The efficiency-frontier approach for health economic evaluation versus cost-effectiveness thresholds and internal reference pricing: combining the best of both worlds?

Authors: Frank G. Sandmann, Sarah Mostardt, Stefan K. Lhachimi & Andreas Gerber-Grote

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ABSTRACT

Introduction: The efficiency-frontier approach (EFA) to health economic evaluation aims to benchmark the relative efficiency of new drugs with the incremental cost-effectiveness ratios (ICERs) of non-dominated comparators. By explicitly considering any differences in health outcomes and costs, it enhances the internal reference pricing (IRP) policy that was officially endorsed by Germany as the first country worldwide in 1989. However, the EFA has been repeatedly criticized since its official endorsement in 2009.

Areas covered: This perspective aims to stimulate the debate by discussing whether the main objections to the EFA are technically valid, irrespective of national contextual factors in Germany with the reservations towards using a cost-per-quality-adjusted life year (QALY) threshold. Moreover, we comparatively assessed whether the objections are truly unique to the EFA or apply equally to IRP and cost-effectiveness thresholds.

Expert commentary: The plethora of objections to the EFA (n=20) has obscured that many objections are neither technically valid nor unique to the EFA. Compared to cost-effectiveness thresholds, only two objections apply uniquely to the EFA and concern intended key properties: (1) no external thresholds are needed; and (2) the EFA is sensitive to price changes of comparators. Combining these policies and developing them further are under-utilized research areas.

Keywords: reference pricing; cost effectiveness; health technology assessment; economic evaluation; decision making

1. INTRODUCTION

Internationally, various pharmaceutical policies aim to balance the access to drugs, ensure their quality, and control the growth of the drug expenditures [1, 2]. In this Perspective Article, we focus on pricing policies adopted by policy makers and third-party payers, particularly the practice of benchmarking drug prices by means of internal (i.e., domestic) reference pricing, to which the efficiency-frontier approach (EFA) can be seen as an extension. We believe that the plethora of objections to the EFA has obscured the strengths and limitations of the approach. This is why the main body of this Perspective Article will aim to stimulate the debate by scrutinizing the various objections voiced against the EFA on their merits, irrespective of national contextual factors. However, we acknowledge that some of the confusion can be attributed to the national setting of Germany, which originally proposed the EFA and has officially endorsed it as the only country so far, and that is why we will frame the main body of this Perspective Article within the German context and draw conclusions for other countries.

To begin with, Germany was the first country in the world to introduce internal reference pricing (IRP) to achieve transparency between similar drugs and to curb their expenditures to an equivalent level in January 1989 [3, 4]. At first, IRP meant clustering drugs with the same active ingredient in the domestic market to determine a common price level per cluster, which was subsequently extended to drugs regarded as therapeutically equivalent in 1991 [4, 5].

From 1996 onwards, all newly marketed, patented drugs were excluded from IRP in Germany to protect the pharmaceutical industry, which led to the launch of many drugs with only minor modification (so-called “me-too” drugs); consequently, patented drugs without additional therapeutic benefit were included in IRP again in 2004 [4]. Three years later, in 2007, the legal framework for pharmacoeconomic evaluations was enacted with the explicit aim of assessing the prices of new interventions to inform maximum reimbursable price [6, 7], thus intending a policy applicable to all newly marketed drugs again, including those with additional therapeutic benefit.

When the Institute for Quality and Efficiency in Health Care (IQWiG), Germany’s main health technology assessment (HTA) agency, was tasked with developing a suitable method to inform maximum reimbursable prices within the stipulated framework, the quality-adjusted life year (QALY) was not promoted to the primary endpoint of interest as in other jurisdictions [8, 9]. The main reasons were ethical, methodological and legal concerns about

using QALYs [10], and the absence of a reasonably determined, justified and officially recognized cost-per-QALY-threshold [11, 12]. Instead, national consultations were held and the advice of an international expert panel sought [13], which led to adopting the so-called "efficiency-frontier approach" (EFA) in 2009 [14]. The EFA aims to explicitly consider the different therapeutic values and costs of comparable interventions in an economic evaluation to assess interventions' prices (note: since 2011 the approach could be used in Germany to inform price negotiations if opted for by either the manufacturer or payer [15, 16]). However, with the law referring twice to the international standards of health economics, in which the theorems of resource allocations and health maximization are deeply rooted, the confusion was made perfect as to whether or not IQWiG's aim is, or indeed should be, to maximize health through resource allocation [10]. Moreover, IQWiG does not have the legal remit to prioritize funds across disease areas [12], nor is such prioritization currently a primary aim or concern of Germany's health policy (no fixed ex-ante budget exists for health-care expenditures of a given year; the Social Health Insurance funds may simply choose to increase levies the following year to balance their accounts).

With the efficiency-frontier approach having been criticized ever since its official endorsement, we took the opportunity of it now being 10 years since introducing the legal framework for pharmacoeconomic evaluations in Germany, and about 30 years since introducing IRP, to place the most common objections to the efficiency-frontier approach into perspective. To stimulate the debate, we aimed to disentangle the German context from the efficiency-frontier approach as an analytical tool by reviewing common objections on (1) whether they are technically valid, irrespective of national contextual factors. Moreover, we explored whether the objections are truly unique to the efficiency-frontier approach by also checking whether they applied to (2) the "blunt" alternative of IRP [17], and (3) the often heard suggestion of using an externally set cost-effectiveness threshold (range).

Section 2 will outline a brief theoretical background on each of the three policy alternatives in their function as potential pricing tools for decision makers like third-party payers. We will thus not predetermine the objectives of the decision maker, other than comparing the relative prices (or ratios) of interventions. Section 3 details how we identified objections and against which criteria we assessed them. Section 4 provides our assessment of the objections based against the theoretical background outlined in section 2 and the much more detailed references there within. Section 5 draws four conclusions from having assessed the objections. Section 6 will provide some commentary on the German context given that the

EFA has been officially endorsed only in Germany, while section 7 will identify learning points and a way forward for international settings alike.

2. (NOT TOO) TECHNICAL BACKGROUND ON REFERENCE PRICING, COST-EFFECTIVENESS THRESHOLDS, AND THE EFFICIENCY FRONTIER APPROACH

Generally, reference pricing is a cost-containment policy that aims to stimulate price competition between manufacturers of interventions that have been classified as substitutes based on chemical, pharmacological or therapeutic equivalence [4, 18]. Interventions are clustered together into one group, for which a maximum reimbursement level is set as the reference price for all interventions within that group (often based on the price of the cheapest intervention, or an average or proportion of existing prices [17]). Manufacturers are still free to set the price of an intervention independently, but the difference of the price and the maximum reimbursement limit is then to be paid out-of-pocket by the patients [18, 19]. Although prices of interventions are often also compared internationally (known as external reference pricing, ERP), it is the comparison of interventions available domestically, i.e. internal reference pricing (IRP) [19], that is in the focus of this paper. For an illustration of IRP see Figure 1A.

Incremental cost-effectiveness thresholds may be seen as representing a pre-defined willingness-to-pay for a given unit of effect, the implied cut-off when the maximum budget was to be exhausted, or they may be inferred from previous reimbursement decisions [18, 20, 21]. We will concentrate on the often-cited cost-per-QALY threshold approach as applied in England [8], which has been implied to be a suitable alternative to the EFA [22-25]. Incremental cost-effectiveness ratios (ICERs) above the upper-bound cost-effectiveness threshold (of e.g. £20,000–£30,000/QALY in England) suggest that further arguments are needed to support reimbursing the launch price of an intervention as proposed by a manufacturer, while ICERs below the lower-bound threshold are generally considered cost-effective. Moreover, the threshold can be used to benchmark interventions by adjusting the price of an intervention until the ICER meets the cost-effectiveness threshold [26, 27]; see Figure 1B.

The efficiency-frontier approach can best be illustrated within a cost-effectiveness plane, which visualizes the costs and health benefits of all relevant interventions on two axes. All interventions that are not subject to simple or extended dominance are connected in an

ascending order of effectiveness. The resulting curve consists solely of efficient interventions; see Figure 1C. It thereby aids in determining the most appropriate, i.e. non-dominated, comparator of an intervention in an economic evaluation.

[Figure 1 about here]

The efficiency-frontier approach extends this concept by differentiating between comparators and (new) interventions under investigation, and drawing the curve of the efficiency frontier solely based on the comparators [15]. With the efficiency-frontier approach, a reimbursable price for the (new) intervention under assessment must then be set in such a way that the associated costs and effects come to lie on the curve; see Figure 1D. In case the benefit of the (new) intervention exceeds the highest benefit established with the comparators, the last segment of the efficiency frontier is linearly extrapolated, hence using the same trade-off rate for costs and health effects as for the most effective efficient comparator relative to the second most effective efficient comparator; cf. dashed line in Figure 1D. Consequently, an increase in effectiveness is valued by using the observed trade-off between costs and effects of the non-dominated comparators, which has been called a "proportional rule" [28].

The efficiency-frontier approach is thus intended to provide guidance to decision makers in determining by how much the price of an intervention needs to be adjusted for it to become part of the curve of the non-dominated comparators [13]. Clearly, the same idea is realizable with an exogenously set incremental cost-effectiveness threshold, as occasionally done in England [26, 27].

3. IDENTIFYING AND ASSESSING OBJECTIONS

We searched for objections to the efficiency-frontier approach by means of a pragmatic systematic literature review in PubMed and Embase (last search date 03.08.2015). Free text terms used were (cost benefit* and iqwig") as well as (frontier and (efficiency or approach* or method*)). We used further search techniques like the "similar articles" function in PubMed and forward citation searching in Web of Science and Google Scholar using relevant articles known beforehand. Inclusion criteria were publications with objections to the efficiency frontier, written in English or German. In addition, we considered all objections to the efficiency-frontier approach raised by stakeholders during the formal hearing of IQWiG's first-ever health economic evaluation on antidepressants [22, 29].

We provide for each objection a short statement summarizing its key concern in quotation marks, followed by the result of our assessment in three steps: (1) We assessed the technical validity of each objection with regard to the efficiency-frontier approach. Here, we define "technically valid" as representing a sound attribute or comment on the efficiency-frontier approach as a decision tool that applies to the proposed concept within the theoretical framework outlined above in section 2, independent of any national context. Moreover, we assessed whether the objection is truly unique to the efficiency-frontier approach by also considering the "technical validity" of the objection for (2) internal reference pricing (IRP), which can be seen as the historical context leading to the EFA in Germany, and (3) the cost-per-QALY threshold, which has been proposed by many stakeholders as an alternative to the EFA [22-25]. If relevant, we separated considering the cost-effectiveness threshold (CET) as a hard-decision rule from its use as a benchmark for the (value-based) price level of interventions with regards to the threshold (i.e., adjusting the price until the ICER meets the cost-effectiveness threshold) [26, 27].

In cases where an objection also applied to the two alternative approaches (i.e., IRP and CET), we concluded that the objection was not truly unique to the efficiency-frontier approach. Otherwise, we concluded that it was truly unique to the efficiency-frontier approach.

All three policy options have been assessed from the viewpoint of decision makers like third-party payers/insurers, as originally intended for the EFA. Hence, we are comparing the three policy options with regard to their ability of being drug pricing tools, not in terms of resource allocation tools. Also, we compared each policy as an independent option without complementing each other, while section 5 discusses potential combinations.

4. OUR ASSESSMENT OF OBJECTIONS

The systematic literature search identified 39 publications that fulfilled the study inclusion criteria. In addition, we considered the formal comments of 8 stakeholders (i.e., five pharmaceutical companies, two pharmaceutical industry associations, and one health economics society) [22]. In total, 20 distinctive objections to the efficiency-frontier approach were raised, which included topics on allocation (n=4), comparators (n=2), endpoints (n=3), input parameters (n=4), the practical implementation (n=3), and the epistemological roots (n=4). For an overview of our assessment of objections see Table 1.

[Table 1 about here]

4.1 Objection 1: "The approach avoids externally set cost-effectiveness thresholds." [22]

EFA: Valid. The efficiency-frontier approach does not require any externally set cost-effectiveness thresholds as it derives flexible thresholds from the incremental cost-effectiveness ratios of the non-dominated comparators analyzed (which, in turn, constitute the segments of the curve of the efficiency frontier) [13, 15].

IRP: Valid. Reference pricing schemes do not use or require cost-effectiveness thresholds given their exclusive focus on prices once interventions have been classified as equivalent [17, 18].

CET: Invalid. By default, cost-effectiveness thresholds require an exogenously set and explicit incremental cost-effectiveness threshold (range) to allow making any statements about interventions being cost-effective [30].

4.2 Objection 2: "The approach does not prioritize funds across disease areas." [22-25]

EFA: Invalid. The efficiency-frontier approach aims to limit the expenditure of (new) interventions to an amount justified by the available comparators [6, 7], thereby prioritizing funds implicitly by restricting funding in one area that are freed up for another. By considering any subtle differences in health outcomes explicitly, however, the efficiency-frontier approach improves the rather "blunt" IRP schemes [17]. Nonetheless, the focus of the EFA rests on pharmaceutical pricing within disease areas and not on an intentional, deliberate

way of prioritizing resources across disease areas explicitly. When employing the EFA in isolation, without a subsequent appraisal, the slope of the efficiency frontier in a disease area may thus be a potentially historical chance result (cf. objection 10 and 11). In our opinion, the absence of enough comparators to draw a frontier can be regarded as an indicator for the need of prioritization in its own right; cf. rare diseases. Lastly, the explicit use of the EFA to prioritize funds across disease areas requires a similar comparison across endpoints, e.g. with some form of aggregated measure of outcomes (cf. objections 7 and 8).

IRP: Invalid. Reference pricing aims to limit the expenditure on interventions in indications for which comparable alternatives exist; as such, funds are prioritized on disease areas with fewer alternatives, if at all available [18]. Similar to the EFA, reference pricing can only be applied with sufficient comparators.

CET: Invalid. Cost-effectiveness thresholds aim to maximize health by prioritizing funds to disease areas where the most QALYs are gained, irrespective of whom [31]. In practice, this aim may not be achieved, particularly when used only as a funding threshold that ignores the related issues of affordability and the budget impact [32-34].

4.3 Objection 3: "The approach does not represent societal preferences or the maximum willingness-to-pay for new drugs." [22-25]

EFA: Valid. By default, the efficiency-frontier approach may not reflect the maximum willingness-to-pay of society, especially in disease areas with only generic competition [13]. When based on the price level of patented comparators, however, the slope of the last segment of the frontier may at least reveal the current willingness-to-pay of payers [13].

IRP: Valid. Reference pricing likewise benchmarks the price of new drugs to existing comparable alternatives [18]. Nonetheless, the maximum reimbursement limit does not equate to the maximum willingness-to-pay as demonstrated by patients who are willing to make out-of-pocket co-payments for the non-reimbursed price difference [4, 18].

CET: Valid. Ideally, cost-effectiveness thresholds represent the forgone opportunity costs, which is why e.g. the threshold proposal of the World Health Organization (WHO) based on a country's gross domestic product has been heavily criticized for the missing link to actually displaced or unfunded services [34]. In practice, however, these thresholds rather often also reflect the willingness-to-pay of payers (most prominently seen for the threshold proposed for

the USA [21]), not necessarily societal preferences or their maximum willingness-to-pay for new drugs [35-37].

4.4 Objection 4: "The approach avoids explicitly rationing effective drugs on economic grounds." [38]

EFA: Valid. The efficiency-frontier approach avoids rationing effective drugs on economic grounds due to its aim of providing guidance on appropriate reimbursable prices in relation to existing comparators (which can be achieved by reducing the price of interventions whose effectiveness is lower than that of the comparators) [39]. The EFA has not been intended as a binary decision rule [13].

IRP: Valid. Reference pricing also avoids rationing effective drugs on economic grounds by offering a lower reimbursed price, with any difference needed to be paid by patients [17, 18].

CET: Invalid. Cost-effectiveness thresholds could be used to ration effective but inefficient drugs on economic grounds [36], while using it to benchmark the price of an intervention for its ICER to meet the cost-effectiveness threshold may also avoid rationing effective drugs on economic grounds [26].

4.5 Objection 5: "The approach could be used with an inadequate comparator." [22]

EFA: Valid. The efficiency-frontier approach could lead to biased results when using an inadequate comparator [40]. However, as the approach is intended for multiple-technology assessments that include all relevant alternatives as possible comparators [13, 14], an intervention should inevitably be compared with the most efficient, non-dominated (and thus most adequate) comparators.

IRP: Invalid. Reference pricing only applies to interventions once they have been classified as substitutes based on chemical, pharmacological or therapeutic equivalence [4, 18].

CET: Valid. Similar to the efficiency-frontier approach, using an inadequate comparator in the analysis could also lead to biased results with exogenously set cost-effectiveness thresholds [41]. The risk of choosing an inadequate intervention as comparator might even be higher when avoiding multiple-technology assessments [40].

4.6 Objection 6: "The approach is open to manipulation by adding a 'meaningless' alternative to the market." [22]

EFA: Invalid. Given that the efficiency-frontier approach has been intended to assess the prices of new interventions, a newly marketed "alternative" was to be assessed itself, meaning that it should not be considered for the efficiency frontier of non-dominated comparators [13, 14]. A newly added "alternative" could only affect the slope of the curve if it was misclassified as a comparator [40], and even then only if it became a constituting part of the frontier (cf. objection 5; for the related concern of strategic pricing of existing alternatives see objection 12).

IRP: Valid. Any newly marketed "alternative" that is considered comparable to existing interventions was to be clustered with them, or it would enable clustering existing interventions [17]. As such, its price would potentially alter the reference price of that cluster [4].

CET: Invalid. Similar to the efficiency-frontier approach, a scientifically sound analysis based on a cost-effectiveness threshold was to use the newly marketed "alternative" as the main intervention of interest, not as the comparator [41].

4.7 Objection 7: "The approach purposely avoids using the QALY as an endpoint." [42]

EFA: Invalid. Drawing an efficiency frontier in a cost-effectiveness plane does not forestall the choice of health effects used [43, 44], and neither does the efficiency-frontier approach [13, 15]. It largely depends on the national context whether the QALY will be used as an endpoint, and particularly whether it is promoted to the primary endpoint of interest (cf. Introduction) [8, 9]. An overview of the strengths and limitations of the QALY is outside the scope of this Perspective Article and has been given elsewhere [31, 45].

IRP: Valid. Reference pricing does not consider QALYs given the focus on prices once interventions have been classified as equivalent [17, 19].

CET: Invalid. Cost-effectiveness thresholds conventionally use an externally set cost-per-QALY threshold, and thus do not avoid the QALY by default [45].

4.8 Objection 8: "The approach avoids aggregating endpoints." [22]

EFA: Invalid. The efficiency-frontier approach could be used with aggregated endpoints such as the QALY [13, 15], or the results for different endpoints could be aggregated by means of multi-criteria decision analysis (MCDA) techniques [46, 47].

IRP: Valid. Reference pricing does not consider aggregated endpoints given the focus on prices once interventions have been classified as equivalent [17, 19].

CET: Invalid. Cost-effectiveness thresholds conventionally use an externally set cost-per-QALY threshold, and thus intentionally apply an aggregated endpoint by default [45].

4.9 Objection 9: "The approach requires cardinally-scaled endpoints." [22, 23]

EFA: Valid. The efficiency-frontier approach requires cardinally-scaled endpoints, at least in the relevant area of analysis [48].

IRP: Invalid. Reference pricing does not require cardinally-scaled endpoints given the focus on prices once interventions have been classified as equivalent [17, 19].

CET: Valid. Cost-effectiveness thresholds effectively also require cardinally-scaled endpoints, at least in the relevant area of analysis [45, 48].

4.10 Objection 10: "The approach does not consider life-cycles of on-patent drugs (from high prices to generic, and thus lower, prices) by comparing them to historic pricing decisions." [22]

EFA: Valid. The efficiency-frontier approach does not consider the life-cycle of drugs explicitly as the approach was intended for indication-specific analyses using the current prices of the existing alternatives [13]. However, it is not inherent to the approach but the context (and research question) whether the value of the price is chosen to be current, historic, or varying over time.

IRP: Valid. Reference pricing does not consider life-cycles of drugs given the focus on current prices at the time of establishing, or updating, a cluster of equivalent drugs [17, 19].

CET: Valid. Similar to the efficiency-frontier approach, life-cycles of drugs are usually not considered, with a rare example in Hoyle (2011) [49]. Implicitly, the fixed-threshold approach may consider historic pricing decisions when the thresholds are based on patented

interventions whose costs were previously accepted for reimbursement, but not necessarily when the threshold is based on e.g. the value of a statistical life [9].

4.11 Objection 11: "The approach does not properly acknowledge the research and development costs of drugs." [22, 24, 25]

EFA: Valid. The efficiency-frontier approach does not consider the research and development costs of drugs explicitly. When using it without a separate appraisal that addresses such additional concerns, disease areas where the prices of the comparators do not (even implicitly) reflect their research and development costs may be disadvantaged (e.g. indications with only generic comparators).

IRP: Valid. Reference pricing also does not consider the research and development costs of drugs explicitly, which, however, has not been shown to dis-incentivize pharmaceutical innovation [18].

CET: Valid. Cost-effectiveness thresholds also do not consider the research and development costs of drugs explicitly [21, 36]. Arguably, research and development costs are implicitly considered when the threshold is derived from past decisions for patented drugs.

4.12 Objection 12: "The approach could be influenced by altering prices of interventions." [42]

EFA: Valid. The slope of the efficiency-frontier approach could be influenced by changes in the price of comparators (which may result in changes of uptake, and lower healthcare expenditures). However, this presumes for the price-changing company to know beforehand the price level (and associated costs) at which its intervention becomes part of the frontier without incurring substantial profit losses. It also needs to become part of that particular segment of the curve that is used for the assessment (given that the frontier may consist of more than one segment; cf. Figure 1D). If the comparator is owned by a different manufacturer it is not apparent why they would lawfully reduce the price (and voluntarily accept lower profits) to the advantage of a competitor.

IRP: Valid. Given that the reference price is set based on the prices of the existing interventions in a cluster [17, 18], changing the price of existing interventions may impact the level of the price cap in a cluster. Moreover, there are strong incentives for manufacturers to

price their interventions at a higher level than they would have without being subjected to reference pricing [18].

CET: Invalid. Cost-effectiveness thresholds cannot be influenced by altering prices (as it is explicitly set ex ante), but the ICER can be influenced similarly through strategic price changes, which may lead to obtaining less QALYs from a fixed budget [26, 37].

4.13 Objection 13: "The approach requires data that may not always be available." [22]

EFA and CET: Valid. Adequate data are a universal requirement of scientifically sound analyses [41]. Nonetheless, key data on necessary input parameters may be missing for any given disease (in case no indirect treatment comparisons are possible), and the chance of data missing may increase with the number of interventions analyzed.

IRP: Valid. Reference pricing can only be performed once sufficient interventions are available that can be classified as equivalent [18].

4.14 Objection 14: "The approach assumes constant returns to scale and perfect divisibility." [50]

EFA and CET: Valid. Assuming constant returns to scale (i.e. constant marginal health benefits of interventions, irrespective of the amount purchased) and perfect divisibility of interventions is a fundamental limitation of all continuous, linear thresholds [51].

IRP: Invalid. Reference pricing does not make these assumptions in the absence of a linear threshold and the focus on marginal unit prices [18].

4.15 Objection 15: "The approach is very onerous." [22, 23]

EFA: Invalid. The efficiency-frontier approach is intended to include all relevant interventions. However, the approach itself does not require unduly greater effort than any other health economic evaluation performed as a multiple technology assessment (cf. objection 13). Previous research also explored a "shortcut"-application of the efficiency-frontier approach to allow for rapid assessments [52, 53].

IRP: Invalid. Reference pricing is not very onerous given the exclusive focus on prices once interventions have been classified as equivalent [17, 18], which may arguably be the most onerous part.

CET: Invalid. Like the efficiency-frontier approach, applying a cost-effectiveness threshold range is not the most onerous part of an economic evaluation; the complexity rather increases with the choice of the analysis, i.e. whether it is performed as multiple-technology assessment or single-technology assessment [17, 33].

4.16 Objection 16: "The approach could lead to negative ex-factory prices if all trade margins are deduced." [22]

EFA: Valid. If the efficiency-frontier approach let to recommend reducing the price of a drug, the price could become negative if the distance between the location of the intervention and the efficiency frontier was very large, indicating an intervention's inefficiency in relation to the existing comparators. Any low price level could lead to negative prices if all trade margins were deduced, and if the results were implemented mindlessly without an appraisal.

IRP: Valid. If a reimbursement cap based on reference pricing was to be set at very low levels, it is conceivable that ex-factory prices could become negative when deducing all trade margins. However, it has been observed that manufacturers anticipate this when pricing interventions potentially subjected to IRP [18].

CET: Invalid/Valid. Negative ex-factory prices do not occur for cost-effectiveness thresholds used as hard decision rule given that interventions with very high ICERs would be deemed cost-ineffective, and access to the market denied [54]. However, it obviously also applies to cost-effectiveness thresholds used to benchmark prices (when they need to be drastically reduced).

4.17 Objection 17: "The approach deviates from international health economic standards." [22-24]

EFA: Invalid. Using an efficiency frontier to inform decision makers has been officially adopted in two other countries [55, 56], albeit not to benchmark prices as proposed with the efficiency-frontier approach in Germany [13, 15]. However, the comparison of ICERs from non-dominated comparators bears close resemblance to the comparison of the ICER for the

most expensive intervention funded in the USA [21], and the Programme Budgeting Marginal Analysis (PBMA) approach in Australia [33].

IRP: Invalid. Reference pricing of drugs has been conducted in domestic markets for nearly 30 years [5], with at least 20 European countries using internal reference pricing [18].

CET: Invalid. Using cost-effectiveness thresholds to assess interventions' cost-effectiveness has been applied for decades [23, 57], though it has become the national standard in only a few countries [9] and some see its importance diminishing [58], partly due to the issues associated with having one single metric that may not capture all relevant effects [20]. Using cost-effectiveness thresholds to benchmark prices (and costs) of interventions is seen rather critically by some [26, 27].

4.18 Objection 18: "The approach lacks theoretical embedding in economic theory." [22, 50]

EFA and CET: Invalid. The efficiency-frontier approach builds on the well-known concept of the efficiency frontier in (health) economics and decision sciences [43, 44, 59-64]. It is based on the same theoretical foundations as the fixed-threshold approach [65, 66].

IRP: Invalid. Reference pricing is based on the idea that similar goods with nearly identical characteristics (i.e. interventions classified as substitutes based on chemical, pharmacological or therapeutic equivalence [17, 18]) should be selling for the same price.

4.19 Objection 19: "The approach lacks an international debate." [22]

EFA: Invalid. The efficiency-frontier approach was subjected to an extensive formal hearing organized by IQWiG in Germany in 2008, and since then the approach has been debated at national and international conferences and in scientific journals [13, 23-25, 38, 48, 52, 67-74].

IRP: Invalid. The Organization for Economic Co-operation and Development (OECD), the WHO, the European Commission (EC), the Cochrane Collaboration and various academics have all discussed the advantages and disadvantages of reference pricing [2, 4, 17-19, 75].

CET: Invalid. Cost-effectiveness thresholds continue to be extensively debated, which has been ongoing for a much longer period of time [2, 18, 20, 32, 34, 36, 65].

4.20 Objection 20: “The approach uses an arbitrary method to inform decision makers about uncertainty.” [22]

EFA: Invalid. The efficiency-frontier approach has been suggested to be used in conjunction with the interquartile range of the recommended reimbursable price as an aid for subsequent price negotiations [29, 76], which has been misunderstood to be an aid to inform decision makers about uncertainty. Exploring uncertainty in the EFA is indeed an active research area; for the impact of uncertainty on the price recommendation see Corro Ramos et al. [77].

IRP: Invalid. Reference pricing does not inform decision makers about uncertainty given the focus on prices once interventions have been classified as equivalent [17, 19].

CET: Invalid. For cost-effectiveness thresholds, elaborate uncertainty analyses have been an important research area to inform decision makers [78, 79].

5. CONCLUSION

Having assessed 20 objections to the efficiency-frontier approach, we found 11 objections that, in our opinion, could be classified as technically valid.

Many of the objections aimed at properties of the efficiency-frontier approach that are intended to improve the existing reference pricing system in Germany by explicitly considering health endpoints (cf. objections 7-9). Compared to a cost-effectiveness threshold, only two objections are truly unique to the efficiency-frontier approach and concern intended key properties: 1) the efficiency-frontier approach does not require external thresholds due to being derived from existing comparators, and 2) the efficiency-frontier approach is thus supposed to be sensitive to price changes of comparators.

Based on these findings, we draw the following four conclusions: First, a plethora of objections to the efficiency-frontier approach has been raised, with many applying equally to alternative policies and indeed any threshold approach. We appreciate that the relevance of (some of) the objections listed here may be questioned, which was meant to give a comprehensive overview of the criticism that the EFA has been attracting. Instead of speculating about the reasons why this has been happening, we merely opted to assess whether the objections actually have some technical merit. Knowing that the topic, the EFA and these "objections" may be considered controversial by some, we have thus opted for a Perspective Article.

Second, there appear to us to be fewer differences between the efficiency-frontier approach and a cost-effectiveness threshold than may be suggested by the sheer amount of objections. While we acknowledge that there may be disagreement with our assessment and some, or indeed all, of the objections may be judged differently by researchers in terms of their "technical validity", we have included our judgement as an anchor against which the public is invited to base his/her own judgement on. Overall, however, the key distinction between the EFA and CETs is by default their aim and how they reach it, although both approaches may arguably serve both purposes [28]: The efficiency-frontier approach has been intended for the assessment of prices by deriving flexible thresholds to benchmark the relative efficiency of (new) interventions; the fixed-threshold approach has been intended for judging on (new) interventions' cost-effectiveness with implications for their reimbursement based on an external threshold (cf. objection 1 and 12).

Third, it seems important to stress that, unlike IRP, neither of the other two approaches bears the appraisal in itself nor qualifies for an automated reimbursement process (a misunderstanding shared by WHO's threshold proposal; see Bertram et al. [34]). The primary aim of these approaches is to provide guidance to decision makers for a subsequent multi-criteria appraisal, in which various factors in favor for and against reimbursing the launch price of an intervention are to be considered (including opportunity costs, potential weaknesses of the approaches for e.g. rare diseases [80, 81], and research and development costs; cf. objection 11). Any unfavorable assessment with either approach would thus highlight the need for additional arguments to support an intervention's reimbursement (at a higher premium).

Fourth, there is an under-utilized opportunity for researchers to develop policies further. For instance, in our view it would be worth exploring using historic market-entry prices within indications (cf. objection 10) or the on-patent prices across indications. Also, policies could be used simultaneously to complement each other, where the exogenous threshold may indicate health opportunity costs while the efficiency frontier approach may then indicate how the intervention compares to existing alternatives.

6. EXPERT COMMENTARY

Without the historical context of healthcare legislation in Germany set out in the introduction of this paper, it may be difficult to understand the reasons that led to the idea of the efficiency-frontier approach for reimbursement decision-making. When policy makers enacted the legal framework for health economic evaluations in Germany in 2007, they attempted to close a regulatory loophole for patented drugs that had not been covered by internal reference pricing since 1996 anymore. Moreover, the established reference pricing system was to be expanded (again) but this time informed by a much more elaborate process that explicitly considered any subtle differences in benefits and costs between interventions with additional therapeutic benefit. Accordingly, the approaches and standards valid in other countries with different legal and cultural contexts were not easily transferrable to the German setting [12]. Instead, the efficiency-frontier approach appears to have been responding closely to the ideas of the legal framework by combining the price efficiency of the reference pricing system (familiar in German reimbursement policy) with the explicit cost-to-benefit consideration of economic evaluations (unfamiliar in German reimbursement policy); it was thus striving to combine the best of both worlds.

From an international perspective, however, this pricing policy clashed with the alternatively used cost-effectiveness thresholds and the economic idea of resource allocation, and it led to the efficiency-frontier approach being widely opposed. This did not go unnoticed by German policy makers, and by 2011 they have had effectively adopted a reimbursement system based largely on comparative effectiveness when enacting the 'Act on the Reform of the Market for Medicinal Products' (AMNOG) [16]. Under this system, in brief, if a new drug is able to demonstrate an additional therapeutic benefit in randomized controlled trials to a (usually non-placebo) comparator, the manufacturer and the payer enter into price negotiations. Without such a proven additional therapeutic benefit, pricing of the new drug is capped at the price of the comparator (cf. IRP) [18]. If the manufacturer disagrees with the price cap, or negotiations fail, either party could ask for an economic evaluation being conducted to inform renewed price negotiations [82-84]. So far this has never happened, likely due to the disincentives for either party; payers benefit from lower prices of the "blunt" IRP system [17], while manufacturers face the entire financial burden when commissioning an economic evaluation of uncertain outcome to them and possibly negative impact in case a lower price was recommended. Thus, unsurprisingly, no economic evaluation has been commissioned since AMNOG was introduced in 2011 (as of June 2018) [85].

With it now being ten years since enacting the legal framework for health economic evaluations in Germany, the initial attempts to link health economic considerations to the drug pricing system must be judged as having failed; cost-effectiveness relationships play de-facto currently no role for drug pricing in Germany. However, evidence-based health technology assessments in the form of comparative effectiveness research have been successfully integrated in the reimbursement system since 2011 [82-84], providing a more structured system to investigate in potentially clustering drugs based on their health impact. From a societal perspective, it seems obvious to us that it would be desirable to have a similar rigorous system for the costs of drugs, and the relationship of cost-to-benefits between different drugs. For the time being, the optimists among us hence hope for health economic evaluation being only a "sleeping beauty" in Germany [85]. However, for as long as the financial and political pressure is not strong enough (as in the build up to the 1989 reform), the current system in Germany is unlikely to change soon. As such, the prices negotiated may only by chance reach a level considered appropriate [20, 86], which may raise avoidable opportunity costs.

7. FIVE-YEAR VIEW

In 2019, it will be 30 years since Germany, as the first country, introduced internal reference pricing [3]. In general, Germany is a prime example for the international struggle of policy makers trying to find a way that determines appropriate prices for patented drugs while honoring the commitments of access, quality and price control. At this point, however, it seems highly desirable to us to include health economic considerations explicitly into the drug pricing and reimbursement system of any country to avoid ignoring the opportunity costs of funding decisions, and the relative differences in the achievable health and costs. At least three issues need to be reconsidered:

1. While comparative effectiveness research remains undoubtedly pivotal for analyzing the therapeutic value of interventions, it should be the first step in a process complemented by analyzing the opportunity costs associated with the different benefits and expenditures of alternative therapies, particularly those currently not subjected to reference pricing (i.e., interventions with a proven additional therapeutic benefit). The Netherlands are a good example to show that combining these policies is feasible, as the reimbursement system established there complements reference pricing with cost-effectiveness analyses [17, 87].

2. Moreover, it will need sufficient political will to change the current system in order for society to benefit from cost-effectiveness considerations as a whole. To achieve this goal, the procedure for economic evaluations may need to change to raise the appeal and perceived usefulness for policy makers: The conventional IRP is conducted in Germany on an annual basis [82-84], while the comparative effectiveness assessment is usually also concluded within one year [85]. It will thus need a rapid assessment of the health economic aspects to appeal to decision makers, with a short-cut having been proposed before [52, 53]. Australia's Programme Budgeting Marginal Analysis (PBMA) approach provides another example for a rigorous assessment system that suffices with a robust reference/base case, as adding further complexity to the analysis has seldom changed past funding decisions [33].

3. In addition, risk-sharing arrangements need to be explored so as to share the uncertainty associated with the financial burden of additional research among manufacturers and payers (as representatives of society) [88]. In Germany, for instance, manufacturers are currently obliged to pay for the economic evaluation if requested by them. This one-sided financing arrangement provides disincentives for both payer and manufacturers to commission economic evaluations, as the gains from the conventional IRP scheme seem to unduly

advantage the payer and disproportionately burden the manufacturers. One needs to bear in mind that neither the concentration of market power with the manufacturers in monopolies nor with the payers in monopsonies will lead to efficient prices [89]. It may thus indeed need more independent research with the necessary support to investigate in prices in the best interest of both industry and payers, which is ultimately to benefit society as a whole.

8. KEY ISSUES

- The efficiency-frontier approach (EFA) benchmarks intervention's prices based on the relative efficiency to comparators' incremental cost-effectiveness ratio (ICER).
- In Germany, the EFA can be regarded as following in the footsteps of internal reference pricing (IRP), a successful cost-containment strategy celebrating its 30th anniversary in 2019 that was once applicable to all drugs but has been excluding patented drugs with additional therapeutic benefit for 20 years since 1996.
- The EFA aims to combine the savings achievable with IRP and the explicit consideration of cost-effectiveness ratios of economic evaluations, or indeed the best of both worlds, to inform drug pricing negotiations.
- The plethora of objections to the EFA, however, has obscured that many objections are neither technically valid nor unique to the EFA.
- There is an under-utilized opportunity to research into these policies to further develop them, e.g. by using them complementary where exogenous cost-effectiveness thresholds may indicate health opportunity costs while the EFA may indicate how the intervention compares to existing alternatives.

9. FIGURES

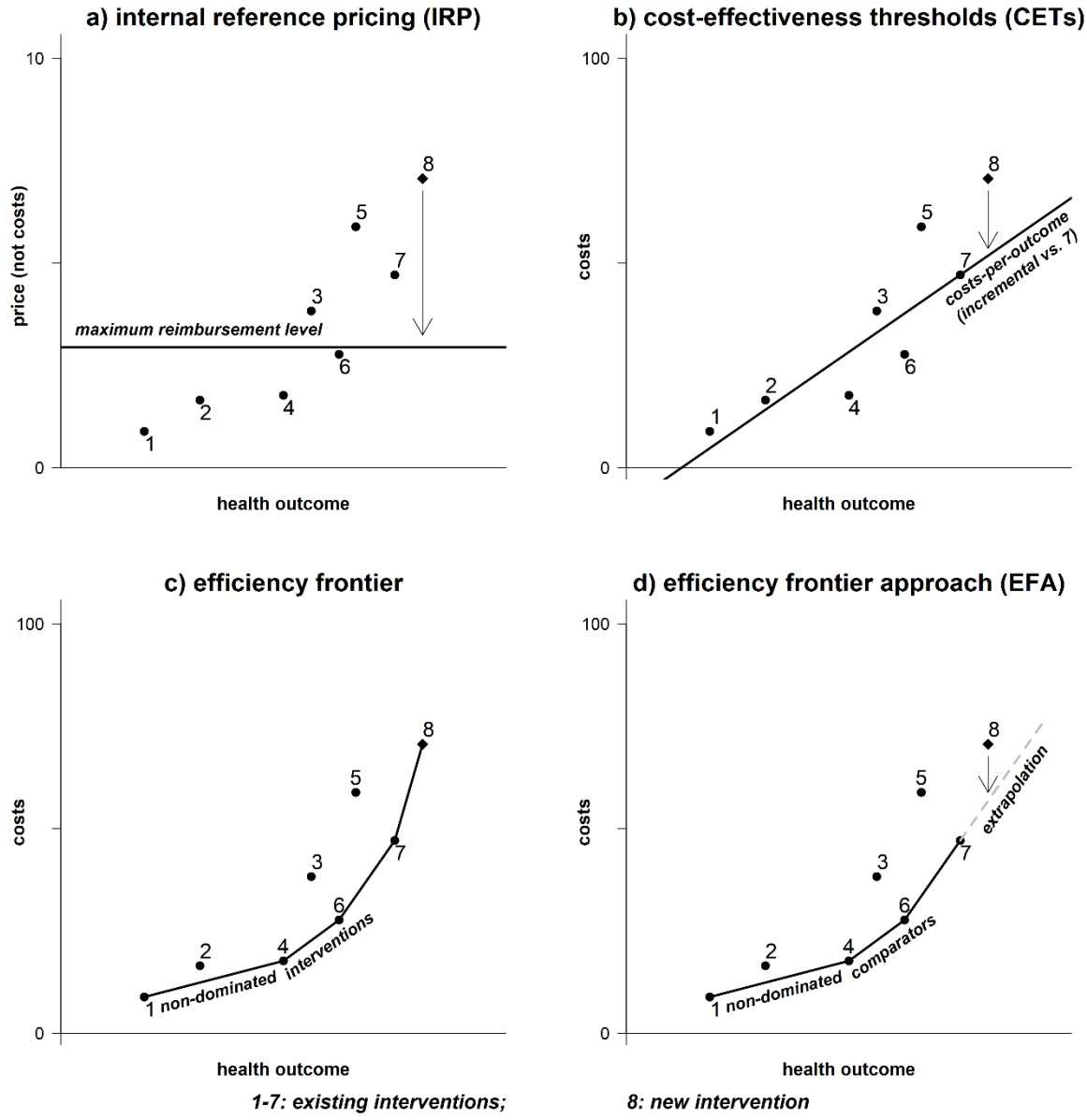

Figure 1. Illustration of the different policies and approaches discussed in this Perspective Article for 8 interventions in a cost-effectiveness plane. Panel a): Internal reference pricing (IPR), with a set maximum price reimbursement level. This level could e.g. be based on an average, meaning that the price above the line is not paid for by third-parties; the new intervention 8 would either require copayments from patients or needing to reduce its price to the maximum reimbursement level. Panel b): Cost-effectiveness threshold (CET) applied incrementally to the new intervention 8 versus the most-appropriate comparator intervention 7. The new intervention 8 is deemed cost-ineffective, and without additional arguments it becomes cost-effective only when reducing its price, i.e. shifting intervention 8 downwards until it lies on the cost-effectiveness threshold. Panel c): The curve of the efficiency frontier

604 indicates the non-dominated interventions. Panel d): Efficiency-frontier approach (EFA) as
605 adopted by IQWiG , with inverted axes for the ease of comparison. Interventions 1 to 7 are
606 used as comparators to assess the new intervention 8. The curve comprises the non-dominated
607 comparators, with the slope of the last segment being extrapolated forward to account for the
608 higher benefit achieved with the new intervention 8. In this example, the EFA would lead to
609 the recommendation of a price reduction, i.e. shifting intervention 8 downwards until it lies on
610 the efficiency frontier. Also note the potential pricing implications for the dominated
611 comparators 2, 3 and 5.

612

613 **TABLE**

614 **Table 1.** Validity and uniqueness of objections to the efficiency-frontier approach

Objection	Step 1: Valid for EFA?	Step 2: Valid for IRP?	Step 3: Valid for CET?
Objections concerning allocation			
1: "does not use explicitly set thresholds"	yes	yes	no
2: "does not prioritize funds across disease areas"	no	no	no
3: "does not represent societal preferences or maximum WTP"	yes	yes	yes
4: "does not ration effective drugs on economic grounds"	yes	yes	no/yes[a]
Objections concerning the comparator			
5: "could be used with an inadequate comparator"	yes	no	yes
6: "is open to manipulation by adding a 'meaningless' alternative to the market"	no	yes	no
Objections concerning endpoints			
7: "does not use the QALY as an endpoint"	no	yes	no
8: "does not use aggregating endpoints"	no	yes	no
9: "requires cardinally-scaled endpoints"	yes	no	yes
Objections concerning input parameters (costs, prices, other data)			
10: "does not consider life-cycles of drugs (using historic prices)"	yes/no[b]	yes	no/yes[c]
11: "does not properly acknowledge R&D costs of drugs"	yes	yes	yes
12: "could be influenced by altering prices"	yes	yes	no
13: "requires data that may not always be available"	yes	yes	yes
Objections concerning practical implementation			
14: "assumes constant returns to scale and perfect divisibility"	yes	no	yes
15: "is too onerous"	no	no	no
16: "could lead to negative prices if all trade margins are deduced"	yes	yes	no/yes[a]
Objections concerning the epistemological roots			
17: "deviates from international health economic standards"	no	no	no
18: "lacks theoretical embedding in economic theory"	no	no	no
19: "lacks international debate"	no	no	no
20: "uses an arbitrary method to inform about uncertainty"	no	no	no

CET: cost-effectiveness threshold, EFA: efficiency-frontier approach, IRP: internal reference pricing, N/A: not applicable, QALY: quality-adjusted life year, R&D: research and development, WTP: willingness-to-pay.
a: not valid when used as a hard decision rule; valid when used to benchmark (value-based) prices to meet the cost-effectiveness threshold.
b: valid for the initial proposal of using current prices of the comparators; not valid as the initial proposal was context-specific and not inherent to the efficiency-frontier approach.
c: not valid when the value of a threshold implicitly accounts for it (e.g. when based on the costs of patented interventions that were previously accepted for reimbursement); valid when not implicitly account for (e.g. when based on the value of a statistical life).

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** = overview of the current drug reimbursement system in Germany (mostly unchanged as of June 2018), with a particular focus on economic evaluations and the efficiency frontier approach

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