3 July 2024
EMA/CHMP/ICH/301589/2024
Committee for Medicinal Products for Human Use

Outcome of public consultation on ICH Reflection paper on pursuing opportunities for harmonization in using real-world data to generate real-world evidence, with a focus on effectiveness of medicines

Summary report of comments received during the public consultation

Release for information	3 July 2024

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1. Background and consultation

The Reflection Paper (RP) was endorsed by the ICH Assembly in June 2023. It aims to engage ICH on the convergence of terminology for Real-World Data (RWD) and Real-World Evidence (RWE), on the format for protocols and reports of studies based on RWD submitted to regulatory agencies throughout the lifecycle of medicinal products, and on the registration of protocols and reports for these studies. The document presents a long-term plan with a stepwise approach for the development of two ICH guidelines, which will ultimately further enable the integration of RWE into regulatory submissions and timely regulatory decision-making.

The RP was published on the ICH and international regulatory agencies' websites in June 2023 for public consultation up to September 2023. ICH would like to thank all the commenters for their input.

This document should be read in conjunction with the updated and final version of the RP. It provides a high-level overview of the comments received from relevant interested parties, with indications on how these will influence the next steps in this ICH strategic priority area.

2. Contributors

In total, 151 individual comments were received from 16 interested parties including learned societies, clinical research organisations, academia, industry associations and international regulators.

3. Summary of main points raised during the consultation

Generally, there was strong support for the initiative and for the development of the guidelines as outlined in the RP. This support was received across the broad range of interested parties responding. Some examples:

"We welcome the initiative of international harmonisation of real-world evidence terminology and convergence of general principles regarding planning and reporting of studies using real-world data, with a focus on effectiveness of medicines."

"We welcome the proposal to convergence and harmonisation of terminology and convergence of guidance related to RWD/RWE to further enable the integration of RWE into regulatory submissions globally and timely regulatory decision-making across different regions."

"We recognize the challenges acknowledged by ICH in the reflection paper and are therefore supportive of the need for harmonization of terminology and general principles in order to enable the use of RWE in regulatory decision-making."

"The RP is a valuable compilation of a variety of RWD/RWE initiatives and an important initiative for the design of future studies and world-wide harmonization of terms and definitions."

"The purpose of this reflection paper is a great initiative and kudos to ICH for taking on a topic that certainly needs standardization within the field."

ICH Reflection papers are intended to lay out an area where harmonisation work is needed, and articulate ideas for potential future harmonisation work. As harmonisation is achieved through the

development of ICH guidelines via a process of scientific consensus, ICH has considered the current consultation by categorising the majority of the input into 4 areas:

- Comments on the scope of the proposed ICH guidelines;
- Comments on the fundamental concepts presented, and requests for clarification;
- Proposals for minor edits with no impact on scope nor concepts presented;
- Other statements/comments requiring no update of the RP, but which should be considered by the future ICH expert working group in the context of the guidelines' development.

Comments on the scope of the proposed ICH guidelines

- Suggestions were made to incorporate principles for data collection, data quality management and conduct of studies based on RWD, including considerations on study design and data analysis. These aspects go beyond the current scope of the proposed guidelines' objectives. As the RP represents the initial step of an incremental approach towards harmonisation of regulatory RWE guidance, these topics have been noted and should be considered priorities for subsequent ICH guidelines.
- Some comments recommended to make the "Transparency" topic of the second proposed guideline a mandatory requirement. This feedback was not implemented because mandatory publication of some RWE studies (e.g., non-interventional) may conflict with current regional regulatory and legislative requirements for the public registration of these types of studies.

Comments on the concepts presented and requests for clarification

- Several suggestions were made to replace the standalone term "effectiveness", by e.g., "efficacy/effectiveness", or "benefits and risks". ICH recognises that these terms are currently used differently across jurisdictions, depending on the development phases of medicinal products. However, this topic requires detailed discussions at the level of a future expert working group. It is therefore considered premature to decide on the final terms to use in the guidelines, hence the world "effectiveness" is used throughout the final RP.
- Comments were received on the need to consistently use the terms "RWD" and "RWE" across the RP. Amendments were made accordingly with the assumption that RWE (and not RWD) is submitted within regulatory applications on medicinal products to inform the decision.
- Additional explanations on the concepts presented were requested, e.g., on the potential roles of RWD and RWE in various contexts of use, and on their potential challenges. The text was revised to provide clarifications where possible, whilst keeping the level of details intended for ICH RPs.
- Some commenters expressed the need for more granularity on what is entailed by 'medicines', in particular if this term includes non-prescription/over-the-counter drugs, biologically active herbals, or medical devices. ICH confirms that the RP covers drugs with and without prescription, vaccines, and other biologics. The text was amended accordingly. However, medical devices were considered out of scope of the proposed guidelines.

- Based on several comments, edits were incorporated to acknowledge patient-generated data, including but not limited to patient engagement data (PED), patient preference, patient reported outcome, as a type of RWD.

Proposals for minor edits with no impact on scope nor concepts presented

Edits were implemented whenever considered relevant to improve the readability and clarity of the text, whilst keeping the conventional level of granularity for ICH RPs.

- Examples of amendments made in line with the comments received include updates of references to latest available versions of regulatory guidelines (e.g. FDA guidance Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (2023), CADTH Guidance for Reporting Real-World Evidence), references to new regulatory guidelines ICH was made aware of (e.g. ANVISA, Brasil and TFDA, Taiwan), and addition of a few relevant publications[1] emphasising the need for harmonisation of operational definitions of the terms RWD and RWE. The mention of "Randomised Clinical Trials" was corrected to "Randomised Controlled Trials".
- The request to extend the list of suggested expertise required for the development of the initiative with "RWE professionals" and "data source experts" was declined as it was considered too specific for the ICH RP, since the list is not intended to be exhaustive. Instead, the list was simplified by referring to "a large number of interested parties", to be more inclusive. A few suggested publications were not included in view to limit the number of references, as ICH felt that their conclusions were already conveyed by references existing in the text, or that their scopes were limited to only specific types of medicines, diseases (e.g., rare diseases), or too specific to methodological aspects of using RWD/RWE.

Other statements/comments requiring no update of the RP, but to be considered by the future ICH working group in the context of the guidelines development

- Regarding the proposed Topic 1: Attention should be paid to PED as part of the future guideline on RWE terminology. Better defining the overlaps between "big data" and "real world data" will be useful. Other terms such as "externally controlled trial" and "external comparator studies" were highlighted as important concepts in need for clarification.
- Regarding the proposed Topic 2: The expert working group should carefully consider the level of details the future guideline will include on the format for protocols & reports of studies based on RWD, e.g., 1) whether it will take into account the different types of study designs, data sources and registration stages (during discussions with regulatory agencies pre-registration, or after

[1] Example: Bloomfield-Clagett, B., Rahman, M., Smith, K. and Concato, J. (2023), Use of Real-World Evidence in Neuroscience-Related New Drug and Biologics License Applications for Novel Therapeutics. Clin Pharmacol Ther, 114: 1002-1005. https://doi.org/10.1002/cpt.3018

registration?); and 2) if feasibility and early validity checks to assess the fitness for purpose of RWD sources and designs will be covered. Of note, "format" in Topic 2 does not necessarily entail "template". An important aspect to consider will be the timing of study registration relative to the stage of protocol development to ensure transparency.

In addition, the title of the ICH RP was amended to improve readability[2]. This change does not impact the scope of the proposal.

4. Summary

Overall, the feedback received from a broad range of interested parties widely supports the initiative for the development of guidelines on convergence of terminology for RWD and RWE, on the format for protocols and reports of study based on RWD, and on advocating registration of these studies. There were no major objections raised or significant obstacles foreseen for the development of the two proposed guidelines. A substantial proportion of comments highlights the importance of the momentum and encourages ICH to initiate the work as soon as possible, as well as to engage appropriately with non-ICH interested parties throughout the process.

The updated, and final, version of the RP reflects the comments accepted by ICH. Other input considered too detailed at the RP stage, but still treated as relevant, will be taken into account when guideline work commences.

[2] Previous title included in the ICH RP published for public consultation June-September 2023: *International Harmonisation of Real-World Evidence Terminology and Convergence of General Principles Regarding Planning and Reporting of Studies Using Real-World Data, with a Focus on Effectiveness of Medicines.*