A scoping review of HTA and Regulatory RWD/RWE policy documents

Executive Summary

IDERHA (Integration of Heterogenous Data and Evidence towards Regulatory and HTA Acceptance) is a European Innovative Health Initiative (IHI) project launched in 2023 that aims to enable the safe, secure, streamlined sharing of heterogenous healthcare data. Heterogenous health data is an umbrella term that encompasses a wide range of data types that are relevant to individual and population health, health care delivery, and research, and includes Real-World Data (RWD), traditional clinical trial data, social determinants of health, and potentially other data that capture factors that affect health such as air pollution.

With the digitization of the health care system, the ability to capture data (i.e., RWD) on the actual delivery of care and patient outcomes is becoming technically more feasible. As a result, Real-World Evidence (RWE) is a relatively new field of research. Given the innovative state of the field, policies that clearly outline how to conduct, assess, and evaluate RWE for public health decision making are lagging behind. The goal of the IDERHA policy-focused activities is to accelerate the pace of policy development by building consensus on the use of RWD and RWE in regulatory and Health Technology Assessment (HTA) decision-making for medicines and medical technologies.

Real-world data (RWD) is information pertaining to health status and health care delivery that is collected routinely from sources other than traditional clinical trials.

Real-world evidence (RWE) is derived from analyses of RWD.

This report is one of the deliverables completed in the first phase of the project, and the objective is to identify priority issues where additional clarity is needed based on the current policy landscape that IDERHA should focus on addressing. Similar reviews have been conducted, but as far as we are aware, this will be the first report that looks across regulatory and HTA policies, has a global scope, and covers medicines and medical devices policies. Based on this analysis, and insights from previous reviews, we have identified the following areas for further exploration in the next phase of the IDERHA project policy-focused work.

Advance Emerging Best Practices
Several organizations and countries have been working on programs and pilots over the last decade to explore various aspects of how to appropriately use RWD and conduct RWE studies. IDERHA will seek to identify and support efforts to accelerate progress on:

- Development of RWE-specific good research practices
- Alignment and refinement on foundational definitions and terms
- Sharing research and submission standards, tools and checklists
- Identifying key lessons from pilot and implementation program experiences

Address Policy Gaps
The analysis revealed that though much progress has been made on various technical and methodological approaches, additional analysis and work is needed to improve European policies on the following areas:

- Increased alignment for assessing the RWE study design and the data “fitness for use”
- Alignment on analytical approaches (e.g., bias, confounding, generalizability and transportability of findings)
- Gaps in implementation for challenging areas (i.e., IVDs and digital health)
- Gaps in the use of RWE to support medical devices regulatory activities under EU Medical Device Regulation
- Explore intersections between RWD, RWE and AI
- Improving alignment, where appropriate, between regulatory and HTA evidence standards

Public Engagement and Transparency
Tackling difficult policy questions requires that diverse perspectives are heard, and input incorporated into pragmatic approaches. To that end, outreach and engagement with experts in the field and the boarder health care community is essential. This report will be released for public consultation to seek input on how to prioritizes the policy gaps identified. This information will be used to shape the next phase of the work which will be to start the development of draft policy recommendations on the use of RWD and RWE. The team will convene a series of workshops with external experts and release a draft of the recommendations in 2025 for public consultation. Based on the public consultation and consensus building workshops, a final report with policy recommendations will be issued in the 2027.

1. Discussion [Extracted from the full report]

This review clarifies our understanding of the dynamic and complex landscape of policies on the use of RWD and RWE in regulatory activities and HTA processes. The insights from this analysis coupled with the finding from similar reviews highlighted a pivotal shift towards the integration of RWE into the clinical evidence portfolio. Our findings also reflect the nascent nature of policy in this field with early adopters developing and iterating policies as other decision-makers lag. It is also important to note that even organizations with policies in place appear to have a nuanced approach that both acknowledges the potential value of RWD and RWE while also seeking to balance concerns about the rigor of the evidence for key public health decision-making. The findings are intended to provide direction for the project's future work and have been organized around the categories of:

- Evolving organizational perspectives
- Emerging best practices for further development and broader adoption
- Gaps in current policies where further analysis and policy development is needed

1.1. Evolving organizational perspectives

As this review was looking specifically at policies that have been published, it does not fully represent the opinions and attitudes of countries and organizations who have not produced policies and guidance in this area. The analysis insights are focused on those organizations that are most likely to be early adopters and who may have a variety of drivers for policy change, including legislated requirements. It is worth noting that even for organizations with policies, the documents reflect underlying concerns and scepticism about the quality of RWE and limitations of its use to support decision-making. A potential area for further exploration would be a more comprehensive mapping of the stated uses of RWE for regulatory activities and HTA (see section **Error! Reference source not found.**) to identify additional trends across regions and organization types to better understand the underlying considerations.

Of those policies in the analysis, several noted the potential benefits of RWE as complementary and supplemental to traditional clinical trials. There were also various sources that cited the value of using RWE to address evidence gaps in difficult to study areas such as rare diseases and paediatric populations. In the regulatory policies, the most support was seen for the use of RWD/RWE to improve clinical trials, enhance post-market surveillance and increase information about underrepresented and hard to study patient populations. ICER & OHE's evaluation of HTA guidance[9] found that RWE is most likely accepted when complementing RCTs, filling evidence gaps, identifying and evaluating new safety concerns, or analyzing drug classes with multiple competitors.

Amongst regulators, there are notable differences in the approaches supported for medicines as compared to medical devices. For medicines, the interest is primarily in post-market activities and interest in improving information about potential patient populations and clinical trial improvements. For medical devices, there appears to be emerging support for the use of RWE in pre-market regulatory activities. Given the differences in development, innovation cycles, regulatory frameworks, and the resulting scientific and clinical questions between these product types, this is to be expected.

While there has been an explosion of new policies focused on RWD and RWE (over 60 approximately) in the last five years, these policies continue to be relatively uncommon across markets and are more likely to be seen in well-developed regulatory systems (see **Error! Reference source not found.**) and HTA agencies. As noted above, the potential for an expanding policy gap between early adopters and other jurisdictions may undermine global research approaches and hinder broader harmonization efforts.

There were clear concerns with the potential to draw inaccurate results and opportunities for poor quality research and misuse. Due to concerns with data mining and manipulation, multiple policies focused on transparency to the research process such as requirements for pre-specified, and a preference to more structured data collection methods like registries.

Some of the policies reflect ongoing concerns that allowing the use of RWD/RWE is reducing the scientific and evidentiary bar and potentially jeopardising the public health. Several of the documents seek to address these concerns with specific statement indicating that RWE studies will be evaluated with the same rigour as traditional clinical trials. For example, the MHRA guideline states "…protocol for the study should be of the same standard that would be expected for a traditional RCT".[41] Some policies allow the use of RWD but only in very limited situations such as in the case of European Medical Device Regulation[59] where RWD may be used per the MDCG guidances as a source of clinical data but only for clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC, in the Post-market Clinical follow up Plans, and the Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software.[55]

The review identified one document from Swissmedic[19] that specifically state that RWE is not acceptable for use in the authorisation of new therapeutic products. Additionally, IQWiG have expressed concerns about the use of RWD in regulatory and policy decision-making, especially when measuring treatment effects of new medicines[1]. These attitudes may be due to several factors and reflect the limitations of the legal authorities and/or of the more conservative attitudes on the use of RWE.[45] In order to advance the appropriate use of RWD and RWE, it is critical to better understand these concerns and identify possible approaches to address them in future work. The project team plans to actively identify and engage with other stakeholders who may have concerns about the use of RWD/RWE in regulatory and HTA contexts.

1.2. Emerging best practices

1.2.1. Refining and aligning on foundational definitions and terms

The field is quickly evolving and as a result there is continued refinement in the terms, definitions, and language used. There has been general alignment on the high-level terms such as RWE and RWD. However, it was found that nuanced differences in the types of RWD sources included in the descriptions could create confusion or differences between what RWD is accepted across decision-makers. The increasing use in regulatory documents of the terms data "relevance", "reliability" as key components of data quality (e.g., whether data is "fit-for-purpose") is a key example of the rapid evolution and hopefully growing clarity in this field. For example, in 2023, US FDA CDRH[10] updated a 2017 draft guidance to provide more data relevance and reliability when using RWE to support regulatory decision-making for devices. While this is an example of increased clarity, the review also found other terms used to describe the evaluation of data quality in various documents such as data "suitability"[23]. Supporting additional alignment on foundational terms and definitions will create more consistency.

1.2.2. Learning from experience

There are several programs which have focused on RWD infrastructure development and piloting RWE studies (e.g., EU IMI funded EHDEN[46] project and EMA's DARWIN EU®[47], China NMPA BoAo[48] and Great Bay Area pilot zones, US FDA Sentinel[49] and NESTcc initiatives[40]). While it was not within the initial extraction categories for the review, reviewers found some of the documents included examples of successful and unsuccessful submissions. US FDA CDRH issued a report in 2021[50] on RWE examples used to support regulatory decisions. Based on these findings, it could be beneficial to the field to pool and analyze these pilots and examples to identify best practices and common errors that would support both study sponsors and decision-makers.

1.2.3. Creating RWE-specific research practices

Based on the external literature and the documents in this analysis, there appears to be growing momentum towards the standardization of RWD/RWE research practices. Several third-party organizations (e.g., ISPOR, ISPE, Duke-Margolis Center for Health Policy, OHDSI network, EEPIA and the NESTcc) have proposed approaches to bolster trust through transparency in RWD-based research. These typically include similar sets of guidance and expectations as noted in the section on Ethics, Trust, and Transparency. These include publication and registration of study protocols, detailed documentation of operational decisions, broader dissemination strategies and adherence to Open Science principles. Several of the policies cited third-party papers and/or included similar types of approaches. Additional work to build consensus on trust and transparency policies could advance broader adoption and support more standardized policies moving forward.

As a potential component of this work, further assessment of the new category "Procedural Guidance" introduced in the Burns *et al.*(4) paper could be a good foundation. Their paper noted that this is an emerging area of guidance within the documents reviewed on procedural aspects related to submissions to regulatory and HTA agencies. While not the focus of our analysis, we did find that some of the guidance documents include directions on what information should be included in submissions. Some directions were focused on elements to include in the cover letter, but others were presented in tables and charts. Future analysis on these components could be a useful addition to RWE guidance documents moving forward, as it helps standardise what is to be included for those submitting and sets the expectations of the reviewers. Given that most of the guidance's focus on components that will need to be documented for submission, more consistency could support more shared expectations, transparency and harmonized approaches. Developing reporting standards and checklists focused on different types of RWE would also be a welcome area of further work.

1.3. Possible gaps for further exploration

1.3.1. Harmonizing the assessment of data quality and fitness for use

As noted in the analysis, there is no clear position amongst regulatory authorities or HTA agencies regarding expectations for demonstrated quality and fitness for use. In almost all the documents, there is an acknowledgement that the study needs to be a "tailored approach to match the evidentiary bar"[30] and that there needs to be a fitness for use approach in the valuation of the individual study to the research question. While there is a growing alignment around the concept of fit-for-purpose assessment of data there is uncertainty about what criteria will be used in the assessment. However, there are organizations looking at these challenges. For example, NICE's RWE Framework[23] also includes a "Data Suitability Assessment" (DataSAT) tool detailing how to assess whether RWD is suitable for the purpose it is being used for. While not included in this review, the draft ICH RWE reflection paper[51] proposes several areas where harmonisation/convergence may be addressed, one of which is data quality.

1.3.2. Data collection and documentation standards

We found that there is general consensus on the need to provide detailed documentation on the data collection process to ensure data quality and integrity. However, there are not shared expectations on what that should include. There tends to be more clarity on more well understood data sources such as registries. Other RWD sources for which research was not the primary purpose (e.g., claims, administrative and EHR) are more challenging. The secondary use of these RWD reflect issues with patient consent and privacy requirements, extraction and curation processes, and the need to RWD provenance for decision-makers (e.g., traceability and auditability). One approach to address these challenges is the adoption of common data models which could support more standardization of data collection. These challenges are even more problematic when considering more novel data sources such as apps, wearables, and complex data from imaging and video.

1.3.3. Guidance for RWE interpretation

In our review, only the CADTH guidance[29] for reporting RWE included a specific section addressing interpretation of RWE results. Data interpretation is a combination of having trust in the evidence through being confident in data quality and having transparent and rigorous processes. It could be useful to see whether further guidance is released by other organizations to see if there is agreement with the principles laid out by CADTH.[29] It may be that some of this information is included in other documents, but not in discrete sections on interpretation, making it harder to draw out. It is suggested that guidance documents include a separate section on interpretation.

1.3.4. Advancing analytical methods development

Adoption of more detailed information on types of analytical approaches including ways to mitigate bias found in documents from EMA, NICE, and IQWiG could be useful in countries where limited guidance is provided. It would be important to get consensus on whether there is agreement on the types of methods being suggested. Although we are not suggesting that there needs to be a consensus on a single best practice method, it would be helpful to have guidance on the range of techniques that could be used and where they would be most appropriate.

Reviewers noted that some of the documents included references to the potential use of data from sources outside the country or region, increasingly being referred to as “transportability” (e.g., US FDA, Australian TGA). Additionally, there are recommendations regarding the need to assess the generalizability of these RWD and the RWE to the local populations. However, there appeared to be little guidance on potential approaches to do so. This was not a specific extraction element in this analysis. The team concluded that this is an important area for further policy research and development as we seek to build global evidence portfolios and use valid clinical data from other regions.

1.3.5. Challenging medical product types and emerging innovations

As the pace of innovation continues, there is an increasing need to advance evidence generation for emerging therapies and diagnostic tools across the care pathway. This review identified the following areas where there were gaps in the current RWD and RWE specific policies and where additional analysis and policy development may be needed – in vitro diagnostics, DHTs and AI use in health care, and personalized- or precision-medicine products.

1.3.5.1. In vitro diagnostics

This review did not include guidance specific to in vitro diagnostics (IVDs). A preliminary assessment found that there are very few policy guidelines available that address the unique nature of IVDs when using RWE in regulatory decision making. The strengths and limitations of the use of RWE with IVDs are unique to these types of devices and may require separate analysis and recommendations for policy considerations. The Medical Device Innovation Consortium released a paper in 2020 focused on helping developers plan for the use of RWE and RWD when preparing premarket submissions for review of new or modified IVDs[54]. Additional analysis of this and other relevant documents could inform recommendations on considerations unique to IVD. Given the importance of these products in the care pathway, this is a gap in this field where additional policy development is needed.

1.3.5.2. AI use in health care

The advancement of AI and ML present significant opportunities for enhancing the extraction, analysis, and utilisation of RWD. Despite existing challenges, such as data extraction from unstructured sources and the need to mitigate algorithmic bias, the ongoing development of AI offers potential for solutions. To leverage

these technologies effectively and improve healthcare outcomes, it will be essential to update current methodologies and practices continually.

To keep pace with these technological advancements, further AI-specific guidance is crucial and much needed. EMA and the Heads of Medicines Agencies (HMAs) have recently drafted an AI workplan through 2028.[53] This comprehensive strategy aims to maximise AI's benefits and address potential risks by providing ongoing support for product development, establishing guidelines for AI integration throughout a medicine's lifecycle, and engaging in public consultations. Preparations to align with the forthcoming EU AI Act in 2024 are also underway, intending to create frameworks that enhance efficiency, data analysis, and decision-making processes within the bounds of data protection legislation. Additionally, the US FDA, has initiated discussions to engage stakeholders and address considerations for employing AI/ML in drug and biological product development. This initiative reflects the agency's commitment to refining regulatory science and gathering input to shape future frameworks. Within HTA, NICE have published an Evidence Standards Framework for Digital Health Technologies (DHT)[28] which addresses the design considerations necessary to mitigate algorithmic bias, ensuring equitable impacts across different user groups. It emphasised the importance of continuous monitoring of DHT performance over time, particularly for technologies based on AI or ML. The rapid development of new products using AI and SaMD requiring regulation makes it is difficult for policies to keep pace.

1.3.5.3. Personalized medical products

The South Korean MFDS guidance noted the potential value of RWD and RWE for emerging product areas such as 3D printed, patient specific, and/or rare products.[15] The analysis did not identify other guidance with these specific product areas specified. While these are relatively new fields, the project team indicated that it would be valuable to monitor the evidence generation needs of regulators and HTA agencies.

1.4. Analysis limitations and strengths

The dynamic nature of the policy environment and variability in definitions and terminologies across documents presented considerable challenges in data extraction, potentially impacting the review's comprehensiveness. The reliance on publicly accessible documents in English may have introduced selection bias. Additionally, limiting the scope of the review to documents that are explicitly focused on RWD and RWE policies means that potentially relevant documents were not reviewed. Some policy documents were not included in our analysis but show a trend towards the potential acceptance of RWD but also limitations in how it might be used in decision-making. For example, Singapore's Health Sciences Authority (HSA) draft GN-20 Guidance on Clinical Evaluation includes the use of RWD as a source of clinical data.[54] Another example is the Medical Device Coordination Group (MDCG) guidance documents around clinical investigation and evaluation under the EU Medical Device Regulation 2017/745 (e.g. MDCG 2020-6, MDCG 2020-7 and MDCG 2020-1) which include RWD as a source of clinical data.[55] However, there is no European Medical Device guidance on the specifics of the use of RWD and mechanisms surrounding the generation of RWE.[59]

Additionally, since the end of our data collection, there have been other reviews on this topic published. In February, Jansen *et al.* (2024) released findings on how RWE was being used in regulatory and HTA decision-making, *Real-World Evidence to Inform Regulatory Decision Making: A Scoping Review*.[56] As our data collection was already completed at the time of publication, we were not able to incorporate their findings into this report. We intend to use this to inform our future work. In March 2024, the Margolis Institute for Health Policy at Duke University released the *International Harmonization of Real-World Evidence Standards Dashboard*.[3] This dashboard provides a comprehensive overview of the regulatory landscape surrounding RWE and highlighting the gaps in regulation across other regions. We were unable to include this resource in our analysis due to the timing of its release, however it will be a valuable tool moving forward.

In the EU, the European Health Data Space (EHDS) will be established, following the finalization of related legislation. In preparation for this, the Recommendations on a Data Quality Framework[57], comprising 13 detailed recommendations. While this included discussion of the secondary use of data, it was not specifically focused on RWD/RWE, and therefore not included in this review. Also not evaluated in this review but referred to in several documents was the EU ENCePP guidance related to conduct of pharmacoepidemiology studies.[58]

During our analysis, we encountered difficulties due to the varied structures and terminologies used across different policies. Many documents contained general statements on certain aspects, along with broad suggestions for implementation, which were often dispersed or categorised under different sections due to overlaps in topics. This fragmentation was especially noticeable in discussions on data collection, quality, governance, and transparency, complicating the extraction of specific components.

A key strength of this review lies in its systematic approach to identifying and analysing the current stance on RWE among leading health policy bodies. The detailed examination of organizational sentiments, differences in RWE application across devices and pharmaceuticals, and the distinction between regulatory and HTA perspectives provides a comprehensive overview of the field. This structured approach builds on previous reviews and ensures that the key findings are grounded in a robust analysis of contemporary documents, offering valuable insights for policymakers, researchers, and healthcare practitioners.

1.5. Further work and next steps

This report is intended to fill gaps in the current research by looking across fields, regions, and types of health products. The scoping review includes policies for both medicines and medical devices and reflects the current perspectives of regulatory and HTA agencies from different parts of the globe. Based on this analysis, and insights from previous reviews, we now have a clearer understanding of the current policy landscape and have identified the following areas for further exploration in the next phase of the IDERHA policy project work.

The analysis found that there are encouraging signs that significant progress has been made to provide clearer and more consistent approaches that will support broader adoption. More specifically, there are emerging concepts around what constitutes good research practices specific to RWD sources and RWE studies intended to support the public health. New resources including submission checklists, study design tools, and research transparency practices could be consolidated and shared to increase consistency in the implementation of studies, as well as establish shared expectations between sponsors and decision-makers. The project will work to engage with the other organizations leading this work to identify approaches to both advance current efforts and support broader adoption.

The analysis also revealed that although a lot of progress has been made on various technical and methodological approaches, additional work is needed to harmonize policies for the assessment of data quality and identify appropriate analytical approaches to address concerns about bias, confounding, and generalizability of findings across different populations. Several organizations in different regions are actively working to pilot RWD access and RWE research programs. The IDERHA project team will look at how to gather and consolidate the lessons learned from these projects to help identify best practices and support efforts to focus on areas where more development is needed.

Through the course of the analysis, the team identified areas where there are potential gaps that hinder the use of RWD and RWE. The analysis suggests that there is a need to do additional exploration around well-established, as well as new and emerging technological and policy fields. For example, IVDs are a critical component of patient care and have a long history of regulation and market access. As seen in the recent pandemic, the need to quickly use the data collected in everyday care to support the ongoing effectiveness of

these products remains limited. The US FDA CDRH's recent guidance on RWE explicitly includes the use of RWD and RWE as an acceptable approach to generate evidence for IVDs but in practice this is challenging.[10]

The use of AI in health care is a high-priority area for policy development globally. The focus of this study and the eventual policy recommendations will be on the use of RWD and RWE to support decision-making and not on the development of AI regulations or policies for market access. However, it is relevant to understand the relationship between AI, RWD, and RWE. The project team will work to identify how to support policies where these issues intersect.

We found that there remain significant differences between different product areas, types of organizations (e.g., HTA, regulatory and third-party), and regions in organizational perspectives about the use of RWD and RWE. Many of these perspectives reflect concerns about scientific rigor in decision-making. There appears to be a relationship between the types of acceptable uses of the RWD and RWE and the implicit indications of the various organizations' perspectives, concerns, and aspirations regarding the potential to use these data and studies to support decision-making. The goal of this work is to support more consistent and harmonized approaches to advance the appropriate use of RWE. Additionally, a key component of the work moving forward will be focused on better understanding diverse concerns and views about the use of RWD and RWE.

All of these factors will shape and inform how RWD and RWE may be used in the future to support critical public health decisions. It will not be possible to address them all within the scope of this project and the next phase of the work will require that we identify priorities and focus our work.

The findings from this report will be released for public consultation. The consultation will focus on gathering input from diverse stakeholders in the health ecosystem on how to prioritizes the policy gaps identified. The findings in this report will also be summarised into a public-facing document for publication. After the consultation period, the team intends to convene a series of small workshops with external experts and organizations to gather diverse views to develop pragmatic policy recommendations on the use of RWD and RWE in the EU and support global harmonization efforts. A draft of the recommendations will be released in 2025 with the final report issued in the 2027.

2. Conclusion

This is the first scoping review to look across policies for regulatory and HTA, cover both medicines and medical devices and have a global scope. The review illustrates the cautious yet progressive integration of RWE in health technology assessment and regulatory frameworks, identifying both the policy advances and challenges. Based on this analysis and insights from previous reviews, we have identified the areas for further exploration in the next phase of the IDERHA policy project work. We also hope that this report will be a useful reference for other groups working on these challenging topics. By highlighting the need for better alignment of expectations on the emerging field of RWE in terms of standardization, clarity, and utilisation, this work contributes significantly to the ongoing dialogue on optimising health data for the betterment of patient care and serves as a basis for further policy development.