduce payer risk surrounding the success or failure of treatment.	There is a decrement to the likelihood that a treatment results in success after a certain length of time.
Pay by result	Bring costs down and reduce payer risk surrounding the success or failure of treatment.	Decision uncertainty is mainly associated with treatment success and failure.

Table 6. The example scenarios for the MEA techniques.

MEA technique	Scenario
Financial-based agreement	
Discount	The discount strategy of 10% on drug cost.
Free initiation treatment	The first cycle of the drug was offered for free. Thereafter, full drug price was paid.
Utilisation cap	The payer paid for the drug for up to three cycles. The pharmaceutical company subsequently provided free-of-charge drugs for those patients who received more than three cycles.
Performance-based agreement	
Conditional treatment continuation	The payer paid for the drug for up to three cycles. Only patients who demonstrated an adequate response (complete or partial) to the therapy continued with treatment. The pharmaceutical company subsequently provided free-of-charge drugs for these patients.
Pay by result	Full drug costs were reimbursed by the pharmaceutical company for patients who did not show a partial or complete response within four cycles.

agreement is the discount technique (Aguiar Júnior et al., 2019; Amdahl et al., 2017; Squires et al., 2018; Stevenson et al., 2018; Williamson et al., 2010), followed by the rebate technique (Blommestein et al., 2016; Ramaekers et al., 2017). For the performance-based agreement, two techniques were applied: the pay-by-result technique (Clopes et al., 2017; Holleman et al., 2019), and the cost-sharing technique (Navarria et al., 2015),

Although there are rationales for each MEA technique selection, there may be a variety of circumstances that dictate the choice of a different MEA technique. This is because decisions are not based only on the achievement of predetermined conditions but also the magnitude of the various factors that may affect the decision. A quantification of risk is therefore inevitable.

Dissemination and projected impact

1. The appropriate MEA technique will benefit on lowering the drug procurement costs.
2. The national budget in the health care system will be sustainable from drug procurement with the proper MEA technique.
3. The accessibility to high-cost drugs will be increased even though the national budget in health care system is limited.

Conclusion

MEA can help reduce drug expenditures. Therefore, the budget in health care system could be sustainable and the patient access to high-cost drug could be increased. However, it might not be suitable for implementing to the procurement process of some high-cost drugs. MEA should not be accepted when lack of certain evidence on research and development process and clinical safety. Finally, MEA should not be implemented to determine drug price or used as regular reimbursement.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Authors contributions

PO, CS, and TP initiated the idea of this research work and drafted the proposal. PO performed review literature. PO, CS, TP, and HR contributed to study design and protocol development. TP, CS, and HR drafted manuscript. CS, TP, and HR provided academic support and supervision. All authors proofread and approved the final version of this manuscript.

Ethics approval and consent to participate

This research uses data from Thammasat University Hospital database. Data entry in this research is anonymous and de-identify data. The research protocol was approved by the Human Research Ethics Committee of Thammasat University (Science), (HREC-TUSc) COE No. 015/2567.

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ORCID

Piyapat Owat http://orcid.org/0009-0001-1595-6123
Chaoncin Sooksriwong http://orcid.org/0000-0002-6188-882X
Hataiwan Ratanabunjerdkul http://orcid.org/0009-0008-2129-2221
Tuangrat Phodha http://orcid.org/0000-0001-7793-0327

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