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Integration of Heterogeneous Data and Evidence towards Regulatory and HTA Acceptance

WP6 Policy recommendations to enable Regulatory and HTA decision making

D6.2 Report on Global Regulatory Best Practices Analysis: A scoping review of HTA and Regulatory RWD/RWE policy documents

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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.

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Acronyms and Abbreviations

AEMPS	Agency of Medicines and Medical Devices (Spain)
AI	Artificial intelligence
AIFA	Italian Medicines Agency
CADTH	Canadian Agency for Drugs and Technologies in Health
CDE	Center of Drug Evaluation (China)
CDM	Common Data Model
CDRH	Center for Devices and Radiological Health (US)
CMDE	Center of Medical Device Evaluation (China)
DHT	Digital Health Technology
EHDS	European Health Data Space
EHR	Electronic Health Record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology & Pharmacovigilance
EUA	Emergency Use Authorization
EUNetHTA	European Network for Health Technology Assessment (Europe)
EUreccA	European initiative of new Reimbursement and aCCess Approaches
FDA	U.S. Food and Drug Administration
HAs	Health Authorities
HAS	National Authority for Health (France)
HDE	Humanitarian Device Exemptions
HMA	Heads of Medicines Agencies
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
HTW	Health Technology Wales
ICER	Institute for Clinical and Economic Review (U.S.)
ICH	International Council for Harmonisation
IDAGC	Integrated Data Access Governance Council
IHI	Innovative Health Initiative
IMDRF	International Medical Device Regulators Forum
IMI	Innovative Medicines Initiative (Europe)

IQWiG	Institute for Quality and Efficiency in Health Care (Germany)
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MDCG	Medical Device Coordination Group
MFDS	Ministry of Food and Drug Safety (South Korea)
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
ML	Machine Learning
NEST	National Evaluation System for Health Technology (U.S.)
NICE	National Institute for Health and Care Excellence (England)
NIFDSE	National Institute of Food and Drug Safety Evaluation (South Korea)
NPMA	National Medical Products Administration (China)
OHE	Office of Health Economics
OMOP	Observational Medical Outcomes Partnership
PBAC	Pharmaceutical Benefits Advisory Committee
PECO	Patient, Exposure, Comparison, Outcome
PGHD	Patient-generated Health Data
PICOTS	Patient, Intervention, Comparison, Outcome, Timing, Setting
PICO	Patient, Intervention, Comparison, Outcome
PMA	Premarket Approval
PSEHB	Pharmaceutical Safety and Environmental Health Bureau (Japan)
RCT	Randomised Controlled Trial
REALISE	Real World Data in Asia for Health Technology Assessment in Reimbursement
ROBINS-I	Risk Of Bias in Non-randomised Studies - of Interventions
RWD	Real World Data
RWE	Real World Evidence
SaMD	Software as a Medical Device
TEHDAS	Joint Action Towards the European Health Data Space
TGA	Therapeutic Goods Administration (Australia)
WP	Work Package
ZIN	National Health Care Institute (Netherlands)

1. Introduction

IDERHA (Integration of Heterogenous Data and Evidence towards Regulatory and HTA Acceptance) is a European Innovative Health Initiative (IHI) project that aims to enable the safe, secure, and streamlined sharing of heterogenous healthcare data. While there is not a broadly adopted definition, 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. This may include data from real-world data (RWD) sources, traditional clinical trial data, social determinants of health, and potentially other data that capture factors that affect health such as air pollution.

The IDERHA project aims to integrate, analyze, and use heterogenous health data, including RWD, to better support doctors, researchers, and patients with insights that can improve the treatment and management of disease and allow for more personalized care. Real-world evidence (RWE) is derived from analyses of RWD. While the merits of RWD and RWE are recognized, policies for the use and adoption of it in regulatory and health technology assessments (HTA) decision making are not broadly available. Even in areas where there is a commitment from regulators to use it, there remain concerns about the scientific rigor.[1]

Given that RWD and RWE are not as well defined for policy makers, IDERHA seeks to accelerate policy development in this field to enable patients and healthcare providers to benefit from novel health research and solutions.

In recent years, the number of guidance documents and policies related to the use of RWE in regulatory and HTA contexts, has been steadily increasing, particularly regarding drugs and biologics (Figure 1).[2,3] Similarly, for medical technology there is an acceleration in the development and publication of RWE specific guidance globally (e.g., United States, South Korea, China, Japan and Australia).

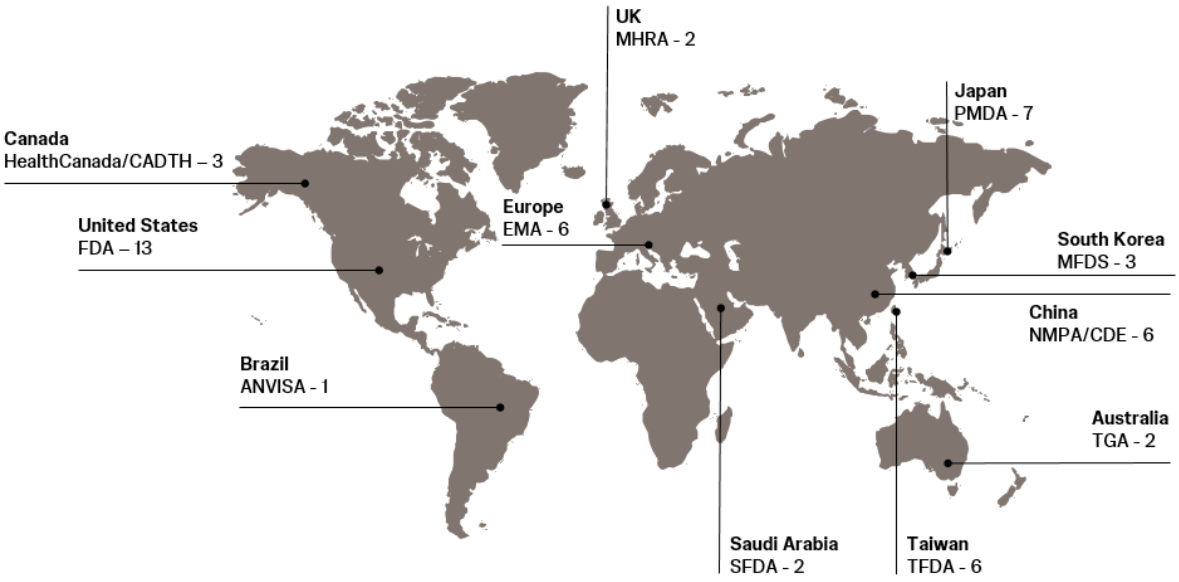

Figure 1. Number of RWE guidance documents and frameworks from regulatory agencies as of 2023. Adapted from the Margolis Institute for Health Policy dashboard[3]

This report is an analysis of the current policy and guidance documents on the use of RWD and RWE in HTA and regulatory decision-making for medicines and medical devices. For the purposes of this report, we use the term 'policies' to encompass documents that provided recommendations and information on the use of RWD and RWE studies such as best practice guides, frameworks, methodological guidance, quality standards, and organizational policies. The documents included in the analysis were primarily issued by HTA agencies and regulatory authorities, however a small number of policy-related documents from key third-party

organizations (e.g., ISPOR), were also included. The analysis focused on emerging best practices, areas of policy alignment or divergence, and identifying critical topics where a lack of policy exists. This report will be issued for public consultation to solicit additional feedback.

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. We have used the insights from previous reviews[2,4] to build a picture of current best practices and identify areas where developing recommendations for future policy on the acceptance and use of RWE in regulatory and HTA may be needed.

This report is the foundation for the next phases of the project work, which are focused on drafting, disseminating, and developing consensus recommendations to support the acceptance of heterogeneous health data research in regulatory and HTA decision-making. The team will use the findings from the report, public consultation, and future expert workshops to draft policy recommendations. These draft recommendations will also be released for public consultation to solicit public feedback, build consensus, and inform the final report, which will be issued in 2027.

2. Objective and scope

The goal of IDERHA Work Package 6 is to develop recommendations to accelerate RWE policy development to meet the current and future advances in the digitization of health data, research methods, and health care innovations. The long-term goal of Task 6.4 is to develop consensus policy recommendations supporting the acceptability of RWE for key public health decision-making (i.e., regulatory and HTA). Where possible, the final recommendations will seek to advance global harmonization.

This report is not intended to be a comprehensive overview of every document available on this topic. The team focused on the most recent documents and prioritized those from well-established regulatory, HTA, and third-party organizations.

The review explores:

- what current policies cover: definitions, scope, geographical region, link to broader policies and initiatives;
- where there is consensus on best practice policy for broader adoption;
- where there are policy gaps for the use of RWD and RWE in decision-making; and
- where additional foundational work and/or consensus development is needed.

3. Methodology

3.1. Scoping review

As an overall framework for the review, the JBI methodology for scoping reviews, was chosen.[5]

3.1.1. Search strategy

A literature search was conducted by information specialists at NICE. The search strategy was developed, and test searches were conducted. The final search was conducted in both MEDLINE ALL and Embase, where individual search strategies were developed for both. An example search strategy used for MEDLINE ALL can be found in Appendix 1. As not all organizational policies may appear in these databases, individual searches of relevant organizations' websites were conducted (i.e., US FDA, EMA, EUNetHTA, NICE, HAS, IQWiG, AEMPS, AIFA, ZIN, DEFACTUM, CADTH, ICER, PBAC, SMC, SHTG, AWTTC, and HTW), and some

documents were identified through review group expertise. Searches were carried out on 20th June 2023 and limited to references from 2017 onwards. We continued to include new documents up until January 2024. The review team prioritized documents that referred specifically to the use of RWD/RWE by regulatory and HTA agencies and a small number of third parties (e.g., international societies, research organizations), who had published documents of relevance.

At least two researchers screened all references to determine eligibility. If disagreement arose, a third party was included, and consensus was reached on the eligibility of the document. In total, 17 researchers participated in the data extraction and drafting of the report.

3.1.2. Eligibility criteria

Documents were assessed for eligibility against a set of inclusion and exclusion criteria:

- Types of sources: The review incorporates both published and grey literature. Additionally, documents that provide context to policies, even if they are not policies themselves, were considered for inclusion. Documents can originate from any country, or they may be global or non-country specific in nature.
- Language: Eligible documents must be in English, including those that have been translated into English, with active efforts made to seek translations where possible.
- Timeframe: Only documents published between 2017 and January 2024 were considered for inclusion. It is likely that policy documents prior to 2016 will be outdated.
- Exclusion criteria: Any documents that had been superseded by an updated version were to be excluded.

3.1.3. Data extraction and analysis

Data was extracted using a standardized extraction template (Appendix 2). The template was finalized following a pilot on ten documents. Extraction criteria included, but were not limited to, details surrounding whether the document included guidance on the use of RWE, study design, data quality, and transparency. Reviewers extracted data, with at least 25% of the documents extracted and compared by two independent reviewers. The remaining document extractions were validated by a second reviewer. In both approaches, any discrepancies were resolved through discussion.

3.2. External expert workshop

On 30th October 2023, a two-hour workshop was convened under Chatham house rules with five experts from regulatory and HTA agencies. This workshop was held to solicit expert input on the landscape analysis. This included details on the research objectives, document inclusion criteria, the list of the organizations and initiatives whose policy or guidance documents were included in the review, the analysis extraction categories, and a summary of the current findings. Participants were asked to provide feedback on both the review process and emerging areas. Feedback on the review process included the recommendation for separate analyses for regulatory and HTA documents, as well as policies related specifically to either medicines or medical devices. The participants were particularly interested in identifying areas of alignment across different policies and countries.

3.3. Consultation with IDAGC

The IDERHA Integrated Data Access Governance Council (IDAGC) was established to provide guidance to the project team. On 14th February 2024, the IDAGC reviewed the methods and process, as well as some early high-level findings. Similar to the feedback from the external workshop, the IDAGC wanted the report to identify areas of potential alignment and divergence, as well as where there might be gaps in the current

policies. They urged the team to consider how to communicate the benefits and risks to patients, clinicians, providers, and other stakeholders related to the use of RWE.

3.4. Building on existing landscape analyses

Several landscape reviews by other groups were identified and it was found that most of these analyses focused primarily on policies from regulatory authorities, rather than HTA. These reviews also tended to focus on a single medical product type covering either medicines or medical devices but not both. The following publications informed our work.

The paper *Real-World Evidence for Regulatory Decision-Making: Updated Guidance from Around the World*, published by Burns *et al.*[4], analyzed global documents regarding the use of RWE for drugs and biologics and reviewed progress towards its acceptance for medicines. The authors grouped the documents into four following categories:

- Regulatory RWE Frameworks provide guidance and policy on the regulatory requirements of health authorities.
- RWD Quality Guidance set standards for the data used in studies.
- Real-World Study Methods Guidance describe how RWE studies should be conducted.
- Procedural Guidance describe internal organizational procedures related to RWE.

There was a significant overlap in the documents included in this review and our analysis. We considered adopting a similar categorization. However, after careful consideration, we decided that our analysis was focused on different primary topics.

Insights were also included from the *Current Landscape for Global Regulatory Acceptance of Real-World Evidence for Medical Devices* by Cavanaugh *et al*.[6] This paper's findings provided details of uses of and sentiments regarding RWE for medical devices around the world. This report details twelve examples where RWD was used to support regulatory decision-making, primarily from the U.S. Food and Drug Administration (US FDA). It also includes polling by country on success rates of RWE use and institutional barriers that remain.

4. Results

4.1. Overview of Analysis Documents

The analysis included 50 individual policy or guidance documents from 29 organizations (Appendix 3). Although our analysis has a wider scope than either the Burns *et al*.[4] or Cavanaugh *et a*l.[6] analyses, it overlaps with both significantly. Burns *et al*. analyzed 36 documents from 10 organizations and Cavanaugh *et al.* analyzed 28 documents from 10 organizations, though their analysis included additional polling and survey data. This analysis' broader scope complements these two analyses, which were both important resources in our research.

Some organizations have produced multiple documents on the use of RWD/RWE which cover different aspects of policy considerations. To simplify the analysis, findings were combined by organization to provide a more comprehensive view of each organization's position. A set of simple categories were developed (Table 1) to enable classification of the types of documents within the review. For a complete listing of how each of the documents are categorized please see Appendix 3.

Category	Definition
Regulatory Submission Guidance	Guidance for use of RWE in submissions to regulatory agencies. Possible topics include study and research methods, data quality requirements, procedural guidance, and accepted use.
HTA Submission Guidance	Guidance for use of RWE in submissions to health technology assessment agencies. Possible topics include study and research methods, data quality requirements, procedural guidance, and accepted use.
Strategic Plans	Organizational strategy documents, organizational policies, and white papers.
Research Practices	Tools and protocols to facilitate RWE research.

Table 1. Document categorization system

The analysis of the regulatory documents included 32 documents (29 from regulatory organizations and 3 documents from third-party organizations). Of these, 17 were specific to medicines, 12 were specific to medical devices, and three covered both. Of the regulatory documents, 28 were regulatory guidance, three were strategic plans, and one was a research practices document.

The HTA analysis included 14 individual documents (11 from HTA agencies and 3 documents from third-party organizations). Of these, four documents were specific to medicines, one was specific to medical devices, and nine covered both, or did not mention if they were specific to either. Nine of these were HTA methods guidance documents, three were strategic plans, one was a research practices document, and one was both a regulatory and HTA guidance document.

The analysis also covered four third-party documents from three organizations, covering both Regulatory and HTA sectors. Of these documents, three covered medicines alone and one covered both medicines and medical devices. Three of these documents were both regulatory and HTA guidance and one was a research practices document (Figure 2).

In our analysis, we found that some documents were focused on specific RWD sources. There were six documents that specifically addressed the use of registry data for RWE studies, one covered the use of electronic health records (EHRs), and one covered the use of both EHR and claims data. These documents were predominantly from regulatory agencies.

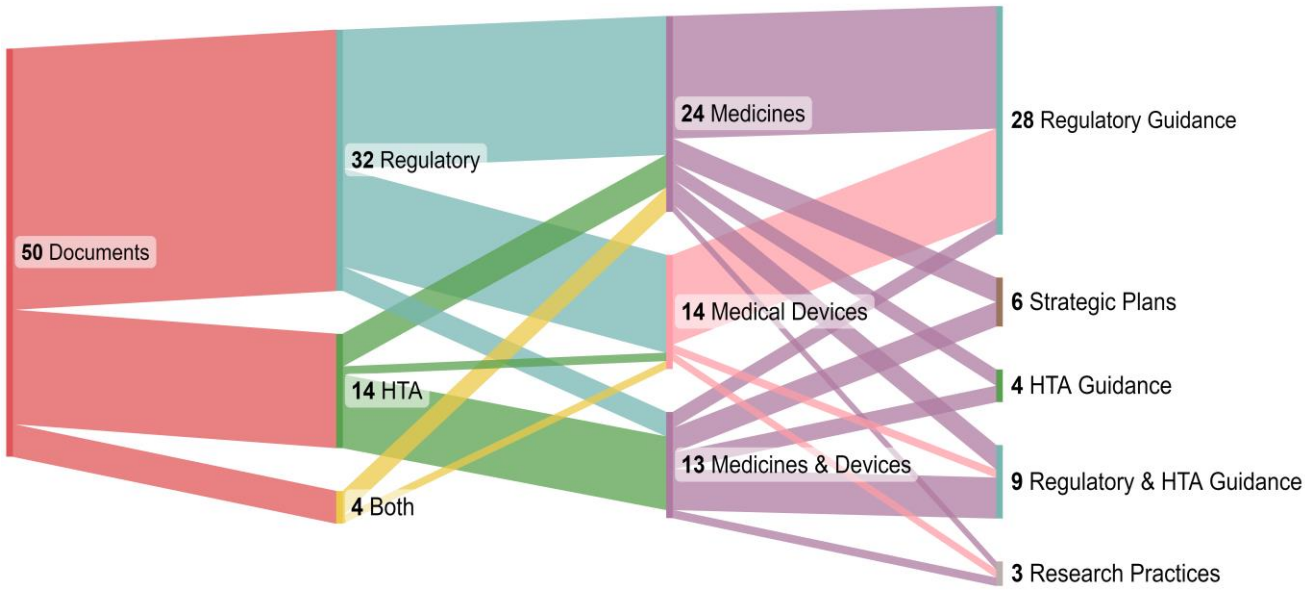

Figure 2. Breakdown of analysis documents by category

4.2. Definitions of RWD/RWE

Over the last decade there has been an evolution of the language and definitions of RWD and RWE. Standardized definitions are important to ensure consistency in interpretation of what is included as RWD and RWE. Given this rapid evolution, our review looked at the definitions and found that most organizations included 1) a definition of either RWD, RWE, or both in the policy and that 2) the core aspects of the definition appear to be aligned with small differences found in the definition of what constitutes RWD (Table 2).

Definitions of Real-World Data	Definitions of Real-World Evidence
RWD can be defined as information pertaining to health status and health care delivery that is collected routinely from sources other than traditional clinical trials.[1]	RWE refers to the evidence derived from analysis of RWD regarding the usage and potential benefits or risks of an intervention.

Table 2. Core definitions of RWD and RWE derived from analysis.

There appears to be broad adoption of early definitions released by ISPOR[7] and US FDA[8], with some of the documents citing them as sources. Similarly, the examples of RWD data sources are generally aligned with some differences between documents. For example, in the US FDA definition, examples of RWD sources include EHRs, claims and billing data, data from product and disease registries, patient-generated data including home-use settings, and data from mobile devices. The EU definition also includes those sources but additionally specifies primary and secondary care records and administrative birth and death data. While the primary types of RWD are generally consistent, subtle differences in the definitions should be evaluated as

[1] Variations in terminology exist, such as using "routine practice data" or "real world clinical data".

they could hinder efforts at harmonization of research practices, interpretation across decision-making (between HTA and regulatory), and across jurisdictions (in different countries).

Key Findings

- There is general alignment in the core definitions of RWD and RWE across HTA, regulatory, and third-party organizations.
- Subtle differences in definitions and lists of types of RWD sources may hinder harmonization efforts.

4.3. Uses of RWD and RWE

In this review, the areas of use of RWD and RWE to support regulatory and HTA decision-making were assessed. The analysis identified some common themes and diverging policies across regulatory and HTA documents. Both regulatory bodies and HTA agencies advocated for the integration of RWE throughout the product lifecycle, recognizing its complementary role alongside traditional clinical trials. While most documents emphasized the use of RWE to complement clinical trials, this support is primarily complementary to traditional clinical studies such as randomized trials, both in their planning phase and in other aspects such as analysis and interpretation. Both regulatory and HTA guidance and policies acknowledged the usefulness of RWD and RWE in assessing the generalizability of trial results to local contexts or specific populations, and in post-market surveillance to assess long-term performance, efficacy, and safety data. HTA methods guidance also included the use of RWD and RWE to derive inputs for and validate assumptions and extrapolations made within economic modelling. There also appeared to be differences in focus and granularity between HTA and regulatory documents. For example, regulatory guidelines tended to provide more prescriptive recommendations. HTA documents exhibited variability in depth and specificity.

The review found that while often listed together, there were distinctions between how RWD/RWE can be used, and where RWD/RWE could then be used within the regulatory activities and HTA processes.

4.3.1. How RWD/RWE is used in research

A variety of ways in which RWD can be used as a data source were identified in the review and organized into overarching categories listed in Table 3. While many of the listed uses were relevant for either regulatory or HTA activities, there were often differences in the types of studies and scientific questions these could be applied to address. For example, regulators more frequently listed the use of RWD for post-market surveillance and vigilance applications, while HTA bodies focused on effectiveness and understanding if the assumptions that informed economic modelling and HTA recommendations were valid. Detailed discussions of the individual categories with findings from specific policy documents are found below.

Supporting trial design

- Assessing feasibility during the planning phase of a clinical study
- Generating hypotheses for clinical studies (e.g. estimating treatments effects or failure rates)
- Identifying relevant outcomes
- Identifying targets for the development of new therapies and design of the drug development pathway
- Estimating test accuracy or reproducibility of test results such as biomarkers
- Testing/validating surrogate endpoints

Cohort characterization and contextualization of trial results

- Understanding natural history/disease progression/epidemiology
- Understanding care pathways
- Identifying relevant patient populations/population characteristics
- Identifying biomarkers or clinical characteristics relevant to the outcomes of interventional and non-interventional studies
- Identifying and characterising underserved/underrepresented audiences and areas of health inequalities against target population
- Assessing the applicability of trial results to patients in real life and/or a specific context /healthcare system
- To monitor use, adherence and experience of using health technologies
- Estimation of utility scores/mapping data to Quality of Life tools

Estimating intervention effects (population-level estimation)

- Extrapolation of trial results
- Estimating comparative effects in countries in which the technology was available
- Estimating effects for combination therapies (including sequences) or decision strategies not examined in randomised controlled trials
- Allowing head-to-head comparisons between interventions in absence of head-to-head trials
- Filling evidence gaps in network meta-analysis
- External control arm for single arm trials
- Assessing long-term efficacy and safety
- Assessing effectiveness and safety in off-licence indications
- Exploring heterogeneity in intervention effects
- Estimating economic burden (e.g. resource use and costs)
- Measuring patient QoL

Innovative technology and algorithm optimisation

- A mechanism for training and re-training artificial intelligence and machine learning-enabled medical devices
- Validating software as a medical device (SaMD) product
- Developing clinical prediction models

Table 3. Identified uses of RWD/RWE sources (This table is a compilation of all uses of RWD identified in the analysis and does not represent consensus by the authoring organizations included in the review)

4.3.1.1. Supporting trial design

Several of the policies identified the use of RWD/RWE to support the design of trials through supporting hypothesis generation, feasibility assessments, and identifying relevant outcomes of interest. The ICER and the Office of Health Economics Research[9] from the US also reported that RWD/RWE is utilized in drug development to identify targets for the development of new therapies and design the drug development pathway. RWD/RWE can also be used in the validation and choice of surrogate endpoints and biomarkers to

be used in trials. For example, in situations where it would not be feasible to conduct a trial for the length of time to measure a direct clinical outcome, RWD can help validate the link between the two, by providing the longer-term follow-up data.

4.3.1.2. Cohort characterisation and contextualization of clinical trial results

Characterization of target populations, standards of care, comparators, care pathways, disease progression, and natural history is one of the most frequently mentioned uses of RWD/RWE, particularly in HTA documents. Multiple regulatory and HTA documents identified the use of RWD/RWE to address challenges associated with conducting controlled clinical trials in populations traditionally underrepresented in research (e.g. children, elderly, racial/ethnic minorities, pregnant and/or breastfeeding people). For example, the US FDA CDRH guidance[10] notes the potential of RWD/RWE to better understand health disparities and inform regulatory decision-making. Several of the documents also noted the potential for RWD/RWE as vital in supporting research efforts where clinical trials are difficult due to small patient populations (e.g., rare or neglected diseases).

RWD/RWE are also used to contextualise trial results (i.e., comparison of results to real-life practice). This was highlighted by multiple regulatory and HTA documents as being particularly important when assessing if clinical trial results can be generalized beyond the trial to real-world healthcare system practice. Other uses included post-market monitoring.

4.3.1.3. Estimating intervention effects

Regulators and HTA bodies often make decisions based on limited or immature trial evidence bases, where gold standard randomised clinical trials will only be able to provide evidence for a specific population over a specific time-period. RWD may be used to support better estimations of intervention effects and impacts. This can be done by extrapolating the trial results beyond the parameters set in a trial. In HTA, these types of extrapolations of overall survival are essential to allow economic modelling of long-term cost-effectiveness. RWD can also be used to provide control arms in single-arm trials or comparator arms when specific analyses are needed (e.g. head-to-head comparisons which can allow comparisons of a new intervention with standards of care, instead of placebo).

Several regulators support the use of RWD for monitoring post-market safety. For example, the European Medicines Agency (EMA)'s Data Quality Framework for EU medicines regulation[11], indicated that routinely collected RWD has long been utilized to inform regulatory decision-making regarding drug safety during the post-authorization phase. Similarly, the Pharmaceutical Safety and Environmental Health Bureau (PSEHB) of Japan advocates for the utilization of RWD/RWE, particularly registry data, in post-marketing evaluations of efficacy and/or safety.[12] Other regulators note that RWE can serve as a valuable tool for identifying post-market safety signals, and aid in the assessment of the benefit-risk profile throughout their lifecycle. In some cases, RWE can support post-marketing studies of conditionally authorized devices and facilitate long-term evaluations of safety and/or performance, especially for high-risk implantable medical devices.

4.3.1.4. Innovative technology and algorithm optimisation

There are a few examples where RWE is seen as an approach to support innovative product areas. In 2023, the US FDA released guidance on RWE to support regulatory decision-making for medical devices. Among the potential applications identified, one significant purpose is to utilize RWD as a mechanism for re-training artificial intelligence and machine learning-enabled medical devices.[13] The Therapeutic Goods Administration's (TGA) guidance also includes factors to consider when using RWE to validate software as a medical device (SaMD) product and also includes considerations for RWD generated by a SaMD product.[14] The Ministry of Food and Drug Safety (MFDS) of South Korea includes RWE for supporting clinical trials to verify the safety and performance of rare medical devices, 3D printed medical devices, and regulated digital

technologies (such as big data and artificial intelligence).[15] Additionally, the US FDA authorized a next generation sequencing-based tumour profiling test based on RWE extracted from a retrospective review of medical records, which was used to estimate somatic mutation prevalence, validate a cut-off, and support evaluation of claims.[16]

This review found that the use of RWD and RWE to support more innovative technologies such as training and validating artificial intelligence (AI) and digital health technologies (DHT) is starting to be included in some of the more recent documents (e.g., US FDA CDRH 2023[10], TGA 2023[14]). Additional analysis of the intersection of RWD, RWE, and AI policies is included in section 4.8 of this report.

The NICE RWE framework noted that RWD could be used for 'developing and validating digital health technologies including prognostic models' [23]. Clinical prediction models 'predict a diagnostic or prognostic outcome based on a combination of patient characteristics (e.g. demographic information, disease history, and treatment history[17]). Large-scale RWD sets can provide information on the outcomes of large numbers of patients with different characteristics, allowing machine learning analytical techniques to be used to develop prediction models for individual patients based on their specific characteristics. These models can have various applications as predictive, diagnostic, and prognostic and can be employed as part of clinical decision support systems, SaMD and in other contexts.

4.3.2. Where RWE is used in regulatory activities and HTA processes

The use of RWD/RWE is most likely to be associated with expedited approval pathways and conditional approvals, as well as expanding indications or updating labels. Increasingly, RWE is being used both in pre and post marketing authorisation stages and for reimbursement decision-making. The majority of documents broadly suggested ways that RWE could be used but did not make definitive statements on when it would be accepted. Table 4 summarises the types of uses noted for RWE in regulatory activities and HTA processes. This table is a compilation of all the potential uses identified throughout all the documents.

A key focus of the use of RWE in HTA documents is on its role in understanding the generalisability of trial results to the local context, characterising the target population and the natural history of the disease and supporting economic modelling. Most HTA documents acknowledge RWE's role in deriving inputs for economic models including those relating to the natural history of the disease, baseline risks, the associated resource use and costs of a treatment/intervention, and quality of life. Characterization of healthcare conditions, care pathways, and natural history is one of the most frequently mentioned uses in HTA documents as it provides valuable information to ensure economic models are as reflective of real-life and localised contexts as possible. Post-reimbursement, RWE can be used to validate assumptions made in these models, potentially allowing re-evaluation and reviewing of reimbursement and payer coverage decisions. The HTAi Global Policy Forum also discussed the possibility of using RWE to drive disinvestment decisions. [63]

Attitudes towards the use of RWE appear to vary significantly across countries. As noted, the FDA have indicated that RWE could be used as a primary clinical evidence source, however, Swissmedic explicitly stated that "new marketing authorization applications based solely on RWE are deemed unacceptable, given the current legal, scientific, and regulatory frameworks necessary for such acceptance have yet to be established."[19]

There were differences noted between medicines and medical devices. For medicines, RWE has primarily only been recommended for use as a supplementary or complementary evidence source to clinical trials in regulatory or HTA decision-making. For medical devices, most regulatory policies state that RWE can only be used as supplementation clinical evidence (e.g., China NMPA[18,62], TGA[14]). A notable exception is the US FDA CDRH guidance that indicated that it is possible to use RWE as primary clinical evidence across a wide range of pre-market submission types (i.e., PMA, 510k, de novo, HDE, EUA). While there is Medical Device

Coordination Group (MDCG) guidance [55] on the use of RWE, there is not a regulatory framework for RWE within the EU Medical Device Regulation. [59]

For medical devices, use of RWE as a primary data-source has been much more common as it is often not possible to run randomised clinical trials in these settings. It is unsurprising then, that differences between medicines and medical devices emerged regarding the types of evidence accepted for regulatory and HTA submissions (e.g., observational studies are more acceptable for medical devices). For instance, the US FDA's guidance[10] on medical devices outlined a broader spectrum of uses compared to drug-related recommended uses. TGA also suggested that separate guidance for medical devices and medicines will be required because the generation of such evidence is often quite different to warrant such, even though some technologies may increasingly require reference to both.[14]

Pre-marketing authorization

- Primary clinical evidence to support marketing authorization
- Supplementary evidence to support marketing authorization
- Conditional approvals
- Expedited approval pathways
- Expanding indications or assessing off-license efficacy

HTA

- Economic modelling
  - Providing inputs for modelling
  - Adapting models to local contexts
- Primary clinical evidence to support HTA and reimbursement decisions
- Supplementary clinical evidence to support HTA and reimbursement decisions

Post-marketing authorization/ reimbursement decision

- Regulatory
  - Pharmacovigilance (monitoring adverse events)
  - Postmarket clinical follow-up (PMCF) for medical devices
  - Vigilance for medical devices
  - Product reclassification
- HTA
  - Outcome-based contracting/managed entry agreements/ early value assessments
  - Reimbursement re-evaluations
  - Informing disinvestment decisions
  - Expanding indications or assessing off-license efficacy
  - Payer coverage decisions

Table 4. Regulatory activities and HTA processes where there are opportunities to use RWE

Key Findings

- RWE is generally considered complementary evidence to the gold standard RCT for both regulatory and HTA of all health products.
- The most frequently recommended uses of RWE in regulatory policy documents are Clinical Trial Support and Post-Market Surveillance.
- In HTA, the use of RWE in economic modelling is well established for deriving inputs other than relative effectiveness.

- Divergence in uses of RWE between medicines and medical devices is driven by the differences in products, types of evidence needed to demonstrate safety, performance, and effectiveness and regulatory requirements.
- Few documents provided clear descriptions on the circumstances where RWE would be accepted.

4.4. Guidance on study design and conduct

Study design and methods include some of the key areas considered when planning a research study, including developing a research question, choosing the study design, analysis, and interpretation of results. In this review, data collection and curation processes were considered separately. Ensuring robust study design practices and methodologies is crucial to ensure high quality research is undertaken to engender trust in the results produced. It also links strongly with ensuring a transparent and reproducible process.

4.4.1. Developing the research question

There appears to be growing consensus between HTA and regulatory documents on structuring a research question. Some policies recommended using frameworks like PICO, PICOTS or PIRO. Some regulatory organizations (e.g. EMA[21], Health Canada[22], and Swissmedic[19]) mention defining estimands explicitly, which contributes to the transparency and reliability of statistical analyses. The NICE RWE framework discusses the use of prevalence and incidence as target metrics.[23]

There appears to be differences between some HTA and regulatory expectations. The key difference is that regulatory organizations question if RWE can address the research objectives while HTA agencies focus more on evidence gaps and the need for RWE. Although many documents mentioned justifying the choice of observational vs experimental study designs, it is not clear how to determine if RWE can adequately answer the research question posed. Additionally, policies published by EUNetHTA[24], ICER[25] and ISPOR[26], appear to require more comprehensive details on the research question than regulatory policies.

4.4.2. Choosing a study design

There is consensus within HTA and regulatory documents on the principles of choosing a rigorous study design justified for the research question, developing a study protocol that involves design details, and engaging stakeholders early in the process. Almost all the documents stated the superiority of randomised clinical trials for establishing casual relationships. When guidance is provided, the focus is on the justification for conducting an RWE study instead of a clinical trial rather than providing guidance on preferred designs of RWE studies.

The regulatory documents provided several recommendations. They expressed a preference for prospective observational studies over retrospective ones. They also frequently recommended early engagement with regulatory authorities when possible. Some also suggested conducting feasibility assessments and pilot studies to ensure the data quality is sufficient for the intended study design.

HTA guidelines offered slightly different advice. They did not include a preferred study design but noted that the chosen design should be explicitly justified based on the study's objectives. For objectives aimed at understanding routine practice, observational studies that incorporate methods to address potential biases were prioritized. HTA guidelines also recommended initiating early discussions among developers, payers, and regulators to agree on suitable study designs.

4.4.3. Analytical methods

This category examined the guidance on analytical methods and bias mitigation strategies across reviewed documents. Most regulatory documents suggested pre-defining an analytical or statistical analysis plan within the study protocol. This ensures clarity and transparency in how data will be analyzed, and biases addressed

before data collection begins. For instance, the US FDA emphasized the importance of submitting these documents for review prior to finalisation, while Japan's PSEHB highlighted the need for clear extraction conditions to avoid arbitrary data selection.[12]

Despite the variability in detail, there was clear agreement on the importance of a structured analytical approach to address potential biases and confounding. This was particularly evident in documents from both regulatory and HTA bodies, with no significant distinction in the suggested standards or methods. Both EMA [21,27] and NICE[23] recommended their own guidance on missing data and confounding, respectively, and there is also some wider alignment on the use of tools like the ROBINS-I checklist. A more unified approach to analytical tools and methodologies could further strengthen the guidance provided across organizations.

HTA documents also described the necessity of documenting analytical plans and bias mitigation measures. However, detailed methodological guidance, such as that provided by NICE[23] and IQWiG[20], delved into specific strategies like direct adjustment and propensity score matching. The US FDA and EMA offered broader guidance, acknowledging the variability in appropriate analysis methods and the importance of tailored advice.

4.4.4. Interpretation of results

This category was exploring whether the documents reviewed contained any reference or guidance on how RWE results should be interpreted or used (i.e., how the evidence should be used to make decisions based on it). There did not appear to be any major discernible difference between HTA and regulatory guidance.

Several documents made the general recommendation to provide relevant information to aid in interpreting study results. The Canadian Agency for Drugs and Technologies in Health (CADTH)'s guidance[29] stood out for its comprehensive advice, highlighting the need to summarize key findings, cautioning against drawing causal inferences from associations, and recommending a thorough interpretation that considers the study's goals, limitations, and the broader evidence context. It stressed the differentiation between clinical and statistical significance and the assessment of adverse event implications. There is consensus on addressing study limitations, the necessity of sensitivity analyses for accurate interpretation, and including caveats related to analytical assumptions and missing data. Agencies like the US FDA and TGA also noted the complexities that can obscure results' interpretation, especially concerning health equity.

Involvement of diverse stakeholders, including patients and field experts, in result analysis and dissemination is advocated to ensure comprehensive interpretation (e.g., NICE[23], ICER[30], OHE[36]). However, the responsibility for interpreting results lies with decision-makers or sponsors, indicating the need for a critical evaluation of RWE's relevance and credibility (ISPOR[31], NMPA[32]).

In its guidance, TGA[14] highlighted challenges in interpreting results of studies for medical devices that used RWD sources. TGA specifically pointed out that RWD might lack the detailed information necessary for accurately capturing key safety and performance endpoints, as well as identifying the specific medical device under evaluation. This limitation can obstruct reliable conclusions about a device's performance and safety.

Key Findings

- There is consensus between regulatory and HTA policies on the need for robust study design and methods when using RWD.
- Some policies recommend frameworks for study design (e.g., PICO, PICOTS or PIRO).
- HTA documents are more likely to recommend specific types of analytical methods, and justification of choice of method is often required.
- Specific analytical methods for medical devices may be required.
- There is a lack of explicit discussion on interpretation of results in most documents.

4.5. Data collection, curation, and characterization

4.5.1. Data collection

Data collection refers to the systematic approach to gathering data for a specific purpose from various sources, which can include the design of collection tools, methodologies for data acquisition, and the identification of data sources. This process is crucial for ensuring that the data are relevant, accurate, and comprehensive for its intended use.

The analysis of regulatory documents on data collection reveals a consensus on several key points and current guidance aimed at ensuring the reliability, validity, and integrity of data within clinical and regulatory settings.

- Emphasis on structured methodologies and data quality: Regulatory documents underscored the importance of employing structured methodologies in data collection to uphold data quality. The guidance was oriented towards ensuring that data collected are not only accurate but also reliable and consistent across different studies and contexts. For instance, the EMA and the US FDA highlighted the necessity of standardised data collection protocols that are rigorously followed to minimise variability and bias in data.
- Importance of detailed documentation: A recurring theme in the regulatory documents was the importance of detailed documentation of the data collection process. This included clear descriptions of the methods used for data collection, the rationale behind the choice of methods, and the procedures in place to ensure data quality and integrity. Such detailed documentation is crucial for regulatory review and approval processes, as it provides transparency and facilitates the assessment of data reliability.

HTA documents focused on the systematic and standardized methodologies necessary for the collection of data that support the assessment of health technologies. Documents from Canada, Germany, and the international community detailed the need for transparent data handling practices and the importance of data integrity in HTA. These documents discussed the challenges associated with integrating diverse data sources, emphasising the need for clear guidelines and standards to ensure that the collected data are robust and comprehensive, supporting evidence-based healthcare decisions.

The analysis revealed a consensus on the critical role of data collection, with regulatory documents generally providing more detailed guidance compared to HTA documents. Notable differences emerged in the emphasis on data quality and methodological rigor, reflecting varying requirements across regulatory and HTA contexts. The documents did not explicitly address differences between medicines and medical devices, indicating potential areas for further guidance development.

Key Findings

- There is a consensus on the necessity of detailed documentation of the data collection process, including clear descriptions of methods used, rationale behind method choices, and procedures for ensuring data quality and integrity.
- While there is overlap in requirements for data collection, given the differences between the evidentiary needs of regulators and HTA agencies, there are divergent requirements.
- There appears to be a preference for prospectively designed RWD sources such as registries.
- RWD sources (e.g., medical records and claims) that are primarily collected for purposes other than research are seen as more problematic given their heterogeneity across health systems and providers.

4.5.2. Data extraction and curation

Data extraction and curation involves the process of retrieving relevant information from collected data and preparing it for analysis. This includes data cleaning, transformation, and harmonisation to ensure it meets

quality standards for analysis. Curation may also involve the annotation and integration of data from diverse sources to make them usable for specific research or decision-making processes. These components play a central part in establishing the provenance of the RWD and ensuring that it has not been mismanaged (see Data Provenance section below).

Approximately half of the documents provided insights into data extraction and curation processes. Of these, most were regulatory documents from organizations across Europe, Japan, USA, Canada, International, UK, China, Australia, and South Korea. The remaining include HTA documents originated from Canada, Germany, UK, Europe, and Asia, and third-party organizations.

Regulatory documents offered comprehensive guidance focusing on ensuring data integrity, quality, and reliability essential for regulatory compliance and decision-making. For example, the EMA's 2023 document detailed the necessity of rigorous data quality assessment protocols across evidence generation processes.[11] It emphasized systematic approaches to data management, ensuring that data utilised in regulatory submissions uphold the highest standards of accuracy and reliability. Similarly, the US FDA's[33] guidelines provided insights into leveraging existing datasets for retrospective studies, highlighting the critical importance of meticulous data curation practices to mitigate biases and enhance the validity of research findings.

HTA documents underscored the critical role of data extraction and curation in evaluating medical interventions and health technologies. CADTH's 2023 guidance[29], for instance, outlined detailed processes for data cleaning and validation, reflecting the stringent requirements for data quality in health technology assessments. These documents often discussed the challenges of integrating diverse data sources and emphasized the need for transparent and standardised data handling methodologies to support evidence-based decision-making.

The analysis revealed a consensus on the importance of data extraction and curation across regulatory and HTA documents, with regulatory documents generally offering more detailed guidance. Key similarities included the emphasis on data quality and the use of standardised methodologies. However, the scope and detail of guidance varied by region and organization, reflecting different regulatory environments and data management practices. Notably, the documents did not explicitly address the unique challenges associated with medical device data versus medicines. Gaps identified included a lack of specific guidance on handling novel data types and emerging data sources, underscoring the need for ongoing updates to regulatory and HTA guidelines to accommodate advances in data generation and analysis technologies.

Key Findings

- Regulatory and HTA documents consistently emphasize the importance of maintaining data integrity and quality throughout the extraction and curation processes.
- There is a recurring theme of advocating for standardized methodologies in data extraction and curation to ensure consistency and reliability across different processes and studies.
- Transparency in data handling practices is highlighted as essential, particularly in HTA documents.
- Processes for data validation and cleaning are consistently emphasized, underscoring the need to ensure the accuracy and reliability of datasets used in regulatory submissions and health technology assessments.
- There is a lack of specific guidance on handling novel data types and emerging data sources.

4.5.3. Data linkage

Data linkage refers to the methods and technologies used to connect data elements from different sources, enabling the integration of diverse datasets for comprehensive analysis. This process involves matching

records that relate to the same entity across different databases, often requiring sophisticated algorithms to ensure accuracy and privacy preservation.

Regulatory documents underscored the importance of data linkage in enhancing the regulatory oversight of medicines and medical devices. Notably, the EMA's "Good Practice Guide for the use of the Metadata Catalogue of Real-World Data Sources"[27] provided detailed guidance on data linkage practices to enhance the utility of RWE in regulatory evaluations.

HTA documents collectively emphasized the strategic importance of data linkage in conducting comprehensive health technology assessments. For instance, CADTH's 2023 guidance underscored the need for transparency in stating whether studies involve linked data, reflecting a broader trend towards ensuring the validity of HTAs through robust data linkage practices.[29] Similarly, IQWiG[34] and ISPOR[35] addressed the methodological challenges in using data from various sources, advocating for precision and methodological integrity in data integration. This focus on methodological rigor is crucial for the accuracy of HTA findings, as further highlighted by NICE's real-world evidence framework, which pointed to the essential role of thorough data linkage.[23]

Additionally, OHE delved into the prerequisites for successful data linkage, emphasising data standards and governance as key elements.[36] This underscores the necessity for established protocols and ethical considerations in the use of linked health data, underlining the nuanced approach HTA bodies take towards maximising the potential of data linkage.

Regulatory documents, particularly from the EMA, detailed the methodologies and standards required for effective data linkage, aiming to ensure data integrity and support regulatory decision-making. HTA documents, seen in the guidance from CADTH[29] and NICE[23], underscore the significance of data linkage in evaluating health technologies, focusing on methodological rigor and the impact of linked data on outcomes assessment. Together, these documents reflect a comprehensive approach to leveraging data linkage in health data management, emphasising the need for continued innovation, ethical data use, and international collaboration.

Among the documents reviewed, the EMA documents stood out for providing detailed guidance on data linkage, particularly in identifying suitable data sources for RWE studies. This contrasted with other documents that offered minimal or no specific details on data linkage practices, indicating a disparity in the depth of coverage across the dataset. The areas of data standards, technological advancements, and ethical considerations generally received good coverage, whereas explicit methodologies for data linkage and integration challenges are less comprehensively addressed.

The current guidance on data linkage revealed gaps, particularly in the explicit detailing of methodologies and in addressing the practical challenges of integrating diverse data sources. There's an implied need for more comprehensive frameworks that not only address data quality and privacy concerns but also provide clear instructions for executing data linkage in varied research and regulatory contexts.

Key Findings

- Common themes include the need for detailed descriptions of data linkage processes, transparency regarding data sources, and methodologies used for linkage. Ensuring data integrity and protecting patient privacy are universally emphasized.

- While all guidelines stress data integrity and transparency, the level of detail and specific requirements vary. Regulatory bodies tend to focus more on the scientific validity and regulatory compliance aspects, while HTA agencies and third parties may emphasize practical considerations for data use in healthcare decision-making.
- Regulatory guidelines, particularly from bodies like the US FDA and EMA, provide the most detailed requirements, including specific methodologies for data linkage, validation processes, and the handling of heterogeneity across data sources.

4.5.4. Common data models

Data standardization, a key process for harmonizing data into a universal format, is crucial for enabling cooperative research, extensive analytics, and the exchange of advanced tools and techniques. This process is particularly important in healthcare, where data collection and storage methods vary significantly across organizations and countries. Despite efforts to standardise terminology, concepts can differ widely from one healthcare setting to another. The adoption of a common data model (CDM) by converting disparate databases into a uniform format, can facilitate data sharing, integration, and analysis by ensuring that data from varied sources can be compared and combined effectively. This approach promises the rapid and effective examination of large datasets from multiple sources to identify and assess potential drug safety risks. CDMs are standardised frameworks or schemas for organising, structuring, and storing data that enable consistency in data format and terminology across different studies or databases. CDMs facilitate data sharing, integration, and analysis by ensuring that data from varied sources can be compared and combined effectively.

Regulatory documents emphasized the critical role of CDMs in ensuring data harmonisation and quality. The EMA, through its "Guideline on registry-based studies"[21], mentioned the Observational Medical Outcomes Partnership (OMOP) model, highlighting the significance of standardised data collection frameworks to enhance interoperability and analysis across Europe. Similarly, the US FDA focused on leveraging CDMs to streamline data integration, ensuring that health data from diverse sources can be effectively combined and analysed. These documents collectively advocated for the adoption of CDMs to facilitate more efficient review processes and cross-border cooperation in safety monitoring and post-market surveillance.

HTA documents presented a spectrum of perspectives on the use of CDMs. CADTH (29) provided practical guidance on data cleaning and linkage, underlining the necessity for clear methodological practices. Meanwhile, IQWiG expressed reservations about forming a ‘common data pool’ when analysing several registries.[20] Instead, it suggested using identically designed studies in the individual registries and then summarizing these studies meta-analytically. NICE and other HTA bodies discussed CDMs in the broader context of data quality and integrity, indicating a cautious but open approach towards their use in health technology assessments.

Contributions from international task forces, such as the ISPE-ISPOR, stressed the importance of reproducibility and data sharing. They recognised the potential benefits of CDMs in standardising practices but also note the challenges in ensuring data integrity and relevance.

The analysis revealed a broad consensus on the potential benefits of CDMs, though perspectives varied significantly between regulatory, HTA, and other documents. Regulatory documents tended to emphasize harmonisation and international collaboration, while HTA documents showed a more varied approach, reflecting concerns about methodology and data quality. Third party documents contributed valuable insights into reproducibility and the challenges of data integration. Key differences emerged in their approach to data quality, recommendations of CDMs, and data linkage practices. Regulatory documents often emphasized harmonisation for data integrity and to increase the suitability of the data for regulatory review, occasionally suggesting specific CDMs like OMOP for broad interoperability. HTA documents, while valuing data quality, focused more on the data relevance and methodological rigor required for health technology assessments,

often discussing CDMs' benefits and challenges without offering firm recommendations. These distinctions highlighted varied perspectives on the utility and implementation of CDMs in health data management.

Key Findings

- While not universally recommended, several guidelines mention the use of CDMs as a potential approach for standardizing data.
- No documents advocate for a specific CDM, however some included examples, such as the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) and the Sentinel Common Data Model.
- Most notably, IQWiG expresses reservations about forming a 'common data pool' when analyzing several registries. Instead, it suggests using identically designed studies in the individual registries and then summarizing these studies meta-analytically.

4.5.5. Data characterization

Data characterization, or metadata, aims to identify the strengths and weaknesses of original data sources, covering aspects such as the purpose of data collection, site types, data types (e.g., administrative claims, clinical notes), and patient demographics. This information is critical for evaluating data suitability for study questions, supporting study protocol development, and contributing to findings' relevance and reliability assessments. A positive finding was that there is movement toward the standardization of documentation such as resources like the EMA's Metadata catalogue[27], guidance on submission in the NICE RWE framework[23], and recent guidance from US FDA[10], and South Korea[15] (e.g., tables, and checklists).

Most of the documents in both HTA and regulatory categories broadly defined RWD sources. Several provided information on the types of information and assessment needed to characterize the strengths and weaknesses for specific types of data sources. For both medicines and devices, there was more information on the use of data from pre-specified RWD sources such as disease, patient, or product specific registries. Some policies were specific to other RWD sources such as EHRs and claims. There appeared to be a gap or lack of guidance on other sources, such as patient-generated health data (e.g., apps, wearables, monitors), device-generated data, and complex data sources such as radiographic images and video.

However, even in documents with minimal descriptions, it was noted that submissions would be expected to include information on the RWD sources such as the data standards, quality check procedures, whether the data were collected prospectively or retrospectively, and traceability.

Key Findings

- Generally, there was significant overlap in the concepts of data source characterization, data collection, and the general assessment of data relevance and reliability.
- There appears to be movement toward standardization of how these components are documented for submission to decision-makers.
- Current guidance on less well understood RWD sources such as patient-generated health data, device-generated data, and complex data types such as images is limited.

4.6. Data quality assessment

The use of data of suitable quality in RWD studies is one of several considerations that are fundamental to engendering trust and credibility in the resulting RWE. Across the different policies, the concepts of data quality

were highlighted. However, there is variation in how it was described and defined. The US FDA described fit-for-purpose assessment of the RWD as an evaluation of both the relevance and reliability with the key criteria comprised of various components such as accuracy, timeliness, representativeness, etc. While definitions of relevance and reliability were the two key data quality criteria assessed in this review, there are multiple parameters and assessment tools that can be considered for evaluating data quality.

Regulatory authorities/bodies have published more documents than HTA bodies and the regulatory documents tended to be more detailed than HTA. The most comprehensive regulatory bodies were EMA and US FDA, both in the context of medicines. For HTA agencies, NICE and HAS have also published extensively with their guidance applying to medicines and medical devices. ISPOR also stood out as providing a detailed perspective with multiple documents. Across regulatory and HTA bodies, there was more guidance on data quality in documents for medicines than those for medical devices.

Across different documents, similar topics were discussed but the level of detail varied (e.g., NMPA's medical device guidance[62] defines key elements of data but does not elaborate on these). Several documents referred specifically to data relevance (e.g., EMA, US FDA, Health Canada, NMPA, TGA, MFDS, ISPO, ICER, HAS, NICE, and NESTcc). Similarly, several referred specifically to data reliability (e.g., EMA, US FDA, Health Canada, NMPA, TGA, PSEHB and ISPOR). Nevertheless, while several documents did not cite these terms specifically many included references to individual aspects of relevance and reliability. The EMA data quality framework[11] outlined a comprehensive framework of five dimensions (reliability, extensiveness, coherence, timeliness, relevance) and 16 sub-dimensions.

A limited number of organizations referred to quality in the context of a feasibility study in their guidance (e.g., EMA, MHRA, IMI, and Health Canada). While both EMA and US FDA had guidance on quality related to registries, EMA also included extensive description of aspects of quality related to a study based on registries. US FDA's guidance[10] noted that when used in regulatory submissions, patient-level data should be submitted to US FDA in accordance with applicable legal and regulatory requirements and that specific provisions apply where such data are owned by a third party. The MHRA[41] reflected on the use of digital health technologies (such as wearable devices, mobile applications, etc) to collect data during routine clinical care but relevance of measurements should be considered when adopting this approach. US FDA also noted the limitation of EHRs as these may not be sufficiently comprehensive.

The review found two organizations, EMA[11] and NESTcc[43] that published data quality frameworks. EMA's framework is agnostic to data type but indicated that they will shortly publish an annex to the framework that is specific to RWD. This annex was not available at the time of this review, however.

Some policies have indicated that they are influenced by other organizations' approaches. For example, TGA[14] indicated that its approach for data quality is similar to that of the US FDA. ISPOR noted the possibility of data qualification or accreditation and EUNetHTA's tool[24] evaluates registries and quality standards. Additionally, EMA has available the option of qualification[11] that would include addressing the suitability of a given data source for a particular context of use.

Key Findings

- There is no clear consensus amongst regulatory authorities or HTA bodies regarding expectations for demonstrated quality; with variability around the quality related parameters that are discussed.

- There is a trend towards the need for data to be "fit for purpose" and/or reflect the intended use but little guidance on how that will be assessed.
- "Reliability" and "relevance" and/or related elements are key quality parameters with several related components defined, such as accuracy, timeliness, and representativeness.
- Feasibility studies can include evaluation of data quality.
- Monitoring and alignment of data quality standards for the EHDS will be important in Europe.

4.7. Ethics, governance, trust, and transparency

There are established policies, standards and procedural steps built throughout the traditional clinical studies process to ensure transparency and establish trust in the research and its findings. Currently, there are not a similar set of broadly accepted policies for RWE studies. Without these types of policies there are decision-maker concerns about the potential for inaccurate, biased and in some cases, fraudulent research being used to support important public health decisions. For the purposes of this analysis, the information extracted from the policies has been roughly broken up into the following categories.

4.7.1. Pre-specified protocols

Several of the documents recommended that the development and communication (e.g., posting and/or registering) of study protocols be done prior to conducting the research. It is generally agreed that "transparency in what researchers initially intended to do protects against data dredging and cherry picking of results."[31] Accordingly, the majority of the policies stipulated that an a priori protocol be developed. Of those, the majority also recommended registration of the protocol, with some including specific registries (e.g., HARPER, ClinicalTrials.gov, ENCePP European EU-PAS registry, China Clinical Trial Registry, PROSPERO, World Health Organization's portal) depending on the country/region of the authoring organization. Though less commonly documented in the policies, there were also additional requirements about documentation of deviation from or amendments to the protocol.

4.7.2. Publishing requirements

Our analysis also looked for any stated expectations on publishing study results, as well as additional information on recommended practices (e.g., checklists, standards), and recommendations to share specific methods/codes used in the analysis to support replication of results. About half of the policies had expectations regarding the publication of the study. The minimum requirement was that the study be published, while some discussed additional details about the publication of studies (e.g., favorable or unfavorable, significant or insignificant). Some of the more detailed documents included criteria about publishing the analytical code. On this point, ICER noted that "some manufacturers have raised the concern that sharing of analytic code could constitute a "transfer of value" to payers raising regulatory scrutiny, and efforts are needed to clarify this point in order for true collaboration in sharing code between manufacturers and payers to proceed."[30] There was not clear consensus on preferred models of publishing (e.g., peer reviewed, white paper).

4.7.3. Research procedures

Recommendations were made on the different phases of the study such as the timing of data collection and analysis (e.g., multi-phase study approach), external validation or review expectations, use of standardized reporting tools and restrictions on use/applications of secondary analyses. It is noteworthy that a relatively small number of documents included specific methods or criteria for evaluation that could be used to support transparency. An example was a two-phase approach using independent experts to balance the propensity models and then a second phase for the statistical analysis noted in the recent US FDA CDRH[10] guidance. Another approach included in a few documents addressed restrictions on the use of and the criteria to describe and present any unplanned analyses performed secondarily (not defined a priori).

4.7.4. Stakeholder communication

Policies regarding stakeholder communications typically included discussions with reviewing organizations (e.g., regulatory authorities, HTA agencies) during any phase of the research (prior to, during, after completion and during review). However, we found that some policies also recommended communications with other key stakeholders such as clinicians, providers, and patients.

Several of the regulatory guidance encouraged engagement between study sponsors and regulators throughout the process. Of these, a few included specific guidance on which processes to use within the current regulations for communications. For example, the US FDA CDRH[10] notes the pre-submission meeting process as the point of communication.

Some of the documents included specific statements recommending the inclusion of key stakeholders in the process. For example, a recommended best practice was to "include key stakeholders (e.g., patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, and manufacturers) in designing, conducting, and disseminating the research."[31]

4.7.5. Data provenance

Data provenance seeks to ensure transparency in RWD use by detailing the data's origin, including its capture process, quality assurance, and governance. It also involves documenting how data were transformed for research, focusing on extraction methods and curation. Notably, not all documents used the term data provenance. Some of the documents included examples which could be used to identify, refine, and promote broader adoption of best practices.

A prevalent concern was the perception that the use of RWE might lower the scientific and evidentiary standards. Documents from regulatory bodies such as the US FDA emphasize the need for RWE study protocols to match the rigor expected of traditional clinical studies and RCTs. This approach aims to tailor RWE studies to meet the required evidentiary standards, improving RWE study quality and reducing the potential for biased outcomes.

Organizations such as ISPOR, ISPE, Duke-Margolis Center for Health Policy, and NESTcc are proposing approaches to bolster trust through transparency in RWD-based research. These include mandating the publication of study protocols, detailed documentation of operational decisions, and broader dissemination strategies. Despite these efforts, some organizations cautioned against industry-sponsored registry ownership, advocating for healthcare providers or patients to maintain registry control to ensure unbiased data availability. NICE have also developed the Data Suitability Assessment Tool (DataSAT) to help the consistent and structured presentation of data suitability at the point of assessment.[23]

4.7.6. Data governance and ethics

Data governance can be defined as a strategy for the overall management of the usability, availability, integrity, quality, and security of data to ensure their maximum potential. As in clinical research, effective data governance is vital for any real-world research because it ensures that data is consistent and trustworthy. However, a 2023 EUreccA (European initiative of new Reimbursement and aCCess Approaches) report[39] noted that there is a lack of consensus on appropriate data governance practices for RWD/RWE. The report also recognized that the overall trust in RWD is still limited, especially regarding data management, despite the progress that has been made in improving the reliability of the data. Therefore, an effective data governance strategy is necessary to increase confidence in RWD/RWE for regulatory and HTA decision-making.

The key data governance criteria assessed in this review were informed consent processes and considerations, data privacy, and data access and sharing policies. Additional considerations that are relevant to data governance, including data collection, linkage, and transparency, are covered in other sections of this review. Most of the discussions around data governance in both the regulatory and HTA documents were high-level and focused on documentation and reporting requirements. HTA documents tended to provide more detailed guidance. The documents did not explicitly address differences between medicines and medical devices, indicating potential areas for further guidance development.

Key themes that emerged included the protection of personal data, informed consent, transparency and documentation of data governance processes and procedures, ethical oversight, and adherence to good clinical practices. In documents specifically relating to registries the general principles of data governance were underpinned.

The two themes with the greatest consensus related to the protection of personal information and informed consent. Regarding the protection of personal information, the documents emphasized the importance of the ethical use of data and compliance with data privacy and data protection laws. Consultation with experts on data privacy issues during study design was recommended(44) to ensure compliance (e.g., appropriate use of deidentification mechanisms).(19)

The issue of consent was repeatedly mentioned across documents. Informed consent was emphasized in regulatory documents.(19) The MHRA explicitly stated that "patient consent is required before enrolment."(41) NMPA(18,32) advised that ethical review and informed consent for real-world research must be in accordance with various regulations and guidelines including the World Medical Assembly Declaration of Helsinki.(61) NICE's guidance(23) emphasized consent but qualified this by stating that it must be provided 'when appropriate', and the OHE(2) and CADTH(29) discussed consent 'and/or alternative legal bases according to the intended use' highlighting the varied nature of consent mechanisms.

The two other data governance themes that were less common, but notable, were ethics body oversight and good clinical practice (GCP). Several countries' regulatory agencies, including the US FDA, Health Canada, and NMPA, provided recommendations for ethics bodies to oversee research involving RWD. Regarding the use of good clinical practice, US FDA noted that conducting "a clinical investigation in accordance with GCP provides assurance that the data and results from the clinical investigation are credible and accurate and that the rights, safety, and well-being of subjects are protected." (10) Although the term GCP was not seen in many of the documents, many of the underlying components were included and work is being done to expand the application of GCP by third party organizations (ISPOR(26), ISPE(38)).

Key Findings

- Policies reflect underlying concerns and skepticism about the quality of RWE studies and the potential for biased findings.
- Communication between sponsors and decision-makers throughout the research process is encouraged and could be a mechanism to support transparency.
- There is not a clear set of expectations regarding level of granularity in publication, and concerns about intellectual property could create challenges.
- Third party organizations are developing tools, templates, and processes that could become a standard for "good research practices" specific to RWD and RWE.
- Data set characterization and provenance extraction focused on the documentation of how the research data set is derived from the original data sources and is the foundation for the assessment of data relevance and reliability and also in establishing good research practices.
- In both regulatory and HTA documents, the discussions of data governance were high level and related to processes and procedures.

- The two themes with the greatest consensus in both regulatory and HTA documents related to the protection of personal information and informed consent, with HTA documents, especially from UK's Office of Health Economics, generally providing more detailed guidance compared to regulatory documents.
- Other data governance themes that were less common, but notable, were ethics body oversight, data sharing, and data access.

4.8. Intersection of RWD/RWE and artificial intelligence

AI is an interdisciplinary field encompassing computer science, statistics, and engineering, focused on creating algorithms and models capable of learning, decision-making, and predicting outcomes. Machine Learning (ML) is a subset of AI and involves training algorithms to develop models through data analysis, rather than through direct programming. For this review, AI and ML specific guidance's were out of scope, however, RWD is frequently used in the development, training, retraining, and ongoing validation of AI and ML applications. There is also emerging research seeking to use AI to extract key clinical data elements from unstructured data sources (e.g., EHR clinical notes) to support RWE studies. Given these intersections, we examined if and how the RWD and RWE specific policies included in this review addressed these topics. Despite the very few documents in the review that discussed AI in any detail, they collectively underlined AI's potential role in tackling challenges such as extracting data from unstructured sources, and bolstering data analysis and predictive modelling.

The challenge of extracting high-quality data from unstructured sources such as free-text notes in electronic patient records is significant. IQWiG[20] highlighted the difficulty in employing text-mining applications and natural language processing (NLP) tools for automatic data extraction, pointing to this as a considerable obstacle in the near term. The ISPOR task-force report[35] further elaborated on the extensive labour and resources required to transform unstructured information into analysable data, noting that the involvement of trained clinical experts following standardised protocols remains the gold standard. However, the ISPOR task-force report [35] also acknowledged the increasing role of NLP, ML, and AI as complementary or alternative solutions to manual abstraction, anticipating significant advancements in converting unstructured EHR information into analysable data due to the rapid advancement of these technologies.

Various regulatory and HTA agencies have recognised the potential of AI methods, such as ML and neural networks, to supplement clinical trial results and predict health technology effects in new contexts. HAS[42] discusses the possibility of extending the applicability of clinical findings to broader populations through AI. NESTcc[40] and MFDS[15] see AI-enhanced RWE as critical for verifying the safety and performance of medical devices. ANVISA[44] highlights the utilisation of data-driven methods, including machine learning algorithms, for selecting study covariates, merging traditional clinical knowledge with modern data analytics to refine research designs and outcomes.

Regarding AI products, HTAi[63] and TGA [14] discussed the integration of real-time data with AI, stressing the need for the data (including RWD) used in AI products to be representative of the target population to avoid algorithmic bias.

Additionally, the role of DHTs in the health ecosystem may enable them to generate more granular patient-generated health data (PGHD) that could be harnessed for research. PGHD is seen as a potential mechanism to better engage patients and reduce burden to generate meaningful data outside the traditional clinical setting. PGHD is cited in some policies as a source RWD (e.g., TGA[14] and the US FDA CDRH[10]).

Key Findings

- Few organizations provided guidance surrounding the use of AI in the extraction and analysis of RWD and generation of RWE.

- The most promising area of use is likely to be in extracting data from unstructured sources like electronic patient records, which currently poses a significant challenge and is where improvements could be made with AI's rapid advancement.
- AI methods could potentially be used to support enriching clinical trial populations and extending findings to broader populations, as well as being used for safety verification and research design optimisation.

5. Discussion

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

5.1. 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 4.3) 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 Figure 1) 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.

5.2. Emerging best practices

5.2.1. 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.

5.2.2. 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.

5.2.3. 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.

5.3. Possible gaps for further exploration

5.3.1. 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.

5.3.2. 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.

5.3.3. 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.

5.3.4. 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.

5.3.5. 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.

5.3.5.1. 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.

5.3.5.2. 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.

5.3.5.3. 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.

5.4. 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.

5.5. 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.

6. 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.

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Appendix

Appendix 1 – Search strategy

Database: MEDLINE ALL

1 *Electronic Health Records/ (15967)

2 exp *Registries/ (29613)

3 (("Real world" or registry or electronic health* record or EHR or claim or claims or "patient generated") adj2 (evidence or data or study or studies or research or trial*)).tw. (78847)

4 ("heterogenous data" or "heterogeneous data").tw. (1897)

5 (routine* adj3 data).tw. (13700)

6 (RWE or RWD).tw. (1062)

7 or/1-6 (133840)

8 exp *Technology Assessment, Biomedical/ or *Comparative Effectiveness Research/ (8670)

9 (regulator* or "technology assessment" or HTA or "comparative effectiveness research" or cer or payer or payor).tw. (738766)

10 or/8-9 (743561)

11 exp Guidelines as Topic/ (172755)

12 st.fs. (767179)

13 policy/ (8557)

14 Checklist/ (8606)

15 (standard* or policy or policies or framework* or policy or policies or approach* or guidance or guideline or guidelines or advice or checklist* or "check list*" or template* or design* or "best practice*").tw. (6375178)

16 or/11-15 (6898191)

17 7 and 10 and 16 (2138)

18 animals/ not humans/ (5097865)

19 17 not 18 (2123)

20 limit 19 to yr="2018 -Current" (1245)

Appendix 2 – Extraction template

Field Name	*Description*
Initial data extracted by and date	
Reviewed by (initials)	
Title	
Author	*Include centre if relevant e.g. FDA CDRH, but not country*
Year	*Year of publication*
Country/Geographical region covered	*Geographical areas covered by document, write 'not specified' if not clear*
Regulatory/HTA/Both/Other	*Select one of: Regulatory, HTA, Both, Other*
Medicine/MedTech/Both/Other/ Unclear	*Does document relate to Medicines, Medtech or both*
Document type (organizational policy/framework/white paper etc…)	*Suggested fields are:* *-Organizational policy/guideline* *-RWE initiative guidance*
URL	*Link to document*
Document Aim/Purpose	*Include any aims written in the document, or if none summarise aims yourself*
Document scope	*What areas does the document cover- what settings, what are the major areas covered*
Overall position on RWE/RWD source	*Summary of position taken on use of RWE/data source by authors, try to summarise if not explicitly stated*
Definitions of heterogenous data /RWE/RWD	*Provide any definitions given. If definitions have been sourced from elsewhere include details of original reference(s) e.g. have used ISPOR definitions*
Provides recommendations for when RWE should be used?	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details for when RWE is recommended for use	*Areas or uses that have been identified as suitable for use of RWE*
Provides examples for when RWE should not be used?	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details of caveats/exclusions of use of RWE (when it should not be used)	*Areas or uses that have been explicitly stated as not suitable for RWE use*
Provides recommendations on research question?	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details of recommendations on research question	*E.g. do they mention use of a framework such as PICO to devise*
Provides recommendations on study design?	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details of recommendations on study design	*What considerations need to be taken into account when designing the study?* *Do they suggest specific study design types?*
Provides recommendations on data characterisation/provenance?	*Select one field* *-Detailed description*

	-Minimal description *-No description*
Details of recommendations on data characterisation/provenance	*Data set characterisation, where does data come from e.g. claims, large hospital etc.*
Provides recommendations on data collection?	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details of recommendations on data collection	*Who and how was the data collected for its original purposes /initial entry. What were the aspects of quality e.g. who entered it, were they trained, checks and balances on initial data entry, what was its original purpose?*
Provides information on assessing data provenance (detailed/minimum/no description)	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details on assessing data provenance	*Chain of custody - Can you identify where the original data comes from, and can we access that?* *Can you track data back to original sources?*
Discusses data extraction and curation processes?	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details of data extraction and curation processes	*Extraction protocol for use in study, curation is the clean-up*
Suggests use of Common Data Model- specify model(s)	*Yes/No (if yes, which?)*
Provides description on assessing data quality including relevance and reliability (detailed/minimum/no description)	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details of assessing data quality criteria- what criteria/parameters is data quality assessed against?	*Does it discuss reliability? Does it discuss relevance?*
Recommends analytical methods and ways of minimising bias	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details of analytical methods including ways of minimising bias suggested	*Are analytical methods to be used described and in what level of detail? Note any specific analytical methods suggested or if reference to other documents/sources, do not include full details of what analytical method entails* *State any areas of potential bias mentioned and what they state to do about it (if included)* *State any areas of potential bias mentioned and what they state to do about it (if included)*
Methods for minimising bias	*State any areas of potential bias mentioned and what they State any areas of potential bias mentioned and what they state to do about it (if included)* *state to do about it (if included)*
Discusses data linkage /data linkage capabilities (detailed, minimal, no description)	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details of Data linkage	*What are methods for data linkage?*
Transparency requirements (detailed, minimal, no description) such as	*Select one field* *-Detailed description*

protocol posting, IDE requirements, protocol changes etc	*-Minimal description* *-No description*
Transparency/ reporting requirements/expectations such as protocol posting, IDE requirements, protocol changes etc	*Details of transparency requirements/expectations in document Priori/during and post study*
Guidance on interpretation of results	*Does the document include any reference or guidance on how RWD/RWE results should be used/interpreted?*
Provides recommendations on data governance and/or ethical considerations	*Select one field* *-Detailed description* *-Minimal description* *-No description*
Details of data governance and ethical consideration information/recommendations	*Include any information/recommendations on data access & sharing policies* *Consent processes/considerations* *Ethical considerations*
Gaps, limitations or concerns noted	*Record any gaps, limitations or concerns about the RWE guidance noted by the authors e.g. this guidance does not cover xxx, further guidance is needed on xxx* *OR areas you have noted as being missing or limited*
Any other issues raised	*Capture any other issues of information relevant that has not been captured in previous fields*
Reviewers note	*This field is intended to capture any initial thoughts by the reviewer(s) as they extract the data which may not be explicitly captured by the data e.g. feelings on adequacy of document, where areas seem well developed or underdeveloped*

Appendix 3 – Included landscape review documents

#	Title	Author	Publication Date	Region	Issuing Body	Sector	Category
1	Real World Evidence and Patient Reported Outcomes in the Regulatory Context	TGA	2021	Australia	Regulatory	Both	Strategic Plans
2	Guidance on Real World Evidence: Considerations for Medical Device Regulatory Decision-Making (DRAFT)	TGA	2023	Australia	Regulatory	Medical Devices	Regulatory Guidance
3	Clinical Evidence Guidelines for Medical Devices	TGA	2023	Australia	Regulatory	Medical Devices	Regulatory Guidance
4	Best Practices Guide for Real-World Data Studies Guide No. 64/2023 – Version 1	Anvisa	2023	Brazil	Regulatory	Medicine	Regulatory Guidance
5	Elements of RWD/E Quality Throughout the Prescription Drug Product Life Cycle	Health Canada	2019	Canada	Regulatory	Medicine	Strategic Plans
6	Health Canada's Position on the CADTH Guidance for Reporting RWE to Support Decision-making	Health Canada	2023	Canada	Regulatory	Medicine	Strategic Plans
7	Guidance for Reporting Real-World Evidence	CADTH	2023	Canada	HTA*	Both	Regulatory & HTA Guidance
8	Guidelines for Use RWE Support Drug Development and Registration (Interim)_EN	NMPA - CDE	2020	China	Regulatory	Medicine	Regulatory Guidance
9	Guidelines for the Use of Real-World Data in Clinical Evaluation of Medical Devices (Interim)_EN	NMPA - CMDE	2020	China	Regulatory	Medical Devices	Regulatory Guidance
10	Guidelines for Real-World Data Used to Generate RWE (Interim)_EN	NMPA - CDE	2021	China	Regulatory	Medicine	Regulatory Guidance
11	Communication of RWE to Support Drug Registration Applications (Interim)_EN	NMPA - CDE	2023	China	Regulatory	Medicine	Regulatory Guidance

12	CDE Design and Protocol Framework of Real-World Studies of Drugs (Interim)_EN	NMPA - CDE	2023	China	Regulatory	Medicine	Regulatory Guidance
13	CMDE Guidelines for Registration Review of Design and Statistical Analysis of Real-world Studies of Medical Devices (Exposure Draft) _EN	NMPA - CMDE	2023	China	Regulatory	Medical Devices	Regulatory Guidance
14	Methodology for the Clinical Development of Medical Devices	HAS	2021	France	HTA	Medical Devices	HTA Guidance
15	Real-World Studies for the Assessment of Medicinal Products and Medical Devices	HAS	2021	France	HTA	Both	HTA Guidance
16	Concepts for the Generation of Routine Practice Data and their Analysis for the Benefit Assessment of Drugs According to §35a Social Code Book V (SGB V)1	IQWiG	2020	Germany	HTA	Medicine	HTA Guidance
17	Basic Principles on Utilization of Registry for Applications	PSEHB	2021	Japan	Regulatory	Both	Regulatory Guidance
18	Guidance on the Review and Approval of Digital Therapeutics	NIFDSE	2020	South Korea	Regulatory	Medical Devices	Regulatory Guidance
19	Guideline for RWE for Medical Devices	MFDS	2023	South Korea	Regulatory	Medical Devices	Regulatory Guidance
20	International Strategic Agenda 2020: National Health Care Institute	ZIN	2020	Netherlands	HTA	Both	Strategic Plans
21	Swissmedic Position Paper on the Use of Real-world Evidence	Swissmedic	2022	Switzerland	Regulatory	Medicine	Regulatory Guidance
22	NICE Real-World Evidence Framework	NICE	2022	England	HTA	Both	HTA Guidance
23	MHRA Guidance on the Use of Real-World Data in Clinical Studies to Support Regulatory Decisions	MHRA	2021	UK	Regulatory	Both	Regulatory Guidance
24	MHRA Guideline on Randomised Controlled Trials Using Real-World Data to Support Regulatory Decisions	MHRA	2021	UK	Regulatory	Medicine	Regulatory Guidance
25	NESTcc Methods Framework	NESTcc	2020	USA	Third-party (Regulatory)	Medical Devices	Regulatory Guidance
26	NESTcc Data Quality Framework	NESTcc	2020	USA	Third-party (Regulatory)	Medical Devices	Regulatory Guidance

27	Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry	US FDA	2021	USA	Regulatory	Medicine	Regulatory Guidance
28	Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry: Draft Guidance for Industry	US FDA	2021	USA	Regulatory	Medicine	Regulatory Guidance
29	Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry	US FDA	2021	USA	Regulatory	Medicine	Regulatory Guidance
30	Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products	US FDA	2023	USA	Regulatory	Medicine	Regulatory Guidance
31	Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. Draft Guidance for Industry and Food and Drug Administration Staff	US FDA	2023	USA	Regulatory	Medical Devices	Regulatory Guidance
32	A Framework to Guide the Optimal Development and Use of Real-World Evidence for Coverage and Formulary Decisions	ICER	2018	USA	HTA	Medicine	HTA Guidance
33	Real World Evidence for Coverage Decisions: Opportunities and Challenges A Report from the 2017 ICER Membership Policy Summit	ICER	2018	USA	HTA	Both	Strategic Plans
34	2020-2023 Value Assessment Framework	ICER	2020	USA	HTA	Both	HTA Guidance

35	Use of Real-World Data and Real-World Evidence to Support Drug Reimbursement Decision-Making in Asia	REALISE Working Group [2]	2021	Asia	HTA**	Medicine	HTA Guidance
36	Guideline on Registry-based Studies	EMA	2021	EU	Regulatory	Medicine	Regulatory Guidance
37	Good Practice Guide for the use of the Metadata Catalogue of Real-World Data Sources (DRAFT)	EMA; HMA	2022	EU	Regulatory	Medicine	Regulatory Guidance
38	Data Quality Framework for EU Medicines Regulation (DRAFT)	EMA; HMA	2022	EU	Regulatory	Medicine	Regulatory Guidance
39	Big Data for Better Outcomes: a Practical Toolkit for the Identification, Selection and Measurement of Outcomes Including in Real-World Settings	IMI	2018	Europe	Third-party (Both)	Both	Regulatory & HTA Guidance
40	The Registry Evaluation and Quality Standards Tool (REQueST)	EUNetHTA	2019	Europe	HTA	Both	Research Practices
41	International Harmonisation of Real-World Evidence Terminology and Convergence of 4 General Principles Regarding Planning and Reporting of Studies Using Real-World Data	ICH	2023	International	Third-party (Regulatory)	Medicine	Regulatory Guidance
42	Principles of International System of Registries Linked to Other Data Sources and Tools	IMDRF	2016	International	Regulatory	Medical Devices	Regulatory Guidance
43	Methodological Principles in the Use of International Medical Device Registry Data	IMDRF	2017	International	Regulatory	Medical Devices	Regulatory Guidance
44	Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making	IMDRF	2018	International	Regulatory	Medical Devices	Research Practices

45	Real-World Evidence in the Context of Health Technology Assessment Processes – From Theory to Action	HTAi Global Policy Forum	2018	International	Third-party (HTA)	Medicine	Strategic Plans
46	Real-World Evidence: Current Best Practice for Reimbursement Decision-Making	OHE	2023	International	Third-party (HTA)	Both	HTA Guidance
47	Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0	ISPE	2017	International	Third-party (Both)	Medicine	Regulatory & HTA Guidance
48	Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making.	ISPOR/ ISPE	2017	International	Third-party (Both)	Medicine	Regulatory & HTA Guidance
49	Harmonize Protocol Template to Enhance Reproducibility of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects: A Good Practices Report of a Joint ISPE/ISPOR Task Force	ISPE/ ISPOR	2022	International	Third-party (Both)	Medicine	Research Practices
50	Using Data from Electronic Health Records for Health Technology Assessment: An ISPOR Emerging Good Practices Task Force Report (DRAFT)	ISPOR	2023	International	Third-party (HTA)	Both	HTA Guidance

* CADTH is an HTA agency, however its guidance covers both HTA and regulatory

**The REALISE working group is a consortium of 11 Asian health systems working to create a framework guiding the use of RWE in drug reimbursement in Asia.