Experience in using HTA for expanding UHC benefit package to cover rare diseases and high-cost drugs among seven middle and high-income countries: A targeted literature review.

Dian Faradiba
Kumaree Pachanee

Issue#24
May 2023

HTAP
Health Intervention and Technology Assessment Program

policy brief

Key messages

- Treatment for rare diseases is typically more expensive than medications for common diseases given high cost of research and development and small patient population from whom to recoup costs.
- The term "high-cost drugs" and "rare diseases" are closely associated and often used interchangeably. In general, however, while countries have a clear definition of rare diseases, the definition of what constitutes high-cost drugs is still debated.
- Among seven countries reviewed, most countries have similar definition of rare diseases, and only one country, England, explicitly define high-cost
- Australia, Republic of Korea, and England, have special pathway for reimbursing high-cost rare disease drugs with certain requirements that must be met and the requirements must be met. The pathway must be reviewed, its cost-effectiveness assessed, and approved by the decision-making authority.

Background

A rare disease is a chronic disease that can cause disability or can lead to premature mortality in patients. For drug companies, recouping research and development costs from a small patient population is harder compared to drugs developed for common conditions. As a result, treatments for rare diseases are typically more expensive than medications for common diseases.[1] The term "high-cost drugs" and "rare diseases" are closely associated and often used interchangeably. In general, however, while countries have a clear definition of rare diseases, the definition of what constitutes high-cost drugs is still debated.

Health Technology Assessment (HTA) is a multi-disciplinary tool to help inform decisions around the development of the health benefits package for the population of the country and is being increasingly adopted by many countries seeking to achieve or sustain Universal Health Coverage (UHC). However, for rare diseases, the use of HTA to support decision-making for developing the benefits package poses challenges in terms of them not being cost-effective.[2] Therefore, treatment of rare diseases is rarely included in the benefits package of many countries.

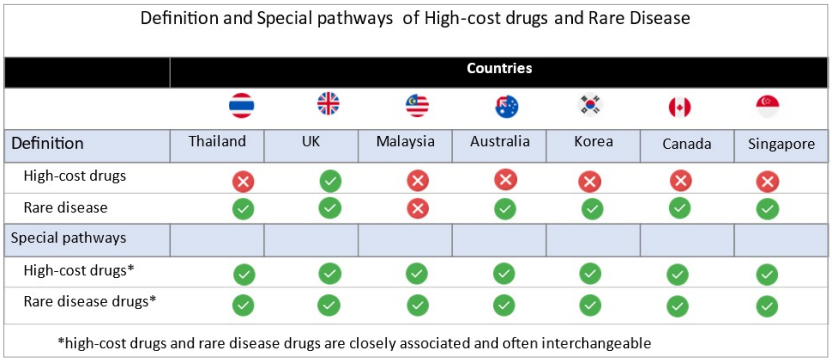
This policy brief provides a summary of a recent review of the definition of rare diseases, high cost and how HTA has been used in the case of rare diseases in seven countries. The countries were purposively selected based on them having established HTA policies and availability of resources in the public domain. This review will give readers a better understanding of the current situation of rare diseases in the healthcare system, as well as the potential role of HTA in providing support, allowing them to adapt these processes to their own context.

Definition of rare disease and high-cost drugs.

Based on a targeted review of seven countries, namely Thailand, England, Malaysia, Australia, the Republic of Korea, Canada, and Singapore, it was found that all countries, except Malaysia, have explicitly defined rare diseases. Six countries reported a definition of rare diseases: Thailand, England, Australia, Republic of Korea, Canada and Singapore. In Thailand, a rare disease is defined as one with fewer than 10,000 cases per year, whereas ultra-rare disease is defined as a disease with fewer than 1,000 cases per year. The topic of rare diseases is important for health policy development in Thailand because Thailand aligns with and prioritizes the Sustainable Development Goals (SDGs) principle of 'Leaving no one behind,' and the goal of its UHC policy is to provide equitable access to essential health services for everyone, as well as to protect households from bankruptcy due to high health care costs.

The definition of high-cost was only discussed in the England where a drug is considered high cost if (*i*) the drug and its expected associated costs of care are disproportionately high compared to the other expected costs of care within the Health Resource Group (HRG), a standard grouping of clinically similar treatments which use comparable levels of healthcare resource (ICD-10 and OPCS), which would affect fair reimbursement, and (*ii*) there are, or expect to be, more than a £1.5 million spend or 600 cases in England per annum. All countries reviewed have a special pathway and /or consideration to reimburse drugs for rare diseases (Figure 1).

Figure 1.
Definition and special pathways of high-cost and rare disease



Special pathway for accessing rare diseases and/or high-cost drugs and its criteria.

Given the scarcity of literature describing rare disease pathways, we selected three countries as case studies (the Republic of Korea, Australia, and England) to elaborate on these processes in the section below.

Australia

Starting in 1995, the Australian government has provided a special pathway to increase access to rare disease drugs through the Life Saving Drug Program (LSDP) which applies the "Rule of Rescue" (ROR) principle. Australia has set up a "Rare Disease Benefit Review Policy Framework", adding to the existing general benefits review process. When any new drugs are being considered by the Pharmaceutical Benefits Advisory Committee (PBAC) and are found to be "clinically effective but not cost-effective", they will be considered further under the LSDP. [3]

To meet the ROR claim, a few factors must be considered: there is no alternative treatments exist in Australia, it is a life-threatening disease (a severe, progressive disease that can lead to premature death), it is a rare disease (affecting a very small number of people), and the proposed drugs provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition.[4] See **Table 1** for specific criteria for inclusion in the LSDP.

Table 1. Decision-making criteria for LSDP (adapted from procedure guidelines).[3]

	Criterion	Notes
A1	The drug is a proven therapy for a rare but clinically definable disease	• ≤1 per 50,000 • High lifelong cost burden
A2	The disease is identifiable with reasonable diagnostic precision	
A3	Evidence of significant reduction in age-specific life expectancy due to the disease	• Data for disease progression without treatment • Life extension can be represented by disability reduction
A4	Evidence of significant life extension due to the drug	• Or significant disability reduction • Surrogate outcomes data is acceptable if there is no survival data
A5	The drug is clinically effective but rejected for PBS listing due to the lack of cost-effectiveness	
A6	No lifesaving alternatives on the PBS listing or available through public hospitals	
A7	No suitable and cost-effective non-drug therapy	Such as surgery or radiotherapy
A8	The cost of the drug is required per year is an unreasonable financial burden for the patient	
B1	The proposed confidential price of the drug compared with effective price in comparable oversea markets	
B2	The proposed cost of the drug compared with the cost of comparable drugs already funded through the LSDP	

Source: Policy Brief, The Life Saving Drug Program: Australia's pathway for high-cost drugs, available at https://www.hitap.net/documents/185668

Republic of Korea

In the Republic of Korea, the task of HTA is now being conducted by the National Evidence-based Healthcare Collaborating Agency (NECA) under the Medical Service Act.[5] Since for newer therapeutics targeting rare diseases or diseases for cancers, there is difficulty in providing pharmacoeconomic evaluation (PE) evidence and usually lack alternatives treatment, pathways such as: a) listing as essential drugs b) Risk Sharing Agreement (RSA) and c) PE exemption and d) price negotiation waivers that are different from there traditional route as shown in Table 2 have been adopted by the Republic of Korea's government. The process of pricing and reimbursement for any new drug is heavily influenced by the presence or absence of available alternatives. Alternatives are drugs that are currently being used for an equivalent therapeutic indication on the regulatory label.[6]

Table 2. Criteria for P&R pathways for drugs with no alternatives

Pathway	Criteria	Notes
When no alternatives		
Essential Drug	• No alternatives • Treat life threatening conditions • Treat small patient groups • Significant improvement in clinical efficacy or patient survival	*Life threatening*- 2 years or less of life expectancy Unclear definition of small groups
Risk Sharing Agreement	• No alternatives • Anticancer agent or serious life-threatening diseases • Should be approved via drug review committee on severity, social and ethical influences	*Refund based* RSA most used (mandatory PE evidence) *Contract term*- 4 years can't be extended if alternatives exist. *No expansion* of indications for P&R
Pharmacoeconomic evaluation exemption	• Rare disease and rare cancers • Clinically effective proven by single arm RCT or phase -II trial. • Drugs to be listed in at least three of A7 countries	*Expenditure cap RSA*- with the pharmaceutical sector *Price*- based on lowest adjusted list price from A7 countries.
Price negotiation waiver	• If pharmaceutical companies accept the weighted average price, it is allowed to pass the negotiation period of 60 days	-

PE, Pharmacoeconomic evaluation; RCT, Randomized controlled; RSA, Risk-sharing agreement; trials.
Source: Lee JH. Pricing and Reimbursement Pathways of New Orphan Drugs in South Korea: A Longitudinal Comparison. Healthcare (Basel). 2021 Mar 8;9(3):296. doi: 10.3390/healthcare9030296. PMID: 33800373; PMCID: PMC8000795.

England

The National Institute for Health and Care Excellence (NICE) in in England has a special guidance to consider reimbursement for high-cost rare disease drugs known as Highly Specialized Technologies (HST). This evaluation is based on factors such as 1) the nature of the condition, 2) clinical efficacy, 3) value for money and 4) the technology's impact beyond immediate health benefits.[7]

Decisions are made based on the findings of an economic evaluation study for HSTs, which are benchmarked against an Incremental Cost-effectiveness Ratio (ICER) of £100,000 per quality adjusted life years (QALYs) gained. The Evaluation Committee will apply a weight between 1 and 3, which corresponds to the incremental QALYs gained per patient over a lifetime horizon of 10 to 30. For example, if incremental QALYs gained (per patient, using lifetime horizon) is 10, then the weight applied is equal to 1. For QALYs gained in the range of 11 to 29 and greater than or equal to 30, weights applied are between 1-3 and 3, respectively.

See **Table 3** for summary of special pathways from three countries.

Table 3. Summary of the special pathway for rare diseases and/or high-cost drugs

	Countries		
	England	**Australia**	**Republic of Korea**
1. Definition			
1.1 Rare Disease	Number of cases less than 1 in 2,000	Number of cases less than 5 in 10,000	< 20,000 patients, or for which the prevalence is unknown owing to difficulties in diagnosing the disease
1.2 High-cost drug	There is, or is expected to be, more than a £1.5 million spend or 600 cases in England per annum	-	-
2. Pathways	Highly Specialized Technologies (HST)	Life-Saving Drug Program (LSDP)	1. Essential drug 2. Risk sharing agreement 3. Pharmacoeconomic evaluation exemption 4. Price negotiation waiver
2.1 Criteria	1) Nature of the condition, 2) clinical efficacy, 3) Value for money 4) Technology's impact beyond immediate health benefits.	**Criteria for LSDP** • **A1** The drug is a proven therapy for a rare but clinically definable disease • **A2** The disease is identifiable with reasonable diagnostic-precision • **A3** Evidence of a significant reduction in age-specific life expectancy due to the disease • **A4** Evidence of significant life extension due to the drug • **A5** The drug is clinically effective but rejected for PBS listing • **A6** No lifesaving alternatives on the PBS listing • **A7** No suitable and cost-effective non-drug therapy • **B1** The proposed confidential price of the drug compared with the effective price in comparable oversea markets • **B2** The proposed cost of the drug compared with the cost of comparable drugs already funded through the LSDP	**Criteria for Essential drug :** • No alternatives • Treat life threatening conditions • Treat small patient groups • Significant improvement in clinical efficacy or patient survival **Risk sharing agreement:** • No alternatives • Anticancer agent or serious life-threatening diseases • Should be approved via drug review committee on severity, social and ethical influences **Pharmacoeconomic evaluation exemption:** • Rare disease and rare cancers • Clinically effective proven by single arm RCT or phase -II trial. • Drugs to be listed in at least three of A7 countries **Price negotiation waiver :** • If pharmaceutical companies accept the weighted average price, it is allowed to pass the negotiation period of 60 days
2.2 Agency	National Institute for Health and Care Excellence (NICE)	Pharmaceutical Benefits Advisory Committee (PBAC)	National Evidence-based Healthcare Collaborating Agency (NECA)

Case study: Topic prioritization for high-cost drugs in England

The overall flow of topic prioritization for high-cost drugs can be seen in Figure 2.

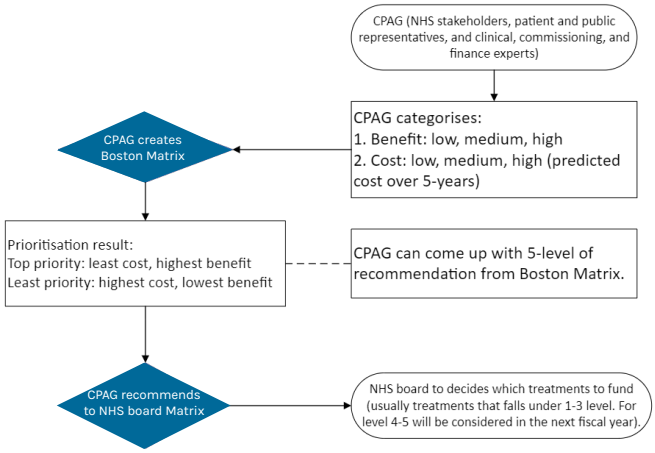
To determine which high-cost drugs to fund, the NHS consults with a committee known as the Clinical Priorities Advisory Group (CPAG). This committee oversees reviewing drugs and therapies including those used to treat expensive and/or rare diseases. Members of the CPAG represent a diverse range of expertise and include NHS stakeholders, patient, and public representatives, and clinical, commissioning, and finance experts. The CPAG is not a decision-making body, but it plays a significant role in developing recommendations.

CPAG creates a "Boston Matrix" to aid in determining which drugs should be prioritized when they are all more expensive but provide greater clinical benefit than current practice (i.e., drugs which falls in top-right quadrant of cost-effectiveness plane). This matrix divides the top-right quadrant of the cost-effectiveness plane into nine additional compartments, dividing the benefit (x axis) into three categories (low, medium, and high benefit) and the cost (y axis) into three categories (low, medium, and high cost). See figure 3 for Boston Matrix example by NHS.

CPAG will classify the clinical benefit and cost of drugs into three categories (low, medium, and high). There will be clinical and economic experts who will forecast and provide input, particularly on drugs costs over a 5-year period. CPAG will summarise the drugs into the Boston Matrix and forward the recommendation to NHS England once all information has been gathered. NHS England will then decide which drugs they could commit to funding. See figure 3b for 5-level of priority by NHS.

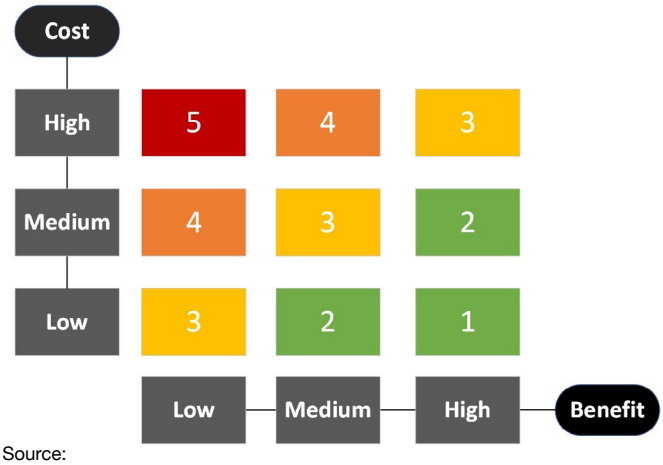
If some drugs are not considered to be funded in the next fiscal year, CPAG will review those treatments within six months, and these drugs can be considered up to three times. The final decision is made by NHS England, which must be approved by the NHS Board.

Figure 2. England topic prioritization for rare disease and/or high-cost drugs



CPAG, Clinical Priorities Advisory Group; NHS, National Health Services
Source: Simplified and/or adapted flowchart prepared by authors based on information available in NHS website[8]

Figure 3. Example of Boston Matrix



Source:
NHS website[8]

Figure 3b. 5-level of priority from Boston Matrix

Source: NHS website[8]
Note: CPAG forwards the recommendation to NHS. Due to resource constraints NHS cannot commit to all 5-level priority, therefore they will commit to fund drugs which fall in level 1-3. However, there is possibility to fund drugs in level 4-5. These drugs will be reconsidered (up to three times) in the next CPAG meeting in 6 months period.

References

1. Groft SC, Posada M, Taruscio D. Progress, challenges and global approaches to rare diseases. Acta paediatrica (Oslo, Norway : 1992). 2021;110(10):2711-6.
2. Canada's Drug and Health Technology Agency (CADTH). Drugs for Rare Diseases: A Review of National and International Health Technology Assessment Agencies and Public Payers' Decision-Making Processes. CADTH; 2023.
3. Department of Health and Aged Care of Australian Government. Procedure guidance for drugs funded through the Life Saving Drugs Program (LSDP) 2018 [cited 2013 March, 1st]. Available from: https://www.health.gov.au/resources/publications/procedure-guidance-for-drugs-funded-through-the-life-saving-drugs-program-lsdp?language=en.
4. Department of Health and Aged Care of Australian Government. Basis for any claim for the 'rule of rescue' 2016 [cited 2023 March, 1st]. Available from: https://pbac.pbs.gov.au/section-5/5-4-basis-for-any-claim-for-the-rule-of-rescue.html#:~:text=When%20all%20four%20factors%20apply,the%20criteria%20of%20the%20restriction.
5. Health Insurance Review & Assessment Service (HIRA). Healthcare Benefit Management [cited 2023 March, 1st]. Available from: https://www.hira.or.kr/eng/about/05/02/06/index.html.
6. Lee JH. Pricing and Reimbursement Pathways of New Orphan Drugs in South Korea: A Longitudinal Comparison. Healthcare (Basel, Switzerland). 2021;9(3).
7. National Institute for Health and Care Exellence (NICE). Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes: NICE; 2022 [cited 2023 March, 1st]. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf.
8. NHS England. Clinical Priorities Advisory Group (CPAG) [cited 2023 March, 1st]. Available from: https://www.england.nhs.uk/commissioning/cpag/.

Acknowledgement

This paper is a part of research project titled "Development of policy options to support reimbursement decisions on high-cost health interventions in Thailand's public healthcare system". HITAP was commissioned by the National Health Security Office (NHSO) in Thailand to conduct this study with funding from the Health Systems Research Institute (HRSI). This policy brief was written in consultation with Prof. Alec Morton from University of Strathclyde UK, and Saudamini Dabak and Assoc. Prof. Wanrudee Isaranuwatchai from HITAP.

About the author

1. **Dian Faradiba,** Project Associate, Health Intervention and Technology Assessment Program (HITAP)
2. **Kumaree Pachanee,** Researcher, HITAP

Contact: hiu@hitap.net

This policy brief can be downloaded from www.hitap.net