Real-world Evidence: Requirements and Recommendations for Regulatory Submissions

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Contents

Revision History

Version	Date	Summary
1.0	2023-May-10	(Committee, 2020) (CDER, 2021) White Paper 2021/2022 – RWE project Real-world Evidence: Requirements and Recommendations for Regulatory Submissions

Overview: Purpose of This Document

The PHUSE Real World Evidence project released the first white paper on Basic Considerations for the Use of Real World Evidence (RWE) in Support of Regulated Clinical Trial Submissions in July 2020. Since then, the inclusion of real-world data (RWD) in regulated clinical trials has gained significant prevalence.

During the Computational Science Symposium (CSS) 2021, it became clear that companies are still insecure about the use of real-world data for regulatory submission trials due to lack of clear guidelines and standards. Since then, the FDA has released a number of draft guidelines on the use of real-world data for public review, which we discuss here.

In this white paper the RWE project aims to provide an overview of the learnings, challenges and best practices around RWD data sources, collection, cleaning, standardisation, reporting and regulatory submissions. This paper also aims to serve as a reference for relevant guidelines and articles related to the use of RWD/RWE for regulatory submissions.

Real-world Data and Real-world Evidence

In the guidance document Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision Making for Drug and Biological Products (CDER, 2021), the FDA defines RWD as routinely collected data related to patient health status or delivery of healthcare. This data can be collected from different sources, such as electronic health records (EHRs), medical claims data and patient-generated data.

RWE is defined as any evidence based on RWD to assess the risk and benefits of a medical intervention or device.

Data Selection

By definition, RWD is not designed or collected to address a specific research question, due to which data selection becomes critical. There are two key considerations for selecting the 'right' data:

1. Data relevance
2. Data reliability

Data Relevance

Data relevance depends on the availability of key data elements to support the analysis and good sample of patients meeting the study requirements. This includes:

Identifying appropriate data source(s)

Since real-world data is not collected to support clinical trials it may lack the necessary information for a proper analysis. Therefore, usability of real-world data to generate real-world evidence for regulatory submission collectively depends on the research question at hand and the data source(s) used to gather the data. For example, if the outcome of the RWD/RWE study is lower than A1C level, then does the RWD source capture all lab information?

During the EMA learnings initiative webinar for optimal use of big data for regulatory purposes (Committee, 2020), it was specifically underlined that research questions should be defined before the appropriate real-world data source is selected to avoid bias in the research or study design. Claims data, pharmacy data, GP data, registries and hospital data all have their advantages and drawbacks.

Retrieving baseline patient and disease characteristics, lines of therapy, dose information (exposure), adverse event occurrences and efficacy endpoints can be quite complicated. In addition, geographical differences can influence data collection and linkage between the different data sources. Furthermore, the data residency (the place where the data is stored – the US, the EU, etc.) and sovereignty (i.e. local government regulations) can be critical to the availability of the data to address the research question as well.

Ensuring fit-for-purpose data

An important aspect of preparing real-world data analyses is to assess whether the data is fit for purpose to address the research question. Section III-B of the draft FDA guideline Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry (CDER, 2021) specifically addresses this question of the 'relevance of source data'. Fit-for-purpose assessment is based on the completeness of the minimum of the source data, such as exposure, health-related outcomes and covariates, or at least unbiased approximations. For example, assumptions are in most cases needed for date of death.

Data Reliability

The reliability of the data should be assessed, which includes the accuracy, completeness, provenance and traceability. Although originating from the same data source type, when combining data from different healthcare providers and information systems, heterogeneity will occur, which implies a risk for bias. The less bias is observed, the better the perceived reliability of the data source.

The potential sources of biases should be appropriately identified in the study design, the impact should be evaluated, and methods to address these should be defined before the start of the analysis. For example, removing patients from the cohorts because of missingness or lost to follow-up is discouraged as this might result in bias of study results. Instead, inferences for missingness and assessments of impact of missingness should be made.

When evaluating RWD sources the following must be considered:

- Step 1: Develop a protocol for the RWE study
- Step 2: Establish a data selection plan
  - Is the data fit for purpose?
  - Is the data reliable?
- Step 3: Establish a Data Quality Review Plan
- Step 4: Establish data handling rules for data anomalies (e.g. missing data)
  - If not using randomisation, consider how to control for unknown biases or show that the cohorts are comparable, especially if the RWD is used as the comparison arm and an RCT for the treatment arm
  - Proper documentation of matching algorithm and any specific checks, conversion, or handling rules for the input data

- Step 5: Establish stable data transfer agreement, to align on data transfer and ingestion
  - Ensure systems used for data storage and acquisition transformation are CFR Part 11 compliant (if necessary, ensure proper auditing)
- Step 6: Agree on the internal data model for ingestion and storage and determine how/if conversion to SDTM is required (relevant in case data will be submitted to regulatory authorities)
- Step 7: Define the analysis data model (ADaM) (relevant in case data will be submitted to regulatory authorities)

Data Standards

Standards for data collection, organising, formatting, managing and transmitting real-world data (RWD) follow different procedures compared to conventional clinical trials. For example, electronic healthcare (EHR) data is currently transmitted using HL7 V2 messages and is mandated by the Office of the National Coordinator (ONC) to change to HL7 FHIR as of 2022. Randomised clinical trial data collection and submission standards are governed by the FDA, who has mandated the use of Clinical Data Interchange Standards Consortium (CDISC) standards for the submission of study data. The FDA currently has the authority to request RWD in CDISC format but recognises the standard may present a challenge as it was not designed with RWD in mind. When designing a prospective or retrospective trial using RWD, involve relevant integrated data analytics & reporting (IDAR) functions (Statistical Programming, Data Management, Data Acquisition and Data Transparency), as well as Data Science, Privacy and Epidemiology, in discussions around data ingestion and submission. Also, consult with the FDA review team to ensure the RWD is fit for purpose.

Some differences between data standards in typical clinical trials and RWD:

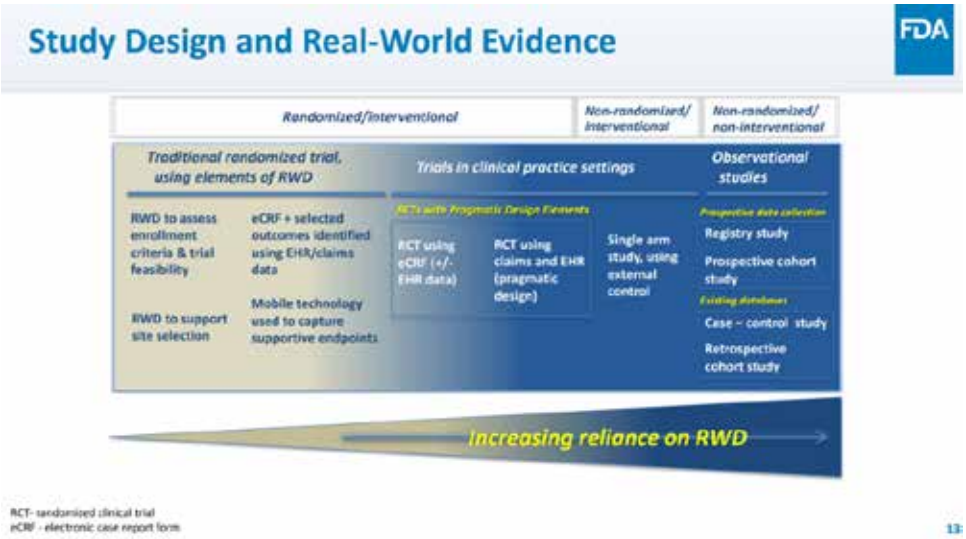
- Clinical trials:
  - Current standards required by the FDA
    - Study Data Tabulation Model (SDTM)
    - Analysis Data Model (ADaM)
    - Standard for Exchange of Nonclinical Data (SEND)
    - Study data definition (Define-XML)
- Real-world data:
  - Non-standard, non-normalised
  - OMOP
- Government agency, commercial and organisation-specific common data models (CDMs)
    - Fast healthcare interoperability resources (FHIR): Currently, FHIR is being used by leading EHR vendors, and government agencies of the United States, Canada, Australia and Europe. Medical insurance companies initiated a project called Da Vinci to accelerate FHIR adoption.
    - Observational Medical Outcomes Partnership (OMOP) OMOP Common Data Model: This is observational health outcomes data with medical terminologies around the world aligned in a standard format and is used by researchers for adverse event surveillance of the marketed drugs.
  - Common data models, e.g.
    - Sentinel (designed for claims data and being expanded for EHR data): The FDA leads and is the primary user of this data model initiative.
    - Informatics for Integrating Biology & the Bedside (i2b2): This is a USA NIH-funded initiative directed to address computational challenges while dealing with heterogenous data obtained from clinical care settings.
    - Accrual to Clinical Trials (ACT): This model is used to integrate the i2b2 repositories that are linked with the shared health research information network platform.
    - Patient-Centered Outcomes Research Network (PCORnet): This is a patient-reported outcomes data model collected through EHR systems, which ensures the data collected is thoroughly screened for conformance and completeness.
    - United States Core Data for Interoperability (USCDI): This standard is developed with an application programming interface certification criteria in accordance with the Cures Act Final Rule.
    - U.S. Department of Veterans Affairs Electronic Health Record (EHR) System.
    - National Cancer Institute (NCI) Cancer Data Standards Registry and Repository (caDSR).

Data Analysis

Study Design

To conduct an RWD study in order to document or assess the usage of a medical device or treatment, observational, descriptive or non-comparative designs are the most appropriate. These study designs can help gain information about the modalities of prescription and usage of the product in real-world settings (e.g. patient and HCP characteristics, therapeutic strategies, off-label use), patients' quality of life (QoL) and the security profile of drug usage, amongst other insights. Although these study designs help identify contextual elements regarding the potential effect of a drug on a patient, these cannot be used to claim any causal relationships.

If the purpose of an RWD study is to analyse the effectiveness and/or safety of a drug compared to another therapeutic schema, comparative study design could be considered. For studies without randomisation, regulatory authorities recommend implementing measures to minimise indication bias, in particular due to the use of causal inference methods in an observational situation, such as adjustment, matching or the weighting when the conditions for applying these methods are met. Other types of study designs can be used depending on the research question. The chart shows that although RWD can be used to address various research questions, certain types of analysis have a higher prevalence of RWD use than others.



Study Data

To ensure relevant and reliable source data is used for analysis, particularly for submission studies, the following should be accounted for:

- Detailed documentation of the inclusion/exclusion criteria and the representativity of patients per country included within the RWD study.
- Ensuring the preselected population is representative of the future population treated by the drug after registration.
- Identifying the variables and corresponding assumptions needed to create computable phenotypes of required values, such as baseline characteristics, lines of therapy, drug usage, efficacy endpoint and date of death.

Missing Data

Handling missing data is important to ensure that correct conclusions are drawn from the data, specifically the treatment effect. Traditionally, simple methods of analysis, such as analysing complete cases or data imputation (e.g. last observation or mean observation carried forward) were used. More recently, researchers are being encouraged to consider the mechanisms behind the missing data, i.e. missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR), and assumptions made to analyse the missing data. The estimands framework guides the formulation of these mechanisms in terms of intercurrent events and formally describes the estimated treatment effect (Committee, 2020) [Ref 3] (ISPOR 2022).

Confounding Variables

Confounders (or confounding variables) affect both the dependent and independent variables and are an important factor to account for and control in statistical modelling. Presence of confounders can result in incorrect treatment effect estimates. In traditional clinical trials, confounding is controlled by regulated and randomised data. However, in RWE studies, randomisation is not possible.

The FDA has released draft guidelines (Appendix A item 8) on how to account for and control confounding effects in randomised clinical trials. Principles offered in the guidelines, such as stratification, matching and weighting, can also be applied to RWD/RWE studies. This is particularly important if using RWD/RWE as the comparator arm for registrational purposes.

Matching

Comparable treatment arms are important to make accurate safety and efficacy assessments of treatments under study. In a traditional clinical trial, 'comparability' is ensured by randomisation or strict inclusion/exclusion criteria. In RWD/RWE studies, which are not randomised, patients selected from RWD sources are 'matched' to patients from the clinical trial data. Two matching methodologies are described below:

Eligibility criteria

Key eligibility criteria from the clinical trial protocol is used to match patients. Eligibility criteria used are generally selected based on literature reviews and/or statistical methodologies.

Propensity matching

Propensity scoring (to ensure comparable treatment arms) can be done if the same variables are present in both the RWD and clinical trial data. Based on all relevant covariates, a score is calculated for each patient in each arm. Patients are then matched based on this score.

Weighting can also be applied when developing the matching algorithm. In case of missing data, correct assumptions and inferences need to be made when calculating the score. Based on sample size tests and the number of patients available in RWD and clinical trial databases, matching can be done on a ratio of 1:1, 1:2, etc.

Heterogeneity and Bias Assessments

- Heterogeneity is an inherent characteristic of RWD due to varied and non-standardised data sources. There can be multiple reasons for heterogeneity to occur in RWD (several are listed below) and if not handled properly, these can result in biased results.
- Use of different treatment protocol in regular clinical practice (medication tiering and formulary decisions)
- Use of multiple information systems for data entry and metadata assignments
- Variability of data entry policies and protocols followed by HCPs
- Different national registration requirements
- Different populations in the database
- Different length of patient follow-up
- Different visit schedules affecting the accuracy of the window selection

Insufficient pre- and post-study data can also result in assessment bias. Therefore, the protocol should account for potential left truncation/censoring and other types of data-limiting issues that can occur in RWD. Assessment bias can also occur due to lack of proper tracking of prior treatment in a real-world setting. This can result in under- or overestimation of the effect of the drug.

Regulatory Considerations

Although this white paper summarises regulatory guidelines and frameworks for the EMA and FDA, other regulatory authorities, such as Australia's Therapeutic Goods Administration (TGA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA), also have defined guidelines on the use of RWD/RWE. It is the responsibility of the sponsor to ensure all local regulations are followed.

The U.S. Food and Drug Administration (FDA):

- The FDA requires that sponsors submit the protocol and SAP for review and approval before conducting the study. This is to ensure all essential elements of study design – data source, collection and analysis; study conduct; and final reporting – are predefined to avoid bias. For each element, the protocol and final study report should describe how that element was ascertained from the selected RWD data source including applicable validation studies.

The 21st Century Cures Act (1), enacted on 13 December 2016, mandated the FDA to create a framework to evaluate RWE to support marketing applications for new drugs or new indications for drugs already approved. In response, the FDA published its Framework for FDA's Real-World Evidence Program in December 2018 (2). The framework outlined three areas of consideration for the FDA when evaluating any analysis based on RWD in support of a marketing application: whether RWD is fit for use, whether the study design can provide adequate evidence to support the hypothesis and whether the study conduct meets regulatory requirements.

In the fourth quarter of 2021, the FDA issued four guidelines which expanded on the previous version, as well as provided implementation strategies for using RWD to support marketing applications for drugs or biological products:

- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision Making for Drug and Biological Products (3): This guidance primarily focuses on three areas related to the use of RWD extracted from EHRs and claims data: selection of data sources to appropriately address the research question; development and validation of study design elements; and preserving data provenance and quality throughout the study life cycle.

- Data Standards for Drug and Biological Product Submissions Containing Real-World Data (4): This guidance outlined the FDA Data Standards Catalogue (5), which is the accepted set of data standards principles required when submitting RWD in support of a marketing application. The catalogue follows the CDISC principles. The guidance also included RWD to CDISC mapping formats and required documentation.

- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry (6): This guidance provides assessment criteria to assess and ensure data registries are fit to use for regulatory decision-making analysis.

- Considerations for the Use of Real-World Data and Real World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (7): This guidance discusses the applicability of 21 CFR Part 312 (Investigational New Drug Application) to studies that use RWD in support of a regulatory decision for the safety and effectiveness of a drug.

European Medicines Agency (EMA)

On 22 October 2021, the EMA finalised their new guideline for registry-based studies (EMA/426390/2021). The purpose of this new guideline is to give recommendations to marketing authorisation applicants and holders on the methodology for using patient registries to run registry-based studies. Our white paper will summarise the main points discussed in the EMA's guideline surrounding this initiative for using patient registries to run registry-based studies.

First, to avoid any confusion on the concept of registries, a clear comparison is made between registry and registry-based studies in that a patient registry is an organised, open-ended real-world data collection system to identify specified outcomes for a population defined by a particular disease, condition or exposure. On the other hand, a registry-based study is driven by a specific research question, as per the instructions given in the protocol, which draws upon data collection infrastructure or patient population of one or more patient registries. Subsequently, the differences in duration of follow-up, patient enrolment, data collection, analysis plan and data quality management are also discussed.

In terms of looking at each component of differences in more detail, it is made clear in the guideline that the timelines in the duration of the follow-up for patient registries tends to be long term and open-ended, whereas the timelines for registry-based studies are driven by the study objective(s) along with the study data collections and analysis plans. Similarly, patient enrolment for registry-based studies is defined by the research question(s) and may contain a subset of the patient registry population, which is confined to these criteria in comparison to patient enrolment in a patient registry, whereby this involves the general enrolment of all patients with the particular disease or condition.

The data collection for registry-based studies is also restricted by the procedures outlined in the protocol and additional data may be required that is not routinely collected by the patient registry. The scope of data collection within a patient registry covers a fairly large range of elements depending on the purpose of the registry. The statistical analysis plan in registry-based studies is specific to the research question(s) within a separate document from the study protocol and registry protocol, whereas in a patient registry, data analysis is performed at routine intervals as described in the predefined outcomes at time points which can be found in the registry protocol. Data quality management among registry-based studies is specific to the study and its implementation is via a risk-based approach; by contrast, in patient registries, data quality management is applied on a routine basis.

Further to discussing the differences between registry and registry-based studies, the EMA delves into how marketing authorisation applicants and holders will be able to use the findings of registry-based studies. The acceptability of this evidence as a source for regulatory purposes is dependent on the regulatory assessment criteria for the medicinal product being studied, and the EMA's advice is for the study protocol to be published and to seek early consultation via national competent authorities and the EMA's scientific advice and protocol assistance when marketing authorisation applicants and holders wish to propose the use of a registry-based study. The use of registries depends on the stage or type of clinical trial the registry data is based on, for example the pre-authorisation phase or the post-authorisation phase. The use of registries will also apply when assessing scenarios such as the effects of the medicinal product administered during pregnancy and breastfeeding.

Once the uses of registry-based studies are addressed, the EMA provides a methodology as to how marketing authorisation applicants and holders can plan a registry-based study, along with the legal obligations and regulatory requirements for each activity performed for using registry-based studies. A detailed overview is also provided regarding good practice to have in mind for the use of patient registries, which is followed by a useful checklist for assessing the suitability of using registries for registry-based studies.

Abbreviations

CDER	Center for Drug Evaluation and Research
HCP	Healthcare Provider
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
RWD	Real-World Data
RWE	Real-World Evidence

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Appendix A – Guidances

(1) https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf
(2) https://www.fda.gov/media/120060/download
(3) https://www.fda.gov/media/152503/download
(4) https://www.fda.gov/media/153341/download
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