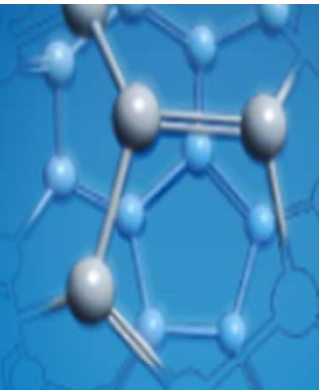


FÓRUM DO MEDICAMENTO

A PARTILHA DE RISCOS NA PROMOÇÃO DE GANHOS EM SAÚDE

ORGANIZAÇÃO APAH

PATROCÍNIO AstraZeneca

Innovation and managed entry agreements: general issues and the Italian case-study

Claudio Jommi

Scientific Coordinator of the Pharmaceutical Observatory, Cergas, Università Bocconi

Associate Professor, Department of Pharmaceutical Sciences, Università del Piemonte Orientale

(Past) President of the Italian Health Economics Association

Lisbon, 17th of November, 2017

Managed entry agreements …

… different names same thing …

- Risk-sharing
- Managed Entry Agreements
- Managed Market Entry Agreements

MEA !!!

Agenda: General Issues

- **Rationale and Taxonomy of MEA**
- Statistics on MEA
- Organizational and practical issues
- Impact evaluation
- The Italian case-study

Rationale for MEA: uncertainty about performance

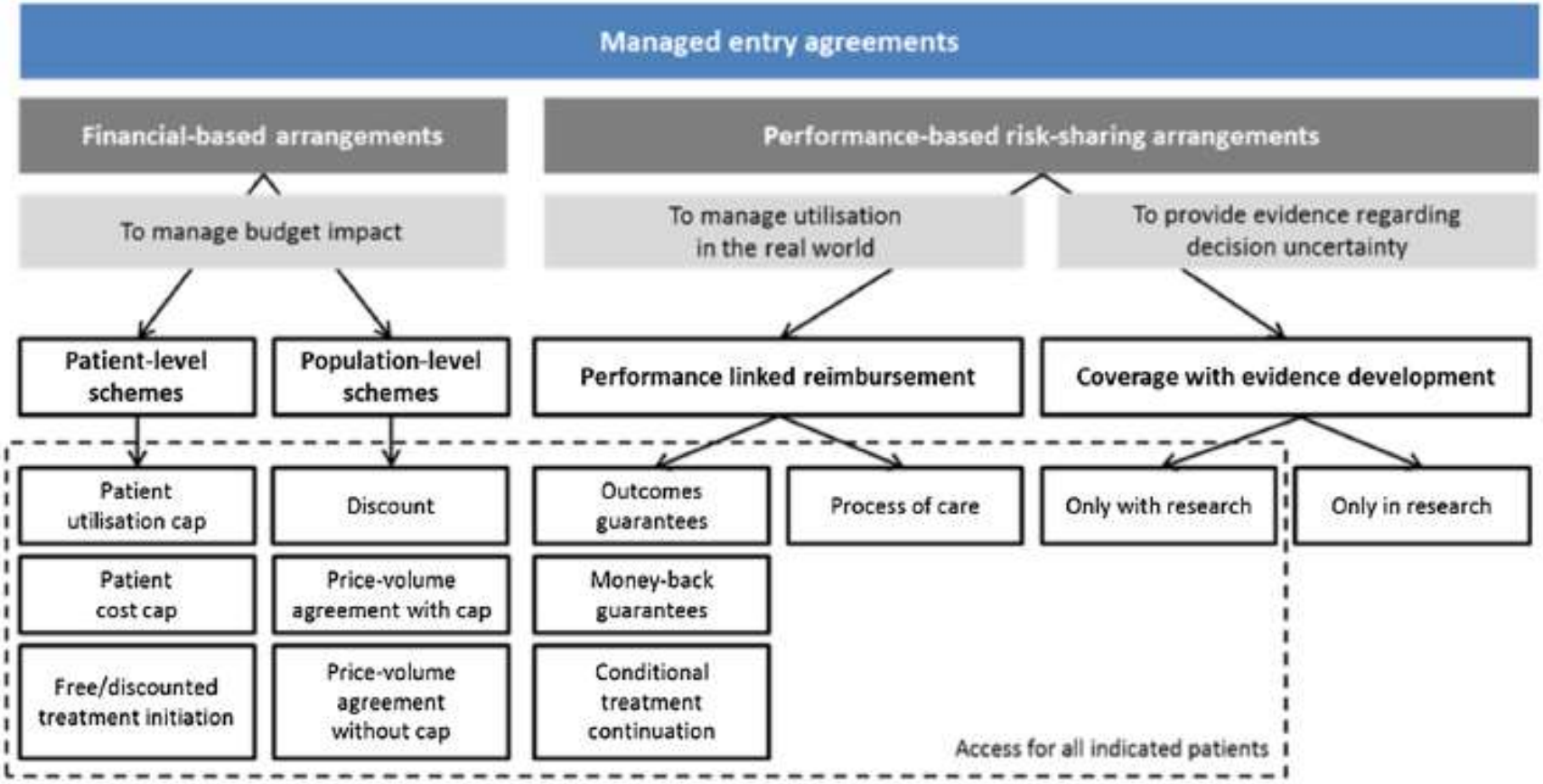
- (Comparative) Effectiveness
- Long-term safety
- Number of patients treated (volume)
- Adherence and Persistence
- Actual unit drugs cost per patient treated
- Patient path and resource utilization

Taxonomy of MEA

	POPULATION LEVEL	PATIENT LEVEL
FINANCIAL / UTILISATION BASED (FU)	Discount Price/volume agreement	Capping per patient Manufacturer funded treatment initiation (MFT)
OUTCOME BASED	Coverage with evidence development (CED)	Conditional treatment continuation (CTC) Performance-linked reimbursement (PLR)

Source: Carlson et al, Health Policy 96 (2010) 179–190

More specific taxonomy of MEA

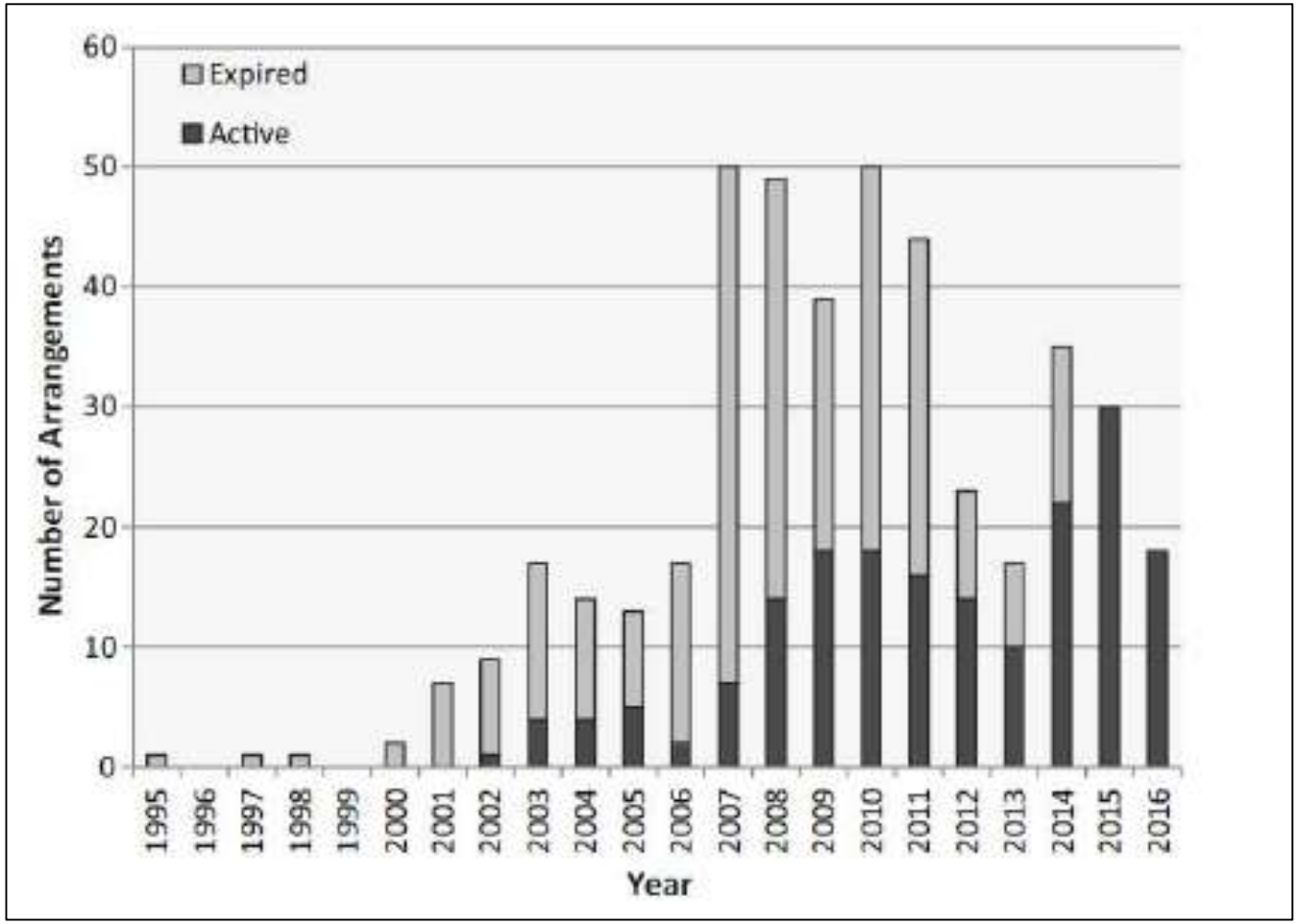


Source: Morel et al, Orphanet Journal of Rare Disease, 2013, 8:198

Agenda

- **Rationale and Taxonomy of MEA**
- **Statistics on MEA**
- Organizational and practical issues
- Impact evaluation
- The Italian case-study

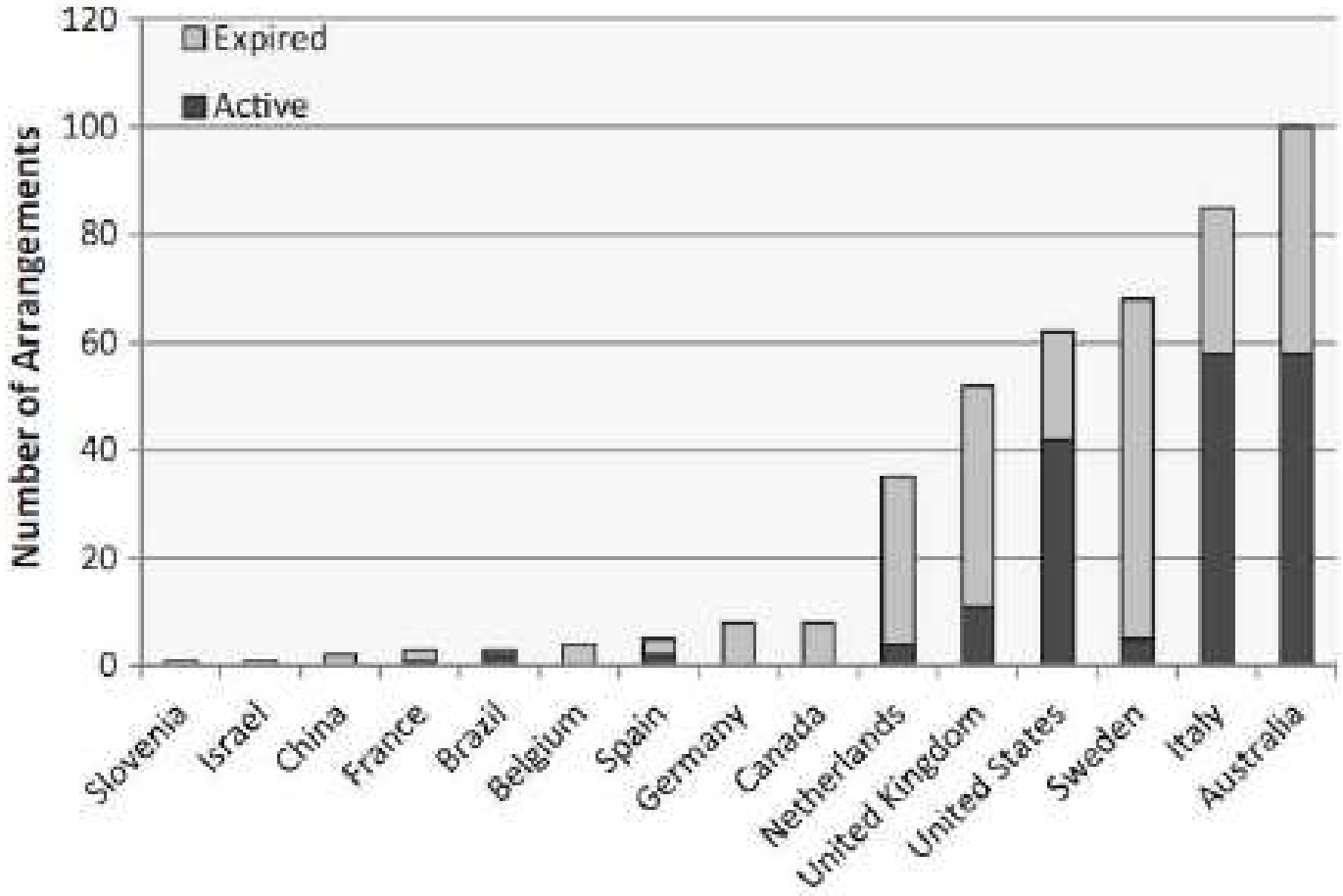
Worldwide diffusion



42% active
56% expired

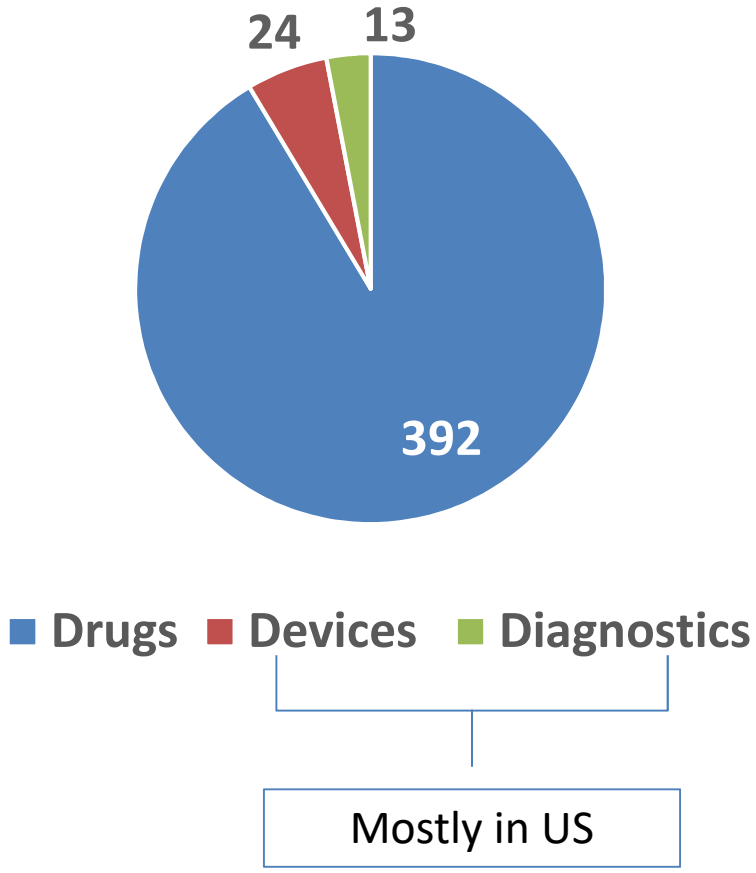
Source: Carlson JJ et al 2017. Performance-Based Risk-Sharing Arrangements: An Updated International Review. Pharmacoeconomics. Jul 10

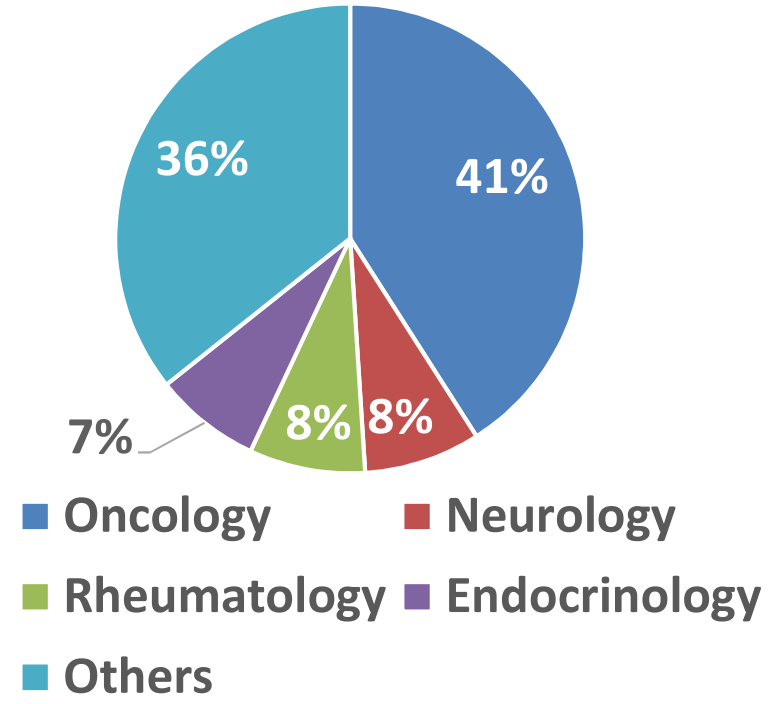
Interested countries



Source: Carlson JJ et al 2017. Performance-Based Risk-Sharing Arrangements: An Updated International Review. Pharmacoeconomics. Jul 10

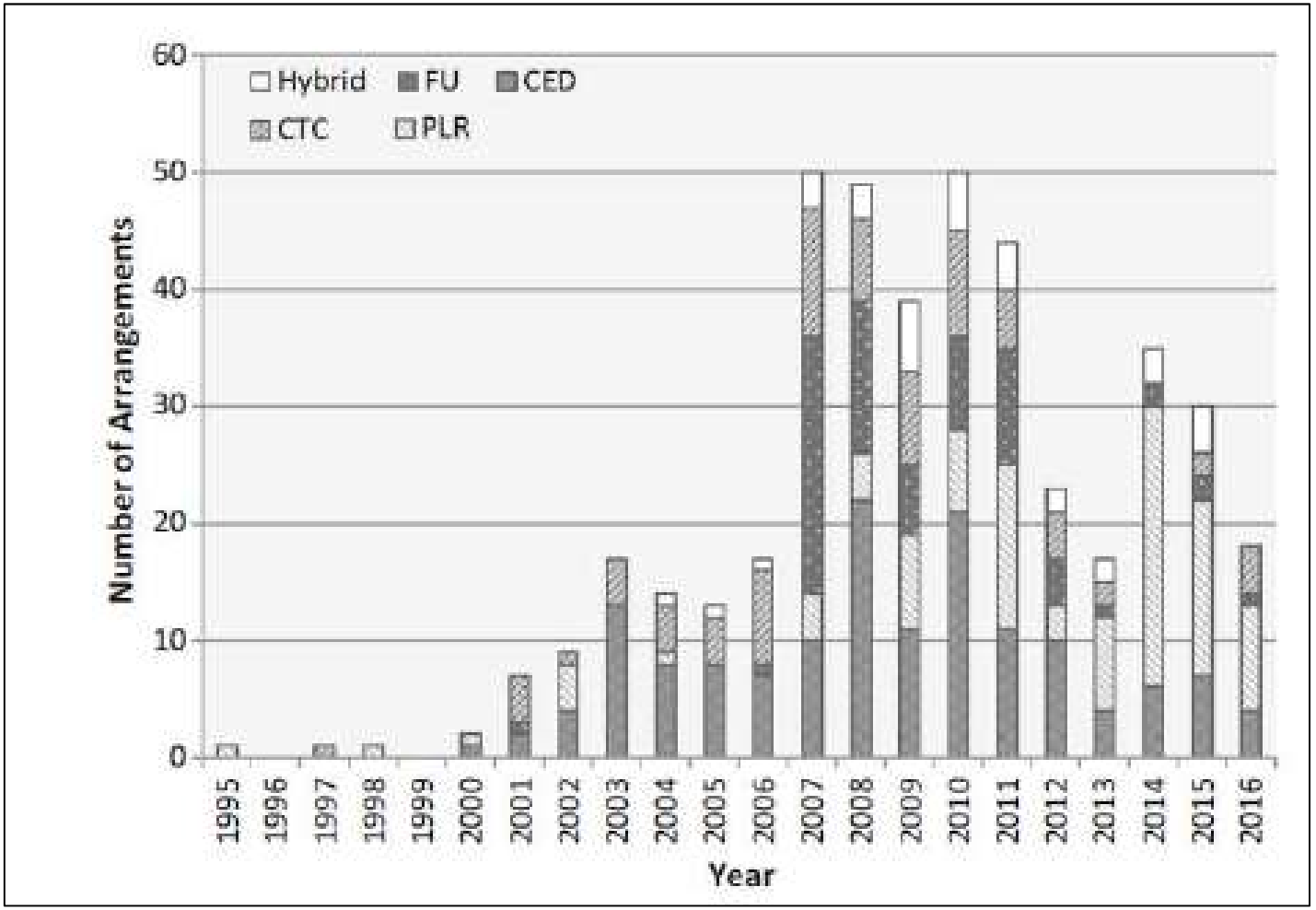
Interested technologies





Source: Carlson JJ et al 2017. Performance-Based Risk-Sharing Arrangements: An Updated International Review. Pharmacoeconomics. Jul 10

Kinds of MEA



Number of financial-based could be under-estimated (confidential)

Source: Carlson JJ et al 2017. Performance-Based Risk-Sharing Arrangements: An Updated International Review. Pharmacoeconomics. Jul 10

Agenda

- **Rationale and Taxonomy of MEA**
- **Statistics on MEA**
- **Organizational and practical issues**
- Impact evaluation
- The Italian case-study

Pros

The industry

- To avoid list prices below the price corridor (that would imply cross reference pricing and parallel trade)
- To avoid negative reimbursement decisions
- To improve local access
- To improve company's image in supporting sustainability
- To strengthen relationships with payers

The health care payer

- To prioritize drugs truly essential
- To prevent media critics on negative reimbursement decision
- To share the risk of failure and control expenditure
- To collect Real World Data

Cons

The industry

- Transaction costs
- Actual reimbursement rate non certain (and possibly much lower than nominal price)
- Rebound effects if health care professionals do not comply with procedures

The health care payer

- Transaction costs
- Criticism on lower transparency
- Actual savings not certain
- Relationships with healthcare professionals may get worsen
- Companies may incorporate the expected impact of MEA on their requests on list prices

Ispor Guidelines on Outcome-Based MEA

VALUE IN HEALTH 16 (2013) 703–719

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

ISPOR TASK FORCE REPORTS

Performance-Based Risk-Sharing Arrangements—Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force

Louis P. Garrison Jr., PhD (co-chair)[1,], Adrian Towse, MA, MPhil (co-chair)[2], Andrew Briggs, MSc, DPhil[3], Gerard de Pouvourville, PhD[4], Jens Grueger, PhD[5], Penny E. Mohr, MA[6], J.L. (Hans) Severens, PhD[7], Paolo Siviero, BA[8], Miguel Sleeper, ACMA[9]*

[1]Pharmaceutical Outcomes Research & Policy Program, Department of Pharmacy, University of Washington, Seattle, WA, USA; [2]Office of Health Economics, London, UK; [3]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK; [4]ESSEC Business School, Cergy Pontoise, France; [5]F. Hoffmann - La Roche AG, Basel, Switzerland; [6]Center for Medical Technology Policy, Baltimore, Maryland, USA; [7]Institute of Health Policy & Management, Erasmus University Rotterdam, Rotterdam, The Netherlands; [8]Agenzia Italiana del Farmaco, Rome, Italy; [9]Access to Medicines GlaxoSmithKline plc, Brentford, UK

ABSTRACT

There is a significant and growing interest among both payers and producers of medical products for agreements that involve a "pay-for-

governance processes are also essential. The information generated as part of PBRSAs has public good aspects, bringing ethical and profes-

Key issues in (outcome-based) MEA

- Choice of methodology (which agreement?)
- Protocol design
- Quality and independence of monitoring
- Data management capacities
- Timing (with price negotiation)
- Completeness of contract
- Publicity of financial clauses
- Publicity of results
- Funding

The Multiple Sclerosis CED case in UK (1)

BMJ

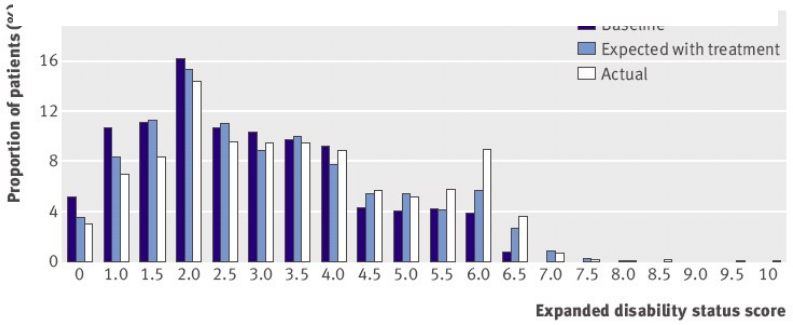
RESEARCH

Multiple sclerosis risk sharing scheme: two year results of clinical cohort study with historical comparator

Mike Boggild, consultant neurologist,[1] Jackie Palace, consultant neurologist,[2] Pelham Barton, senior lecturer in mathematical modelling,[3] Yoav Ben-Shlomo, professor of clinical epidemiology,[4] Thomas Bregenzer, director, biostatistics,[5] Charles Dobson, senior projects officer,[6] Richard Gray, director[7]

Results In the primary per protocol analysis, progression in disability was worse than that predicted and worse than that in the untreated comparator dataset ("deviation score" of 113%; excess in mean disability status scale 0.28). In sensitivity analyses, however, the deviation score varied from −72% (using raw baseline disability status scale scores, rather than applying a "no improvement" algorithm) to 156% (imputing missing data for year two from progression rates for year one).

Conclusions It is too early to reach any conclusion about the cost effectiveness of disease modifying treatments from this first interim analysis. Important methodological issues, including the need for additional comparator datasets, the potential bias from missing data, and the impact of the "no improvement" rule, will need to be addressed and long term follow-up of all patients is essential to secure meaningful results. Future analyses of the cohort are likely to be more informative, not least because they will be less sensitive to short term fluctuations in disability.



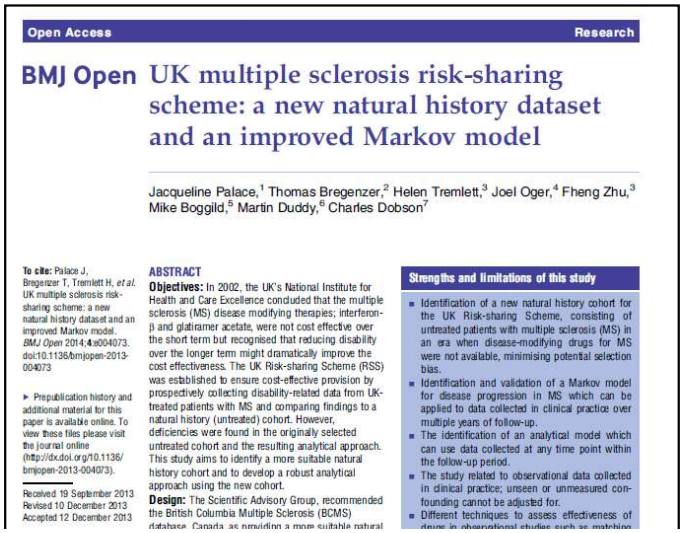
Costly failure of a risk sharing scheme

The NHS is paying for thousands of patients with multiple sclerosis to receive drugs that monitoring data suggest are not effective. **James Raftery** examines what went wrong with the access scheme that facilitated their use

Continuing the scheme is unjustified

Christopher McCabe and colleagues examine the claims behind the decision not to reduce drug costs in the multiple sclerosis risk sharing scheme

The Multiple Sclerosis CED case in UK (2)



Open Access Research

BMJ Open UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model

Jacqueline Palace,[1] Thomas Bregenzer,[2] Helen Tremlett,[3] Joel Oger,[4] Fheng Zhu,[3] Mike Boggild,[5] Martin Duddy,[6] Charles Dobson[7]

To cite: Palace J, Bregenzer T, Tremlett H, *et al*. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. *BMJ Open* 2014;**4**:e004073. doi:10.1136/bmjopen-2013-004073

► Prepublication history and additional material for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2013-004073).

Received 19 September 2013
Revised 10 December 2013
Accepted 12 December 2013

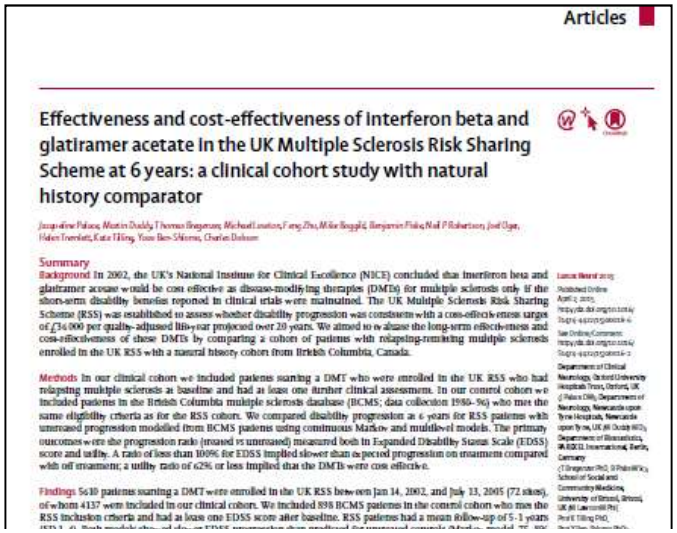
ABSTRACT

Objectives: In 2002, the UK's National Institute for Health and Care Excellence concluded that the multiple sclerosis (MS) disease modifying therapies; interferon-β and glatiramer acetate, were not cost effective over the short term but recognised that reducing disability over the longer term might dramatically improve the cost effectiveness. The UK Risk-sharing Scheme (RSS) was established to ensure cost-effective provision by prospectively collecting disability-related data from UK-treated patients with MS and comparing findings to a natural history (untreated) cohort. However, deficiencies were found in the originally selected untreated cohort and the resulting analytical approach. This study aims to identify a more suitable natural history cohort and to develop a robust analytical approach using the new cohort.

Design: The Scientific Advisory Group, recommended the British Columbia Multiple Sclerosis (BCMS) database, Canada, as providing a more suitable natural

Strengths and limitations of this study

- Identification of a new natural history cohort for the UK Risk-sharing Scheme, consisting of untreated patients with multiple sclerosis (MS) in an era when disease-modifying drugs for MS were not available, minimising potential selection bias.
- Identification and validation of a Markov model for disease progression in MS which can be applied to data collected in clinical practice over multiple years of follow-up.
- The identification of an analytical model which can use data collected at any time point within the follow-up period.
- The study related to observational data collected in clinical practice; unseen or unmeasured confounding cannot be adjusted for.
- Different techniques to assess effectiveness of



Articles

Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator

Jacqueline Palace, Martin Duddy, Thomas Bregenzer, Michael Lawton, Fang Zhu, Mike Boggild, Benjamin Fisher, Neil P Robertson, Joel Oger, Helen Tremlett, Kate Tilling, Yoav Ben-Shlomo, Charles Dobson

Summary

Background In 2002, the UK's National Institute for Clinical Excellence (NICE) concluded that interferon beta and glatiramer acetate would be cost effective as disease-modifying therapies (DMTs) for multiple sclerosis only if the short-term disability benefits reported in clinical trials were maintained. The UK Multiple Sclerosis Risk Sharing Scheme (RSS) was established to assess whether disability progression was consistent with a cost-effectiveness target of £34 000 per quality-adjusted life-year projected over 20 years. We aimed to re-assess the long-term effectiveness and cost-effectiveness of these DMTs by comparing a cohort of patients with relapsing-remitting multiple sclerosis enrolled in the UK RSS with a natural history cohort from British Columbia, Canada.

Methods In our clinical cohort we included patients starting a DMT who were enrolled in the UK RSS who had relapsing multiple sclerosis at baseline and had at least one further clinical assessment. In our control cohort we included patients in the British Columbia multiple sclerosis database (BCMS; data collection 1980–96) who met the same eligibility criteria as for the RSS cohort. We compared disability progression at 6 years for RSS patients with untreated progression modelled from BCMS patients using continuous Markov and multilevel models. The primary outcomes were the progression ratio (treated vs untreated) measured both in Expanded Disability Status Scale (EDSS) score and utility. A ratio of less than 100% for EDSS implied slower than expected progression on treatment compared with off treatment; a utility ratio of 62% or less implied that the DMTs were cost effective.

Findings 5610 patients starting a DMT were enrolled in the UK RSS between Jan 14, 2002, and July 13, 2005 (72 sites), of whom 4137 were included in our clinical cohort. We included 898 BCMS patients in the control cohort who met the RSS inclusion criteria and had at least one EDSS score after baseline. RSS patients had a mean follow-up of 5·1 years

Findings 5610 patients starting a DMT were enrolled in the UK RSS between Jan 14, 2002, and July 13, 2005 (72 sites), of whom 4137 were included in our clinical cohort. We included 898 BCMS patients in the control cohort who met the RSS inclusion criteria and had at least one EDSS score after baseline. RSS patients had a mean follow-up of 5·1 years (SD 1·4). Both models showed slower EDSS progression than predicted for untreated controls (Markov model, 75·8% [95% CI 71·4–80·2]; multilevel model, 60·0% [56·6–63·4]). Utility ratios were consistent with cost-effectiveness (Markov model, 58·5% [95% CI 54·2–62·8]; multilevel model, 57·1% [53·0–61·2]).

Interpretation Findings from this large observational study of treatment with interferon beta or glatiramer acetate provide evidence that their effects on disability in patients with relapsing-remitting multiple sclerosis are maintained and cost effective over 6 years. Similar modelling approaches could be applied to other chronic diseases for which long-term controlled trials are not feasible.

CED versus PLR outcome-based

Population	Individual
Requires a precise research question	It assumes that the single patient cannot be generalized
Requires a protocol to address the question	It requires drugs registry
Requires a good governance	It requires health care professionals commitment

Increasing role of PLR

- Clear and manageable indicator of patients' response
- Short-term impact of the therapy
- Limited size of target patient population

- Controversial response measure
- Chronic treatment
- Company not ready to cover IT expenses

Which outcomes?

- Health (Mortality / QALYs) or Cost-effectiveness: more frequent in Sw, NL, UK, Aus (where cost-effectiveness matters)
- Avoided events (e.g. hospitalisation, relapses, exacerbations): more frequent in France where they matter to get a good ASMR (added therapeutic value) rank
- Surrogate endpoints (e.g. Overall Response Rate / Progression Free Survival in Oncology): more frequent in Italy (PLR)
- Adherence / Persistence / Patients preferences not considered

Agenda

- Rationale and Taxonomy of MEA
- Statistics on MEA
- Organizational and practical issues
- Impact evaluation
- The Italian case-study

Which impact? Very few evidence

VALUE IN HEALTH 16 (2013) 703–719

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

ISPOR TASK FORCE REPORTS

Performance-Based Risk-Sharing Arrangements—Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force

Louis P. Garrison Jr., PhD (co-chair)[1,], Adrian Towse, MA, MPhil (co-chair)[2], Andrew Briggs, MSc, DPhil[3], Gerard de Pouvourville, PhD[4], Jens Grueger, PhD[5], Penny E. Mohr, MA[6], J.L. (Hans) Severens, PhD[7], Paolo Siviero, BA[8], Miguel Sleeper, ACMA[9]*

[1]Pharmaceutical Outcomes Research & Policy Program, Department of Pharmacy, University of Washington, Seattle, WA, USA; [2]Office of Health Economics, London, UK; [3]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK; [4]ESSEC Business School, Cergy Pontoise, France; [5]F. Hoffmann - La Roche AG, Basel, Switzerland; [6]Center for Medical Technology Policy, Baltimore, Maryland, USA; [7]Institute of Health Policy & Management, Erasmus University Rotterdam, Rotterdam, The Netherlands; [8]Agenzia Italiana del Farmaco, Rome, Italy; [9]Access to Medicines GlaxoSmithKline plc, Brentford, UK

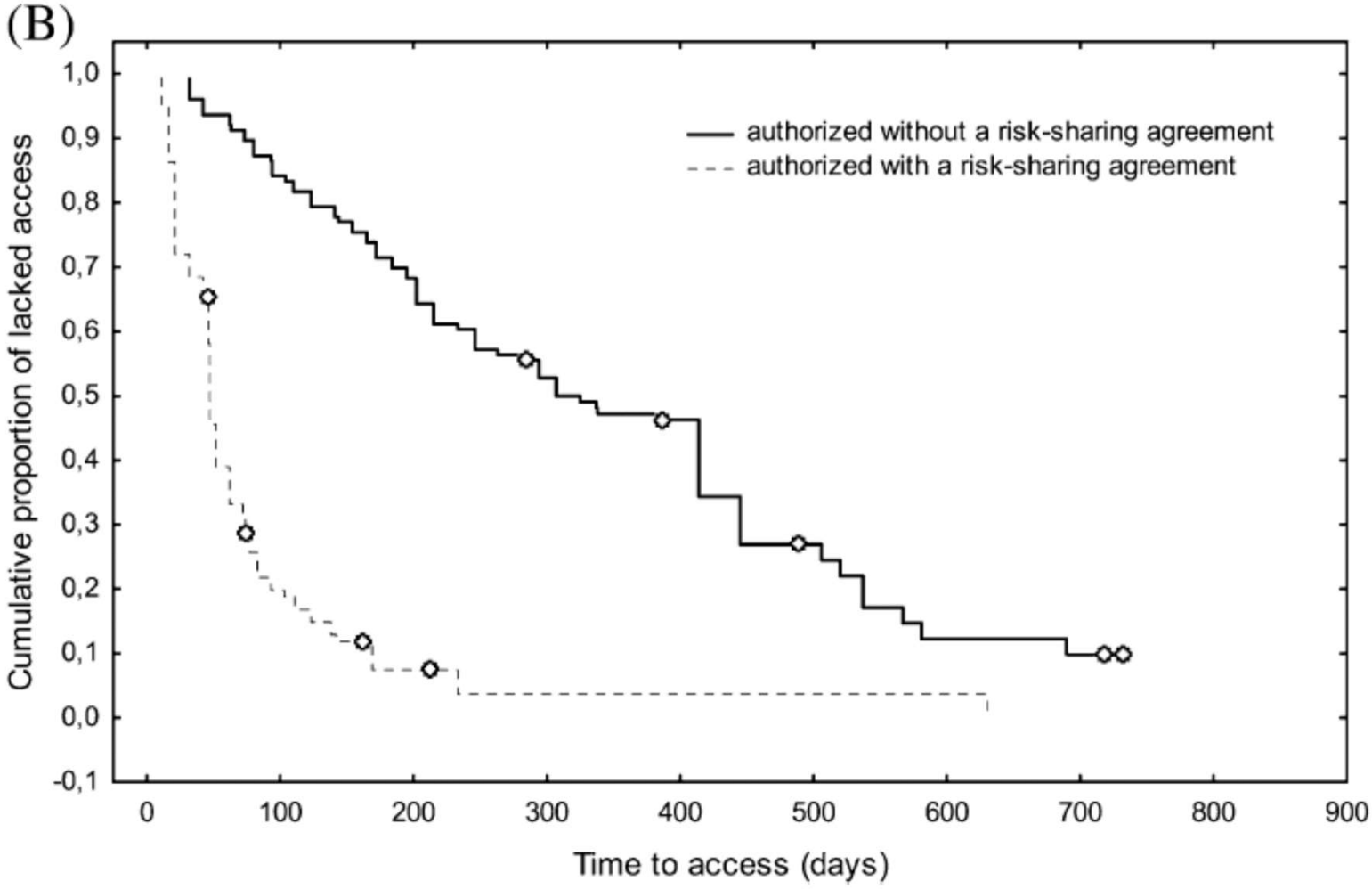
ABSTRACT

There is a significant and growing interest among both payers and producers of medical products for agreements that involve a "pay-for-

governance processes are also essential. The information generated as part of PBRSAs has public good aspects, bringing ethical and profes-

- Transactions costs
- Governance issues (UK case-study)
- Innovation rate (only theoretically investigated)
- Market access

Impact of PLR in Italy on Market Access for onco drugs

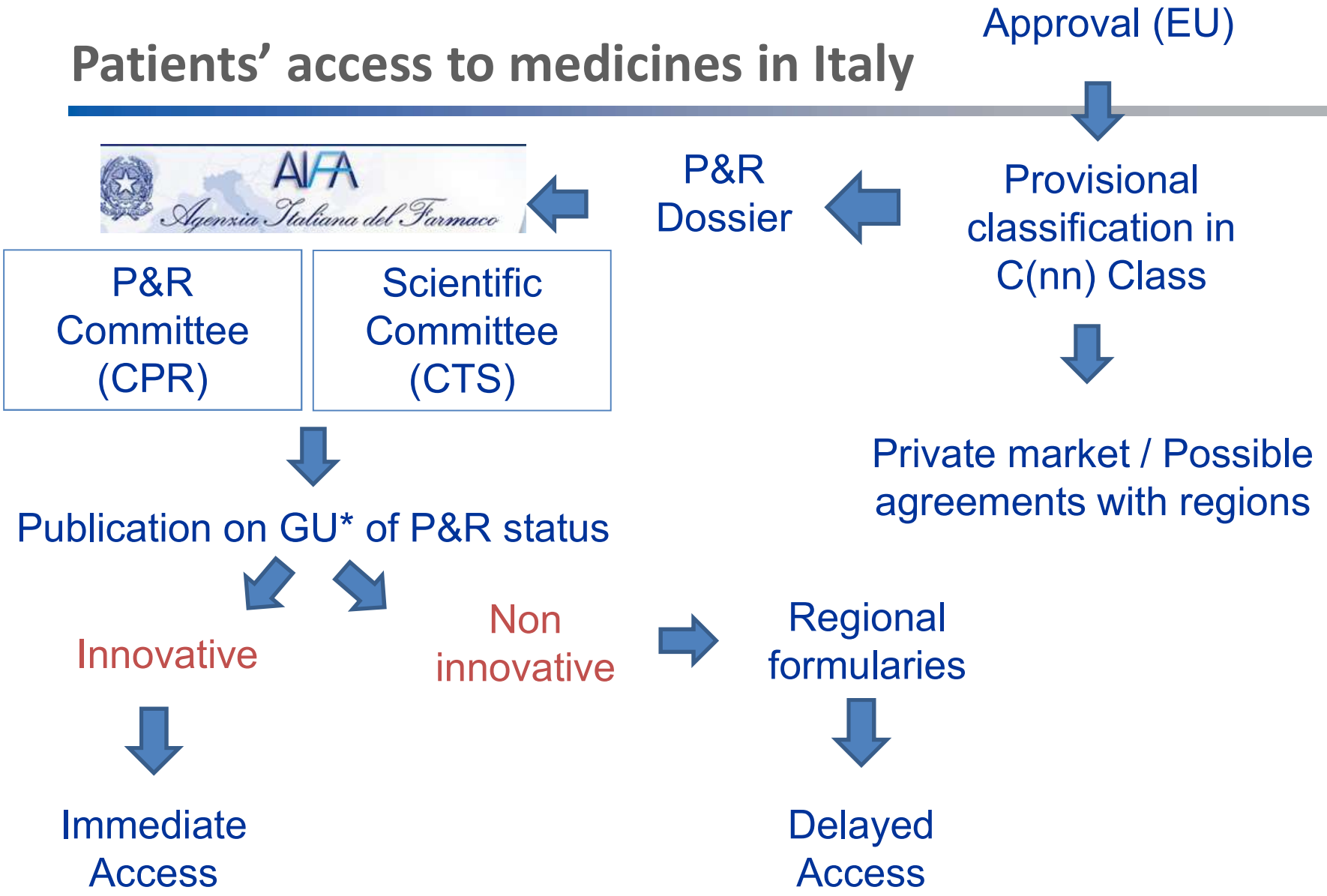


Source: Russo, et al, Annals of Oncology, 21, 10, 2081-2087

Agenda

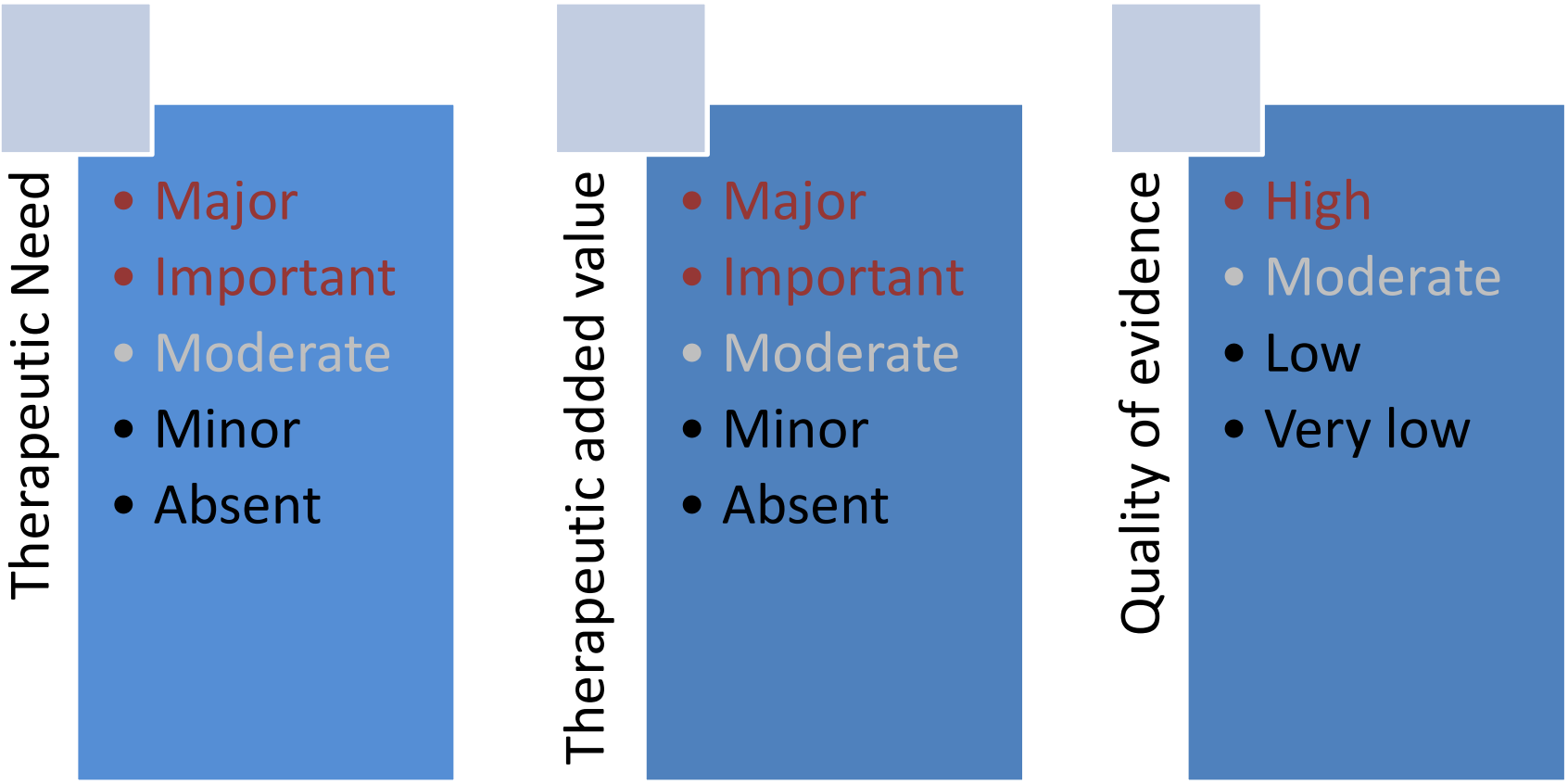
- Rationale and Taxonomy of MEA
- Statistics on MEA
- Organizational and practical issues
- Impact evaluation
- The Italian case-study

Patients' access to medicines in Italy



* Gazzetta Ufficiale

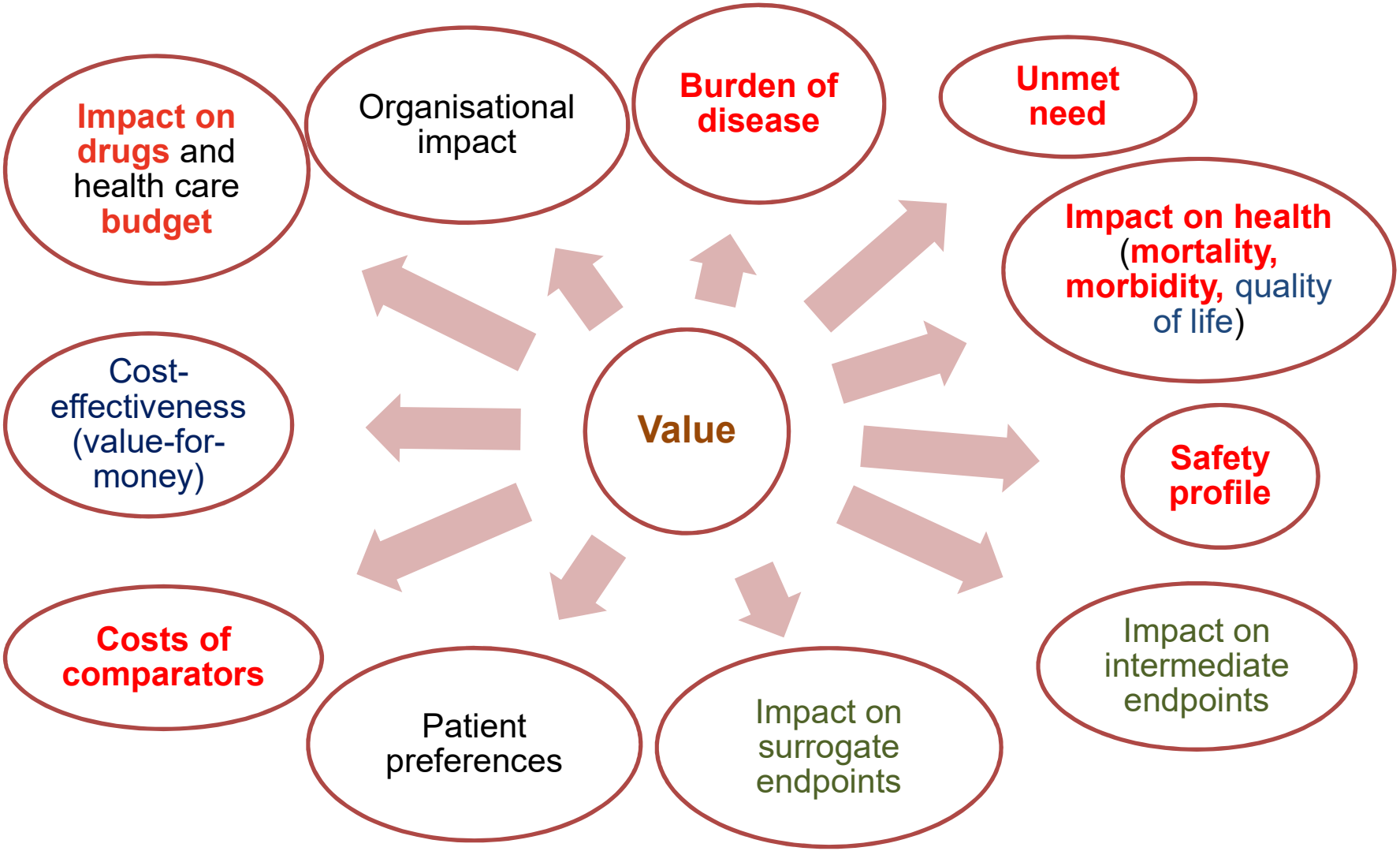
Drugs innovativeness criteria



Possibly innovative, Grey Area, Not innovative

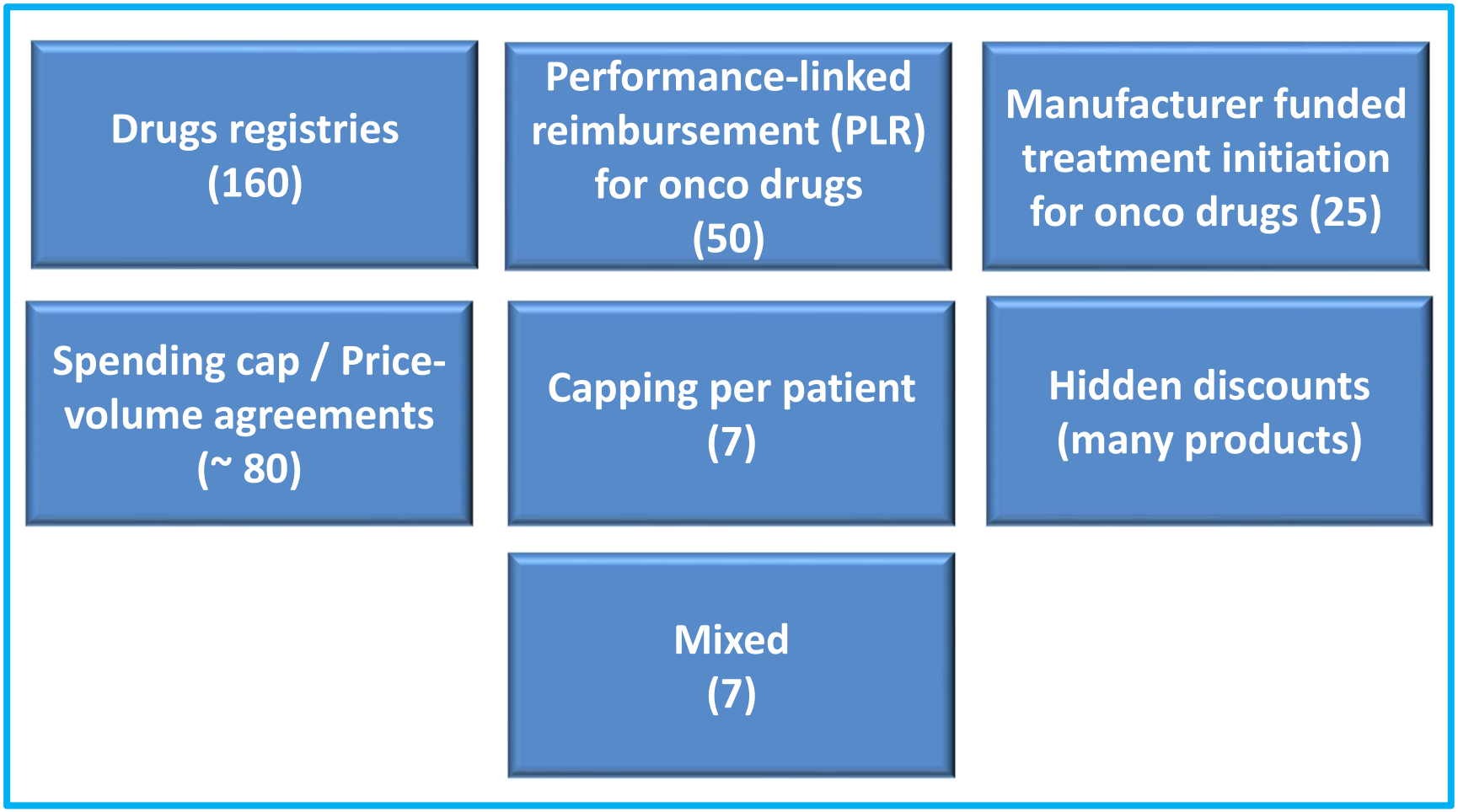
(Margins of tolerance on Grade's criteria for drugs for orphan and rare diseases)

The role of HTA domains in the negotiation of P&R

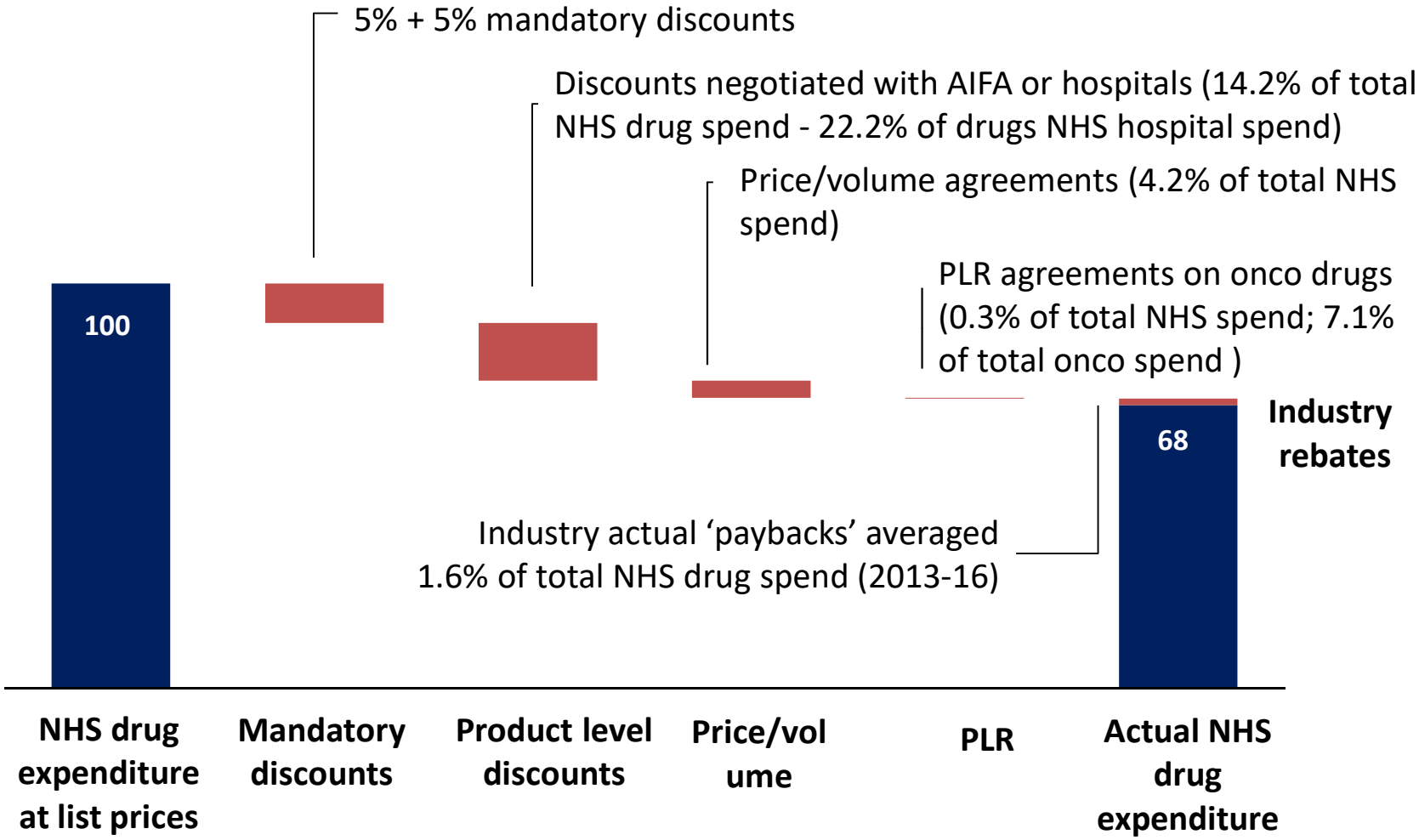


Very important, Rather important, Less important, Disregarded

Extensive use of MEA (2016)



The financial (cash) effects of MEA: gross vs net drugs expenditure



Source: our elaboration on Rapporto Osmed and Monitoraggio spesa

PLR in Oncology: how do they work (1)

AIFA Agenzia Italiana del Farmaco

P&R Dossier

P&R Committee (CPR)

Scientific Committee (CTS)

Publication on GU of P&R status

PLR

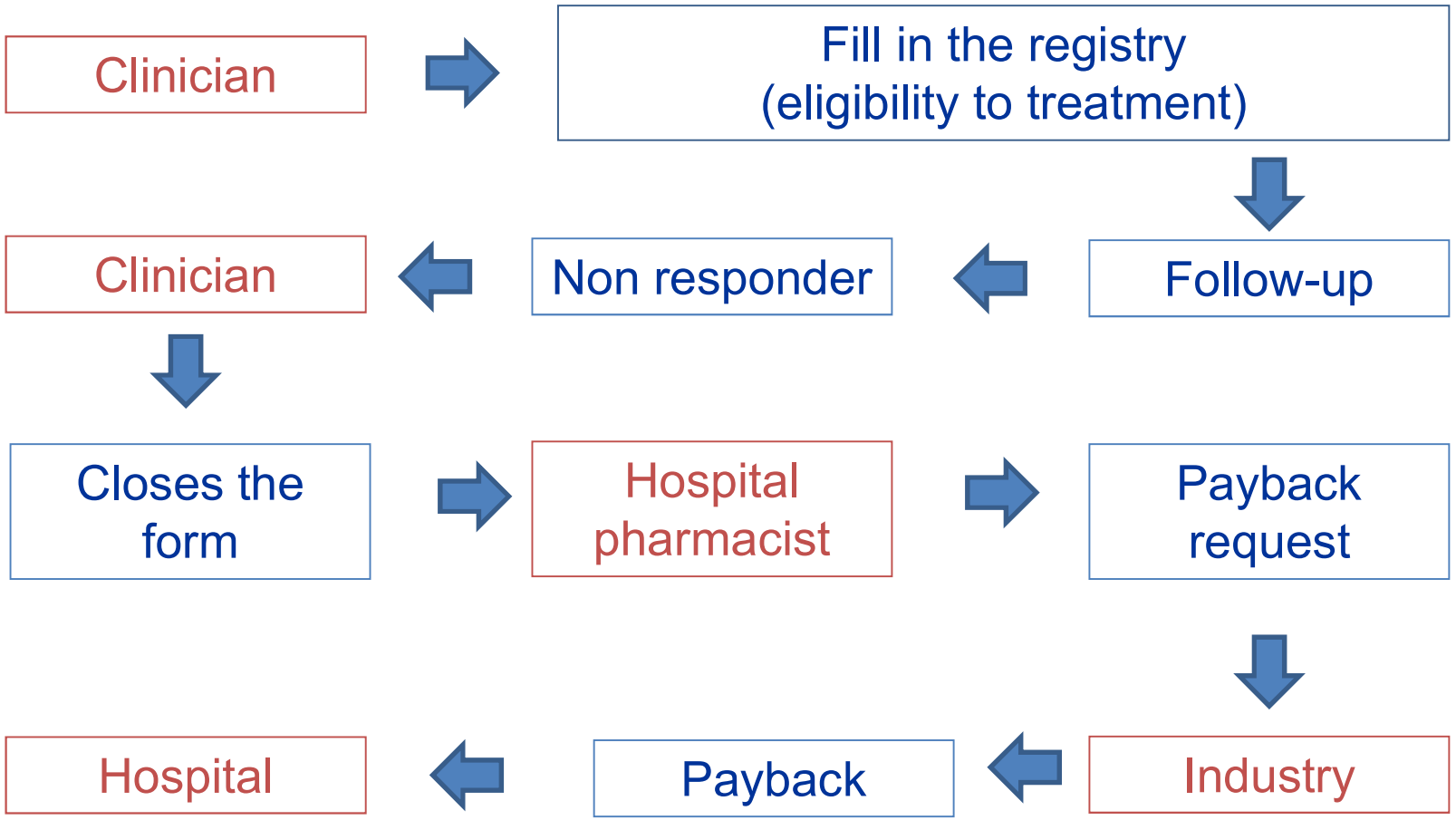
Endpoint (e.g. PFS) Follow-up expected date

Paper Registry

Web-based Registry

Fee paid by the industry for the IT system

PLR in Oncology: how do they work (2)



Pros and cons

Pros

- It has permitted access to many cancer drugs
- It allows different reimbursement rate across indication
- It implies real world data collection

Cons

- Administrative burden for clinicians (compliance?)
- Sunk costs for health care organizations
- Actual savings (100 million Euros in 2016 cash) lower than expected

Take home messages

- MEA are expanding due to uncertainty on effects and high costs of new technologies
- Drugs is the preferred target (more evidence, easier data collection, less confounding variables)
- Governance issues mainly disregarded in MEAs
- Impact evaluation limited, but it seems that market access and penetration favoured
- Clinical endpoints used as “performance” indicators
- Other benefits, like adherence/persistence, acceptability to patients or patients preferences, not considered
- Limited financial impact (cash) of PLRs in Italy so far (compared to financial-based agreements)

Thank you !!!

claudio.jommi@uniupo.it

claudio.jommi@unibocconi.it

FÓRUM DO MEDICAMENTO

ORGANIZAÇÃO

APAH

ASSOCIAÇÃO PORTUGUESA DE ADMINISTRADORES HOSPITALARES

PATROCÍNIO

AstraZeneca