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Methodology

## The Effect of the Drug Life Cycle Price on Cost-Effectiveness: Case Studies Using Real-World Pricing Data



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### ABSTRACT

**Objectives:** Cost-effectiveness analyses (CEAs) generally assume constant drug prices throughout the model time horizon, yet it is known that prices are not constant, often with price decreases near loss of exclusivity (LOE). This study explores the impact of using dynamic drug-specific prices on the incremental cost-effectiveness ratio (ICER) using selected reproduced case studies.

**Methods:** Case studies were selected following explicit criteria to reflect a variety of drug characteristics. For each drug, a published CEA model was identified, replicated, and modified with dynamic real-world pricing data, to compare ICERs based on constant drug prices with estimates obtained when including drug life cycle pricing. The impact of dynamic real-world pricing—inclusive LOE—was analyzed using a single patient cohort and multiple cohorts over time.

**Results:** Fluvastatin, alendronic acid + colecalciferol combination therapy, letrozole and clopidogrel were selected as case studies. Inclusion of real-world pricing data compared with applying constant prices reduced the ICER in a single-cohort setting up to 43%. In the multicohort analyses, further reductions of the ICERs were observed of up to 113%. The ICERs were sensitive to the period of drug usage relative to the models' time horizons, the relative proportions of drug costs in the overall treatment costs, and timing of LOE compared with the cost year of the original analysis.

**Conclusions:** Assuming dynamic drug prices may lead to more representative ICER estimates. Future CEAs for drugs could account for predicted and disaggregated life cycle price developments based on retrospective data.

**Keywords:** cost-effectiveness, drug product lifecycle, dynamic drug prices, loss of exclusivity, patent expiration, real-world data.

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### Introduction

In many high-income countries, cost-effectiveness analyses (CEAs) are part of the reimbursement decision-making process. In these analyses, disease- and cost-modeling approaches are used to identify the health outcomes and incremental costs of a health technology relative to current practice. Typically, cost parameters are assumed to be constant for the whole duration of the model simulation.<sup>1–4</sup> In particular, drug costs, which are often one of the key drivers of the cost-effectiveness outcome, are held constant even though it is known that drug prices change over the drug life cycle and decrease significantly after loss of exclusivity (LOE) and potentially already before, for example, due to increasing competition and possible price or volume agreements.<sup>5</sup>

Including such price dynamics in CEAs might have a significant impact on the incremental cost-effectiveness ratio (ICER). Indeed, several studies have previously shown that incorporating future price decreases—inclusive those due to LOE—of the analyzed drug or alternatively its comparator relevantly affects the drugs'

cost-effectiveness profile in a positive or negative manner.<sup>6–10</sup> Previously, for example, British real-world price data for 1980 to 2006 were analyzed, showing a mean annual decrease of 3.8% for an individual drug, resulting here in decreasing ICERs, especially for chronic long-term conditions.<sup>10</sup> This study was expanded by additionally introducing the varying sizes of future incident patient cohorts into the drug life cycle,<sup>6</sup> highlighting the necessity to look beyond just the first cohort that starts drug treatment, as reduced prices over time increasingly affect cost-effectiveness. This impact is expected to vary with the duration of the utilization of a drug in a population, especially, but not solely, in multicohort analyses.<sup>11,12</sup> In the analyses, a constant annual price decrease was used, which was a simplification of reality in which prices may initially drop slowly and more rapidly close to and after LOE with potential consequences for ICERs, in particular in disaggregated multicohort analyses.<sup>13,14</sup>

To the best of our knowledge, real-world drug price dynamics have so far not been used in conventional CEAs apart from assumed aggregate price decreases. This article aimed to give

simple examples, illustrating the impact of including historically observed dynamic real-world pricing data over the drug life cycle on the cost-effectiveness, in specific reproduced case studies. Notably, dynamic real-world pricing data from The Netherlands were used as the illustration.

## Methods

To estimate the impact of dynamic real-world pricing data over the drug life cycle on the cost-effectiveness of drugs, we used example cases that were carefully selected, using explicit criteria. Below we describe how these criteria were set, Dutch real-world pricing data were gathered,<sup>14</sup> the corresponding CEAs were identified and replicated, and the impact of the drug life cycle pricing on cost-effectiveness results was estimated.

### Case Study Selection

We used 3 main criteria to select the example cases: (1) availability of Dutch drug-specific dynamic real-world pricing data,<sup>14</sup> (2) the selected cases should represent the characteristics of a wide variety of drugs, and (3) the published CEAs should be reproducible.

Concerning the first criterion, the case examples were selected out of a data set containing information on 250 unique drugs that went out of patent over a period of 17 years.<sup>14</sup> For the second criterion, characteristics considered were indication area, duration of drug use, model horizon, and revenue before patent expiry, categorized as low, medium, and high sales (see below). The categorization after sales was adopted from previous research<sup>14</sup> and was applied because it is expected that products with different revenue volume or budget impact drive different pricing and price negotiation outcomes. For the third criterion, appropriate publications of CEAs were identified by the means of a scoping review in PubMed, a preselection of eligible cases was done, and a limited number of suitable cases were identified for analysis. Notably, straightforward reproducibility represented an important final selection criterion. The final number of cases was made based on the authors' opinions on a good balance between the second and third criteria. Given that Dutch real-world pricing data were used, models from The Netherlands were preferred. If unavailable, models for other European settings were selected.

### Real-World Pricing Data

Recently, drug-specific sales and real-world pricing data were analyzed for the Dutch setting.<sup>14</sup> The median drug price fell by 41% in the 4 years after patent expiration. Drug-specific mean monthly prices per defined daily dose (DDD) were calculated as weighted averages of all available packages and types at the level of anatomical therapeutic chemical-classes. The data set for these price analyses, combining 2 proprietary national databases with prescription and price data from 1999 to 2016 (Z-Index, The Hague<sup>15</sup> and Close-Up national sales database, Amersfoort<sup>16</sup>), was further processed in our study.

### Model Reproduction

The relevant parts of the selected cost-effectiveness models were reproduced in R (version 4.2.0, R Foundation for Statistical Computing, Vienna, Austria)<sup>17</sup> using the package *heemod*.<sup>18</sup> All reproduced models used the same model structure, cycle length, time horizon, inputs parameters, and discount rates as the original published cost-effectiveness models. Given that the dynamic real-world pricing was considered to only influence costs and not effects in the CEA, the results of the reproduced cost-effectiveness

models were calibrated and validated by comparing the incremental costs of the reproduced model with the costs reported in the published model. The model was deemed to be accurately reproduced if costs were in the  $\pm 10\%$  range of the published values.

Subsequently, combining the original study effects with the reproduced costs, the resulting ICERs were used as a base to further compare the cost-effectiveness using dynamic real-world pricing data and constant prices, respectively. First, the model was analyzed with the constant price of the year applied in the original case study. Second, the model was reanalyzed using dynamic real-world pricing data.

### Single-Cohort and Multicohort Analyses

As a first step to analyze the impact of dynamic real-world pricing, a single-cohort approach was used. Within the single-cohort approach, a single cohort faces treatment during the drug utilization period/time horizon. As in real life, patients—grouped together in, for example, annual cohorts—keep successively starting after each other using a specific drug; in addition, a multicohort analysis was performed as a second step. Notably, when a next cohort starts 1 year after the previous one, the drug price might have already decreased with beneficial consequences for the cost-effectiveness for that particular cohort. Ergo, with decreasing prices, cost-effectiveness potentially improves for each subsequent future cohort. Obviously, a single cohort can also experience relevant decreases in price when for instance the drug utilization period is long, but effects can be expected to be more pronounced in the multicohort setting. In addition, the particular importance of applying multicohort models for analyzing value over the lifetime of a drug has been indicated in previous studies.<sup>6,9,19</sup>

To the best knowledge of the authors, no formal guidance exists on the number of cohorts to include in a multicohort analysis. For the multicohort analyses, the number of yearly cohorts was pragmatically set at 10 to reflect the approximate period from market introduction to LOE, also considering that CEAs for drugs are mostly conducted soon after market approval.<sup>20</sup> Both individual ICERs for separate cohorts and a multicohort ICER were calculated. The multicohort ICER was derived through dividing accumulated costs by effects over all 10 cohorts. One should note that, as the health effects were kept constant in the denominator of cost-effectiveness formula and therefore only the costs in the numerator are being varied, negative ICERs can be considered meaningful indicating changes in cost savings only. In particular, more negative ICERs would indicate increased net savings in the CEAs in the framework of this specific study.

Cohort-specific results were discounted with the rates reported in the original studies, except if differential discounting was applied. In case differential discounting was originally applied, an equal discount rate at that of the costs was chosen. This was done to eliminate the effect of differential discounting that cost-effectiveness ratios decrease for next cohorts merely due to differential discounting per se.<sup>21</sup>

### Extrapolation and Incorporation of Real-World Pricing Data

Because the drug utilization period in our analysis could be longer than the period for which dynamic real-world pricing data was available, extrapolation of the price development could be necessary for the multicohort approach. This necessity was determined by the cost year applied in the original study and the length of the period for which the drug was used.

**Table 1.** Model characteristics of the analyzed drugs as derived from original publications (except when indicated otherwise).

Model	Comparator	Disease area	Time horizon	Price year original model	Year generic entry*	Drug utilization	Cycle length	Discount rates	Country	Drug revenue year before entry (in €)*
Alendronate acid + colecalciferol <sup>23</sup>	No treatment	Osteoporosis	10 years	2004	2013	Maximum first 5 cycles	1 year	Equal at 4%	NL	Low
Fluvastatin (on top of dietary counseling) <sup>24</sup>	Dietary counseling	Cardiovascular	10 years	2002	2008	Health state dependent; maximum 10 cycles	1 year	Equal at 4%	NL	Medium
Clopidogrel (on top of aspirin) <sup>25</sup>	Aspirin	Cardiovascular	1 year	2006	2009	First cycle	Variable	Equal at 4%	NL	High
Letrozole <sup>26</sup>	No treatment	Oncology	40 years	2004	2011	Health state dependent; maximum 5 cycles	1 year	Equal at 3.5%	UK	Medium

NL indicates The Netherlands; UK, United Kingdom.

\*Derived from van der Schans et al.<sup>14</sup>

For the purpose of the extrapolation, the development in price was depicted by the means of a monthly ratio, with the numerator being the mean monthly price per DDD and the denominator being the mean monthly price per DDD in the month before LOE. Thus, the resulting price ratio indicates the relative price of a drug over time compared with the month before LOE. If needed, this monthly approach was adapted if the cycle length in the model differed from 1 month. Subsequently, the price ratio data were fitted with nonlinear regression equations in the software STATA (version 16, StataCorp LLC, College Station, TX) following the National Institute for Health and Care Excellence Decision Support Unit survival analysis guidelines.<sup>22</sup> All function types listed in these guidelines were fitted and the best fits were selected based on the Akaike information criterion (AIC) coefficient. As the AIC is not necessarily selecting the most appropriate function type for extrapolation in all cases, also visual inspection was performed for final selection. Although these functions were developed in particular for the multicohort part of the analysis, for consistency and if needed, they were implemented in the single-cohort approach.

Given the retrospective approach of this research, using observed dynamic real-world pricing data, and the specific nature of drug prices, the prices were not adjusted for inflation. Notably, drug prices are potentially more driven by specific pricing regulatory mechanisms, competition, and agreements rather than the country-specific deflator.

### Case Studies

The following 4 drugs and respective published models were selected for this study: alendronic acid + colecalciferol combination therapy (indicated for osteoporosis),<sup>23</sup> fluvastatin (indicated for elevated cholesterol),<sup>24</sup> clopidogrel (indicated for antiplatelet therapy),<sup>25</sup> and letrozole (used in oncology).<sup>26</sup> The treatment comparator for alendronic acid + colecalciferol combination therapy and letrozole was no treatment. Fluvastatin was compared with dietary counseling and clopidogrel to aspirin. Notably, the 4 selected examples all consider prices changes to the drug under assessment and not to the comparator therapies against which they are assessed.

Fluvastatin, alendronic acid + colecalciferol combination therapy, and letrozole had relatively long assumed (chronic) drug

utilization periods of 10 years, 5 years, and 5 years, respectively. In contrast, clopidogrel was assumed to be used relatively short in an acute setting. Consequently, the model of clopidogrel had a short time horizon, whereas the other drugs were simulated for longer time periods of 10 years (fluvastatin and alendronic acid + colecalciferol combination therapy) and 40 years (letrozole). The drug-specific details and model characteristics are listed in Table 1.<sup>14,23-26</sup> Notably, for letrozole, no Dutch model could be found, and a UK analysis was selected and—as mentioned—combined with the Dutch dynamic real-world pricing data. All reproduced models involved single cohorts in the original publication.

## Results

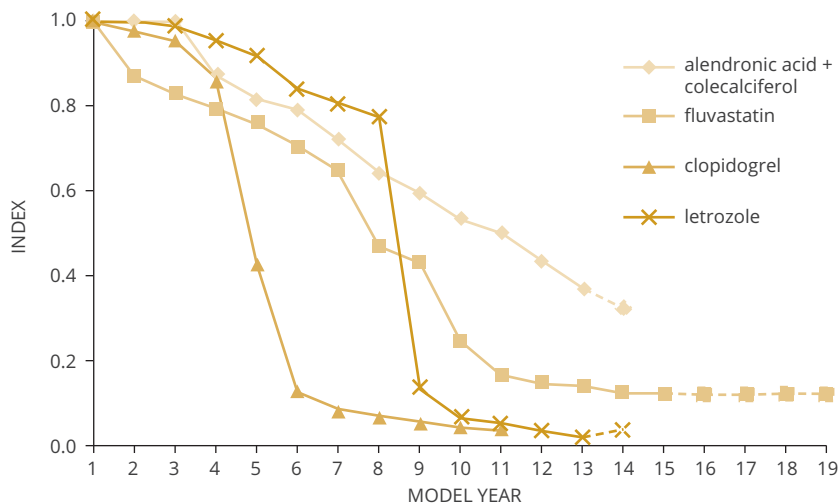
### Model Reproduction and Validation

Estimated incremental costs in the respective models only slightly deviated from the original studies ranging from -8% (clopidogrel) to 8% (letrozole). Given that the reproduced models used the original study health effects, deviations in the obtained ICERs from their original study were solely caused by the incremental costs. Most reproduced models used equal discount rates; nevertheless, in 1 case, equal discounting was implemented in our reproduced model as opposed to differential in the original publication. The model validation specifics are reported in Appendix Table 1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2022.06>.

### Observed and Fitted Price Developments

The price ratios of all drugs decreased over time. Comparing the values of the last model year with their corresponding values in the original studies, reductions of 63% for alendronic acid + colecalciferol up to 98% for letrozole were found (Fig. 1). Price ratios of clopidogrel and letrozole dropped sharply after their respective LOE, whereas the ratios for alendronic acid + colecalciferol and fluvastatin decreased more constantly over the respective model horizons. All drug prices already decreased before LOE (from 14% for clopidogrel to 47% for alendronic acid + colecalciferol) and persistently continued to do so afterward. Three of the 4 drugs had best curve fits with a single nonlinear function, whereas the price ratio data for letrozole were fitted best

**Figure 1.** Annual price development for all 4 drugs compared with price in first model year. Model year 1 is representing the cost year in the original study, whereas the last year per drug marks the last year of data included in the multicohort analysis. For all drugs, the year of generic entry or LOE is indicated with a red dot in the figure. The dashed line indicates extrapolated data based on the available data (solid line) using the respective functions for the specific cases.



LOE indicates loss of exclusivity.

with a piecewise approach due to a particularly slow decreasing price before LOE and a comparatively late occurrence of LOE. In the latter case, a log-logistic and an exponential function were combined. All absolute annual price curves, price ratios, and estimated fits and function types and AIC values are reported in the Appendix Figures 1.1 to 4.1 and Table 2 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2022.06>.

**Extrapolated Prices**

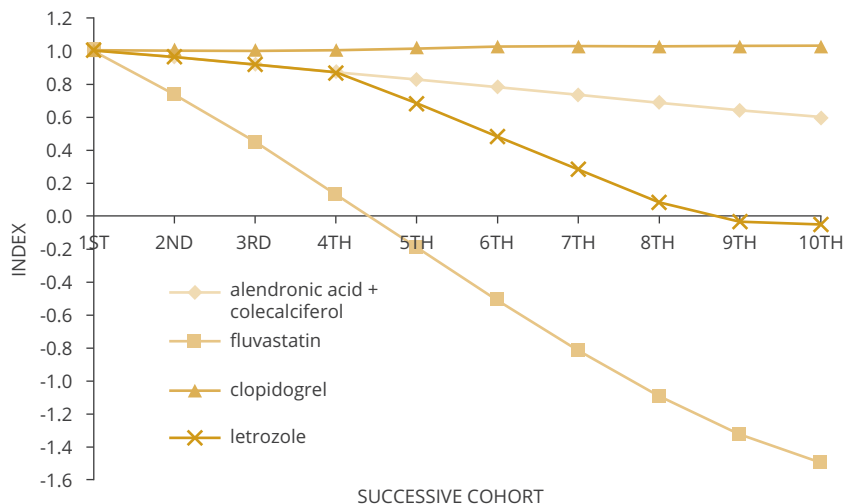
For the multicohort approach, extrapolation of dynamic real-world pricing data was necessary for all cases except clopidogrel. Notably, prices for letrozole, alendronic acid + colecalciferol, and fluvastatin were extrapolated for 1, 1, and 4 years, respectively. In general, considering these extrapolation timeframes, it can be noted that the extrapolation of price data was very limited.

Fluvastatin may serve as an illustrative example for the extrapolation of prices. Notably, the original fluvastatin model applied a drug utilization period for a maximum of 10 years, with cost year 2002. For the single-cohort approach, no extrapolation was required given that dynamic real-world pricing data were available until 2016. Nevertheless, the multicohort approach for 10 subsequent cohorts required 4 additional years of extrapolated real-world pricing data (2002 + 9 [additional years] + 9 [additional cohorts] – 2016 = 4). The extrapolations of the fitted real-world pricing data are shown in Figure 1.

**Single-Cohort Results**

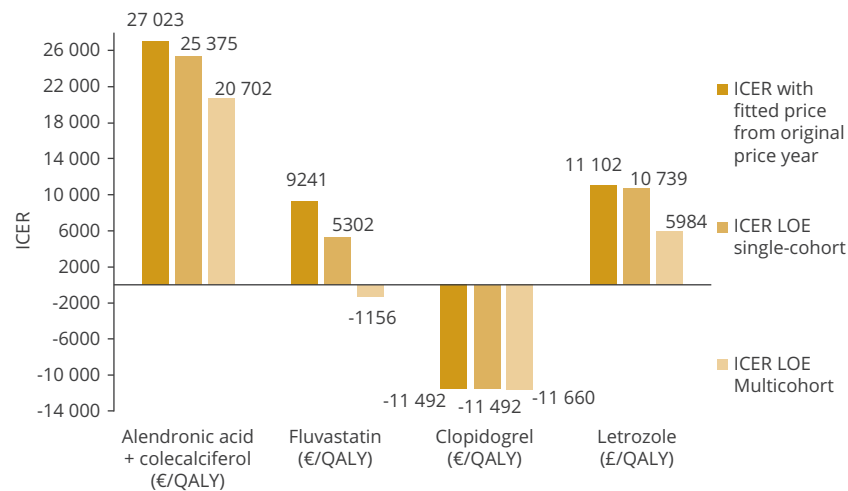
In the single-cohort setting, the effect on the ICER of dynamic real-world pricing compared with constant prices was largest for fluvastatin with 43%, whereas smaller decreases were observed for

**Figure 2.** ICERs per drug and cohort are reported as ratio relative to the drug-specific ICER of the starting cohort. The cohort-specific ICERs of clopidogrel are negative (cost saving) with health effects being kept constant in the ICER, hence an increase in the ratio corresponds to a further decreased ICER, thus an increase in cost savings.



ICER indicates incremental cost-effectiveness ratio.

**Figure 3.** ICERs (cost per QALY) per analytic approach for all drugs. The reproduced model is used to calculate a base ICER with the constant fitted price in the original price year of the respective study. The ICERs of the single-cohort and multicohort analyses are calculated incorporating dynamic real-world pricing data. The multicohort ICER reflects the division of the discounted and summed up cohort-specific costs and effects per drug. Currency units are reported in brackets.



ICER indicates incremental cost-effectiveness ratio; LOE, loss of exclusivity; QALY, quality-adjusted life-year.

alendronic acid + colecalciferol at 6% and letrozole at 3%. The ICER of clopidogrel did not change in the single-cohort approach, given the relatively short drug utilization period, all happening within the first year.

### Multicohort Results

The development of the drug-specific ICERs over the included cohorts in the multicohort approach is shown in Figure 2. The ICERs of all drugs improved markedly over the successive cohorts compared with the initial single cohort. Considering the cohort-specific ICERs per drug, those for fluvastatin and letrozole decreased relevantly and reported negative (cost-saving) ICERs after 5 and 9 cohorts, respectively. The cohort-specific ICER of alendronic acid + colecalciferol decreased by 40% if we compare the last and the first cohort. In Figure 2, clopidogrel shows a slight 3% increase in the reported ratio after 10 cohorts due to further decreased negative ICERs, indicating increased cohort-specific cost savings at the same quality-adjusted life-year gains. In the Supplemental Materials (Appendix Figure 5 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2022.06>), we present an alternative representation using a cumulative average approach.

The cumulative multicohort ICERs for fluvastatin, letrozole, and alendronic acid + colecalciferol decreased compared with the reproduced results with 113%, 46%, and 23%, respectively, whereas for clopidogrel the cumulative multicohort ICER decreased further with 1.5% (again indicating increased cost savings). The ICERs of the reproduced model with the fitted price of the original cost-year, single-cohort and multicohort analyses are reported in Figure 3.

### Discussion

To the best of our knowledge, this is the first study showing the impact of including historically observed dynamic real-world pricing data over the drug lifecycle in reproduced CEAs. Our results from 4 selected cases indicate that inclusion of dynamic real-world pricing data versus constant prices reduced the ICER up to

43% in the single-cohort setting. Acknowledging the increasing influence of the drug life cycle over multiple cohorts of future patients, a multicohort analysis highlighted further ICER reductions up to 113% in the exemplar cases.

### Driving Factors

In our case studies, fluvastatin showed the largest decrease in its single-cohort and multicohort ICERs when including dynamic real-world pricing data. The relatively long drug utilization period—up to 10 years—was one of the key factors driving the substantial impact in the CEA. In addition, the relative share of drug costs compared with the total costs included in the economic model can be considered as an important driver of the impact dynamic real-world pricing has on the cost-effectiveness. In the specific case of fluvastatin, the share of medicine costs was highest in all case studies at 43%. In contrast to fluvastatin, clopidogrel had both a short utilization period (less than 1 year) and a relatively low drug cost share of only 0.05%, resulting in a relatively small change in the ICER of 1.5% if dynamic real-world pricing data were used. The observations on long drug utilization periods and high drug cost shares being highly influential are aligned with previous research.<sup>10</sup>

The 2 drugs with the most significant reductions in the ICERs in the single-cohort approach, fluvastatin and letrozole, also showed the largest decreases in the multicohort ICERs of 113% and 46%, respectively. Notably, the letrozole case study presented an example of a relatively late LOE (9th model year), which illustrated that timing of LOE clearly has an impact on the ICER results when examining cohort-specific ICER values. When real-world prices were included, the cohort-specific ICER of the letrozole cohort to experience the first post-LOE price in its timeframe (5th cohort) was the first cohort-specific ICER that substantially decreased (32% compared with the starting cohort and 19% compared with the previous cohort). Therefore, the timing of the price decrease is of great influence on the ICER.

The case of clopidogrel illustrated that the incorporation of dynamic real-world pricing is not necessarily always of influence under all conditions and scenarios. In the single-cohort setting,

the estimated ICER with dynamic prices was the same as under the original constant price due to the short drug utilization period. Given that this study kept health effects constant over cohorts, in the particular case of clopidogrel, the negative and further decreasing multicohort ICER illustrated an increase in cost savings through a reduction in price. Although this example of a negative ICER is not highly relevant in reimbursement decision setting as such, it highlights that factoring in dynamic prices, even in cost-saving circumstances, does provide further insights in economic consequences, in particular, if a multicohort approach is applied.

### Previous Studies

The price life cycle of drugs has been studied previously. A recent literature review found price decreases ranging from 6.6% to 66% up to 5 years after LOE,<sup>5</sup> yet there have been methodological differences in the incorporation of the impact of LOE, and decreasing prices in general, on the ICER results.<sup>6–10,27–30</sup>

Some studies analyzed the impact of dynamic prices of the new drug on the ICER<sup>6,9,10,27</sup> assuming static annual price decreases<sup>10</sup> and life cycle correction factors,<sup>6</sup> analyzing varying cohort sizes and efficacy estimates<sup>9</sup> or one-off reductions in the price of the new drug.<sup>27</sup> These studies found that exclusion of dynamic real-world pricing and LOE in the analysis leads to an undervaluing cost-effectiveness. Other studies<sup>7,28</sup> focused on the impact of LOE on the comparator drug through mathematical models<sup>7</sup> or theoretical frameworks,<sup>28</sup> potentially leading to too low estimates of the ICERs.

Three studies<sup>8,29,30</sup> have explored the impact of incorporating the LOE on both the intervention and the comparator drug by applying mathematical models,<sup>29</sup> assumptions about relative price decreases,<sup>30</sup> and price index calculators.<sup>8</sup> These studies highlight the interplay of generic availability and change in pricing and timing of price decreases due to generic entry. From the above, it appears that our approach innovates on existing literature, in particular, in the use of dynamic real-world prices in reproduced models, but also that further challenges remain, for example, extending the presented framework of this study with an active comparator that has a dynamic price based on real-world data.

### Strengths and Limitations

The methodology of this study distinguishes itself from previous research by highlighting the isolated effect of including real-world pricing data in CEAs using multiple reproduced case studies representing a variety of drug characteristics. As such, this study was able to retrospectively incorporate the prices that society actually paid into reproduced CEA models and subsequently show the influence of real-world decreasing prices on the ICERs. Additionally, our results, based on retrospective price data, provide a first indication of the influence of different drug characteristics on the magnitude of the effect on the ICER. Thus, the current retrospective analysis can contribute to further discussions on the potential implementation of including price development estimations in future prospective health-economic analyses.

Following the earlier elaborated aim of this study to give simple examples of the impact of dynamic real-world pricing and LOE on the cost-effectiveness of drugs, the authors chose to isolate this effect from any other dynamic characteristics that might occur in the real world. This includes cohort sizes that are known to vary in size over the product life cycle,<sup>6</sup> drug life times have been shown to vary<sup>12</sup> and adherence is rarely 100% of the patient population. The authors of this study were faced with a trade-off between enhanced realism of the analysis and simple messaging of the approach-benefit in which they chose for the latter. Hence, the isolation of the effect of LOE on the intervention drug is able to

(“*ceteris paribus*”) highlight the benefits of adding a dynamic in a simple manner. Although excluded in this study, the authors want to explicitly state that introducing an active comparator, which is experiencing LOE before the analyzed drug or does so in a more pronounced manner, could lead to a scenario in which the inclusion of life cycle price developments causes the cost-effectiveness of the analyzed intervention to actually deteriorate. Compared with our starting point of reference with constant prices, decreasing prices considered for both the index and the comparator drug can lead to both improved and worsened cost-effectiveness. Actual change in cost-effectiveness depends on the specific individual trajectories of both drugs included in the analysis.

The LOE impact found in this study should for 2 reasons be considered as conservative, given that inflation correction and potential negotiated price discounts were not included.<sup>31</sup> This could lead to an overestimation of the actual drug costs.

A limitation of this research can be found in the fact that the authors based their analysis on the reproduction of published models for which not all necessary information (eg, background mortality or disease) was available. In addition, for one of the 4 drugs in this study (letrozole), no Dutch cost-effectiveness model could be found, and hence, pragmatic choices needed to be made applying Dutch real-world pricing data within a UK model. Finally, the choice of not reproducing effects might expose this study to the risk of incorrect estimation in the reproduced models, which would be detected when both costs and effects were reproduced, yet this risk was seen as inferior to the risk of a general reproducing error caused by difficulties in replicating the full model.

### Further Work

A recent literature review has elaborated on the need for national CEA guidelines to examine the inclusion of assumptions related to future drug price developments, as only one-third of the analyzed national guidelines mentioned the dynamics of LOE.<sup>32</sup> Following the benefits of retrospectively quantifying the impact of the drug life cycle costs on health-economic outcomes to inform decision making, it would be advisable to further assess the role of predicted prospective future drug price development in cost-effectiveness outcomes. In particular, more research needs to be performed on how exactly to design and use dynamic pricing models for healthcare decision making on reimbursement. The hypothesis is that a dynamic digital platform or tool for prospective estimation of price development of drugs could contribute to more representative cost-effectiveness outcomes, particularly relevant when outcomes are close the willingness-to-pay thresholds.

Additionally, given the found effect of dynamic real-world pricing data over multiple cohorts, further research should elaborate on the inclusion of multicohort analysis and extrapolated real-world pricing data as a potential standard scenario analysis for national reimbursement decision making. Finally, the effect of LOE and other regulatory mechanisms on price through international reference pricing should be examined, given that this research purposefully did not consider this to avoid further complexity. Therefore, further research should be conducted on how to include the effect of the product life cycle cost development to inform healthcare decision making.

### Conclusion

When analyzing the cost-effectiveness of drugs through disease- and cost-modeling approaches, assuming dynamic drug prices throughout the entire model time horizon may well lead to

more representative ICER estimates. Drug prices decrease over time and are associated with their modeled cost structure and magnitude and timing of the LOE price drop. Therefore, future CEAs for drugs could include scenario analyses predicting disaggregate life cycle price developments based on retrospective drug price development patterns to inform decision makers.

## Supplemental Materials

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2022.06.007>.

## Article and Author Information

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*Critical revision of the paper for important intellectual content:* Schöttler, Coerts, Postma, Boersma, Rozenbaum

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