

# Effectiveness of national pricing policies for patent-protected pharmaceuticals in the OECD: A systematic literature review

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## **Effectiveness of national pricing policies for patent-protected pharmaceuticals in the OECD: A systematic literature review**

### **Abstract**

**Objectives:** The aim of this review is to assess the current state of empirical research regarding the effectiveness of national pricing regulations of the patent-protected market for prescription pharmaceuticals. Effectiveness is understood as the capacity of policies to have a desired impact on outcomes, such as health status, patient access, healthcare expenditure, and research investments, among others.

**Methods:** A systematic review of the published literature on pricing regulations in OECD countries was performed. The PubMed, MEDLINE, Scopus, Web of Science, Cochrane Library and the OECD iLibrary databases were searched in September 2016 and December 2017, with an update in August 2018. Interrupted time series studies and additional empirical studies were included, as well as systematic reviews if appropriate methods were applied. The risk of bias was assessed based on the recommendations of the BMJ guidelines, Cochrane EPOC criteria, QHES instrument, HTA good practice guidelines, CRD's guidance and the CHEC criteria. The quality of evidence was evaluated using the suggestions from EPOC and GRADE.

**Results:** Thirty-one publications met the inclusion criteria. Most of the assessed empirical research included therapeutic (TRP) and/or external reference pricing (ERP), with a clear majority focusing on TRP. The main outcomes that were analysed were drug prices, expenditures and drug use. For value-based pricing (VBP), only limited empirical data were found.

**Conclusions:** We found evidence that TRP may reduce pharmaceutical prices and expenditures in the short term. Furthermore, TRP may lead to substitution effects towards lower-priced pharmaceuticals. The effects of TRP on patient access, healthcare utilization and R&D investments

were found to be uncertain. No conclusions were drawn for ERP and VBP. No evidence was found for the effects on health outcomes for any of the analysed policies.

There is a strong need for evidence generation regarding effective pricing policies, particularly for value-based policies, managed entry agreements and non-financial outcomes.

### **Key Points for Decision Makers**

- We found evidence that therapeutic reference pricing may reduce pharmaceutical prices and expenditures in the short term and may lead to substitution effects towards lower-priced drugs in the short term.
- Apart from the above, the existing research does not provide credible evidence that the current policies have an impact on healthcare utilization, patient access, health outcomes or R&D investments.
- There is a strong need for evidence generation regarding effective pricing policies, particularly for value-based pricing policies and for non-financial outcomes.
- Policy makers should systematically define the assessment of policy effectiveness during the policy formulation process. In addition, experimental research on the topic could augment the scarce amount of available evidence, especially for value-based pricing policies.

## 1. Introduction and background

### *1.1 Description of the policy issue*

In most OECD (Organisation for Economic Co-operation and Development) countries, laws regulate the pricing of prescription pharmaceuticals. Parliaments and governments aim to control public spending on pharmaceuticals, while securing access to innovative treatments for their citizens.

Desired policy outcomes of pricing and reimbursement regulations are focused on short-term reduction and mid-term stabilization of health expenditures [1]. In light of the financial and economic crisis, a majority of the countries in Western Europe in recent years decreed one-off as well as permanent, cost-containment policy measures to increase the control of spending on pharmaceuticals [1,2]. However, these policies face increasing criticism that they are not sufficiently effective, not only regarding impacts on public finances, but even more due to their potential consequences on access for patients to new treatment options [3,4], although new procedures for early access (conditional approval) and managed entry (coverage with evidence) have been introduced in Europe to make new therapies with “unsettled benefit–risk profiles” available [5].

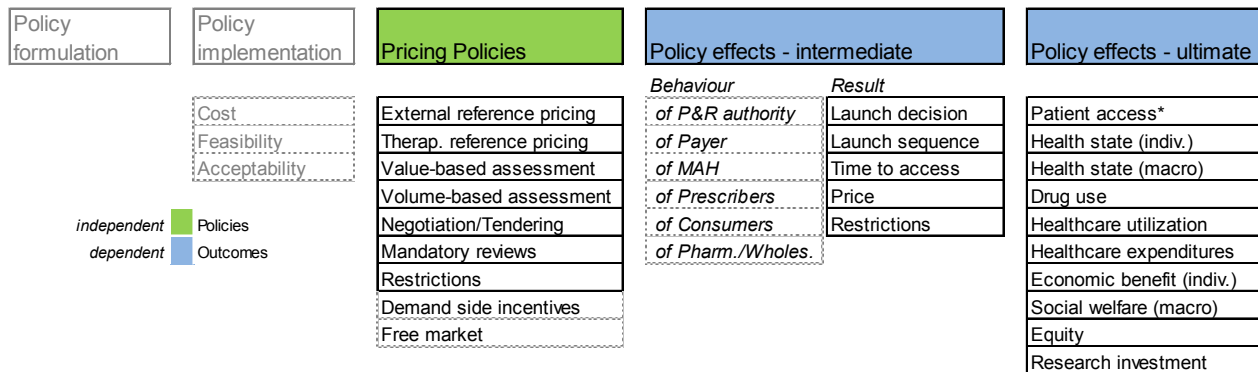
Currently, the calls for reform are getting louder, in light of a growing number of new molecules and increasingly complex treatments, especially in oncology. According to IMS, the R&D pipeline for oncology “has expanded by more than 60% over the past decade”, amounting to 710 late-phase therapies in 2017 [6,7]. Knowledge of the clinical benefits of the new therapies is often scarce at the time of marketing authorization [8], and the promised survival benefits imply a longer therapy duration, and therefore, additional budget impacts. Additionally, an increasing number of molecules are used in combination with other medications [6,7]. Most of the national health systems have struggled to adapt to this new challenge, resulting in the reduced availability and coverage of new treatments [6].

The current regulations might have not only adverse incentives for short-term availability, they are also claimed to have further undesirable effects on the long-term research decisions of industry, reducing related investments [9,10].

Finally, the ongoing change in the pharmaceutical sector, shifting from a “traditional blockbuster model” to more segmented markets offering therapies for smaller patient populations, leads to the discussion among authorities of whether current national policy approaches set the right incentives for industry to optimize research towards “value for money” [1,11,12]. In general, new drugs entering an established market can address previously unmet needs or target new populations for existing therapies (e.g., paediatric) and, consequently, increase treatment options [1]. While new therapies with high cure rates (e.g., for hepatitis) may be considered as cost-effective even at high nominal costs per patient and month, other innovations may seem hardly worth a premium compared to existing standards [13]. Most recently, OECD classified “many high-cost cancer drugs” as low-value (“type C”) technologies, if value is “based solely on the cost per life year or per quality-adjusted life year” [13]. From a health system perspective there is a clear need for the evolvement of current reimbursement policies in industrialised countries to better reflect “value for money” of new treatments [14]. This calls for pricing regulations that promote fast access to essential innovations, while not incentivizing investments in “me-too” compounds that offer no additional benefit. The challenging part of such policy reforms towards a more value-based assessment is not only a technical but also a normative one: how to find consensus on which technologies are “essential” (funded on a system level) and which are “nice to have” (individual funding). The discussion on how to measure value for money and whether the new pricing schemes are increasing is still ongoing [15-17]. Figure 1 provides an overview of our policy analysis, summarizing the most common pricing policies and the most discussed policy outcomes. The latter were defined

with consideration to recent policy papers from the WHO and the OECD, as well as existing reviews of the topic [1,12,18-22]. We refined the effect taxonomy after the first abstract screenings. The differentiation between intermediate (behaviour, result) and ultimate policy effects represents our own proposal, which reflects the screened study designs.

**Figure 1: Layout of pharmaceutical pricing policy analysis**



**Fig. 1** \* includes affordability and availability (supply), P&R: pricing and reimbursement, MAH: marketing authorization holder

### 1.2 Description of current policy designs to address the policy issue

The most common pricing policies for pharmaceuticals in industrialised countries are therapeutic (internal) reference pricing, international (external) reference pricing and value-based assessments. These are generally combined with positive reimbursement lists (formularies), regular price reviews (individual or in groups) and tendering. These direct pricing policies are often supplemented with measures on the demand side to set desired incentives for prescribers, pharmacies and patients. Finally, authorities can link reimbursement authorisations to managed entry agreements, including coverage with evidence obligations and pay-for-performance schemes. The definitions below closely follow the suggestions of the “Glossary of Pharmaceutical Terms” issued by the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies.

### *Therapeutic (internal) reference pricing (TRP)*

TRP is defined as the governmental practice of using the prices of identical (ATC 5 level) or similar medicines (ATC 4) or therapeutically equivalent treatments (beyond medicines) in a country. One or a set of therapies are used as benchmark or reference to set or negotiate the reimbursable price of a product in a given country. [20,23] The concrete mechanics can differ between the national systems (average or lowest of “equal” treatments, weighted for multiple indications, or not, measured per cycle, month or year). TRP can also be combined with other pricing instruments, such as ERP, and may also allow for an “innovation premium” for added therapeutic value (both are currently the case in Switzerland, based on Art. 65b KVV [24]). TRP sets the reimbursable price and thus implies that a third party, normally the patient (or insurance), has to cover the costs beyond the fixed price.

### *International (external) reference pricing (ERP)*

ERP is the practice of using the prices of a medicine in one or several countries to derive a benchmark or reference to set or negotiate the price of a product in a given country [20,23]. All but two EU member countries (Sweden, UK) have implemented some type of ERP [15]. While the policy intends to affect the national market of the issuing state, its external effects are the subject of debate, since marketing authorization holders are incentivized to launch new therapies in countries with higher prices first and delay in others [15].

### *Value-based pricing (VBP)*

The value-based assessment for pharmaceutical pricing is also referred to as “cost effectiveness-based”, “outcome-based” or “pharma economic” pricing. There is still “no widely accepted definition” of the value part of this instrument [23]. Following the WHO glossary, when referring to VBP, we mean the practice of authorities of “setting prices for new medicines and/or deciding on reimbursement based on the therapeutic value which the medicine offers, usually assessed through

a health technology assessment (HTA)”. VBP can be combined with cost-effectiveness thresholds, such as in Sweden or the UK, to define a range for the acceptable price of a treatment. VBP agreements are predestined for combination with managed entry schemes (see below), such as the Patient Access Scheme (PAS) in the UK, which allows the manufacturer to adjust the offer to the authorities (bringing the ICER down). However, most MEAs and PASs are still volume-based and not value-based. [1,2,23,25,26]

#### *Managed entry agreements (MEAs)*

An MEA is an “arrangement between a manufacturer and a payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions” [27]. It has established itself as the overarching term for arrangements such as “performance-based schemes”, “risk-sharing agreements” (RSAs), “patient access schemes” (PASs) or “coverage with evidence” schemes. MEAs aim to address uncertainties of new health technologies regarding clinical performance, cost-effectiveness, effective use or long-term budget impacts. [23,27]

While some MEAs focus on real-world evidence collection after the market authorization, others are set up as profit controls, volume-based agreements or other forms of predefined (“capped”) quantities or annual expenses for a new treatment. According to the ISPOR taxonomy, “cost-sharing” arrangements fall outside the definition of performance-based risk-sharing arrangements (PBRSA), since they are not linked to underlying cost-effectiveness [28]. While we do not limit our analysis to “financial schemes” [26], our focus lies on MEAs as part of or linked to pharmaceutical pricing regulations, following the WHO definition [23] (see inclusion criteria below under section 2.1).

#### *Other pricing and reimbursement policies*

In addition, the simple instrument of issuing a positive (or negative) reimbursement list is a widely used component of pharmaceutical pricing regulation. Further, in several countries, the official



reimbursement label is subject to negotiations for official reimbursement authorization. In addition to price, it often defines additional limitations of reimbursable use, e.g., the eligible population, sometimes including mandatory tests to prove eligibility, subject to approval by a medical examiner (insurance physician). This practice was recently applied to control costs of the new hepatitis C therapies, which led to a controversial discourse on politics and health sciences [1,13,29].

Finally, an interesting complement to TRP, VBP and other pricing policies under discussion is “indication-based pricing”, which aims to “capture the differential value of drugs across indications or patient groups” [25]. Thus far, this has been applied to only a very few special therapies across the European countries [30]. One example is Bevacizumab, which in Switzerland has the same official list price for all of its seven reimbursable indications. However, for two of these, the official reimbursement label defines an indication-specific (renal cell carcinoma and breast cancer) pay-back that is reimbursable by the health insurance of the treated patient [31]. One common challenge for indication-based pricing is that existing administrative structures in many countries are not designed to “track patients’ indications” for reimbursement purposes [32].

### ***1.3 Why this review is important***

Since the nineties, scientific interest in pharmaceutical pricing regulation has steadily increased, with a clear rise in publications in PubMed since 2013 [33]. In recent years, there have been a few systematic reviews published on existing evidence regarding pharmaceutical pricing regulation. Most of these reviews are limited to specific policies and have not been updated to reflect the most recent studies published on various health system and policy changes, especially regarding value-based pricing. The Cochrane Library has published seven systematic reviews in the research area in which we are interested. The review by Acosta et al. (2014) entitled “Pharmaceutical policies:

effects of reference pricing, other pricing, and purchasing policies” was found to be a very comprehensive, but was also a very restrictive, structured review [20].

Acosta et al. included only interrupted time series (ITS) and repeated measures (RM) studies. A more inclusive analysis of the existing body of research is necessary to provide a broader picture on current state of the discourse, which often takes place in the political arena. Otherwise, the analysis might reach only an exclusive expert audience. Finally, and most importantly, the previous reviews did not focus on the patent-protected market and did not simultaneously include all relevant policies. Most studies actually did the opposite—including or focusing on the off-patent market, while limiting the analysis to a single or a few selected policies. Against the background of the mentioned challenges for financing and incentivizing new, innovative health technologies, we consider the inverse focus to be essential.

#### ***1.4 Objectives***

The aim of this review is to assess and summarize the current state of empirical research on the effectiveness of national pricing regulations on the patent-protected market for prescription pharmaceuticals. Effectiveness is understood to be the capacity of policies to have a desired impact on outcomes such as health state, patient access, drug use, healthcare utilization, drug prices, healthcare expenditure, research investment, individual or organizational benefit, overall welfare, behaviour other than drug use and equity.

The study aims to contribute to the discourse around reform options of pricing regulations for new (“innovative”) pharmaceuticals in developed health systems with established public policies. Therefore, the analysis focuses on high-income OECD countries. There is undoubtedly a high need for health systems and related pharmaceutical policies to evolve in developing countries. However,

the majority of the respective policy settings and the data and evidence availability and quality were rated to not be supportive for the overarching research aims of this review.

## **2. Methods**

### ***2.1 Inclusion criteria for studies***

#### *Type of studies*

Controlled before-after studies (CBA), interrupted time series studies (ITS) and repeated measures studies (RM) were included. Inclusion was generally based on the recommendations from the Effective Practice and Organisation of Care (EPOC) for review authors [34]. However, to gain a broader picture of the current research, empirical studies not fulfilling the EPOC criteria were included if appropriate quantitative data and methods for inductive statistics were used. Additionally, existing systematic reviews were included if appropriate methodologies were applied.

#### *Type of policy designs*

National pricing regulations for patent-protected pharmaceuticals, including international (external) reference pricing, therapeutic (internal) reference pricing, value-based pricing (based on clinical and pharma economic data), managed entry agreements, positive reimbursement lists (formularies), and regular price reviews (individual or in groups) were included if they were linked to price decisions. Not included were studies focusing on demand-side policies only, such as co-payments (patients), prescription quotas or budgeting (physicians), and substitution and margins (pharmacists).

Our definition of “pricing policies” follows the Glossary of Pharmaceutical Terms, published by the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies: “Regulations and processes used by government authorities to set the price of medicine as part of exercising

price control” [23]. Based on this definition, we excluded analyses of MEAs not linked to price setting.

In contrast to the definition of the WHO CC and the Cochrane review by Acosta et al. [20], our scope was limited to official pricing policies issued by public authorities (i.e., national parliaments or governments, but not regulations issued by single health plans). Furthermore, effects of national pricing policies were considered only if they were realized in the addressed (sovereign) territory. In consequence, impact assessments of local policies on other countries, especially of ERP, were excluded. We acknowledge, however, that international effects are indirectly affecting the performance of national pricing policies [35].

#### *Type of outcome measures*

Outcomes of interest were policy effects such as health state (individual/societal), patient access, drug use, healthcare utilization, drug prices, healthcare expenditure, research and development (R&D) investments, welfare (economic benefit for an individual or organization, along with overall social welfare), behaviour other than drug use and equity (see Figure 1).

#### *Scope of the studies: health systems considered*

Only research focusing on “high-income” (World Bank classification) OECD countries was included, considering the historical changes of countries in their classification [36]. The reason for the defined scope is laid out above (1.4 Objectives).

## **2.2 Search methods**

Published studies were identified by an electronic database search using the following sources: PubMed, MEDLINE, Scopus, Web of Science, Cochrane Library, and the OECD iLibrary.

Searches with different word variations and combinations of “pharmaceutical” and “pricing” or

“prices”, as well as “policies” and “regulation” were performed. Publications on “reference pricing”, “value-based pricing” and combinations with “patient access” and “innovative” were also searched. Further, a supplementary check on publications on “managed entry” or “risk sharing” agreements not flagged with “pricing” keywords was performed. The complete search strategy is listed in Table 3 of Appendix 1.

The searches were performed in September 2016, December 2017 and August 2018 (update of PubMed, Scopus and Web of Science search) and were restricted to records published in 2005 or later. No additional filters for language or quality of evidence (e.g., “peer-reviewed journal only”) were applied at this stage. Only duplicate records (394) were excluded for initial abstract screening. Four additional publications not identified through the keyword search were added manually for abstract screening, since they were cited by at least one of the included systematic reviews on the topic.

### ***2.3 Data extraction and analysis***

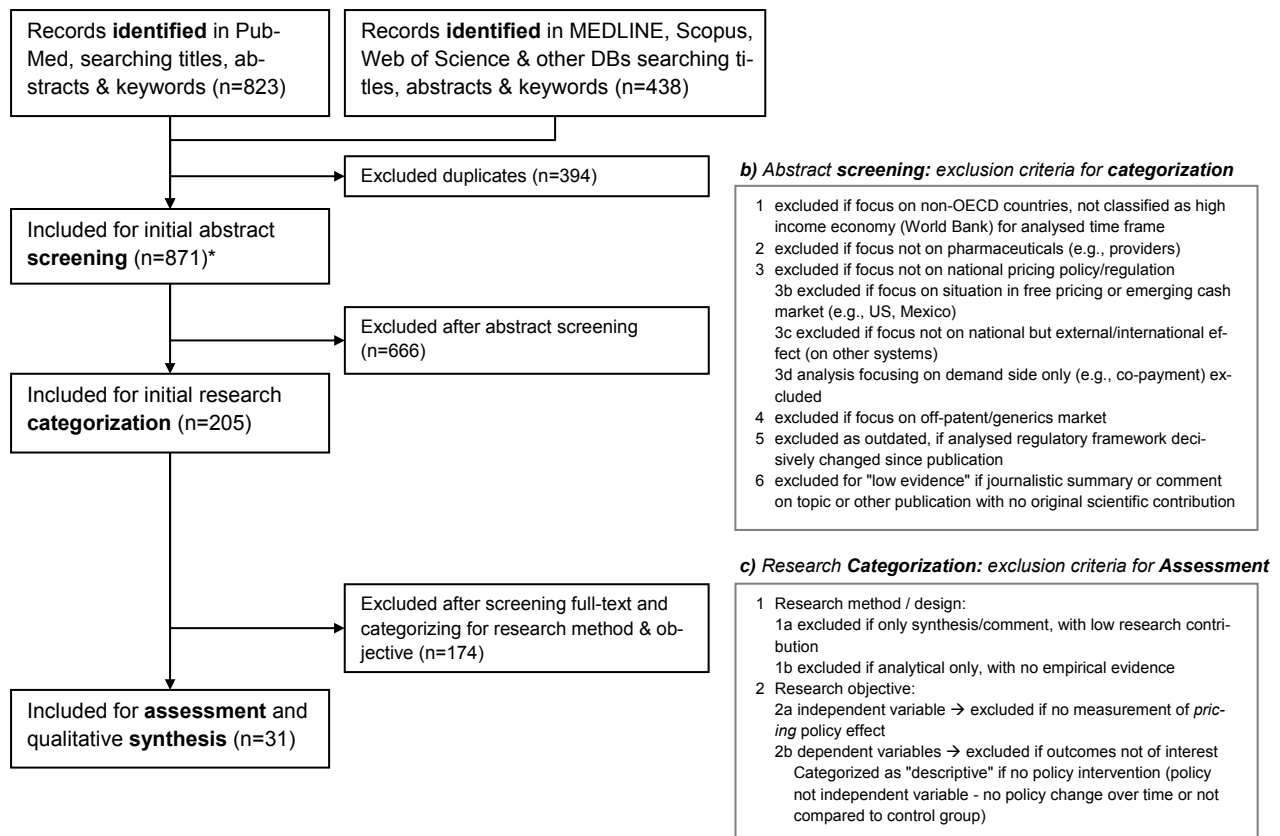
As revealed in the PRISMA study flow [37] in Figure 2, the review was performed in five main phases: a) identification (electronic database searches), b) abstract screening, c) research categorization (full text), and d) assessment of risk of bias with e) subsequent qualitative synthesis. The first author (DJW) conducted the literature search and extracted the articles for initial abstract screening and research categorization. When articles met any of the exclusion criteria, they were excluded from further assessment. If the assignment was ambiguous or unclear, the first author (DJW) consulted with the second author (SB) to reach an agreement.

In the abstract screening, the exclusion criteria (Figure 2) were tested sequentially. If no exclusion criteria were met, then the publication was included in the research categorization step (c).

In the research categorization step (c), the full text of the selected publications were analysed, and they were classified according to “research type” (16 types, see Appendix 1, Table 4) and “research objective” (see Appendix 1, Table 5). If the publication was not classified as one of the six predefined research types, it was excluded. At the same time, the research objective of the publication was assigned to one of 24 predefined research objective pairs (see Table 5 in Appendix 1, based on the policy analysis layout in Figure 1). Studies were excluded if pricing policy was not the independent variable. Further, if no policy change was analysed (no change over time or no comparison with another country or district with a different policy setting), then the study was categorized as "descriptive" and was excluded.

For poster abstracts included after screening, research categorization was performed on the available abstract text. If, based on the available information, no exclusion criteria were applicable, then the abstract was included in the risk of bias assessment and qualitative synthesis.

**Figure 2: Study flow (PRISMA diagram)**



**Fig. 2** \*4 studies were added manually because they were cited by at least one of the included systematic reviews; DB: databases

## 2.4 Assessment of risk of bias

The assessment of the risk of bias was based on a synthesis of existing tools. The reason for this was that none of the commonly used tools were designed for an inclusive analysis of all of the types of research included in this analysis: empirical research, analytical microeconomic models and systematic literature reviews. The most common tools were designed for health interventions and had to be adjusted for health policy designs. The integrated questionnaire was based on a selection and synthesis of the recommendations from:

- the BMJ guidelines [38] and a later, additional questionnaire by Drummond et al. [39],
- the Cochrane EPOC criteria [40],

- the Quality of Health Economic Studies (QHES) instrument [41],
- the good practice guidelines for modelling in HTA by Philipps et al. [42],
- the CRD's guidance for reviews [43] and the criteria list from the Consensus on Health Economic Criteria (CHEC) project [44].

The questionnaire comprised of total 18 questions, four on the study design (S1-S4), four on the data source and handling (D1-D4), three for the analytical modelling (M1-M3) and seven on the empirical analysis, synthesis and conclusions (E1-E7). The full questionnaire is given in Appendix 1, Table 7.

For each publication and each question, the risk of bias was assessed with either low, unclear or high, following the EPOC suggestions [40]. Since the EPOC criteria were integrated with other assessment questionnaires, the scoring recommendation had to be adapted. In general, the score “unclear” was used restrictively. This was a necessary adaption for the rating of policy “interventions” compared to specific health interventions. If a question could not be answered since it was “not specified in paper” [40], the risk was rated high. The rating “unclear” was assigned only if credible arguments against relevant bias of the conclusion were indicated in the publication. For example, D4 (intervention dependent on other changes) was only rated low if it was plausible that the stated impact of the policy on the defined outcome was not influenced by other changes. It was rated unclear if efforts were displayed to control one or some of the most important confounders (e.g., other pharmaceutical policies implemented in parallel, other relevant healthcare policy measures in parallel, changes of the relevant market structure, relevant trends in technology, or relevant macroeconomic factors on the distribution or demand side).

Missing information from assessed poster abstracts was rated with a high risk of bias.

Low was scored with 2 points, unclear with 1 and high with 0. The final SCORE per record was the ratio of scored points to the total possible points, in percent. With the risk of bias defined as 1-



SCORE, the grouping was set as: 0% no risk, 1-19% low, 20-39% moderate, 40-59% medium, and 60-100% high risk of bias.

## ***2.5 Synthesis of results***

For each of the assessed publications all policy-outcome pairs analysed were listed and grouped into the four main policy designs (TRP, ERP, VBP, other), as described in section 1.2. The results per pair and publication were assigned to one of the following six policy-outcome effects:

- positive (↑),
- negative (↓),
- contradictory/inconclusive (↕),
- effect exists (different directions possible, →),
- no effect (X),
- no conclusion (-).

The effects were contrasted with the risk of bias for the respective analysis for a qualitative synthesis per policy-outcome pair. We used the GRADE method [45] to rate the quality of evidence (high, moderate, low, very low), and based on that, followed the EPOC guidelines [46] to report the effect per pair.

## **3. Results**

### ***3.1 Included studies***

A total of 31 publications met the inclusion criteria, and none were classified as CBA or RM. Eight publications were based on interrupted time series studies (ITS), and seven were included because they met the requirements for quantitative data and methods. A further four publications presenting analytical models were included, since empirical validation was performed. Finally, 12 systematic reviews were also included.

*Included ITS:* Armeni et al. 2016, Augurzky et al. 2009, Barros et al. 2010, Grootendorst et al. 2005, Grootendorst et al. 2006, Morgan et al. 2008, Stargardt 2010, Yfantopoulos 2007. [[47-54](#)]

*Additional empirical research included (inductive statistics but no qualified ITS):* Golec et al. 2010, Kalo et al. 2012, Kanavos et al. 2011, Kyle 2007, Leopold et al. 2012, Stargardt 2011, von der Schulenburg et al. 2011. [[10,55-60](#)]

*Included analytical models with empirical validation:* Atella et al. 2012, Comanor et al. 2018, Kaiser et al. 2014, Koenig et al. 2011. [[61-64](#)]

*Included systematic reviews:* Acosta et al. 2014, Espin et al. 2011, Galizzi et al. 2011, Green et al. 2010, Lee et al. 2012, Lee et al. 2015, Morgan et al. 2009, Puig-Junoy 2005, Relakis et al. 2013 (poster abstract), Rémuzat et al. 2015, van der Gronde et al. 2017, Zhou et al. 2014 (poster abstract). [[19-22,65-72](#)]

Table 1 provides an overview of the included studies.

### **3.2 Excluded studies**

Of the 871 publications included for initial abstract screening, 666 did not meet the inclusion criteria. Most of them (281) did not focus on pharmaceutical pricing regulations according to the definition. A total of 169 did not focus on OECD and/or on high-income countries; 82 focused on the off-patent market. Of the 205 records included for full-text research categorization, 174 were excluded because they did not analyse a policy change (134) and/or did not classify as an appropriate research type (147). Full details on every screened record and summary per criteria are given in Appendix 2, Table 9.

The main reasons for the exclusion of empirical studies, which were included in other systematic reviews on the topic (included in this review as well), were that they were either published before

the defined time frame (23), did not meet our definition of pricing policy (17), or focused on the off-patent (4) or free-pricing (2) market. Details are displayed in Appendix 1, Table 6.

**Table 1: Overview of included publications**

Database	Publication	Type of economic research	Dependent variable	Methods	Scope / setting of analysis	Policy analysed	TRP	ERP	VBP	in general	Other	Outcomes
pubmed	Atella_2012 [61]	Economic model (analytic, empirical data)	Prices	OLS regression	US, Italy	Price controls vs none					X	Drug prices and drug quality (R&D invest)
scopus	Comanor_2018 [64]	Economic model (analytic, empirical data)	Prices	Ratio & linear regression	US, UK	Price controls vs none				X	X	drug prices
pubmed	Kaiser_2014 [62]	Economic model (analytic, empirical data)	Welfare***	Log-linear regression, random coefficients logit (RC logit) model	Denmark 2005, statins	Change from external to therap. reference pricing	X					Drug prices, demand (drug use), expenditures, (co-payment)
pubmed	Koenig_2011 [63]	Economic model (analytic, empirical data)	Invest (R&D)	Random parameters logit model	27 European countries	External, therap. reference pricing price controls overall	X	X		X		Location choice (incl. R&D investment)
pubmed	Armeni_2016 [47]	Interrupted time series study (ITS)	Expenditures	ITS	Italy	Therap. reference pricing, quotas, [co-payment]		X				Drug expenditures
pubmed	Augurzky_2009 [48]	Interrupted time series study (ITS)	Prices	ITS	Germany	Therap. reference pricing		X				Drug prices
pubmed	Barros_2010 [49]	Interrupted time series study (ITS)	Expenditures	ITS	Spain	Administrated price reductions, therap. reference pricing		X			X	Drug expenditures
pubmed	Grootendorst_2005 [50]	Interrupted time series study (ITS)	Expenditures	ITS	Canada, NSAIDs	Therap. reference pricing		X				Drug expenditures, drug use
pubmed	Grootendorst_2006 [51]	Interrupted time series study (ITS)	Prices	ITS	Canada, ACE Inh. & CCBs	Therap. reference pricing		X				Drug expenditures, drug use
pubmed	Morgan_2008 [52]	Interrupted time series study (ITS)	Invest (R&D)	ITS	Canada	Therap. reference pricing		X				R&D investment (local)
pubmed	Stargardt_2010 [53]	Interrupted time series study (ITS)	Usage**	ITS	Germany, statins	Therap. reference pricing		X				Drug use (adherence), healthcare utilization (visits), drug expenditures
pubmed	Yfantopoulos_2007 [54]	Interrupted time series study (ITS)	Prices	ITS	Greece	Positive list pricing					X	Drug expenditures
pubmed	Golec_2010 [10]	Statistical analysis - inductive (not ITS)	Invest (R&D)	OLS regression	US, EU	Price regulation by government vs none				X		Profitability, stock return, R&D investments
pubmed	Kalo_2012 [55]	Statistical analysis - inductive (not ITS)	Usage** & Exp	Aggregated linear regression	Hungary, asthma (2 prod.)	Therap. reference pricing		X				Drug expenditures (daily cost of therapy)
pubmed	Kanavos_2011 [56]	Statistical analysis - inductive (not ITS)	Prices	Random effects panel data analysis	OECD	Therap. & external reference pricing free pricing	X	X				Drug prices
Scopus	Kyle_2007 [57]	Statistical analysis - inductive (not ITS)	Access*	Negative binomial regression	OECD	Price controls vs none	X		X	X	X	Patient access (countries launched, time to launch)
pubmed	Leopold_2012_II [58]	Statistical analysis - inductive (not ITS)	Prices	Linear regression model	14 EU countries, 14 products	External reference pricing			X			Drug prices
Scopus	Stargardt_2011 [59]	Statistical analysis - inductive (not ITS)	Prices	Hierarchical multi-level random intercept model	Germany	Therap. reference pricing, price freeze		X			X	Drug prices
pubmed	vonderSchulenburg_2011 [60]	Statistical analysis - inductive (not ITS)	Prices	Fixed/random effects panel data analysis	6 EU countries ACE Inhibitors	Therap. reference pricing, cost-effectiveness analysis (value-based), profit controls, etc.	X		X		X	Drug prices
pubmed	Acosta_2014 [20]	Systematic Review	Diverse	Systematic review of ITS, RM, CRM, CBA	18 articles included	Therap. & external reference pricing maximum pricing, index pricing	X	X			X	Health outcomes, healthcare utilization, drug expenditures and drug use
haiweb.org	Espin_2011 [19]	Systematic Review	Prices	Systematic review [plus case studies]	21 articles included	External reference pricing			X			Drug prices
pubmed	Galizzi_2011 [65]	Systematic Review	Prices	Systematic review of theoretic and empiric research	35 articles included	Therap. reference pricing		X				Drug prices, drug expenditures, other effects
pubmed	Green_2010 [21]	Systematic Review	Diverse	Systematic review of ITS, RM, CRM, CBA	29 articles included	Restriction of reimbursement					X	Drug use, healthcare utilization, health outcomes, drug expenditures
pubmed	Lee_2012 [66]	Systematic Review	Diverse	Systematic review of empiric research	16 articles included	Therap. reference pricing		X				Drug prices, drug expenditures, drug use and healthcare utilization
pubmed	Lee_2015 [22]	Systematic Review	Expenditures	Systematic review of ITS, RM	29 articles included	Policies to control expenditure (incl. therap. reference pricing)	X			X		Drug expenditures, drug prices, drug use, healthcare utilization, health outcomes, [behaviour]
pubmed	Morgan_2009 [67]	Systematic Review	Diverse	Systematic review of ITS	3 [plus 12] articles included	Therap. reference pricing [and tiered formularies]	X					Drug expenditures (patient, insurer), drug use, healthcare utilization
pubmed	Puig-Junoy_2005 [68]	Systematic Review	Welfare***	Systematic review of empiric research	10 articles included	Therap. reference pricing		X				Overall social welfare, drug prices, healthcare utilization, [level of competition]
Web of Science	Relakis_2013 [69]	Systematic Review	Diverse	Systematic review of published evidence	na	Price controls					X	R&D investment, patient access (availability), drug expenditures, welfare
pubmed	Rémuzat_2015 [70]	Systematic Review	Prices	Systematic review of empiric research [plus survey]	234 articles included	External reference pricing			X			Drug prices, patient access, R&D investment, [international spill-over effects]
pubmed	vanderGronde_2017 [72]	Systematic Review	Diverse	Systematic review of scientific (peer-reviewed) and newspaper (journalistic) articles	221 (153+68) articles included	various	X	X	X	X	X	Drug prices, expenditures, access, various
pubmed	Zhou_2014 [71]	Systematic Review	Expenditures	Systematic review of theoretic and empiric research	na	Therap. reference pricing		X				Drug prices, drug use, drug expenditures, patient access

IST: Interrupted Time Series Study, TRP: Therapeutic Reference Pricing, ERP: External (International) Reference Pricing, VBP: Value-Based Pricing, R&D: Research and Development, na: not applicable [ ] not included in analysis, \* includes affordability and availability (supply), \*\* includes drug use and healthcare utilization, \*\*\* includes individual benefit and overall welfare

### ***3.3 Summary of risk of bias***

*Study design:* For all the non-ITS empirical studies and empirically verified theoretical studies, the risk of bias was rated high. The main reasons for this were the lack of measures to control relevant underlying trends and confounding variables and limited time points before and after the analysed policy change. Further, the policy intervention for some of the studies was not clearly defined. [73-76] For example, Kaiser et al. defined the policy intervention as a “change from external to internal reference pricing” in Denmark in 2005 [62], while Atella et al. bundled “regulatory regimes” with or without price controls for the US and Italy [61]. In the latter, since effective (potentially interacting) policies remained unspecified, and no indication and justification for the data range was given, the risk of bias for the section study design was rated as high. Golec/Vernon investigated the impact of overall price controls on R&D spending and profitability of EU vs. US firms [10]. However, the basic design lacks plausible methods to isolate the policy effects from confounding drivers for R&D spending or stock market returns.

*Data:* Most studies did not report techniques, evidence or plausible arguments to prevent outcomes from being influenced by other confounding variables during the analysed period. [40] Both Grootendorst/Steward and Morgan/Cunningham analysed the implementation of TRP policies in British Columbia [51,52]. The first study reports a negative (decreasing) effect on drug expenditures, while the latter concluded that there was no impact on local R&D spending. While the risk of bias for the analysis of Grootendorst/Steward was rated low overall, they admit that the introduction of low-cost generics during the analysed period could not be adequately controlled for [51]. Morgan/Cunningham neither control for nor discuss changes in the market in their analysis. Differences between the two systems regarding market structure (e.g., R&D intensity, companies entering/leaving the market) were neither controlled for, nor disclosed or discussed. [52]

*Empirical analysis:* Disaggregated results were missing for some of the studies and for some of the reviews. Additionally, some of the conclusions were enriched with opinion statements that were not founded on the analysed data and presented results. Yfantopoulos concludes that the introduction of positive list pricing in Greece was not effective in controlling pharmaceutical expenditures [54]. However, the underlying parameter is not significant, and many more details on the expenditure data that was used would be needed to reduce the risk of bias. The literature review from Espin/Rovira/Labry and that of Rémuzat et al. lacked an assessment of the evidence quality and risk of bias [19,70]. For both, it remains unclear whether the summary and the reported conclusions were based on the performed systematic review; additionally, no potential limitations of the analysis were disclosed.

*Overall risk:* The average risk of bias for the included ITS studies was rated low. Only the analysis from Yfantopoulos [54] left concerns, since information was missing on the independence of the effects from other changes, as well as on the aggregation of data and basis for conclusions, resulting in a medium risk of bias. The included analytical models with empirical verification scored lower, with moderate risk, mainly due to leaving doubts regarding the independence of the analysed changes and due to the lack of data reported on a disaggregated level. The non-ITS empirical studies were assessed only partly, since their risk of bias was judged as high after the initial assessment of the study design and data selection (except Kyle and Stargardt 2011, which was medium [57,59]). Most of the selected systematic reviews had a credible low risk of bias, with the exception of Rémuzat [70], Espin [19] and van der Gronde [72]. In Espin et al., more than half of the included studies were classified as opinions, while information on the included research designs was found to be incomplete. For the analysis of Relakis [69] and Zhou [71], no full results completing the published poster abstracts were found. Van der Gronde et al. [72] provided a comprehensive and up-to-date overview on the topic of pharmaceutical pricing; however, their paper did not disclose relevant information on the exclusion

criteria (screening, eligibility), criteria for additional inclusions, the chosen time period, and selection criteria for newspapers. Furthermore, no assessment of the risk of bias or the method of synthesis was disclosed (see PRISMA recommendations [37]), and central statements were either based on a single publication or not referred at all. An overview of the assessment of the risk of bias is provided in Appendix 1, Table 8.

### ***3.4 Effects of the policy changes and quality of evidence***

Table 2 provides an overview of the synthesized effects of the policy changes reported in the assessed empirical publications, as well as in the analysed systematic reviews. We found result statements for eight outcome categories. The only outcome category completely missing in the assessed publications was “equity”. No research intention was formulated for seven potential policy-outcome pairs, leading to 17 potential effects for synthesis. A conclusive statement could be derived for only 11 pairs.

*TRP on drug prices:* Five of the empirical studies and six systematic reviews performed an analysis of the impact of TRP on drug prices. Three of the original studies found evidence for prices to decrease after the introduction of TRP, one study reported inconclusive results (increase as well as decrease) and one study did not find an impact. Four of the reviews concluded that the introduction of TRP was likely to have a negative (reducing) impact on prices, while one publication reported “minimal” impact, with no details. For a general statement of the respective correlations, the evidence quality was rated low. We conclude that TRP may reduce drug prices. [22,48,56,59,60,62,65,66,68,71,72]

*TRP on healthcare expenditures:* Seven of the empirical studies and six systematic reviews performed a respective analysis. Four of the original studies reported reduced reimbursed expenditures. One study stated a transitory reduction with no impact on the trend. Furthermore, one study found that TRP did not reduce expenditures, and a recent (2016) analysis concluded

that TRP leads to higher expenditures. Of the systematic reviews, all five reported that TRP reduced the amount of drug expenditures. However, the definition of savings and expenditures was heterogeneous, and uncertainties on sustainability of the effects were reported. Although the average risk of bias was moderate, the effect was ambiguous, and for half of the studies the evidence was limited to a specific therapy or substance. In consequence, the overall quality of evidence for a general statement was rated as low for short-term expenditures and very low for mid-term expenditures. We conclude that TRP may reduce drug expenditures in the short term, while the long-term effect is uncertain. [[20](#),[22](#),[47](#),[49-51](#),[53](#),[55](#),[62](#),[65-67](#),[71](#)] This finding is in line with that of Acosta et al. [[20](#)].

*TRP on drug use:* Four of the empirical studies and five systematic reviews reported a respective analysis. All of the publications reported, in some form, shifts, switches or substitutions due to TRP between reference and referenced drugs. Very limited information and evidence was reported on overall drug use for the affected therapies. The empirical studies were limited to four therapeutic/pharmacological subgroups: ACE inhibitors, calcium channel blockers, NSAIDS (ATC level 3) and statins (ATC level 4). Consequently, the overall quality of evidence for a general statement was found to be low, although the average risk of bias was low for the reported substitution effects. We found that for a “moderate” rating, broader empirical research is needed that includes different therapies. [[20](#),[22](#),[50](#),[51](#),[53](#),[62](#),[66](#),[67](#),[71](#)]

For TRP and the outcomes *healthcare utilization*, *patient access* and *R&D investment*, the quality of evidence was rated very low, and we conclude that it is uncertain whether a respective policy impact exists. No evidence was reported for effects on *health outcome* or overall *welfare*. As displayed in Table 2, the body of research was markedly limited for ERP and very limited for VBP policies. We found the negative impact of both policies on *prices* and *patient access* to be uncertain, similar to the impact of ERP on research investments. For all other possible outcomes, no clear conclusion (or no conclusion) was reported in the analysed literature.



Further effects were reported for other policies such as administered price reductions (Spain) [49], positive list pricing (Greece) [54], price freeze (Germany) [59] or profit controls [60]. A Cochrane review from 2010 found that “Implementing restrictions to coverage and reimbursement of selected medications can decrease third-party drug spending without increasing the use of other health services” based on the results from six ITS studies [21]. We found no evidence for impacts from MEA in the context of pricing policies. There is a growing interest, with a corresponding increase of publications, on “use, advantages and disadvantages” [77], while evidence on these outcomes remains scarce [26,78,79].

#### **4. Conclusions and Discussion**

OECD countries have implemented numerous policy reforms on pharmaceutical pricing in the last decade [1]. The scientific evidence of whether these policy adjustments have the desired or unwanted effects on debated outcomes is, however, still scarce. In particular, for patent-protected pharmaceuticals (“new innovative technologies”), qualified evidence on policy effects remains very limited. The majority of empirical studies and reviews included in this review focused on therapeutic reference pricing. We found evidence that TRP may reduce pharmaceutical prices and expenditures in the short-term and may lead to substitution effects towards lower priced drugs in the short term. Apart from that, the existing research does not provide certain evidence that the current policies have an impact on healthcare utilization, patient access, health outcomes or R&D investments.

The aim of this paper was to analyse qualified empirical research on the effectiveness of existing policies. It was not the aim to perform an impact analysis of the existing research on current policy debates. To consider potential reasons for the scarce evidence that we found, we investigated the inclusion of the analysed research in selected topical policy publications from the

OECD and the European Union. Of the 205 publications included in our initial research categorization, only two (Paris et al. [12] and Vogler et al. [80], both qualified as “descriptive”) were referenced in the recent 231 page OECD paper on “New Health Technologies: Managing Access, Value and Sustainability” [13]. Additionally, the very recent report from the European Commission (Expert Panel on Effective ways of Investing in Health EXPH) on “Innovative payment models for high-cost innovative medicines” [14] refers only to one study (again, Paris et al. [12]). The cited OECD working paper No. 63 “Value in Pharmaceutical Pricing” [12] itself refers to one of the categorized studies (Leopold [81], qualified as “descriptive”). The more recent OECD working paper No. 87 on “Pharmaceutical Expenditure And Policies” [1] makes reference to one of the included and assessed studies, the systematic review from Lee et al. [66], without placing it into context of other systematic reviews or original research.<sup>1</sup>

For a general conclusion, a proper impact analysis would be needed that would consider the sequential influence of original research (e.g., using a “payback model”, see [82,83]) in a broader selection of recent policy papers. Yet the conclusions might be noted for their discrepancy between imminent legislative discussions and available scientific evidence. While external and therapeutic reference pricing are still broadly applied and are not expected to be abandoned, new “innovative payment models for new medicines” are desired by authorities [14] and by the pharmaceutical industry [84]. There seems to be a high-level consensus that new models should reflect therapeutic value added for the society and focus on patient-relevant outcomes. Several OECD countries have already incorporated value-based elements into their pharmaceutical pricing policies; for example, Sweden has been doing this for more than 10 years [12,18]. The trend in OECD countries is clear, with HTA being “increasingly used to inform coverage decisions” [1]. In this context, the lack of evidence on value-based pricing policies is consternating, if not alarming, especially given the current scepticism of the European Parliament,

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<sup>1</sup> The three papers from the OECD and EXPH refer to few of the recent literature on MEAs, which we excluded since none of them provides a policy effect analysis (see above).

where value-based pricing “can be misused as a profit maximizing economic strategy” [85]. As was very recently stated by Vogler (WHO) and Paris (OECD) et al. “regular reviews and evaluations of the impact of pricing and reimbursement policies” are critical to determine their effectiveness in “achieving the intended aims” [15]. There is a particular “need for impact assessments of managed entry agreements, value-based pricing and HTA” [15,77].

Why is the value-based pricing policy debate not informed by a more solid body of empirical evidence? There are admittedly methodological challenges with the empirical analysis of such policy changes in general. The different settings of the included studies in this paper reveal an unsurprising picture. The reported results (regarding TRP) with a lower risk of bias focused on only a few, established therapies or substances with a certain technological “stability” over a few years. Some of those studies could hardly be repeated for current oncologic treatments, where an increasing number of completely new therapies (e.g., targeted immune oncology) are coming to the market. This technological trend is “multiplied” by the increasing number of interdependent policy changes in recent years in most OECD healthcare systems.

These scientific challenges are confronted by the changing needs of the policy makers—the emerging legislative necessity to move from generally valid, static regulations to adaptive policies based on a mix of models [14]. In addition, the effort of designing and evaluating policy adaptations is a disproportionately higher burden for smaller countries [86].

Finally, value-based, performance-oriented agreements are often linked to MEAs and RSAs [78]. The resulting prices and conditions are, in the majority of countries, confidential and are therefore difficult to access for scientific evaluation [19,26,28,78,87].

It has never been more obvious that the interaction of health policy formulation and academic policy research needs to move beyond an “iterative” process (Habermas [88]) to a more “co-creative”, “co-evolutionary” process (Jasanoff [89]). This could also increase legitimacy. In the

concrete example of value-based pricing of new pharmaceutical therapies, this should mean the following:

- Need for the early and regular involvement of policy makers in the design of new policy research. Define the concept of qualified policy effectiveness analysis in the policy formulation phase, and roll it out jointly with the regulation change in the policy implementation phase.
- Need for research institutions to proactively approach the changing needs of the policy formulation process with appropriate research tools. Promote applicable empirical tools to analyse smaller, faster and interdependent policy changes. Additionally, complement the classical empirical tools, such as interrupted time series studies, with economic (field or laboratory) experiments to test policy hypotheses at an early stage.
- Need for the pharmaceutical industry, healthcare providers and insurance companies to set up and cooperatively participate in health economic studies beyond established clinical trials (post-marketing authorization), using real-world data on clinical and non-clinical outcomes.

Main limitation: While our restrictive focus on qualified study designs and the chosen methodology to adjust for the risk of bias follows the current practices [34,40], it comes at a cost. The current state of the underlying policy reform might call for a broader analysis of survey data, discussion papers and policy statements—from scientific and from political stakeholders. These data were not included in the findings of our study. On the other hand, the broader selection of designs, as recommended by EPOC [34,40], and the inclusion of meta-literature might also have skewed our findings.

Nevertheless, we conclude that there is a high need for evidence generation on effective pricing policies. In particular, the emerging value-based pricing policies and managed entry agreements should be assessed continuously on a scientific basis to inform policy formulation processes in

OECD countries [15]. In general, it is recommended to define policy effectiveness analysis in the policy formulation and implementation process.

### **Compliance with Ethical Standards**

**Funding:** No funding was received for the research performed or the writing of the manuscript.

**Conflict of interest:** DJW is an external PhD student at the University of Lucerne and was employed at the pharmaceutical company Takeda Pharma while performing this research. Neither the former employer of the first author nor any other private or public entity supported or influenced this research in any relevant way. SB has no conflicts of interest to declare. All of the authors submitted a signed Conflict of Interest disclosure form.

**Author contributions:** All of the authors (DJW and SB) fulfilled the authorship criteria and contributed to the design of the study, review of the search protocol, analysis and interpretation of the results, and writing and review of the manuscript. DJW prepared the search protocol, performed the database searches, screenings, categorizations, and assessments and prepared the draft of the manuscript. All of the authors are aware of the submission and are in agreement with the manuscript.

**Table 2: Summary effects of policy changes and quality of evidence**

Policy	Outcome	Orig. studies	Syst. reviews	Effect		Risk of Bias <sup>1</sup>	Quality of evidence <sup>2</sup>	Synthesis <sup>3</sup>							
TRP	Drug prices	5		Kanavos_2011 [56]	not significant	-	69% high	LOW	TRP may reduce drug prices.						
				vonderSchulenburg_2011 [60]	results inconclusive	↑	69% high								
				Kaiser_2014 [62]	Substantial reduction in prices	↓	19% low								
				Augurzky_2009 [48]	no full but fast price adjustment, manufacturers seem to compensate TRP prices with non-TRP prices	↓	17% low								
				Stargardt_2011 [59]	TRP reduces prices	↓	44% med								
		6		Galizzi_2011 [65]	After intro of TRP prices are likely to drop	↓	8% low								
				Lee_2012 [66]	reduced drug prices	↓	8% low								
				Lee_2015 [22]	minimal impact on prices	→	4% low								
				vanderGronde_2017 [72]	lower prices	↓	96% high								
				Zhou_2014 [71]	reference pricing could reduce prices	↓	92% high								
				Puig-Junoy_2005 [68]	(descriptive/no conclusion)	-	8% low								
				Healthcare expenditures		7				Grootendorst_2005 [50]	reduced drug expenditures, due to substitution of lower cost for higher-cost drugs, coupled with reduced reimbursement of higher-cost drugs	↓	0% no	LOW for short-term,	TRP may reduce drug expenditures in the short term.
										Grootendorst_2006 [51]	substitution of lower cost for higher-cost drugs, coupled with the reduced reimbursement of higher-cost drugs, had the effect of lowering drug expenditure	↓	7% low	VERY LOW for mid-term	It is uncertain whether TRP reduces drug expenditures in the long-term.
Stargardt_2010 [53]	decrease in expenditures	↓	10% low												
Kaiser_2014 [62]	Substantial reduction in healthcare expenditures	↓	19% low												
Kalo_2012 [55]	therap. reference pricing does not reduce expenditures	X	69% high												
Barros_2010 [49]	Impact on expenditures transitory: on level but not trend	↓X	17% low												
Armeni_2016 [47]	therap. reference pricing leads to higher expenditures	↑	10% low												
6		Galizzi_2011 [65]	saving effects (short-term) at least on molecule level, due to switches			↓	8% low								
		Lee_2015 [22]	reference pricing may result in cost savings				4% low								
		Acosta_2014 [20]	TRP may reduce drug expenditures in the short term by shifting drug use from cost share drugs to reference drugs. effect on expenditures of cost share drugs is uncertain.			↓	0% no								
		Morgan_2009 [67]	reduced expenditures			↓	17% low								
		Lee_2012 [66]	decreases in expenditures			↓	8% low								
		Zhou_2014 [71]	could reduce expenditures			↓	92% high								
Drug use (substitution/total use)		4		Grootendorst_2005 [50]	substitution of lower cost for higher-cost drugs	→	0% no	LOW	TRP may lead to substitution effects towards lower priced drugs in the short term.						
				Grootendorst_2006 [51]	substitution of lower cost for higher-cost drugs	→	7% low								
				Stargardt_2010 [53]	increase in switches and of non-adherence	→	10% low								
				Kaiser_2014 [62]	reform induced consumers to substitute away from branded drugs	→	19% low								
		5		Acosta_2014 [20]	drug use shifting from cost share drugs to reference drugs	→	0% no								
				Morgan_2009 [67]	increased switching, reduced overall	→	17% low								
				Lee_2012 [66]	increased switching	→	8% low								
				Lee_2015 [22]	no increased use	X									
				Lee_2015 [22]	shifts in use	→	4% low								
				Zhou_2014 [71]	increase use of lower priced drugs	→	92% high								

TRP (cont.)	Healthcare utilization	1		Stargardt_2010 [53]	limited evidence that increased switching leads to increased visits in some sub-groups	↑	10%	low	VERY LOW	It is uncertain whether TRP increases health-care utilization.
			4	Lee_2015 [22]	(nothing reported)	-	4%	low		
				Acosta_2014 [20]	effects on healthcare utilization are uncertain due to lack of evidence	-	0%	no		
				Morgan_2009 [67]	increase in short-term physician visits	↑	17%	low		
				Puig-Junoy_2005 [68]	(descriptive/no conclusion)	-	8%	low		
Patient access		1		Kyle_2007 [57]	TRP leads to earlier launch	↑	56%	med	VERY LOW	It is uncertain whether TRP leads to earlier launches.
			1	Zhou_2014 [71]	no impact on patient access found	-	92%	high		
Health outcome		-	3	Lee_2015 [22]	(nothing reported)	-	4%	low		
				Acosta_2014 [20]	no evidence found	-	0%	no		
				Morgan_2009 [67]	no evidence found	-	17%	low		
Welfare	-	1		Puig-Junoy_2005 [68]	no evidence on found	-	8%	low		
Research investment		2	-	Koenig_2011 [63]	less investments for countries with price controls, but not significant for R&D only	-	33%	mod	VERY LOW	It is uncertain whether TRP has an effect on R&D investments.
				Morgan_2008 [52]	reference pricing did not have impact on local R&D	X	23%	mod		
ERP	Drug prices	2		Kanavos_2011 [56]	not significant	-	69%	high	VERY LOW	It is uncertain whether ERP reduces prices.
				Leopold_2012_II [58]	leads to lower prices, but price level not driven by ERP only	↓	75%	high		
		3	Rémuzat_2015 [70]	inconclusive	↑	63%	high			
			Espin_2011 [19]	no evidence found	-	63%	high			
			vanderGronde_2017 [72]	(nothing reported)	-	96%	high			
	Healthcare expenditures	-	1	Acosta_2014 [20]	(nothing reported)	-	0%	no		
	Drug use	-	1	Acosta_2014 [20]	(nothing reported)	-	0%	no		
	Healthcare utilization	-	1	Acosta_2014 [20]	(nothing reported)	-	0%	no		
	Patient access		2	Rémuzat_2015 [70]	evidence for delay or avoidance of launches	↓	63%	high	VERY LOW	It is uncertain whether ERP has a negative effect on patient access.
				vanderGronde_2017 [72]	countries with a lower willingness to pay could see a drug launch delayed or no launch at all	↓	96%	high		
Health outcome	-	1	Acosta_2014 [20]	(nothing reported)	-	0%	no			
Research investment		1	Koenig_2011 [63]	less investments for countries with price controls, but not significant for R&D only	-	33%	mod	VERY LOW	The effect of ERP on R&D investments is uncertain and unclear.	
			Rémuzat_2015 [70]	(descriptive/no conclusion)	-	63%	high			
VBP	Drug prices	2	vonderSchulenburg_2011 [60]	cost-effectiveness analysis has a negative impact on price	↓	69%	high	VERY LOW	It is uncertain whether VBP reduces drug prices.	
			Comanor_2018 [64]	VBP leads to same prices as free-market pricing	X	97%	high			
		1	vanderGronde_2017 [72]	VBP incentivizes high prices for innovative drugs	↑	96%	high			
Patient access	1	-	Kyle_2007 [57]	pharmaco-economic evidence requirement seems to delay launch	↓	56%	high*	VERY LOW	It is uncertain whether VBP has a negative effect on patient access.	

**Policies:** TRP: Therapeutic reference pricing, ERP: External reference pricing, VBP: Value-based pricing

**Effect:** ↑ positive effect, ↓ negative effect, ↑ contradictory/inconclusive effect, → effect (different directions possible), X no effect, - no conclusion

**<sup>1</sup> Risk of bias:** 1-SCORE (0% no risk, 1-19% low, 20-39% moderate, 40-59% medium, 60-100% high), overall outcomes are per publication unless stated otherwise.

\* Risk for this policy-outcome pair adjusted, since it was considerably higher than for the publication overall.

**<sup>2</sup> Grades of evidence** according to the **GRADE** Working Group [45]:

HIGH: We are very confident that the true effect lies close to that of the estimate of the effect.

MODERATE: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

LOW: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

VERY LOW: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**<sup>3</sup> Synthesis of the effect** following the EPOC guidelines on how to report the effects of interventions [46].

R&D: Research and Development



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## Appendix 1

**Table 3: Search strategy**

#	descriptor	proceeding	PUBMED	MEDLINE	Scopus	Web of Science	OECD iLibrary	COCHRANE	Other	TOTAL
1	pharmaceutical OR medicine AND pricing OR prices	AND, OR, 2005-		162						
2	"pharmaceutical pricing" OR "*" prices" OR "*" price"	exact OR, 2005-	180		131	101	19			
3	"pharmaceutical pricing" OR "*" prices" OR "*" price" OR "medicine prices" OR "drug prices"	exact OR, 2005-						5		
4	"medicine prices" OR "drug prices" AND NOT #2	exact OR, AND, 2005-	174							
5	pricing, pharmaceuticals, innovative	AND, 2005-	66							
6	patient access pricing pharmaceuticals policies	AND, 2005-	51							
7	pharmaceutical, "pricing policies"	AND, 2005-	24							
8	"pharmaceutical policies"	exact, 2005-	82							
9	"value-based pricing" OR "value based pricing"	exact, OR, 2005-	46							
10	pharmaceutical, pricing, policies	AND, 2005-					20			
11	"price regulation", pharmaceutical	exact, AND, 2005-	49							
12	"reference pricing"	exact, 2005-	151							
99	[manually added since cited by included systematic review]		1						3	
<b>Search results</b>			<b>824</b>	162	131	101	39	5	3	<b>1265</b>
<i>duplicates</i>			99	126	58	79	27	5	0	394
<b>Initial abstract screening</b>			<b>725</b>	36	73	22	12	0	3	<b>871</b>
<i>excluded</i>			550	31	64	15	4	0	2	666
<b>Initial research categorization</b>			<b>175</b>	5	9	7	8	0	1	<b>205</b>
<i>excluded</i>			149	5	6	6	8	0	0	174
<b>Assessment</b>			<b>26</b>	0	3	1	0	0	1	<b>31</b>

Additional checks:

#	descriptor	proceeding	PUBMED
A1	"managed entry" NOT #2 NOT #9 NOT #12	exact, OR, 2005-	44
A2	"risk sharing agreements" OR "risk sharing schemes" OR "risk sharing contracts NOT #2 NOT #9 NOT #12	exact OR, 2005-	67
A3	"managed entry" OR "risk sharing" AND pharmaceutical OR pharmaceuticals OR drugs NOT #2 NOT #9 NOT #12	AND, OR, 2005-	106
<u>Additional inclusions</u>			0

Search fields: title, abstract, key words. Word variations if supported.

**Table 4: Categorization type of research**

<b>Type of economic research</b>	<b>Empirical/ analytical</b>	<b>excluded</b>
Economic model (analytic)	analytic	Y
Economic model (analytic, empirical data)	combined	N
Cost-effectiveness analysis (CEA)	combined	N
Cost-utility analysis (CUA)	combined	N
Cost-benefit analysis	combined	N
RCT, NRCT	empiric	N
Controlled before-after study (CBA)	empiric	N
Interrupted time series study (ITS)	empiric	N
Repeated measures study (RM)	empiric	N
Statistical analysis - inductive (not RCT/NRCT, CBA or ITS)	empiric	N
Statistical analysis - descriptive	empiric	Y
(Retrospective) Observational study	empiric	Y
Survey / (Structured) Interviews	empiric	Y
Case study	empiric	Y
Systematic Review	empiric	N
Literature Review (not systematic)	empiric	Y
Legal analysis	empiric	Y
Synthesis/Comment	empiric	Y
Guideline	combined	Y

**Table 5: Categorization research objective**

<b>Research objective (independent &gt; dependent var.)</b>	<b>excluded</b>
Prices (descriptive)	Y
Prices > Behaviour	Y
Prices > Access*	Y
Prices > Health outcome	Y
Prices > Usage**	Y
Prices > Expenditures	Y
Prices > Equity	Y
Prices > Invest (R&D)	Y
Prices > Other	Y
Other (non_Policy) > Prices	Y
Other (non_Policy) > Other	Y
Policy (descriptive)	Y
Policy > Prices	N
Policy > Behaviour	N
Policy > Access*	N
Policy > Health outcome	N
Policy > Usage**	N
Policy > Expenditures	N
Policy > Usage** & Exp	N
Policy > Welfare***	N
Policy > Equity	N
Policy > Invest (R&D)	N
Policy > diverse	N
Policy implementation	Y

\* includes affordability and availability (supply)

\*\* includes drug use and healthcare utilization

\*\*\* includes individual benefit and overall welfare

Y: yes, N: no, R&D: Research and Development

**Table 6: Reason for excluded studies included in other systematic reviews**

<b>Publication</b>	<b>Acosta_2014</b>	<b>Green_2010</b>	<b>Lee_2012</b>	<b>Reason for exclusion</b>
Aronsson 2001	X			Out of defined time-frame
Bjerrum 2001		X		Out of defined time-frame
Brekke 2003	X			Out of defined time-frame
Brekke 2009			X	Off-patent market
Brekke 2011	X			Off-patent market
Burse 2000		X		Out of defined time-frame
Carroll 2006		X		No pricing regulation (search key words)
Delate 2005		X		No pricing regulation (search key words)
Farley 2008		X		No pricing regulation (search key words)
Fischer 2004		X		Out of defined time-frame
Fischer 2007		X		No pricing regulation (search key words)
Fretheim 2007		X		No pricing regulation (search key words)
Grootendorst 2002	X		X	Out of defined time-frame
Grootendorst_2004			X	Out of defined time-frame
Hartung 2004		X		Out of defined time-frame
Hartung 2006		X		No pricing regulation (search key words)
Hazlet 2002	X	X	X	Out of defined time-frame
Jackevicious 2008		X		No pricing regulation (search key words)
Keith 1994		X		Out of defined time-frame
Kephart 2005		X		No pricing regulation (search key words)
Kibicho 2012	X			Free pricing market
Law 2008		X		No pricing regulation (search key words)
MacCara 2001		X		Out of defined time-frame
Marshall 2002	X	X		Out of defined time-frame
Marshall 2006		X		No pricing regulation (search key words)
Marshall 2007		X		No pricing regulation (search key words)
McManus 2001	X			Out of defined time-frame
Morden 2008		X		No pricing regulation (search key words)
Moreno-Torres_2011	X		X	Off-patent market
Motheral 2004		X		Out of defined time-frame
Narine 2001	X			Out of defined time-frame
Pavcnik 2002	X			Out of defined time-frame
Puig-Junoy 2004			X	Out of defined time-frame
Puig-Junoy 2007	X		X	Off-patent market
Roughhead 2006		X		No pricing regulation (search key words)
Sakshaug 2007		X		No pricing regulation (search key words)
Sawyer 1983	X			Out of defined time-frame
Schneeweiss 2002	X		X	Out of defined time-frame
Schneeweiss 2003	X		X	Out of defined time-frame
Schneeweiss 2004		X	X	Out of defined time-frame
Schneeweiss 2006		X		No pricing regulation (search key words)
Smalley 1995		X		Out of defined time-frame
Soumerai 2008		X		No pricing regulation (search key words)
van Driel 2008		X		No pricing regulation (search key words)
Mabasa 2006			X	No pricing regulation as defined
Pavcnik 2000			X	Out of defined time-frame
Johnson 2011			X	Free pricing market

**Table 7: Questionnaire for assessment of risk of bias**

		Interrupted time series study (ITS)	Statistical analysis - inductive (not ITS)	Economic model (analytic, empirical data)	Systematic Review
<b>Study design</b>					
S1	Research question stated and answerable?	X	X	X	X
S2	Intervention and potential alternative clearly defined and pre-specified?	X	X	X	X
S3	Study design appropriate to address question, following conventions?	X	X	X	
S4	Setting and scope justified and appropriate to answer question (time frame, coverage)?	X	X	X	X
<b>Data</b>					
D1	Sources of data described and justified (quality, relevance, etc.)?	X	X	X	X
D2	Outcomes clearly stated, predefined & meaningful? Measures valid and reliable? Abstractions clear?	X	X	X	X
D3	Reasons for selection/ exclusion of data stated and plausible?	X	X	X	X
D4	Intervention independent from other changes?	X	X	X	
<b>Model</b>					
M1	Economic model (structure) displayed in a clear, transparent manner?			X	
M2	Evidence for the model structure applied provided?			X	
M3	Structural assumptions transparent and justified? Are they reasonable given the overall objective?			X	
<b>Empirical analysis</b>					
E1	Shape of the intervention effect prespecified?	X		X	
E2	Major outcomes presented in disaggregated as well as aggregated form?	X		X	X
E3	Data analysed appropriately? Details of statistical tests given?	X		X	X
E4	Incomplete outcome data addressed?	X		X	X
E5	Method of synthesis or meta-analysis of estimates described?	X		X	X
E6	Conclusions & recommendations justified and based on the results (data) reported? Theoretical (model) conclusions valid given the data presented?	X		X	X
E7	Limitation and potential biases discussed?	X		X	X

IST: Interrupted Time Series Study, TRP: Therapeutic Reference Pricing, ERP: External (International) Reference Pricing, VBP: Value-Based Pricing



**Table 8: Assessment risk of bias: scoring table**

Publication	Type of economic research	Research objective	STUDY DESIGN				DATA				MODEL			EMPIRICAL ANALYSIS							SCORE
			S1 Research question stated and answerable?	S2 Intervention and potential alternative clearly defined and pre-specified?	S3 Study design appropriate to address question, following conventions?	S4 Setting and scope justified and appropriate to answer question (time frame, coverage)?	D1 Sources of data described and justified (quality, relevance, etc.)?	D2 Outcomes clearly stated, predefined & meaningful? Measures valid and reliable? Abstractions clear?	D3 Reasons for selection/exclusion of data stated and plausible?	D4 Intervention independent from other changes?	M1 Economic model (structure) displayed in a clear, transparent manner?	M2 Evidence for the model structure applied provided?	M3 Structural assumptions transparent and justified? Are they reasonable given the overall objective?	E1 Shape of the intervention effect prespecified?	E2 Major outcomes presented in disaggregated as well as aggregated form?	E3 Data analysed appropriately? Details of statistical tests given?	E4 Incomplete outcome data addressed?	E5 Method of synthesis or meta-analysis of estimates described?	E6 Conclusions & recommendations justified and based on the results (data) reported? Theoretical (model) conclusions valid given the data presented?	E7 Limitation and potential biases discussed?	
Atella_2012	Economic model (analytic, empirical data)	Policy > Prices	Y (LOW)	N (HIGH)	N (HIGH)	N (HIGH)	unclear	unclear	Y (LOW)	N (HIGH)	Y (LOW)	Y (LOW)	unclear	N (HIGH)	N (HIGH)	Y (LOW)	unclear	Y (LOW)	N (HIGH)	N (HIGH)	44%
Comanor_2018	Economic model (analytic, empirical data)	Policy > Prices	unclear	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	3%
Kaiser_2014	Economic model (analytic, empirical data)	Policy > Welfare***	Y (LOW)	Y (LOW)	N (HIGH)	unclear	Y (LOW)	Y (LOW)	unclear	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	unclear	Y (LOW)	81%
Koenig_2011	Economic model (analytic, empirical data)	Policy > Invest (R&D)	Y (LOW)	unclear	N (HIGH)	Y (LOW)	N (HIGH)	unclear	unclear	N (HIGH)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	N (HIGH)	Y (LOW)	Y (LOW)	unclear	Y (LOW)	Y (LOW)	67%
Armeni_2016	Interrupted time series study (ITS)	Policy > Expenditures	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	unclear	-	-	-	Y (LOW)	unclear	Y (LOW)	Y (LOW)	unclear	Y (LOW)	Y (LOW)	Y (LOW)	90%
Augurzky_2009	Interrupted time series study (ITS)	Policy > Prices	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	unclear	Y (LOW)	N (HIGH)	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	N (HIGH)	Y (LOW)	83%
Barros_2010	Interrupted time series study (ITS)	Policy > Expenditures	Y (LOW)	unclear	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	N (HIGH)	unclear	-	-	-	unclear	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	83%
Grootendorst_2005	Interrupted time series study (ITS)	Policy > Expenditures	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	100%
Grootendorst_2006	Interrupted time series study (ITS)	Policy > Prices	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	N (HIGH)	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	93%
Morgan_2008	Interrupted time series study (ITS)	Policy > Invest (R&D)	Y (LOW)	Y (LOW)	unclear	Y (LOW)	Y (LOW)	N (HIGH)	Y (LOW)	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	N (HIGH)	77%
Stargardt_2010	Interrupted time series study (ITS)	Policy > Usage**	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	unclear	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	N (HIGH)	Y (LOW)	90%
Yfantopoulos_2008	Interrupted time series study (ITS)	Policy > Prices	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	unclear	Y (LOW)	unclear	N (HIGH)	-	-	-	Y (LOW)	N (HIGH)	N (HIGH)	unclear	Y (LOW)	N (HIGH)	N (HIGH)	57%
Golec_2010	Statistical analysis - inductive (not ITS)	Policy > Invest (R&D)	Y (LOW)	N (HIGH)	N (HIGH)	unclear	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	-	-	-	-	-	-	-	-	-	-	19%
Kalo_2012	Statistical analysis - inductive (not ITS)	Policy > Usage** & Exp	Y (LOW)	Y (LOW)	N (HIGH)	N (HIGH)	unclear	N (HIGH)	N (HIGH)	N (HIGH)	-	-	-	-	-	-	-	-	-	-	31%
Kanavos_2011	Statistical analysis - inductive (not ITS)	Policy > Prices	Y (LOW)	N (HIGH)	N (HIGH)	N (HIGH)	unclear	Y (LOW)	N (HIGH)	N (HIGH)	-	-	-	-	-	-	-	-	-	-	31%
Kyle_2007	Statistical analysis - inductive (not ITS)	Policy > Access*	Y (LOW)	N (HIGH)	N (HIGH)	Y (LOW)	Y (LOW)	N (HIGH)	unclear	N (HIGH)	-	-	-	-	-	-	-	-	-	-	44%
Leopold_2012_II	Statistical analysis - inductive (not ITS)	Policy > Prices	Y (LOW)	Y (LOW)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	-	-	-	-	-	-	-	-	-	-	25%
Stargardt_2011	Statistical analysis - inductive (not ITS)	Policy > Prices	Y (LOW)	Y (LOW)	N (HIGH)	N (HIGH)	unclear	Y (LOW)	Y (LOW)	N (HIGH)	-	-	-	-	-	-	-	-	-	-	56%
vonderSchulenburg_201	Statistical analysis - inductive (not ITS)	Policy > Prices	unclear	unclear	N (HIGH)	N (HIGH)	Y (LOW)	N (HIGH)	unclear	N (HIGH)	-	-	-	-	-	-	-	-	-	-	31%
Acosta_2014	Systematic Review	Policy > diverse	Y (LOW)	Y (LOW)	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	-	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	100%
Espin_2011	Systematic Review	Policy > Prices	Y (LOW)	Y (LOW)	-	Y (LOW)	N (HIGH)	unclear	N (HIGH)	-	-	-	-	N (HIGH)	unclear	unclear	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	38%
Galizzi_2011	Systematic Review	Policy > Prices	Y (LOW)	Y (LOW)	-	Y (LOW)	Y (LOW)	Y (LOW)	unclear	-	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	unclear	Y (LOW)	Y (LOW)	Y (LOW)	92%
Green_2010	Systematic Review	Policy > diverse	Y (LOW)	Y (LOW)	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	-	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	100%
Lee_2012	Systematic Review	Policy > diverse	Y (LOW)	Y (LOW)	-	Y (LOW)	Y (LOW)	Y (LOW)	unclear	-	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	unclear	Y (LOW)	Y (LOW)	Y (LOW)	92%
Lee_2015	Systematic Review	Policy > Expenditures	Y (LOW)	Y (LOW)	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	-	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	unclear	Y (LOW)	Y (LOW)	Y (LOW)	96%
Morgan_2009	Systematic Review	Policy > diverse	Y (LOW)	Y (LOW)	-	Y (LOW)	unclear	Y (LOW)	unclear	-	-	-	-	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	N (HIGH)	Y (LOW)	83%
Puig-Junoy_2005	Systematic Review	Policy > Welfare***	Y (LOW)	Y (LOW)	-	Y (LOW)	unclear	Y (LOW)	Y (LOW)	-	-	-	-	unclear	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	Y (LOW)	92%
Relakis_2013	Systematic Review	Policy > diverse	Y (LOW)	unclear	-	Y (LOW)	Y (LOW)	N (HIGH)	N (HIGH)	-	-	-	-	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	29%
Rémuzat_2015	Systematic Review	Policy > Prices	Y (LOW)	Y (LOW)	-	Y (LOW)	unclear	unclear	unclear	-	-	-	-	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	38%
vanderGronde_2017	Systematic Review	Policy > diverse	unclear	N (HIGH)	-	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	-	-	-	-	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	4%
Zhou_2014	Systematic Review	Policy > Expenditures	Y (LOW)	N (HIGH)	-	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	-	-	-	-	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	N (HIGH)	8%

Y: yes, N: no, IST: Interrupted Time Series Study, TRP: Therapeutic Reference Pricing, ERP: External (International) Reference Pricing, VBP: Value-Based Pricing  
 \* includes affordability and availability (supply), \*\* includes drug use and healthcare utilization, \*\*\* includes individual benefit and overall welfare

ERIC/ERIC	b) Abstract screening							c) Research categorization				ID	Title	Author (sorted, update separate)	Details	Date	PubDate	PubYear														
	ERIC1/Date	ERIC2/Date	ERIC3/Date	ERIC4/Date	ERIC5/Date	ERIC6/Date	ERIC7/Date	ERIC1	ERIC2	ERIC3	ERIC4								ERIC5													
10	20160828	OECD Library	Y											Pharmaceutical Pricing Policies in a Global Market (OECD) Erratum: Perceptions of general practitioners towards pharmaceutical price war and assessment medicines EU judges overruled price fixing: Foreign consignments must not be by the Pharmaceutical Price Order Few regulations in pharmaceutical pricing [Per il prezzo dei farmaci poche regole da seguire] More and more drugs under the Pharmaceutical Prices Act (WGP) [Steads meer geneesmiddelen onder de 25272635 (Chapter 1. A contemporary history of the Japanese pharmaceutical industry (1980-2010). A contemporary 26887181 A Campaign to Cut Drug Prices. 19127766 A few specialty drug prices fall—all generics. (No authors listed) 16110523 AIDS activists defy steady hikes in HIV drug prices. (No authors listed) 16365977 Australia: new free trade agreement with US targets drug prices. (No authors listed) 15572563 Commerce: Market-set drug prices abroad wouldn't cut U.S. prices. (No authors listed) 26417639 Discounted drug prices for hospitals: result in prescriptions for expensive drugs in the community. (No authors listed) 20446567 Drug prices on the rise as coverage gaps loom. (No authors listed) 26594733 Exorbitant drug prices harm research. (No authors listed) 20355274 How insurers' bargaining power affects drug prices in Medicare Part D. (No authors listed) 27459793 Is There a Cure for High Drug Prices? A Special Investigation From Consumer Reports Best Buy Drugs. (No authors listed) 16250202 Managed care payments, drug prices rise for savings efforts. (No authors listed) 16240494 Medicare should bargain for lower drug prices, study says. (No authors listed) 16158504 National foundation: AIDS drug prices still too high for poor. (No authors listed) 18179656 Better pharmaceutical price comparison studies are needed for meaningful evaluation of price-control pol (Schaffner et al) 16625648 The cost of US pharmaceutical price regulation: A financial simulation model of R&D decisions (Aaserud M, Dahlgren AT, KÅesters JP, Odmæ 20160828 Y	20160828	Y						Y										
2	20172131	Scopus	Y											Pharmaceutical Pricing Policies in a Global Market	Acosta A, Ciapparo A, Aaserud M, Vietto V, J Aggarwal S	Cochrane Database Syst Rev. 2014 Oct 16;10: CD005991	create date:2014/10/16	2011	2011													
4	20172131	Scopus	Y											Pharmaceutical Pricing Policies in a Global Market	Aggarwal S, Khan MU, Patel I, Ahmad A	J Pharm Pract. 2015 Jan-Mar;41(1):3-3. doi: 10.1010/j.jpp.2014.11.003	create date:2015/02/25	2015	2015													
2	20172131	Scopus	Y											Pharmaceutical Pricing Policies in a Global Market	Akalephan C, Wuboluprasert S, Sakulabumr R, Luanguangrong P, Jitrakathae A, Aekeasangsri R	J Eur J Pharm Sci. 2015 Sep 29;72(1):402-5. doi: 10.1016/j.ejps.2015.07.004	create date:2015/07/04	2015	2015													
7	20160828	pubmed	Y											Pharmaceutical Pricing Policies in a Global Market	Ali E E, Gilani A H, Gedif T, Aji GK, Yaha Y	East Mediterr Health J. 2012 Aug;18(8):811-20. create date:2012/08/24	2012	2012														
2	20160828	pubmed	Y											Pharmaceutical Pricing Policies in a Global Market	Almeida AD, da Silva AL, Cherchiglia ML, Andrad E, de Oliveira GL, Accurio Fde A, et al	Cochrane Database Syst Rev. 2014 Oct 16;10: CD005991	create date:2014/10/16	2011	2011													
4	20160828	pubmed	Y											Pharmaceutical Pricing Policies in a Global Market	Almeida AD, da Silva AL, Cherchiglia ML, Andrad E, de Oliveira GL, Accurio Fde A, et al	Cochrane Database Syst Rev. 2014 Oct 16;10: CD005991	create date:2014/10/16	2011	2011													
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	b) Abstract screening										c) Research categorization					
	Records found	Duplicates	INCL_1	EXCL_1a1_ORCID_1a4	EXCL_1a2_ORCID_1a4	EXCL_1a3_Orphan	EXCL_1a4_Orphan	EXCL_1a5_Orphan	EXCL_1a6_Orphan	EXCL_1a7_Orphan	EXCL_1a8_Orphan	Type of economic research	EXCL_evidence2	Research objective	EXCL_1a9_Orphan2	INCL_3
First search	1028	322	706	146	21	199	68	8	73	16	175		125		109	29
Update	137	72	165	33	1	82	14	0	14	0	30		22		16	3
Overall	1265	394	871	169	23	281	82	8	87	16	205		147		124	31

Sequential text (no double entries) EXCL\_2 666 Parallel text (double entries) EXCL\_1 124

