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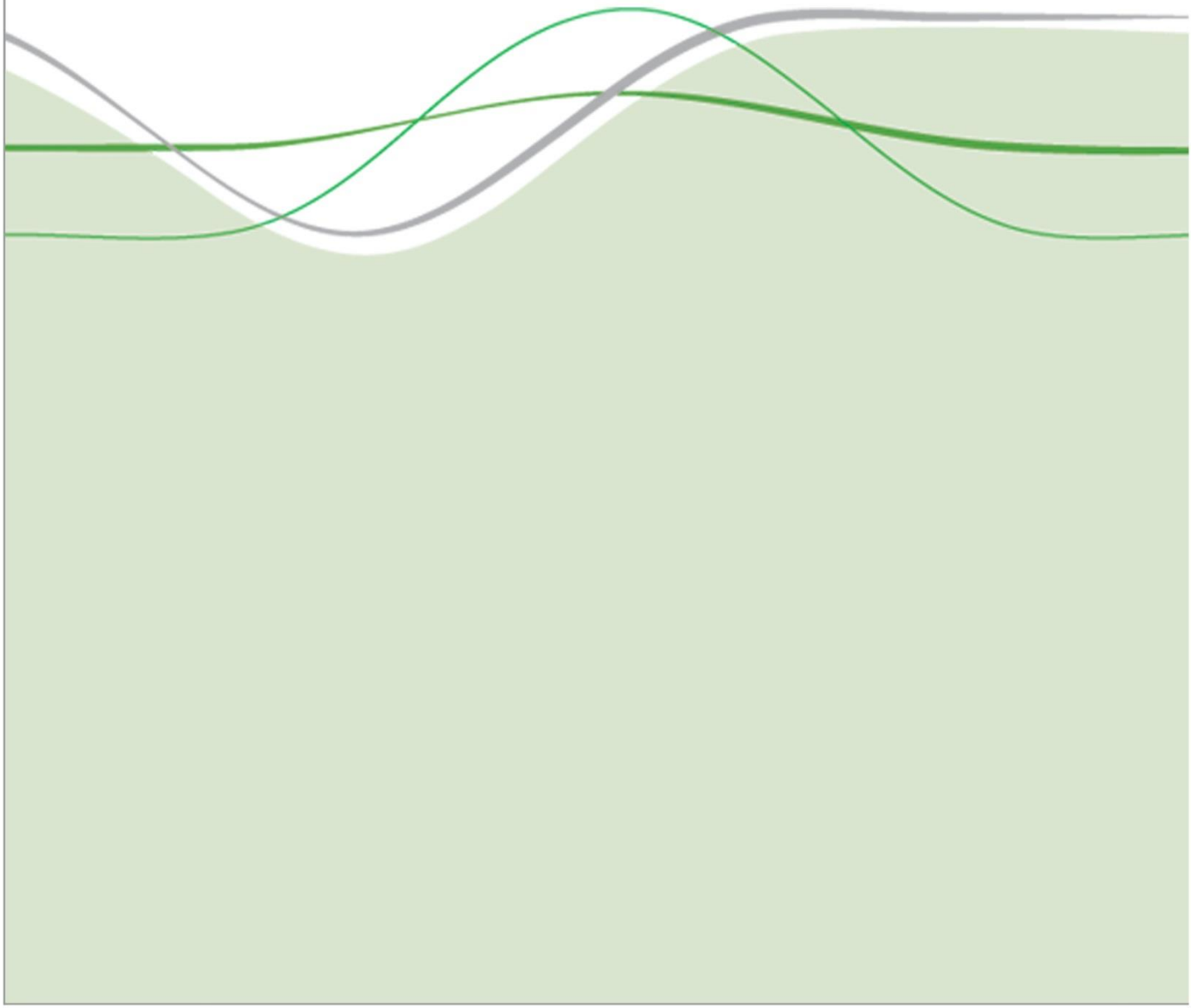
Research Paper

The WHO Technical Report on the Pricing of Cancer Medicines: Missing a Central Role for Value Assessment

April 2019

Simon Brassel, Olga Rozanova and Adrian Towse



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ABSTRACT

At the end of 2018 the WHO Technical Report: Pricing of cancer medicines and its impacts ("the Report") was published in order to address requests made in a resolution adopted by the 2018 Seventieth World Health Assembly WHA70.12 on *Cancer prevention and control in the context of an integrated approach.*

The Report dismisses value assessment and the fundamental role of value assessment in delivering value for money. This is inconsistent with both existing WHA policy on HTA and the reality that more and more payers in WHO Member States are using value assessment analyses to support their purchasing decisions. Secondly, the Report lacks proposals to enable differential pricing and managed entry agreements to happen. Both can increase access while setting the right incentives for future innovation if implemented correctly. Lastly the report calls for price transparency and price caps which are likely to have a negative impact on differential pricing and managed entry agreements, reducing access to treatment for patients and producing less innovation in the future.

Much of the emphasis of the Report is that the R&D "supply side" is not working as the authors would like, but we are not convinced that this is the major challenge. Supply responds to demand and the real challenge is to get demand side reforms that use new treatments efficiently and send the right signals to industry about the new cancer treatments (and associated health gains) that payers want to fund.

The Report fails to promote mechanisms and processes (value assessment and related pricing and purchasing arrangements) that are key to efficient pricing and use of cancer medicines. This is a missed opportunity.

1. HISTORY AND CONTEXT FOR THE WHO'S TECHNICAL REPORT "PRICING OF CANCER MEDICINES AND ITS IMPACTS"

1.1. WHA requests a report on cancer pricing

A resolution adopted by the 2018 Seventieth World Health Assembly WHA70.12 on *Cancer prevention and control in the context of an integrated approach*, included a request for a comprehensive technical report on pricing approaches for cancer medicines and their impact on availability and affordability. The WHO Technical Report: Pricing of cancer medicines and its impacts ("the Report") was published at the end of 2018.

The starting point for the Report is the public health and system challenge generated by the many forms of cancer. It stresses the improvements in the diagnostic and treatment options available, enabling early detection, and more effective use of surgery, radiotherapy and drugs. While the Report outlines progress in increasing survival rates, the authors emphasise the variations in survival rates by types of cancer and among people living in different regions of the world (World Health Organization, 2018, p.2).

The Report, however, is concerned about growth in medicines expenditure and, in particular, the role played in that growth by the prices of new cancer medicines. It states that "expenditure on cancer medicines has grown at rates higher than the growth rates in patient population and overall health expenditure" (World Health Organization, 2018, p.2). We can note in this context that spending (as a share of health expenditure) has historically been below the share of cancer in the overall burden of disease (Cole et al. 2016).

1.2. Related WHO initiatives on UHC, HTA and the "Fair Pricing Forum"

The World Health Assembly (WHA) has previously strongly supported Member State moves towards Universal Health Coverage (UHC). In the 2014 WHA, a resolution on *'Health intervention and technology assessment in support of universal health coverage* was adopted. The WHO is aspirational as to the use of HTA, seeing it as a route enabling UHC to be implemented. It is a tool to help Member States decide "what is going to be provided, given the resources available".

The WHO has also launched a Fair Pricing Initiative which led to a ''Fair Pricing Forum'' which took place in Amsterdam in 2017 (Garner, Rintoul and Hill, 2018). Its report on the Fair Pricing Forum (World Health Organization, 2017) led to a critique in form of an open letter by Anthony Culyer in which the author argues for "a rethink of the economic advice provided through WHO" (Glassmann, 2017).

1.3. The real challenge is to get demand side reforms

In this paper we comment on a number of points raised by the Report. The selection of relevant areas is briefly outlined in Box 1. We focus on the way forward to improve access to cancer treatments, given health budgets, and given the priority within those budgets for cancer treatments. Much of the emphasis of the Report is that the R&D "supply side" is not working as the authors would like. We comment briefly on this later, but we are not convinced that this is the major challenge. Supply responds to demand and the real challenge is to get demand side reforms that use new treatments efficiently and send the right signals to industry about the new cancer treatments (and associated health gains) that payers want to fund.

Access to cancer care is not just about drug prices for on-patent cancer medicines, or indeed the cost of associated surgery, radiotherapy and off-patent drugs. Having an ecosystem of care, which includes diagnostics and therapy, is crucial to the health system's ability to delivery of care. A key element is the resource made available for UHC in the form of budgets for health care. Many countries are seeking to increase financing for UHC to levels that reflect both population preferences for spending on health and governments' desire to deliver health outcomes for their populations. Within the budget available, the priority given to cancer medicines will depend not only on the value of cancer treatments (the incremental benefits delivered relative to the incremental cost – of which price is a key part), but also on the alternative uses of the budget, in treating other diseases. These elements are brought together in the use of HTA and value assessment.

In this respect therefore, there are some key problems with the analysis presented in the Report:

- It **dismisses value assessment** and the fundamental role of HTA in delivering value for money. The Report is inconsistent with both prior stated views by the WHO on HTA and the reality that more and more payers in WHO Member States are using such analyses to support their purchasing decisions.
- It **lacks proposals to enable differential pricing and managed entry agreements to happen** as both can increase access while setting the right incentives for future innovation if implemented correctly.
- It **calls for price transparency and price caps** which are likely to have a negative impact on differential pricing and managed entry agreements, reducing access to treatment for patients and less innovation in the future.

Box 1: Selection of points of relevance from the Report

The Report is a deliverable upon the request of the resolution WHA 70.12 adopted by the 2018 Seventieth World Health Assembly on *Cancer prevention and control in the context of an integrated approach.*

It analyses the impacts of pricing approaches on price, availability and affordability of cancer medicines, identifying "four determinants of medicine prices from the industry perspective", one of which is the "value" of medicines. However, it sees "many uncertainties associated with estimating value" and that "value-based pricing may lead to unaffordable prices."

The Report sets out **24 options** that, in the view of the authors, have the potential to enhance affordability and accessibility of cancer drugs.

It not feasible to comment on every option put forward and we focus on the following selection:

- **Option b1:** Prioritizing the selection of medicines with higher clinical value.
- **Option b2:** Considering managed entry agreements only in specific cases
- **Option c1:** Disclosing the net transaction prices of cancer medicines to relevant stakeholders
- **Option d1:** Sharing information on medicine prices and technical assessments
- **Option a1:** Enforcing price caps for cancer medicines

We have selected the first two options (b1 and b2) despite the report lacking a clear commitment to Health Technology Assessment. Related sections in the report criticise the current value assessment methods and provide no proposals to overcome related challenges or to promote alternatives. This threatens the implementation of useful, efficiency-raising approaches such as value-based pricing and managed entry agreements.

We have selected Option c1 and d1 of the Report despite underestimates of the negative consequences of the disclosure of prices of on-patent medicines on availability and affordability.

We selected Option a1 of the Report as price caps ignore potential negative impacts on availability.

2. THE MISSED OPPORTUNITY OF PROMOTING VALUE ASSESSMENT

2.1. Value assessment enabled through HTA

The Report states the case for "prioritizing the selection of medicines with high(er) clinical value" (World Health Organization, 2018, p.105), but fails to put forward value assessment as a route to understand what it is worth paying for the clinical value on offer. The Report's approach is not compatible with WHO's commitment to "continue to undertake activities to raise awareness, promote knowledge and encourage the practice of HTA and its uses in evidence-informed decision making" (World Health Organization, 2015).

2.1.1. HTA must be built on robust methods

The Report is sceptical of setting the price at a level that reflects that value. It claims that the implementation of a value-based pricing approach is challenging due to the high degree of uncertainty in the quantification of the value of an intervention. The reasons given are: the variation in robustness and capacity of the evaluation frameworks, the lack of suitable comparators and evidence to inform clinical and economic value, as well as different perceptions of value by different stakeholders (World Health Organization, 2018, pp.20–21).

Measuring even the most basic value element of a medicine, namely the gain in health for the patient is not trivial. Uncertainty will be always present in decision making around non-deterministic interventions. However, progress has been made with respect to both methodologies and dealing with uncertainty, see for example Barnsley et al., (2016) and to the use of scientific judgement and deliberation in an HTA appraisal process (Culyer and Lomas, 2006). Debate continues on the breadth of societal and patient elements to be included in value assessment, and on the potential for introducing more structure into decision making (Garrison et al., 2018). The type of assessment to be used is also debated, with some countries using cost-effectiveness analysis and others, therapeutic added value approaches (Towse, 2014). The WHO Report should be encouraging the development of value assessment methods and processes. Instead it cites WHO's 2015 survey to point out that "the capacity for authorities to undertake value assessment through health technology assessment and appraisal is highly variable in comprehensiveness and robustness". Yet that survey was conducted in response to a 2014 WHA resolution on HTA in support of UHC which urged member states "to consider establishing national systems of health intervention and technology assessment". The 2015 survey was intended to map the landscape so that WHO could support Member State HTA developments, not provide a pretext for the WHO Report on cancer pricing to ignore HTA.

2.1.2. LMICs must be supported in building up HTA capacity

The Report argues that "operationalization of value-based pricing often faces various practical challenges" (World Health Organization, 2018, p.35). These challenges and capacity constraints are particularly present in middle - and low-income countries (MLICs). Yet, value assessment is crucial to priority setting and can help countries attain and sustain UHC (Chalkidou et al., 2016b). Many countries have set up national HTA institutions, including MIC countries such as Brazil and Thailand.

Value assessment is fundamental to the selection of medicines that deliver the highest value to the health system and society. Academic commentators have called on global health funders to formally introduce HTA to improve their decision making processes (Chalkidou and Madan Keller, 2017). Yet using HTA and value-based assessment requires significant resources in a country or region and this can indeed be a challenge, especially in MLICs, though hardly a reason for quitting before even starting. However, the efforts required to build-up the necessary capacities should be a good investment. Regional hubs might be beneficial and could serve several countries that share systemic and socio-economic factors. A degree of regional commonality is needed because some have questioned whether some global activities (see for example the WHO CHOICE project) that produce global evidence and global guidance are effective as they ignore the local political context in a country (Chalkidou et al., 2016b; Baltussen et al., 2016).

An international reference case for methods has been developed by the iDSI with funding from the BMGF (Wilkinson et al., 2016). Good practices have also been put forward by the ISPOR HTA Task Force (Kristensen et al., 2019). Approaches to good practice for value assessment in the US have been put forward in Sanders et al. (2016) and Garrison et al (Garrison et al., 2018). Chalkidou, Culyer and Nemzoff (2018) argue that these reference case and good practice guides can inform the development of a Reference Case by policy makers locally. Local ownership will ensure that adaption to the local context occurs.

2.2. Value should inform pricing and purchasing in the local context

The Report states that access to cancer medicines is linked to many systemic factors including the insurance coverage of the population (World Health Organization, 2018, p.viii) and that "different health care settings have vastly different system capacity" (World Health Organization, 2018, p.68). This is not, however, an argument against the use of value assessment but a recognition that because of this heterogeneity, it has to be applied according to its local context. Two things are of special importance.

Firstly, the perspective taken by any HTA must depend on the specific question it aims to address. This includes the health of the underlying population; the availability of analytical capacity to gather and utilise information; as well as the local cultural, historical, and political landscape (Chalkidou, Culyer and Nemzoff, 2018).

Secondly, the decision context and the elements of value must be regarded as relevant by local decision makers. There is widespread recognition that health gain for the patient and cost savings to the health system are important, as well as getting the correct comparator (how else might this patient be treated?). However, other elements of value may also be important, for example the impact on families including caregivers, the impact on productivity (both paid and unpaid supply of labour) and the option value of keeping a patient alive until new treatments become available. One route that has been proposed is to have a two-part reference case, with core elements in the base case and the additional elements of social value in a supplementary assessment. This leaves open the question as to what should be included. To follow the discussion, see: Wilkinson et al. (2016); Garrison et al. (2018); Sanders et al. (2016) and Chalkidou, Culyer and Nemzoff (2018).

Value-based pricing and purchasing carried out using carefully implemented HTA would solve many of the issues in the Report. It would reduce the likelihood of payers including medicines of only marginal health benefit if the price was high (see (World Health Organization, 2018, p.15). It would support countries to "consider the full spectrum of

interventions from prevention to palliation" (World Health Organization, 2018, p.5) and select those cancer-related intervention with the highest return on investment (measured in health gain of the population per unit of cost). On a wider level, it would support priority setting in the context of MLICs seeking to develop a benefits package as part of a move to UHC (see also (Chalkidou et al., 2016a). It would help to ensure that "improved access to cancer medicines comes not at the expense of health care in other disease areas" (World Health Organization, 2018, p.viii).

In general, it is also important to understand that in MLIC interventions have to be put in the context of:

- UHC priorities, which need to be reflected in reimbursement and formulary listing decisions (see (Towse et al., 2011; Hernandez-Villafuerte et al., 2017a; b));
- health system strengthening (at its simplest adopting a technology may require investment in an infrastructure which would already be present in a HIC, yet that infrastructure, once in place, may enable many other health services to be supplied (see Hauck et al. (2019)).

2.3. The affordability challenge

The authors claim that value-based pricing may result in the unaffordability of cancer medicines (World Health Organization, 2018, p.ix). The related WHO Fair Pricing Forum Report argued that value-based pricing was "insensitive to the questions of affordability" and this is a point made by others (UCL Institute for Innovation and Public Purpose, 2018, p.19).

Yet anchoring value in the context of local budgets is a key component of the use of HTA in value assessment. A value-based price in one country might not be cost-effective in another. Differential pricing, as we discuss below, then becomes crucial to the implementation of price differences.

The answer to the question as to what a health system can afford to pay for the health gains that a specific medicine delivers must be answered in the country-specific context. As outlined by Culyer (2016) the threshold is determined by three fundamental things, namely:

- the underlying demographics and disease burden
- local environments, customs and values
- and the budget available.

Hence, such a threshold can be implicit or explicit, but it must be local and will always be closely linked with the budget available in the specific context. Inevitably, per capita income will be a key influencer of budgets. Poorer countries will have lower value-based prices reflecting limited local resources and more alternative options for delivering low cost health gain.

The challenge of high budget impact treatments, such as those for HCV, can also be addressed by various routes within a value-based pricing framework (Towse and Mauskopf, 2018). We have seen the impact of competition (Berdud et al., 2018) in enabling payers to pay lower prices. Affordability is addressed in HTA.

2.4. Value assessment enables managed entry but requires constructive proposals to overcome challenges

In selective cases, the Report explicitly recommends the application of managed entry agreements (MEAs) as they have the potential to raise efficiency levels in a market (World Health Organization, 2018, p.xv). MEAs are agreements between manufacturer and payer or provider to enable access to a medicine subjected to specific conditions. Those conditions can be financial-based by being linked directly to the price (as with price discounts) or total expenditure (a budget cap), or they can be performance-based, in which case the payments are linked to changes in a defined health outcome. This can be at a patient level, as applied for example in Italy, with an ex-post payment to the manufacturer only for treatments that enable a particular patient to hit a target outcome (Navarria et al., 2015), or linked to evidence collection on a patient population, which can be through a clinical trial or an observational study.

According to the authors of the Report, **MEAs should be limited to specific circumstances** such as a clear clinical need for the treatment and a likely refusal to use the drug in the absence of a MEA. Most importantly to the authors is that **their implementation should avoid confidential terms wherever possible** as this compromises transparency and good governance (World Health Organization, 2018, p.106). We address the second point (avoidance of confidential terms) in section 4.2. , here we focus on the rational of the Report to limit the use of MEAs.

The authors claim that MEAs may be associated with high transaction and administrative costs and that they "may not address clinical uncertainties unless a robust data collection and scientific approach are in place, which in turn, would add to the overall costs of implementing such policy" (World Health Organization, 2018, p.106).

We agree on the complexity of contractual agreements that can come with all types of MEA and the demands they put informational infrastructure. Thus, many countries are not yet ready to start implementing performance-based health care on a broader basis. Activities related to value assessment and the implementation of local HTA processes will, however, serve as the base for designing suitable MEAs. There are several advantages of performance-based MEA to be weighed in the balance. For example, they:

- may provide faster access to innovative drugs when current pricing mechanisms fail (e.g. during coverage with evidence development agreements)
- send a clear signal to the pharmaceutical industry that they will be paid for value, but not for medicines that fail to deliver benefit (Cole et al., 2019)
- can increase the focus on structures and services that are built on accurate measurement on health outcomes under real world conditions.

Hence, MEAs are a useful approach in principle and practice. However, there is still work left to be done with respect to ex-post evaluations to identify what worked well and in which context (see for example (Garrison et al., 2013)). The WHO could contribute to those efforts and share resulting best practice between member states.

3. HOW DIFFERENTIAL PRICING MIGHT ENHANCE SOCIAL WELFARE

3.1. The economic case

Differential pricing is recommended by the authors of the report (World Health Organization, 2018, chap.5), although at the same time, price discrimination is criticised. Differential pricing in this context refers to the price for the drug being country-specific.[1] It implies that the profit-maximizing price set by the drug manufacturer of a product will be higher in higher-income countries than in low-income countries. The drug price is a function of the country's willingness to pay for the product.

Price differentiation can guarantee greater access to medicines worldwide (without threatening innovation and sustainability). It supports dynamic efficiency by enabling developers of innovative pharmaceutical products to recoup the costs of R&D, while minimising the impact on access to medicines (Danzon, 1997; Danzon and Towse, 2003). Danzon et al. demonstrate that efficiency[2] is achieved when each payer negotiates pharmaceutical prices using a local threshold for willingness-to-pay for health and when health related gain reflects the preferences for health gain of those they are buying for, given the relevant budget constraint and other competing demands on that budget. In other words, countries agreeing to prices that reflect local circumstances combines in total to give the correct global incentive to industry as to where to invest in R&D.

Differential pricing benefits some market participants (like drug manufacturers and patients in low-income countries) but may lead to higher prices for payers in high-income countries. Where a uniform price with no differentiation leads to MLIC markets not being able to afford the drug the benefits are straight forward, price differentiation increases access in MLIC markets and has no impact on prices in HICs. Where it does increase prices in HICs as compared to a uniform price, patients will in the long-run still benefit from price differentiation if the prospect of higher profits translates into higher investments in R&D and the development of new drugs (see (Ridley, 2005; Ikeda and Toshimitsu, 2010)). This implies that in the long-term differential pricing should improve the availability and quality of the drugs for patients in both MLICs and HICs.

3.2. Contradictions in the WHO Report

The authors of the Report advocate differential pricing. They recognize that it may be useful in ensuring drug affordability and availability in low-income countries. Hence the promotion of price differentiation practices is recommended (see ((World Health Organization, 2018, chap.5)).

On the other hand, price discrimination is discussed in a critical and negative tone (see (World Health Organization, 2018, p.30)). Differential pricing is criticised because it does not address public health objectives: "The monopolist would undertake price discrimination for different markets insofar as there are barriers in place to prevent the consumers in various markets from taking advantage of the differences in price and

[1] For a rigorous and detailed discussion of this approach – termed third-degree price discrimination - and its welfare implications see, for example, Tirole, 1988.

[2] Strictly second-best static efficiency and dynamic efficiency.

make a profit from it (i.e. arbitrage). As medicine markets often depend on the health systems [sic] or patient's ability to pay, the market outcomes would often not meet public expectations as well as public health objectives." (see World Health Organization ((2018, p.30)). But, as we set out in section 3.1. above, the theory is clear. A switch from uniform pricing to differential pricing is likely to lower prices for MLICs, enhancing welfare and improving access to medicines.

4. THE NEGATIVE CONSEQUENCES OF PRICE TRANSPARENCY

According to the authors, price transparency "should be encouraged on the grounds of good governance" (World Health Organization, 2018, p.xiii) and hence it is strongly advocated. Transparency as a principle of good governance is not the same as transparency for improving access by lowering prices. In fact, the former often carries an opportunity cost on the latter (Chalkidou and Towse, 2019). The Report concedes "…there is limited context-specific evidence that improving price transparency has led to better price and expenditure outcomes. Nonetheless, improving price transparency should be encouraged on the grounds of good governance." As a recent report suggests (Berdud et al., 2019) this is confusing transparency of process – which increases competition – with disclosing prices, which can undermine price differentiation and also lead to supplier collusion.

4.1. Impacts of price transparency on differential pricing

Non-arbitrage is a critical condition for implementation of differential pricing. In other words, if I supply you at a lower price than I supply your neighbour and you then start supplying the neighbour yourself with my product, so undercutting my price, I can no longer sustain the differential. I have to supply you both at the same uniform price.

Price transparency stimulates arbitrage. If prices are higher in the high-income countries compared to those in the low-income countries, payers in the high-income country have incentives to buy the medicines from wholesalers in the lower income countries rather than from the manufacturer. However, this form of parallel trade does not have to take place. Instead reference pricing can be used. The high-income country references its price to the price being paid in the low-income country. The two markets are linked and the manufacturer is therefore forced to regard them as one and supply at a uniform price.

Ridley (2005) formulates this idea in the following way: "Transparency facilitates parallel trade and creates political pressure for lower prices in higher-income countries. Because manufacturers do not want to undermine their higher prices in higher-income countries, they are motivated to increase prices in lower-income countries. Lower prices for the rich and higher prices for the poor create price compression." Scott Morton (1997) provides evidence that price transparency tends to increase the lowest price offered by the manufacturer. This may even lead to the refusal by the manufacturer to supply because of the fear that other purchasers may insist on getting the same low price. Alternatively, by insisting on a uniform price to avoid referencing, the low-income country may be unable to afford the drug.

In short, price transparency is in complete conflict with differential pricing. Since differential pricing promotes affordability and availability of the drugs in the low-income countries, price transparency harms drug accessibility. The only way it would be

compatible would be with a global agreement on tiered pricing by region and market. As the argument for price transparency made in the WHO Report is that it enables a payer to insist on getting the same (low) price as another payer, the authors are not proposing a tiered pricing agreement.

4.2. Impact of price transparency on Managed Entry Agreements

As outlined in section 2.4. MEAs enable payers and manufacturers to agree prices based on a discount or budget cap (financial-based MEAs) or based on the therapeutic effects of the drugs (outcome-based MEAs). To date, most MEAs are financial-based and are implemented through (usually undisclosed) discounts. MEAs are (almost always) confidential in nature. Ferrario et al. (2017) assessed the implementation and impact of MEAs in East and Central Europe and found that 73% are designed as confidential discounts.

However, In the same way as price transparency prohibits differential pricing implementation, manufacturers may be reluctant to enter MEAs with price transparency because it will affect the prices agreed with other buyers. Ridley (2005) puts it in the following way: "There is a good reason for keeping rebate information private. In general, a seller is less willing to offer a large discount to a buyer if the amount of that discount will be public knowledge and will undermine other prices." Price transparency make MEAs less attractive for manufacturers and may affect adversely medicines' affordability and accessibility.

4.3. Risk of price collusion an unintended consequence of price transparency

Another possible adverse effect of price transparency is that it may make the tacit price collusions among manufacturers more sustainable. The punishment for the deviation from the collusive outcome may be more severe than the one under non-observable prices. Under price transparency, if one firm deviates from a collusive solution, non-deviating firms immediately detect the deviation. In response to this deviation, the non-deviating firms stop behaving cooperatively and enter a tough price competition. As a result, price transparency may prevent firms from lowering their prices in anticipation of these price wars with competitors.

Unobservable price-cuts, however, are more difficult to detect (Stigler, 1964) and may soften the reaction of the non-deviating firms. Hence there may be fewer negative consequences (and more incentives) for the deviating firm from lowering prices if prices are unobserved.

Thus, from our perspective, the improved sustainability of collusion may translate into higher prices under price transparency (as compared to the situation of the non-observable price). Higher prices, in turn, mean lower affordability and availability of drugs.

5. THE EFFECTS OF PRICE CAP REGULATION

The authors of the Report advocate "considering the enforcement of price caps for cancer medicines" (World Health Organization, 2018, p.104).

They argue that price caps are likely to reduce prices of cancer medicines and improve related affordability and availability in the short-run. However, the obvious question is how will the price caps be set? If this is not by reference to the value of the drug – using HTA and value assessment - then the wrong incentives for R&D investment will be given

(Kidokoro, 2002). Price caps disincentivise manufacturers from competing on price and if set too low, may reduce entry to or motivate exit from the market (see Zhang et al. (2016).

One study (Hill, Barber and Gotham, 2018) proposed generating estimates of the cost of manufacturing essential medicines to set drug prices. An OHE analysis (Towse, Hernandez-Villafuerte and Shaw, 2018) critiqued the methods used to generate the cost estimates. The model is not a good predictor of price for the three countries analysed. As a result, imposing prices at the level predicted by the model is likely to lead to an increase in generic drug shortages. Towse et al. argued that the way to tackle generic drug prices is through increasing competition by more effective procurement arrangements which bring in competitive global suppliers, rather than using price controls.

The WHO Report gives Australia as a case study where price caps have restrained pharmaceutical expenditure. However, Australia was the first country to introduce HTA and value-based assessment into the systematic appraisal of drugs for inclusion in its Pharmaceutical Benefit Program. This can be viewed as an indirect form of price control in the sense that it is controlling for the price of health and health related benefits. The price of the pill depends on the expected health value to be delivered to the patient. Australia also has a long history of using financial risk sharing agreements to lock in budget expenditure to the numbers of patients for which the drug is expected to be cost-effective. More recently it has been experimenting with outcomes-based agreements for cancer medicines, in which provisional coverage approval is given subject to additional evidence collection. Australia's expenditure control comes from using HTA, value assessment, and various forms of market entry agreement, not from price controls in the sense that the Report uses them[3]. There is a cost – not all drugs launched globally are accessible by Australian patients.

The Report also cites the UK Cancer Drugs Fund (CDF) as an "anti-competitive business practice." This is incorrect. As the Report points out, the original CDF was a government policy to deliver additional cancer medicines to patients, but at a cost that could not be justified. Advocates of reform (Buxton et al., 2014) were listened to and, with industry support, the CDF is now under the control of NICE and operates as a ring-fenced budget to fund coverage with evidence development, i.e. use of cancer drugs that are expected to be cost-effective by the NHS for a maximum of 2 years, whilst additional evidence is collected. Following a revised value assessment, the drug is either fully funded or rejected. The CDF has evolved to become a potentially successful example of the use of MEAs.

6. THE ERRONEOUS FOCUS ON SUPPLY SIDE FAILURE

The emphasis of the Report is that the R&D side is not working. We are not convinced that this is the major challenge. The Report argues, for example, that R&D returns are too high, using an R&D cost study by (Prasad and Mailankody, 2017) which shows a range of $204m -$2.6bn, using data from 10 biotech companies on 10 oncology drugs. Each company has only one drug. Data and calculations are not disclosed. New work is

[3] Ironically, and as the Report notes, Australia has struggled to buy generics efficiently, using various forms of price control mechanism that have not worked well (Clarke, 2014).

in progress by DiMasi and Grabowski on R&D costs for oncology drugs (personal communication). No doubt the numbers generated will produce controversy. This is ultimately not the key policy issue, however, because it just does not make sense for payers to contemplate moving to a cost-plus pricing model, turning the industry into a regulated utility:

- The need to include both failure rates and the cost of capital means that calculating cost is complex. Even if it were doable at a global level, how would R&D costs be allocated across countries?
- Cost-plus takes away the incentive to keep costs down. It encourages scientists to keep projects going when the expected value is low given other options, and they should be "killed".

Most R&D investment ends in failure. If demand for cancer drugs is high and prices are high, then industry will invest in R&D and find new drugs. The key is to ensure that the demand signals are right. That means paying only for value.

7. FUTURE PRIORITIES FOR THE WHO

We have commented on selected points in the WHO Technical Report on the pricing of cancer medicines and its impact. The Report fails to promote mechanisms and processes (HTA, value assessment and related pricing and purchasing arrangements) that are key to efficient pricing and use of cancer medicines. This is a missed opportunity. Worse, the Report sends readers off in directions that focus on the R&D supply side of the pharmaceutical market rather than seeking to fix the demand side. In our view the priorities for WHO should be to:

1. Provide support for Member States introducing effective HTA and related priority setting mechanisms in order to support both the introduction of UHC and more efficient pricing and reimbursement mechanisms based on value-based pricing.
2. Ensure HTA reflects the context both in terms of the elements of value deemed relevant, and in the impact on the healthcare system. There may be important differences between HIC and MLIC countries as to the character of HTA.
3. Advocate differential pricing of drugs and vaccines. This is crucial to increasing access to on-patent products.
4. Oppose transparency of on-patent pricing. This will reduce both access to medicines and R&D.
5. Recognise that most products that underpin health care provision (by value and volume in MLICs and by volume in HICs) are off-patent multi-source generics (and, in the future biosimilars). Advice on the effective procurement of these products is key.
6. Acknowledge that R&D is best incentivised by use of value-based assessment of health and health related outcomes and by value-based pricing. Additional incentives may be needed for ultra-orphan drugs in oncology and other diseases. Effective management of the demand side of the health system is a far more effective way to get R&D that meets patient and health system needs than seeking to restructure R&D.

8. REFERENCES

Baltussen, R., Jansen, M.P., Mikkelsen, E., Tromp, N., Hontelez, J., Bijlmakers, L. and Van der Wilt, G.J., 2016. Priority Setting for Universal Health Coverage: We Need Evidence-Informed Deliberative Processes, Not Just More Evidence on Cost-Effectiveness. *International Journal of Health Policy and Management*, 5(11), pp.615–618. 10.15171/ijhpm.2016.83.

Barnsley, P., Cubi-Molla, P., Fischer, A. and Towse, A., 2016. *Uncertainty and Risk in HTA Decision Making*. Research Papers. [online] Office of Health Economics. Available at: https://ideas.repec.org/p/ohe/respap/001764.html [Accessed 17 Jul. 2018].

Berdud, M., Garau, M., Neri, M., O'Neill, P., Sampson, C. and Towse, A.K., 2018. R&D, Competition and Diffusion of Innovation in the EU: The Case of Hepatitis C. [OHE Reserach Paper 18/06] London: Office of Health Economics. Available at: https://www.ohe.org/publications/rd-competition-and-diffusion-innovation-eu-case-hepatitis-c [Accessed 8 Apr. 2019].

Berdud, M., Chalkidou, K., Dean, E., Ferraro, J., Garrison, L., Nemzoff, C. and Towse, A., 2019. *The Future of Global Health Procurement: Issues around Pricing Transparency*. [online] Office of Health Economics. Available at: https://www.ohe.org/publications/future-global-health-procurement-issues-around-pricing-transparency# [Accessed 29 Mar. 2019].

Buxton, M., Longworth, L., Raftery, J., Sculpher, M. and Towse, A., 2014. Reforming the Cancer Drug Fund. *BMJ*, 349(nov28 2), pp.g7276–g7276. 10/gdtkc9.

Chalkidou, K., Culyer, A.J. and Nemzoff, C., 2018. Perspective in Economic Evaluations of Health Care Interventions in Low- and Middle-Income Countries—One Size Does Not Fit All. p.18.

Chalkidou, K., Glassman, A., Marten, R., Vega, J., Teerawattananon, Y., Tritasavit, N., Gyansa-Lutterodt, M., Seiter, A., Kieny, M.P., Hofman, K. and Culyer, A.J., 2016a. Priority-setting for achieving universal health coverage. *Bulletin of the World Health Organization*, 94(6), pp.462–467. 10.2471/BLT.15.155721.

Chalkidou, K., Li, R., Culyer, A.J., Glassman, A., Hofman, K.J. and Teerawattananon, Y., 2016b. Health Technology Assessment: Global Advocacy and Local Realities Comment on 'Priority Setting for Universal Health Coverage: We Need Evidence-Informed Deliberative Processes, Not Just More Evidence on Cost-Effectiveness'. *International Journal of Health Policy and Management*, 6(4), pp.233–236. 10.15171/ijhpm.2016.118.

Chalkidou, K. and Madan Keller, J., 2017. Six Reasons Why the Global Fund Should Adopt Health Technology Assessment. *Center For Global Development*. Available at: https://www.cgdev.org/publication/six-reasons-why-global-fund-should-adopt-health-technology-assessment [Accessed 29 Mar. 2019].

Clarke, P., 2014. Pharmaceuticals, pharmacists and profits: a health policy perspective. *Australian Prescriber*, 37(5), pp.148–149. 10.18773/austprescr.2014.058.

Cole, A., Lundqvist, A., Lorgelly, P., Norrlid, H., Karlsberg Schaffer, S., Lewis, F., Hernandez-Villafuerte, K., Lindgren, P., Garau, M., Welin, K.-O., Bianchi, S., Althin, R., O'Neill, P., Persson, U. and Towse, A., 2016. Improving Efficiency and Resource Allocation in Future Cancer Care. Consulting Reports. [online] Office of Health Economics. Available at: https://ideas.repec.org/p/ohe/conrep/001748.html [Accessed 17 Jul. 2018].

Cole, A., Cubi-Molla, P., Pollard, J., Sim, D., Sullivan, R., Sussex, J. and Lorgelly, P., 2019. Making Outcome-Based Payment a Reality in the NHS. p.127.

Culyer, A.J. and Lomas, J., 2006. Deliberative processes and evidence-informed decision making in healthcare: do they work and how might we know? *Evidence & Policy: A Journal of Research, Debate and Practice*, 2(3), pp.357–371. 10.1332/174426406778023658.

Culyer, A.J., 2016. Cost-effectiveness thresholds in health care: a bookshelf guide to their meaning and use. *Health Economics, Policy and Law*, 11(04), pp.415–432. 10.1017/S1744133116000049.

Ferrario, A., Arāja, D., Bochenek, T., Čatić, T., Dankó, D., Dimitrova, M., Fürst, J., Greičiūtė-Kuprijanov, I., Hoxha, I., Jakupi, A., Laidmäe, E., Löblová, O., Mardare, I., Markovic-Pekovic, V., Meshkov, D., Novakovic, T., Petrova, G., Pomorski, M., Tomek, D., Voncina, L., Haycox, A., Kanavos, P., Vella Bonanno, P. and Godman, B., 2017. The Implementation of Managed Entry Agreements in Central and Eastern Europe: Findings and Implications. *PharmacoEconomics*, 35(12), pp.1271–1285. 10.1007/s40273-017-0559-4.

Garner, S., Rintoul, A. and Hill, S.R., 2018. Value-Based Pricing: L'Enfant Terrible? *Pharmacoeconomics*, 36(1), pp.5–6. 10.1007/s40273-017-0567-4.

Garrison, L.P., Jr., Towse, A., Briggs, A., de Pouvourville, G., Grueger, J., Mohr, P.E., Severens, J.L. (Hans), Siviero, P. and Sleeper, M., 2013. Performance-Based Risk-Sharing Arrangements—Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force. *Value in Health*, 16(5), pp.703–719. 10.1016/j.jval.2013.04.011.

Garrison, L.P., Neumann, P.J., Willke, R.J., Basu, A., Danzon, P.M., Doshi, J.A., Drummond, M.F., Lakdawalla, D.N., Pauly, M.V., Phelps, C.E., Ramsey, S.D., Towse, A. and Weinstein, M.C., 2018. A Health Economics Approach to US Value Assessment Frameworks—Summary and Recommendations of the ISPOR Special Task Force Report [7]. *Value in Health*, 21(2), pp.161–165. 10.1016/j.jval.2017.12.009.

Glassmann, A., 2017. Where Does WHO Get Its Economic Advice? *Center For Global Development*. Available at: https://www.cgdev.org/blog/where-does-who-get-economic-advice [Accessed 28 Mar. 2019].

Hauck, K., Morton, A., Chalkidou, K., Chi, Y.-L., Culyer, A., Levin, C., Meacock, R., Over, M., Thomas, R., Vassall, A., Verguet, S. and Smith, P.C., 2019. How can we evaluate the cost-effectiveness of health system strengthening? A typology and illustrations. *Social Science & Medicine*, 220, pp.141–149. 10.1016/j.socscimed.2018.10.030.

Hernandez-Villafuerte, K., Garau, M., Towse, A., Garrison, L. and Grewal, S., 2017a. *Policy Options for Formulary Development in Middle-income Countries*. Consulting Reports. [online] Office of Health Economics. Available at: https://ideas.repec.org/p/ohe/conrep/001784.html [Accessed 17 Jul. 2018].

Hernandez-Villafuerte, K., Garau, M., Towse, T. and Garrison, L., 2017b. *Policy Options for Formulary Development in Middle-income Countries: Mexico Case Study*. Consulting Reports. [online] Office of Health Economics. Available at: https://ideas.repec.org/p/ohe/conrep/001781.html [Accessed 17 Jul. 2018].

Hill, A.M., Barber, M.J. and Gotham, D., 2018. Estimated costs of production and potential prices for the WHO Essential Medicines List. *BMJ Global Health*, 3(1), p.e000571. 10.1136/bmjgh-2017-000571.

Ikeda, T. and Toshimitsu, T., 2010. Third-degree price discrimination, quality choice, and welfare. *Economics Letters*, 106(1), pp.54–56. 10.1016/j.econlet.2009.09.024.

Kidokoro, Y., 2002. The Effects of Regulatory Reform on Quality. *Journal of the Japanese and International Economies*, 16(1), pp.135–146. 10.1006/jjie.2001.0490.

Kristensen, F.B., Husereau, D., Huić, M., Drummond, M., Berger, M.L., Bond, K., Augustovski, F., Booth, A., Bridges, J.F.P., Grimshaw, J., IJzerman, M.J., Jonsson, E., Ollendorf, D.A., Rüther, A., Siebert, U., Sharma, J. and Wailoo, A., 2019. Identifying the Need for Good Practices in Health Technology Assessment: Summary of the ISPOR HTA Council Working Group Report on Good Practices in HTA. *Value in Health*, 22(1), pp.13–20. 10.1016/j.jval.2018.08.010.

Morton, F.S., 1997. The Strategic Response by Pharmaceutical Firms to the Medicaid Most- Favored-Customer Rules. *The RAND Journal of Economics*, 28(2), p.269. 10.2307/2555805.

Navarria, A., Drago, V., Gozzo, L., Longo, L., Mansueto, S., Pignataro, G. and Drago, F., 2015. Do the Current Performance-Based Schemes in Italy Really Work? "Success Fee": A Novel Measure for Cost-Containment of Drug Expenditure. *Value in Health*, 18(1), pp.131–136. 10.1016/j.jval.2014.09.007.

Prasad, V. and Mailankody, S., 2017. Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. *JAMA Internal Medicine*, 177(11), p.1569. 10.1001/jamainternmed.2017.3601.

Ridley, D.B., 2005. Price differentiation and transparency in the global pharmaceutical marketplace. *PharmacoEconomics*, 23(7), pp.651–658. 10.2165/00019053-200523070-00002.

Sanders, G.D., Neumann, P.J., Basu, A., Brock, D.W., Feeny, D., Krahn, M., Kuntz, K.M., Meltzer, D.O., Owens, D.K., Prosser, L.A., Salomon, J.A., Sculpher, M.J., Trikalinos, T.A., Russell, L.B., Siegel, J.E. and Ganiats, T.G., 2016. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA*, 316(10), pp.1093–1103. 10.1001/jama.2016.12195.

Stigler, G.J., 1964. A Theory of Oligopoly. Journal of Political Economy, 72(1), pp.44–61. 10.1086/258853.

Tirole, J., 1988. *The theory of industrial organization*. Cambridge, Mass: MIT Press.

Towse, A., Devlin, N., Hawe, E. and Garrison, L., 2011. *The Evolution of HTA in Emerging Markets Health Care Systems: Analysis to Support a Policy Response*. Consulting Reports. [online] Office of Health Economics. Available at: https://ideas.repec.org/p/ohe/conrep/000192.html [Accessed 17 Jul. 2018].

Towse, A., 2014. Value of Drugs in Practice. In: A.J. Culyer, ed., Encyclopedia of Health Economics. San Diego, CA: Elsevier, pp.432–440.

Towse, A., Hernandez-Villafuerte, K. and Shaw, B., 2018. A critique of the paper "The estimated costs of production and potential prices for the World Health Organization Essential Medicines List". p.16.

Towse, A. and Mauskopf, J.A., 2018. Affordability of New Technologies: The Next Frontier. *Value in Health*, 21(3), pp.249–251. 10/gdtkcx.

UCL Institute for Innovation and Public Purpose, 2018. *The people's prescription: Re-imagining health innovation to deliver public value*. [IIPP Policy Report,] London: IIPP, Global Justice Now, Just Treatment, STOPAIDS. Available at: https:// www.ucl.ac.uk/bartlett/public-purpose/wp2018-10 .

Wilkinson, T., Sculpher, M.J., Claxton, K., Revill, P., Briggs, A., Cairns, J.A., Teerawattananon, Y., Asfaw, E., Lopert, R., Culyer, A.J. and Walker, D.G., 2016. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. *Value in Health*, 19(8), pp.921–928. 10.1016/j.jval.2016.04.015.

World Health Organization, 2015. *2015 Global Survey on Health Technology Assessment by National Authorities. Main findings.* Geneva.

World Health Organization, 2017. *Report on the Fair Pricing Forum 2017*. Geneva: World Health Organization.

World Health Organization, 2018. *Pricing of cancer medicines and its impacts*. World Health Organization.

Zhang, W., Guh, D., Sun, H., Marra, C.A., Lynd, L.D. and Anis, A.H., 2016. The Impact of Price-cap Regulations on Exit by Generic Pharmaceutical Firms. [online] info:doi/10.1097/MLR.0000000000000577.