

Defining Intent, and Guiding Harmonization and Ethics Standards for Real-World Data and Real-World Evidence in Regulatory Decision-Making

I. INTRODUCTION

There is increasing interest in the use of Real-World data (RWD) to support regulatory decision making across the product life cycle. Key sources of RWD are electronic health records, claims data, prescription data, and patient registries. Real-world evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from an analysis of RWD. For decades, such evidence has been well accepted for satisfying post-approval safety monitoring requirements but has not been used commonly to demonstrate drug effectiveness, which is a relatively new concept.

As applications are increasing, it is proposed that CIOMS develop a consensus report and recommendations for the use of RWD and RWE in regulatory decision-making related to biopharmaceutical products. This report would cover three key areas:

- Articulate the different RWD/RWE requirements depending on the intent of use e.g. Regulatory, Payers, and Public Health;
- Propose harmonized practices and guidance for using RWD and RWE for regulatory purposes (given that there are no existing consensus guidelines);
- Articulate point of view (POV) on key ethical issues relevant to RWD and RWE and a provisional set of standards to address those issues (the high-level POV may lead to a separate/satellite group of ethicists to deal with it).

Among other important objectives, stakeholder consensus will enable global cooperation to facilitate future harmonization amongst key stakeholders, including regulatory authorities, expanding opportunities for the appropriate and effective use of this important approach.

II. THE ISSUES

II.1 RWD and RWE in Effectiveness Decision-Making

Premarketing Phase I-III interventional clinical trials are conducted under well-controlled conditions in which both efficacy and safety data are carefully collected and analysed. Data from these studies form the basis for regulatory authorization for the marketing of a product. Generally, only highly selected subjects with clear-cut syndromes or diseases are eligible for these trials, which are primarily designed and statistically powered to evaluate efficacy. The number of subjects enrolled in premarketing clinical trials is constrained by prospective subjects who meet inclusion and exclusion criteria, their willingness to participate in a clinical trial, investigators with appropriate experience and training to conduct the study, available resource and timeframe, etc. Thus, when a product is authorized, the available data are scientifically sound, but may not represent conditions of actual use in the broader healthcare setting. Indeed, important safety information is often not available when a product is first marketed. For example, sub-groups such as the elderly, children, women of child-bearing potential, pregnant women, and subjects with organ dysfunction are routinely excluded from pivotal Phase III clinical trials. Additional examples of typical exclusions are subjects with severe manifestations of disease, co-morbidities or those who require co-medication(s). Other common limitations inherent in the design of premarketing trials are the relatively short duration of exposure and the inability to detect very rare or delayed adverse reactions.

In real-world healthcare, patients may have co-morbid conditions or a more severe disease or use concomitant medications and, as a result, treatment conditions are less controlled than in clinical trials. Variations in diet, use of herbal medications or natural substances, genetic heterogeneity, idiosyncratic responses, or other confounders may also contribute to the challenges encountered by the healthcare system when introducing a novel therapy. When a new medicinal product is introduced to treat actual patients in hospital, at home or at work, and when a large patient

population has been exposed under conditions of chronic use, understanding of the safety profile can be enhanced by properly designed and conducted Phase IV studies; studies which are often time-consuming and expensive. Indeed, use of RWD and RWE might accelerate, i.e., facilitate gleaning insights or drawing conclusions earlier than via more traditional means. Scientific safety studies, whether interventional or non-interventional, may serve a key role in addressing important safety concerns, and data from such studies, complement existing routine passive and active safety surveillance, as well as the safety profile developed from Phase I-III data. However, while RWE from observational studies is well accepted for post-approval safety monitoring, it has been viewed sceptically for its contribution to regulatory decisions around effectiveness. Indeed, these studies can have their own limitations often due to the reliance on secondary data, and evidence quality can be compromised by confounding by indication or a general lack of rigorous collection standards.

More recently, hybrid trial designs that combine features of clinical trials and studies with RWD, have started emerging to support regulatory decision-making in an ever-increasing number of cases. Although the methodologies for these innovative studies are not currently well established, they may offer a way to combine the advantages, and minimize the limitations of both traditional clinical trials and observational studies. This raises the likelihood that they will play an increasingly important role in regulatory decision-making as regulators, researchers, and clinicians gain more experience with them.

As questions remain as to whether RWE can be used to assess the effectiveness of drugs, it would be expected and needed to evaluate the increasingly novel methodologies that are being used to design studies, collect and analyse data. This output could serve to articulate requirements and appropriateness to support this specific intent versus addressing safety or payer questions. This will also reinforce the need for collaboration across all stakeholders, from regulators to payers, health technology assessment bodies, patients, academia and industry.

II.2 Global Regulatory Harmonization

The absence of consensus guidelines and clear routes to obtaining pilot guidance from agencies for the use of RWD and RWE in drug effectiveness decision-making and subsequently, approval, has potentially slowed the adoption of, and investment in, RWD and RWE among researchers and biopharmaceutical manufacturers. While certain regulatory authorities have articulated their unique guidelines and expectations, differences exist among the major global regulators. Harmonization of guidelines including clear definitions, terminology and other key elements of an RWD and RWE guideline would help set standards for study design, data acceptability, and ethical guidelines, among other factors and define the “rules” for acceptance of evidence in regulatory decision-making.

The existence of harmonized standards would reduce confusion and the use of inappropriate or ineffective methodologies, while spurring utilization of, and investment in, RWD and RWE research models. Gaining consensus across major global regulators will take time, however, a CIOMS report and recommendation would help to expedite uniform standards.

II.3 RWD and RWE Ethics POV

The ethical guidelines set forth for interventional studies have evolved over time, largely in response to identified abuses by researchers and research sponsors, and due to gaps in earlier regulatory frameworks. Current regulator-endorsed ethical standards are inspired by the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, and CIOMS International Ethical Guidelines for Health-related Research Involving Humans, among other statements of ethical principles. These documents were written in response to failures identified throughout the history of human subjects research and to address changing research environment.

We have an opportunity to avoid similar missteps in the realm of RWD and RWE by proactively developing a POV on relevant ethical considerations. While certain human subject protections are not as relevant in RWD and RWE, significant ethical issues remain, including the appropriate use of

individualized medical data, privacy, consent, data ownership and financial considerations, and the sharing of insights and results with study populations, among others.

While developing a final set of ethical guidelines for RWD and RWE may take years, an opportunity exists to identify the key ethical challenges posed by these approaches, with an objective of establishing a baseline POV on how these challenges can be navigated.

III. NEED FOR A CIOMS WORKING GROUP

III.1 Background

The rapidly evolving technology and data landscape is making newer research models, including the use of RWD and RWE, more effective and reliable. RWD and RWE have proved to be valuable approaches for improving biopharmaceutical product safety and clinical decision-making. They have also demonstrated their utility in regulatory decision-making in the realm of effectiveness. To help RWD and RWE to be more broadly adopted for this purpose, however, a new stakeholder consensus is required in the areas of 1) appropriate use of RWD and RWD in drug approval decision-making, 2) harmonization of global regulatory standards, and 3) RWD and RWE ethical standards. CIOMS is well positioned to develop this consensus report.

The CIOMS guideline would create a reference worldwide for regulators and researchers involved in RWD/RWE studies, as well as pharmaceutical and biotechnology companies involved in product development and marketing.

III.2 Aim of the working group (WG)

The primary remit of the proposed CIOMS WG would be to develop, for global use, a consensus report and recommendations on principles to be applied regarding triggers, objectives, research questions, design features, and timing of RWD and RWE as part of the regulatory process for products in the peri-approval stage of development or for authorized products.

The working group would also be expected to evaluate the increasingly novel methodologies that are being used to design studies, collect and analyse data, and use the output in the regulatory process to assess how RWE can contribute to effectiveness decisions.

Supporting this, the proposed CIOMS WG would propose an approach and standard guidelines supporting harmonization across global drug regulatory authorities and develop a POV on ethical considerations and challenges related to RWD and RWE.

III.3 Composition of the group

Senior scientists with relevant scientific and research background will be invited from regional and national drug regulatory authorities, leading innovative biopharmaceutical companies, clinicians, academicians, WHO, and non-commercial research organizations.

Additionally, bioethicists, privacy experts, and others with experience identifying and analysing life sciences ethics issues will be engaged to support the development of an RWD and RWE ethics POV.

A balanced approach will be used for selection of experts such that no constituency would have a preponderance of influence within the WG.

III.4 Gaps to fill in

The contemplated CIOMS report will ensure that stakeholders have consensus principles to guide decisions regarding triggers, objectives, research questions, study design features, and timing of RWD and RWE integration into the regulatory process for products in the peri-approval stage of development or for authorized products. Considerations to be addressed by the WG might include:

- Articulating different RWD/RWE requirements depending on the intent of use, e.g., Regulatory, Payers, Public Health, etc., including discussion on reliability and scientific validity, i.e. non-promotional study design and conduct;
- Defining the appropriateness of study designs including hybrid approaches, data collection and handling methods to address the research question in a regulatory context;
- Determining the role of novel ways to collect data e.g., wearables, clinical trial decentralization, direct to patients approaches;
- Discussing the role of new analytical approaches and statistical considerations in establishing causality e.g. machine learning, and natural language processing;
- Laying the groundwork to facilitate global harmonization work amongst key stakeholders to define a path forward to the desired state;
- Identifying key ethical challenges and concerns; and
- Other points to consider that are introduced during deliberations of the WG.

III.5 Work process and miles stones.

The established CIOMS process and procedures should be followed. If the Concept Paper is agreed by end 1Q2020, it is expected that the work of the WG will be completed within this general schedule:

Milestone	Anticipated timing
Consultation on WG composition and funding	4Q2019
Brainstorming meeting (meeting number zero)*	1Q2020
First face-to-face meeting of WG	2Q2020
Draft of WG report	3Q2021
Consultation with external experts on penultimate draft WG report	2Q2021
Publication of WG report	1Q2022

Face-to-face meetings of the WG are contemplated minimum four times per WG duration, of which three meetings are recommended for the year 2020; between meetings work will be conducted via email, teleconferences, and/or videoconferences. It is anticipated that one of the first activities of the WG will be to evaluate the existing regulatory landscape, i.e., review current regulations and guidance, as well as other relevant initiatives on use of RWD and RWE in regulatory decision-making. It is likely that at least one month will be required for consultation with external experts on the penultimate draft report prepared by the WG. Final deliverables and timelines will be agreed by the first WG meeting.

* Optional, may be replaced by the first WG meeting

III.6 Deliverables

We have listed below some possible deliverables. It will be the first task of the group to agree a final list.

- Draft articulating the RWD/RWE intent of use/type of decision to be made to inform appropriate methodology
- Draft harmonized guidance including clear definitions and terminologies to be adopted by global drug regulatory authorities
- Draft POV on RWD and RWE ethical considerations

IV. CONCLUSION

There is a strong need to launch the Working Group to develop consensus-based recommendations

to address the issues listed above. Furthermore, the collaborative efforts brought together to accomplish this task could create the environment to hold an annual conference on RWD and RWE jointly with industry, academia, scientists, clinicians, SME and regulatory authorities to advance our use of this important approach.