International experiences with managed entry agreements

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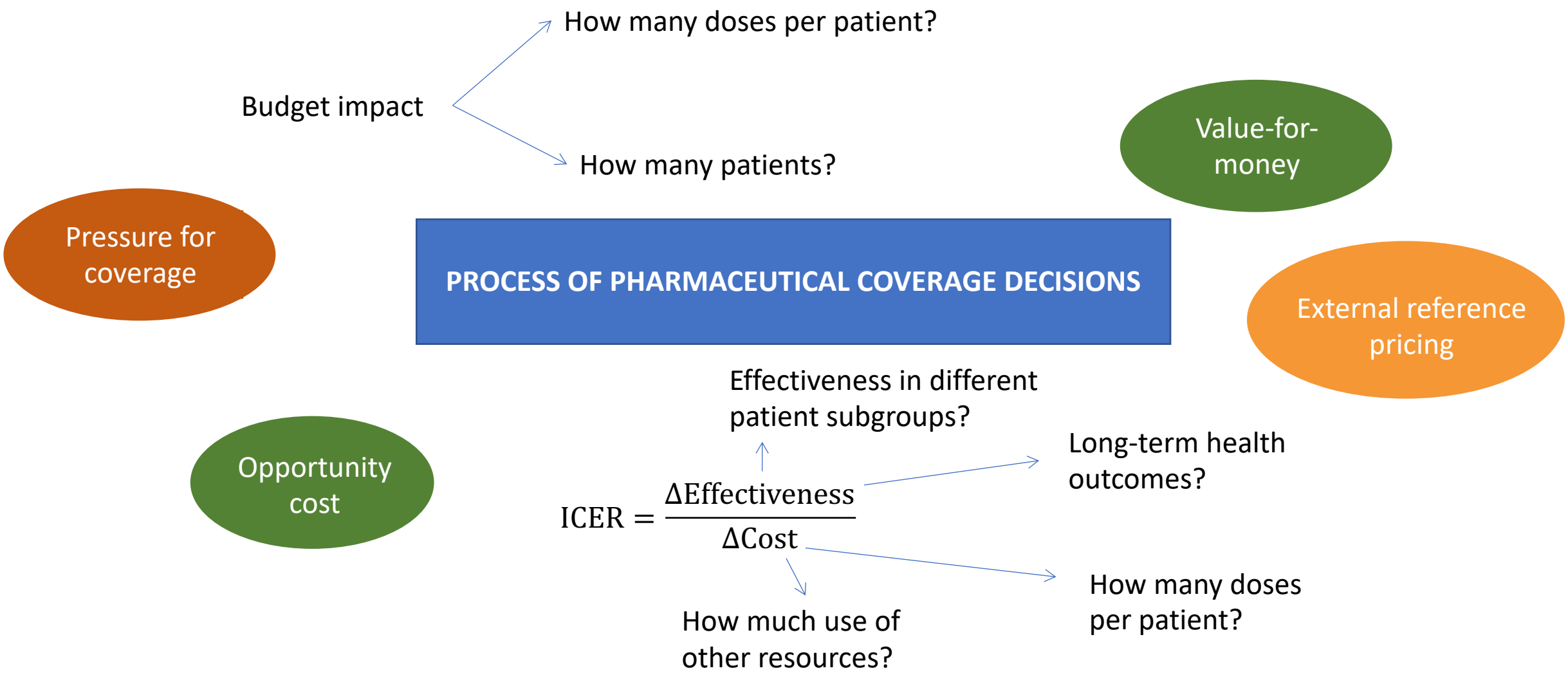
Outline

- The context in which MEAs are introduced
- Overview of the type of agreements implemented
- Examples of health outcome based agreements
- Lessons learned
- Equity considerations
- Summary

The context in which MEAs are introduced



Managed entry agreements (MEAs)

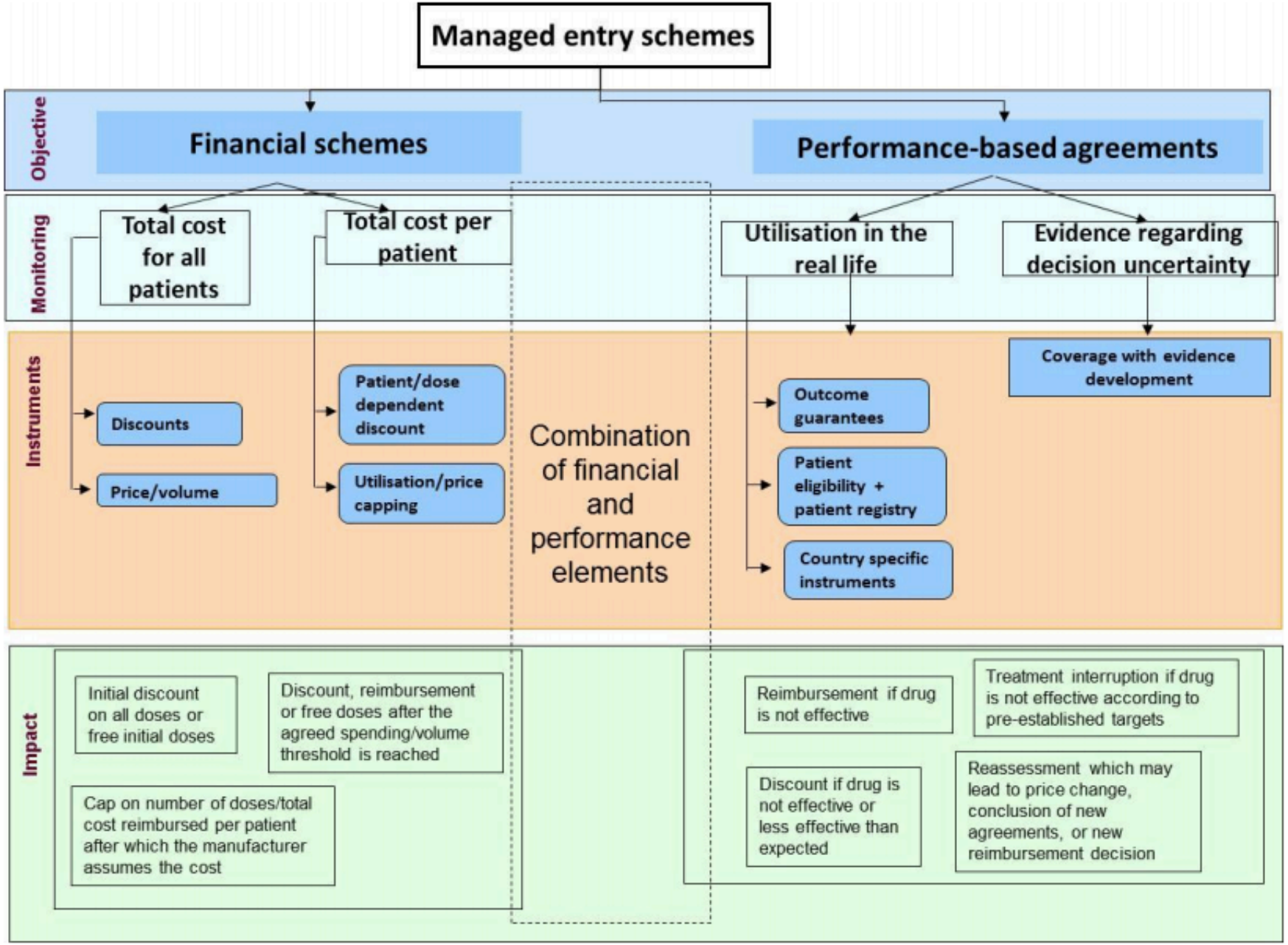
- A MEA is an arrangement between a manufacturer and payer/provider that enables the reimbursement of a medicine subject to specific conditions (Klemp, *et al.* 2011)

- MEAs aim to:
  - mitigate the impact of **uncertainty** and **high prices** on cost-effectiveness and expenditure
  - enable patients to access promising new drugs in a context of uncertainty
- Two main groups:
  - health outcome based
  - financial based

Klemp, M, KB Frønsdal, K Facey, and HTAi Policy Forum. 2011. What principles should govern the use of managed entry agreements? *Int J Technol Assess Health Care* 27 (1):77-83

Many names are used to define ‘managed entry agreement’

- **Managed entry agreements:** summary term encompassing both financial and health outcome based agreements
- **Performance based agreements** relate to the health outcome based agreements
- **Risk sharing schemes** has been used to define both financial and health outcome based but it is debatable whether all financial agreements have a risk sharing component
- Country specific terms: patient access schemes (UK), conventions (Belgium)



Performance in real-life

Health technology performance assessment (HTpA)

Sources: Ferrario A & Kanavos P, EMINet, 2013 and Guerra et al. Int J Technol Assess Health Care, 2017

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HEALTH TECHNOLOGY PERFORMANCE ASSESSMENT: REAL-WORLD EVIDENCE FOR PUBLIC HEALTHCARE SUSTAINABILITY

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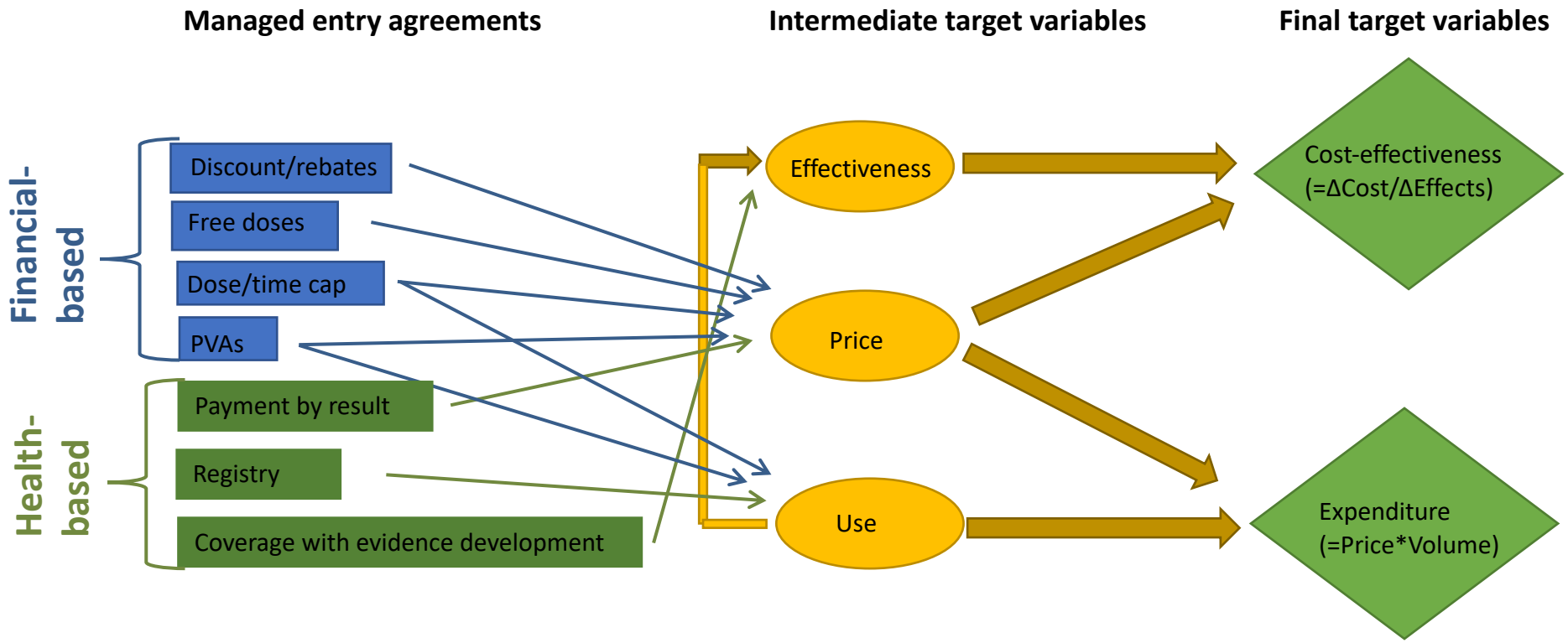
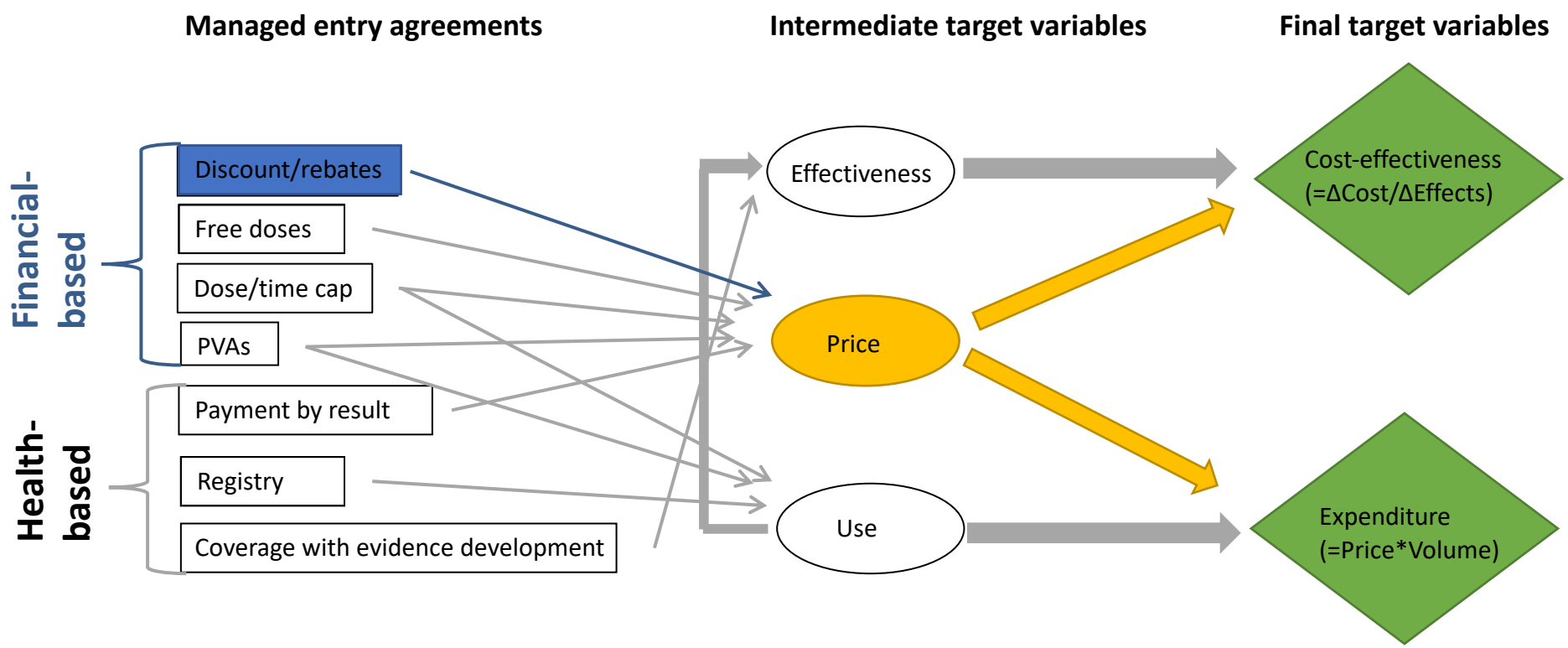
How MEAs influence key parameters



Source: Ferrario A, Kanavos P, Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. *Soc Sci Med.* 2015 Jan;124:39-47.

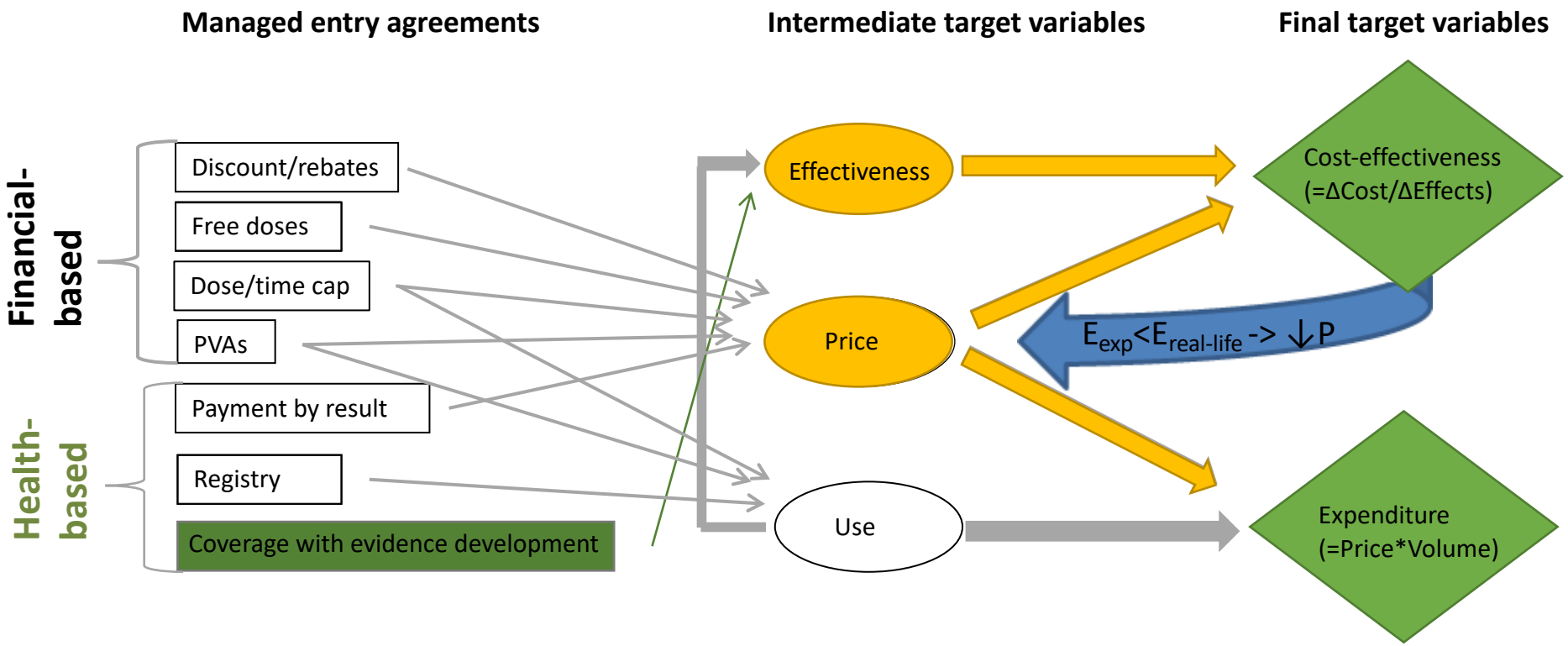
Example: Patient access schemes in England involving confidential discounts for neoadjuvant pertuzumab

The regulatory approval of pertuzumab for neoadjuvant treatment had limited the clinical trial evidence
-> the available evidence was suboptimal for the purposes of long-term modelling and health technology assessment.
The discount on the cost of pertuzumab increased the likelihood that pertuzumab would be cost effective.



Source: Ferrario, A and Kanavos, P (2014), 'Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden', Social Science and Medicine and https://www.nice.org.uk/guidance/ta509/resources/pertuzumab-with-trastuzumab-and-docetaxel-for-treating-her2positive-breast-cancer-pdf-82606727940037 (accessed May 11, 2019

Example: Coverage with evidence development in Sweden



Levodopa/Carbidopa (Duodopa®) 2003-2008[1]

Temporal component

Source: Ferrario A and Kanavos P (2014), 'Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden'; [1]Willis, M, Persson U, Zoellner Y, and Gradl B. Reducing Uncertainty in Value-Based Pricing Using Evidence Development : the case of continuous intraduodenal infusion of levodopa/carbidopa (Duodopa®) in Sweden. Appl Health Econ Health Policy. 2010;8(6):377-86

United Kingdom: Patient access schemes (PAS)

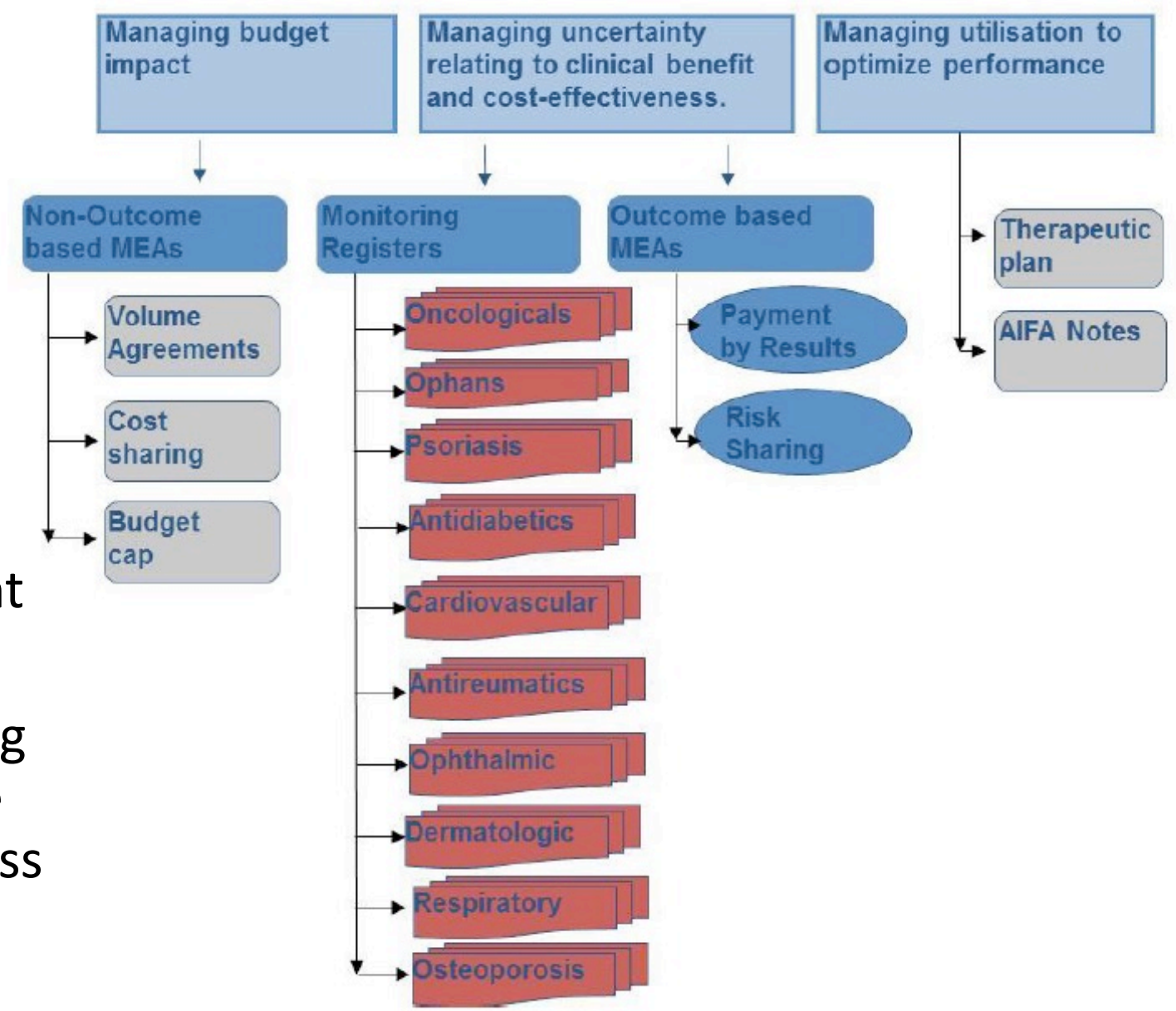
- Some health outcome based agreements up until about end of 2009
- An early review of PAS highlighted challenges for frontline health care workers which led to a gradual phase out of health outcome based agreements
- Currently, the majority of schemes is financial: a mix of simple discounts, free stock, dose or time capping schemes

- Refunds for two of the common PASs (sunitinib and bortezomib) may not have been passed on to the funding PCT in 50% of cases
- 73% of respondents reported that they did not have capacity to take on any more schemes
- Funding needs to be found for staff time dedicated to tracking and managing PASs, preventing missed claims and reducing the risk to the NHS
- There is no one preferred scheme; however, simpler schemes with fewer requirements for data collection and monitoring are preferred
- The development of a set of national standard templates for PASs to allow manufacturers to select a familiar "off the shelf" scheme would benefit the NHS
- There is a need for flexibility around any time limits for processing claims; ideally at least 90 days should be allowed to process claims
- In general, schemes linked to measurement of a clinical response took longer to administer and were associated with more problems

Source: Williams S and Thomson D, A report into the uptake of patient access schemes in the NHS. 2010; NHS: National health service; PCT: Primary care trust

Italy:
Monitoring registries

- Focus on limiting use to well defined patients in specialised centres
- Monitoring registries linking prescribing with reimbursement
- Successful in controlling use, relatively successful in obtaining substantial refunds, limited use of health outcome data to assess performance in real life



Sources: Ferrario A & Kanavos P, EMINet, 2013 and Garattini S et al. European J of Health Econ, 2015

Netherlands

Conditional financing (CF) of expensive hospital drugs was applied in the Netherlands between 2006 and 2012

Eligibility for CF
Budget impact > EUR 2.5 million/year
Proven added therapeutic value
Uncertainties on appropriate use, cost-effectiveness

Initial assessment T=0
Therapeutic value
Budget impact
Outcome research proposal

Outcome research study
Conducted by the manufacturer together with clinicians, professional societies and hospitals

Re-assessment and appraisal and final decision T=4 years

Source: Makady et al. Health Policy, 2019

Experience with conditional financing in the Netherlands

12 drugs underwent the full procedure

- 11 out of 12 drugs: T > 4 years
- Re-assessment: 10 out of 12 drugs recommended for continuation of reimbursement, with 6 needing yet more time for evidence generation.
- Advice to discontinue reimbursement for 2 out of 12 drugs has not yet been implemented in Dutch healthcare practice.

Financial and health outcome based have now replaced conditional financing

Source: Makady et al. Health Policy, 2019

Challenges and lessons learned in the Netherlands

- For acute conditions 4 years may be sufficient to collect meaningful data, for other conditions (e.g. chronic and orphan diseases) longer follow-up period will be needed
- Little incentive to collect data once reimbursement was granted
- Quality of outcome research was generally poor. Recurring problems included lack of control group or intervention and control groups that were not comparable. Low patient recruitment (participation was voluntary)
- Interim evaluation would have helped addressing challenging before T=4
- Rapidly changing drug landscape particularly for oncology
- Time, effort and resources to set up ad-hoc registries

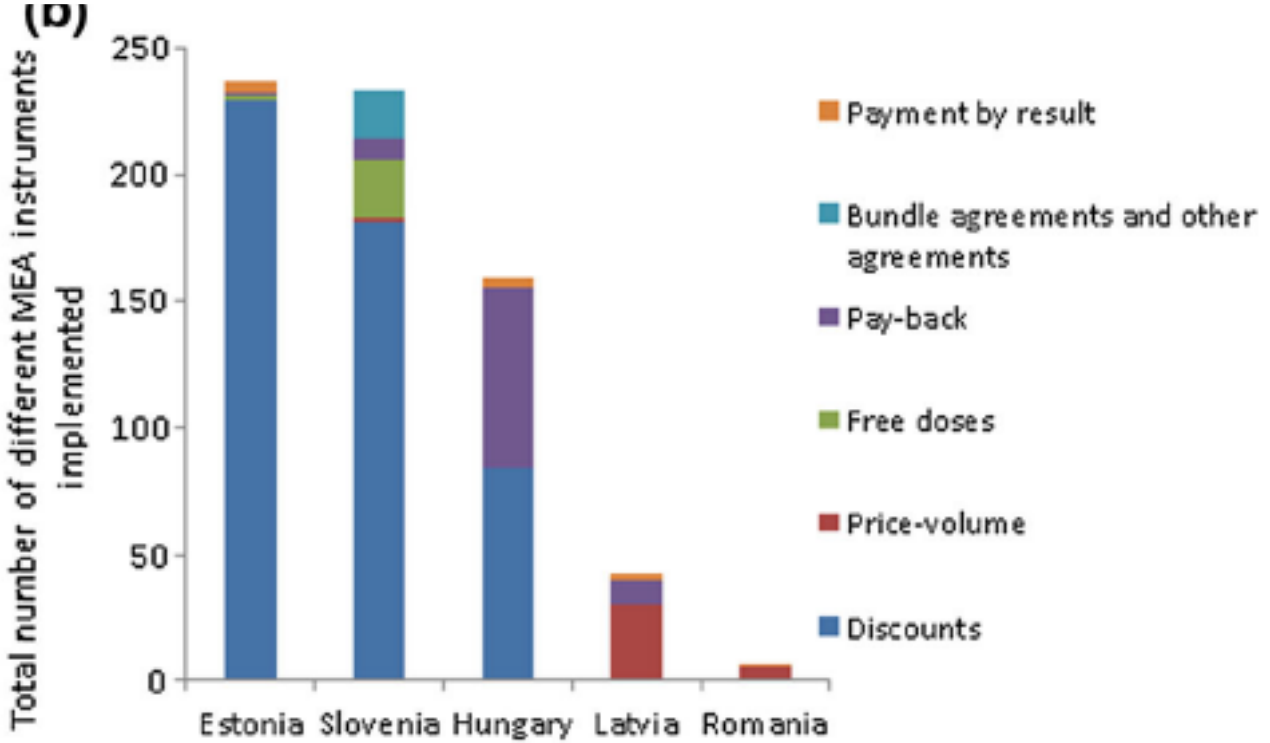
Source: Makady A, van Acker, et al. Value Health, 2019

Table 2 Types of MEAs implemented in Central and Eastern European countries

	Financial					Health outcome-based agreements	
	Discounts	Price-volume agreements	Free doses	Payback	Bundle agreements and other agreements	Payment by result	Coverage with evidence development
Albania	Not implemented						
Bosnia and Herzegovina (applies to both *The Federation of Bosnia and Herzegovina* and *Republika Srpska*)	√		√		√		
Bulgaria	√	√		√	√[b]		√
Croatia	√	√	√	√	√[d]	√	
Czech Republic	√	√		√		√	[a]
Estonia	√	√	√	√		√	
Hungary	√	[c]	√	√	√	√	
Kosovo							
Latvia		√		√		√	
Lithuania		√		√			
Poland	√	√		√	√[e]	√	
Romania		√				√	
Russia	Not implemented						
Serbia			√	√	√[f]		
Slovakia	Not yet implemented						
Slovenia	√	√	√	√	√		

Source: Ferrario et al. Pharmacoeconomics 2017

Only a minority of MEAs implemented in Central and Eastern Europe are health outcome based



Source: Ferrario et al. Pharmacoeconomics 2017

Performance based risk sharing agreements in the US

Public payer: Medicare coverage with evidence development (CED)

- 26 national coverage determination with CED between 1996-2017
- Mostly used for procedures
- The greatest number of CED was for cardiovascular diseases (9/26, 35%)
- Four CEDs, all cardiovascular therapies, had CED requirements removed after 4-12 years.
- Public reporting of results from CED-related studies/registries is rare across all areas

Sources: Zeitler et al. J Am Coll Cardiol, 2019

Performance based risk sharing agreements in the US

Medicare coverage with evidence development

- Experience has highlighted the costs and complexities of data collection
- Specific issues include: study design flaws, insufficient funding, lack of adequate data collection systems
- There were more difficulties in implementing studies based on clinical trials than those using registries

Sources: https://www.cms.gov/medicare/coverage/coverage-with-evidence-development/ accessed May 8, 2019; Neumann & Chambers, Health Affairs Blog 2013; Carlson et al. Pharmacoeconomics 2017

Performance based risk sharing agreements in the US

Private payers: Health insurers

Outcome based agreements

- 1997-2012: 5
- 2015-2017: 16
- Cardiometabolic (n=13); Multiple sclerosis (n=3); others (osteoporosis, RA, anemia, lung cancer) (n=5)

Types of outcomes

- Most measurable in health insurance claims data: e.g. hospitalizations, adherence/compliance, cost, ER visits
- Electronic medical records needed: test results (e.g. low-density lipoprotein, blood sugar), survival

Source: Yu JS, Chin L, et al.*J Managed Care Spec Pharm.* 2017

Lessons learned

- Experiences with health-outcome based agreements and coverage with evidence development were mixed so far
- Enabling factors include existing data collection infrastructure (e.g. being able to leverage on existing registry data), mandatory data collection, existing links between data collection on outcomes and the reimbursement process
- Challenges included lack of robust study design and a rapidly evolving drug landscape, particularly for oncology
- Other considerations: time required to negotiate and manage the schemes including time required data collection and evaluation

Are managed entry agreements enough to enable universal access to effective medicines?

Achieving universal access to high value medicines

- The National Institute for Health and Care Excellence (NICE) was originally **set up** in 1999 as the National Institute for Clinical Excellence, a special health authority, **to reduce variation in the availability and quality of NHS treatments and care.**
- Until recently, cost-effectiveness was its main criterion for making recommendations and medicines deemed cost-effective by NICE had to be made available to all NHS England patients within 3 months of the decision
- As of April 2017, a new affordability criterion was introduced: The budget impact test
- Technologies costing more than GBP 20 million in any of the first three years the NHS may engage in commercial discussion with the manufacturer

Source: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/budget-impact-test

Equitable access to new therapies

- New high cost health technologies carry the risk of enhancing inequalities
- Between public and privately insured patients
- Depending on ability to afford co-payments

Access to trastuzumab as an illustration for the need for affordable prices to enable universal access to effective therapies

Approval year of trastuzumab for early and metastatic breast cancer

Drug/indication	FDA approval (year)	ANVISA approval (year)	SUS access authorization (year)
Trastuzumab/metastatic	1998	1999	2017
Trastuzumab/adjuvant	2005	2006	2012

Between 2008 and 2009, **9% SUS vs. 53% privately insured women** with breast cancer overexpressing HER-2 received trastuzumab (stage adjusted) (Barrios at al. 2019).

Source: Barrios et al. ecancer, 2019

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IMPLICATIONS OF GLOBAL PRICING POLICIES ON ACCESS TO INNOVATIVE DRUGS: THE CASE OF TRASTUZUMAB IN SEVEN LATIN AMERICAN COUNTRIES

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Objectives: Differential pricing, based on countries' purchasing power, is recommended by the World Health Organization to secure affordable medicines. However, in developing countries innovative drugs often have similar or even higher prices than in high-income countries. We evaluated the potential implications of trastuzumab global pricing policies in terms of cost-effectiveness (CE), coverage, and accessibility for patients with breast cancer in Latin America (LA).
Methods: A Markov model was designed to estimate life-years (LYs), quality-adjusted life-years (QALYs), and costs from a healthcare perspective. To better fit local cancer prognosis, a base case scenario using transition probabilities from clinical trials was complemented with two alternative scenarios with transition probabilities adjusted to reflect breast cancer epidemiology in each country.
Results: Incremental discounted benefits ranged from 0.87 to 1.00 LY and 0.51 to 0.60 QALY and incremental CE ratios from USD 42,104 to USD 110,283 per QALY (2012 U.S. dollars), equivalent to 3.6 gross domestic product per capita (GDPPC) per QALY in Uruguay and to 35.5 GDPPC in Bolivia. Probabilistic sensitivity analysis showed 0 percent probability that trastuzumab is CE if the willingness-to-pay threshold is one GDPPC per QALY, and remained so at three GDPPC threshold except for Chile and Uruguay (4.3 percent and 26.6 percent, respectively). Trastuzumab price would need to decrease between 69.6 percent to 94.9 percent to became CE in LA.
Conclusions: Although CE in other settings, trastuzumab was not CE in LA. The use of health technology assessment to prioritize resource allocation and support price negotiations is critical to making innovative drugs available and affordable in developing countries.

Base Case Results per Country

Life-years

Quality-adjusted life-years

Costs

Incremental cost-effectiveness ratios
Indicative price of trastuzumab to be cost-effective under a willingness to pay thresholds of one GDP per capita per QALY (2012 USD).

Country	LYs	QALYs	Costs USD (thousand)	ICER in USD	ICER in GDPPC	Current Tzb Price (USD)	CE price (USD)
Argentina							
No Tzb arm	*10.07*	*8.12*	*12.2*				
Tzb arm	*11.03*	*8.70*	*57.2*				
Difference	0.97	0.58	45.0	**77,273**	**8.47**	**2,696**	**350**
Bolivia							
No Tzb arm	*9.42*	*7.59*	*20.1*				
Tzb arm	*10.29*	*8.11*	*56.2*				
Difference	0.87	0.51	36.1	**70,202**	**35.47**	**2,260**	**115**
Brazil							
No Tzb arm	*9.77*	*7.88*	*9.1*				
Tzb arm	*10.69*	*8.43*	*69.9*				
Difference	0.92	0.55	60.8	**110,283**	**10.30**	**3,743**	**400**
Chile							
No Tzb arm	*10.24*	*8.26*	*16.6*				
Tzb arm	*11.24*	*8.86*	*50.2*				
Difference	1.00	0.60	33.6	**55,928**	**4.50**	**2,099**	**500**
Colombia							
No Tzb arm	*10.04*	*8.10*	*71.6*				
Tzb arm	*11.01*	*8.68*	*117.2*				
Difference	0.96	0.58	45.7	**78,946**	**12.65**	**3,264**	**700**
Peru							
No Tzb arm	*9.83*	*7.93*	*21.0*				
Tzb arm	*10.77*	*8.49*	*52.2*				
Difference	0.93	0.56	31.2	**55,821**	**10.34**	**1,981**	**260**
Uruguay							
No Tzb arm	*10.10*	*8.15*	*14.9*				
Tzb arm	*11.07*	*8.73*	*39.6*				
Difference	0.97	0.59	24.7	**42,104**	**3.62**	**1,565**	**475**

Summary

- MEAs are a tool and can provide short time solutions but alone they are unlikely to deliver equitable access and ensure long term financial sustainability of universal health coverage systems
- Monitoring drug performance in real-life is very important (Health technology performance assessment)
- The issue of high launch prices remains
- Addressing high prices for effective medicines is key to enable equitable access as part of universal health coverage

Thank you!

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