International Collaboration Progress

HMA/EMA Big Data Stakeholder Forum
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"…challenges exist, due for example to heterogeneous data sources, different levels of data quality, and various governance models for data sharing and access. Close collaboration between regulators across the world can help address these challenges"

ICMRA statement on international collaboration to enable real-world evidence (RWE) for regulatory decision-making, July 2022

Overview

To address challenges in the Real-World Data and Real-World Evidence (RWD/RWE), and clinical trial spaces, regulators have been collaborating on key initiatives to enhance harmonization, improve methodologies, and strengthen evidence generation. These include:

International Coalition of Medicines Regulatory Authorities (ICMRA):

- The COVID-19 Real-World Evidence (RWE) and Observational Studies Working Group (WG)
- The WG on RWE for Public Health Emergencies

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH):

- M11 Guideline - "*Clinical electronic Structured Harmonised Protocol (CeSHarP)"*
- M14 Guideline - "*General principles on the plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines*"
- Reflection Paper and New Topic Proposal - "*Pursuing Opportunities for Harmonisation in Using Real-World Data to Generate Real-World Evidence, with a focus on Effectiveness of Medicines*"

ICMRA RWE Working Group – COVID-19

- The ICMRA COVID-19 RWE and Observational Studies Working Group was created in April 2020 to identify areas for RWD/RWE international collaboration in the context of the pandemic

- Was co-chaired by EMA and HC, and included three technical workstreams:
  - Vaccine Pharmacovigilance Network (VPN) led by MHRA and TGA
  - Pregnancy observational research led by EMA
  - Building international cohorts of COVID-19 patients led by HC

- Demonstrated numerous achievements including new collaborations, effective sharing of data, knowledge and experience in relation to observational studies, a regulators workshop on RWE, several publications, and ICMRA statements

ICMRA RWE Working Group – Public Health Emergencies

- The COVID-19 WG was officially closed out at the end of February 2024 and its lessons learned have been published
  - *Collaborative real-world evidence among regulators: lessons and perspectives*

- Based on the lessons learned, a proposal was presented to, and received the endorsement of, the ICMRA Executive Committee to repurpose the WG more broadly to focus on RWE in public health emergencies (PHEs)

- The first meeting of the ICMRA RWE WG for PHEs was held in July 2024, and was co-chaired by EMA and HC
  - Included a presentation of the members and how they utilize/consider RWD/RWE and a discussion of the WG mandate
  - Areas of focus in the near-term include governance and a proposed workplan that includes the exploration of topics for future collaborative projects
  - Next meeting to be held in December to discuss governance principles and processes for collaborative studies

ICH M11 - Clinical electronic Structured Harmonised Protocol

- **Guideline is a high-level document**
  - Provides the background on why a harmonized clinical protocol template is needed, and
  - Describes design principles on how the template & technical specification were developed

- **Template**
  - Includes identification of headers, common text, instructions, data fields and terminologies

- **Technical Specification**
  - Serves as a technical representation of the ICH M11 protocol template to support the exchange of protocol information

ICH M11 - Progress Made in Montreal (November 2024)

Consensus Achievements:

- Adjudicated *Regional Party Review* comments for the Template
- Reached agreement on majority of *Regional Party Review* comments for the Technical Specification
- Reached consensus on *Terms, Definitions, and Valid Value Sets (38 out of a total 120 still under review)*

Training Material Development:

- Collaboration with Harvard MRCT ongoing to create comprehensive training materials for ICH M11
- Materials to be hosted on the ICH website
- Proposal to utilize MRCT's training platform for advanced learning, akin to E6 (R2) training

ICH M11 - Conclusions

M11 Milestones:

- Significant progress made; all milestones remain on schedule

Collaborations:

- *M2 Partnership*
  - Provided timely clarification on SDO partnerships, streamlining processes
  - Continued collaboration critical for ongoing success
- *Statistical Integration*
  - Regular engagement with ICH EWG statistical experts has ensured accurate incorporation of E9 (R1) principles

ICH M14 - RWD for Safety Assessment of Medicines

- HC is participating in the establishment of a new ICH guideline on "*General principles on the plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines*"

- This guideline will focus on post-approval non-interventional pharmacoepidemiological studies using RWD on drugs, vaccines and other biologics
    - Studies with treatment assignment are excluded but basic principles presented may be applicable to these studies when RWD elements are included

ICH M14 - Progress and Current Status

- Expert Working Group formalized in May 2022
- Initial first draft circulated for internal party review June 2023
- Draft guidance posted on ICH website May 24, 2024
- Public consultation ended on October 22, 2024
- The EWG is now beginning to go through more than 1,200 comments submitted by interested parties
- Anticipating finalization as a Step 4 document to be implemented in the local regional regulatory system in May 2025


ICH harmonisation for better health

ICH M14 Step 2

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EMA/FDA/HC RWE Cluster, ICH RWE Reflection Paper and New Topic Proposal

- EMA/FDA/HC RWE Cluster is a monthly forum to discuss RWE topics
  - Was leveraged to develop an ICH RWE Reflection Paper focusing on key areas identified through the 2022 ICMRA Regulatory Workshop and Statement

- ICH Reflection Paper on "*Pursuing Opportunities for Harmonisation in Using Real-World Data to Generate Real-World Evidence, with a focus on Effectiveness of Medicines*"
  - Underwent public consultation that closed on September 30, 2023, and comments were incorporated
  - Adopted by the ICH Assembly in June 2024
  - New topic proposal targeted for December 2024 and development is currently underway by EMA, FDA and HC

	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

"*By consolidating resources, expertise, and data on an international scale, these global collaborations were seen as a strategic approach to navigate uncertainties and enhance the robustness of evidence*"

Beck AE, Kampman M, Huynh C, Simon C, Plueschke K, Cohet C, Verpillat P, Robinson K, Arlett P. Collaborative Real-World Evidence Among Regulators: Lessons and Perspectives. Clin Pharmacol Ther. 2024 Oct 21.

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