Relative Effectiveness Assessment of Pharmaceuticals: Similarities and Differences in 29 Jurisdictions

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ABSTRACT

Objective: Assessment of the effectiveness compared with alternative treatment(s) plays an important role in many jurisdictions in determining the reimbursement status of pharmaceuticals. This type of assessment is often referred to as a relative effectiveness assessment (REA) and is carried out by many jurisdictions. Increased sharing of information across jurisdictions may save costs and reduce duplication. The objective of this study was to explore the main similarities and differences in the major methodological aspects of REA in multiple jurisdictions. Methods: Data were gathered with a standardized data extraction form by searching publicly available information and by eliciting information from representatives at relevant organizations. Results: Of the initially included 35 jurisdictions, data were gathered for 29 jurisdictions. There seem to be substantial similarities on the choice of the comparator, the role of indirect comparisons, and preferred end points in REAs (except for the use of health state utilities). Jurisdictions, however, differ in whether effectiveness (usual circumstances of health care practice) is estimated in case no (comparative) effectiveness data are available and how this is done. Conclusion: Some important methodological aspects for REA are approached in a similar way in many jurisdictions, indicating that collaboration on assessments may be feasible. Enhanced collaboration in the development of methods and best practices for REA between jurisdictions will be a necessary first step. Important topics for developing best practice are indirect comparisons and how to handle the gap between efficacy and effectiveness data in case good quality comparative effectiveness data are not yet available at the time of reimbursement decisions.

Keywords: comparative effectiveness, health technology assessment, pharmaceuticals, policy, reimbursement.

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Introduction

Funding or reimbursement of a pharmaceutical by the health service or health insurance is one of the factors that determine timely access for patient to the pharmaceutical. The decision on whether a pharmaceutical is reimbursed is based on multiple factors. The efficacy and/or effectiveness compared with alternative interventions is typically considered one of the most important criteria in determining reimbursement status [1]. This type of assessment is often referred to as a relative efficacy/effectiveness assessment (REA) (for definition used in this article, see Fig. 1) [2–4]. An REA is a specific element of health technology assessment (HTA) that focuses on the clinical benefit of the intervention, whereas HTA is broader and can also include other aspects, such as ethical, cost, and cost-effectiveness considerations.

There are two types of REA, a rapid assessment and a full assessment. A rapid assessment is an assessment of one pharmaceutical within a limited time frame in comparison with one or more relevant alternative interventions. It can be the assessment of a new pharmaceutical launched into the market, or the reassessment of a pharmaceutical for a new indication or when new relevant data are available. For a full assessment, multiple technologies within a disease area are assessed. The latter type of assessment is typically conducted several years after the technologies have been introduced to the market. Such an assessment may not have to be carried out within a certain time frame. This analysis focuses on rapid assessments.

While there is general consensus that the decision-making process on reimbursement decisions should be undertaken within national and local contexts, there are potential efficiencies to be gained from enhanced collaboration around the collection of evidence underpinning these decisions. Increased sharing of information (e.g., methods, data requirements, and results) across jurisdictions may save costs and reduce duplication. A working group of the High Level Pharmaceutical Forum, a high-level political platform, was set up to support member states of the European Union in applying REAs in order to allow containment of pharmaceutical costs as well as a fair reward for innovation. After the completion of the High Level Pharmaceutical Forum 2005–2008, the European Network for Health Technology Assessment...
Relative efficacy: the extent to which an intervention does more good than harm under ideal circumstances, compared to one or more alternative interventions [2]

Relative effectiveness: the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice [2]

Surrogate endpoint: a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives [5]

Composite endpoint: An endpoint that consists of multiple endpoints that are combined into a new single outcome measure by using a predefined algorithm [6]

Health state utility: value assigned to the quality of life in a health state, normally on a scale of 0 (dead) to 1 (full health)

Fig. 1 – Definitions.

(EUnetHTA) was identified as an appropriate candidate for developing scientific recommendations for improvements in REA of pharmaceuticals in Europe. The overarching objective of EUnetHTA Joint Action is to put into practice an effective and sustainable HTA collaboration in Europe that brings added value at the European, national, and regional levels.

As a first step, an analysis was conducted of the arrangements and the scientific methods used for REA in current national practice. The objective of this study was to explore the main similarities and differences in the major methodological aspects of REA in multiple jurisdictions: the choice of comparator, the use of indirect comparisons, the use of outcome measures, and the use of efficacy data for effectiveness assessments.

Methods

Data were captured with a standardized data extraction form developed by seven EUnetHTA partners (AETSA [ES], AHTAPol [PO], CVZ [NL], HAS [FR], ESKI [HU], IRF [DE], and the National Institute for Health and Clinical Excellence [UK]) that conduct HTAs of pharmaceuticals. The form included 38 open or multiple-choice questions (the multiple-choice questions were to be answered with yes/no or always/sometimes/never). Data were gathered by searching publicly available information and by eliciting information from representatives at relevant organizations (see Fig. 2). The answers were checked by the researchers for inconsistencies and clarity, and if needed were queried.†The results were double-checked by representatives of the respective organizations.

Originally, we included 31 European jurisdictions and four English-speaking non-European jurisdictions, most of which are known to have a well-established HTA process for pharmaceuticals (Canada, Australia, and New Zealand) or is known for its interest in REA (the United States).

For each jurisdiction, in particular, the major methodological aspects of the “comparative analysis” were collected. The comparative analysis refers to assessing the efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternatives. Relevant definitions that were used are provided in Figure 1 [2,5,6]. The results were double-checked by representatives of the respective organizations.

Data were gathered between May 1, 2010, and May 1, 2011.

Results

Of the originally included 35 jurisdictions, data were gathered for 29 jurisdictions (Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Luxembourg, Malta, the Netherlands, New...
Zealand, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom (separate data extraction for England/Wales and Scotland). Data were not available for Bulgaria, Cyprus, Greece, Lithuania, and Romania, because no suitable sources for these jurisdictions were identified. No data were collected for the United States, given that there is no single entity or standardized approach for REA in the United States because of its multipayer environment.

The organizations that were selected for eliciting information for each jurisdiction are listed in Appendix 1 at Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2012.04.010.

For the United Kingdom, separate data were abstracted of the methods used by the National Institute for Health and Clinical Excellence and the Scottish Medicines Consortium, as both have well-established procedures and methods.

Of the jurisdictions included, all conduct rapid assessments whereas 17 jurisdictions conduct full assessments. The results presented in this article are specific to rapid assessments.

As part of a rapid assessment, relative efficacy was stated to be assessed in all jurisdictions (83% state to do so always and 17% sometimes). More than 95% of the jurisdictions state that they look at the relative effectiveness (41% always and 55% sometimes). It was stated by some of the jurisdictions that effectiveness is assessed only when direct data on this parameter are available, whereas other jurisdictions estimate the effectiveness if the data are not available. In addition, more than 95% include a cost-effectiveness assessment (62% sometimes and 34% always).

**Choice of comparator**

In many jurisdictions, several options can exist for the choice of comparator. For example, in Poland, the primary comparator for the assessed intervention must be the so-called existing practice. It is also recommended, however, to perform a comparison with other comparators (the most frequently used, the cheapest, the most efficient, and compliant with the standards and guidelines for clinical management). Only five jurisdictions (almost 20%) state that “whatever was used in the registration trials” can be an option for the choice of the comparator (Belgium, Slovakia, Slovenia, Spain, and Switzerland) (see Table 1). The majority (almost 70%) of the jurisdictions state “best standard care” and/or “other” (almost 50%) as an option for the choice of comparator. The jurisdictions were asked for their definition of the choice of comparator. For both categories (“best standard care” and “other”), the definitions that jurisdictions use are similar. Examples of definitions are “the treatment(s) used in current clinical practice” (England/Wales), “most frequently (or widely) used therapy” (Belgium, Estonia, Finland, and Latvia), “the validated care in the field” (France), and “the therapy that prescribers would most replace with the proposed pharmaceutical in practice” (Australia).

In 83% of the jurisdictions, the comparator(s) for the assessment can include one or more nonpharmaceutical interventions. In practice, however, the comparison with nonpharmaceuticals is an exception in some of these jurisdictions. It was also mentioned that for pharmaceuticals used in an inpatient setting than in the outpatient setting it is more common to include nonpharmacological interventions. The comparator is limited to pharmaceuticals in Belgium, Canada, Denmark, Italy, and Norway.

**Indirect comparison**

When there are no head-to-head trials available that include a direct comparison between the pharmaceutical to be assessed and the relevant comparator, all jurisdictions, except for Turkey, may use indirect comparisons (see Table 1). Only few jurisdictions state to have a preference for the type of indirect analysis; for example, Australia and New Zealand indicated a preference for the Frequentist method and in Scotland, Bayesian analysis is preferred.

**Outcomes**

In general, all clinically relevant outcomes are accepted for the assessment. Several jurisdictions prefer outcomes related to mortality, morbidity, and/or quality of life. Final outcomes (preferably patient-relevant and clinically significant end points) are preferred over surrogate end points by all jurisdictions. The results on individual end points are presented in Table 1 and Figure 3.

In all jurisdictions, surrogate outcomes are accepted for the assessment. However, many jurisdictions state that surrogate outcomes are not preferred, considered less relevant for the decision making than clinical outcomes, and are accepted only if considered clinically relevant and/or validated. Composite outcomes are also generally accepted but not preferred.

Most jurisdictions accept quality-of-life data with the premise that the instrument used should be validated. Disease-specific quality-of-life measurements are accepted slightly more widely (90%) than generic quality-of-life measurements (almost 80%). Almost half of the jurisdictions (48%) state that health state utilities can be used for determining the relative effectiveness.

Almost all jurisdictions take safety data into account for the assessment. Various outcomes such as dropout from study due to side effects, deaths due to side effects, major side effects, and irreversible side effects were mentioned as particularly relevant safety end points.

**Efficacy versus effectiveness data**

All jurisdictions consider to some degree (“always” or “sometimes”) whether clinical trial data available at the time of the assessment are also applicable to the general patient population (also referred to as external validity) (Table 1). The organizations were asked how effectiveness is assessed if no effectiveness data from clinical studies are available. They were asked whether they would do always/sometimes/never 1) a qualitative extrapolation (estimate of the effectiveness of a treatment based on the efficacy data that are available) or 2) a quantitative extrapolation (e.g., modeling). A qualitative extrapolation is done at least sometimes by 75% of the organizations. A quantitative exercise to extrapolate efficacy data to effectiveness data is done at least sometimes by 50% of the organizations (Table 1). In the absence of long-term data, short-term data are extrapolated qualitatively in almost 70% of the jurisdictions (always or sometimes) and quantitatively (through modeling) in more than 60% (always or sometimes) of the jurisdictions.

**Methodological guidelines**

More than 80% of the jurisdictions state that some form of guideline is available in which the methodology that is used for the comparative analysis is described. Of the countries that have such national guidelines, more than 60% indicate to have it available in English. The methodological guidelines are publicly available in most jurisdictions. The guidelines vary substantially across countries in the type of content (methods vs. other information regarding procedure of reimbursement submission) as well as the level of detail on methods (evidence and methodological requirements).

Some of the national guideline documents focus mainly on the procedure of a reimbursement submission (how to do a submission and the timelines involved) or, for example, on which reimbursement criteria are used for the assessment. The information in these guidelines on how to perform/assess the REA can be limited. Other jurisdictions, such as the Czech Republic and Portugal, use the national guideline for pharmacoeconomics as guidance to inform the REA. An example of a detailed guideline on the methods used to perform/assess the REA is Section B of the guidelines of the Australian Pharmaceutical Benefits Advisory Committee. This guideline focuses on how marketing authorization holders should perform an REA and present the data.
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<th>Are safety data taken into account?</th>
<th>Is the generalizability of the study data (e.g., RCTs) to the proposed treatment population considered (external validity)?</th>
<th>How is the effectiveness assessed if not available through clinical trial data?</th>
<th>If data on long-term effects are absent, are short-term clinical data extrapolated?</th>
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</tr>
<tr>
<td>SE</td>
<td>BS, O</td>
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<tr>
<td>CH</td>
<td>BS, RP, BS</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>TU</td>
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<td>Y</td>
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</tr>
<tr>
<td>Percentage (%)</td>
<td>R = 17</td>
<td>Y = 17</td>
<td>Y = 97</td>
<td>Y = 100</td>
<td>Y = 97</td>
<td>Y = 79</td>
<td>Y = 48</td>
<td>Y = 90</td>
<td>Y = 97</td>
<td>A = 66</td>
<td>S = 34</td>
<td>S = 50</td>
<td>S = 36</td>
<td>S = 59</td>
<td>S = 52</td>
<td>N = 17</td>
</tr>
<tr>
<td>BP = 24</td>
<td>N = 83</td>
<td>N = 3</td>
<td>N = 0</td>
<td>N = 0</td>
<td>N = 17</td>
<td>N = 52</td>
<td>N = 10</td>
<td>N = 3</td>
<td>S = 48</td>
<td>A = 10</td>
<td>A = 10</td>
<td>A = 32</td>
<td>A = 14</td>
<td>A = 25</td>
<td>A = 14</td>
<td>Y = 83</td>
</tr>
<tr>
<td>BS = 69</td>
<td>O = 48</td>
<td>N = 0</td>
<td>N = 17</td>
<td>N = 52</td>
<td>N = 10</td>
<td>N = 3</td>
<td>S = 48</td>
<td>S = 50</td>
<td>S = 36</td>
<td>S = 59</td>
<td>S = 52</td>
<td>S = 52</td>
<td>S = 52</td>
<td>S = 55</td>
<td>S = 55</td>
<td>N = 17</td>
</tr>
</tbody>
</table>

A, always; AU, Australia; AT, Austria; BE, Belgium; BP, best possible care; BS, best standard care; CA, Canada; CZ, Czech Republic; DK, Denmark; EN/WA, England/Wales; EE, Estonia; FI, Finland; FR, France; GE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LA, Latvia; LU, Luxembourg; M, data are missing; MA, Malta; N, no; NE, never; NL, Netherlands; NZ, New Zealand; NO, Norway; O, other; PL, Poland; PT, Portugal; R, whatever is used in registration trials; RCT's, randomized controlled trials; REA, relative effectiveness assessment; S, sometimes; SC, Scotland; SK, Slovakia; SI, Slovenia; ES, Spain; SE, Sweden; CH, Switzerland; TU, Turkey; Y, yes.
Analysis by Sorenson et al. [1], it is referred to as routine treatment.

Understood as a comparator is very similar; in most jurisdictions, the comparator varies across jurisdictions, the meaning and what is available. Our findings confirm the reality, morbidity, and quality of life were mentioned as preferred comparisons are usually accepted if no direct comparisons are available. In addition, direct comparisons are preferred; however, indirect comparisons are usually accepted if no direct comparisons are available.

Similar to the results of Sorenson et al. [1], the outcomes mortality, morbidity, and quality of life were mentioned as preferred outcomes by various jurisdictions. Our findings confirm the results of Levy et al. [8] regarding surrogate outcomes; these are generally not preferred, but accepted under certain circumstances (if considered clinically relevant and/or validated). Most jurisdictions include quality-of-life data with the premise that the instrument used should be validated; however, health state utilities are not used uniformly across jurisdictions. Although most countries are interested in the relative effectiveness, effectiveness data are often not available around the time of market authorization of a new pharmaceutical. Our data show that in such cases some countries limit their assessment to relative efficacy. The majority of the jurisdictions, however, sometimes or always attempt to extrapolate effectiveness data from randomized controlled trials to daily clinical practice. In some countries, they refer to a qualitative extrapolation, which is an interpretation (estimate) of the effectiveness of a treatment based on the efficacy data that are available. Some jurisdictions use modeling exercises to extrapolate efficacy data. This does not seem to be common practice in the majority of European jurisdictions and is probably mostly done in countries in which modeling is carried out for a cost-effectiveness or cost-utility assessment.

On the basis of these findings, we conclude that there are more similarities than differences between the major methodological aspects used in the jurisdictions. There seems to be substantial similarities regarding the choice of the comparator and preferred end points, except for the use of health state utilities in REAs. However, there is more divergence in whether effectiveness is assessed and whether effectiveness is estimated if no effectiveness data are available. Our conclusion is also supported by results of other studies. Levy et al. [8] concluded for Australia, Canada, Netherland, Scotland, and Sweden that the same type of data are evaluated with a preference for head-to-head comparisons and trials that approximate routine clinical practice as much as possible. Clement et al. [10] concluded that differences in reimbursement decisions resulted less often from the interpretation of the clinical or economic evidence and more from differences between processes used by different organizations. A less recent comparison between 12 countries regarding comparative evaluations of pharmaceuticals also found many similarities between these countries, but the authors also concluded that international agreed standards for doing assessments are lacking [13].

The research methods used in this study have some limitations. The results addressed in this article were gathered by eliciting information from representatives at relevant organizations. A lack of standardization of terms may have led to differences in the individuals’ interpretation of the terms. Some representatives completed the survey by themselves, whereas others were interviewed by telephone. Because of the size of the study, it was not possible to use one single method for eliciting the information. We have, however, minimized difference in interpretation by the representatives by cross-checking the results for inconsistencies, challenging these, and asking queries. In addition, final results from literature and interviews were validated by the interviewee’s interpretation of the terms. The results addressed in this article were gathered by eliciting information from representatives at relevant organizations.

Under ideal circumstances the comparator for an assessment that is shared across jurisdictions would be the reference treatment according to clinical practice guidelines at European or international level with good quality evidence on effect size and adverse effects from scientific literature, and with a European Union marketing authorization for the respective indication and line of treatment. If such reference treatment, however, does not exist and usual care differs between jurisdictions, sharing of information on assessments across jurisdictions is challenging and industry have to prepare submission files for different jurisdictions with different comparators. Clinical practice patterns can vary between jurisdictions because they are defined by a number of factors, including organization of the health care system, availability of resources, and economic patterns [4]. Nevertheless, in most assessments in various jurisdictions, the same pivotal trials are used, indicating that the same comparator is used in these jurisdictions. Where care patterns differ between jurisdictions, direct and indirect comparisons may be used to include all context-relevant comparisons. In addition, as Jönsson [4] pointed out, variation in usual care may diminish over time because of convergence of patterns of clinical practice and an increase in evidence-based decision making.

The aim of REA is to compare health care interventions in daily practice on the basis of the synthesis of available evidence. Although data from comparative studies (direct comparisons) are
mostly preferred, for a considerable number of pharmaceuticals such data are not available around the time of marketing authorization because no active control study was performed or the results are not published [14,15]. In addition, surrogates are often the main end points in the clinical studies that form the basis for the reimbursement submission [10], indicating that trials are not ideal for reimbursement decision making. Decision makers struggle with the challenge associated with the limited availability of or quality of the evidence [7]. Clement et al. [10] identified significant uncertainty around clinical effectiveness as a key issue in reimbursement decisions. The increased interest in comparative effectiveness data worldwide and increased resources for conducting these types of studies, through, for example, The American Recovery and Reinvestment Act of 2009 [16], may boost the amount and quality of effectiveness data that will be available in the future [17,18]. This will result in a better understanding of the effectiveness of pharmaceuticals in clinical practice and will improve the ability to make evidence-based decisions for individual patients as well as for the development of national recommendations.

Partly to address the problem of limited evidence, some jurisdictions are exploring the use of conditional reimbursement or coverage with evidence development [7]. However, even such an approach has to be based on the available evidence at the time. Hence, an REA shortly after market authorization often has to include an estimate of how efficacy data in experimental studies can predict (comparative) effectiveness in clinical practice. Therefore, indirect comparisons currently play an important role in the REA of pharmaceuticals directly after market authorization. The use of indirect comparisons for evaluating health care interventions has been studied in detail [19–22]. So far, however, relatively few jurisdictions provide clear guidance on which techniques are preferred for REA [23,24]. There is a clear need for internationally agreed guidelines in this area. In addition, harmonization and/or standardization in the approaches how to extrapolate from efficacy to effectiveness data would also be an important step to sharing assessments. Although not applicable to all countries, our findings confirm the finding by Zentner et al. [13] that methodologies for REA are less well described than pharmacoeconomic methodologies or other drug evaluation aspects. Hence, there is a need for detailed guidelines on methodological requirements for REAs.

This article specifically focuses on the methods for an REA. Although a very relevant step, harmonization of methods and best practices for REA between jurisdictions is not identical to harmonization of market access in various jurisdictions. The reimbursement decision-making process is a national/regional responsibility. Other criteria such as cost-effectiveness and budget impact can be relevant for the decision, and differences in the process of reimbursement evaluations can lead to variance in the timing of market access. Even more, jurisdictions can make different reimbursement decisions on the basis of the outcome of the same REA if there is difference in perception of the value of the available data, for example, for cultural reasons. One jurisdiction may value improvement of progression-free survival as clinically relevant, while another jurisdiction may not find this sufficient and require data on overall survival. Furthermore, one jurisdiction may be willing to accept a higher level of uncertainty than the other. Nevertheless, this does not diminish the benefits of harmonizing REA as this harmonization has the potential to lead to efficiency gains for assessment agencies as well as industry, which in the end may lead to faster access for patients to new pharmaceuticals.

REA has attained an increasing role in reimbursement decisions of pharmaceuticals. Not only does it contribute to evidence-based clinical decision making, it also forms an integral part in identifying the pharmaceuticals that offer the most value for money [1]. Enhanced collaboration and development of methods and best practices for REA between jurisdictions may improve efficiency in the assessment of health technologies [1,3,4].

Conclusion

The results presented in this article show that some important methodological aspects for REA are approached in a similar way in many jurisdictions, indicating that collaboration on assessments may be feasible. Enhanced collaboration in the development of methods and best practices for REA between jurisdictions will be a necessary first step. Important topics for developing best practices are indirect comparisons and how to handle the gap between efficacy and effectiveness data in case no good quality comparative effectiveness data are available at the time of reimbursement decisions.

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Supplemental Materials

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References


