**Variations in External Reference Pricing Implementation – Does it Matter for Public Policy?**

Jennifer Gilla\*, Anna-Maria Fontriera, Dionysis Kyriopoulosa & Panos Kanavosa

Author Affiliations: a Department of Health Policy and LSE Health - Medical Technology Research Group, London School of Economics and Political Science, Houghton Street, London, WC2A 2AE, UK

\*Corresponding author:

Dr Jennifer Gill

Department of Health Policy

LSE Health - Medical Technology Research Group

Cowdray House

London School of Economics and Political Science

Houghton Street

London WC2A 2AE

UK

Tel: +44 (0)20 7106 1195

Email: J.Gill7@lse.ac.uk

**Abstract**

**Background** - External reference pricing (ERP) seeks to rationalize prices and contain costs by using foreign prices as a reference for the determination of domestic prices and is often used as the starting point for the facilitation of negotiations between health authorities and pharmaceutical manufacturers.

**Methods** - A systematic literature review was used to identify characteristics of ERP implementation across 29 countries. Primary data collection, in the form of surveys directed at key stakeholders, were also used to supplement data in instances where information received from the systematic literature review was outdated or minimal. Findings from the systematic literature review and primary evidence from key stakeholders were bench-marked against 14 best practice principles inherent to an optimal ERP system.

**Results** - Significant heterogeneity in ERP implementation across countries was identified. Country basket size, pricing calculation, frequency of price revisions varied between countries. Belgium, France, and South Africa were more likely to adhere to the best practice principles whilst Bulgaria, Hungary and Romania had the most instances of non-adherence.

**Conclusion** - The observedheterogeneity has policy implications for governments including globally declining pharmaceutical prices, launch delays in lower-income countries, reduced incentive for continued R&D and reduced access to medicines. Overcoming this issue to ensure that ERP is beneficial to all stakeholders will require a focus on developing sustainable, transparent, simple and stable systems using a set of key guidelines that should maximise the benefits of the pricing policy.

**Key Words:** External reference pricing; Pharmaceutical policy; Regulation of Pharmaceuticals; Systematic Review; Expert consultation.

**JEL Classification:** I, I1, I10,I11, I18

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**Background**

External reference pricing (ERP), also known as external price referencing or international price comparison/ benchmarking, is a commonly used pricing policy with high global research interest. Officially defined as “*the practice of using drug prices in several countries to derive a benchmark or reference price for the purposes of setting or negotiating prices in countries*” [1-3], the primary aim is the control of in-patent drug prices [4] via the containment of pharmaceutical prices and expenditure [5]. The widespread use of ERP is generally a result of government cost control requirements with authorities using prices from other settings to evaluate the fairness or appropriateness of the actual price related to comparative cases [6]. The actual process of ERP implementation varies significantly between countries [7]. The size of the country reference basket used, the method of price calculation and the type of country used in the basket can all differ between countries which can impact price levels and price containment achieved.

One of the most significant concerns around the use of ERP is related to the fact that it could lead high-income countries to demand low prices enjoyed by the lower-income countries they reference, creating difficulties for the latter. ERP-related price leakages can trigger a manufacturer to set either a single price or narrow band of prices before launch takes place. Whilst in the short run imported lower prices may be beneficial in high-income countries, in the long run, lower revenues can lead to reduced return on R&D investment and consequently fewer new medicines [8]. Furthermore, marketing authorization holders may initially prefer to promote their products to high-price countries rather than low-price countries so that these high prices are used as reference in countries performing ERP [9]. At the same time, the accuracy of international comparisons may be distorted due to methodological issues and differences across countries in strength, formulation and pack sizes available [10]. ERP assessment is considered complex compared to other pricing methods. The promotion of transparency around the use of ERP may improve the accountability of decision-making, which could reduce uncertainty for manufacturers and eliminate discrimination and corruption [7].

Via a combination of primary and secondary evidence the present study aims to contribute to the review, analysis and body of evidence around the variety of ERP methods and techniques implemented by 29 countries: Austria, Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Turkey, Brazil, Egypt, Jordan, Kuwait, Lebanon, Qatar, Saudi Arabia, South Africa, South Korea and United Arab Emirates. To determine the quality of ERP systems implemented by the countries of interest we benchmark findings from a systematic literature review and primary evidence from key stakeholders against 14 best practice principles that an ERP system should follow [11]. Whilst previous studies have aimed to review different methods of ERP implementation across countries, to our knowledge this is the first time that literature review data has been combined with primary evidence from key experts and then used to benchmark these different methods of implementation against a set of best practice principles.

**Methods**

The primary aim of this study was to identify the characteristics of ERP implementation across countries in order to inform subsequent discussion and analysis. Relevant evidence was collected based on both primary and secondary sources. The evidence base covered 29 countries that were known to implement ERP during the 2000-2016 period. Secondary sources of evidence comprised a systematic literature review, including peer-review studies and grey literature using a set of pre-determined endpoints to investigate practices. The resulting impact, both within and across country borders, was also analysed, although this information is presented in two accompanying studies [12,13]. Evidence from the literature was validated and complemented via primary data collection from key stakeholders across all 29 countries.

**Study endpoints**

A number of defined endpoints relating to the structural elements of ERP were analysed (see Table 1). The main role of ERP in each country of interest was examined in order to determine cross-country differences in application. We also investigated the role of stakeholders in the design of ERP systems and their involvement in any appeals processes. The number of basket countries and the criteria used for their selection was also evaluated alongside the methods used for price calculation. The role of the patent status and innovation was taken into account. Furthermore, investigation around the inclusion of wealth adjustments, price revisions and exchange rate fluctuations was necessary given their impact on price determination [14]. The sources, dissemination and accessibility of price data were also assessed as key issues in price setting. As far as interaction with other policies is concerned, the alignment of the pricing process with the reimbursement process was examined and the combination of ERP with different negotiation tools for reimbursement was used as an endpoint. The interaction of other pricing processes such as value-based pricing (VBP) and health technology assessment (HTA) with ERP was also examined.

<Table 1 about here>

**Systematic literature review**

The systematic literature review methodology was based on the Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews in healthcare.

*Inclusion criteria (country selection and study period)*

The study countries were Austria, Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Turkey, Brazil, Egypt, Jordan, Kuwait, Lebanon, Qatar, Saudi Arabia, South Africa, South Korea and the United Arab Emirates, all of which are known to have implemented ERP at some point [15,14,16-19]. Whilst initial searches were not restricted in terms of country, in order to ensure that evidence was representative of a wide geographical range, once the search was concluded the study was limited to the countries mentioned above.

The study period for inclusion of relevant published material was from January 2000 to December 2016. The year 2000 was selected as the start date because countries started to implement ERP in the late 1990s. As a result literature describing these processes is thought to have been available from 2000 onwards.

*Identification of evidence*

Seven electronic databases (Web of Science (WoS), CINAHL, EconLit, MEDLINE, ProQuest, Cochrane Library and Scopus) were searched for peer-reviewed literature. A combination of broadand policy keywords were used to ensure that all relevant literature was captured. All synonyms and different phrasings of External price referencing were included in the search. The search run was (“Pharmaceutical Price Regulation” OR “Pharmaceutical Regulation” OR “Cost Containment” OR “Pharmaceutical Pricing” OR “External Price Referencing” OR “External Price Referencing” OR “International Price Comparisons” OR “International Reference Pricing” OR “International Price Referencing”) AND (drug OR drugs OR medicine OR medicines OR pharmaceutical OR pharmaceuticals) AND (Austria OR Belgium OR Bulgaria OR Czech Republic OR Estonia OR France OR Germany OR Greece OR Hungary OR Italy OR Latvia OR Poland OR Portugal OR Romania OR Russia OR Slovakia OR Slovenia OR Spain OR Turkey OR Brazil OR Egypt OR Jordan OR Kuwait OR Lebanon OR Qatar OR Saudi Arabia OR South Africa OR South Korea OR “United Arab Emirates” OR UAE). The search was restricted to keywords present within abstracts only, to limit the number of irrelevant papers being returned, and articles in English.

In order to minimize bias and to capture all relevant information a targeted and comprehensive search of the grey literature was also conducted using the WHO, the WHO Collaborating Centres for Pharmaceutical Pricing and Reimbursement policies, the OECD online databases and the European Commission to ensure that no valuable reports were excluded. The keywords used to search these were “External price referencing” OR “External Price Referencing” OR “International Reference Pricing” OR “International Price Referencing”. Relevant information was recorded and combined with the results of the systematic literature review.

*Study selection, data extraction, evaluation and synthesis*

Identified articles were selected according to a four-stage process as outlined in Figure 1. In the first stage, all titles and abstracts were reviewed. Abstracts that were not relevant to the topic were excluded. In the second stage articles that were not in English or did not relate to one of the pre-determined study countries of interest were also excluded. In the third stage full-texts were assessed for eligibility based on the mention of ERP implementation in relation to one of the pre-determined study endpoints (Table 1). In addition, relevant studies identified from reference screening and grey literature were incorporated at this stage. Finally, in the fourth stage, full articles were reviewed and relevant data was extracted. An Excel template listing the study endpoints was used for data extraction. Data were extracted in free text form in order to avoid loss of information. Results from other systematic literature reviews were included if the selected endpoints of interest in those reviews were different to the respective endpoints of interest in the present study in order to minimize result bias. A comprehensive synthesis of the literature was carried out to identify key trends related to ERP implementation across countries.

**Primary Data Collection**

Upon analysis of the data retrieved from the systematic literature review it became obvious that in some cases the data was not conclusive, was potentially outdated and may not have reflected actual practice. As a result, primary evidence was used to validate and supplement information from the systematic literature review. A short survey was sent to at least one key stakeholder in each of the 29 countries of interest between January and July 2017.

Stakeholders were affiliated with national competent authorities (regulatory bodies, ministries of health, health insurance organisations, reimbursement committees), academic and research institutes and the pharmaceutical industry. The survey focused on the salient features of ERP and was divided into four areas. These were: (i) Objectives and Scope of External Price Referencing Systems; (ii) Administration and Operations; (iii) Methods for the Conduct of External Price Referencing; and (iv) Implementation of External Price Referencing.

*The 14 best practice principles for Benchmarking*

To increase our understanding of the ERP-related performance of the countries in question, findings from both the literature review and survey were bench-marked against a framework of 14 best practice principles thought to be valuable for an optimal ERP system [11]. These 14 principles emerged as a method for approaching the issue of heterogeneity in ERP systems in a non-partisan, systematic way. In doing so, the authors built on work by the WHO, which analysed the pros and cons of various ERP features [5], utilising both analysis of relevant literature as well as stakeholder input from countries implementing ERP in 2013 (when the work was conducted), to refine a larger set of potential principles to a list of 14 key principles described in more detail below. The 14 principles are organized into four sections which mirror the four sections of the survey used in this study. The principles are shown in Box 1.

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| **Box 1****The fourteen best practice principles for Benchmarking**1. **Objectives and scope of external price referencing system**

***ERP system objectives should be clear and align with country specific health system objectives***: Outlining the objectives scope and monitoring mechanisms are important first steps in ERP system design. They should be contained within a scoping document, should be legislated and routinely reassessed. Health system goals should also be considered so that the ERP system functions cohesively and does not focus too narrowly or on the short-term only. ***ERP systems should focus on in-patent products considered for the purposes of coverage, pricing and reimbursement decisions***: Without external controls, the relative lack of competitive forces for newly launched, in-patent pharmaceutical products can result in very high prices. With this in mind, ERP is most appropriately applied to in-patent pharmaceuticals. Off-patent pharmaceuticals are naturally subject to greater competitive forces, which drive down prices. In addition, there are other mechanisms available for directly or indirectly influencing prices of off-patent pharmaceuticals, such as price capping or internal price referencing, the latter being used extensively to set a price ceiling on reimbursement. ***Prices developed using ERP should not override conclusions of HTA or VBP approaches***: Several countries utilize ERP as an adjunct to explicit methods of value assessment (e.g. cost-effectiveness analysis). In principle using multiple approaches should be encouraged. However, some approaches, such as health technology assessment (HTA) and value-based pricing (VBP) have a stronger theoretical underpinning, in that they directly consider the overall value of a pharmaceutical agent to a population in order to make coverage decisions and determine prices. Therefore, ERP-based prices should not override those developed via other more robust evidence-based approaches, if they disagree. 1. **Administration and operations**

***The ERP system should have administrative simplicity and transparency***: Simple and transparent systems are easier to manage, less prone to manipulation and easier to audit, which means that fewer resources will be required in order to establish and maintain them and, through that, efficiency can be improved. Uncertainty surrounding pricing mechanisms may cause suppliers to delay or even prevent entry into certain countries. In addition, price negotiations will likely be more straightforward if all parties concerned clearly understand the country’s pricing mechanisms, especially if these prices are strictly enforced. ***Stakeholders should participate in the design and review of the ERP system***: Stakeholders representing a wide variety of interests, including patients, health care professionals, industry and academic experts, should be consulted in the design of the ERP system and periodic input from these groups should be requested to ensure that the system remains relevant. At a minimum, stakeholder feedback should be elicited on the scoping document or the draft legislation. Involving a variety of stakeholders can result in a system that best balances the needs and concerns of all groups involved and can also lead to greater transparency and decreased uncertainty. ***Stakeholders should be able to appeal regulator decisions***: A process should be developed and opportunities should be provided for stakeholders to appeal pricing decisions made explicitly using ERP. Allowing for appeals with a finite timeline is essential, given the inherent uncertainty in prices developed via ERP. The appeals process may also illuminate issues with the ERP system’s design or management and will allow extenuating circumstances to be presented and considered. ***Reference countries should be selected based on similarities in economic status and health system objectives***: Selecting reference countries with a similar economic status and health system objectives increases the likelihood of arriving at appropriate price levels, which align with other healthcare decisions made within the country. Demanding the same price in lower-priced markets as in higher income markets could cause innovative pharmaceuticals to become prohibitively expensive for low- or middle-income countries; the remedy in this case includes the use of purchasing power parity- (PPP) based exchange rates or wealth adjustment based on per capita income adjustments. In addition, heavily referencing lower-income countries could lead pharmaceutical companies to delay launches in those countries. ***International implications of ERP implementation should be considered***: The wide use of ERP often has a number of unintended consequences internationally, which may have broader impact. Worldwide decreases in drug prices may lead to decreases in research and development of new products. The value of pharmaceutical innovation to the healthcare system should always be considered and reflected in drug prices which will require systems to consider the international implications of their pricing policies. 1. **Methods for the conduct of external price referencing**

***Publicly available ex-factory prices should form the basis of the ERP system***: Ex-factory prices are most reflective of actual prices compared to retail or wholesale prices, which incorporate additional costs; these costs vary across countries and usually are subject to national regulatory practices. Using publicly available sources to locate price information is ideal because it encourages transparency. ***The mean of prices in reference countries should be used***: Most ERP systems use the mean, median or minimum price of referenced countries when developing a national target price. Assuming that reference country selection is based on similar economic status and health system objectives, using the minimum price is generally not appropriate, since countries with the lowest prices may have unusual public health or economic circumstances, which could justify a lower price. Therefore, an average price rule should form the basis of ERP systems with the median being used if outliers are a concern. ***Patent status should be respected***: When determining target prices for in-patent products, whose patents may have expired in one or more reference countries, referring to prices of off-patent products within the reference countries should be avoided. Ignoring patent protection may lead companies to avoid launching in certain markets, which would decrease access in those regions. ***ERP formula should avoid the impact of exchange rate volatility***: Exchange rates can vary dramatically over time, so using an exchange rate at a single time point may result in unstable or perverse price estimates. To avoid this, using a moving average of the exchange rate, is suggested. European Economic and Monetary Union (EMU) countries could also consider excluding non-euro currencies, to avoid volatility. As exchange rates do not completely adjust for a currency’s purchasing power, countries could consider using purchasing power parity (PPP) exchange rates or wealth adjustments in the actual country relative to its comparators.1. **Implementation of external price referencing**

***Price revisions should be kept to a minimum and should be carried out consistently to avoid the perception of opportunistic behavior***: Price revisions should occur on an infrequent but scheduled basis and the schedule should be made public to ensure transparency and fairness. Typically, price comparisons would take place at launch, and price revisions could take place perhaps once annually to ensure stability, predictability and administrative simplicity, whilst reducing uncertainty. ***ERP-based prices should be aligned with other tools used when negotiating reimbursement***: Many countries utilize price setting through ERP as an adjunct to other methods of value determination and risk management including HTA and managed entry agreements. Countries entering into these arrangements will need to consider how the prices developed using ERP align with such agreements. Countries with value-based pricing systems should proceed with caution in their thinking about introducing ERP, since potential reference countries may not be establishing prices based on product value.  |

Source: The authors, adapted from [11].

**Results**

Figure 1 shows a flowchart of the review process and the respective number of articles in each stage. The database search yielded 6,877 peer reviewed and grey literature studies whilst additional sources provided by our network numbered 143. Following removal of duplicates 3,979 studies were screened based on relevant titles and abstracts. Of these, 549 studies were identified as potentially useful and read in full to assess for eligibility. The remaining 283 texts were then assessed for strength of evidence. The content of 48 studies were finally used to inform the findings. Respondents from 20 countries (Belgium, Brazil, Bulgaria, Egypt, Estonia, France, Germany, Greece, Hungary, Italy, Jordan, Latvia, Poland, Qatar, Romania, Russia, Slovakia, Slovenia, South Africa and Spain) completed the survey. Two respondents contributed on behalf of both Brazil and Hungary whilst only one respondent supplied information from each of the remaining 18 countries. Respondents were asked to provide evidence, and their personal perspective, on the implementation of ERP within the countries they were responding on behalf of. It is important to highlight that the responses of the experts represent their personal view and not the view of their institution. In this paper, stakeholders’ responses in the survey are referred to as ‘Survey of key experts on the regulation of medical technology’ [20].

A combination of both primary and secondary evidence is presented in this section. When evidence from the systematic literature review was used, primary data were used to validate the findings. In cases where minimal or outdated evidence was drawn from the systematic literature review, primary data was used to draw conclusions. The evidence shown in the tables throughout the remainder of the results section refers to the latest available source.

<Figure 1 about here>

**Objective of ERP and alignment with health system objectives**

Generally, ERP has three main aims [21]: (a) negotiate or set prices within a country, (b) negotiate coverage and reimbursement and (c) authorize product marketing. The use of ERP has increased significantly as a price control method [22] in in-patent medicines and as a cost containment measure due to issues like the global financial crash in 2008, increases in life expectancy and increases in the prevalence of chronic conditions [16].

Most countries studied used ERP in order to set low domestic prices to limit pharmaceutical spend. Greece implemented price controls through ERP to limit pharmaceutical and budget spending [23], Turkey introduced ERP in 2004 in order to control pharmaceutical expenditure [24], Slovenia uses ERP as a tool to regulate the growth of public and private drug expenditure [25], and in 2010, Russia promoted ERP to regulate prices [15]. In Spain, ERP was implemented to control drug prices for which there are no alternatives available on the market [16]; Latvia implements ERP to reimburse drugs at manufacturer prices [26]; and in Bulgaria, ERP aims to estimate a ceiling price for innovative and generic prescription drugs [27].

However, complicated interrelations between countries can lead to issues around the achievement of these low prices [28] due to variations in the basket of reference countries, the type of price compared, calculation methods employed, exchange rate fluctuations and data availability [3]. Two other studies in this series examine the impact of variations in ERP system design within- and across-countries on a number of different endpoints including pharmaceutical price levels, launch delays and price convergence [12,13].

**Characteristics of products subject to ERP price regulation**

There are a number of variations in terms of the type of medicines subject to ERP systems. For example, the system can focus only on in-patent, originator drugs that are reimbursable (included in the national positive list), or, less commonly, on off-patent, generic drugs that are paid out of pocket. Generally the use of ERP is limited to originator products [17,1] but it can be applied to all marketed medicines, or particular categories of medicines such as reimbursable medicines, prescription-only medicines or innovative medicines [3,1] (Table 2). The rationale for limiting ERP to in-patent medicines is twofold: first, there are more dynamic and effective methods to enhance competitive prices in the off-patent market and, second, price comparisons between in-patent and off-patent drugs may undermine patent protection and intellectual property characteristics.

Whilst there is some evidence describing the type of medicines covered by ERP policies in individual countries, ERP implementation mainly relates to reimbursable medicines (Table 2) [29]; Bulgaria, Romania, Slovenia and Poland set prices for generic prescribed drugs based on international reference pricing policy [27]; Latvia, Poland and Austria use reimbursed drugs [7].

<Table 2 about here>

**The use of ERP as the main or supportive tool in pricing**

Results show that 16 of the countries of interest use ERP as their main pricing policy, with the remaining 13 using ERP as a supportive tool, or additional criteria, with which to trigger or conduct negotiations rather than set prices (Table 3).

In Europe an increasing number of countries of interest tend to use ERP as a supportive or supplementary tool. This is the case in Belgium [14], Poland [30], Spain, Estonia, France, Germany, Hungary, Latvia and Russia. Notable exceptions, where ERP is still used as the main method for price setting are Austria, Czech Republic, Greece, Portugal, Romania, Slovakia, Slovenia, and Turkey. Bulgaria and Portugal have been using ERP as the main method for price setting, but have recently moved to implement HTA based on cost-effectiveness principles as one of the main criteria in determining price and reimbursement but ERP is still a key criterion informing prices. In Italy, the original role of ERP has changed from being the main method of price setting to a supplementary role taken into account when conducting negotiations between industry and the Italian Medicines Agency [31,32]. This increase in the ‘supportive’ role of ERP highlights the limits of its effectiveness as it is based on list prices rather than net prices.

## Presence of appeals process for stakeholders

Limited information on the presence of an appeals process for stakeholders was highlighted via the systematic literature review. Information was only isolated in one country – the Czech Republic, where in June 2008 a newly implemented ERP system set maximum prices for 3,944 products. As a result, at the end of 2008, price cuts led to a number of appeals by industry due to distortion in price regulation [33]. Expert opinion and survey data suggest that most European countries, either directly, or indirectly, do have appeals processes in place, whereby manufacturers are in a position to appeal if they feel that a price is wrongly ‘constructed’ based on national ERP principles [20] (Table 3). This can be done formally (and forms part of a statutory process, or informally, through an appeal to competent authorities. If the former, there are strict timelines for processing the appeal.

<Table 3 about here>

**Number of basket countries and frequency of price revisions**

The number of countries in a basket, and the specific countries chosen, can have a significant impact on resulting drug prices [34] - a small number of reference countries could give significant weight to few countries whilst a large basket size can increase administrative difficulty without necessarily adding any value.

EU members generally elect to use a reference basket that contains 5 to 20 countries [4]. Table 4 (adapted from Kanavos et al., 2010 [21] and Toumi et al., 2014 [14]) highlights the size of country baskets in European countries and the number of times each country is used as a reference in the basket of another country. In recent years there has been a trend to increase the basket size [35], potentially as a means to reduce medicine prices further. The number of basket countries quoted incorporates all countries where list prices may be used. In some instances countries chose to pick only the lowest priced of these ‘basket countries’, or the average of some number of these countries. However, the number of basket countries includes all countries that may be used.

Austria expanded its basket of countries from 14 to 24 countries, while the Czech Republic used only 8 countries until 2009 [17]. In recent years, Greece has increased its basket to all EU countries in order to achieve further reductions in pharmaceutical prices in response to the financial crisis. Other countries have also increased or have expressed interest in increasing the number of reference countries they use: Slovakia (from 8 countries in 2009 to all EU members recently) and Latvia (which is carrying out negotiations for the expansion of the number of reference countries used).

France, Germany and the UK are the most referenced countries, because they launch drugs early and the latter two employ free pricing methods for in-patent drugs [6], with Germany deploying complete pricing freedom during the first year of a new medicine’s introduction [36] and the UK allowing free pricing subject to profit control based on the Pharmaceutical Pricing Regulation Scheme (PPRS) [37].

Alongside the number, and choice, of countries, in the basket the frequency of price revisions can affect the prices derived using ERP. Many EU countries have a legal framework that calls for price renewals on a regular basis with regular intervals lasting from three months to five years [16]. Frequent price revisions may distort the role of the market, as they may reduce predictability and produce errors, especially when large baskets of countries are used [2]. Nevertheless, the appropriate interval of price revisions depends on the respective national policy [3] and there is significant variation in the rate of price revisions (Table 3).

<Table 4 about here>

**Criteria for basket country selection**

In terms of basket content, countries mainly take into account the following components to create a basket: (a) geographical characteristics, (b) financial similarity [38], (c) availability of price data, (d) public health status and health insurance and (e) investment and contribution of pharmaceutical industry in financial performance.

There is limited information on the criteria that most countries use to choose their basket. Most EU countries use other EU members as reference [6]. For instance, the three Baltic countries (Estonia, Latvia and Lithuania) use each other in their reference baskets as they have common socioeconomics factors [39,40], while northern and southern EU countries follow a similar trend [3]. Nevertheless, there are some examples such as Brazil, South Africa, Jordan and Lebanon, which implement ERP based on both EU and non-EU countries [4]. In Poland, GDP of countries is considered as an important factor to determine the reference basket.

**Type of comparator prices used in ERP**

ERP is generally based on officially published prices. Since price negotiations and discounts are kept confidential within a country most countries will be using reference prices that may be higher than the negotiated price enjoyed in the reference country. Most countries use ex-factory prices in their international comparisons [18], because this helps minimize price deviations that may arise due to differences in distribution mark-ups [41]. The implementation of ERP using the ex-factory price is considered to be more suitable than other methods, for example, using the wholesale price, as distribution margins and tax rates are different across countries leading to difficulties in international comparisons [2]. However, there are some countries that use the wholesale price and some that use the pharmacy retail price [7] (see Table 2).

**Method of calculation of reference price**

Some studies have argued that an average price-based calculation should be used to enhance fairness of ERP [2]; however, most countries studied in this paper used a lowest basket price-based calculation, or an average of the *n* lowest prices based calculation. Only Austria, Belgium, Italy, Jordan and South Korea [17,42,43,20] used the average basket price, although the implementation of ERP has ceased in Italy and only has a marginal role in Belgium.

**Sources of information for pricing decisions**

The implementation of ERP requires access to price information which should be publicly available and reliable. Non-availability, price heterogeneity, non-reliability and a lack of transparency can reduce the effectiveness of ERP [16]. Many countries support free access to price data, although the extent that different stakeholders contribute to the accessibility of information varies across countries (see Table 5). Generally, in EU countries the necessary price data is provided by the marketing authorization holder, public and information sources, although some countries also use information from confidential sources such as EURIPID [44].

<Table 5 about here>

**Inclusion of wealth adjustments in ERP calculations**

Whilst most countries reference those with similar economic criteria there are cases of countries referencing those with a higher GDP – for example Bulgaria, with a GDP of $6,819 references France, Spain and Italy [3]. In principle, countries can account for differences in GDP by making wealth adjustments based on Purchasing Power Parity (PPP) or GDP growth. However, evidence shows that none of the studied countries perform such adjustments meaning that countries referencing those with higher GDP than themselves may be exposed to artificially high prices and vice versa. Slovenia had originally implemented a price adjustment based on GDP differential and applying a 15% discount to the average price derived from Italian, Austrian and German prices, but this is no longer the case. Germany reports that a formal weighting of prices by the estimated yearly turnover of a pharmaceutical and PPP of other countries could be applied.

**Accounting for exchange rate fluctuations**

If countries reference those with different currencies then exchange rate fluctuations can influence the calculated reference price [21]. If weaker currencies and/or poorer countries are used in the reference basket, a downward adjustment is usually seen as exchange rates are used to contain prices. In Estonia, valid exchange rates are taken into account in the price calculation [40]. In the Czech Republic, price estimation is based on the average exchange rates for the three months prior to the review [33] and similar is the case in Greece, while in Jordan, exchange rates are taken into account due to possible price changes [2]. In Turkey, which references Portugal, Spain, Italy and Greece, reference prices are converted to 70% of the previous year's average exchange rate between the euro and the Turkish lira [24]. In contrast Saudi Arabia is one of many countries that do not consider exchange rates in price determination [45] and take current exchange rates. Some countries in the Eurozone, notably Spain, have moved to using Euro only countries in their reference basket to avoid multiple currencies and decrease price fluctuation.

**Link between (list) price and reimbursement**

ERP can be aligned with the reimbursement processes to contribute to price reduction [21] (Table 5). Concerns arise from the determination of reimbursement prices using ERP. These concerns centre around the “appropriateness” of chosen reference countries (for example, countries with higher levels of GDP or bigger markets), and the confidentiality of negotiated prices in the reference. In Slovenia the introduction of ERP is an additional tool to improve the drug reimbursement system [25]. In 2011, Slovakia introduced pharmacoeconomic analysis of publicly reimbursed drugs to control pharmaceutical expenditure in parallel to ERP [46].

**Interaction of ERP with HTA and VBP**

ERP implementation can limit the ability of other methods to regulate drug pricing [47] and any combination of approaches can present difficulties when determining the most effective pricing policy. ERP does not take into account the role of VBP, which is related to the contribution of drugs to patients’ health and society [2]. This is because ERP is often thought of as a more technical and administratively complex process than VBP, due to the requirements of large amounts of price data [48]. In addition, the value of drugs, which is considered under VBP, can differ across countries [42]. The alignment of the two methods is complex as price determination should be based on value, which is subject to various assessments [14].

As far as price setting based on HTA recommendations is concerned, its inefficient implementation may lead to ERP use, ultimately aiming to contribute to drug spending control. The final assessment of HTA and the outcomes of cost-effectiveness analysis (which are supposed to reflect society’s willingness to pay) may not be taken into account due to the parallel use of ERP [47].

**ERP alignment with other negotiation tools of reimbursement**

The use of ERP can facilitate the negotiation and reimbursement processes [1]. It is generally seen as one of the criteria used in price negotiations, with other criteria including clinical efficacy, budget impact, a form of cost-effectiveness analysis and R&D expenditure [21], [49]. In Italy and Estonia, pricing negotiations and reimbursement processes are based on a combination of ERP and internal reference pricing [32,40]. In France, Italy and Spain, ERP operates as a criterion in negotiations between authorities and industry for innovative drugs of high therapeutic value [4], whereby the price in these countries cannot exceed the average price determined by their respective baskets. Countries and health authorities may apply some informal evaluation methods for reimbursement, while other governments can use different ERP designs to enhance negotiations with the in-patent drug industry [50,7].

**Link between ERP regulation and patent status**

Countries should take into account the value of innovation in ERP design. Drug authorization and patent-expiry vary across countries and thus the same product can be in-patent in one country and off-patent in another at the same time. In most cases, when a drug loses patent protection the price is reduced compared to its in-patent price. Therefore, it is possible that a country where the drug is still in-patent is using reference prices from a country where the drug has lost its patent protection and is therefore cheaper. This could lead to artificially low prices in the referencing country which could lead to spillover effects such as parallel trade. Evidence in the literature on whether ERP respects the patent status is scarce to non-existent, however, it has been recorded that the Czech Republic does not take into consideration the patent protection status in the comparison of drugs [51], which was confirmed in the stakeholder surveys [20]. Estonia, Portugal, Slovakia, Egypt, Brazil and Russia have also been reported to take the cheaper or generic product price to inform their basket.

**Country Adherence to 14 Best Practice Principles**

Using the latest evidence drawn from the systematic literature review and the results from primary data collection, we analysed the extent to which the 29 countries of interest followed the 14 best practice principles (Table 6). It emerges that none of the countries in question seemed to follow all 14 of the principles with most not using the mean price of the basket and an administratively simple and transparent system which involved stakeholder participation. Most countries use the lowest price in the basket, or the average of the lowest *n* prices, have large baskets, reducing administrative simplicity. Similarly, whilst external stakeholders may be consulted, their contribution to the actual decision-making related to ERP is practically null, it is an administratively driven process that excludes active participation by stakeholders. Belgium, France, and South Africa adhered to the most principles whilst Bulgaria, Egypt, Hungary and Romania had the most instances of non-adherence. Most countries adhered to using ex-factory prices, aligning ERP systems with negotiation tools and keeping price revisions to the minimum.

<Table 6 about here>

**Discussion**

The objective of this study was to analyse ERP implementation in different geographical jurisdictions and to determine levels of interaction between ERP and other pricing and/or reimbursement policies. Systematic literature review evidence was validated and supplemented with primary evidence from stakeholders in 20 of the 29 countries of interest with primary evidence missing from Austria, Czech Republic, Portugal, Kuwait, Lebanon, Saudi Arabia, South Korea, Turkey and UAE.

This evidence-base has enabled us to analyse specific endpoints related to ERP design and implementation. The analysis has highlighted significant heterogeneity in the salient features of ERP across the 29 countries of interest. Such variations may be the result of the different health system policy objectives in individual countries, differing health requirements, different working budgets, and different pricing policies. Differences in the perception of the value of innovation and of the importance of R&D may also result in such variations in the ERP design, some of which could be suboptimal.

There are a number of policy implications resulting from some of these potentially suboptimal practices included in certain ERP systems such as launch delays in low-income countries, parallel trade reducing drug stock levels, inflated prices in low-income countries, downward convergence in pharmaceutical prices, the likelihood of reduced incentives for continued R&D and reduced access to medicines in some regions. During the design phase of ERP governments are likely to focus on the short-term financial gains that could be the result of a newly implemented ERP system that uses a “lowest price in the basket” style calculation. However, such decisions could negatively impact healthcare systems in the long term.

These issues may be the result of “path dependence”, for which ERP has been criticized, i.e. the features of the ERP system influence the overall outcome achieved [21,52,16]. For instance, regular price revisions can lead to greater short-term cost-containment, due to lower price levels in a country. The level of price reduction also depends on the countries selected for the basket and the price considered in the basket.

In a simulation exercise by the European Commission, it was shown that more frequent price revisions resulted in higher healthcare savings. In this scenario, the European Commission tested the extent of the price reduction if all countries re-evaluated their prices every six months. This resulted in a decrease of about 6% on the average medicine price in all 28 European countries [3].

Basket country choice can impact the effect of ERP. In Slovakia, ERP tends to result in higher prices relative to neighbouring countries, with similar income levels. Slovakia uses the German price and the price of the originator country to calculate their reference price, but Germany tends to have higher ex-manufacturer prices and the country of manufacture tends to be a high-priced country. As a result of these apparent high prices, in 2009 Slovakia began calculating reference prices using the mean of the six lowest-priced countries across Europe [53,17].

Such changes to EPR implementation can have implications for market access within the country. For example, in Slovakia following the 2009 change manufacturers began either disregarding the newly implemented prices or lobbied for exemptions of their products, leading to access delays [17]. Such market access issues are most likely to occur in countries that are highly regulated and/or small markets. Markets with flexibility on pricing, or markets that are large in size, with higher GDP, increased public healthcare spending, a higher percentage of GDP on health expenditure and a higher price level of pharmaceuticals are less likely to suffer from reduced availability [7,54]. For example, out of 15 European countries, Germany, where pricing is not regulated at ex-factory level, had the highest pharmaceutical prices and availability [52].

Over and above the impact of ERP design within a country, the policy can have cross-border spillover effects. These include price instability, launch delays, unwillingness of manufacturers to launch in low price countries and price convergence towards the international average. ERP design determines whether price convergence results in higher or lower prices but the trend appears to be for convergence to the lowest rather than the average. Larger baskets, and an increase in basket size over time, are associated with some price convergence between European pharmaceutical prices [35,52,55]. It has also been argued that ERP can lead to a downward price convergence in Europe when the lowest price in the country basket rather than the average price is used to calculate the reference price [14].

The path dependent nature of the process means that design can go some way to alleviating the issues discussed above. Countries should be encouraged to design systems that both work for them, but also promote industrial policy and follow key design principles.

A specific set of 14 best practice principles have been proposed as a method for approaching the issue of ERP heterogeneity in a non-partisan, systematic way [11]. Despite the existence of these best practice principles our analysis shows that none of the 29 countries of interest follow all available principles. Belgium, France, and South Africa seemed to adhere to most principles – an average of ten principles each, although, of course, the importance of ERP has become secondary in Belgium and France over time. Overall within Europe, countries tend to follow around half of the principles, with low income countries such as Hungary, Romania and Bulgaria reducing the average price in a quest to reduce the prices of medicines in their countries. The lack of adherence to these principles suggests that many of the ERP systems in place are sub-optimal, could be having a negative impact on the effectiveness of the systems and could adversely affect access.

There are some potential methodological limitations in our analysis. Literature was identified from online databases, where the results were limited to the English language. As a result, relevant studies published in a language other than English could have been excluded. Furthermore, as pharmaceutical pricing policies are constantly undergoing changes and being updated, the evidence presented in this study may not reflect the policy landscape in future years. However, this study provides a benchmark at a specific point in time for further comparisons to be undertaken in the future.

**Conclusion**

This study aimed to identify detailed evidence on the methods by which ERP is implemented in 29 countries using a systematic review process combined with a survey of key informants. Of these 29 countries, 17 were EU member states with the remainder being from the Middle East, Latin America, Africa and Asia.

Our findings showed that there is significant heterogeneity between countries in terms of the design of their ERP systems. Subsequent analysis highlighted that none of the countries in question adhered to the 14 best practice principles thought to form an ‘optimal’ ERP system. There are a number of policy implications arising from heterogeneity and suboptimal practices, particularly when countries focus on using lowest price calculations and high-income countries reference lower priced countries with no wealth adjustment. These practices could undermine any potential beneficial ERP effects for government payers such as cost-containment and low pharmaceutical prices. Suboptimal practices can cause spillover effects such as launch delays in low-income countries, inflated prices relative to GDP in some countries, globally declining pharmaceutical prices, reduced incentive for continued R&D and reduced access to medicines in some regions. This is in direct contrast to the aims of ERP.

Rapidly evolving healthcare costs and increases in life expectancy and chronic disease prevalence mean that reduced drug prices are the ultimate aim for most country governments. But, carelessly employed ERP, which could be detrimental to all stakeholders, should be avoided. ERP systems should be designed with both health and industrial policy aims in mind. Schemes have to represent the requirements of all stakeholders including patients, manufacturers and governments in order to ensure that patients get access to well-priced medicines as and when required, governments can spend within their means and manufacturers have enough incentive to continue investing in future R&D in order to benefit future patient populations. Developing such a system will require input from all actors during the design and review of ERP systems.

Results from this study have shown that heterogeneity and suboptimal ERP practices can have detrimental effects for all stakeholders. Overcoming such issues in a non-partisan, systematic way can be achieved using the set of 14 best practice principles discussed here. By following such guidelines, it is hoped that ERP systems that are of benefit to all stakeholders and lead to fair pricing and equitable access to health technologies, whilst improving the sustainability of pharmaceutical pricing practices and encouraging innovation, can be developed.

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