FACT SHEET

Real-World Evidence (RWE)

Benchmarking quality and compliance standards

Data quality standard to be defined

Real-World Data (RWD) is any data that is collected in the context of the routine delivery of care, as opposed to data collected within a clinical trial where study design controls are established around what is collected in the form of source data, with the requisite data elements available for sound clinical and statistical analysis.

We also expect to see greater sharing and harmonization of definitions for data quality and the expected data quality checks as we collaborate across organizations able to link datasets from multiple sources or run data quality checks from one healthcare network to another. We need to establish the minimum requirements for data curation that will vary depending on the dataset and the study, but for now the data curation process must at least indicate whether the data can answer the research question within the context of the intended use.

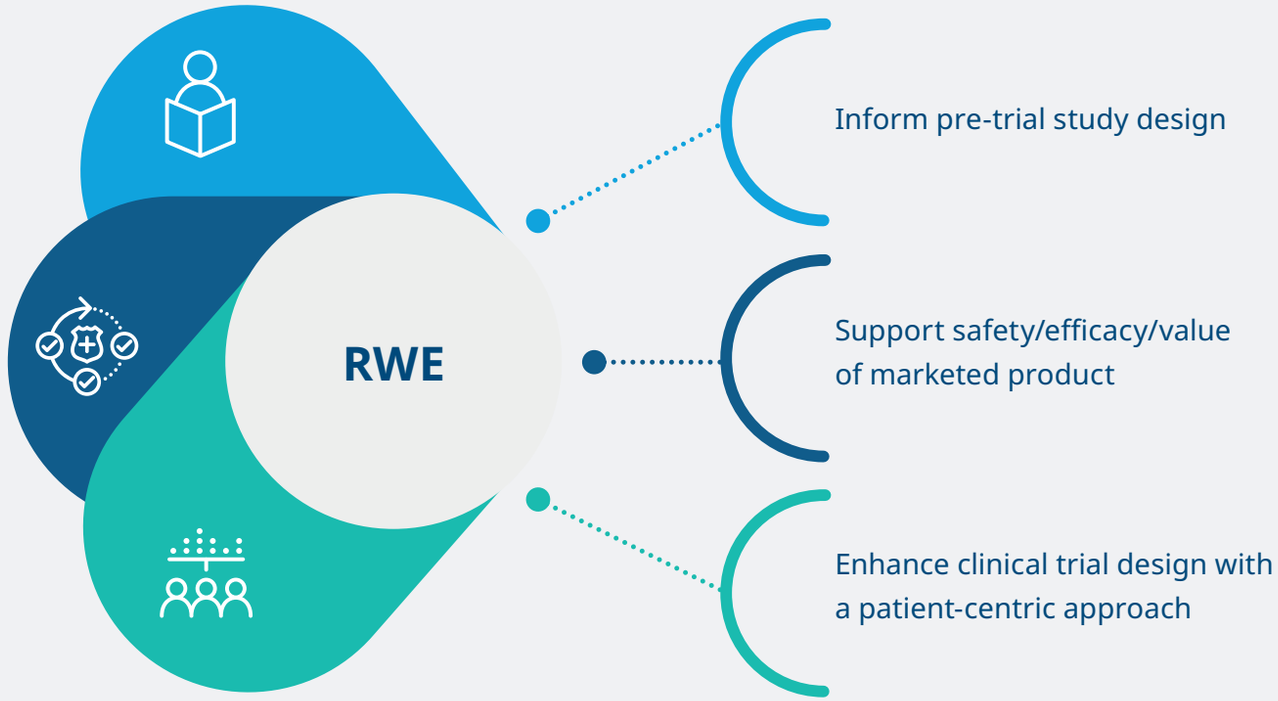
Until the regulatory standards for RWE/RWD are established with definitive criteria for requirements for data quality we must consider building out our existing quality management system (QMS) with parameters set by FDA's Quality Framework.

FDA's Quality Framework

- RWD is fit for use
- The trial or study design generates convincing and reliable data to answer the regulatory question
- Whether study conduct meets FDA regulatory requirements e.g., study monitoring and data collection

The goal isn't data quality, it is "evidence quality" and making the convincing argument to the regulators that the Real-World Data (RWD) is suitable for regulatory use. Not all studies require the same level of certainty and regulatory determination when it comes to evidence of quality. For example, studies of overall utilization patterns for exploratory analyses will require a different level of certainty than a comparative study intended for policy or regulatory decision-making.

RWE VALUE-ADDED PROGRAM



A sponsor has already framed the clinical QMS around the tenets of assuring data quality and performance compliance have been achieved prior to submitting data to the regulatory authority. As we look towards augmenting the traditional clinical QMS to include constraints impacting the Real-World Evidence (RWE) program, we can add value throughout the drug and device development and commercialization lifecycle from pre-launch to post-marketing applications.

ALCOA-CCEA vs. SPIFD

Good Clinical Practice (GCP) and the attributes for data quality have been known by the acronym ALCOA-CCEA: Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available. In the clinical trial setting, we operationalize ALCOA-CCEA through key study-related workflows that are standardized, validated and controlled through structured data collection methods. These workflows are tied to GCP responsibilities for the Clinical Investigator, which are reaffirmed in auditable regulatory — also called essential — documents and, of course, verifiable through the collection of the original "primary" data referred to as source documentation.

However, in the RWE setting, the standardization and validation of tried-and-true methods are not regulated, therefore the ability to verify the reliability of the RWD is not that simple. The Structured Process to Identify Fit-For-Purpose Data (SPIFD) framework is considered a data feasibility decision tool that provides the step-by-step process to assess both data relevance and operational data issues to justify the data selection when assessing source documentation wherein ALCOA-CCEA cannot be achieved.

Verifiable source documentation for RWD elements includes, but is not limited to, paper or electronic inpatient and outpatient medical records and case histories, diagnostic laboratory and imaging data, patient preference information, patient-reported outcome measures, UDI and other device identifiers, and performance data that exists within the device such as self-diagnostics, error codes, and patient diagnoses/treatments delivered.

ALCOA-CCEA will continue to be the goal, with the SPIFD decision tool providing the constructs as we retool and restructure the clinical QMS framework.

QMS in the RWE setting

Before we look organizationally at the sponsor to determine any gaps in key functional areas that would support the RWE program, let us remember step one of the study feasibility process, which is to identify appropriate RWD sources to address the specific regulatory question.

We will consider this framework as we develop programmatic enhancements towards the existing QMS leveraging GCP functional area resources, systems, processes and procedures. Organizations should perform an initial gap assessment to determine areas to which additional standardized processes and quality control measures should be applied. Step two is after we identify the RWD source, which may be sources held "in-house", which makes it easier to conduct your own data queries due to internal access to data i.e., with closed studies, you may need to consider other data sources and data assets external to the organization, such as patient registries. That brings us to new roles, responsibilities and possible new regulations, or at least more guidance from the regulatory authorities.

RWE CLINICAL QUALITY MANAGEMENT SYSTEM (QMS)

New roles, responsibilities and regulations

Traditionally, we have roles and regulatory responsibilities for the sponsor, Clinical Investigator and the IRB/IEC in the ¬clinical trial setting. ICH E6(R2), ICH E8 and FDA 21CFR312/812 and 21CFR 56 delineate these roles and responsibilities quite clearly with defined contracts, agreements and reporting structures. In the RWE setting, these roles will need to be assessed not just from a regulatory expectation, but also from a legal patient privacy and data security perspective. Therefore, at this time, the FDA has not established legally enforceable responsibilities but instead has provided guidance documents describing the Agency's current thinking on the topic of RWE.

The RWE program now involves new roles that do not have defined regulatory responsibilities. Without these definitions, the way we collect RWD to support RWE could lead to cases of unreliability of the data source.

These new roles include the patient, which in the GCP setting we establish an agreement with through the Informed Consent Document (ICD). In the case of the decentralized clinical trials (DCT) model, the vendor is responsible for collection of data instead of the Clinical Investigator.

Are we shifting from the roles of the Institutional Review Board (IRB), Independent Ethics Committee (IEC), Data Safety Monitoring Board (DSMB) and DMC (Data Monitoring Committee) to other oversight committees responsible for assuring no bias and conflict of interest (CoI) are suggested in the design of the RWE study as well as introducing additional responsibilities and

activities surrounding adjudication and determining whether supplemental data sources are available and sufficient to provide any missing information or evidence required for an informed decision? What does the monitoring effort look like — not the typical onsite monitoring visit when data is collected at the patient's home or through a DCT model?

From the Clinical Investigator owning the responsibility for the primary data (source data) collection to other data owners or institutions (e.g., government body, non-governmental organization, university, healthcare system) requires additional legal and proprietary adherence to compliance standards.

So, from legal back to establishing new regulations to govern the RWE program may be difficult due to the multiple jurisdictions responsible for making regulatory and legal decisions across localities and global regions. How do we transverse across the patient journey, particularly in the U.S., without a national healthcare system that would provide the linkages between record sources to support common data elements?

How should you design your RWE QMS?

Are you confident your traditional clinical QMS is built on a foundation with the capability to expand and flex with the uncertainties the RWE program will bring while we wait for "gold standards" to be defined by the regulatory authorities? We can start with sound methodologies that can be replicated for identifying the provenance and characterization of the data source and set the parameters around standardization with an understanding that the chronological record of data flow, including stop-gap measures when adjudication is required, will lead us to confirming that the data extracted for analytical purposes is reliable and relevant to optimize the reliability, quality and usefulness of the data. IQVIA can work with you to determine your QMS needs.

IQVIA TECHNOLOGIES

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