「2022年罕見疾病醫療照護之挑戰與前瞻論壇」

罕藥給付決策之經濟評估
- ICER/QALY國際標準比較及運用

蒲若芳
2022/9/27

ICER (incremental cost-effectiveness ratio) 是衛生經濟特有的經濟指標

Incremental Cost-Effectiveness Ratio (ICER)

公式: $ICER = \frac{\Delta cost}{\Delta effectiveness}$ (common: cost per QALY)

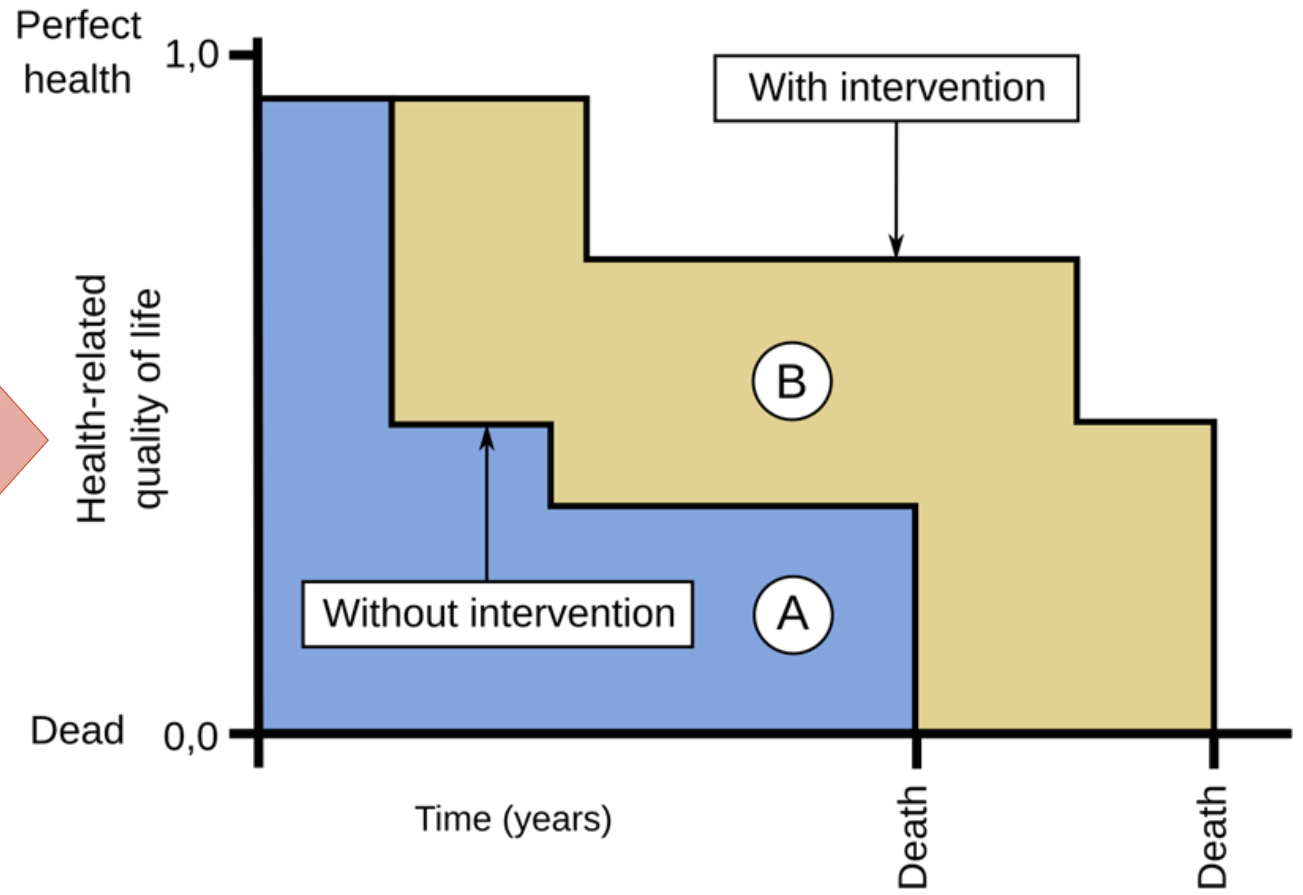
基本的成本效益研究結果:

Strategy	Total Cost	Incremental Cost	Expected QALYs	Incremental QALYs	ICER
藥物A	300,000		4.4		
藥物B	400,000	100,000	4.8	0.4	250,000

"比上原來的藥物(A)，以新藥物(B)來治療，每多得一個QALY，必須多花$250,000"

$$ICER = \frac{\Delta cost}{\Delta effectiveness} = \frac{100{,}000}{0.4} = 250{,}000$$

QALY
(quality-adjusted life years)



https://en.wikipedia.org/wiki/Quality-adjusted_life_year

Direct	Indirect
Visual analogue scale	EuroQol-5 Dimension (EQ-5D)
Time trade-off scale	Health utilities index
Standard gamble	Short form-6 dimension (SF-6D)

Table 1: QOL Measurement Methodologies.

Pettitt DA, Raza S, Naughton B, Roscoe A, Ramakrishnan A, et al. (2016) The Limitations of QALY: A Literature Review. J Stem Cell Res Ther 6: 334. doi:10.4172/2157-7633.1000334

Utility怎麼來的?

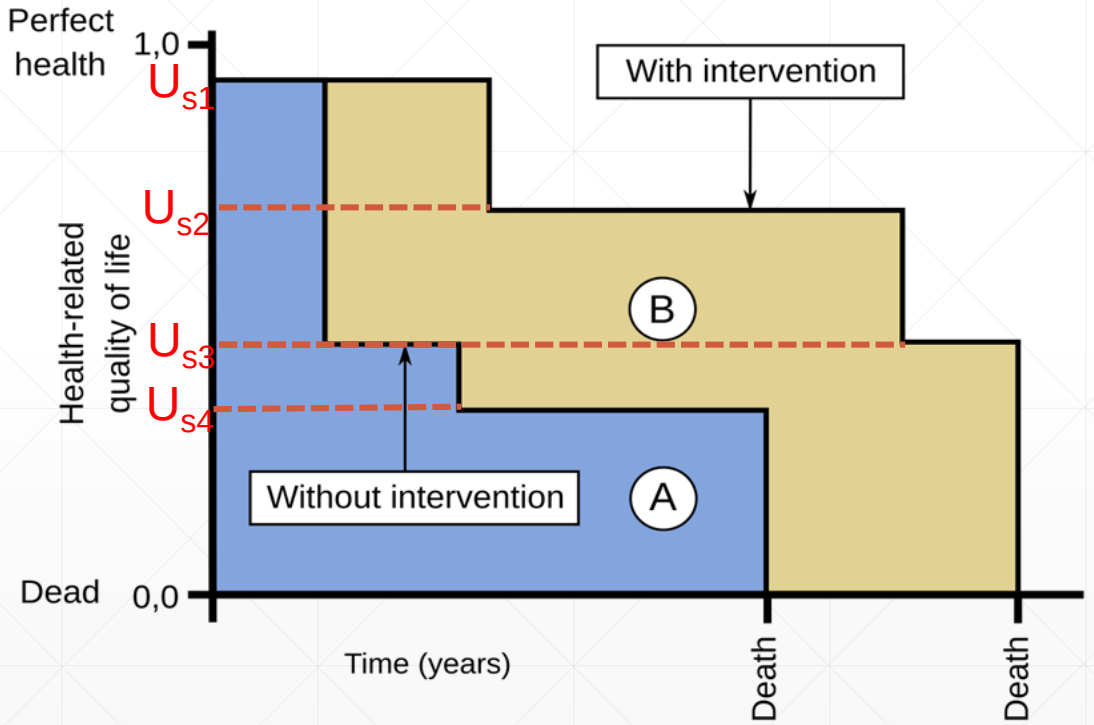
針對S1病人狀況進行EQ5D問卷

(1)行動能力、(2)自我照顧、(3)平常活動、(4)疼痛/不舒服、及(5)焦慮/沮喪等 (各有1-5等級勾選)

根據EQ5D問卷回答結果，代入台灣公式得出Utility

EQ5D S1 = (1,1,2,1,1) 則 U_{S1} = ?

同樣估算出 U_{S2}, U_{S3}, U_{S4}



https://en.wikipedia.org/wiki/Quality-adjusted_life_year

臺灣EQ-5D-5L健康狀態權重

面向 / 健康狀態 (1-3面向/4-5面向)	(1) 行動能力	(2) 自我照顧	(3) 平常活動	(4) 疼痛/ 不舒服	(5) 焦慮/沮喪
1. 沒有困難/沒有	0	0	0	0	0
2. 有一點困難/有一點	0.1076	0.0757	0.0726	0.0868	0.0637
3. 有中度的困難/有中度的	0.1996	0.1322	0.1234	0.1578	0.1829
4. 有嚴重的困難/有嚴重的	0.3652	0.2644	0.2802	0.3402	0.3401
5. 無法進行/非常嚴重	0.4767	0.3241	0.3505	0.4534	0.4212

11133

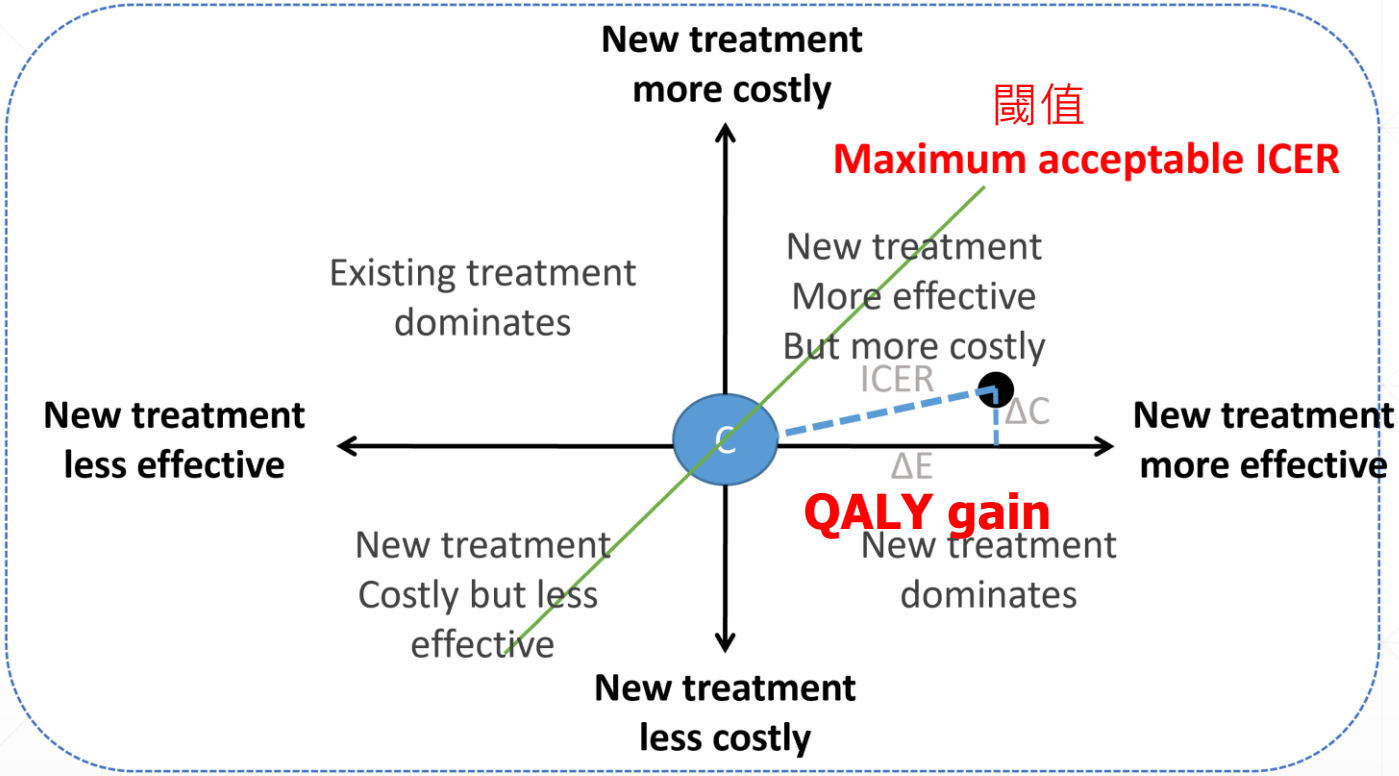
效用損失
=0+0+0+0.1578+0.1829
=0.3407
效用值=0.6593 (1-0.3407)

22221

效用損失
=0.1076+0.0757+0.0726+0.0868+0
=0.3427
效用值=0.6573 (1-0.3427)

Lin, H.W., et al., Valuation of the EQ-5D-5L in Taiwan. PLoS One, 2018. 13(12): p. e0209344.

投影片來源：吳慧敏博士



$$ICER = \frac{\Delta cost}{\Delta effectiveness}$$

A. H. Briggs 2001. “Handling uncertainty in economic evaluation and presenting the results." In Economic Evaluation in Health Care: Merging Theory with Practice, ed. M. Drummond and A. McGuire, 174. Oxford, U.K.: Oxford University Press

The cost-effectiveness plane

由於種種的不確定性，特定方案的ICER也不會只有一個"最正確的"值

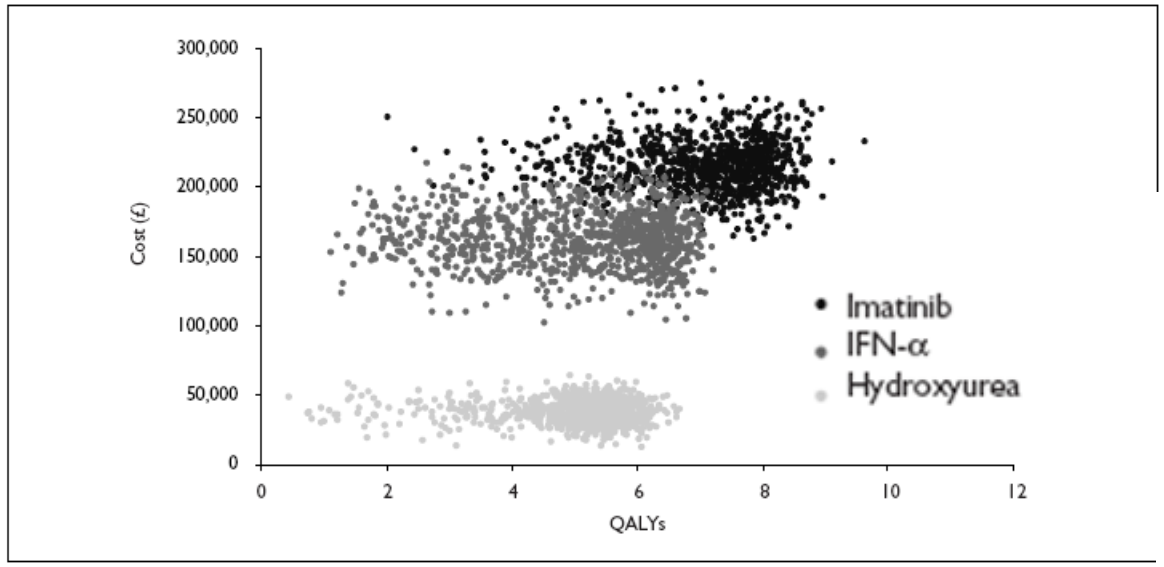


FIGURE 13 *Cost-effectiveness plane for the independent probabilistic economic analysis*

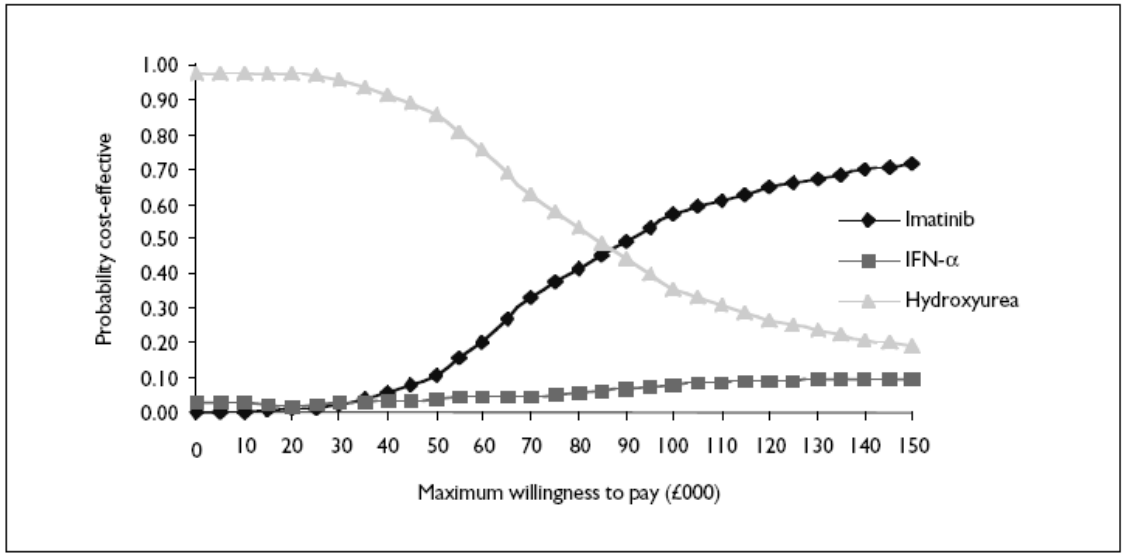


FIGURE 14 *Cost-effectiveness acceptability curve for IFN-α, imatinib and hydroxyurea*

ICER為什麼是效率的指標?

BRIEFING PAPER

The NICE Cost-Effectiveness Threshold

What it is and What that Means

Christopher McCabe,[1] *Karl Claxton*[2] and *Anthony J. Culyer*[3,4]

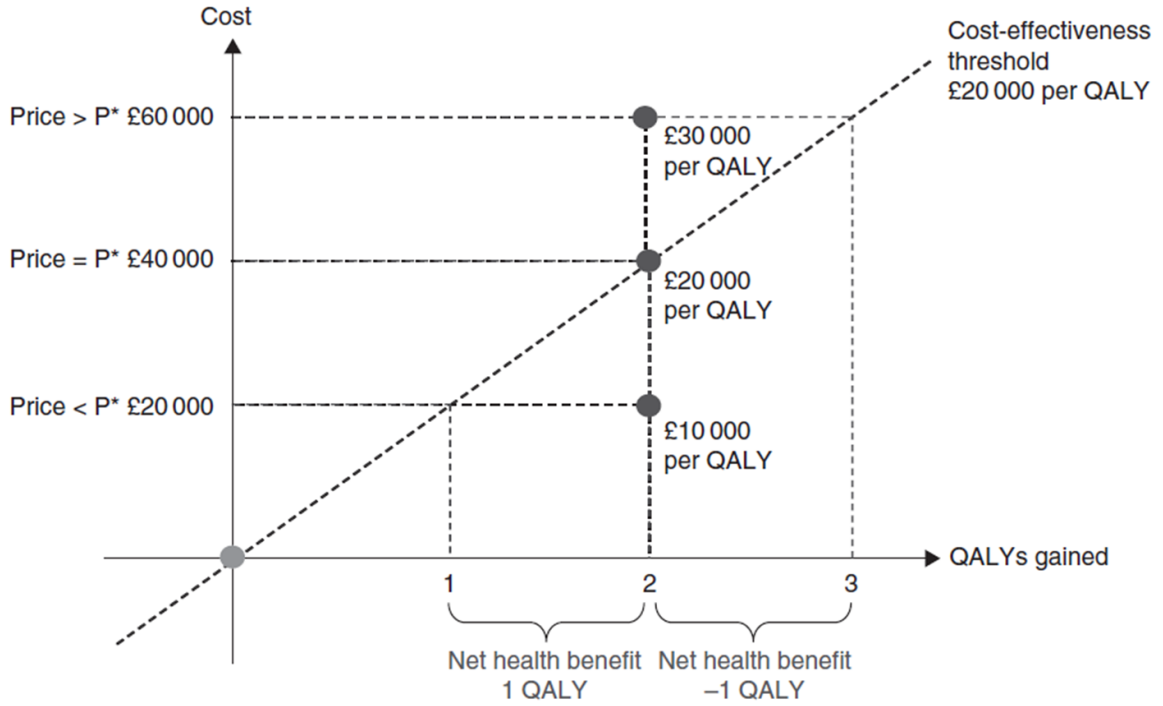


Fig. 3. Threshold and health gain (reproduced from Claxton et al.[19]). **P*** = maximum price the NHS can afford or the value of the technology.

Pharmacoeconomics 2008; 26 (9): 733-744

罕藥就是不一樣

因為「罕見」

所以...

1. 相較於一般性疾病，罕病診斷不易、能納入的試驗人數少、數據難收集
2. 常常無法做到雙盲對照研究
3. 就算研發、上市及營運花費相同，但每個接受治療者須攤提的單價成本–相當高
4. 就算取得藥證上市，但市場小

藥廠研發缺乏研發動機

潛力新藥 (尤其是unmet need) 歐美查登單位會給快速通關

療效不確定性高

因為「罕見」

所以...

1. 病人延遲、或根本沒有得到正確診斷、合適的轉介 (EIU: 40%)
2. 很多時候，甚至連醫師都不知道能用甚麼方法治療
3. 一人得病，全家奔波，家庭照護負擔重
4. 病人及家庭成員的生產力損失，收入的損失
5. 社會、教育、國家需提供各種環境支持，納稅人的承擔
6. 嬰幼兒期罹病，不會有商業保險願意承保
7. 就算有商業保險，不見得在承保疾病範圍，不見得獲全額給付

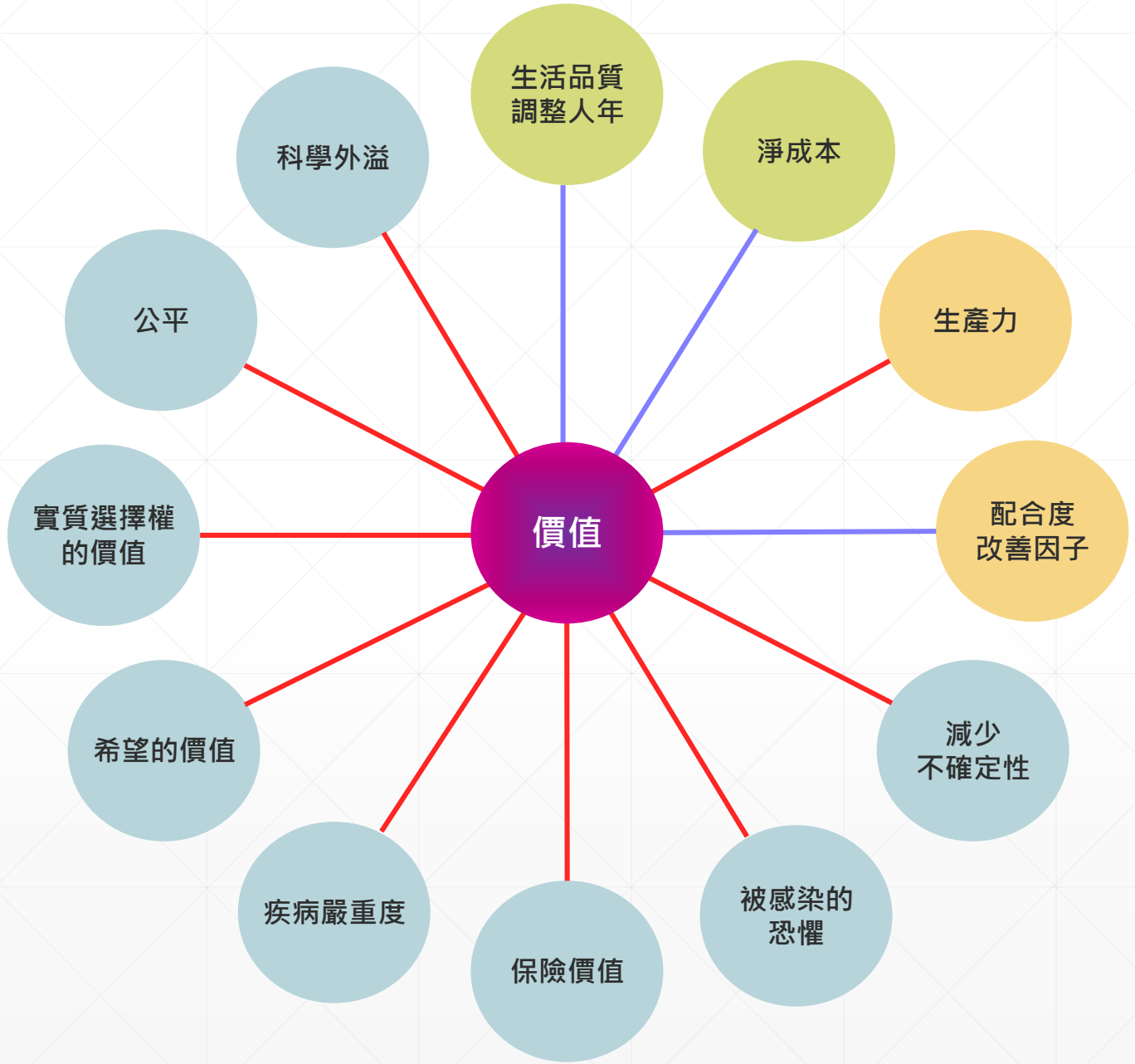
需要能及早診斷的檢驗/查、需要能維持生活功能及維繫生命的治療

？公費/健保給付？

給付決策的決定過程
沒有辦法跟非罕藥相同

疾病、診斷、治療效果、長期影響...很多不確定性
「少數人」的權益與經濟效益的平衡

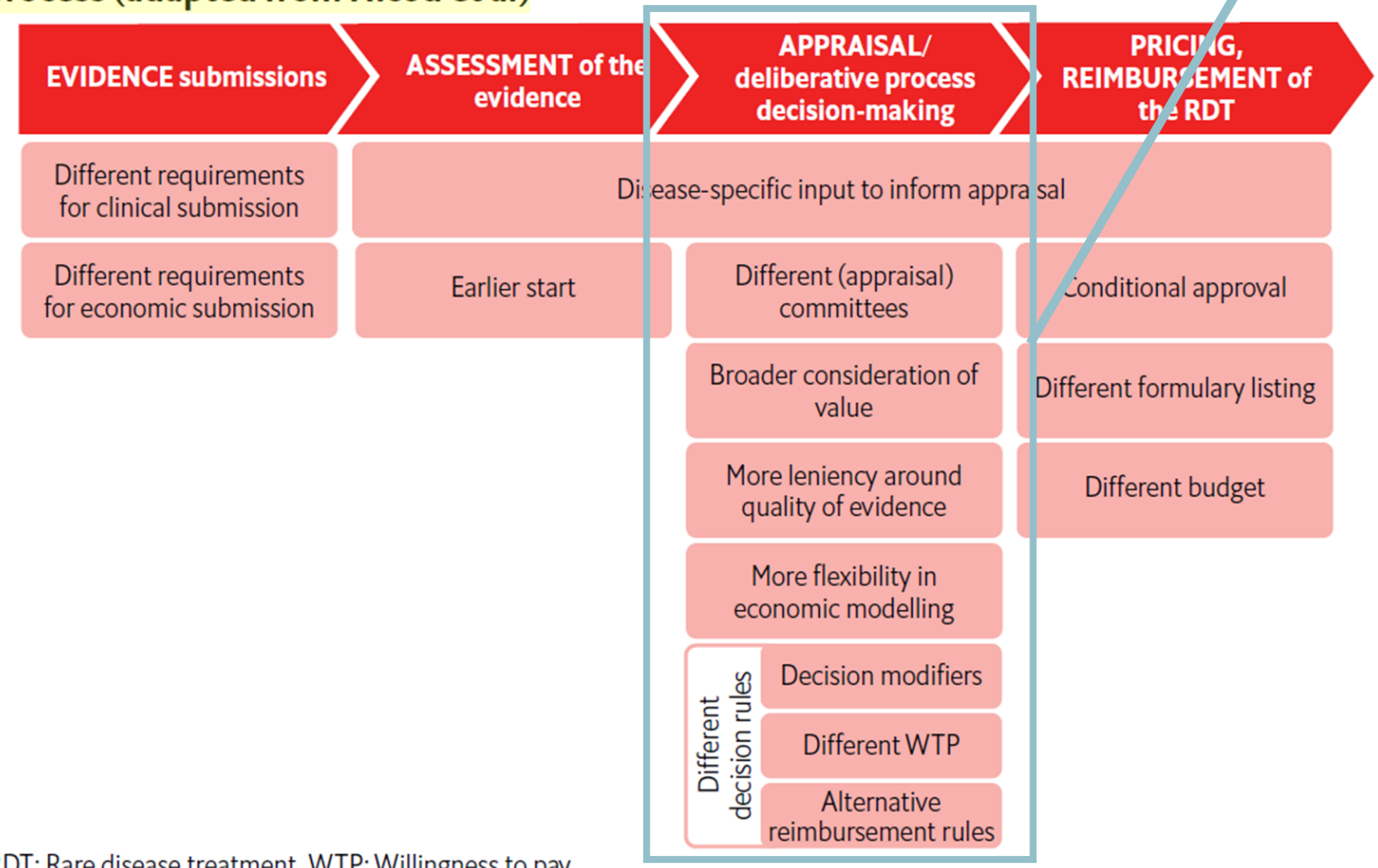
新藥的價值不只在療效與成本效益



Garrison et al. Value Health. 2019 Jun;22(6S):S12-S17.

原有的HTA程序也許不合適

Figure 1: Features included in supplemental processes for rare diseases across the HTA process (adapted from Nicod et al)[81]



RDT: Rare disease treatment, WTP: Willingness to pay

罕藥價值評斷的審辯過程，需要:

1. 疾病的相關資訊
2. 專門的委員會
3. 考量層面更廣的價值
4. 對證據品質的要求較寬鬆
5. 對經濟模型的要求較彈性
6. 不同於一般藥物的決策規則
   - Decision modifier (考量其他因素)
   - WTP 願付價格 (閾值修正)
   - 不同的給付規則

The Economist Group 2022 Connecting the dots: Embedding progress on rare disease into healthcare

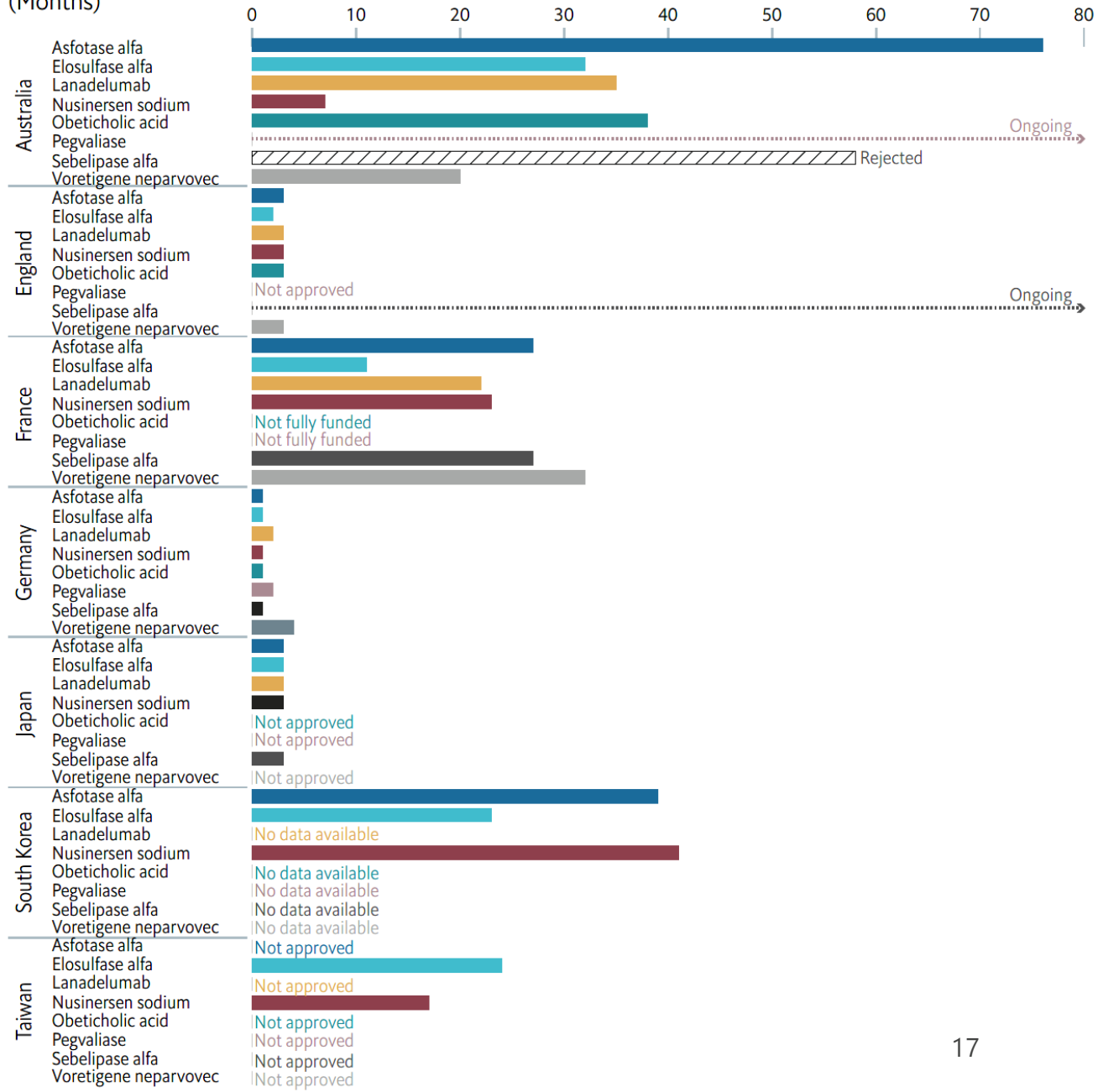
國際經驗 (EIU報告)

Table 1: List of comparison treatments in Economist Impact's analysis of time between regulatory approval and reimbursement decision[84-86]

Medicine (brand name)	Disease/condition	Prevalence (per 100,000)
Lanadelumab	Hereditary Angiodema	5
Pegvaliase (Palynziq)	Hyperphenylalaninaemia	0.2
Obeticholic acid (Ocaliva)	Primary biliary cholangitis	21.05
Sebelipase alfa (Kanuma)	Lysosomal acid lipase deficiency	2
Asfotase alfa (Strensiq)	Childhood- or juvenile-onset hypophosphatasia	1
Elosulfase alfa (Vimizim)	Mucopolysaccharidosis type IVA	15
Nusinersen sodium (Spinraza)	Spinal muscular atrophy	10
Voretigene neparvovec (Luxturna)	Leber congenital amaurosis	2.5

這8項藥品是從 International Rare Disease Research Consortium's Rare Disease Treatment Access Working Group於 2021年所擬定的 **"Essential list of medicinal products for rare disease"**中挑選出來。

Figure 2: Time between marketing authorisation and when public health systems agreed to reimburse them for eight treatments across seven jurisdictions



Source: Economist Impact.

德國

- 一般而言，藥品一旦拿到上市許可，就以藥廠的訂價給付一年。如果這一年的所有相關支出少於5千萬歐元，則藥廠價繼續維持。過於昂貴的藥品，GBA將會評估其療效(added therapeutic benefit)，並據以跟藥廠重新議價。
- 罕藥一開始取得藥證所需的證據較寬鬆。但一年之後如果沒有更充足的證據，就會被認為沒有可量化的療效證據，必須重新議價。
- 病人近用速度較快，但有較高比例的藥品在後續評估時被認為沒有足夠的療效價值。

GBA: Gemeinsame Bundesausschuss (聯邦共同審議委員會)

The Economist Group 2022 Connecting the dots: Embedding progress on rare disease into healthcare

英國

- 罕藥也要經NICE評價，但主要走HST (highly specialised technology)路徑。
- HST的評價過程，對相關證據的考量較為寬鬆，例如觀察性研究也可參考。一般NICE接受ICER在 £ 20,000~ £ 30,000 (per QALY)的新藥，但HST的ICER閾值至少為 £ 100,000。而且如果預期可以有很高的健康效果 (QALY gain 在30 以上)，則閾值可以到 £ 300,000 。
- 這些評價過程也需要時間。但EIU報告中，英國的病人近用速度與德國相差無幾。其主因在於，早在查登期，就開始評價作業。

NICE: National Institute for Health and Care Excellence (國家健康與照顧卓越研究院)

The Economist Group 2022 Connecting the dots: Embedding progress on rare disease into healthcare

法國

- 先經HAS進行一般HTA程序，包括成本效益評估。但委員會理解罕藥在證據彙集上的困難性，會在評價過程上稍做調整，改為進行相對療效評估、加上考量治療之後對病人健康效果的改善(包括質性與量性)、以及其未滿足之臨床需求(unmet need)程度。
- HAS將評估結果轉送給CEPS，如果所有衛生體系相關支出少於3千萬歐元，則接受廠商的訂價。
- 沒有ICER的把關。藥價討價還價的過程可能會很長。不過病人近用問題可經由ATU的方式讓真正非常有需求的病人，甚至在藥品拿到許可證之前就可公費使用。

HAS: Haute Autorité de Santé (健康監管高級委員會)；CEPS: Comité Economique des Produits de Santé (衛生產品經濟委員會)；ATU: Autorisation temporaire d'utilisation (臨時授權使用)

The Economist Group 2022 Connecting the dots: Embedding progress on rare disease into healthcare

澳洲

- EIU報告的幾個亞太地區國家中，已給付最多的國家。
- 如同一般藥品，必須經PBAC進行評價；但沒有對罕藥有特殊的規則，而且罕藥常常在第一次PBAC審議時被拒絕 – 造成近用延遲及多次規費 (成本增加)。另外，缺乏有經驗的藥物經濟學者能夠評估罕藥的價值。
- 傳統的HTA成本效益評估，被認為是多年來造成病人無法取得或延遲取得罕藥的主因。
- 如果PBAC建議不予收載，罕病治療可以另走LSDP (life saving drugs plan)途徑，LSDP條件如：預期治療可以增加病人壽命，且會對病人造成過分巨大的財務負擔(unreasonable burden)…等。

PBAC: Pharmaceutical Benefits Advisory Committee (藥品給付諮詢委員會)

日本

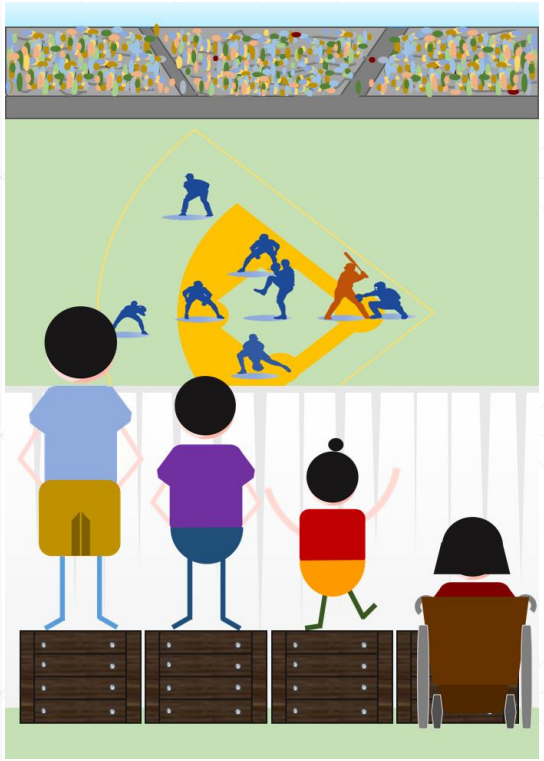
- 自2019年之後，採取類似德國的制度，在藥品獲得上市許可的60-90天之內，健保即以廠商定價開始給付。
- 跟一般藥品不同的是，只用於治療罕病的藥品可以不必進行之後的HTA評估(用以藥價調整)。
- 也有conditional early access program，不過2017-2020間只有一個藥品符合資格。

南韓

- 在EIU報告中所分析的8項罕藥，南韓只有給付3項。跟台灣一樣，因為市場小、醫療費用佔GDP比例小、給付決策難以預料 (reimbursement is not straightforward)，很難吸引藥廠引入新藥。
- 2014年以前的HTA過程，使得罕藥很難得到給付。2014-2015年間修正(reform)之後，將罕藥分成兩類，其中沒有其他治療方法的嚴重疾病且新藥可以獲得明顯療效(demonstrated substantial clinical effectiveness)的，被列為基本藥品(essential drugs)，參考7大國家的價格給價。
- 2014-2018間罕藥的費用大幅成長(為原來的四倍)，但還是只占全部藥費支出的1.4% (台灣2.3%)。

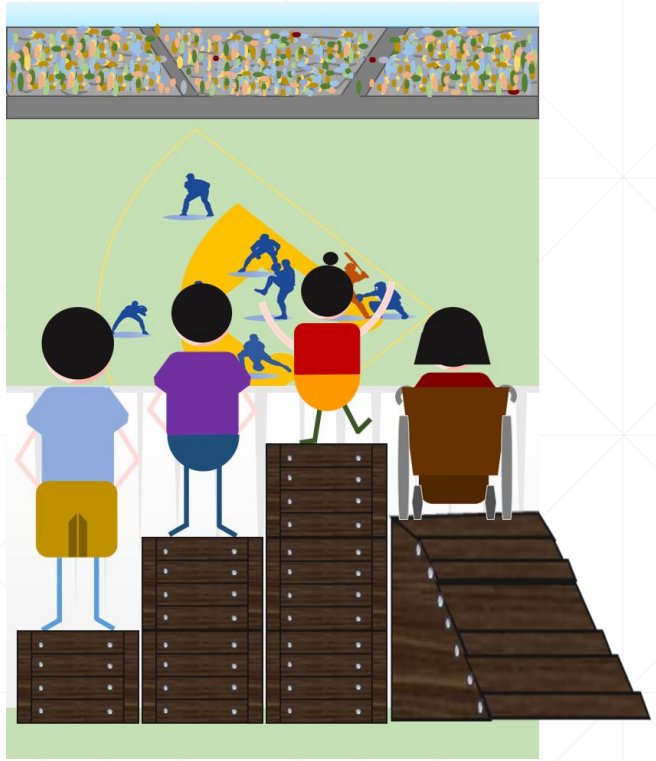
罕藥的評估考量，公平(equity)可能比成本效益 (efficiency)重要

所以在一定的條件下，ICER的要求可以不比照一般藥品。



平等

獲得相同補助？



公平

依不同需求
獲得補助，大家
都有機會

有些罕藥的QALY gain非常好

Product	Indication	QALY gain
Luxturna (voretigene naparvovec)	Inherited retinal disease due to mutations in both copies of the RPE65 gene, a condition that may lead to blindness	Between 12.1-17.7 QALYs compared to best supportive care accounting for uncertainty (NICE 2019).
Zolgensma (onasemnogene abeparvovec)	Spinal Muscular Atrophy.	For SMA type 1, 18.6 QALYs compared to best supportive care (NICE 2021).
Strimvelis (autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence)	Rare metabolic disorder adenosine deaminase deficiency-severe combined immunodeficiency (ADA-SCID) which causes serve immunodeficiency and recurring infections in patients.	13.6 QALYs compared to hematopoietic stem cell transplant from a matched-unrelated donor (NICE 2018).

TABLE 2: EXAMPLE GENE THERAPIES AND MAGNITUDE OF QALY GAIN

Firth I, Schirrmacher H, Zhang K, Hampson G, Towse A, 2021. Exploring the financial sustainability of gene therapies. OHE Consulting Report, London: Office of Health Economics.

有些新藥的QALY gain非常好

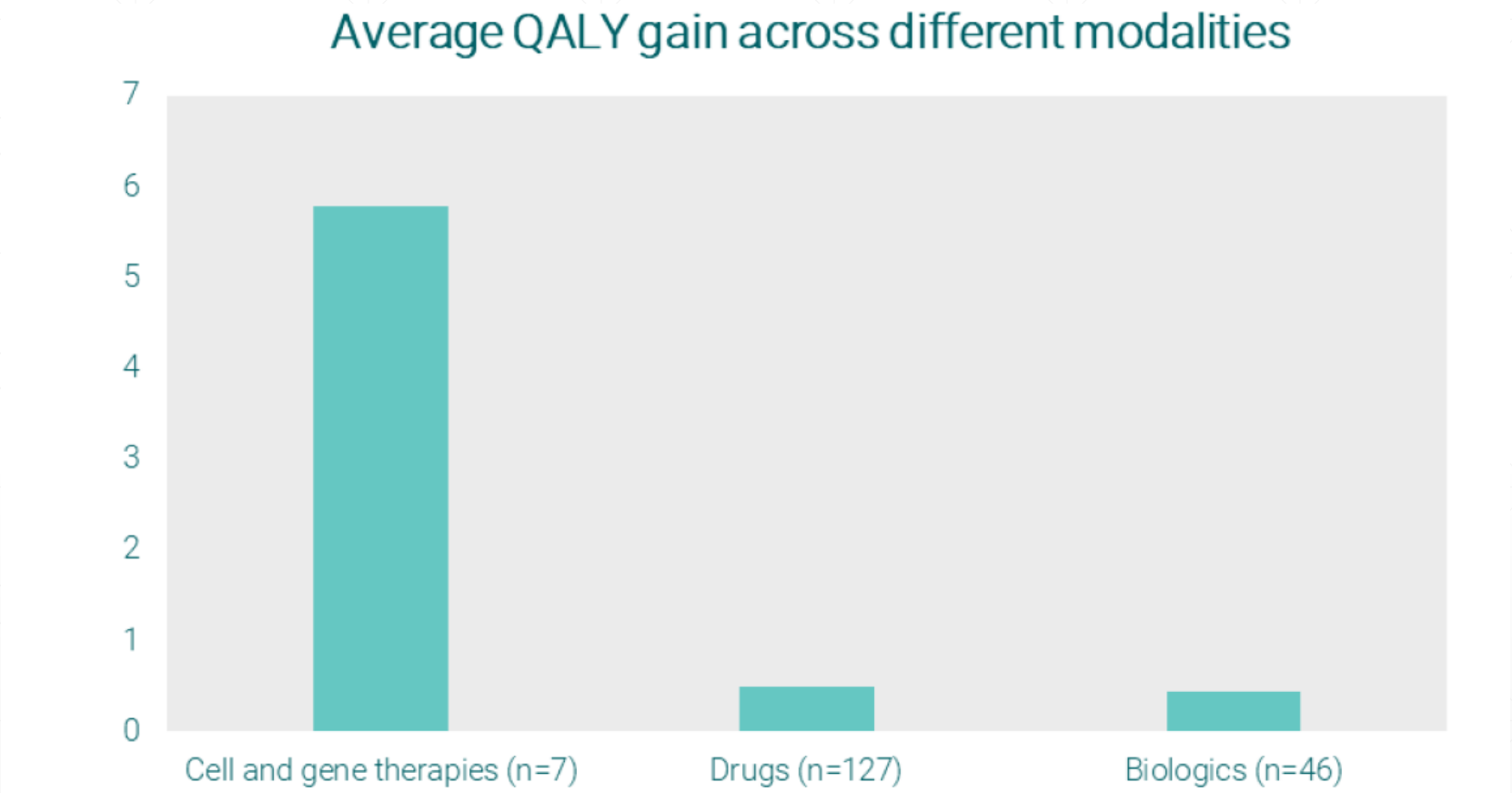


FIGURE 1 THE AVERAGE QALY GAINS OF A SAMPLE OF CELL AND GENE THERAPIES, OTHER BIOLOGICS AND SMALL MOLECULES (COHEN ET AL. 2019)

Firth I, Schirrmacher H, Zhang K, Hampson G, Towse A, 2021. Exploring the financial sustainability of gene therapies. OHE Consulting Report, London: Office of Health Economics.

“Equity(公平)”考量很重要

Fairness and Equity. Equity issues of orphan drugs and rare diseases due to the nature of these diseases (low patient population, high costs, and low health gain) are highly important. Since the ICERs of these treatments are so high and the amounts of health resources are limited, most of them would not fall under standard thresholds of CE. It has been suggested that patients with rare diseases have a human right to treatment raising issues of equity in terms of access to orphan drugs (19). Therefore, this criterion has been mentioned as a one of the contextual criteria in new methods of priority setting in determining a social value for orphan drugs (13;16;19).

Mohammadshahi M, et al (2022). Methods and criteria for the assessment of orphan drugs: a scoping review. International Journal of Technology Assessment in Health Care, 38(1), e59, 1–13 https://doi.org/10.1017/S0266462322000393

對罕藥進行特殊考量之倫理依據

Table 2 Ethical principles that favours price premium of orphan drugs and their criticism

Ethical principle	Description	Critics
"Non-abandonment"	• Society should not abandon individuals who are suffering from a serious and rare condition [19, 96]. • Reimbursement of ODs promotes the appearance of social solidarity where vulnerable groups are supported [35]. • Social justice requires treating everybody with dignity and respect as a human being [97].	• Public healthcare should guarantee the best supportive care for everyone. Restrictions made only for drugs that are far from being cost-effective [8, 44].
"Rule of rescue"	• Society puts greater value on health gains of individuals who are in immediate peril, and there are a small number of cases where no alternative treatments are available [34]. • Identifiable individuals are an essential part of this principle [98]. • Lifesaving ability should be considered in the reimbursement decision, but more specifically, only for therapies of life-threatening diseases, which have no alternative treatments. In this later case, the drugs should be financed irrespectively of their cost [28, 31, 96].	• Immediate, life-threatening peril also characterized several other diseases, for which treatment can be more cost-effective [19, 90]. • Since every person faces imminent death in certain periods of time, this cannot be a differentiating characteristic of rare diseases [8]. • It is not right to select one orphan drug over another as having particular social value, because it is not equal to value lifesaving drugs more than cosmetic drugs [26]. • "Rule of rescue" cannot be feasible at population level in an era of constrained resources [90].
"Rights based approach"	• Social solidarity requires that all members of the society have access to a decent minimum standard of healthcare because it is the right and fair thing to do [92, 97]. • Right of access to high-quality health care is embedded in the legislation of the developed countries [36, 75, 96].	• "Right-based approach" would not necessarily favour the treatment of rare conditions over more prevalent conditions, because these patients also receive the same standard of care [34].
"Equality of opportunity"	• Every member of the society should have the same opportunities to receive treatment and this must be true for rare disease patients as well as other patients with more frequently occurring disorders [60, 96]. • Everybody should have a fair chance to receive not only some treatment, but also the best available treatment [47]. • The equality of opportunity should be the paramount consideration in determining social value [65].	• Effectiveness of ODs is not sufficiently proven in several cases (See section Efficacy, effectiveness)

無遺棄

救援

(基本)權利

機會平等

Zelei et al. Orphanet Journal of Rare Diseases (2016) 11:72

一定要用ICER…?

針對罕藥的ICER特殊處理

Table 1 Proposed solution to handle higher ICERs of ODs

Proposed Solution	Description	References
Weighted QALY 對QALY gain給予更高加權	*"Weighted QALYs* (according to disease prevalence, severity) *attach a higher value to the health gain of a person with a rare disease. Therefore the ICER will decrease, increasing the likelihood of meeting the* (standard) *threshold."*	[32, 34–36, 62, 75, 76, 93, 94]
QALY categorization 對QALY分類	Prioritization of rare disease groups could be achieved by categorizing QALY's based on e.g., disease states	[75]
Higher CE-threshold for ODs 比較寬鬆的ICER閾值	Accepting a higher cost-effectiveness threshold for ODs increases the probability that these drugs will be cost-effective	[36, 92–94]
Special rules above the CE-threshold 高於ICER閾值者有其他配套方法	• Above the cost-effectiveness threshold special support funds or specific political decisions may be needed. • Assess the profitability of ODs on different price levels (cost is warranted and based on a careful consideration of the manufacturer's cost and returns on investment.)	[95] [47]

Zelei et al. Orphanet Journal of Rare Diseases (2016) 11:72

使用ICER也是有變通的時候

TABLE 2 COST-EFFECTIVENESS THRESHOLDS (COMMONLY OBSERVED RANGES, WITH MODIFIERS) BY COUNTRY

Country	Threshold	Currency	Modifiers (quantitative[10])	Modifiers (qualitative)	Reference
Australia	Not specified	-		Rule of rescue / unmet needs, Equity	Taylor and Jan, 2017
Canada	140,000	CAD		Oncology	Skedgel, Wranik and Hu, 2018
Czech Republic	Not specified	-		Innovation, Severity	Skoupá, 2017
England and Wales	50,000 100,000 - 300,000	GBP	End of Life, HST, Ultra-rare		NICE, 2018
Ireland	100,000	EUR	Ultra-rare		Interview
Japan	7,500,000	JPY	Rare, Paediatric, Oncology		Towse, 2019
Netherlands	20,000-80,000	EUR	Severity (proportional shortfall)		Reckers-Droog, van Exel and Brouwer, 2018

Zhang, K. and Garau, M., 2020. International cost-effectiveness thresholds and modifiers for HTA decision making. OHE Consulting Report, London: Office of Health Economics.

Norway	1,000,000	NOK		Ultra-rare	Ottersen et al., 2016
	275,000 - 825,000	NOK	Severity (absolute shortfall)		Interview[11]
Poland	n/a				
Scotland	Not specified	-		See SMC modifiers list (above)	Scottish Medicines Consortium, 2012
South Korea	Not specified	KRW	Severity, Availability of substitutes		Bae et al., 2018
Sweden	1,220,000	SEK		Severity, Rare	Persson et al, 2012
	2,000,000	SEK			Interview
Taiwan	n/a				
Thailand	Not specified	THB		Equity	HITAP, 2014
United States	500,000	USD	Ultra-rare		Institute for Clinical and Economic Review, 2018

[10] Where a specific value is attached to the modifier (e.g. £300,000 for HST in England and Wales)
[11] Severity of illness and priority setting in Norway. Summary of a report from a working group, November 2015: Available from: https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/summary_the_magnussen_report_on_severity.pdf

Zhang, K. and Garau, M., 2020. International cost-effectiveness thresholds and modifiers for HTA decision making. OHE Consulting Report, London: Office of Health Economics.

Postma *et al.*
Orphanet Journal of Rare Diseases (2022) 17:157
https://doi.org/10.1186/s13023-022-02283-z

Orphanet Journal of Rare Diseases

REVIEW Open Access

Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose?

Maarten J. Postma[1,2], Declan Noone[3], Mark H. Rozenbaum[4], John A. Carter[5], Marc F. Botteman[5], Elisabeth Fenwick[6] and Louis P. Garrison[7*]

三大因素，讓**使用傳統CEA**來評估罕藥是困難或不適當的：

1. **基本原則衝突**：罕藥的特質與利用CEA評估新藥的立意是相衝突的。
   - 倫理與經濟的衝突
   - 到底要在相同資源下買到最大健康效果，或優先照顧有緊急需求的人 (maximized good for all vs. favoritism toward those in dire need…)
2. **QALY的特性**：是否能抓到罕藥的價值?
   - Complex nature and limited scope
3. 療效、成本、自然史、影響性：都有**很高不確定性**，此情形下再怎麼嚴謹執行傳統CEA，也只會生成非常高不確定性的結論。

ICER成為決策主要依據，在台灣合適嗎?

基礎工程尚未啟動 (不是尚未完成)

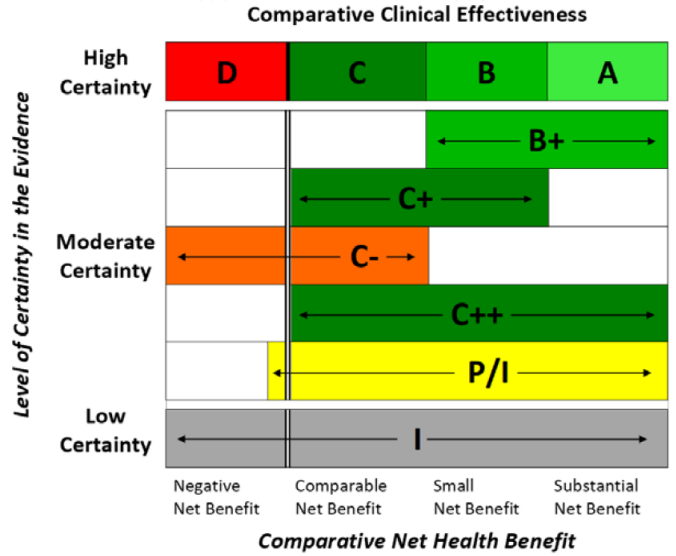
一般新藥使用ICER評估

- 各種元素
  - 模型建構：流行病學、自然病史、建模能力
  - 成本
  - 健康生活品質權數 (utility, QoL, EQ-5D台灣tariff)
- 台灣特殊健保核價過程
  - 用廠商價? 用健保專家會議(或PBRS)核訂的價格? 來計算ICER
- 人力資源與報告評析素養 (capacity and capability)
  - 有合適的執行指引
  - 有認真執行與批評能力的專業團隊
  - 決策討論時能夠「不役於ICER這個數」，有看透價值的洞察力

基礎工程尚未啟動 (不是尚未完成)

罕藥使用ICER評估

- 價值觀討論
  - 公平重不重要? 該花多少資源在罕藥上?...
- 評估框架建立
  - 要不要看ICER?
  - ICER用來做甚麼?
- "high-cost drugs" 是問題，罕藥是高成本藥物，但ICER是解方嗎?
- ICER之外？



ICER Evidence Rating Matrix. https://icer.org/evidence-rating-matrix/

Limited effectiveness → Life-changing

謝謝聆聽，歡迎指教!