الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Framework on the Use of Real-World Data (RWD) and Real-World Evidence (RWE) to Support Effectiveness and Safety for Marketing Authorization of Medicinal Products

Version 1.0

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Saudi Food & Drug Authority

Drug Sector

For Comments Drug.Comments@sfda.gov.sa

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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1. Introduction

The Saudi Food and Drug Authority (SFDA) plays a vital role in public health in Saudi Arabia by ensuring the effectiveness and safety of medicines and vaccines. Advances in data science and medical health records systems can significantly contribute to achieving the transformation of health care services and regulations in line with the SFDA fourth strategic objective and ultimately the Saudi Vision 2030. The transformation is likely to impact evidence for medicine applications, in particular, the way it is generated, ranked and interpreted.

As a part of its mission, and to keep pace with the transformation in health care, the drug sector at the SFDA is outlining a framework to regulate the use of Real-World Data (RWD) and Real-World Evidence (RWE) in support of medicines marketing authorizations.

2. Scope of this Framework

This framework aims to define RWD and RWE and provide an outlook to demands and issues in this context such as data quality and confounding. Moreover, it implies SFDA's views and possible initiatives related to the RWE/RWD ecosystem to improve its utilization, appropriateness and quality.

3. Defining Real-World Data and Real-World Evidence for Medicine Regulatory Decision

3.1. Real-World Data

Real-World Data (RWD) is defined as any data routinely collected from patients concerning their health conditions, the healthcare services they receive, or data that supports the healthcare services provided to them.

3.2. Fit-for-Purpose Real-World Data

Fit-for-purpose RWD refers to a source of RWD that captures accurate longitudinal information, meeting the needed sample size, on consistent time-fixed or time-varying treatments, necessary covariates to reduce confounding, and outcomes of interest considering the clinical question in the study. The data source must be quality-assured, and the study sample should be generalizable to the target population.

3.3. Real-World Evidence

Real-World Evidence (RWE) is generated from the analysis of fit-for-purpose RWD. The analysis usually aims to answer a clinical question of interest on the effectiveness and safety of a human medicinal product or vaccine in a clinical condition. These questions are typically framed using well-defined parameters "e.g. estimands" that precisely describe the treatment effect to be estimated.

4. Randomized vs Non-Randomized Clinical Trials

A clinical trial is any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study the pharmacokinetics of an investigational product(s) to ascertain its safety and/or efficacy.

In Randomized Clinical Trials (RCTs), participants are randomly assigned to the different treatment groups, ensuring comparable numbers and baseline characteristics. Randomization, blinding, and the use of control groups are approaches to minimize bias and confounding in clinical trials.

On the other hand, in non-randomized clinical trials researchers tend to assign participants to treatment groups based on other factors rather than by random assignment. Although this study design might be useful in rare cases where RCTs are unethical or inapplicable, it introduces a higher risk of bias and confounding.

5. Examples of RWD and RWE

5.1.Examples of Appropriate Data Sources of RWD

Generally, any data source used to generate RWE must be of high quality, reliable, and relevant "fit-for-purpose" to capture the outcome of interest. Some examples of appropriate data sources include Electronic Health Records (EHR), medical claims data, patient/ disease registries, wearable devices and Patient- Reported Outcomes (PRO).

5.2. Examples of Study Designs for RWE

5.2.1. Observational Studies

Observational studies are non-interventional studies that generally collect and observe cases or case series and identify the associations among the observed variables. It can be primary data collection studies or secondary data use studies including, cohort and case-control studies, etc. Observational studies can provide data assessments with high applicability and generalizability to the real-world clinical practice. However, data obtained from this study design are highly susceptible to bias and confounding.

5.2.2. Target Trial Emulation

One approach to address causality questions in observational studies is the emulation of a hypothetical clinical trial “target trial” using observational datasets and an appropriate methodology. This study design could enhance the validity of causal inferences drawn from RWD and yield clinically interpretable findings.

5.2.3. Hybrid Trials

Hybrid trials combine the elements of traditional clinical trials and real-world evidence. Initially, the data are collected through case report forms (CRFs); for the remainder of the study, data are extracted from real-world sources such as electronic health records and medical claims. Hybrid trial designs tend to have stronger external validity and generalizability due to their large sample size and heterogeneous populations. However, hybrid trials are prone to risk of lower data quality compared to data actively collected in clinical trials.

5.2.4. Pragmatic Trials

Pragmatic trials are conducted to assess the correlation between different interventions in a routine clinical setting. This design usually explores the outcomes and applicability of any interventions in everyday real-world settings. It typically includes diverse populations by setting broader inclusion/exclusion criteria, making the results more generalizable.

5.2.5. Registry-Based Trials

Registry-based trials utilize patient/ disease registries for data collection to investigate a specific research question. Some of the advantages of using registries include their ability to permit the long-term data collection and to provide prospective data on disease progression. However, one limitation of using data from registries is the lack of harmonization in data formats and used terminology across registries. Moreover, maintaining the quality of the registry is challenging yet crucial to increase confidence in the validity and reliability of the extracted data.

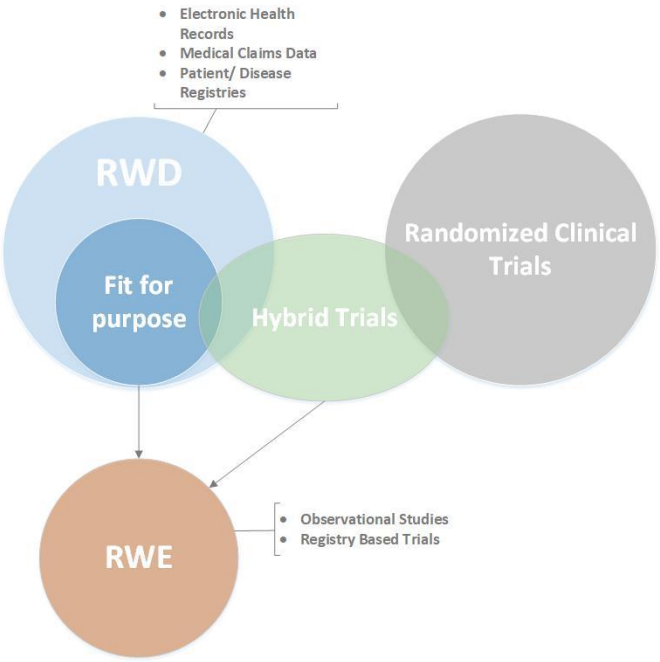

Figure 1: Linking RWD and RWE Concepts

6. Data Quality

Data quality is a key element for optimizing the utilization of RWE in regulatory decision-making. The selected data and its source must be fit-for-purpose, relevant and accurately representing and addressing the research question, complete information, coherent with no differences across the data sets, and timely providing up-to-date data.

Standardization of RWD help improves the data quality by ensuring the accuracy, consistency and reliability of the extracted data and its source. Many frameworks can be

applied to standardize the data, for example, using Common Data Models (CDMs) enable better quality control and offers uniform and consistent data across the different datasets.

7. Bias and Confounding in RWE

Uncontrolled confounding is a challenge that may affect the validity and limit the interpretation of the results from observational studies. Such confounders arising from the use of large databases (measured and unmeasured confounders) can be handled through the choice of appropriate study design and analysis method of the data (e.g. stratification, standardization, regression models, propensity scores and combining with machine learning tools with a high-dimensional propensity score (hdPS) method).

Additionally, biases can possibly arise from the inappropriate handling of data used to generate RWE such as selection bias and information bias. These biases need to be addressed in order to have valid and reliable results from RWE (e.g. matching patients and target trial emulation).

8. Potential Uses for RWD and RWE for Regulatory–Decision Making

8.1. Hypothesis Generation

RWD and RWE can help advance drug discovery. First, repurposing an approved drug to be used in another disease. Second, comparing two strategies before going into a randomized clinical trial (RCT) to inform the decision. Third, utilizing genetic data to identify drug leads. This can include data from biobanks for drug discovery.

8.2. Augmenting Single Arm Studies

RWD can augment single-arm studies by serving as an external comparator to the intervention arm. This is usually applied in early-phase trials or in rare diseases, especially those with few or no treatment options or for testing certain medicinal products. Historical and external controls may be used in single-arm trials to develop orphan drugs when clinical trials are not feasible or unethical in the proposed settings.

8.3. Transportability and Local Data

Given that clinical trials are currently conducted as multi-regional trials, where different regions may have different distributions of effect modifiers, local RWD can

be used to transfer the causal effect observed in such trials to the target population by providing local data on significant covariates.

8.4. Inform Prior Assumptions

In the era of growing use of Bayesian statistics, RWD can be valuable in informing which prior assumptions to use to optimize the sample size, treatment dosage, or patient selection criteria.

8.5. Investigating Under-Represented Populations in RCTs

RWE can be used to investigate under-represented populations by including a diverse, broader demographic representation to test a research question.

9. Conclusion

SFDA is initiating this framework as part of a continuous effort to guide further establishment of an understanding of utilization, potential uses, and to optimize the evaluation of such data, with a view to informing future regulatory decisions.

10. Glossary

- **Common Data Model (CDM):** A standardized format that allows data from diverse sources to be harmonized and analyzed using standard code.
- **Disease Registries:** a centralized system that collects information about specific diseases and usually focuses on the disease progression and outcomes.
- **Electronic Health Records:** an electronic system used to collect, store, and manage patients' health information such as diagnosis, treatments, laboratory tests, allergies and immunization.
- **Estimand:** a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at the population-level what the outcomes would be in the same patients under different treatment conditions.
- **Medical Claims Data:** an administrative record that collect information that healthcare providers submit to insurance payers for reimbursement of medical services.
- **Patient Registry:** a centralized system that gathers data on patients' diseases, exposure, and treatments.
- **Patient Reported Outcomes (PRO):** a measurement reported directly from the patients about their health status, symptoms, and quality of life without interpretation by a clinician.
- **Wearable Devices:** an electronic device that can be worn on the body such as smartwatches and fitness trackers. These devices can collect and monitor various physiological parameters, such as heart rate, blood pressure, sleep patterns, and physical activity.

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