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Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies

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ABSTRACT

Background: Randomized controlled trials provide robust data on the efficacy of interventions rather than on effectiveness. Health technology assessment (HTA) agencies worldwide are thus exploring whether real-world data (RWD) may provide alternative sources of data on effectiveness of interventions. Presently, an overview of HTA agencies' policies for RWD use in relative effectiveness assessments (REA) is lacking. **Objectives:** To review policies of six European HTA agencies on RWD use in REA of drugs. A literature review and stakeholder interviews were conducted to collect information on RWD policies for six agencies: the Dental and Pharmaceutical Benefits Agency (Sweden), the National Institute for Health and Care Excellence (United Kingdom), the Institute for Quality and Efficiency in Health-care (Germany), the High Authority for Health (France), the Italian Medicines Agency (Italy), and the National Healthcare Institute (The Netherlands). The following contexts for RWD use in REA of drugs were reviewed: initial reimbursement discussions, pharmacoeconomic analyses, and conditional reimbursement schemes. We identified 13 policy documents and 9 academic publications, and conducted 6 interviews. **Results:** Policies for RWD use in REA of drugs notably differed across contexts. Moreover, policies differed between HTA agencies. Such variations might discourage the use of RWD for HTA. **Conclusions:** To facilitate the use of RWD for HTA across Europe, more alignment of policies seems necessary. Recent articles and project proposals of the European network of HTA may provide a starting point to achieve this.

Keywords: policy study, real-world data, real-world evidence, relative effectiveness assessment.

Introduction

In light of rising health care costs and the introduction of innovative, yet expensive, pharmaceutical products, health technology assessment (HTA) agencies are seeking robust methods for relative effectiveness assessments (REAs) of drugs in routine clinical practice. *The relative effectiveness of an intervention* is defined as "[t]he extent to which an intervention does more good than harm, when compared to one or more intervention alternatives for achieving the desired results and when provided under the routine setting of health care practice (i.e. real-world setting)" [1].

Conventionally, data on treatment effects for drugs are collected in the context of randomized controlled trials (RCTs), whereby a selected, homogeneous group of patients is randomly assigned to either the experimental drug or a comparator (e.g., placebo or active comparator) under highly controlled conditions. This study design is ideal to demonstrate the efficacy of a drug, because of its ability to minimize problems with confounding, information bias, and selection bias. Nevertheless, once a drug gains marketing authorization, it is administered to a heterogeneous patient group in routine clinical practice whereby patients present with differing comorbidities, comedications, and genetic profiles. Consequently, it is challenging to extrapolate results from RCTs to drug effects in clinical practice [2].

Because of limitations associated with the use of RCT-generated efficacy data to predict the relative effectiveness of drugs, HTA agencies worldwide are currently exploring the possibilities for using real-world data (RWD) to supplement and enrich the evidence for REA of drugs. Examples of national and international collaborations exploring these possibilities include the Patient-Centered Outcomes Research Initiative and the Innovative Medicines Initiative GetReal Consortium (IMI-GetReal). The IMI-GetReal is a 3-year project aiming at investigating policies and methodologies for the collection and use of RWD in drug development and assessment. It combines a broad array of stakeholders across Europe to collaborate on developing a policy framework for RWD use and good practices for its integration in the evidence base.

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In addition, HTA agencies are exploring the use of evidence development strategies that provide effectiveness research data earlier during drug development in the framework of medicine adaptive pathways to patients [3]. One example, the IMI-ADAPT SMART project, is a 3-year project enabling a platform for multiple-stakeholder discussions on questions relating to the implementation of medicine adaptive pathways to patient activities in the European setting. Moreover, numerous publications have highlighted the growing need for RWD use in HTA decision making to inform clinical effectiveness parameters, natural history of disease, adherence to treatment and health-related quality of life, or information on demand and supply constraints for health economic evaluations in specific settings [4–9].

Research conducted by the IMI-GetReal identified three contexts within which RWD is currently being used for REA of drugs: as supplementary input for initial REA after market authorization, as input for pharmacoeconomic analyses (PEA), and for the re-assessment of relative effectiveness in conditional reimbursement schemes (CRSs) [8]. Nevertheless, an overview of the similarities and differences between different HTA agencies' policies for the use of RWD in the three aforementioned contexts seems to be lacking. Given the recent efforts and growing interest for the harmonization of HTA activities across Europe (e.g., as demonstrated by activities of the European network of HTA [EUnetHTA]), an initial comparison of policies for RWD use by HTA agencies across a number of European jurisdictions may provide a good starting point for further discussions on the harmonization of policies on this topic.

Therefore, this article aims to review the policies of six HTA agencies in Europe on RWD use in REA of drugs. More specifically, the article considers agencies' policies regarding RWD accepted or requested as well as policies for the appraisal of RWD in the following three contexts: initial reimbursement discussions (IRDs), PEA, and CRS. It is important to note that this article does not aim to provide a comprehensive overview of RWD policies of HTA agencies in all 29 European jurisdictions but rather aims to present a comparison across several relevant jurisdictions in Europe.

Methods

Six European HTA agencies were selected for analysis: the Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket [TLV], Sweden), the National Institute for Health and Care Excellence (NICE, the United Kingdom), the Institute for Quality and Efficiency in Healthcare (Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen [IQWiG], Germany), the High Authority for Health (Haute Autorité de Santé [HAS], France), the Italian Medicines Agency (Agenzia Italiana del farmaco [AIFA], Italy), and the National Healthcare Institute (Zorginstituut Nederland [ZIN], The Netherlands). HTA agencies in France, Germany, Italy, and the United Kingdom were selected because they represent the four largest European jurisdictions (the so-called Big Four)—jurisdictions bearing most influence on European policies on several aspects, including health [10–12]. Meanwhile, HTA agencies in Sweden and the Netherlands were selected because of their pioneering roles, both historically and currently, in cutting-edge European HTA projects, such as the EUnetHTA [13]. To ensure that all relevant information on agencies' policies on RWD use in REA of drugs was collected, three methods were used to retrieve information: a review of agencies' guidelines and policy papers, a review of academic publications by HTA affiliates on RWD use in REA of drugs, and semistructured interviews with representatives from the selected agencies.

First, the Web sites of the six HTA agencies were searched for guidelines and policy papers in the three contexts: IRD, PEA, and CRS. Documents were included if they were published in English, German, French, or Dutch. Second, a search for academic articles published by agency affiliates relating to RWD use in REA of drugs was conducted in MEDLINE using the PubMed interface (for the search strategy, see the Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.12.003). To minimize chances of missing relevant literature, a time span of 10 years was selected. Articles were included if they 1) were published between January 1, 2006, and June 21, 2016 (date of search); 2) explicitly discussed the use of RWD in REA of drugs; 3) were published in English, German, French, or Dutch (Swedish and Italian documents were excluded because the study authors do not master these two languages); and 4) comprised more than an abstract. Articles were excluded if they did not meet all inclusion criteria. Documents retrieved from agency Web sites and PubMed searches were evaluated independently by two authors. Any disagreements regarding inclusion or exclusion of articles were resolved by consensus.

Third, semistructured interviews were conducted with representatives from the six HTA agencies. Representatives were selectively sampled on the basis of seniority and function, with a preference for senior HTA assessors and research and development senior officers. Information for identifying representatives was retrieved from agency Web sites and/or the authors' professional network. All representatives were approached by email using a standardized invitation. A standardized questionnaire was sent to all representatives who agreed to participate 2 weeks before the interview to guide discussions (see Appendix Figure i in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.12.003). To increase the validity of stakeholder views, participants were provided the freedom to invite colleagues they deemed relevant to take part in the interviews. Interviews were conducted, recorded, and subsequently transcribed for further analysis. The sampling of representatives and interview protocols were compared with the consolidated criteria for reporting qualitative studies to ensure good quality [14].

It is important to note that the interviews were conducted as part of a broader review of stakeholder policies and perspectives on RWD [8]. Therefore, the scope of questions posed in the interviews extended beyond the aims of this research.

A standardized coding scheme was developed using MaxQDA 11.0 software (Berlin, Germany) to extract data from all compiled documents and transcripts on two aspects: 1) RWD accepted or requested and 2) the appraisal of RWD for REA of drugs within IRD, PEA, and CRS (see Fig. 1). The scheme was developed by iterative assessment of included documents and interview transcripts, in accordance with the directed content analysis approach for qualitative research [15]. Two authors independently performed data abstraction and coding. Any discrepancies were resolved by consensus.

The results from the coding analysis of the compiled documents and transcripts reported in this article were subsequently verified with the interviewed representatives of all six agencies to ensure factual correctness.

For the purpose of this article, we based our definition for RWD on the IMI-GetReal definition:

> An umbrella term for data regarding the effects of health interventions (e.g. safety, effectiveness, resource use, etc) that are not collected in the context of highly controlled RCTs. Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data. Data collected include, but are not limited to, clinical and

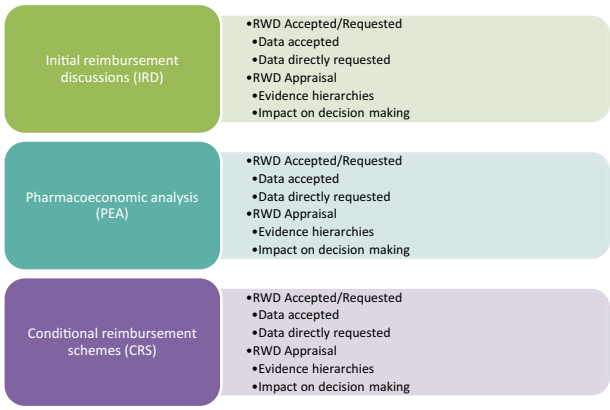

Fig. 1 – Coding scheme developed to conduct coding analysis. CRS, conditional reimbursement scheme; IRD, initial reimbursement discussion; PEA, pharmacoeconomic analysis; RWD, real-world data.

economic outcomes, patient-reported outcomes and health-related quality of life. RWD can be obtained from many sources including patient registries, electronic medical records, and claims databases. [16].

Results

The search for guidelines and policy papers on RWD use on agency Web sites yielded 13 documents (see Table 1). All six agencies had guidance and policy papers available for IRD, five agencies for PEA, and three agencies for CRS. The number and nature of documents varied per institute. Some agencies (e.g., TLV, HAS, and ZIN) had separate guidelines for IRD and PEA, whereas others (e.g., NICE) combined both in one document.

The PubMed search initially yielded 284 hits; 9 were selected for further analysis and 275 were excluded because they did not meet all inclusion criteria (see Fig. 2 for diagram on article selection). Of the 9 selected articles, 1 involved affiliates from several HTA agencies [17], 4 were specific to AIFA affiliates [18–21], 3 were specific to NICE affiliates [22–24], and 1 was specific to an HAS affiliate [25] (see Table 1).

Of the nine agency representatives approached across the six agencies, all agreed to participate (response rate = 100%). For two of the six agencies, one additional colleague was invited by the approached representatives to participate in the interview. Two interviews included one agency participant, three included two agency participants, and one included three agency participants (see Table 1). In total, 22 documents and 6 interview transcripts (labeled as a–f in Table 1) were included in the analysis.

Initial Reimbursement Discussions

All HTA agencies accept all available evidence on the drug undergoing REA, which implicitly includes RWD (transcripts a–f) [26–30]. Agencies do not specify which sources of RWD nor which methodologies for RWD collection the applicant should resort to (transcripts a, b, d–f) [26,27,29,30]. Nevertheless, several do provide suggestions for specific RWD sources as well as preliminary guidance on the suitability of these sources to answering different scientific questions (transcripts b, c, f) [27,28,31,32].

Agencies iterate that RWD may be used to demonstrate treatment effects of the assessed drug but only under specific circumstances. For example, RWD may be used in the absence of RCT evidence on drug efficacy (transcripts b and f) [27,28,30]. In the absence of RCT data on head-to-head comparisons between treatments, RWD may be drawn upon to provide information on estimates of effectiveness to enable indirect treatment comparisons (transcripts b and f) [27,30]. Finally, RWD may be used to supplement RCT data on treatment effects if data on specific subpopulations or long-term follow-up are lacking (transcripts b and f) [27,30]. In all the aforementioned situations, agencies require an explicit justification why RWD was used and a clear discussion of the biases associated with the RWD used and its consequences on treatment effect estimates (transcripts a–c and e) [26–30].

Moreover, three agency guidelines iterate that RWD may be used to provide information on aspects other than treatment effect, such as epidemiological data (e.g., incidence and prevalence), resource use data, and cost data [27,28,30].

All agencies adopt similar hierarchies of evidence in accordance with principles of evidence-based medicines [26–30]. Adopted hierarchies unanimously place sources of RWD on a lower level of quality and reliability than those of RCTs. Consequently, agencies iterate that RWD may be used to confirm or supplement, rather than substitute, findings on causal treatment effects demonstrated by RCTs (transcripts b–d and f) [27–30]. Thus, conclusions on treatment effects derived from RWD are generally regarded as more circumspect than RCT-derived conclusions by decision-making committees; examples of quotes to this effect can be found in Table 2. Two agencies, however, explicitly recognize limitations associated with strictly adopting evidence hierarchies in guidelines and state that such hierarchies should not preclude the exclusion of valuable non-RCT evidence from decision making (transcripts b and f) [27,30].

Agencies differ on the acceptability and impact of RWD on decision making in cases in which RCT data are sparse, for example, for orphan diseases; several state that non-RCT data could be resorted to for decision making in these cases (transcripts a, b, and f) [27,30], whereas one states that resorting to non-RCT data presents a greater risk to validity of conclusions and should thus be avoided (transcript c) [28]. Examples of quotes demonstrating agencies' disparity of views on this issue can be found in Table 2.

Table 3 presents a summary of policies on RWD accepted or requested and RWD appraisal in the context of IRD per agency.

Pharmacoeconomic Analyses

Contrary to the first context, RWD is directly requested by five HTA agencies for various aspects of PEA (the sixth agency does not conduct PEA). More specifically, agencies recommend that epidemiological data (e.g., incidence and prevalence), direct and indirect costs, and resource use in routine practice be collected from national RWD sources (e.g., claims databases, registries, and hospital databases) (transcripts b, e, and f) [27,28,32–34]. Other aspects of the evaluation, such as adherence to treatment and compliance, can also be collected from RWD sources such as registries, databases, ad hoc studies, or epidemiological surveys [34].

Several agencies specify that treatment effects used for modeling relative effectiveness should primarily be based on results from RCTs (transcripts b, d, and f) [27,32,34,35]. Alternatively, RWD may provide complementary evidence on treatment effects (transcripts b, d, and f) [27,30,34], be used to valuate the health effects over time in the form of utilities [27,32,35], or provide data on transition probabilities between different disease states in pharmacoeconomic models [27,32].

With regard to RWD appraisal in PEA, the use of RWD for epidemiological data, direct and indirect costs, resource use in routine practice, and adherence to treatment and compliance is largely accepted by HTA agencies. For relative treatment effects, however, the same hierarchies of evidence apply as in the context of IRD, implying that RWD is conventionally placed on

Table 1 – List of policy documents, guidelines, and academic publications retrieved as well as the number of interview participants and transcript reference per agency.

HTA agency	Policy papers and guidelines	Academic publications	Number of interview participants and transcript reference
TLV	Guide for companies when applying for subsidies and pricing for pharmaceutical products [21] General guidelines for economic evaluations from the Pharmaceutical Benefits Board (LFNAR 2003:2) [28] The Swedish Pharmaceutical Reimbursement System [33]	–	1 participant Transcript reference: a
NICE	Guide to the methods of technology appraisal 2013 [22] NICE DSU technical support document 17: The use of observational data to inform the estimates of treatment effectiveness in technology appraisal: Methods for comparative individual patient data [26]	Evidence requirements for reimbursements of pharmaceuticals across Europe [12] Methodological challenges in evaluating the value of registries [18] Evidence informed decision making: The use of "colloquial evidence" at NICE [17] How RWD compensate for scarce evidence in HTA [19] How to improve the quality of evidence when new treatments are funded conditional on collecting evidence of effectiveness and safety [20]	3 participants Transcript reference: b
IQWiG	Allgemeine Methoden version 4.2 [23]	–	1 participant Transcript reference: c
HAS	General method for assessing health technologies [24] Choices in methods for economic evaluation [29] Les etudes post-inscription sur les technologies de santé (médicaments, dispositifs médicaux et actes) [31]	–	2 participants Transcript reference: d
AIFA	–	Evidence requirements for reimbursements of pharmaceuticals across Europe [12] New perspective and new challenges in clinical trial regulation in Italy [13] Feasibility and challenges of independent research on drugs: The Italian Medicines Agency (AIFA) experience [15] The Italian postmarketing registries [14] The nationwide Osmed Health-Db database: A tool to support health-care decision-making and real-world evidence generation [16]	2 participants Transcript reference: e
ZIN	Beoordeling stand van de wetenschap en praktijk [25] Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg [30] Leideraad voor Uitkomstenonderzoek [27] Procedure voorwaardelijke toelating geneeskundige zorg 2015 [32]	Evidence requirements for reimbursements of pharmaceuticals across Europe [12]	2 participants Transcript reference: f

AIFA, Italian Medicines Agency; HAS, High Authority for Health; HTA, health technology assessment; IQWiG, Institute for Quality and Efficiency in Healthcare; NICE, National Institute for Health and Care Excellence; RWD, real-world data; TLV, Dental and Pharmaceutical Benefits Agency; ZIN, National Healthcare Institute.

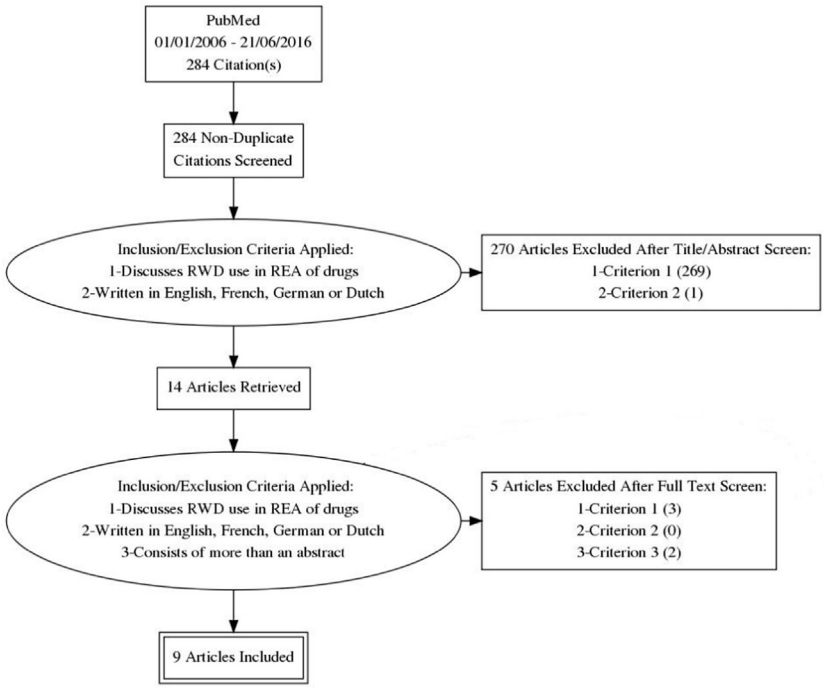

Fig. 2 – PRISMA diagram of inclusion and exclusion of articles retrieved through the PubMed search. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; REA, relative effectiveness assessment; RWD, real-world data.

a lower quality level (transcripts b, d, and f) [27,28,32,34,35]. Therefore, conclusions for relative treatment effects on the basis of RWD are considered as being more circumspect (transcripts b–d and f) [27,28,32,34,35].

Table 4 presents a summary of policies on RWD accepted or requested and RWD appraisal in the context of PEA per agency.

Conditional Reimbursement Schemes

Three of the six HTA agencies implement CRS (transcripts d–f) [19,20,36,37]. A fourth agency stated briefly that reimbursement can be conditionally offered to allow an applicant time to procure more RWD on long-term effects (transcript a) [38]. Meanwhile, a fifth agency recently announced the establishment of a CRS for oncologic drugs (transcript b) [39]. It, however, remains unclear whether the latter two schemes constitute ones as established as those outlined by the other three agencies (transcripts a and b).

Only one of the three agencies clearly defined criteria for the selection of candidates for CRS and a procedure to do so (transcript f) [32,37].

The purposes for RWD collection for CRS differed between the three agencies. For the first agency, a product is nominated for conditional reimbursement on two conditions: that it is highly innovative and data on its effectiveness are highly sparse at initial assessment. Therefore, the purpose for data collection is focused primarily on demonstrating effectiveness, with a preference for RCT data and a supplementary role for RWD (transcript f) [32,37]. For the second agency, a contract is drawn up between the agency and an applicant to conduct postmarketing studies that aim to answer questions raised during initial assessment. These questions may relate equally to issues of effectiveness and/or cost-effectiveness of the drug in national clinical practice and a preference is made for RWD rather than RCT data (transcript d) [36]. For the last agency, recommendations to set up postmarketing studies are similarly based on questions raised during initial assessment with a preference for RWD. Nevertheless, the use of study results for the last agency varies; they can be used to inform re-assessment of effectiveness and/or cost-effectiveness in clinical practice, but may also be used for repricing discussions (transcript e) [19,20].

Notwithstanding these principal differences, two agencies follow the same procedure for conditional reimbursement. First, gaps in evidence presented in submissions for IRD are systematically identified by the agencies. Second, the agencies request that the applicant develop a study protocol to collect the RWD needed to inform such gaps, implying that RWD collected for each drug candidate is highly case-specific. Both agencies provide methodological guidance to applicants on which study designs to choose to answer the scientific questions raised during initial assessment. This guidance also includes detailed examples of existing national RWD sources that may be used to answer specific questions [32,36,37]. Third, the applicant's study protocol(s) are reviewed by independent committees to judge their scientific quality and feasibility. Once relevant adjustments are made to the protocol(s), a contract is drawn up between the agency and the applicant in which the study protocol and the date for submitting additional evidence are specified. Further adaptations to the study protocol by the applicant are possible but only after consultation with the agency [32,36,37]. It is unclear whether the same procedure also applies for CRS implemented by the third agency.

Unlike the first two agencies, which lay the burden of RWD collection on applicants, the third agency often actively participates in, or initiates its own, product or indication registries (transcripts d–f) [18–20,36,37].

All three agencies require that the studies implemented deliver data of adequate quality and robustness to answer questions identified during initial assessment (transcripts d–f) [32,36,37]. Moreover, two agencies require that the study eventually conducted adhere strictly to the protocol agreed upon by all parties. This is to ensure that the scientific quality and outcomes of the study remain valuable for decision making. If these conditions are met, results generated by the studies would form the basis for decision making during re-assessment (transcripts

Table 2 – Examples of interview quotes on RWD use in IRD and CRS.

Context for RWD use	Topic	Quotation A	Quotation B
IRD	Appraisal of RWD vs. RCT data for treatment effect estimates in general	"There is this red flag in there. If you use non-randomized and non-controlled evidence, you have to be more careful, more circumspect about the relative treatment effect drawn from those studies. Ideally you should use more than one independent source of such evidence, as a back-up."[b]	"Of course we accept those data. We are forced by law to accept those data but we don't have to conclude the benefit from such data."[c]
IRD	RWD use to inform treatment effect estimates for orphan diseases	"Yes, RWD certainly plays a role in orphan diseases since RCTs are difficult to conduct in that area. In this case, patient registries may be the most ideal source for RWD."[f]	"… we would then need a registry with a very, very, very, high quality. In terms of having all patients in the registry, no selection criteria and no selection bias. We could imagine that we would only then accept these registry analyses for very rare diseases, but not in general."[c]
CRS	Use of RWD generated in CRS for decision making	"So, we are used to using that kind of data, though we know the bias and the problems that are related to the robustness of that kind of [RWD] data. For the re-evaluation for the pricing and reimbursement of the product, this kind of data are robust enough for the analysis that we need to do for the reevaluation of pricing and reimbursement of the product."[e]	"You can't really rely on it. You can use the RWD as a confirmation of the expectation you have on initial assessment and the data for the first-line population you have, and the data you have had already of the post-hoc subgroup analysis. So it is used as a confirmation of previous conclusions."[f]

CRS, conditional reimbursement scheme; IRD, initial reimbursement discussion; RCT, randomized controlled trial; RWD, real-world data.

d–f) [32,36,37]. Nevertheless, quotes from interviews shed light on varying acceptability of results generated from such studies for decision-making practice (see Table 2). Moreover, there was no guidance on the impact of RWD on decision making if conclusions for treatment effects on the basis of RWD contradict those from RCT-based evidence.

Table 5 presents a summary of policies on RWD use in the context of CRS per agency.

Similarities and differences in policies for RWD accepted or requested and RWD appraisal in IRD, PEA, and CRS are presented in Table 6.

Discussion

Policies for RWD accepted or requested and RWD appraisal for REA of drugs adopted by the six agencies differed between the three contexts analyzed. For example, although RWD use for IRD was accepted but not explicitly recommended, its use was recommended by agencies for PEA and CRS. RWD may provide evidence on numerous parameters of REA: (relative) treatment effects, epidemiological data, resource use data, and cost data.

Policies for RWD accepted or requested and RWD appraisal for REA of drugs differed between the six agencies within the same contexts. An important example relates to RWD use to provide data on treatment effects for IRD in situations in which it may be difficult to conduct RCTs (e.g., orphan diseases). Although some agencies deem this acceptable, others explicitly advise against it. Similarly, policies for CRS differed whereby the aims of the three agencies' schemes, procedures for conducting CRS, as well as agencies' involvement in RWD collection in CRS varied.

Intercontext policy variations may be an issue if the effectiveness and pharmacoeconomic components of HTA dossiers submitted to an agency are examined by two different assessors who subsequently appraise the RWD differently. Another compounding factor presents itself in agencies that offer a possibility for CRS, because the manner with which these different assessors would be required to appraise RWD in the effectiveness and pharmacoeconomic components of a specific dossier will inevitably depend on whether the dossier is submitted as a standard dossier or as a candidate for CRS. Bearing these points in mind, one can argue that standardizing the implementation of policies on RWD use for decision making in practice may be difficult in any single HTA agency.

Meanwhile, variations between agencies' policies may present marketing authorization holders (MAHs) with a multitude of challenging questions when developing strategies for evidence generation across the product life cycle [8,40,41]. For instance, in the context of CRS, MAHs would need to question whether their product qualifies as a candidate for CRS in the different countries; whether questions raised by the various agencies would overlap or differ; and consider whether one study would suffice to collect the RWD needed for all three agencies.

Hierarchies of evidence adopted by HTA agencies prominently featured in documents and interview transcripts assessed. Several agencies implement such hierarchies through tools for classification of evidence quality (e.g., The Grading of Recommendations Assessment, Development and Evaluation working group [GRADE]) [42]. Although evidence hierarchies have well-established roots in evidence-based medicine, it is debatable whether they are applicable to the concept of RWD use for HTA. Conventionally, hierarchies automatically downgrade all RWD without exploring the subtle differences between the advantages, disadvantages, and relevance of different RWD sources (e.g., patient registries or claims databases). More importantly, such evidence hierarchies do not address the differences

Table 3 – Summary of policies on RWD accepted or requested and the appraisal of RWD in the context of IRD per agency.

HTA agency	RWD accepted/requested			RWD appraisal		
	RWD accepted	RWD to inform treatment effects	RWD to inform other parameters	Hierarchy of evidence adopted	Conclusions on treatment effects on the basis of RWD regarded as circumspect	Conclusions on treatment effects on the basis of RWD possible in exceptional circumstances (e.g., orphan diseases)
TLV	Yes	Under specific circumstances	Not mentioned	Yes; with regard to evidence for treatment effects	Yes	Yes
NICE	Yes	Under specific circumstances	Epidemiological data (e.g., incidence and prevalence), resource use data, and cost data	Yes*; with regard to evidence for treatment effects	Yes	Yes
IQWiG	Yes	Under specific circumstances	Epidemiological data (e.g., incidence and prevalence) and resource use data	Yes; with regard to evidence for treatment effects	Yes	No
HAS	Yes	Under specific circumstances	Not mentioned	Yes; with regard to evidence for treatment effects	Yes	Not mentioned
AIFA	Yes	Under specific circumstances	Not mentioned	Yes; with regard to evidence for treatment effects	Yes	Not mentioned
ZIN	Yes	Under specific circumstances	Epidemiological data (e.g., incidence and prevalence), resource use data, and cost data	Yes*; with regard to evidence for treatment effects	Yes	Yes

AIFA, Italian Medicines Agency; HAS, High Authority for Health; HTA, health technology assessment; IQWiG, Institute for Quality and Efficiency in Healthcare; IRD, initial reimbursement discussion; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial; RWD, real-world data; TLV, Dental and Pharmaceutical Benefits Agency; ZIN, National Healthcare Institute.

* However, agency explicitly recognizes limitations associated with strictly adopting evidence hierarchies in guidelines and states that such hierarchies should not preclude the exclusion of valuable non-RCT evidence from decision making.

Table 4 – Summary of policies on RWD accepted or requested and the appraisal of RWD in the context of PEA per agency.

HTA agency	RWD accepted/requested			RWD appraisal		
	RWD recommended	RWD to inform treatment effects	RWD to inform other parameters	Hierarchy of evidence adopted	Conclusions on treatment effects on the basis of RWD regarded as circumspect	Conclusions on other parameters on the basis of RWD regarded as reliable
TLV	Yes	Under specific circumstances	Epidemiological data (e.g., incidence and prevalence), costs (direct and indirect), and resource use	Yes; with regard to evidence for treatment effects	Yes	Yes
NICE	Yes	Under specific circumstances	Epidemiological data (e.g., incidence and prevalence), costs (direct and indirect), and resource use	Yes*; specifically with regard to relative treatment effects	Yes	Yes
IQWiG	NA	NA	NA	NA	NA	NA
HAS	Yes	Under specific circumstances	Epidemiological data (e.g., incidence and prevalence), costs (direct and indirect), resource use, adherence, and compliance	Yes; with regard to evidence for treatment effects	Yes	Yes
AIFA	Yes	Under specific circumstances	Epidemiological data (e.g., incidence and prevalence), costs (direct and indirect), and resource use	Yes; with regard to evidence for treatment effects	Yes	Yes
ZIN	Yes	Under specific circumstances	Epidemiological data (e.g., incidence and prevalence), costs (direct and indirect), and resource use	Yes*; with regard to evidence for treatment effects	Yes	Yes

AIFA, Italian Medicines Agency; HAS, High Authority for Health; HTA, health technology assessment; IQWiG, Institute for Quality and Efficiency in Healthcare; NA, not applicable; NICE, National Institute for Health and Care Excellence; PEA, pharmacoeconomic analysis; RCT, randomized controlled trial; RWD, real-world data; TLV, Dental and Pharmaceutical Benefits Agency; ZIN, National Healthcare Institute.

* However, agency explicitly recognizes limitations associated with strictly adopting evidence hierarchies in guidelines and states that such hierarchies should not preclude the exclusion of valuable non-RCT evidence from decision making.

Table 5 – Summary of policies on RWD use in the context of CRS per agency.

HTA agency	CRS implemented?	CRS aims	CRS procedure	Preference for RWD	Involvement in collection of RWD?	Preference for RWD	Impact of RWD on decision making
TLV	No*	NA	NA	NA	NA	NA	NA
NICE	No*	NA	NA	NA	NA	NA	NA
IQWiG	No	NA	NA	NA	NA	NA	NA
HAS	Yes	Effectiveness and/or cost-effectiveness	1: Identification of evidence gap 2: Consultation on study design 3: Decision making based on results	Yes	No	Yes	Conditional on whether data delivered sufficiently address evidence gap highlighted and adherence to agreed-upon study protocol
AIFA	Yes	Effectiveness, cost-effectiveness, and/or price re-negotiations	Not mentioned	Yes	Yes	Yes	Conditional on whether data delivered sufficiently address evidence gap highlighted
ZIN	Yes	Effectiveness	1: Identification of evidence gap 2: Consultation on study design 3: Decision making based on results	No; in first instance RCT data with RWD as supplementary	No	No; in first instance RCT data with RWD as supplementary evidence	Conditional on whether data delivered sufficiently address evidence gap highlighted and adherence to agreed-upon study protocol

AIFA, Italian Medicines Agency; CRS, conditional reimbursement scheme; HAS, High Authority for Health; HTA, health technology assessment; IQWiG, Institute for Quality and Efficiency in Healthcare; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial; RWD, real-world data; TLV, Dental and Pharmaceutical Benefits Agency; ZIN, National Healthcare Institute.

* CRS schemes implemented by the agencies do not constitute schemes as established as those outlined by HAS, AIFA, and ZIN.

Table 6 – Summary of similarities and differences in policies for RWD accepted or requested and RWD appraisal within the three contexts.

Context	RWD accepted/requested	RWD appraisal
IRD	Summary of commonalities • All sources of data are welcomed in submissions. This implies that RWD is also welcome. • Treatment effects: RWD can be used to inform on treatment effects when RCT evidence is absent on specific head-to-head comparisons. Biases related to RWD must, however, be explored and documented. • Other domains: RWD can be used to provide evidence on epidemiological data, natural history of disease, or resource use data. • Agencies do not specify which kind of RWD should be collected nor the methods for collection. Nevertheless, the choice of which RWD and collection methods should be justifiable given the scientific questions at hand. Summary of differences • One agency recently published a comprehensive list of RWD used in technology appraisals, detailing that comparative IPD, noncomparative IPD, and aggregated data have been used in decision making. In addition, the document included detailed guidance on statistical methods for use of RWD in submissions. • No significant differences further.	Summary of commonalities • All agencies adopt evidence hierarchies in accordance with evidence-based medicine. Hierarchies consistently rank RWD at a lower quality level than RCT data. • Impact of RWD on decision making differs according to contextual factors: ◦ Conclusions regarding causal effects that are based on RWD will be regarded as more circumspect. ◦ RWD can be used to supplement/confirm RCT-based conclusions on treatment effects. ◦ For some agencies, impact of RWD may be higher in cases in which RCTs are difficult to conduct (e.g., rare diseases). • There is lack of clarity on RWD impact in the case of conflicting evidence (cf. RCT) Summary of differences • Two agencies explicitly recognize limitations in adhering to strict evidence hierarchies in guidelines by stating that such hierarchies should not preclude the exclusion of valuable non-RCT evidence from decision making. One agency advises against deviating from evidence hierarchies when considering evidence inclusion for decision making. • Two agencies stipulate that in cases in which RCT data are sparse (especially orphan diseases), RWD may be the only source of data available and thus could be used for decision making. Contrastingly, one agency stipulates that the circumstance of small patient populations (e.g., orphan diseases) does not necessitate deviance from the principles of evidence hierarchies.
PEA	Summary of commonalities • RWD is directly requested by HTA agencies for PEA. • Treatment effects: RWD can be used to inform on treatment effects when RCT evidence is absent on specific head-to-head comparisons. Biases related to RWD must, however, be explored and documented. • Costs and resource use data: National RWD is the preferred source for costs data (direct and indirect) and resource use data. • Other domains: RWD can be used to provide data on quality of life, adherence, epidemiological data, and transition probabilities for models. Summary of differences There are no significant differences.	Summary of commonalities • RWD use to inform parameters other than treatment effects is largely accepted. • Hierarchies of evidence adopted by HTA agencies consistently rank RWD at a lower quality level than RCT data. • Impact of RWD on decision making differs according to contextual factors: ◦ Conclusions regarding causal effects that are based on RWD will be regarded as more circumspect. ◦ RWD can be used to supplement/confirm RCT-based conclusions on treatment effects. Summary of differences There are no significant differences.
CRS	Summary of commonalities • RWD requested in any scheme is case-specific but follows similar processes for two agencies: 1: Identification of evidence gaps during IRD 2: Assessment of study proposal to collect data for scientific quality, feasibility, and	Summary of commonalities • The impact of RWD collected rests on the following conditions: ◦ That applicants take practical guidance available into consideration when designing the study protocol

continued on next page

Table 6 – *continued*

Context	RWD accepted/requested	RWD appraisal
	relevance 3: Agreement on study protocol and date of collected RWD delivery for re-assessment of relative effectiveness • Agencies provide practical guidance for applicants on: ◦ Which scientific questions different study designs can and cannot answer. ◦ Existing national RWD sources and relevance for providing specific information. Summary of differences • Only three of the six HTA agencies implement CRS. • Differing aims of CRS (effectiveness vs. cost-effectiveness vs. repricing discussions) influence the type of data requested in each scheme. • The degree of guidance available for applicants varies between the three agencies: two agencies have guidelines to this effect, yet one does not. • One agency often actively participates in, or initiates its own, product or indication registries. The remaining two agencies lay the burden of data collection on applicants.	◦ That the research conducted delivers the answers to evidence gaps identified ◦ That the research conducted adheres to the protocol agreed upon by all parties Summary of differences There are no significant differences.

CRS, conditional reimbursement scheme; HTA, health technology assessment; IPD, individual patient-level data; IRD, initial reimbursement discussion; PEA, pharmacoeconomic analysis; RCT, randomized controlled trial; RWD, real-world data.

in the type of insights provided by RCT data (efficacy data with high internal validity) and different forms of RWD (long-term data on safety and effectiveness from registry data, resource use data from claims databases, or patient-reported outcomes from pragmatic clinical trials). An increasing body of literature also refers to the relevance of using data from pragmatic clinical trials for more generalizable and translatable evidence on real-world outcomes [43–45], yet guidance on this topic was not always reflected in agency guidelines. This can result in excluding valuable evidence in decision making. Furthermore, some agencies may abandon the rigid framework of evidence hierarchies because of pragmatic reasons (e.g., in situations in which RCTs are difficult to conduct or for CRS), and others even provide methodological guidance on such aspects [27,31,32,36]. Therefore, it may be necessary for HTA agencies to consider how implementation of rigid evidence hierarchies could be adapted to enable effective use of RWD in decision-making processes.

The lack of harmonization of policies for RWD use in REA of drugs may discourage MAHs from collecting or analyzing RWD for HTA purposes [8,40,41]. Therefore, it may be useful for HTA agencies in Europe to align policies on RWD and provide guidance on practical aspects of RWD collection and analysis. This is especially important in light of the increasing trend of new (oncology or orphan) drugs granted conditional marketing authorization on the basis of phase II data or surrogate outcomes rather than phase III RCT data [46–48]. A harmonized set of policies on RWD use for HTA would provide MAHs with the ability to plan alternative evidence generation pathways that rely less on RCTs and more on real-world studies, the latter theoretically yielding outcomes more relevant for HTA purposes [49–52]. The EUnetHTA may provide a platform for discussions on aligning RWD policies. The EUnetHTA has recently published position articles on additional (non-RCT) evidence generation for REA and is finalizing proposals for pilot projects that will address some of the aforementioned issues [53–55].

In addition to studying differences in policies for RWD use in REA of drugs between different contexts and agencies, determining whether differences extend to the implementation of these policies in practice is important. When asked if their agency accepts or requests RWD, one HTA representative stated, “Of course we accept those data. We are forced by law to accept those data but we don’t have to conclude the benefit from such data.” This implies that RWD has quite a low impact on decision making in that agency, in contrast to others. When representatives from two of the three agencies implementing CRS were asked about the impact of RWD in decision making at re-assessment, they displayed contradicting views. One stated, “You can’t really rely on them. You can use the RWD as a confirmation of the expectation you have at initial discussions,” whereas the other stated, “For the re-evaluation of pricing and reimbursement of the product, that kind of data are robust enough.” Therefore, the reality of how RWD is used in practice may differ from policies and should be the focus for future research.

Strengths

To ensure that all available information on RWD policies was gathered for all six HTA agencies, a mixed-methods approach was used that included a review of agency Web sites, academic literature, and stakeholder interviews. This minimized the probability of important information being excluded from analysis. Moreover, the selection of documents for analysis, data abstraction, and coding was conducted independently by two authors.

Limitations

Although six European HTA agencies were included, this does not automatically mean that we provided a representative overview of all European policies on RWD use in REA of drugs. The agencies

selected represent only those vested in the Big Four jurisdictions and two agencies with pioneering roles in cutting-edge European HTA initiatives. Nevertheless, considering the novelty of the topic on RWD use in REA of drugs and the impact of the agencies and jurisdictions included, this sample was deemed as relevant for an initial policy analysis on RWD use in REA of drugs in Europe.

The information available for analysis varied between agencies. Language capabilities of the involved researchers meant that Swedish and Italian documents were excluded from the analysis. As a result, valuable information from documents written by TLV or AIFA may have been overlooked. Moreover, not all agencies published guidelines that specifically focus on the use of RWD in REA. But then, gathering information from several sources through agency Web site searches, the PubMed search, and stakeholder interviews ensured that the impact of excluded information was minimal. Furthermore, TLV published numerous English guidelines on REA [26,33,38] and AIFA affiliates published several English academic articles on RWD use in Italian practice [17–21].

It can be argued that data gathered during interviews may reflect only the interviewees' opinion, rather than represent the agencies' official position. We attempted to account for this through selective sampling of participants, providing all approached participants with the opportunity of inviting colleagues they deemed relevant to the interview and by interviewing more than one person per institute. In addition, information provided during interviews was compared with that from policy documents and academic publications to ensure alignment between data sources.

Conclusions

Individual agencies' policies regarding RWD accepted or requested and appraisal of RWD for REA of drugs vary notably across the three contexts assessed: IRD, PEA, and CRS. In addition, differences are present between each agency's policies on RWD use for IRD, PEA, and CRS. For example, the manner by which RWD is appraised for decision making varies in any given agency, being largely acceptable for numerous PEA parameters and CRS but not for informing treatment effects for IRD. Moreover, the existence of CRS, as well as the manner of the implementation of RWD use in CRS, is different in the agencies examined.

The lack of harmonization of policies on RWD use for REA of drugs may present MAHs with a multitude of challenging questions when they consider collecting and using RWD for HTA purposes. As a result, MAHs may be discouraged to use RWD for HTA. Therefore, HTA agencies in Europe may collaborate to align policies on RWD and provide guidance on practical aspects of RWD collection and analysis. Recently published position articles and future project proposals by the EUnetHTA may provide a starting point for discussions and a suitable platform for HTA agencies to achieve this.

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Supplementary materials

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