Journal of Evaluation in Clinical Practice

WILEY

Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

REVIEW ARTICLE

Using Real-World Evidence for Clinical Development to Address the Gap Between Marketing Authorisation and Reimbursement in European Countries: Insights From Literature Review

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Received: 29 April 2024 | **Revised:** 4 March 2025 | **Accepted:** 21 March 2025

Keywords: evaluation | evidence-based medicine | health policy | structured reviews

ABSTRACT

Background: Health Technology Assessment (HTA) agencies require evidence relevant to elements like the 'added value' of the drug, efficacy and safety in real life, or data regarding the drugs' effects on different subgroups of interest. Using Real-World Evidence (RWE) during drug clinical development can provide the information required for HTA approval.

Objective: Two targeted literature reviews (TLRs) were conducted to narratively describe the reasons for the gap between EMA market authorisation and market access in France and Germany; the possible importance of RWE studies to provide relevant clinical evidence for HTA approval and, therefore, their role to support drug clinical development programmes in Europe.

Methods: Relevant studies were identified by searching Embase using predefined search strategy via the Ovid platform. Additional studies were included from external keyword searches on Google Scholar and PubMed that address the objective of the review. Further searches were conducted in the Haute Autorité de Santé (HAS) and the Gemeinsamer Bundesausschuss (GBA) websites to identify examples of reimbursement submissions.

Results: The average time to access drugs was 128 days in Germany and 508 days in France. Delays in patient access to new drugs resulted in diminished patient benefits. The delays in the approval of new drugs were attributed to several clinical factors, including: (i) lack of safety and efficacy data from the submitted clinical trial; (ii) absence of clinically relevant comparators; (iii) lack of demonstration of added value and (iv) inability to contextualise data to the local population. RWE can be valuable in supporting clinical evidence generation by providing a complementary set of information to address gaps in knowledge regarding the drug's effectiveness and safety. It can also offer an external arm for comparison when randomisation is not feasible. Furthermore, RWE can support the demonstration of a drug's added benefit over existing therapies and help define its role in disease management. However, RWE studies also face several limitations, including variability in data quality, challenges in addressing specific research questions, methodological constraints and concerns about the credibility of analyses.

Conclusion: Access to medication is usually delayed due to the HTA agency's requirements for scientifically robust clinical evidence about the drug's effectiveness and safety assessed in specific subpopulations, with relevant and valid endpoints. The utilisation of RWE is revolutionising the whole clinical development process that supports HTA submissions. Early engagement among stakeholders during the drug's clinical development on how providing high-quality, relevant clinical data might be addressed is crucial for ensuring the robustness, reliability and acceptance of RWE.

1 | Introduction

The journey from drug discovery to patient access is a multifaceted process with two crucial milestones, marketing authorisation and pricing and reimbursement approval. While marketing authorisation signifies a product's safety and efficacy, pricing and reimbursement approval ensures its affordability and accessibility to patients. In the European context, these two milestones operate independently, leading to a disconcerting gap that can impede timely patient access to novel therapies and technologies. Across Europe, the average delay between market authorisation and actual patient access varies more than sevenfold between countries [1, 2]. One of the main reasons for delayed approval is the lack of clinical evidence that supports the added value of the drug over existing therapies or its effects on special populations.

The process of obtaining reimbursement is multifactorial, complex and time-consuming and generally varies depending on the country and the type of drug. Health Technology Assessment (HTA) agencies assess the clinical added value of drugs as well as their cost-effectiveness and cost-utility to determine the overall economic impact [3]. Generally, HTA agencies need submissions to include proof about important aspects of the drug's benefits, like how it adds value to existing therapies or the need to remove uncertainty regarding the drugs' effects on different subgroups of interest [3].

Clinical evidence generation is the fundamental step in the HTA process, aimed at evaluating the safety, effectiveness and value of medical interventions [4]. This process involves rigorous methodologies to gather and analyse data from various sources, including clinical trials and real-world evidence (RWE) studies. Incomplete clinical evidence may lead to delays in the assessment process, as the HTA body may request additional data or clarifications from the submitter.

The European Medicines Agency (EMA) defines RWE as the evidence derived from the analysis of Real-World Data (RWD). RWD encompasses information about the impacts of health interventions gathered outside the controlled environment of RCTs. RWD encompasses both primary data collected directly to mirror standard clinical practice and secondary data sourced from pre-existing, routinely collected datasets [5]. Understanding the role of RWE in providing relevant clinical evidence and identifying the challenges when submitting clinical RWE would help find solutions that meet the HTA agencies' requirement, therefore, leading to early acceptance of drug reimbursement, which would help reduce the access delay, hence subsequent clinical impact.

2 | Objective

Two targeted literature reviews (TLRs) were conducted to narratively describe the possible clinical reasons for the gap between market authorisation and reimbursement of medicines and the possible role of RWE studies in providing relevant clinical evidence and supporting the drug clinical development programme.

3 | Methods

Two TLRs were conducted following the standard methodologies for conducting and reporting systematic reviews as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [6]. The first TLR focused on the gaps in clinical evidence that lead to delays in HTA approval, and the second TLR focused on identifying the ways RWE can help address this gap. This article reports on the synthesis of the two TLRs.

Relevant studies were identified by searching Embase on 26 April 2023, using predefined search strategies via the Ovid platform. MeSH terms and Keywords were used to search the databases. Additional manual searches using Google Scholar were performed. Eligibility criteria for study selection were defined using the PICO framework (Population, Intervention, Comparator, Outcomes).

Studies reporting on any disease area, intervention or comparator with outcomes (such as any reported cause of gaps between market authorisation and reimbursement of medicines or clinical outcomes due to gap, or outcomes that illustrate the role of RWD in addressing challenges related to the gaps between market authorisation and reimbursement of medicines) that were relevant to the objective of the study were included in the respective TLRs.

An investigator was responsible for reviewing abstracts according to the pre-defined selection criteria. All eligible studies identified during title/abstract screening proceeded to the full-text screening phase, where they were assessed for eligibility by the same reviewer. Studies that match the PICO criteria following the full-text screening were included. Examples were extracted from the websites of HTA bodies such as Haute Autorité de Santé (HAS), Gemeinsamer Bundesausschuss (GBA), and IQWiG. The results of the review were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7].

4 | Results

A total of 253 abstracts were identified via Embase search on 26 April 2023 for TLR1, which aimed to identify reasons related to clinical evidence that causes such delay, and 765 abstracts for the objective concerning the use of RWE to address the delay (TLR2). After screening of the literature identified, 22 records were included for TLR1 and 29 for TLR2 (Figure 1).

Studies included for TLR1 were guidelines and systematic reviews ($n = 4$ each), retrospective database searches and webpages ($n = 3$ each), commentary papers and surveys ($n = 2$ each) and book chapters, analytical frameworks, annual reports and multi-year annual metrics study ($n = 1$ each). For TLR2, most of the included records were descriptive reviews ($n = 21$), followed by webpages ($n = 5$) and cohort study, systematic literature review and a template for planning and reporting ($n = 1$ each). Two PRISMA flow diagrams illustrating the study selection procedures are presented in Appendix A.

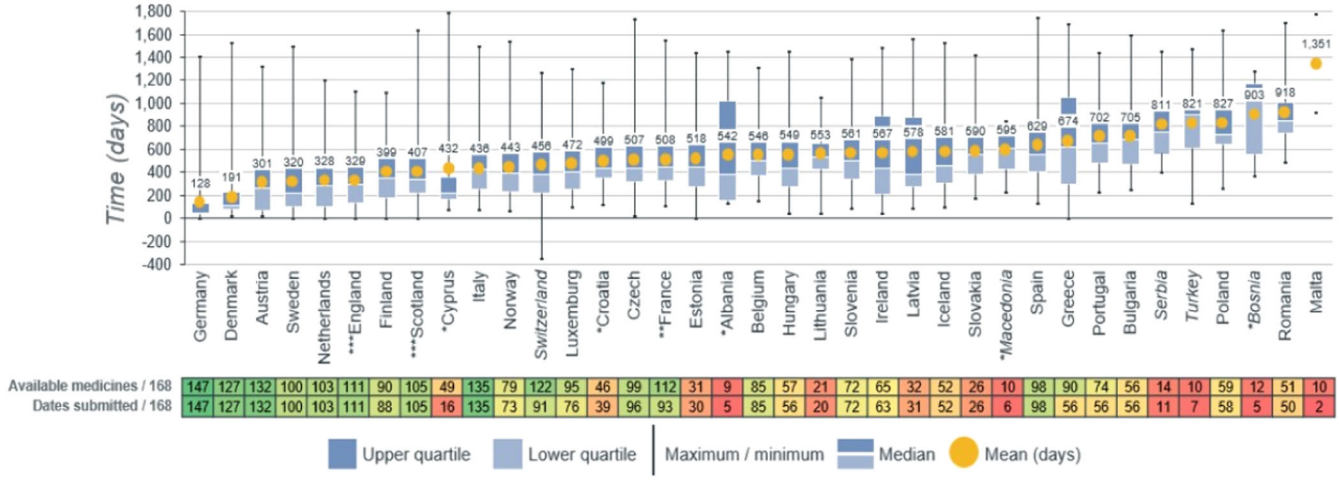

FIGURE 1 | Mean time to availability in days (2018–2021) according to the Patient W.A.I.T Indicator Survey by Newton et al. [8] *This figure was used with permission from the original authors.

4.1 | Documenting the Delay Between Market Authorisation and Drug Reimbursement

The most recent data in the Patient Waiting to Access Innovative Therapies (W.A.I.T.) indicator 2022 survey highlighted that the average time to reimbursement for innovative treatments across EU and European Economic Area (EEA) countries was, on average, 517 days with variations from 128 days in Germany and 508 days in France. The expected time to receive an HTA approval varies widely among countries. Spain, for instance, contends with a protracted reimbursement timeline of approximately 629 days, a reflection of the involvement of multiple HTA bodies in the evaluation process [8].

4.2 | Clinical Consequences of the Delayed Drug Access

Delays in receiving pricing and reimbursement approval can prevent patients from receiving potentially life-saving or essential treatments. The delayed drug access may have an important impact on the patients' life-years, as shown by Uyl-de Groot et al. when studying the variations of access to newly registered cancer drugs in Europe [9]. In Europe, approximately 14,994 patients with melanoma were eligible for treatment with ipilimumab in the first year after EMA approval in 2011. The study derived sales data from IQVIA's MIDAS database, which originates in retail or hospital settings. Moreover, the study assumed that the sales data give an indication of the access and use of drugs [9]. Considering the sales per country in the first year, approximately 11,184 melanoma patients were not treated with ipilimumab. Knowing that the average gain in overall survival (OS) of 3.7 months would have resulted in a loss of 3448 life-years [9]. When the same calculation was applied to prostate cancer patients who were eligible for abiraterone, it resulted in 55,853 patients not receiving treatment, suggesting a loss of 18,152 life-years throughout Europe due to the non-use of abiraterone [9].

4.3 | Lack of Clinical Information as One of the Key Reasons in Drug Reimbursement Delays

Most of the delays in achieving HTA approval were due to limitations of clinical research. Our review identified several reasons to explain the delay between marketing authorisation and pricing and reimbursement:

- Lack of safety and efficacy data from the submitted clinical trial: Clinical trials may fail to present enough efficacy results such as on selected populations or conducting an underpowered study [10]. Endpoints were considered insufficient or unacceptable due to a lack of alignment with regulatory requirements or evidence of relevance to clinical outcomes [11]. Safety is addressed in every phase of clinical trials, but data reliability increases significantly when a larger population is exposed to the drug such as in Phase 3 or post-approval studies [10]. This later solution is particularly relevant for rare diseases that are characterised by small Phase 3 trials.
- Absence of clinically relevant comparators: This can be due to the inappropriate use of an inactive comparator, such as selecting the least effective option for comparison. If any of the treatments chosen for comparison in a trial is known to be inferior to others, not only will some trial participants be deprived of effective treatment, but choosing a suboptimal comparator undermines the overall credibility of the trial [12]. HTA bodies require a well-defined control group to demonstrate that a treatment or intervention is superior to existing approved therapy [13]. Placebo-controlled trials are a valuable methodological approach as they help establish the true efficacy of a new treatment by comparing it to an inactive substance. This design minimises bias and ensures the reliability of the study results. Active comparators help HTA agencies determine whether the new treatment offers any additional benefits over current standard therapies. This is crucial for making informed decisions about resource allocation and ensuring that patients receive the most effective treatments available. On the other hand,

non-inferiority trials often face scrutiny because they rely on assumptions about the performance of the comparator, which can be challenging [14]. Finally, active comparator trials are often more ethically acceptable than placebo-controlled trials, especially when effective treatments are already available [15].

- Lack of demonstration of added value: This reason is given by HTA agencies when evidence is insufficient to establish the superiority of a new drug compared to existing approved therapies. In some cases, the HTA agencies might ask for additional research to support the added benefit of the new drug.
- Inability to contextualise data to the local population: A well-conducted randomised clinical trial is considered to have good internal validity. When the population that will be exposed to the drug is substantially different than the trial population, HTA agencies may request additional data that are relevant to the local population.

One of the main clinical reasons for requesting additional data identified in our TLR was the lack of evidence demonstrating the clinical benefit of the drug. Even after submitting the dossier, HTA bodies required additional evidence to support the assessment [16]. England showed the highest frequency of requesting additional evidence from companies, followed by Germany [16]. The evidence requested across HTA bodies was related to the use of a locally relevant comparator, the need for sub-group analyses and to contextualise the evidence to the local population, and the need to use a different analysis approach, for instance, network meta-analysis [16]. Network meta-analysis is a statistical tool for pooling evidence from multiple studies to compare a set of three or more interventions. It compares each pair of interventions in the set simultaneously by combining all available direct evidence (i.e., head-to-head studies) and indirect evidence (e.g., their performance relative to a common comparator in separate studies). France has extensive experience in requiring RWD/RWE following access to reimbursement. Between 2000 and 2019 and using public sources, 333 postlaunch studies were required [17] to strengthen the drugs' effectiveness in different contexts [18]. The drugs that received a postlaunch study request were either drugs that had a claim of impact on morbidity and mortality or drugs with new mechanisms of action. The main reasons for these postlaunch studies were good usage, effectiveness, compliance and quality of life.

In 2011, the transparency committee in France attributed an insufficient SMR (Service Médical Rendu), which reflects the product's actual medical benefit and determines the reimbursement level, to pazopanib, a drug indicated in advanced renal cell carcinoma, due to the absence of any direct comparison against the already existing medicinal products [19]. The clinical data submitted were based on one pivotal placebo-controlled study and one indirect comparison. In the absence of direct comparison, the applicant performed indirect comparisons against the available drugs. This indirect comparison was considered uninformative by the transparency committee due to several limitations, including wide confidence intervals, unreliable indirect comparison network, absence of heterogeneity assessment and reliance on potentially biased source information derived from an interim analysis.

Overall, the main reasons that contributed to delayed access included the lack of any demonstrated added value of the drug or the lack of demonstrated impact on the organisation of care. The identified reasons for the HTA rejections of various drugs submitted are summarised in Table 1.

4.4 | The Use of Clinical RWE to Address the Delay

Recently, there has been a growing emphasis on incorporating clinical RWE into the decision-making processes of pricing and reimbursement. RWE can help in achieving HTA approval, especially due to the lack of appropriate clinical data. Firstly, clinical RWE complements RCT findings about safety and efficacy and can contribute to enhanced evidence generation. Data from Electronic Health Records (EHRs) can help address various safety issues, especially long-term safety data that are often not detected over a limited duration phase III trial [21, 22]. Claims databases can help detect new adverse events when a larger number of patients are exposed to the drug in regular clinical practice [21, 23]. Table 2 provides examples showing the utility of the RWE to fulfil the needs of HTA organisations.

Some reasons identified include:

- The poor quality of source data: Although administrative and claims data sources are free from recall bias and provide easily accessible data, which are usually relatively large, the weaknesses of these data are the lack of information on potential confounders, disease details and the uncertainty of diagnosis. Moreover, misclassification can also be a problem [30].
- Poorly defined research questions: The research question needs to match exactly the HTA reviewers' requests. This prevents rejections for lack of relevance. Key parameters for research questions should be taken into consideration, including population, intervention and outcomes of interest and the follow-up time needed [31].
- Scientific protocols with weaknesses: Usually, a multidisciplinary team would be developed for planning, designing and implementing a state-of-the-art methodology. The protocol should predefine possible confounders and biases and ways to control for them. Study designs used for RWE are usually subject to selection bias, measurement bias or time-dependent bias, such as immortal time bias and time-lag bias [32].
- The lack of transparency and credibility: Because of high risk of biases and the need of complex analyses, it is important that protocols and statistical analyses plans are sent to the HTA agencies to ensure high integrity of the documents.

5 | Discussion

There is a delay in accessing medications in European countries due to the lack of relevant clinical data required by HTA bodies

TABLE 1 | Overview of the reasons for the delay of HTA approvals identified in our search.

Studies	Reasons for delay from marketing authorisation to reimbursement	Details
Examples from the France HTA (HAS)		
Polivy (Polatuzumab vedotin)	Lack of safety and efficacy data from the submitted clinical trial	• There was a lack of response to the identified patient need, with the lack of evidence providing an additional impact on morbidity–mortality or quality of life *considering the efficacy and safety data available from the POLARIX phase III study.* • There was a lack of demonstrated impact on the delivery of care.
Entrectinib	Absence of direct comparative data for clinically relevant comparators	• There was a lack of response to the identified patient need due to the absence of an additional demonstrated impact on morbidity and mortality or on quality of life, given the *absence of direct comparative data for clinically relevant comparators.* • The absence of data enabling assessment of the impact on quality of life
Palonosetron hydrochloride netupitant	Lack of any demonstrated impact on the resource utilised, such as hospitalisations	• There was a potential presence of chemotherapy-induced nausea and vomiting (CINV), and this medical need is largely already met by the existing alternatives. • *There was a lack of elements supporting no further deterioration in the care and life pathway* due to the absence of robust quality-of-life data. • *There was a lack of demonstrated impact on the organisation of care,* such as hospitalisation. • As the identified need was already largely met by the available alternatives, there was an absence of demonstration of non-inferiority versus the study comparator and the absence of data versus the other existing alternatives.
Prednisolone pivalate	Lack of demonstration of added value	• There was *no evidence of the superiority* of 1% prednisolone eye drops over dexamethasone or fluorocortolone eye drops in robust studies. • *There was a lack of evidence demonstrating the superiority* of 0.5% prednisolone eye ointment over other ophthalmic corticosteroids.
Examples from Germany HTA (G-BA and IQWiG)		
Polivy (Polatuzumab vedotin)	Absence of direct comparative data versus clinically relevant comparators	• There was a lack of comparability with appropriate comparator therapy. • Further evidence of the drug's benefit is awaited. New information on the drug will be reviewed at least annually, and the reimbursement decision will be updated as necessary.
Entrectinib	Lack of demonstration of added value	• On the basis of the results of the STARTRK-2 study and the comparison of single-arm studies (primarily based on the comparison of STARTRK-2 vs. the Flatiron Health Database), derived a *hint of a non-quantifiable added benefit* (the quality and the magnitude of added benefit as assessed by GBA) for entrectinib for the outcomes 'overall survival' and 'tumour response'.

(Continues)

TABLE 1 | (Continued)

Studies	Reasons for delay from marketing authorisation to reimbursement	Details
Palonosetron hydrochloride netupitant	Lack of demonstration of added value	• *Neither the direct nor the indirect comparison was adequate to derive conclusions on the added benefit* of netupitant/palonosetron for the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy in comparison with the ACT specified by the GBA.
Examples from published literature		
The European Federation of Pharmaceutical Industries and Associations [20]	Variations in HTA requirements	• *Acceptance of RWE* is not harmonised across European HTA agencies. • Manufacturers need to prepare different dossiers for different countries, hence adding to the time required for accessing the drug.
Wang 2020 [16]	Requesting additional data due to lack of evidence submitted	• The evidence requested across all HTA bodies was related to (i) using a *locally relevant comparator*, (ii) conducting sub-group analysis, (iii) conducting economic analyses, (iv) *contextualising the evidence to the local population*, (v) the statistical analysis methodology used, (vi) developing a network meta-analysis and (vii) the need to conduct a trial data in the local population. • Locally relevant comparators are generally requested from RWD sources.
Chouaid 2016 [19]	Lack of evidence to prove added value	• In 2011–2013, the French HTA body rejected interventions due to the *absence of any direct comparison* against the already available medicinal products and the absence of blinding in clinical trial data. • Recently, France had extensive experience requiring RWD/RWE following access to reimbursement.
De Pouvourville 2023 [17]	Requesting additional data due to lack of evidence submitted	• When HTA bodies identify gaps in the evidence submitted by the manufacturers, they request *complementary data* from manufacturers in anticipation of a future reassessment, generally with a primary focus on the effectiveness of new treatments. • HTA bodies can also request *additional safety data* after approval of similar drugs. • In France, 333 postlaunch studies were required between 2000 and 2019 that utilised real-world sources.
Real project [18]; examples from the HAS website	Requesting real-life studies, including data on the use of the medication and its effectiveness	• Data requested include the *use of the medication and its effectiveness*. • Transparency Committee of HAS in France may request a *cohort study follow-up of patients treated with the drug*. • For example, for Apixaban, HAS requested a study documenting the therapeutic benefit of apixaban

(Continues)

TABLE 1 | (Continued)

Studies	Reasons for delay from marketing authorisation to reimbursement	Details
		under *actual conditions of use in comparison with the usual management of at-risk patients* with non-valvular atrial fibrillation. After submission of study results, the Commission considered that the data from these studies *did not provide enough information* for clinical value of this treatment. The final decision of HAS was to not recommend this treatment.

to reimburse the drugs. HTA bodies can request additional clinical data during the approval process such as the use of a locally relevant comparator and contextualising the evidence to the local population. The main reasons identified for delayed approval were the lack of comprehensive evidence to support the added value of the new drug, the limited evidence regarding safety and efficacy data from the submitted clinical trials and the absence of direct comparative data versus clinically relevant comparators. Finally, HTA bodies often request additional clinical data from local populations, using real-world studies like registries, for instance.

RWE has been shown to have a clear role in decision-making in the context of drug submission review by addressing data gaps in effectiveness, safety, drug use in clinical practice and overall benefit to society and ultimately be used to inform decision-makers. However, in practice, many RWE studies are rejected because of limited ability to provide credible, relevant data, methodological issues or lack of transparency and poor communication.

Solutions to improve the acceptance of RWE to achieve reimbursement exist. Ensuring the quality of the data source is paramount and involves assessing data completeness, consistency and relevance to the research question, as well as validating the data against external benchmarks wherever feasible. This is especially important when merging multiple databases that were initially developed for administrative purposes. Before using the database for research, data quality needs to be assessed with regard to validity, reliability and capacity to answer the research question in a valid way. Continuous investment in national health information systems and the development of processes and aids for the acceptability and usage of RWE are essential. We observed a trend that favours the development of patients' registries after market access to study the drugs' effects in real life in a systematic way. One good illustration of this process in France is the 'Personalized Reimbursement Model', which is a platform that facilitates the creation of a nationwide database, capable of producing Real-World Evidence (RWE) as required, derived from Electronic Patient Records [33].

Refining the RWE research question is a critical step in increasing the likelihood of HTA approval. Before initiating an RWD/RWE study, the investigator needs to verify that the data source and study design can provide the expected response, for instance, checking outcomes and time points, confounding variables and sample size. Further, aligning with the goals of HTA agencies may help incorporate RWE studies early in the drug development process. Predefining analytic plans and publicly registering protocols before data analysis are key recommendations from ISPOR-ISPE for conducting studies that assess treatment effects through secondary analysis of observational data. Documenting the original plans in a protocol, along with any subsequent amendments, helps ensure that the study results are transparent and not subject to selection or manipulation. ISPOR has recently introduced a registry for RWE study protocols in partnership with ISPE, the Duke-Margolis Center for Health Policy and the National Pharmaceutical Council. This registry is a central component of the RWE Transparency Initiative, which shared its discussions and plans last year [34]. Further, ongoing communication with HTA agencies to describe the RWE development plan facilitates a trustful relationship.

Successful integration of RWE/RWD into clinical evidence required by HTAs for reimbursement decision-making requires collaboration among various stakeholders, including regulatory agencies, payers, healthcare providers and pharmaceutical companies. One remaining challenge is the difference in perception that different HTA agencies may have of RWE data versus data from randomised clinical trials and the specific requirements they may have regarding the 'added value' of a new drug or its economic impact or utility. The European Union has undertaken efforts to harmonise the HTA process across member states. This aims to streamline access to innovative health technologies for patients while ensuring efficient use of resources. A key component of this harmonisation is the EU HTA Regulation [35], which introduces the concept of Joint Clinical Assessments (JCA) [36]. JCAs involve collaboration between national HTA bodies in the EU to jointly assess the clinical value of specific health technologies (medicines and certain medical devices). This collaborative assessment focuses on the clinical efficacy and safety of the technology, aiming to develop a common scientific basis for HTA decisions across member states [36]. Other initiatives propose the development of standards that are useful for all parties involved in either clinical drug development, generating evidence or reviewing HTA reports [37]. The main advantages of these initiatives come from their collaborative nature, scientific rigour and transparency. They pave the way to higher harmonisation of HTA review process across various countries with enhanced efficiency and greater consistency.

TABLE 2 | Summary of reasons for delayed HTA decisions and solutions using RWE.

Use of RWE addressing the clinical reasons for delay	Examples
Lack of safety and efficacy data from the submitted clinical trial	
Use of RWE (retrospective cohorts from EHR data) to support gaps in safety and efficacy data: • RWE provides long-term safety and efficacy data that are often not detected over a limited duration of Phase III and IV studies. • Provides data about adverse events encountered in routine clinical practice when a much larger number of people are exposed to the drug.	• The application of Holoclar to HAS included RWE from three case-series multicentre retrospective studies (HLSTM01, HLSTM02 and HLSTM04), as well as three prospective, uncontrolled study publications. This RWE was incorporated in the dossier to support data on the effectiveness of Holoclar, find the most common adverse event and assess the actual benefit [24]. • The application of Dinutuximab β included RWE from retrospective analyses. • The application of ketoconazole included RWE from three retrospective studies to provide data about the most common adverse events as well as the effectiveness of ketoconazole.
Absence of direct comparative data for clinically relevant comparators	
Use of historical controls and external controls • RWD can serve as a source of external control in single-arm trials. • In some clinical circumstances where randomisation is impossible to undertake, due to ethical concerns and a state of clinical equipoise may not exist, or the scarcity of patients, for example, rare diseases, the development of a single-arm trial is often perceived as the best way to optimise drug learning.	• Assessment of glecaprevir and pibrentasvir is an example of drugs approved by HAS while providing historical control data [25]. The manufacturer used data from the single-arm trial EXPEDITION-8 which was a multicentre, Phase IIIb trial. The manufacturer provided historical control data to compare results. • The application of Dinutuximab β included RWE from retrospective analyses, mainly to support safety and efficacy data [26]. • The application of ketoconazole included RWE from three retrospective studies to provide data about the most common adverse events as well as the effectiveness of ketoconazole [27].
Lack of demonstration of added value	
Use of RWE to support impact on the organisation of care • Some cases where RWD can provide data sooner than traditional controlled trials, such as when there are not enough patients enrolled due to exclusion criteria.	• In the application of ramucirumab to NICE, the manufacturer included findings from a chart review (RWD) to quantify the costs associated with best supportive care, complemented by a survey to establish real-world treatment patterns to determine relevant comparator treatments used in UK clinical practice. Data was supported by an indirect comparison with docetaxel, using the historical comparator from COUGAR-02 trial, which is a multicentre, open-label, randomised, controlled Phase 3 trial [28].
Lack of any demonstrated impact on the disease management (such as hospitalisations)	
Use of real-world utilisation data of the drug and competitor • The exclusion criteria of RCTs do not appropriately account for the heterogeneity of vulnerable characteristics observed in real-world populations. • This prominent difference affects RCTs' external validity and the evidence-based medicine guidelines that are extremely limited when using data from highly selected patients after the exclusion of individuals with comorbidities or using concomitant medications. • RWE can hence be leveraged in addition to RCTs to increase the completeness of evidence-based medicine generated for clinical prescription guidelines.	• The HAS has used data from the ANRS CO22 HEPATHER cohort to determine the therapeutic strategy for using direct-acting antivirals for the treatment of hepatitis C [29].

(Continues)

TABLE 2 | (Continued)

Use of RWE addressing the clinical reasons for delay	Examples
• Increased completeness of evidence-based medicine will better cater to specific prescription guidelines for both patients with a single disease and patients with comorbidities.	

Note: RWE can address the clinical reasons for a delay in HTA approval and hence improve patient access, but they also face some challenges that can lead to their rejection by the HTA bodies.

Although safety and risk/benefit would have already been demonstrated for the market authorisation, additional data is often required post authorisation. Therefore, in some cases, RWD/RWE studies are conducted in the post-marketing phase. Therefore, a conditional pathway has been implemented in Europe to facilitate the marketing of new promising medicines especially in situations where clinical evidence is limited. Between 2018 and 2022, there were 32 conditional approvals in France, and 33 in Germany [38]. Patients' registries are often developed in this context to comply with the HTA requests.

The development of best practice guidelines for conducting RWE studies is a crucial step in optimising the development of high-quality studies. Two recent developments (2022-2023) include the Structured Template and Reporting Tool for RWE (STaRT-RWE) and the HARPER initiative (HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating RWE studies on treatment effect) supported by ISPE and ISPOR with the participation of EMA, FDA, some universities and several pharmaceutical companies [39, 40]. Another initiative is the DARWIN EU which is a platform developed to generate RWE from across Europe on diseases, populations and the uses and performance of medicines. This enables authorities in the European medicines regulatory network to use these data whenever needed throughout the lifecycle of a medicinal product [41].

Finally, it is important to mention that RWE cannot single-handedly solve the problem of delays in HTA approvals. The European Federation of Pharmaceutical Industries Association (EFPIA) has identified additional causes for the delay. These causes include the misalignment of evidence requirements, the speed of the regulatory process and the multiple layers of the decision-making process [42].

6 | Conclusion

Access to medications in European countries is frequently delayed due to HTA review processes, which require specific clinical evidence that often varies between countries. Key clinical reasons contributing to these delays include insufficient data on drug effectiveness and safety in local populations, as well as limited evidence demonstrating the added value of new therapies compared to existing treatments. Although opportunities exist to use RWE in clinical development to address the gap between marketing authorisation and reimbursement, the submitted RWD/RWE studies are often rejected by HTA bodies due to various issues that undermine the credibility of the findings.

The utilisation of RWE is revolutionising the drug clinical development process to facilitate the HTA decision-making process. HTA requirements are multidimensional, combining rigorous clinical trial data with real-world insights, focusing on outcomes that matter to patients and stakeholders while demonstrating cost-effectiveness and safety in a transparent and applicable manner. Robust RWE has the potential to effectively address the gaps in safety and effectiveness data, provide external comparators, aid in demonstrating the added value of the drug and identify patients' preferences. RWE allows for a patient-centred approach, facilitates evidence-based pricing and supports post-market surveillance. Collaboration among stakeholders ensures the robustness and reliability of RWE/RWD, ultimately leading to more informed healthcare pricing and reimbursement decisions. Recent EU initiatives such as JCA are standardising the review process among different HTA organisations, therefore offering higher consistency between HTA organisations and enhancing the efficiency of the whole process. Ultimately, this effort will shorten the delay between marketing access and reimbursement for the benefit of patients who may get faster access to new drugs.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.