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To HTA or Not to HTA: Identifying the Factors Influencing the Rapid Review Outcome in Ireland

Aileen Murphy, PhD [1,*], *Sandra Redmond, MA (Econ)* [2]

[1]*Department of Economics, Cork University Business School, University College, Cork, Ireland;* [2]*Salutem Insights Ltd., Dublin, Ireland*

ABSTRACT

Objectives: Reimbursement systems are evolving and endeavor to balance access and affordability. One such evolution in Ireland is the compulsory rapid review (RR) process, the outcome from which is a recommendation for a health technology assessment (HTA) or no HTA. For drugs that avoid an HTA, evaluation times are shorter, lengthy price negotiations are avoided, and access is faster. In the absence of formal decision-making criteria around the requirement of an HTA, this study examines the factors influencing the outcome of the RR process in Ireland. **Methods:** A database was developed combining data from publicly available sources for drug evaluations conducted by the National Centre for PharmacoEconomics (NCPE) (January 2010-June 2017, n = 296). Because Irish cost data were not publicly available for all drugs, cost data from the Scottish Medicines Consortium were employed as a proxy. Employing logistic regressions, the factors influencing the RR outcome are revealed. **Results:** After an RR, an HTA was recommended for 55% of drugs. The regression results revealed therapeutic area (endocrine, musculoskeletal, and neoplasm), first-in-class and orphan disease increased the probability of an HTA. Furthermore, when proxy costs were included, results revealed that every €1000 increase in annual drug costs per patient increased the probability of an HTA being required by 1% and that an HTA was more likely than no HTA when annual drug costs exceeded €15 000. **Conclusion:** Given the current focus on access and affordability, this study identifies the factors influencing the requirement of an HTA in Ireland.

Introduction

Reimbursement and health technology assessment (HTA) systems globally evolve in response to environmental and economic challenges. In particular, since the global financial crisis, efforts to balance access and affordability are prioritized. A somewhat unique approach was taken in Ireland with the introduction of compulsory rapid reviews (RR) in 2010. While employed in a variety of countries to support decision making, the definition and implementation of RRs vary in practice.[1] Nevertheless, most RRs aim to synthesize evidence in a timely manner without sacrificing scientific rigor.[2]

Before this, only medicines with a significant budgetary impact were considered for an HTA in Ireland, although there was no explicit threshold on what constituted a significant budget impact. Nevertheless, as the financial crisis hit Ireland and recession ensued, budget cuts were necessary. The volume of medicines to be assessed increased at the same time, as did evaluation times. RRs were therefore introduced[3] as a means of optimizing agency resources, which led to shorter evaluation times and faster patient access while ensuring affordability.

Access and affordability of medicines are longstanding issues, particularly in Ireland, where per-capita pharmaceutical expenditure increased dramatically from the 20th highest of 27 Organisation for Economic Co-operation and Development countries in 2000 to third highest of 25 Organisation for Economic Co-operation and Development countries in 2010.[4] After the introduction of international and internal reference pricing, pharmaceutical spending moderated in Ireland but like other countries has been rising since 2014[5] (€1964 million in 2016). The latest rises has been attributed to the introduction of expensive treatments, starting with the allocation of €30 million per year for hepatitis C treatment in the public healthcare system.[6,7] Since this, many high-profile expensive drugs have been approved, such as eculizumab for paroxysmal nocturnal hemoglobinuria and lumacaftor or ivacaftor for cystic fibrosis.[5]

* *Address correspondence to*: Aileen Murphy, PhD, Department of Economics, Cork University Business School, University College Cork, Cork, Ireland.

E-mail: aileen.murphy@ucc.ie

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Previous studies have described the reimbursement process in Ireland in detail[8–10] and examined criteria influencing reimbursement decisions in Ireland after an HTA.[11] To summarize, there are two stages to the reimbursement process, which is governed by the Supply of Medicines to Health Services Agreement between the Government and Irish Pharmaceutical Healthcare Association (IPHA), hereinafter the IPHA Agreement. In stage 1, an RR is required for all new medicines after a licensing decision. The RR is a short dossier submitted by the drug manufacturer detailing the condition and technology, price, regulatory status, placement in therapy, comparator(s), clinical evidence, and budget impact.[12] The National Centre for Pharmacoeconomics (NCPE) assesses the RR within 28 days. There are two outcomes from the RR: full HTA not recommended or full HTA recommended. (In some cases an HTA is initially recommended at submitted price but is avoided after price negotiations.) If an HTA is not required, a positive reimbursement recommendation is made by the national health service (Health Services Executive, HSE). Stage 2 involves an HTA and further engagement with the HSE. The HTA is assessed by the NCPE within 90 days (excluding clock stops for questions). The recommendations after an HTA are a positive decision to reimburse at applied terms; negative reimbursement decision or the decision is referred to the national agency (HSE Drugs Group), who either recommends the drug for reimbursement or not.

In an academic publication, McCullagh and Barry[8] indicate that, when appraising an RR and deciding if a full HTA is required, the following criteria are considered by the NCPE: robustness of clinical efficacy data indicating noninferiority or superiority to comparator while being equal or lower in cost; small eligible population with an unmet need; and low associated budget impact (less than €0.75 to €1 million per annum) or low estimated budget impact, along with existing system infrastructure capable of restricting usage. These criteria, however, are not formalized and do not appear on the NCPE website, the IPHA Agreement, or any other guidance or process documentation used by manufacturers, just the academic publication.[8] Also, it is not clear how these criteria are weighted in the decision-making process.

Whether an HTA is recommended or not has implications for access. As per the IPHA Agreement,[13] the guidance regarding reimbursement timelines for the RR stage and HTA stage is 73 days (28 days RR evaluation plus 45 days to reimbursement) and 163 days (28 days RR evaluation, 90 days HTA evaluation and 45 days to reimbursement), respectively. Although the timelines for the RR stage are generally adhered to and reimbursement almost guaranteed if no HTA is recommended,[8] there are delays in the HTA stage because of clock stops during the evaluation of the HTA and delays in the further engagement phase, which involve price negotiations, with the HSE.[14] Furthermore, 25% of drugs that undergo an HTA do not get reimbursed.[8]

The RR is a practical tool that aims to balance timely decision making, affordability, and access. Attempts at balancing access and affordability are not uniquely Irish. For example, in England NICE has recently introduced a fast-track appraisal process suitable for drugs with an incremental cost-effective ratio under €10 000 per QALY.[15] Elsewhere, there are specific reimbursement routes and considerations for orphan drugs in France and Germany, for example[16]; for innovation status in Italy; and highly specialized technologies in England.

Eight years on from the introduction of compulsory RRs and in the absence of formal decision-making criteria on the necessity of an HTA, this study examines the factors influencing the outcome of the RR process.

Methods

Data

A database was developed combining data from publicly available sources for all drug evaluations conducted by the NCPE from January 2010 to June 2017 (vaccines and devices were excluded). An overview of the variables and sources contained in the database are summarized in Table 1. Table 2 presents a comparison of drugs recommended and not recommended for HTA.

Irish data on patient drug costs were not publicly available from the NCPE website for drugs that did not require an HTA and for approximately two-thirds of those that underwent an HTA. To overcome this, cost data were obtained from the Scottish Medicines Consortium (SMC) website and used as a proxy. The SMC data were used as a proxy for two reasons. First, the populations are similar in size (5.4 m in Scotland[22] and 4.8 m in Ireland[23]). Second, the SMC appraises all new licensed medicines and makes the evaluations publicly available, and so there was a higher likelihood that the data would be available from the SMC compared with other jurisdictions. Drug cost per patient from the SMC was used as opposed to budget impact data because the latter was often not disclosed for confidentiality reasons, and although the populations are similar, the prevalence of diseases can be different, thus impacting transferability.[24] Table 3 presents a summary of SMC cost data (converted to euros using annual average exchange rates).

Analysis

To explore the factors influencing the likelihood that a medicine requires a full HTA, descriptive statistics on the data defined above are produced after which an econometric analysis is employed. With a binary dependent variable—HTA (1) or no HTA (0)—a logit regression is employed using STATA version 14.[25] This predicts the dichotomous outcome of the dependent categorical variable (HTA) based on the explanatory (independent) variables using binomial probability theory. The explanatory variables included here are: year of the review (dummy variable for each year), type of reimbursement scheme (dummy variable for each), first in class, therapeutic area (dummy variable of each), submission company's experience, orphan disease, reassessment and year (See Table 1 for variable definitions). The form of logit regression equation is:

$$\text{logit}(p(x)) = \log\left(\frac{p(x)}{1-p(x)}\right) = a + b_1x_1 + b_2x_2 + \ldots$$

The marginal effects are also estimated using STATA version 14. These measure the effect on the conditional mean of the dependent variable of a change in the independent variables. This provides a good approximation to the amount of change in the dependent variable produced as function of the change in the independent variables and thus are more intuitive particular for logit models.

Because SMC cost data were only proxies, two econometric analyses were conducted—the first without SMC cost data on the full data set (n = 296) and the second with SMC cost data on the restricted data set (n = 212).

Results

NCPE Evaluations 2010-2017

In total 296 evaluations, involving an RR, were conducted by the NCPE between January 2010 and June 2017; in 55% of cases an HTA was recommended (n = 163) (Fig. 1 and Table 2). Table 2 shows that

Table 1 – Data sources and descriptive statistics

Variable	Definition	Source	Description	Mean	SD
HTA	HTA recommended (or HTA not recommended)	NCPE website[17]	Binary: HTA (1), No HTA (0)	0.55	0.5
Therapy area	Therapeutic areas as per WHO ICD-10 classifications	WHO ICD-10 classification[18]	Binary variable per area: Yes (1), No (0)		
			Circulatory	0.11	0.31
			Endocrine	0.13	0.34
			Musculoskeletal	0.07	0.26
			Respiratory	0.07	0.26
			Neoplasm	0.27	0.45
			Infectious disease	0.06	0.23
			Other	0.29	0.45
Reimbursement scheme	General Medical Services (GMS) High Technology Scheme (HTS) Hospital (it was assumed that all IV drugs were reimbursed by hospitals)	NCPE website and in monthly PCRS updates[17]	Binary variable per scheme (GMS, HTS, Hospital): Yes (1), No (0)		
			GMS	0.30	0.46
			HTS	0.34	0.48
			Hospital	0.36	0.48
Year	Year of outcome of RR	NCPE website[17]	Binary variable per year (2009-2017) Yes (1), No (0)		
			2010	0.04	0.20
			2011	0.11	0.31
			2012	0.10	0.31
			2013	0.11	0.32
			2014	0.17	0.38
			2015	0.15	0.35
			2016	0.21	0.41
			2017	0.10	0.31
First in class	Variable indicates unique mechanism of action for treatment as designated by the FDA in their annual report of novel drugs	FDA Annual Reports[19]	Binary: Yes (1), No (0)	0.37	0.48
Orphan status	Drug designated orphan status by the European Commission Community Register of orphan medicines	European Commission Community Register of orphan medicines[20]	Binary: Yes (1), No (0)	0.78	0.41
New drug	Drug designated a new drug if not previously evaluated by the NCPE	NCPE website[17]	Binary: Yes (1), No (0)	0.78	0.78
Experience	Variable indicates the experience of companies navigating the reimbursement process measured by the number of RR and HTA submissions	NCPE website (count of submissions per company)[17]	Continuous	4.15	3.96
Cost	Cost per patient converted to euros using annual exchange rates	SMC website[21]	Continuous (£ converted to € using average annual exchange rates)	*See Table 3*	

Note. PCRS Schemes: General Medicines Scheme (GMS): covering drugs that are prescribed and dispensed in community pharmacies. It is means tested (i.e., dependent on individuals' wealth), and those eligible receive free medicines subject to a €2 prescription charge (up to a maximum €20 a month). High Technology Scheme (HTS): covering mainly oral high-cost drugs that are prescribed in hospitals but dispensed in the community. Hospital scheme: covering IV drugs prescribed and dispensed in hospitals.

FDA indicates Food and Drug Administration; GMS, general medicines scheme; HTA, health technology assessment; HTS, high technology scheme; ICD, International Classification of Diseases; NCPE, National Centre for Pharmacoeconomics; RR, rapid review; WHO, World Health Organization; PCRS, Primary Care Reimbursement Service; SD, standard deviation; SMC, Scottish Medicines Consortium.

there was an increasing trend of HTAs being recommended and that over 70% of first-in-class and orphan drugs were recommended for HTA. Regarding therapeutic area, drugs for neoplasm and circulatory and musculoskeletal disease were more likely to be recommended for HTA compared with other therapeutic areas. Moreover, drugs seeking reimbursement for the high technology and hospital reimbursement schemes were more likely to attract an HTA compared with the general scheme (Table 2).

SMC cost data were available in 212 cases and an HTA was recommended in 62% of these cases (n = 132). Average annual cost per patient was €36 516 (standard deviation €61 171). Regarding

Table 2 – Comparison of drugs recommended and not recommended for HTA

	HTA recommended % (n = 165)	HTA not recommended % (n = 137)
All	55	45
Circulatory	41	59
Endocrine	64	36
Musculoskeletal	62	38
Respiratory	33	67
Neoplasms	88	12
Infectious disease	35	65
Other areas	33	67
First in class	73	27
Orphan disease	78	22
New drug	52	48
GMS scheme	36	64
HTS scheme	68	32
Hospital scheme	58	42
Year 2010	50	50
Year 2011	34	66
Year 2012	58	42
Year 2013	36	64
Year 2014	47	53
Year 2015	58	42
Year 2016	68	32
Year 2017	77	23

GMS indicates general medicines scheme; HTA, health technology assessment; HTS, high technology scheme.

Table 3 – Summary SMC cost data (converted to euro)

	Average SMC cost €	SD €	Sample size
All	36 516	61 171	212
Circulatory	6921	11 640	22
Endocrine	64 869	103 231	29
Musculoskeletal	56 320	147 678	13
Respiratory	17 217	21 068	13
Neoplasms	56 875	33 218	63
Infectious disease	33 269	33 271	15
Other areas	11 749	20 525	57
First in class	53 627	78 080	89
Orphan disease	82 230	92 783	50
New drug	35 430	65 094	160
GMS	11 667	73 677	55
HTS	47 977	51 204	81
Hospital scheme	42 283	56 513	76
Year 2010	36 485	45 956	7
Year 2011	22 981	62 102	19
Year 2012	24 152	48 267	22
Year 2013	17 723	24 828	28
Year 2014	23 053	26 280	38
Year 2015	32 996	39 448	35
Year 2016	60 158	95 680	47
Year 2017	72 714	68 799	16

Note. SMC costs converted from £ sterling to € euros using annual exchange rates.
Time period considered: Jan 2010 to June 2017.
GMS indicates general medicines scheme; HTS, high technology scheme; SMC, Scottish Medicines Consortium.

therapeutic area, average annual drug costs per patient were highest among drugs indicated for endocrine, neoplasms, and the musculoskeletal systems. Average costs for drugs classified as first in class, new, and orphan diseases also exceeded average in the full sample (Table 3).

Factors Influencing Rapid Review Outcome

The logistic regression results reveal that therapeutic area (specifically endocrine, musculoskeletal, and neoplasms), first in class, and orphan disease status are statistically significant in influencing the RR outcome (Table 4). Specifically, a drug indicated for the endocrine system is 21% more likely to require an HTA compared with drugs in the other therapeutic areas category, holding all else constant. In addition, drugs indicated for musculoskeletal and neoplasm systems are 21% and 41%, respectively, more likely to require an HTA than drugs in the other therapeutic area category, holding all else constant. Similarly, drugs that are first in class (19%) and those with orphan status (15%) are more likely to require an HTA.

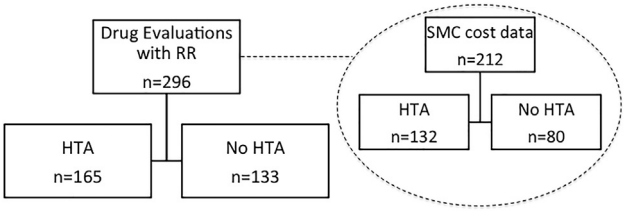


Fig. 1 – National Centre for Pharmacoeconomics submissions 2010-2017.

As indicated previously, a limitation of the publicly available information used to create the data set for this regression was the absence of cost parameters. To overcome this, data on annual drug costs per patient were obtained from the SMC website and used as a proxy for Ireland. These variables were added to the original logistic regression to investigate factors influencing the RR outcome (n = 212). Results reveal a positive relationship between cost per patient and RR outcome. As costs increase, the likelihood of an HTA being recommended increases. Specifically, every €1000 increase in the annual per-patient cost of a drug increases the probability of an HTA being requested by 1%. A drug indicated for the circulatory, endocrine, or musculoskeletal system or a neoplasm is more likely to require an HTA than drugs in the other therapeutic areas category, holding all else constant. Meanwhile a drug indicated for infectious diseases is less likely to need an HTA, holding all else constant. Estimating the predicted values at various cost thresholds (using regression results) indicates that when patient drug costs exceed €15 000 per annum, an HTA is more likely than no HTA (Fig. 2).

Discussion

Previous research elsewhere[26–29] and in Ireland[11] have explored the factors influencing reimbursement decisions after an HTA. Nevertheless, in Ireland reimbursement can be secured without an HTA. In the absence of formal and transparent guidance around the requirement for an HTA, the factors influencing this decision have yet to be explored. This is a particularly important question in Ireland because 45% of drugs evaluated do not require an HTA, and for these drugs reimbursement is almost guaranteed. Consequently, access is much faster for those drugs than when an HTA is required. Furthermore, this analysis contributes to the growing international evidence base on reimbursement systems.

Table 4 – Logistic regression results

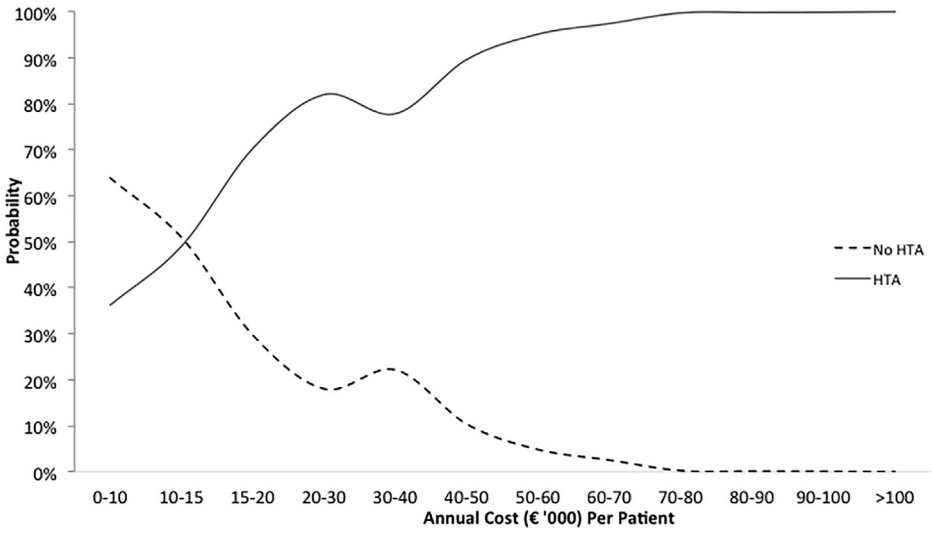
	Full analysis		Cost analysis	
	Marginal effects (SE)		Marginal effects (SE)	
Circulatory	0.08 (0.08)		0.13 (0.08)	***
Endocrine	0.21 (0.07)	*	0.12 (0.07)	***
Musculoskeletal	0.21 (0.10)	**	0.34 (0.11)	*
Respiratory	0.03 (0.10)		−0.01 (0.10)	
Neoplasms	0.41 (0.07)	*	0.22 (0.09)	**
Infectious disease	−0.04 (0.11)		−0.24 (0.12)	**
First in class	0.19 (0.05)	*	0.05 (0.06)	
Orphan drug	0.15 (0.07)	**	0.05 (0.09)	
New drug	−0.04 (0.07)		0.03 (0.07)	
GMS	−0.01 (0.07)		0.05 (0.07)	
HTS	−0.02 (0.07)		−0.11 (0.08)	
Company experience	0.00 (0.01)		0.00 (0.01)	
Year 2011	−0.16 (0.14)		0.02 (0.16)	
Year 2012	0.03 (0.14)		0.28 (0.16)	
Year 2013	−0.16 (0.14)		−0.04 (0.16)	
Year 2014	−0.13 (0.13)		−0.04 (0.16)	
Year 2015	−0.04 (0.14)		0.07 (0.16)	
Year 2016	0.03 (0.13)		0.08 (0.16)	
Year 2017	0.01 (0.15)		0.13 (0.20)	
Cost €'000 (SMC)			0.01 (0.00)	*
LR chi-square	*101.86*		*116.99*	
Prob > chi-square	*0.0000*		*0.0000*	
Pseudo R^2	*0.2501*		*0.4039*	

Note. Dummy variable reference categories: Other therapeutic area; hospital scheme; and year 2010.
Statistically significant at 1% (*), 5% (**), and 10% (***).
GMS indicates general medicines scheme; HTS, high technology scheme; SE, standard error; SMC, Scottish Medicines Consortium.

To analyze the factors influencing whether an HTA is required or not in Ireland, 296 drugs evaluated by the NCPE between 2010 and 2017 were examined, and logistic regression models were employed. Results of the first logistic regression reveal that drugs that are first in class for orphan diseases, cancer, and endocrine and musculoskeletal systems are more likely to require an HTA. These results are unsurprising because these medicines tend to be high cost and the scientific rigor associated with an HTA is required to investigate their cost-effectiveness. Another logistic regression that included annual proxy drug costs from the SMC($n = 212$) indicate that costs are a factor in deciding whether an HTA is required or not. Specifically, it shows that every €1000 increase in annual drug costs per patient increases the likelihood of an HTA by 1%. In addition, whereas the endocrine, oncology, and musculoskeletal remain significant in the second logistic regression, orphan drug status and first in class are no longer significant. This may suggest that it is not first-in-class and orphan status per se that is driving the need for an HTA, but the costs associated with these labels. These results indicate that the RR is fit for purpose; drugs that are likely to have a high budget impact are recommended for HTA.

This study adds to the literature describing and explaining the factors influencing the requirements for an HTA. Specifically, it advances previous studies of the Irish RR system[30] by including more observations and augmenting the NCPE database with secondary data such as orphan status and proxy drug costs from the SMC. This adds to the explanatory power of the logistic regression. In addition, proxy costs allowed for exploration of a cost threshold for RR outcomes. The regression results suggest that for drugs with annual patient costs greater than €15 000, an HTA is the most likely outcome of the RR. Nevertheless, costs employed are only proxies because Irish cost data are not available for drugs that did not require an HTA and for many of those that underwent an HTA. We acknowledge this is a limitation of the study.

Furthermore, we acknowledge that a better indicator of the cost impact of introducing a new drug is the budget impact. Indeed, although not formalized in the reimbursement process, previous commentary on Ireland's HTA process indicates that a low budget impact threshold of between €0.75 and €1 million per annum is one of the criteria that influence the outcome of the RR in Ireland.[8] Unfortunately, Irish budget impact data are not available for many of the drugs evaluated, nor are they easily



Observations from 2010-2017, n =212 and SMC costs employed as a proxy for Irish costs converted to Euros using average annual exchange rates.

Fig. 2 – Predicted probability of the requirement for an health technology assessment.

transferable between jurisdictions, and so proxy budget impact data from SMC could not be used. Therefore, we could not empirically test for the existence of the €0.75 to €1 million budget impact threshold.

Although McCullagh and Barry[8] outline criteria influencing the outcome of the RR (robust clinical data, low budget impact [€0.75-€1m per year], unmet medical need, and systems in place to restrict indication), these are not formalized and lack definition. Also, it is not clear how these criteria are weighted in the decision-making process. The lack of formal criteria, coupled with the compulsory nature of RRs, means that there is often duplication because agency staff are evaluating the same drug twice. Compulsory RRs also mean delays in initiating an HTA. For example, is it necessary for very high cost drugs such as lumacaftor/ivacaftor for cystic fibrosis to undergo both an RR and HTA? Given the new drugs pipeline is dominated by orphan, cancer, and specialty medicines,[31] which this study has shown are more likely to require an HTA to secure reimbursement, can the reimbursement process sustain such duplication? Moreover, how viable is the RR process in its current format; would an opt-in or opt-out approach be a better way to optimize agency resources? Nevertheless, transparent and formal decision criteria would be needed if compulsory RRs were replaced with an opt-in or opt-out approach. This would require significant consideration and capacity for frequent reviews to avoid criteria becoming "out of date," together with mechanisms to avoid moral hazard or gaming behavior. Other jurisdictions have developed formal criteria for opt-in systems; for example, NICE's fast-track appraisal process is deemed suitable for drugs with an incremental cost-effective ratio under €10 000 per QALY.[15]

Conclusions

As new, innovative medicines are diffused and the demand for existing medicines grows, pressure on reimbursement systems in the European Union and beyond will persist. Exploring reimbursement approaches and sharing experiences can be meaningful for HTA agencies designing and evolving their systems,[32] particularly given the shift toward value-based frameworks for reimbursement.[33]

This study describes the RR process employed in Ireland and indicates the factors influencing the requirement of an HTA to secure reimbursement, namely, therapeutic area, first in class, orphan status, and drug costs. These results, coupled with current and expected future trends of high-cost drugs and delays in access to medicines, suggest that better management for their introduction is warranted. Establishing formal decision-making criteria around the requirement for an HTA would represent significant progress.

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