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Towards improving quality of the evidence base for medical decision-making

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Part II.

CHALLENGES RELATED TO TRANSLATION OF EVIDENCE IN DECISION-MAKING

Chapter 6

Real-world evidence to inform regulatory decision-making: A scoping review

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Abstract

Introduction: Real-world evidence (RWE) is increasingly considered in regulatory decision-making. When, and to which extent, RWE is considered relevant by regulators likely depends on many factors. This review aimed to identify factors that make RWE necessary or desirable to inform regulatory decision-making.

Methods: A scoping review was conducted using literature databases (PubMed, Embase, Emcare, Web of Science and Cochrane Library) and websites of regulatory agencies, HTA agencies, research institutes and professional organisations involved with RWE. Articles were included if: (1) they discussed factors or contexts that impact whether RWE could be necessary or desirable in regulatory decision-making; (2) focused on pharmacological or biological interventions in humans; and (3) considered decision-making in Europe or North-America, or without a focus on a specific region.

Results: We included 118 articles in the scoping review. Two major themes and 6 subthemes were identified. The first theme concerns questions addressable with RWE, with subthemes epidemiology and benefit-risk assessment. The second theme concerns contextual factors, with subthemes feasibility, ethical considerations, limitations of available evidence, and disease and treatment specific aspects. Collectively, these themes encompassed 43 factors influencing the need for RWE in regulatory decisions.

Conclusion: Many factors influence the need for RWE in regulatory decision-making. While single factors may not make RWE fully necessary, their cumulative influence could make RWE essential and pivotal in regulatory decision-making. This overview contributes to ongoing discussions emphasising the nuanced interplay of factors influencing the necessity or desirability of RWE to inform regulatory decision-making.

Study highlights

What is the current knowledge on this topic?

Real-world evidence (RWE) is increasingly considered in regulatory decision-making. However, when and to which extent RWE is considered relevant by regulators remains unclear.

What question did this study address?

This review aimed to identify factors reported in literature that make RWE necessary or desirable in regulatory decision-making.

What does this study add to our knowledge?

The need for RWE was found to depend on (1) the type of questions that need to be answered in order to facilitate regulatory decision-making; and (2) contextual factors related to the feasibility and ethical considerations regarding traditional randomized trials, limitations of available evidence, and disease and treatment specific aspects.

How might this change clinical pharmacology or translational science?

The results of our review may help sponsors identify when RWE may be valuable to include in submission dossiers, as well as provide a basis for regulators for their assessment of RWE and whether it could be pivotal in regulatory decision-making.

Introduction

Randomised trials are widely accepted as the gold standard for the benefit-risk assessment of medical treatments, particularly for pharmacological treatments. Consequently, evidence from randomised trials often serves as the foundation for regulatory decision-making and clinical guidelines. However, 'real-world evidence' (RWE) is increasingly considered to complement evidence from traditional trials. RWE is information derived from the analysis of real-world data (RWD), which refers to data relating to a patient's health status or the delivery of health care collected routinely from a variety of sources other than traditional clinical trials.[1]

As the development of complex drugs targeting highly selected patient groups becomes increasingly common, traditional trials to generate pivotal evidence may not always be feasible,[2] or they may be unable to answer all relevant questions (e.g., about heterogeneity of treatment effects, or long-term effects in gene therapies). The COVID-19 pandemic has demonstrated the potential of RWE to accelerate drug development in times of urgent need. Additionally, both the means of collecting and the methods of analysing RWD have advanced over the past few decades (including the continuous advancements in data storage capacity and computational power), presenting opportunities to generate RWE and take it into consideration in regulatory decision-making.

In response to the changing landscape in drug development and increasing opportunities to utilise RWE, regulatory agencies and health technology assessment (HTA) agencies are exploring how to incorporate RWE into their decision-making processes.[2-4] The FDA, EMA and NICE, among others, have developed RWE frameworks and guidance documents, and efforts are ongoing to improve accessibility, quality, outcome harmonisation and governance of RWD.[1, 5-7] Although this work will help increase the potential to generate RWE and enhance its methodological quality, which is ultimately critical in the acceptability of RWE for regulatory purposes, it is still unclear in which scenarios RWE could best be leveraged to aid decision-making.[7, 8] For instance, should RWE studies only be used when traditional trials are unfeasible or unethical, or could RWE studies complement evidence from trials in other scenarios as well? When, and to which extent, RWE is considered relevant by regulators, likely depends on many contextual factors, including the regulatory decision to be made. We conducted a scoping review, in order to identify factors reported in literature that make RWE necessary or desirable to inform regulatory decision-making.

Methods

We followed the PRISMA-ScR statements for reporting our scoping review.[9]

Search strategy

We conducted a comprehensive search of five electronic literature databases (PubMed, Embase, Emcare, Web of Science and Cochrane Library) for articles addressing RWE in regulatory decision-making. The search strategy was developed in consultation with an experienced librarian and included a combination of keywords related to RWD, RWE, and regulatory science. Since the regulatory landscape can vary greatly across different geographical regions, including the potential adoption of RWE into decision-making processes, we decided to focus our review on two primary regions where RWE adoption is most advanced and where we deemed the regulatory frameworks sufficiently similar – specifically, Europe and North-America. Our search strategy incorporated terms targeting the perspectives of countries within these regions. Furthermore, the search strategy included terms to target articles written in English and Dutch only. A detailed search string of the search strategy can be viewed in **Supplementary Material S1**. The search was conducted in November 2022 and did not include restrictions for a specific time period.

In addition to the searching electronic literature databases, we also searched for grey literature addressing RWE in regulatory decision-making. Therefore, official websites of several regulatory agencies (EMA, MHRA, FDA, Health Canada), HTA agencies (EUnetHTA, NICE, ZIN, ICER, CADTH), and research institutes or other professional organisations involved with RWE (Duke-Margolis Center for Health Policy, GetReal Institute, ImpactHTA, ISPE, ISPOR, HTAi, INAHTA), were searched for relevant information (e.g., white papers, frameworks, guidance documents, guidelines – henceforth also referred to as articles). Keywords used included variations of 'real-world data' and 'real-world evidence'. This search was conducted in February 2023. A list of website URLs can also be viewed in **Supplementary Material S1**.

Article selection

Several eligibility criteria were used to select relevant articles. (1) The article discussed factors or contexts that impact whether RWE could be necessary or desirable in regulatory or HTA decision-making. We expanded our scope to HTA decision-making, as we expect there to be relevant overlaps between regulatory and HTA domains regarding the contexts in which RWE could be necessary or desirable to inform decision-making. The current research is also part of a larger project which considers both domains. However, for the purpose of this review, we report specifically on regulatory decision-making (while also including considerations from HTA focused articles that are relevant to the regulatory decision-making); (2) The article focused on pharmacological or biological interventions in humans. We focused exclusively on pharmacological and biological interventions (e.g., drugs, biologicals, gene therapy), and not devices or digital health innovations, as regulatory requirements and means of evidence generation for the latter differ significantly; (3) The article considered decision-making in Europe or North-America, or without a focus on a specific region. We considered articles and studies of any design, but conference abstracts and presentations were excluded. Articles published in languages other than English or Dutch were also excluded.

Titles and abstracts of all identified articles were screened for relevance by two reviewers (MJ and RG). To increase consistency, titles and abstracts of the first 100 articles were screened in duplicate. Discrepancies between the reviewers were resolved through discussion, after which the remaining articles were screened by a single reviewer. A single reviewer (MJ) then reviewed full-text articles for eligibility according to the criteria listed above. Articles that met the eligibility criteria were subsequently included in the scoping review.

Data extraction and synthesis

Data were extracted using a standardised form encompassing general article details (e.g., authors, title, year of publication, journal), along with a concise summary, the decision-making domains discussed in the article (e.g., regulatory or HTA decision-making), and stakeholder perspectives that contributed to the article (e.g., regulators, HTAs, pharmaceutical industry). These stakeholder perspectives were interpreted based on the authors' affiliations listed in the article.

A thematic synthesis approach was used to analyse the content of all included articles for contextual factors impacting the necessity or desirability of RWE in regulatory decision-making. [10] All sections of an article were considered (e.g., introduction, results, discussion/conclusion, appendices, etc.). We used a combination of deductive and inductive coding to identify key themes. Initial coding involved line-by-line coding, summarising the data using both descriptive and interpretive approaches. An iterative process of reviewing and revisiting the articles led to refinement of codes and incorporation of new ones. These codes were subsequently categorised, partially aligning with predefined themes (i.e., deductive coding), and partially under newly emerging themes derived from the data (i.e., inductive coding). Predefined themes were based on an exploratory literature search conducted before the scoping review, and included epidemiology, feasibility, ethical considerations, and generalisability.

The coding and analysis processes were performed by one reviewer (MJ). To ensure consistency of interpretation, the identified factors, including a sample of the corresponding quotes, were scrutinised by a second reviewer (RG). Discrepancies regarding the interpretation of quotes and their corresponding factors were discussed between RG and MJ, and factors were adjusted if needed. Following this process, resulting factors, subthemes and themes were then reviewed within the entire research team and further refined. Finally, themes and subthemes were outlined against a medicine's lifecycle, illustrating potentially varying relevance of contextual factors across its subsequent phases. ATLAS.ti software (GmbH, Berlin, version 23.2.2.27458) was used for the coding process.

Results

Search results and article selection

The combined database searches led to a sum total of 1335 article hits, and 67 articles were identified through the grey literature search. After the removal of duplicates, 710 unique articles remained. Following screening of titles and abstracts, 217 articles were selected for full-text review. Ultimately, 118 articles met the inclusion criteria and were included in the scoping review. **Figure 1** shows a detailed overview of the selection process.

Of the selected articles, 75 (64%) articles covered regulatory decision-making, while 18 (15%) articles covered HTA decision-making. Twenty-five articles (21%) covered both regulatory and HTA decision-making. Additionally, authors from various stakeholder groups contributed to the articles, including (1) regulators, (2) HTAs and payers, (3) pharmaceutical industry, (4) other companies (e.g., consultancy, data providers), (5) academia and research institutes, (6) clinicians and (7) patient representatives. Authors with an academic or research institute affiliation contributed to 70 (59%) articles, regulators to 33 (28%) articles, HTAs and payers to 21 (18%) articles, pharmaceutical industry to 38 (32%) articles, other companies to 32 (27%) articles, clinicians to 14 (12%) articles, and patient representatives to 1 (<1%) article. While about half (58; 49%) of the articles were written by author teams representing one stakeholder group (regulators: 17 (14%) articles; HTA and payers: 9 (8%) articles; pharmaceutical industry: 10 (8%) articles; other companies: 6 (5%) articles; academia and research institutes: 16 (14%) articles; clinicians and patient representatives 0 articles), the other half consisted of collaborations between authors from various stakeholder groups.

Synthesis

In total, 2 major themes, 6 subthemes and 43 individual factors were identified (see **Table 1** and **Figure 2**). A comprehensive description of each individual factor, including illustrative quotes and complete reference list of the included articles, are detailed in **Supplementary Material S2**. Furthermore, **Table S2** of this document gives an overview of the references, including their counts, that contributed to each factor. Here, we describe the major themes and subthemes.

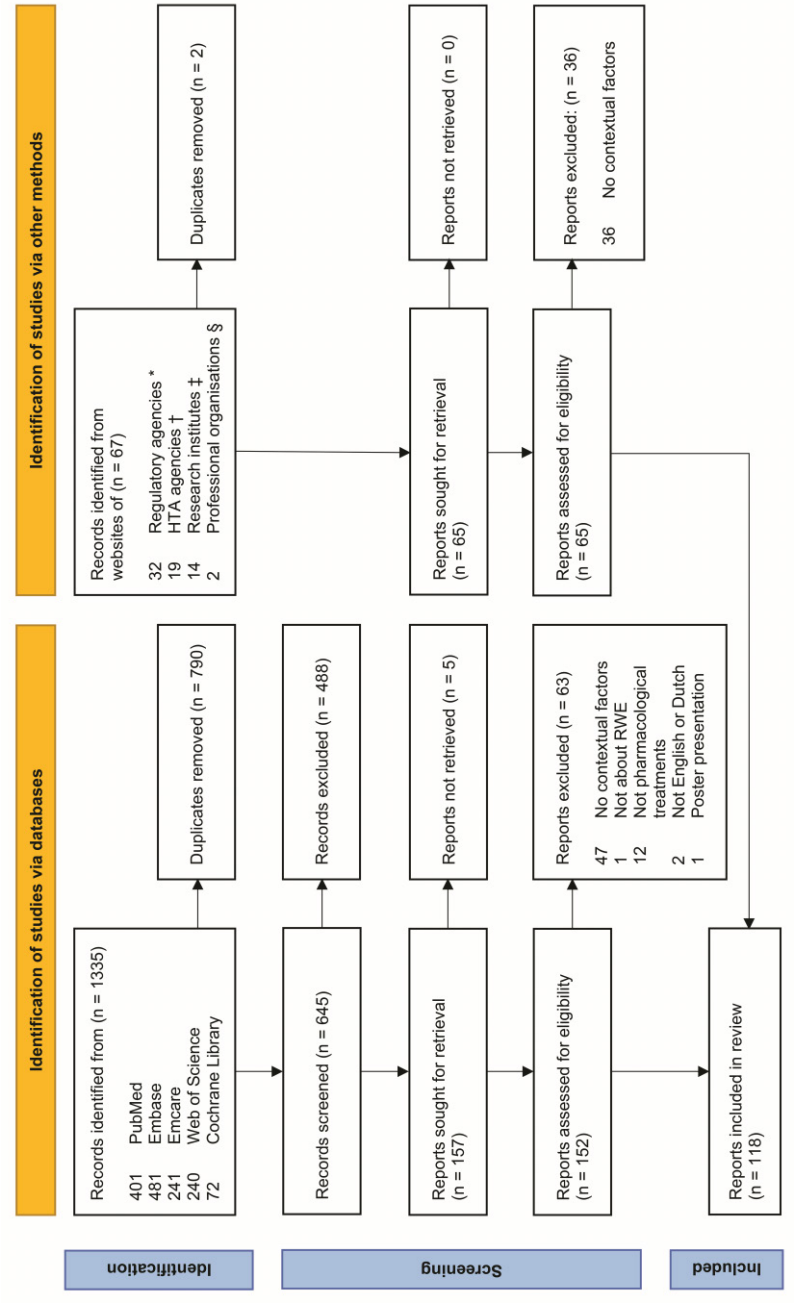

Figure 1. PRISMA flow diagram of the article selection process
*EMA, MHRA, FDA, Health Canada
† EUnetHTA, NICE, ZIN, ICER, CADTH
‡ Duke-Margolis, ImpactHTA, GetReal Institute
§ ISPE, ISPOR, HTAi, INAHTA

Theme 1 Questions that can be answered with RWE and facilitate regulatory decision-making

The first major theme focuses on content-related questions that need to be answered in order to facilitate regulatory decision-making, and which of these questions can be answered with RWE. It comprises two subthemes: questions that are related to epidemiology, and questions that are related to aspects of the benefit-risk assessment.

Subtheme 1.1 Epidemiology

Certain questions naturally lend themselves to be answered with RWE. These include questions related to disease epidemiology, such as disease incidence, prevalence, natural history, patient demographics, and the landscape of standard of care. This information has a myriad of purposes within the realm of regulatory decision-making. It not only provides clinical context to aid in interpreting the results of traditional trials, but it can also specifically be used to contextualise single arm trials, either informally or through the utilisation of external comparator arms. Moreover, epidemiological data holds pivotal value in guiding decisions regarding orphan designations. Additionally, it can serve as substantiation of clinical study design choices, such as the single arm trial, and could be used during scientific advice meetings.

Subtheme 1.2 Benefit-risk assessment

While the randomised controlled trial is widely accepted as the gold standard for benefit-risk assessment of pharmacological interventions, the use of RWE to inform the initial benefit-risk assessment is typically limited, except for expedited or adapted approval pathway settings. In these settings, the conduct of randomised controlled trials is often hampered by feasibility and ethical considerations (e.g., rare diseases with an unmet medical need). Using RWE in benefit-risk assessment particularly pertains to the post-approval setting. A well-known example, and historically the most common use of RWE in regulatory decision-making, includes the continued monitoring of benefit-risk after initial approval, in particular concerning long-term safety aspects. RWE studies offer practical means to track long-term and potentially rare outcomes, where traditional trials would become unfeasible. Similarly, RWE could inform other evidence gaps (e.g., heterogeneity of treatment effects) that pre-approval trials may have been unable to address, sometimes in the form of post-approval obligations imposed by regulators. Additional applications include guiding benefit-risk assessments for label modifications (e.g., potential expansions to new populations and indications) and evaluation of imposed risk minimisation measures at drug approval and/or post-approval.

Theme 2 Contextual factors that increase the necessity or desirability for RWE in regulatory decision-making

The second major theme describes various contextual factors that influence the need for RWE, often stemming from inherent limitations of the traditional trial or the (im-)possibility to conduct one. This theme comprises of four subthemes: feasibility, ethical considerations, limitations of available evidence and disease & treatment specific aspects.

Subtheme 2.1 Feasibility

In some situations, conducting of a randomised controlled trial is unfeasible. RWE studies (e.g., in combination with a single arm trial) may then provide the most viable alternative to generate evidence to inform decision-making. Some of these scenarios are linked to the impossibility to recruit a sufficient number of participants (e.g., extremely rare patient populations or other recruitment difficulties, or rare outcomes requiring exorbitantly large sample sizes). Furthermore, feasibility considerations are often tied to time and resource constraints (e.g., a large required sample size asks for enormous amounts of resources and recruitment may take too long, even if hypothetically enough patients could be recruited;

Table 1. Overview of major themes, subthemes and factors that increase the desirability or necessity of RWE in regulatory decision-making

Theme 1: **Questions that can be answered with RWE and facilitate regulatory decision-making**	**Theme 2:** **Contextual factors that increase the desirability or necessity of RWE in regulatory decision-making**
Subtheme 1.1: Epidemiology	**Subtheme 2.1: Feasibility**
Disease epidemiology	Rare populations
Incidence, prevalence, event rates	Recruitment difficulties
Natural history of a disease	Time constraints
Population characteristics	Resource constraints
Landscape of standard of care	Long-term outcomes
Regulatory purposes of epidemiological data	Rare outcomes
Contextualisation (general)	**Subtheme 2.2: Ethical considerations**
Contextualisation single arm trial (informal)	High unmet need
Contextualisation single arm trial (ECA)	No equipoise
Support orphan designation	Vulnerable populations
Substantiation of trial design	Other ethical considerations
Subtheme 1.2: Benefit-risk assessment	**Subtheme 2.3: Limitations of available evidence**
Pre-approval benefit-risk	Generalisability
Expedited or adaptive approval pathways	Representativeness of endpoint
Post-approval benefit-risk	Representativeness of patient characteristics
Continued monitoring of benefit-risk	Representativeness of patient behaviour
Post-approval safety	Representativeness of treatment setting
Post-approval effectiveness	Representativeness of treatment protocol
Conditional approvals	Less robust trial evidence
Evidence gaps related to benefit-risk	Crossover issues
Heterogeneity of treatment effects	Limited existing knowledge
Optimal dosing and frequency of administration	**Subtheme 2.4: Disease & treatment specific aspects**
Co-prescribing	Complex treatment settings
Label modifications	Vaccine research
Population	Changing drug effectiveness over time
Indication	
Other label changes	
Evaluation of risk minimisation measures	

A comprehensive description of each individual factor, including illustrative quotes and references of the included articles, are detailed in **Supplementary Material S2**. Furthermore, **Table S2** of this document gives an overview of the references, including their counts, that contributed to each factor. ECA: external comparator arm.

late occurring outcomes may require a follow-up time that would become cost-prohibitive in case of a traditional trial; or the conduct of a traditional trial would take too long, while evidence is needed immediately).

Subtheme 2.2 Ethical considerations

Ethical considerations may also preclude the conduct of a randomised controlled trial. For example, when there is a high unmet medical need (i.e., a life threatening or severely debilitating disease without an effective standard of care), it may be considered unethical to withhold a potentially effective treatment and randomise patients to a control arm. Similarly, it may be unethical to randomise when there is no true equipoise. In these scenarios, a single arm trial might be the only viable option, where RWE could be utilised to contextualise its results.

Subtheme 2.3 Limitations of available evidence

Certain limitations tied to evidence of traditional trials could increase the necessity or desirability of RWE to inform regulatory decision-making. For example, an often criticised aspect of traditional trials is the potentially limited generalisability of their results (e.g., due to strict patient populations included or the use of questionable surrogate endpoints). RWE could provide a complementary role in the decision-making process by providing more evidence that has better generalisability. Likewise, if the quality of the trial

evidence is suboptimal, additional RWE of high quality may be useful. Furthermore, in disease areas with very limited knowledge in general, the need for epidemiological data (e.g., natural history) may be emphasised, in contrast to well-known disease areas such as diabetes.

Subtheme 2.4 Disease & treatment specific aspects

Specific diseases and treatments may also influence the need for RWE in regulatory decision-making. In vaccine research, for example, traditional trials may face particular challenges (such as non-serological outcomes that may take a long time to develop or difficulties in catching herd effects). The collection of RWE may also be especially important for complex and innovative treatments for which the biological mechanism is not yet well characterised (e.g., "first-in-class" products) and long-term effects are unknown (e.g., gene therapies). For some innovative therapies, there may be learning effects present (e.g., cell therapies), where RWE could prove useful to investigate potentially changing effectiveness over time.

Contextual factors in practice

While it is helpful to consider the themes and factors that influence the need for RWE in regulatory decision-making in isolation, in practice they do not stand alone. In practice, a combination of factors will play a role, and the factors could also influence each other (see **Box 1**). It is unlikely that a single reason will be a decisive factor in the consideration of including RWE in regulatory decision-making; instead, it will be a combination of reasons that make RWE necessary or desirable to inform regulatory decision-making. Furthermore, several overlaps exist between certain factors (e.g., many of the benefit-risk assessment questions that may be answered with RWE are linked to feasibility considerations). Nonetheless, making more explicit which questions may be answered with RWE as well as which contextual factors play a role, helps to provide a more complete overview of how factors contribute and interact in practice, as well as their potential role across a medicine's lifecycle (**Figure 2**).

Discussion

In our scoping review, we included 118 articles, based on which two major themes and six subthemes were identified, with a total of 43 factors that influence the need for RWE in regulatory decision-making. The first theme concerned the questions that can be answered with RWE (with subthemes epidemiology and benefit-risk assessment). The second theme considered contextual factors, with subthemes feasibility, ethical considerations, limitations of available evidence, and disease and treatment specific aspects.

To our knowledge, a scoping review investigating contextual factors that increase the need or desirability of RWE in regulatory decision-making has not been conducted before. Although guidance documents related to RWE are increasingly developed by regulatory authorities, details specifying when RWE is desired by regulators to inform decision-making has not been covered. Furthermore, publicly available reports on benefit-risk assessments provide limited information on what role RWE has played in the decision-making process.[2, 11] Several studies have scrutinised these reports, uncovering valuable insights regarding various RWE applications, limitations highlighted by regulators, and ultimately decisions made on the basis of the total body of evidence.[12, 13] However, it often remains unclear whether regulators deemed RWE as necessary, and what weight they attributed to RWE in the decision-making process. Furthermore, the inclusion (or lack) of RWE in submission dossiers may not necessarily align with regulator perspectives on its necessity or desirability. The current findings provide a first step in mapping out in which situations and for which regulatory questions and decisions RWE could be desirable or even necessary. Such a framework would be useful for multiple stakeholders.

Box 1. Hypothetical scenario of contextual factors increasing the need for RWE in regulatory decision-making

Consider "Hereditary Syndrome X" (HSX), a rare genetic disorder affecting a small population of patients, that leads to severe organ damage and a drastically reduced lifespan, and does not have an effective standard of care. A novel drug that targets a specific genetic variant of HSX shows promise in halting disease progression based on preliminary data. In this case, a sufficiently powered randomised controlled trial may be challenging to perform, as the target population is small and may be difficult to identify (genetic variant of a rare disease). Furthermore, given there is a high unmet need and preliminary results are promising; randomisation to a control arm could be considered unethical.

In this (hypothetical) scenario, the contextual factors that complicate the conduct of a traditional trial may also be linked to other factors increasing the need for RWE in regulatory decision-making. For example, because the disease of interest is rare, existing knowledge about the disease may be limited, emphasising the need for RWE (e.g., natural history data) to provide additional context for regulators during benefit-risk evaluations. Furthermore, the company developing this novel drug may be more inclined to request scientific advice or apply for alternative approval pathways, for which regulators would require epidemiological data. Since the evidence generation for the benefit-risk assessment in this scenario is likely going to be suboptimal, the need for RWE to confirm and assess benefit-risk long-term is increased as well (e.g., conditional approval obligations).

This example illustrates how certain contextual factors may go hand in hand (diseases with a high unmet need are often rare, and existing knowledge may be limited), how some factors could also influence regulatory decisions to be made and the need for RWE to facilitate these decisions (e.g., orphan designations, scientific advice, alternative approval pathways), and that certain factors are likely to influence the need for RWE throughout the entire medicine's lifecycle.

While only few factors are displayed in this hypothetical example, in reality many intricacies and nuances play a role. Contextual factors are often not a dichotomy but are a continuum (e.g., the "rarity" of a disease), and so is their impact on the need for RWE, and the eventual need or desire for RWE in regulatory decision-making itself.

Box 2. Contextual factors that increase the persuasiveness of RWE

Some contextual factors may not necessarily increase the need or desire for RWE in regulatory decision-making, but if present, could increase its persuasiveness. Notably, these factors do not directly describe the methodological quality of RWE, although they may be linked to certain methodological aspects.

- Clinical plausibility
- Predictable disease progression
- Dose-response relationship
- Evident outcomes
- Large effect size

A comprehensive description of these factors, including illustrative quotes and references, are detailed in **Supplementary Material S2**.

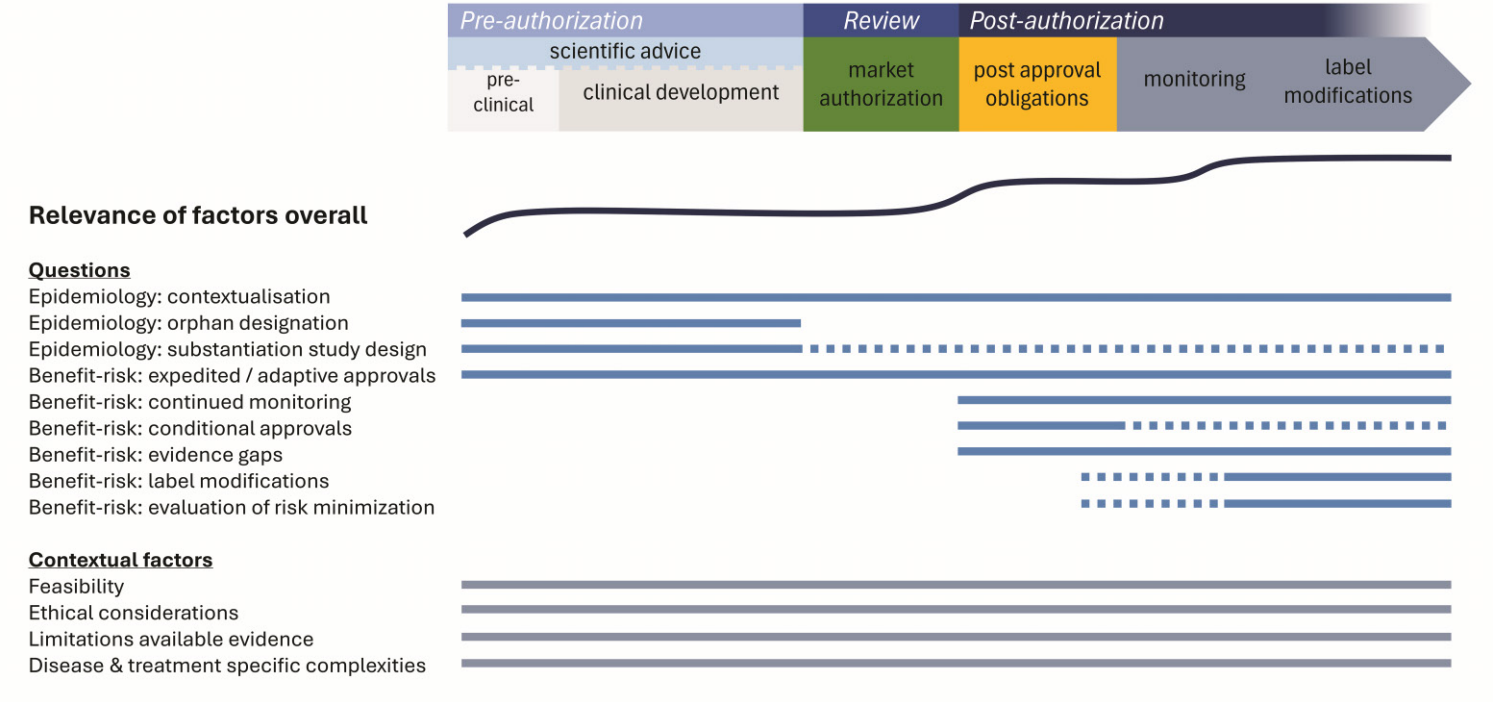

Figure 2. Simplified schematic of a medicine's lifecycle. The potential relevance of identified subthemes is hypothesised against this lifecycle. Questions that can be answered with RWE and facilitate decision-making are most prominent in the post-approval phase. However, supportive epidemiological data to provide clinical context can be helpful at any timepoint. Contextual factors, such as feasibility or ethical considerations, are likely to play a role at any given phase of a medicine's lifecycle (e.g., if a traditional trial is unfeasible to conduct due to certain contextual factors in the pre-approval phase, these factors are likely to continue to play a role in the post-approval phase).

Firstly, it has the potential to help sponsors identify where RWE could be valuable, which might beneficially influence the submission dossier and ultimately the regulatory decision to be made. Secondly, from a regulator's perspective, it could provide an important aspect of the assessment whether RWE could play a pivotal role in the decision-making process. While RWE is always likely to be supportive (e.g., epidemiological data providing clinical context), whether RWE could be pivotal, and thus what weight it should receive in the decision-making process, probably depends on various factors. One of those factors includes the need or desire for RWE. Other critical factors include the methodological quality of RWE (and thereby its validity, including considerations regarding the quality and appropriateness of RWD), the consequences of the decision to be made, and other contextual factors that increase the persuasiveness of RWE (see **Box 2**). The consideration and interplay of all these factors is challenging, and the current overview can contribute to ongoing discussions about the role of RWE in regulatory decision-making.

In light of these discussions, it is important to note that the desire or need for RWE is not a simple dichotomy, but a continuum (e.g., ranging from not useful to absolutely necessary), where certain contextual factors may be more influential than others. For example, a high unmet medical need and an extremely rare patient population rendering a traditional trial unethical and/or unfeasible, might make RWE necessary to inform regulatory decision-making. In contrast, potential generalisability issues regarding traditional trial evidence might only make RWE desirable (not necessary). Future work could focus on further elucidating these intricacies (e.g., how different contextual factors could be valued and how they interact). Furthermore, it would be valuable to obtain validation and further refinement of the themes and contextual factors identified in this scoping review from regulatory authorities and other stakeholders. Notably, EMA's Methodology Working Party is currently charting a roadmap for development of RWE guidance.[14] This roadmap should not only consider methodological aspects of RWE, but should also encompass guidance on when RWE would be desired by regulators.

Lastly, the current research is not intended to promote indiscriminate use of RWE, but to optimise the regulatory decision-making process. A pivotal future step could involve the formulation of a regulatory decision-making framework, where distinct sources of evidence (e.g., traditional trials, RWE) are weighed formally rather than implicitly. Such an approach would not only navigate the complexities that arise when evidence from different sources appears inconsistent or conflicting, but also enhance the transparency and potential consistency of regulatory decision-making. The results of our scoping review could provide a basis for such a framework that can contribute to the multifaceted considerations surrounding the integration and weight of RWE in regulatory decision-making, alongside ongoing developments in RWE methodology and data quality.

Several possible limitations of our study need to be discussed. Firstly, in our scoping review we focused on perspectives that apply globally, or are particular to Europe and North-America. Secondly, we only considered articles published in English and Dutch. Thirdly, because our review relied on literature published in scientific journals and on documents available on public websites, there is a risk that the information presented is incomplete, as discussions about the need for RWE in regulatory decision-making develop rapidly. Finally, coding and analysis was performed by one author, and qualitative analysis can be subject to personal interpretation. However, identified factors, subthemes and themes were reviewed and discussed within the research team and subsequently refined to increase consistency of interpretation.

Conclusion

In conclusion, many factors influence the need for RWE in regulatory decision-making. A single factor on its own may not make RWE fully necessary, but jointly multiple factors could make RWE to be essential and pivotal in regulatory decision-making. This overview provides valuable information that can contribute to ongoing discussions about the necessity or desirability of RWE to inform regulatory decision-making.

Online Supplementary Files

The supplementary files referred to in this chapter are available online at https://doi.org/10.1002/cpt.3218.

References

1. Cave, A., Kurz, X. & Arlett, P. Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. *Clin. Pharmacol. Ther.* 106, 36-39 (2019).

2. Eichler, H.G. *et al.* Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth. *Clin. Pharmacol. Ther.* 109, 1212-1218 (2021).

3. Arlett, P., Kjaer, J., Broich, K. & Cooke, E. Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. *Clin. Pharmacol. Ther.* 111, 21-23 (2022).

4. Concato, J. & Corrigan-Curay, J. Real-World Evidence - Where Are We Now? *N. Engl. J. Med.* 386, 1680-1682 (2022).

5. US Food and Drug Administration. *Framework for FDA's Real-World Evidence Program.* <www.fda.gov/media/120060/download> (2018). Accessed 21 November 2023.

6. National Institute for Health and Care Excellence. *NICE real-world evidence framework.* <www.nice.org.uk/corporate/ecd9> (2022). Accessed 21 November 2023.

7. Jaksa, A., Wu, J., Jonsson, P., Eichler, H.G., Vititoe, S. & Gatto, N.M. Organized structure of real-world evidence best practices: moving from fragmented recommendations to comprehensive guidance. *J. Comp. Eff. Res.* 10, 711-731 (2021).

8. European Medicines Agency. *Regulatory Science - Research needs.* <https://www.ema.europa.eu/en/about-us/what-we-do/regulatory-science-research/regulatory-science-research-needs> (2021). Accessed 21 November 2023.

9. Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. & Group, P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 339, b2535 (2009).

10. Braun, V. & Clarke, V. Using thematic analysis in psychology. *Qual. Res. Psychol.* 3, 77-101 (2006).

11. O'Donnell, J.C. *et al.* Evolving use of real-world evidence in the regulatory process: a focus on immuno-oncology treatment and outcomes. *Future Oncol.* 17, 333-347 (2021).

12. Bakker, E., Plueschke, K., Jonker, C.J., Kurz, X., Starokozhko, V. & Mol, P.G.M. Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making. *Clin. Pharmacol. Ther.* 113, 135-151 (2023).

13. Eskola, S.M., Leufkens, H.G.M., Bate, A., De Bruin, M.L. & Gardarsdottir, H. Use of Real-World Data and Evidence in Drug Development of Medicinal Products Centrally Authorized in Europe in 2018-2019. *Clin. Pharmacol. Ther.* 111, 310-320 (2022).

14. European Medicines Agency. *Consolidated 3-year work plan for the Methodology Working Party (MWP).* <https://www.ema.europa.eu/en/documents/work-programme/consolidated-3-year-work-plan-methodology-working-party-mwp_en.pdf> (2022). Accessed 21 November 2023.