WHO Guideline on Country Pharmaceutical Pricing Policies

Web Annex B

EVIDENCE TO DECISION (EtD) TABLES

What is an EtD framework?

The purpose of EtD frameworks is to help groups of people (panels) making healthcare recommendations or decisions move from evidence to decisions. Frameworks can:

- Inform panel members' judgements about the pros and cons of each intervention that is considered;
- Ensure the important factors that determine a decision (criteria) are considered;
- Provide a concise summary of the best available research evidence to inform judgements about each criterion;
- Help structure discussion and identify reasons for disagreements;
- Make the basis for decisions transparent to guideline users or those affected by a policy decision.

Source: https://www.decide-collaboration.eu/evidence-decision-etd-framework

WHO guideline on country pharmaceutical pricing policies, second edition. Web Annex B. Evidence-to-decision tables

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1. External reference pricing

Questions	1. What is the effect of **External Reference Pricing** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **External Reference Pricing**?	
Population	Medicines and vaccines for human use	**Definition:** External Reference Pricing (ERP; also known as international reference pricing) refers to the practice of using the price of a pharmaceutical product[i] in one or several jurisdictions[ii] to derive a benchmark or reference price. The purpose of ERP is to assess the appropriateness of prices of pharmaceutical products based on the selected benchmark prices, with a view to setting or negotiating the price of the product in a given jurisdiction. Both single-source or multisource supply products could be subject to ERP, but ERP has been used particularly for the pricing of single-source on-patent medicines.
Intervention	External Reference Pricing	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions (administrative units) Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	ERP is a policy widely adopted in many European countries *(1)*, as well as in high- and middle-income countries of other regions (e.g. Brazil, Egypt, Saudi Arabia, Spain, Thailand, Turkey, the United Arab Emirates, South Africa, Iran, Jordan, Lebanon and the Gulf countries) *(2,3)*. Most recently, the government in Malaysia has announced the introduction of ERP *(4)*.	In 2018, the US government has presented a proposal for setting the prices of medicines provided under Medicare Part B (i.e. outpatient physician-administered[iii] medicines) according to an international pricing index (IPI), to be phased in over a five-year period from 2019 to 2023. The IPI would be based on prices from 14 countries: Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Japan, the Netherlands, and the United Kingdom *(5)*.
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☐ Varies ☒ Don't know	**Number of studies included in the systematic review:** No study met the inclusion criteria. The systematic review identified three **other published reviews on ERP**, which have less restrictive inclusion criteria (e.g. inclusion of uncontrolled studies and simulation modelling based on theoretical) *(6–8)*. Main findings from these reviews relating to effects are summarized below for consideration: • Published studies of various methodological designs (e.g. case studies, simulation) have suggested potentially substantial savings for public payers. • The effect size and potential for unintended consequences (see below) are highly dependent on policy design, including country basket, frequency of updates, calculation of reference price. • The policy effectiveness is limited by unavailability price information (e.g. due to prices at different point along the supply chain) and inaccurate information (e.g. due to not having the final net transaction price).	**Co-interventions:** Other criteria considered in ERP price-setting include "the cost of therapy; health gain from the patient perspective; cost-effectiveness; relative benefits compared with treatment alternatives; budget impact analysis; financial resources available for reimbursement and reward for innovation"*(3)*. **Information from excluded studies on the estimated effect size**: Findings cited in *(9)* suggests that €1 price reduction in Germany would lead to a reduction of €0.15 to €0.36 in 15 European countries that used ERR and had Germany in their basket *(10)*. Another study cited in *(9)* (not retrieved) noted that Denmark medicine prices decreased more than 26% after changing from ERP to Internal Price Referencing. The US Department of Health and Human Services projected a savings of "more than $17 billion over its first five years, and more than $50 billion in its first eight years" for Medicare and Medicaid *(11)*. **Duration of effect:** Commentators noted potential "fadeout' effect, where ERP was successful in the short-term but has gradually lost its effectiveness" *(12)* **Frequency of price revision**: A modelling study *(13)* cited in *(6)* "estimated that when systematic price revisions take place every year, the price decrease seen is almost double than the one seen when price revisions take place only every three years".
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ Don't know	**Shortages**: Launch delays, product withdrawals and parallel exports have been noted in the literature *(12)*. **Quality issues**: No information **Safety issues**: No information **Anticompetitive, unethical or illegal conduct**: No information **Other potential unintended effects**: Some commentators suggest that ERP would influence not only national medicine prices but also prices worldwide due to the interlinking of prices *(6,9)*. There were assertion that this might lead to price convergence *(6)*, citing evidence from a study that observed narrower range of pharmaceutical prices among countries with different economic status, compared to the price variations for diagnostic and medical services where ERP was not implemented *(14)*	**Caveats on evidence**: Only theoretical discussion or qualitative case studies of potential undesirable effects have been presented in the literature *(6)*. Where presented, the 'evidence' did not clearly articulate the counterfactual. For example, the 'evidence' did not consider whether products would be launched in lower-priced countries at the same or similar time as countries with higher prices in the absence of ERP. Similarly, regarding parallel trade, a pharmaceutical company refusing to satisfy orders to prevent parallel exports could be considered as abusing its dominant position in violation of trade laws (e.g. in Europe, Article 102 of the TFEU), unless the order was apparently disproportionate with respect to the previous business relationships or market needs. **Effects modifiers:** The feasibility and effects of ERP could be hampered by the lack of transparency on net transaction prices in many jurisdictions because of (1) only list prices are published (2) price variations in healthcare systems with multiple payers.
Evidence certainty	What is the overall certainty of the evidence of effects?	☒ Very low ☐ Low ☐ Moderate ☐ High ☐ Very high ☒ Don't know	No study was included in the systematic review. Studies included in other systematic reviews *(6–8)* and the excluded study *(9)* suggested confounding factors or variable effects, likely to be influenced by market conditions.	The excluded study *(9)* cited that "other confounding factors are that ERP is only one of many pharmaceutical price regulation policies applied in each country and that discounts from negotiated prices are not taken into account while calculating ERP prices due to confidentiality."
Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison?	☐ Favour comparator ☐ Probably favours comparator ☒ Probably favours policy ☐ Favour the policy	ERP is likely to deliver more desirable than undesirable effects, as indicated by: • Some (un-appraised) evidence on price reduction at least in the short run (albeit limited in the quantity and quality of evidence) • A lack of robust evidence attributing undesirable effects to ERP, including launch delays or product withdrawals in lower-income countries	Effective operationalization of ERP would require accurate and verifiable price data from the referenced countries. These data must be, at least with high degree of confidence, considered as comparable and net of all forms of discounts and rebates. Despite its seeming simplicity in principle, the operation could be complex and would therefore require adequate resources and skilled personnel.

[i] A pharmaceutical product, commonly referred interchangeably with drug, medicine or pharmaceutical, is defined as any manufactured or refined substance for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. For the purpose of this review, the scope includes medicines (both small molecules and biological products) and vaccines for human use.

[ii] Jurisdictions refer to countries, regions, or other organized purchasing authorities.

[iii] In some settings, outpatient refers to "a person who goes to a hospital for treatment, but who does not stay any nights there" while other settings (e.g. Europe), "outpatient medicines" could refer to settings outside of hospital (e.g. community pharmacy).

		☐ Varies ☒ Don't know	• Wide adoption or consideration of ERP as one part of the overall pricing policy.	
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	Uncontrolled studies suggest that ERP might be effective in countries, including in 14 European countries *(9)*. Similarly, ERP has been applied in countries outside of Europe but without <u>comparative</u> evidence to demonstrate effectiveness. There is no information about its applicability in low-income countries.	
Equity	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☒ Don't know	Literature suggests the potential occurrence of "beggar-thy-neighbour" practices, that under ERP, higher income countries "seem to want to capitalise on any price differences irrespective of (lower income) country archetype or per capita income level." (i.e. referring to the price of product in a lower-income country) "In principle, such practices nurture inequalities among countries, as wealth differences between referrer and referenced country proliferate" *(12)*. However, no empirical evidence was presented to support the statement.	
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities**: Wide adoption suggests acceptance of ERP. **Patients and community**: No information	<u>Other stakeholders</u> **Insurers**: No information **Manufacturers or suppliers**: Noted a reduction in revenue, competitiveness, and incentive for innovation *(13,15)*. However, no supporting evidence has been presented. **Service providers:** No information
Resources required	How large are the resource requirements for implementing the policy?	☐ Large ☒ Moderate ☐ Small ☐ Neutral ☐ Varies ☐ Don't know	**Human resource:** Skilled personnel is required for data collection and management, including developing methodology, standardizing price information, revising prices regularly to reflect changes in the reference prices in other markets. **Financial resource:** Mostly associated with human resources and data acquisition **Governance**: Legislative framework and procedures for the use of ERP need to be specified, including decision making processes **IT infrastructure**: Database management	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ Varies ☐ Don't know	The feasibility of implementation in low- and middle-income countries is dependent on: • **Reliability of price information**: Pricing authorities rely mostly on list prices rather than net transaction prices because of confidential agreements implemented in many countries. Differences in list price and (undisclosed) net transaction price of medicine have diminished the effectiveness of ERP, particularly in lower income countries. • **Availability of prices from comparable markets**: Lower-income countries appear to have relied on price information countries with a wide range of national incomes, reflecting different timing of product launch and large price variability, resulting in the need for a large sample of reference prices to better inform pricing decision *(2)*. This might increase technical and resource complexity of ERP in these countries.	Feasibility of implementation would require clear definition of: • **Technical methods**, including the number and criteria of reference countries under consideration, type of prices along the supply chain, and sources of information • **Monitoring**: Frequency of price collection, calculation and revision, and choice of exchange rates • **Rules for exceptional circumstances** arising from currency volatility and during shortages of supply
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely neutral ☐ Probably increase ☐ Increase ☐ Varies ☒ Don't know	Only short-term impacts on price were assessed in literature (not appraised in the literature). Long-term financial sustainability is unclear.	

Conclusion

☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☒ Conditional recommendation for the policy	☐ Strong recommendation for the policy

Recommendation

1.A. WHO suggests the use of external reference pricing under the following conditions.
- External reference pricing is used in conjunction with other pricing policies, including price negotiation.
- Adequate resources and skilled personnel are available to implement external reference pricing.
- Selection of reference countries or jurisdictions is based on a set of explicitly stated factors.
- Reference prices are obtained from verifiable data sources.
- Reference prices have accounted for all forms of discounts, rebates and taxes with a high degree of confidence.

- Methods for determining prices follow a transparent and consistent process.

1.B. WHO suggests that countries undertake regular price revisions at pre-specified frequency when using external reference pricing.

1.C. WHO suggests that countries monitor the impacts of implementing external reference pricing on price, affordability and access to medicines.

Justifications

- The GDG recognized the extensive experiences in using ERP across jurisdictions with different health system settings. It also acknowledged a lack of evidence from comparative studies conducted to the standards of the WHO-commissioned systematic review. Considering the totality of evidence and information, however, the GDG reached a consensus that the balance of effects of ERP was in favour of implementing the policy.
- Despite the relative conceptual simplicity of ERP, the GDG recognized the complexity of implementing so-called best-practice ERP, particularly when prices of medicines are often not transparent and their reporting not harmonized. For this reason, the GDG emphasized the importance of having adequate resources and skilled personnel to implement ERP, especially in low- and middle-income countries.

Implementation considerations

- Effective operation of ERP policy should consider the following factors:
  a. sufficient technical capacity, database management, monitoring and evaluation;
  b. a governance structure supported by transparent legislation and appeals process;
  c. an international collaborative network that promotes price sharing and skill transfers;
  d. overall system readiness, including gaining political support.
- Methodology of ERP should consider the following factors:
  a. comparability of price types along the supply and distribution chain (i.e. ex-manufacturer, ex-wholesaler, pharmacy and consumers);
  b. number of jurisdictions included to obtain reference prices;
  c. comparability of referenced jurisdictions, such as market sizes, national income, purchasing power;
  d. legislative measures and operational procedures for methodologically challenging situations, such as availability of data only from non-comparable jurisdictions, missing data and currency fluctuations; and
  e. use for products lacking sufficient competition (to which ERP is most often applied), with prices determined through ERP being used as the point of reference for further price negotiation.

Considerations towards research needs

- Study the impact of ERP on price, availability and affordability, with a focus on specific settings (e.g. low- and middle-income countries) and longer-term impacts.
- Assess the effects of ERP on timing of product launch, with the study design, (i) accounting for factors such as market size, price and dates for dossier submission for product registration and reimbursement; (ii) setting clear null hypothesis (e.g. ERP has no effect on the timing of product launch between jurisdictions expected to have both high and low prices); and (iii) specifying and including a counterfactual (e.g. jurisdictions not using ERP).

2. Internal reference pricing

Questions	1. What is the effect of **Internal Reference Pricing** on the price, volume, availability and affordability of pharmaceutical products? 2. What contextual factors and implementation strategies may influence the effects of **Internal Reference Pricing**?	
Population	Medicines and vaccines for human use	**Definition:** Internal Reference Pricing, or IRP, refers to the practice of using the prices of a set of pharmaceutical products[iv] that are therapeutically comparable and interchangeable, to derive a benchmark or reference price for the purposes of setting or negotiating the price or reimbursement rate of a product. Therapeutic comparability and interchangeability are determined by chemical entity and pharmacological class according to the Anatomical Therapeutic Chemical Classification System (ATC), or by therapeutic indication.
Intervention	Internal Reference Pricing	
Comparison	Other pricing policies or absence of a pricing policy	
Main outcomes	Price, volume, availability, affordability	
Settings	Country jurisdictions; Public, private and mixed public-private	**GDG member(s) with conflicts of interest that led to recusal from the formulation of this recommendation**: None

Assessment

	Criteria	Judgement	Summary of evidence or opinion	Considerations
Policy importance	Is the policy a priority?	☐ No ☐ Probably no ☐ Probably yes ☒ Yes ☐ Varies ☐ Don't know	Many countries with pricing policies for pharmaceutical products have commonly employed Internal Reference Pricing, particularly for linking the prices of (closely) substitutable medicines i.e. generics, biosimilars or therapeutically equivalent or closely substitutable products *(17,18)*.	Internal reference pricing has been used to set the reimbursement rates of closely substitutable products, in healthcare systems with public pharmaceutical insurance, or where reimbursements from private insurers are regulated. For example, patients preferring a branded product would incur the price difference between the branded and reference (generic) product.
Desirable effects	How substantial are the desirable anticipated effects?	☐ Trivial ☐ Small ☒ Moderate ☒ Large ☒ Varies ☐ Don't know	**Number of studies included in the systematic review:** 26 studies. 11 studies on generic reference pricing (**GRP** i.e. ATC 5 level) *(19,20,29,21–28)* and 5 studies on related policies where prices of generic products were set at a proportion of the price of the originator product according to the sequence of market entry (1 study from Sweden and 4 studies from the Republic of Korea) *(30–34)*; 8 studies on therapeutic reference pricing (**TRP** i.e. ATC 4 level) *(35–42)*; 2 studies on mix of generic and therapeutic reference pricing (**GTRP**) *(43,44)*. **Price**: **GRP** was found to reduce prices of both branded and generic medicines, estimated at between 13% *(22)* and 66% *(27)*, with the price reductions largely influenced by generic substitution policies. One study did not observe price reduction because the reference price determined through GRP was higher than the market prevailing price *(29)*. **TRP** was found to reduce the costs of medicines between 10% to 45% *(35,37)*. **Expenditure: GRP** was found to decrease overall expenditure in most studies, but the level of reductions was either not statistically significant, of unknown statistical significance, or smaller than the reduction in average prices *(21)*, possibly reflecting savings being offset by concurrent increase in the quantity of medicines demanded due to lower prices. Studies from the Republic of Korea on policies where prices of generic products were set at 53.55% of the price of the originator product observed statistically significant reduction in expenditure only in the short-term due to concurrent increased in utilization *(31–34)*. **TRP** was found to be associated with a substantial decrease in costs for the insurers *(35–37)* and overall expenditure. **Volume:** The overall evidence suggests that **GRP, TRP** and **GTRP** increased switching to, hence utilization of, generic/lower-cost/fully reimbursed medicines from brand/higher-cost/partially or non-reimbursed medicines without affecting the overall demand. **Availability:** Two studies observed an increase in the number of generics following GRP and a decrease in the number of branded products *(21,25)*. **Affordability**: No information. **Quality:** One study from the Republic of Korea on compulsory price reductions for generic antidiabetic products at a proportion of the originator products found that incidents of medical and surgical procedures relating to diabetic complications were unaffected, but the post-intervention observation period was short *(33)*.	**Co-interventions**: Price cap based on reference price, mark-up adjustment, compulsory price reduction, public tender, policies to encourage generic prescribing/substitutions, in parallel with strengthening of regulatory functions to ensure quality of generic medicines and building public trusts. **Duration of effect:** Most observations are short term (~1 year) post intervention, but one study effects up to 10 years post intervention *(22)*. **Possible externalities:** Global price level and availability and affordability in other countries are not known. **Other systematic reviews:** A review published in Cochrane Library *(45)* found an estimated overall reduction in insurer's expenditure of 18% (range: -53% to 4%), an overall increase in the utilization of the lower priced drugs that set the benchmark price (+15%; range: -14% to +166%) and an overall decrease in the utilization (-39%, range: -87% to -17%) of higher priced drugs for which the patients need to pay the difference in price. Other reviews concluded with similar observations *(46–48)*. citing two studies from British Columbia on the effects of substitutions of ACE Inhibitors within a reference pricing framework, one review *(46)* noted that (therapeutic) reference pricing did not affect patient health outcomes. Review by Galizzi et al made the following qualitative observations on the following effect modifiers that facilitating larger price reduction, savings or market shares: • Generic competition prior to reference pricing • First year of policy implementation • Brand-name drug did not lower price to reference price, launched new formulations, or marketing substitutable on-patent drugs.
Undesirable effects	How substantial are the undesirable anticipated effects?	☐ Trivial ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	**Shortages:** No information **Quality issues:** No information **Safety issues:** No information **Anticompetitive, unethical or illegal conduct**: One study did not observe any additional demand shift from off-patent drugs subject to GRP to on-patent drugs in the same therapeutic category *(22)*.	Some commentators have noted that, in anticipation of price reduction following loss of exclusivity due to generic competition and price linkage within IRP, the originator company may engage in practices, such as switching the market to a new formulation that offers little or no therapeutic benefits (i.e. product hopping) or introduce an additional brand (usually) by the originator companies for their own branded medicine (i.e. 'pseudo-generic' or 'authorized generic')[v]. These might weaken IRP's effectiveness.
Evidence certainty	What is the overall certainty of the evidence of effects?	☒ Very low ☒ Low ☒ Moderate ☐ High ☐ Very high ☐ Don't know	The GRADE assessments presented in the literature review indicated "moderate" level of certainty on the effects of GRP, TRP, or GTRP on price, "moderate" or "low" for volume; but "very low" on expenditure.	Publication bias not assessed.

[iv] For the purpose of this guideline, pharmaceutical product is defined as medicines and vaccines.

[v] A pseudo-generic medicine is an additional brand marketed (usually) by the originator companies for their own branded medicine, but priced lower than their branded medicine. This business practice may discourage other genuinely generic medicines from entering the market because of reduced market share.

Balance of effect	Does the balance between desirable and undesirable effects favour the policy or the comparison?	☐ Favour comparator ☐ Probably favours comparator ☒ Probably favours the policy ☐ Favour the policy ☐ Varies ☐ Don't know	GRP and TRP are likely to deliver more desirable than undesirable effects, as indicated by: • Evidence on price reduction and improved expenditure efficiency (through seemingly higher volume) at least in the short and long term (up to 10 years of observation). • A lack of robust evidence to attribute GRP and TRP to undesirable effects, including switching to therapeutically similar on-patent products not subject to price regulations. • Wide adoption or consideration of GRP and TRP as one part of the overall pricing policy.	Results were presented based on statistical significance; clinical, public health and economic significance are often not discussed.
Generalizability	Has this policy been tested or found to be effective only in specific contexts?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☒ Don't know	The systematic review included only one study from LMIC for TRP conducted in Taiwan Province of China *(24)*. However, the findings of this study were not different from studies conducted in higher income countries.	
Equity	What would be the impact on health equity?	☐ Large positive ☐ Moderate positive ☐ Neutral ☐ Moderate negative ☐ Large negative ☐ Varies ☒ Don't know	No information.	Although there is no formal evidence examining the impact of GRP or TRP on equity, lower costs of treatments arising from GRP and TRP could enhance affordability and broader access.
Acceptability	Is the policy acceptable to government authorities, patients and community?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	**Government authorities:** Wide adoption suggests acceptance of IRP **Patients and community**: GRP and TRP were usually accompanied by rules that retained the rights of the patients for choosing not to switch to lower priced generic or therapeutic equivalent products. However, patients might incur higher level of co-payments. A systematic review noted that "A temporary rise in physician visits was observed, probably owing to an adaptation period for both physicians and patients" *(46)*	Other stakeholders **Insurers:** Evidence suggests cost savings for insurers, particularly TRP. **Manufacturers or suppliers**: Evidence from one study suggested that the joint profits of generic producers were positively affected by Reference Pricing (the increase = 185%), for a given number of generics present in the market *(21)*, but another study found a reduction in producers revenue *(25)*. Prior knowledge of price linkage to the lowest priced medicines has been noted as a possible disincentive for generic producers to supply *(49)*. Country experiences suggests higher level of resistance to TRP than GRP. **Service providers:** GRP and TRP were accompanied by rules that retained the rights of the prescribers to choose not to switch to lower priced generic or therapeutic equivalent products.
Resources required	How large are the resource requirements for implementing the policy?	☒ Large ☒ Moderate ☐ Neutral ☐ Moderate savings ☐ Large savings ☐ Varies ☐ Don't know	**Human resource**: When applying TRP, technical expertise in determining therapeutically equivalent dose is required. **Financial resource:** Mostly associated with human resources **Governance requirements:** Legislative framework and procedures for the use of TRP need to be specified, including decision making processes. **IT infrastructure:** Maintenance of price database to ensure regular revision of prices in accordance to changes in market prices arising from price competition.	
Feasibility	How feasible is the policy to implement in low- and middle-income countries?	☐ No ☐ Probably no ☒ Probably yes ☐ Yes ☐ Varies ☐ Don't know	Feasibility of implementing GRP or TRP is dependent on LMICs' capacity to implement generic substitution policies, or substitution policies for medicines belonging to the same therapeutic group, which have been noted as an important co-intervention effecting price impacts of IRP. Many LMICs currently do not have a generic substitution policy, which may hamper the implementation of GRP. The need for regular revision of prices in accordance to market prevailing prices could have an impact on the overall feasibility too.	Countries have adopted gradual implementation when considering GRP and applied only to a subsample of off-patent substances. In Norway, for example, "this was mainly due to practical reasons and the administrative workload related to implementing reference prices for the relevant products, but also to gain some experience before extending the scheme to more substances." *(21)*
Sustainability	How would the policy affect the long-term financial sustainability of healthcare system?	☐ Reduce ☐ Probably reduce ☐ Likely to be neutral ☒ Probably increase ☐ Increase ☐ Varies ☐ Don't know	Extant evidence suggests that both GRP and TRP could have longer term (2-10 years) impacts on price, although observed impacts were less substantial over time *(22,37)*. This suggests both policies could enhance long-term sustainability of healthcare system.	

Conclusion				
☐ Strong recommendation against the policy	☐ Conditional recommendation against the policy	☐ Conditional recommendation for either the policy or comparison	☒ Conditional recommendation for the policy	☐ Strong recommendation for the policy

2.A. WHO suggests the use of internal reference pricing for generic and biosimilar medicines using the principles of generic reference pricing[vi], under the following conditions.

- IRP is used in conjunction with policies to promote the use of quality-assured generic or biosimilar medicines.
- Reference prices are obtained and validated from verifiable data sources.
- Consistent and transparent criteria for pricing of generic and biosimilar medicines are explicitly evaluated and stated based on an established methodology.

2.B. WHO suggests the use of internal reference pricing for medicines according to the principles of therapeutic reference pricing[vii], under the following conditions.

- IRP is used in conjunction with other pricing policies.
- Reference prices are obtained and validated from verifiable data sources.
- Consistent and transparent criteria, including therapeutic or dose equivalence, are explicitly evaluated and stated based on an established methodology.

Justifications

- The GDG considered the body of literature on IRP assessed in the WHO-commissioned systematic review; the evidence suggests moderate to large reductions in price of medicines when used in conjunction with generic substitution policies and increased utilization of lower cost or fully reimbursed generic medicines. The GDG reached a consensus that the overall balance of effects favours the policy, particularly with consideration of acceptability and financial sustainability to government authorities, patients and the community.
- Despite a lack of evidence relating to the pricing of biosimilar medicines, the GDG considered the policy principles of IRP as applicable to biosimilar medicines. The GDG envisaged the importance of the future market for biosimilar medicines, and anticipated that policies on interchangeability, switching and substitution will be resolved.

Implementation considerations

- Effective operation of internal reference pricing policy requires:
  a. strong national regulatory authorities to assure quality of generic and biosimilar medicines, including established post-market surveillance;
  b. concurrent implementation of policies to promote the use of quality-assured generic and biosimilar medicines, including but not limited to policy options presented in Section 7;
  c. public health campaigns for patients and providers with respect to use of generic medicines, with a view to building trust and acceptance;
  d. a clear understanding of the incentives in the supply chain, including financial incentives to service providers, that may moderate or enhance the overall effects of IRP;
  e. forward-looking policy design in anticipation of growing demand for biosimilar medicines with market characteristics likely to mirror that of generic medicines.
- Internal reference pricing methodology and processes should consider the following factors.
  a. For therapeutic reference pricing, therapeutic equivalence is determined through established scientific methods (e.g. supporting evidence from pharmacokinetic and pharmacodynamic studies).
  b. Where applicable (e.g. health care systems with reimbursement), methodology, policy and legislative processes for specific circumstances should be clearly defined (e.g. when considering the delisting of a product that does not comply with IRP or when authorizing the use of products priced higher than the internally referenced price because of specific patient clinical needs).

Prices of generic medicines could be cross-checked with the prices of raw materials, with a view to informing the pricing by the cost of production

Considerations towards research needs

- Monitor and evaluate the impacts of IRP on the price, availability and affordability of medicines (particularly for biosimilar medicines), and over the longer term (particularly for therapeutic reference pricing).