Updated ICH Reflection Paper

May 2024

Pursuing Opportunities for Harmonisation in Using Real-World Data to Generate Real-World Evidence, with a focus on Effectiveness of Medicines

Introduction

The role of real-world data (RWD) and real-world evidence (RWE) in supporting the evaluation of medicines across the different stages of their development and lifecycle is evolving [US Food and drug Administration (FDA, United States), Framework for FDA's Real-World Evidence Program (2018) and FDA, United States guidance Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (2023); Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making, Health Canada, Canada's 2019; Arlett et al., 2021; ENCePP Guide on Methodological Standards in Pharmacoepidemiology, latest version published].

In July 2022, the International Coalition of Medicines Regulatory Authorities expressed its strong support to strengthening international collaboration on activities to enable the use of RWE in regulatory decision-making [ICMRA, 2022]. This statement emphasises the engagement of regulatory agencies across the globe to address current gaps due to the lack of standardisation of RWD/RWE terminology and formats, the heterogeneity of RWD sources and data quality across RWD sources, and the various study designs used depending on the types of diseases, medicines (referred throughout as including drugs, vaccines, and other biologics), and regulatory contexts. Addressing these challenges should be supported by common definitions and best practices.

This Reflection Paper outlines a strategic approach for ICH to address some of these challenges. The goal is to further enable the integration of RWE into regulatory submissions and timely regulatory decision-making.

Main technical issues to be addressed

Recognising that traditional randomised controlled trials (RCTs) are foundational for generating evidence on safety and effectiveness,[1,2] other approaches including the use of RWD can generate evidence suitable for regulatory decision-making, e.g. to ascertain endpoints in point-of-care RCTs, or serve as a comparator arm in an externally controlled trial (including historically controlled trials) [US Food and Drug Administration (FDA, United States), Framework for FDA's Real-World Evidence Program (2018)]. RWD are also frequently used in non-interventional studies [FDA, United, States guidance on Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products (2023)], for example, to analyse the utilisation of an authorised medicine in routine medical practice, and to generate evidence that supports regulatory decisions on (long-term) post-marketing safety and effectiveness of medicines [Jonker et al., 2022; Flynn et al., 2022]. In addition, RWD can be used to better understand current treatment patterns, co-morbidities, and disease prognosis.

Nevertheless, several challenges exist, including the heterogeneity of RWD types (e.g., electronic health

[1] The principles presented in the reflection paper may also be relevant to clinical studies conducted for purposes other than the evaluation of medicines effectiveness, such as safety and utilisation studies.
[2] Although the terms "efficacy" and "effectiveness" are currently used differently across jurisdictions depending on the development phases of medicinal products, the term "effectiveness" is used in the context of this reflection paper.

records, registry data, claims data, longitudinal drug prescriptions, dispensing or other drug utilisation data, patient experience data, healthcare settings (e.g., primary/secondary/tertiary cares, self-treatable conditions), data source characteristics (e.g., purpose, population coverage, data elements, coding terminology, data privacy), levels of data quality and data validity, and a variety of governance models for data sharing and access [Bakker et al., 2022; Morton et al., 2016], emphasised by distinct or lack of national/regional laws and regulations. The suitability of RWD to generate adequate evidence to support regulatory applications currently requires a case-by-case analysis, which may be driven by different criteria related to the aforementioned factors and depending on the research question(s).

There are currently no internationally harmonised definitions of RWD and RWE.

- RWD has been defined by FDA, United States as "*the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources*", and RWE as "*clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD*. [US Food and Drug Administration (FDA, United States), Framework for FDA's Real-World Evidence Program (2018) and guidance on Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (2023)]".
- RWD has been defined in an EU-led publication as "*routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials*", and RWE as "*the information derived from the analysis of RWD*" [Cave et al., 2019].

Although these definitions (and others such as from learned societies, other regulators, etc.) are similar, the terms RWD and RWE are nonetheless used inconsistently and interchangeably [Concato et al., 2020; Concato & Corrigan-Curay, 2022; ENCePP, 2022; Rahman et al., 2023]. Applying different definitions may complicate efforts among regulators to track such data and evidence, causing potential confusion during communications among regulatory agencies, sponsors, and other interested parties, and precluding an understanding of exactly how and when RWD/RWE may be used to support regulatory decisions.

Recently published studies have attempted to measure the frequency of use of RWD/RWE in medicine approvals and the extent of use for decision-making [Flynn et al., 2022; Purpura et al., 2021; Eskola et al., 2021; Bloomfield-Clagett and Rahman et al., 2023]. Variable interpretation of definitions, heterogenous ways of describing and characterising RWD sources due to the lack of agreed metadata, and diverse methodologies used in these studies have led to a different estimated number of medicines' applications including RWD/RWE. While a significant and increasing proportion of marketing authorisations contain RWE, these observed discrepancies may lead to different levels of acceptance of what is considered to be RWD/RWE across jurisdictions.

Although the contribution of what is now called RWD and RWE has long been recognised for safety monitoring and disease epidemiology across medicines' lifecycles, their use to demonstrate effectiveness is more nascent. Additional work is needed for an in-depth analysis of the actual contribution of RWE to regulatory decision-making, why such information was not considered adequate in some cases, and how it contributed to the approval in other cases [Bakker et al., 2022; Bloomfield-Clagett and Rahman et al., 2023]. This work would also help complement existing recommendations to medicines developers on the submission of RWE (see the Annex including Regulatory Agencies guidance on RWD/RWE as well as the following publications [Simpson et al., 2022 (part 4); Kent et al., 2021; Griesinger et al., 2022; Simpson et al., 2022 (part 8); Jaksa et al., 2021; Angelis et al., 2018]).

National/regional laws and regulations can present challenges to convergence and harmonisation of terminology and convergence of guidance related to RWD/RWE. Reaching common understanding at international level on RWD/RWE definitions, including on a list of metadata, and on principles for structure and content of protocols and reports, would help clarify how RWD/RWE is being integrated into regulatory decision-making.

Objectives and potential benefits

The objectives of this Reflection Paper are:

- To engage ICH on convergence of terminology for RWD and RWE, on the format for protocols and reports of study results submitted to regulatory agencies throughout the lifecycle of medicinal products, and on promoting registration of protocols and reports;
- To inform the assessment of RWD and RWE for regulatory purposes.

The ultimate benefit of this work is expected to be higher quality of RWE that can substantively contribute to the body of evidence supporting the benefit and risk of medicines whilst maintaining evidentiary standards in regulatory decision-making.

The following stepwise harmonisation approach is proposed, with the scope and focus to be reassessed prior to initiating the work:

	Topic	Objective	Deliverables	Tentative timeframe
1.	**RWD/RWE terminology, metadata, and assessment principles**	• Promote a common understanding of the types and scope of RWD/RWE • Guide the discoverability, identification, and description of RWD • Inform the assessment of RWD/RWE for regulatory purposes	• Common operational definitions of RWD and RWE, with clear scope, breadth of potential RWD sources, and level of granularity (e.g., pertaining to RCTs and non-interventional studies)[3] • Core list and use of metadata • General principles for assessment of RWD/RWE	Submit new ICH topic proposal in Dec 2024
2.	**RWD/RWE protocol & report format, and study transparency**	• Agree on common principles regarding formats for RWD/RWE protocols and reports of study results submitted to regulators • Promote transparency by encouraging registration of study protocols and study reports in publicly available registries	• Principles for structure and content of protocols and reports (for medicines developers) • Recommended "best practices" for registration of study protocols/results	Initiate work after the first guideline reaches *Step 4* of the ICH Procedure

[3] Reference to the ICH M14 glossary will be made during development of the Concept Paper.

This Reflection Paper represents the initial step of an incremental approach towards harmonisation of regulatory RWE guidance. The following topics could be considered priorities for subsequent ICH guidelines, based on interested parties' feedback:

- Best practices for data quality including reliability and relevance, building on existing guidance documents [e.g. FDA draft guidance Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision Making for Drug and Biological Products (2021), and FDA, United States guidance Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (2023); Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making, Health Canada, Canada (2019); HMA/EMA Data Quality Framework for EU medicines regulation (2023)];
- Data standards for RWD;
- Appropriate application of study designs and data analyses.

Important considerations

Interested parties and consultation

The complexity of use and impact of RWD/RWE in medicines regulation raise numerous challenges, and the need for involvement of all concerned parties is therefore acknowledged. Should this Reflection Paper be endorsed by ICH, a public consultation is proposed based on the learnings from other ICH guidelines such as ICH E6(R3), ICH E8, ICH E17, ICH M11 and ICH M14 to ensure that all relevant parties are informed and given the opportunity to bring forward their views on technical and operational aspects to be considered when addressing harmonisation of the different focus areas described above. Following the proposed global public consultation on this Reflection Paper and as the guideline work progresses, the Concept Paper and Business Plan should include strategies for extended public consultation and engagement.

Benefits of ICH harmonisation

This proposal will aim to benefit all types of medicinal products at any stage of their lifecycle, i.e., from development/pre-approval to post-marketing monitoring. ICH guidance can increase the efficiency of resources across a large number of interested parties, by aligning expectations of regulators, industry, patient, advocacy groups, contract research organisations, academia, international organizations (e.g., WHO), and others using RWD to generate evidence on medicinal products.

By supporting the delivery of a regulatory system able to integrate RWE in a more harmonised way into submissions for medicines approval and decision-making, this proposal can support timely decisions on the development of innovative treatments, help to address unmet medical needs and support the safe and effective use of medicines.

Interface with existing and upcoming guidances (see Annex)

Several initiatives have been launched in different regions, including but not limited to Europe, the United States and Canada, to evaluate and enable the use of RWE across the spectrum of regulatory use cases that will ultimately lead the development and utilisation of medicines for patients. In December 2018, FDA, United States published a Framework for FDA's Real-World Evidence Program (2018) to address current challenges in using RWD and RWE. This was followed by a series of RWD/RWE guidances starting in 2021 on data sources, study designs, and regulatory considerations. Health Canada, Canada is also working towards optimising the use of RWE to inform regulatory decision-making as described in a Health Products and Food Branch Notice, first published in April 2019. In 2020 the HMA/EMA Big Data Task Force issued ten priority recommendations linked to human medicines, including the development of the European Medicines Regulatory Network Data Standardisation Strategy to allow convergence with partners on standards and guidelines linked to Big Data and RWE.

All these initiatives will support the development of the proposed new ICH guidelines.

Synergies and complementarities are foreseen with other ICH guidelines, for example E6(R3) and its Annex II, ICH M14, as well as ICH M11, currently under development. The ICH guideline M14 on "*General principles on planning and designing pharmacoepidemiological studies that utilize real-world data for safety assessment of a medicine*" focuses on convergence of regulatory guidance and best practices across jurisdictions on planning and designing safety studies that use RWD, whereas the potential for RWE can be broadened to include assessing the effectiveness of medicines. The ICH guideline M11 on "*Clinical electronic Structured Harmonised Protocol (CeSHarP)*" covers general protocol design principles and approach used to develop the separate associated documents, i.e. the CeSHarP Template and Technical Specification, which are acceptable to all regulatory authorities of the ICH regions. The scope of the M11 guideline focuses on protocol of clinical trials only, whereas RWD have been used mostly in non-interventional studies. The proposed guideline on topic 2 includes the convergence of structure of study reports in addition to study protocols. Efforts will be needed to ensure that duplications are minimised, and that knowledge gathered from existing projects are used to the maximum so that we can build on lessons learnt.

In conclusion, recognising the need to leverage the relevant expertise (e.g., pharmacoepidemiology, biostatistics, regulatory science) within regulatory authorities and medicines developers to undertake this initiative, and to leave enough time for the maturation of guidances under development, a long-term plan with a stepwise approach for the development of two ICH guidelines is suggested. This strategy will help effectively progress towards harmonisation of terminology related to RWD and RWE, and convergence of best practices, while ensuring complementarity of scope between the new and existing guidelines.

Annex – Regulatory guidances and other resources related to RWD/RWE

The following table provides examples of existing guidances and other resources related to RWD and RWE. It does not constitute a complete inventory of planned or ongoing activities across jurisdictions. In addition, there are many other non-regulatory initiatives and guidances that will be considered as this work progresses (e.g., from learned societies and other relevant projects and interested parties).

Jurisdictions	Regulatory guidances and other resources	Links
EC, Europe (EMA-EC)	Joint HMA/EMA Big Data Initiative, including: • Data quality framework for EU medicines regulation • Metadata list describing real-world data sources and studies • Good practice guide for the use of the Metadata Catalogue of Real-World Data Sources Other Guidances and resources: • CHMP guideline on registry-based studies • ENCePP Code of Conduct • ENCePP Guide on Methodological Standards in Pharmacoepidemiology • Good pharmacovigilance practices (GVP) Module VIII of post-authorisation safety studies • Scientific guidance on post-authorisation efficacy studies • EU National Competent Authorities-related regulatory guidance, including Nordic health data and registers (e.g. The Danish Health Data Authority)	LINK LINK LINK LINK LINK LINK LINK

FDA, United States	US Food and Drug Administration (FDA, United States). Framework for FDA's Real-World Evidence Program (2018) Individual Guidances: • Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products • Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products • Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products • Data Standards for Drug and Biological Product Submissions Containing Real-World Data • Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics • Use of Electronic Health Records in Clinical Investigations • Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products • Digital Health Technologies for Remote Data Acquisition in Clinical Investigations • Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products	LINK LINK
Health Canada, Canada	• Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making • Elements of real world data/evidence quality throughout the prescription drug product life cycle • CADTH Guidance for Reporting Real-World Evidence	LINK LINK LINK
MHRA, UK	• Guidance on the use of real-world data in clinical studies to support regulatory decisions • Guideline on randomised controlled trials using real-world data to support regulatory decisions	LINK LINK
SFDA, Saudi Arabia	Real-world data in Saudi Arabia: Current situation and challenges for regulatory decision-making	LINK
Swissmedic, Switzerland	Swissmedic, Switzerland position paper on the use of real world evidence	LINK
HSA, Singapore	Digital Health – UNDERSTANDING DIGITAL HEALTH PRODUCTS AND THE REGULATIONS	LINK
NMPA, China	• Guidance for Real-World Data Used to Generate Real-World Evidences • Guidance on the Use of Real-World Evidence to Support Drug Development and Regulatory Decisions • Guidance on Communication with Regulatory Agency on Real-World Studies to Support Product Registration • Guidance on the Design and Protocol Development of Real-World Studies	LINK

MHLW/PMDA, Japan	• Basic Principles on Utilization of Registry for Applications • Basic Principles on the Use of Medical Information Databases in Post-marketing Pharmacovigilance • Points to consider for Ensuring the Reliability in Utilization of Registry Data for Applications • Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases	LINK
MFDS, Republic of Korea	Guideline on the use of Medical Information Database (Real World Data) in pharmacoepidemiologic study	LINK
ANVISA, Brazil	Draft Real-World Evidence Guide (Draft)	LINK
TFDA, Chinese Taipei	• Real World Data: Evaluating Electronic Health Records and Medical Benefit Data to Support Drug Regulatory Decision Guidelines • Guidelines for using electronic health care data to conduct drug epidemiological safety studies • Things to note when using real-world data and real-world evidence as technical documents for drug review applications • Real-world data – assessment considerations for relevance and reliability • Research design for real-world evidence – key considerations for pragmatic clinical trials • Guidelines for using electronic medical record data for clinical research • Real-world evidence supports fundamental considerations in drug development	LINK
Worldwide	ICH guidelines: • ICH M14 "*General principles on planning and designing pharmacoepidemiological studies that utilize real-world data for safety assessment of a medicine"* • ICH M11 "*Clinical electronic Structured Harmonised Protocol (CeSHarP)*" • ICH E6 *"Good Clinical Practice (GCP)"* • ICH E6 (R3) *"Good Clinical Practice (GCP)" and Annex II on the use of RWD* • ICH E8 "*General Considerations for Clinical Studies*" • ICH E9 "*Statistical Principles for Clinical Trials*" • ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on "*Statistical Principles for Clinical Trials*" • ICH E10 "*Choice of Control Group and Related Issues in Clinical Trials*" • ICH E11A "*Paediatric Extrapolation*" ISPE/ISPOR initiatives (non-exhaustive list): • HARPER • EQUATOR • ISPE guidelines for good pharmacoepidemiology practices	LINK LINK LINK LINK

	CIOMS Working Group XIII – Real World Data and Real World Evidence In Regulatory Decision Making	LINK

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