ASSURING AUDIT AND INSPECTION READINESS – CONSIDERATIONS FOR THE USE OF RWD AND RWE IN REGULATORY DECISION-MAKING

A CONSIDERATIONS PAPER PRODUCED BY THE REAL-WORLD DATA AUDIT READINESS INITIATIVE AT TRANSCELERATE BIOPHARMA

DECEMBER 2023

FINAL VERSION

TransCelerate BIOPHARMA INC.
Accelerating Answers.

Contents

Document Intent

As defined by the US Food and Drug Administration (US FDA), Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Similarly, Real-World Evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.[1] RWD reflect the experience of patients in real-world settings rather than clinical trials, and thus, there are inherent challenges in assessing and ensuring data quality. An argument can be made that imposing clinical trial standards (e.g., Good Clinical Practice or GCP) may not always be feasible or appropriate. Health authorities are starting to provide RWD-specific clarity on expectations regarding data quality and how stakeholders can demonstrate that RWD are reliable and relevant for regulatory purposes. This document and the considerations described herein are intended to help sponsors and other stakeholders such as data service providers, in appropriate circumstances, demonstrate to health authorities that specific RWD sources can serve as a reliable basis for regulatory decisions regarding product effectiveness.

This document was informed by regulatory guidance and frameworks intended to help ensure both the reliability and relevance of RWD for regulatory decision making. Considerations related to the accrual, provenance, completeness and accuracy of RWD focus on the processes and procedures followed in order to demonstrate the integrity or reliability of the data. Considerations regarding relevance are intended to help ensure that a RWD source includes data required to answer a specific scientific question. Taken together, the considerations help inform whether RWD are fit for purpose for regulatory decision making. The considerations are robust, but not meant to be exhaustive, and will vary depending on the specific use-case, therapeutic area, and other circumstances. Accordingly, the considerations are not intended to be applied rigidly or exclusively nor to be viewed as the only approach to audit readiness in studies that incorporate and rely on RWD. Each sponsor, data service provider, or any other stakeholder must decide for themselves how best to use RWD/RWE, incorporate RWD into study design and execution, and how best to convince regulators (during the audit and inspection processes or otherwise) that RWD/RWE being proposed is fit-for-purpose to answer specific scientific questions to support regulatory decision-making.

Intentionally, the suggested considerations can be similar or overlapping across the different pillars. The intent of this document is to provide a snapshot of potential considerations based on the information available at the time this document was released. Readers may select which considerations are relevant for their situation or timepoint in the process of assessing and using RWD for regulatory purposes. Although we expect future adaptations, clarifications and changes in the related health authority guidance or regulations, we do not plan to issue updated versions of this considerations document. Organizations may elect to use this version to create or adapt their own set of standards or Quality Management System documents.

TransCelerate is presenting these as considerations and not requirements because: (1) individual companies are best situated to decide whether and to what extent each applies in a given submission; and (2) only regulators have the authority to provide requirements. There are many relevant parties involved in the generation of RWD and RWE. This document outlines some

considerations regarding data quality but does not dictate who is responsible for specific tasks.[a] Sponsors and data service providers will need to work in collaboration, as a practical matter, to define the considerations they find necessary for their specific use-case including role expectations, in other words, who does what.[b] This is an opportunity for data service providers and sponsors to collaborate as a means to find new and novel ways to produce regulatory ready data.

TransCelerate recognizes that while the compliance burden may rest primarily with a sponsor, satisfying compliance requirements often requires substantial support from other stakeholders including sites and data and technology vendors. Sponsors and these other stakeholders may want to consider proactively addressing how any such burden will be managed without unduly burdening any particular stakeholder.

The authors of this document also acknowledge that the considerations listed are not all-inclusive and in addition not all use-cases will require that all considerations are met. It is intended to support sponsor companies and other stakeholders that deal with or manage RWD in efforts to meet the health authorities' expectations regarding data quality when using that data to support a regulatory decision.

[a] This paper is intended to help relevant stakeholders engage with regulators and persuade them that RWD can be used reliably for regulatory decision-making. This paper does not seek to address approaches for complying with any specific regulations or laws. Entities collecting and using data and/or submitting real-world data to health authorities remain solely responsible for ensuring their own compliance with any applicable laws and regulations.

[b] Several of the considerations in this paper may lead a party to consider changes to a clinical trial agreement or other contract. Discussing content of contractual terms or whether a given issue should be addressed in a contract is beyond the scope of TransCelerate initiatives and left to the discretion of individual companies. Similarly, any public comments received asking for contractual language or steer were not addressed as they are beyond TransCelerate's remit.

Background & Rationale

In recent years, increased emphasis has been placed on the potential for RWD and RWE to inform regulatory decision-making related to the effectiveness/safety of pharmaceutical products. Recent activities by regulatory authorities around the world (e.g., US Food and Drug Administration (FDA) release of guidance documents; establishment of the Heads of Medicines Agencies (HMA) / European Medicines Agency (EMA) Big Data Steering Group and its associated outputs) serve to reinforce this emphasis. In 2018, the US FDA published an initial framework related to the use of RWD/RWE to support regulatory decision-making for medical devices.[1] The 2018 framework defined concepts of data reliability, relevance, and quality control all with the goal of assessing whether a given data source is "fit-for-purpose" to address questions on a given medical devices for consideration by regulators. These initial concepts were then expanded by the Duke-Margolis Center for Healthcare Policy (Duke-Margolis) through a series of workshops that included healthcare experts from academia, government, and the pharmaceutical/biotechnology industry.[1–3] These workshops further developed this framework by describing key conceptual components of data reliability, relevance, and quality such as data completeness, provenance, plausibility, and accuracy. Subsequently, in 2021, the US FDA published a series of guidance documents that outlined key considerations for RWD and RWE, including the conduct and use of non-interventional studies which included information on the assessment of RWD quality.[5-7] Similar efforts to develop guidelines for the use of RWD are currently underway by the EMA as well as health authorities in other countries[4–6] and while finalizing this document, the FDA released a final guidance "Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products" that clarifies many of the expectations the agency has for data quality and the resultant needs to aid regulatory decision-making. [7]

While these expansions and clarifications of the data quality assessment frameworks are important to better assess whether a RWD source is "fit-for-purpose", there is a gap in translating them into a functional format for use by data service providers/aggregators as well as end-users such as pharmaceutical product developers to enable these stakeholders to demonstrate to regulators that the RWD/RWE used in specific trials are fit-for-purpose for regulatory decision-making. Indeed, a recent publication suggested that "The research community should prepare for a future in which data quality requirements are carefully calibrated to match the risk and impact of the decision being made."[8]

Several "checklists" assess the quality of RWD that are aligned with the developed frameworks.[9–13] This paper does not attempt to assess the quality or utility of these checklists, which focus largely on downstream aspects of RWD use such as observational or non-interventional study design and the quality of data analysis rather than quality related to the collection and handling of the source data (or the "upstream" efforts). Therefore, additional efforts are needed to develop practical approaches for establishing that RWD sources are suitable and "fit-for-purpose". Approaches would ideally utilize the concepts defined in existing frameworks and incorporate feedback from both providers and users of RWD to generate methods for demonstrating to regulators the quality of RWD sources and building regulators' confidence in the processes used to create data sets that may be used in regulatory decision-making.

The goal is to identify the types of issues/questions that sponsors would need to address in their study documents, which in turn should help stakeholders working with sponsors to determine what documentation about their data collection and database quality assurance processes and records may be sufficient to satisfy the regulatory requirements relating to data quality, depending on the intended use. One key benefit of this project is that it will help all parties contributing to data used for evidence (such as researchers, sponsors and "data suppliers") to better understand why it is important to document how they collect, clean, harmonize, transform, or otherwise curate RWD, and will help to put forward coherent, transparent written explanations on data collection to sponsors and regulators.

The TransCelerate RWD Audit Readiness Initiative was started in 2020 to operationalize the thought leadership stemming from Duke-Margolis/FDA and others on the use of RWD/RWE in regulatory decision-making for product effectiveness. This initiative leveraged health authority and DSP interactions to develop an approach to documentation that supports quality management (quality assurance, quality control, and audit) for RWD sources to assuring health authorities that RWD can be sufficiently reliable to justify use in regulatory decision-making. Specifically, the RWD Audit Readiness Initiative sought to develop a functional list of key considerations of RWD quality that are derived from and meant to complement current frameworks and guidance documents generated by institutions such as the FDA, EMA, and Duke-Margolis. This list of considerations can assist researchers interested in using RWD in (a) helping them to identify factors and circumstances that may affect a health authority's views about data reliability (b) identifying possible types of documentation that would help establish the reliability of RWD/RWE during regulatory audits and inspections. The overall goal of this list of considerations, when used in conjunction with published frameworks and guidance documents from regulatory agencies and other groups of experts, is to help provide insights into what factors and circumstances may affect a health authority's willingness to accept and use RWD as a basis for regulatory decision-making in the drug approval process (understanding that RWD may or may not be used as the sole basis for regulatory decision making). The considerations outlined here are suggestions and the organizational processes, methodologies, and quality activities should be described in organizational Quality Management Systems.

Overview of Methodology

Step 1: The considerations list was developed in a step-wise fashion summarized in **(Figure 1)**. First, a comprehensive literature review was conducted to identify and summarize key concepts of RWD quality.[3,4,8–10,13–36] These key concepts, termed "pillars", were defined as "Relevance"/ "Accrual" / "Provenance" / "Completeness" / "Accuracy" based on prior work by FDA and Duke-Margolis **(Figure 2)**. These five pillars were further categorized under the broad categories of Data Reliability and Relevance based on the findings from the literature review. In addition, key study documentation that could be used as evidence to support each pillar was also identified as part of this literature review.

Step 2: The output of this literature review was presented in draft format to a broad set of stakeholders to obtain feedback on the definitions of the conceptual pillars and the types of supportive documentation that could be used to demonstrate quality of a RWD source. In 2021, the RWD Audit Readiness Initiative sought feedback from data service providers (DSPs) via a survey regarding their views on what would feasible to include in an "Audit Readiness" tool targeting data relevance and reliability, from the perspective of organizations who provide RWD for research purposes. For instance, we were interested in knowing what types of documentation would be feasible for organizations who provide RWD for research purposes to share with their clients/health authorities to help verify the relevance and reliability of the RWD they provide. The survey asked several questions aimed at identifying the types of documents that could ultimately be made available to regulators as a means of building confidence in RWE/RWD for use in regulatory decision-making. The results of that survey made it clear that DSPs would be more comfortable sharing information if tied to a health authority request. We believe that, by working together to allow auditors and inspectors to examine documentation covering methodologies used to collect, manipulate, and report data used in regulatory decision-making, sponsors, other consumers of "purchased" RWD, and DSPs can build regulatory trust in RWD/RWE, collectively expand usage of RWD/RWE, create new business opportunities for DSPs, and thereby capture benefits for DSPs, data users, regulators, and patients.

Step 3: The literature review and feedback received formed the basis for a brainstorming exercise to develop an initial list of considerations under each conceptual pillar. The creation of the considerations list was accomplished by members of the TransCelerate Audit Readiness Initiative team. These considerations were initially phrased as questions about documentation that could help DSPs and/or sponsors demonstrate quality under each conceptual pillar in a real-world data set. Considerations were focused on understanding processes utilized by DSPs/sponsors to evaluate and assure the quality of the RWD.

Step 4: This initial list was then reviewed and refined to make language consistent across each as well as identify potential considerations that may cover multiple conceptual pillars (in this exercise we acknowledged that there may be redundancies across pillars but reasoned that leaving those in brought some value as it enabled each pillar to "stand alone"). Lastly, for each consideration, a rationale was provided to support the inclusion of a given consideration in this document as well as to provide a quick reference for each consideration with respect to its relationship to the underlying conceptual pillar and value in proving to regulators that data are fit-for-purpose.

Step 5: Once the workstream members completed Step 4, the document was released for "Public Review" from November 2022 to February 2023. Direct feedback was sought from pharmaceutical companies, data companies, and thought leaders in the area. Furthermore, TransCelerate sought review through other channels, most notably LinkedIn®. The LinkedIn® post had 188,808 "impressions," 1,185 "clicks," and 1,182 visits to the TransCelerate website where the draft Considerations document was stored. Substantial and detailed feedback on the draft Considerations was received from 26 unique organizations who provided over 250 comments. TransCelerate is very grateful to all commenters for their thoughtful consideration of this paper as well as the effort, knowledge, and thought that went into the comments received.

Step 6: After "Public Review", workstream members reviewed all comments and worked to address them. For comments received that focused on subject matter within this Considerations document's intended scope, the workstream members determined how best and to what extent to address the comment within this document. Some comments did not call for a specific edit or were addressed by edits made in response to other comments. Several comments focused on subject matter outside this document's intended scope. To avoid unmanageable "scope creep", the team decided not to expand this document to address such comments, notwithstanding the insightfulness reflected in many of the comments. Some other comments would have required fundamental changes to the structure of the paper, and accordingly, could not be addressed at this time. This final version of the document is the result of that process.

Figure 1: Audit Readiness Considerations Development Process

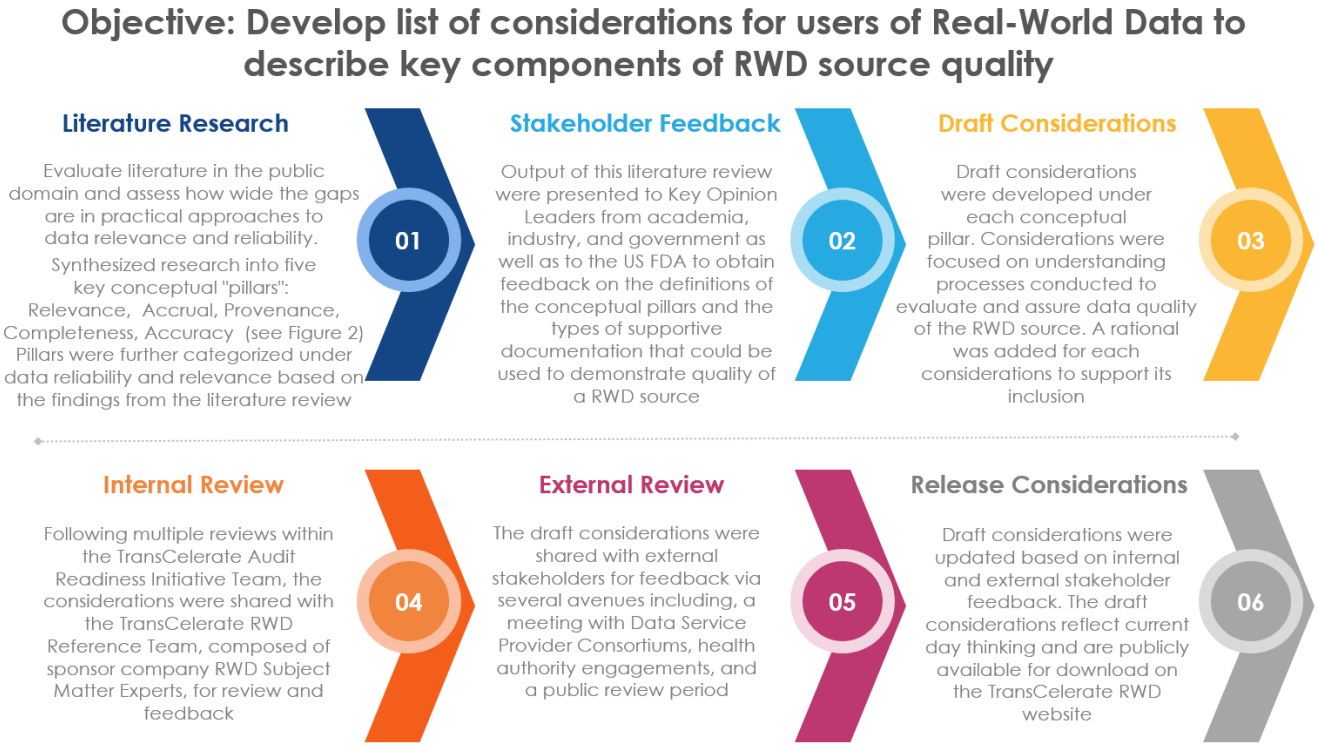
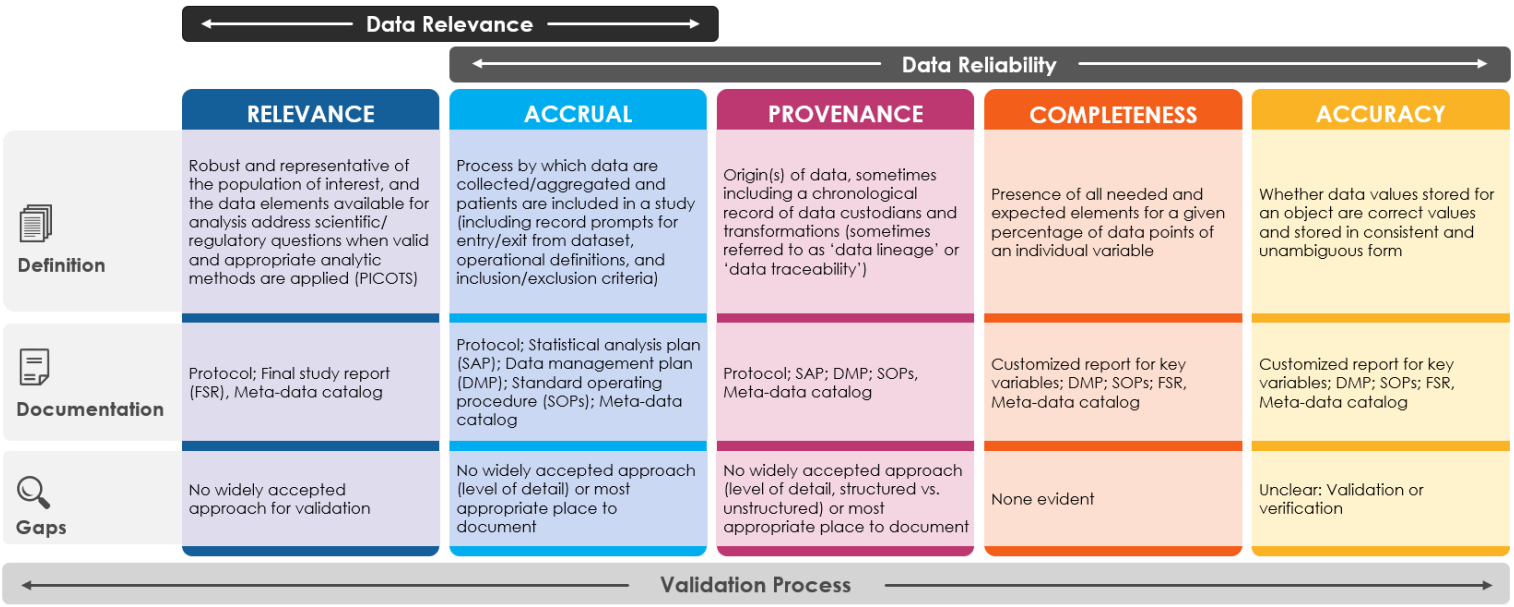


Figure 2: Landscape Assessment Insights Pillars[2,3,10,15,37]



Term Definitions

Throughout this document various terms are used that merit definition. The following glossary defines how the TransCelerate Audit Readiness working group interprets each term as used in this document. Guidance/frameworks from FDA and EMA can provide more details. We acknowledge that there are cases where both variations my exist in definitions within each organization as well as variations between different regulators. Accordingly, we recommend that these terms are defined at a project level to ensure common understanding when using this document.

Accrual

Process by which data are collected/aggregated and patients are included in a study (including record prompts for entry/exit from dataset, operational definitions, inclusion/exclusion criteria and consent/assent).

Accuracy

Whether data values stored for an object are correct values and stored in consistent and unambiguous form. EMA defined accuracy as "defined as the amount of discrepancy between data and reality."[38]

ALCOA/ ALCOA +

ALCOA and ALCOA+ refers to a set of principles used across industry to help articulate the basic requirements of documentation and systems used in regulatory submissions. The ALCOA acronym breaks down as follows: Attributable, Legible, Contemporaneous, Original, Complete. The + refers to the following attributes: Consistent, Enduring, Available, Traceable. More information on these principles is available on the web.[1]

Audit Trail

Documentation that allows reconstruction of the course of events.[20] In the case of an electronic system, an audit trail will indicate the time and date of original entry, who entered it, time and date of any changes made and by whom, as well as the original and updated values as appropriate.

Completeness

Presence of all needed and expected elements for a given percentage of data points of an individual variable. EMA defines completeness as "completeness measures the amount of information available with respect to the total information that could be available given the capture process and data format."[38]

Data Management Plan (DMP) / Data Handling Plan (DHP)

A formal document that outlines what will be done with the data during and after a research project, documents the lifecycle of the data.

Data Dictionary

All the variable names and values that are available in the database.

Data Relevance

Whether the data adequately address the applicable scientific/regulatory question or requirement, in part or in whole, including whether data set appropriately captures exposures, outcomes, and covariate and whether the data are generalizable.

Data Reliability

Whether the data adequately represent the underlying medical concepts they are intended to represent.[1]

Data Service Provider (DSP)

Data holder, owner or aggregator that has the ability to transfer or share data with researchers, inclusive of host or owned data that is captured in the course of the patient journey.

Data Transformations

The process of converting, cleansing, and structuring data into a usable format that can be analyzed to support decision making.

Fit-for-Purpose

In the context of this paper, the term Fit-for-Purpose is used to describe the quality of the data as it pertains to its use in regulatory decision-making. The determinants are based on the specific use of the data and regulatory requirements.

Missing Data

Data that would have been used in the study analysis but were not observed, collected, or accessible.[6]

Marketing Authorization Holder

The Marketing Authorization Holder (MAH) is the entity given license to market, sell and/or distribute a medical product in a specific geography, could be a pharmaceutical or device company, contracted service provider, etc. This term is used in relation to real-world data connected to pharmacovigilance and adverse event reporting for safety surveillance.

Metadata

The descriptive data that characterize other data to create a clearer understanding of their meaning and achieve greater reliability and quality of information.[39]

Provenance

Records that enable tracing the origin(s) of data, sometimes including a chronological record of data custodians and transformations (sometimes referred to as "data lineage" or "data traceability").[40]

Quality Assurance

Consists of proactive and retrospective activities undertaken to evaluate whether prespecified requirements are fulfilled.[1]

Quality Control

Consists of the steps taken during data curation to ensure that the data meet prespecified standards and are reproducible.[1]

Representativeness

The extent to which the population in a data set represents an intended (larger) population.

Record Prompt

The class of events that prompt the creation of a record within a dataset (e.g., emergency room visit, dispensing or order written for a medication).

Sponsor

A clinical study sponsor refers to an individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical study or trial.[41]

Relevance Considerations

The following considerations and potential supporting documentation may help demonstrate whether the data adequately address the applicable scientific/regulatory question or requirement, in part or in whole, including whether data set appropriately captures exposures, outcomes, and covariates and whether the data are generalizable.

#	Relevance Considerations & Potential Supporting Documentation	Purpose of Consideration
1	**PICOTS framework:** Consider employing the PICOTS framework (or alternatives) to clearly lay out justification for relevance of the data source (EHR, claims, registry, other) and design. P: Patient population; I: Intervention; C: Comparator; O: Outcome; T: Timing; S: Setting	Situates this consideration in a broader scientific context and provides accepted framework for thinking through research question(s).[42]
2	**Analysis data sets:** It will be helpful to be able to list and describe all data sources contributing to the analysis. • How are the data considered "Fit-for-Purpose" under the definition described by Duke-Margolis and FDA Considerations? • Inclusion of information on system types, whether public or private, and purpose of original data collection should be thought of as a part of this consideration. What possible gaps or biases are inherent in the original datasets, what methods were used to overcome those issues?	• Showing how the data are considered "Fit-for-Purpose" under widely accepted definitions lends credibility to methods and conclusions.[46,47] • Duke Margolis defines Fit for Purpose as "guided by 4 distinct considerations: the question the research group is seeking to address, the clinical context within which RWE is being generated, the availability of RWD of appropriate relevancy and quality, and the application of trusted methods for turning RWD into actionable evidence. • Fit for purpose can be thought of as a real-world dataset that is meaningful, valid, and transparent, and therefore appropriate to answer a specific question in a particular clinical context. Fit-for-purpose RWD should be characterized as robust and representative of the population of interest, as well as of requisite quality to accurately capture critical endpoints and covariates."[48]
3	**Selection of data set: How was the original dataset selected for use?** • Describe how datasets were assessed for feasibility - which data sources were accessed when designing the study, summarize results from feasibility evaluations or exploratory analyses of those data sources, descriptions of the processes used in this regard will help create a level of transparency that can be used to show relevance. • Be able to explain and provide supportive rationale for the selection or exclusion of relevant data sources from the study. • Audit trails should be used in the datasets to show access and analyses performed.	• FDA states that datasets should be assessed for their feasibility and fitness for use. This can be done prior to writing a protocol to be efficient in the choice of datasets. • "Evaluations of data sources or databases for study design or feasibility purposes serve as a first step to (1) learn about the suitability of the data source or database to address the research question being posed and (2) estimate the statistical precision of a potential study without evaluating outcomes for treatment arms."
4	**Representativeness:** Consider documenting the answers to the following questions about the data sets used: • Is the patient population accurately represented in the selected data source? • Is the population the appropriate age, sex? • Is there adequate representation of racial/ethnic or socioeconomic groups? • Depending on the research question, are there enough patients in the subpopulation(s) of interest? • Is the geographic footprint appropriate? • Are inclusion/exclusion criteria for the study clear and measurable?	The patient population is a crucial aspect of study quality and must be selected so that the research question can be appropriately addressed.
5	**Database description:** Explanatory documentation of the database, including the characteristics of the patient population and a description of care settings (e.g., primary care; specialty care centers; tertiary care centers.) It may be helpful to consider drafting a storyboard to illustrate how: • The included individuals comprise an accurate representation of the population of interest. E.g., that the DISEASE X patients in your dataset are a reasonable representation of DISEASE X patients. • Does the data accurately capture the characteristics, outcomes and key co-variates that are clinically meaningful in a given disease area, e.g. (1) # of patients; (2) Average # of records per patient; (3) # of outpatient/inpatient encounters; (4) average # of healthcare encounters per year; (5) Average age of patient population; (6) Medicare/Medicaid patients (US only)?	• The basic information contained in the data set should be appropriate to the research question and be sufficient to fulfill the needs of the regulatory context for which the data will be used. • Basic info about the patients in used database is helpful to add context and assure that auditors and regulators are made aware of the purpose of each database. • Would provide a decision-action log outlining why data sources were selected.
6	**Measurement validity:** Consider validation and misclassification issues and how to document them. • Is there a potential for misclassification of exposure, outcome, or key covariates? • To what extent? • Is the misclassification differential or non-differential?	Awareness of measurement error as a potential source of information bias is important to understand the suitability of the dataset.
7	**Follow-up:** Consider providing a description of how long a patient is followed in the database (for example: on average, by categories, by time-period (e.g., <1 year, 1-2 years, 2-5 years, 5-10 years, >10 years, etc.). Similarly, it is important to understand population retention (for example, by looking at how much follow-up is available post-index date for study cohorts).	• Shows how the data are fit for purpose; for example, shows that the length of time a patient is followed is sufficient to answer a research question; population stability. • Additionally, this information could help inform RWE study design decisions by potential sponsor, e.g., by specifying how much follow-up time is available after patients' index dates.

#	Relevance Considerations & Potential Supporting Documentation	Purpose of Consideration
8	**Coding:** Consider potential questions about the coding systems and the versions used for capturing diagnoses, prescriptions, and procedures in the database and how to document resolutions in appropriate areas. • Is the system and its data easily able to be used to make like-to-like comparisons (standardized)? • Does the data use ICD10, CPT, LOINC codes? • Do the coding systems/versions available in the database offer the granularity needed to capture key study elements? Shows data usability.	Outlines applicability and robustness of dataset and reinforces that data are fit-for-purpose.
9	**Unstructured data documentation:** Is documentation available that describes the presence of unstructured data (i.e., physician notes, lab/imaging data, other unstructured sources) and methods of incorporation in data source.	Are the data contained in these notes adaptable and/or adapted, extracted, or otherwise characterized to enable use in endpoint evaluation.
10	**Publications:** Has there been any published or publicly available research based on the use of this database? Providing a list of any such research would be helpful (research with regulatory impact would carry more weight).	Can be helpful in establishing relevance in specific disease areas.

Accrual Considerations[iii]

The following accrual considerations and potential supporting documentation may help demonstrate the process by which data are collected/aggregated and patients are included in a study (including record prompts for entry/exit from dataset, operational definitions, inclusion/exclusion criteria and consent/assent).

#	Accrual Considerations & Potential Supporting Documentation:	Purpose of Consideration
1	**Data collection and aggregation:** It is useful to provide descriptions of the process/ methods for data collection and aggregation, such as: • How was the risk of extraction of missing data and implausible values minimized? • How were data discrepancies and duplicates handled?	The FDA Guidance for Industry, Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision Making for Drug and Biological Products states: As a part of the development of a data set, documentation of the processes by which data are extracted from its original source is key to proving data quality and reliability. [Citation]
2	**Quality checks:** What data quality checks were put in place to assure accuracy and completeness for example: • How were data error corrections made, what is the reasoning and timing during the data collection period, were there tolerance limits used? • Were process changes made by data holders, why and when, what was impact on data accrual and/or data quality checks? • Were there updates or changes in coding practices and versioning across the relevant study periods, relevant to variables of interest?	Documentation of these checks will allow the agency to recreate the analyses using the same parameters and datasets, thereby helping to validate conclusions reached.
3	**Timeliness of data:** Providing details about continuity of coverage (enrollment and disenrollment) in the protocol and about documentation when using EHR or claims given that patients may receive care from different providers over time will be a key element in study documentation. Also consider describing the timeliness of data availability, dates spanned by source data sets, continuity of coverage and duration of patient enrollment. • What methods were used to bring new data into a dataset? • How were changes tracked, what did/did not change? • How were new variables defined? • How were changes in patient care norms tracked and their impact? • What methods were used to link patient data from multiple sources?	• The FDA requires that methods and time windows for data accrual be described in documentation up front.49 • The validity of findings from a study using EHRs and/or claims data may depend on documentation of how patients flow into and out of specific health care insurance coverage plans and sites of health care delivery. • FDA has stated that sponsors should evaluate data to assure that it's fit for purpose to answer the research question. "FDA recognizes that evaluation of relevant data sources or databases is an important step in the design of a study and in evaluating a study's feasibility. Such evaluations of data sources or databases for feasibility purposes serve as a way for the sponsor and FDA to (1) assess if the data source or database is fit for use to address the research question being posed and (2) estimate the statistical precision of a potential study without evaluating outcomes for treatment arms."[50]
4	**Quality measures:** • What quality procedures and/or monitoring checks have been put in place to assure data quality? • What criteria was used to determine whether checks were appropriate for the intended use of the data?	Helps to show how the integrity of the data was checked and maintained.
5	**Data migrations:** • How was data migrated over time from the data sources used? • Consider and document any standard forms/tools. Is access to that tool available? If so, consider how access controls could be described, etc.	Shows how, why, when and by whom data may have been changed or updated and is thought to be a fundamental element of proving reliability.
6	**Incentives:** Was data entry incentivized in any way? If so, describe. • How does the pattern of incentives impact data reliability? • By whom is/was the incentive given (Registry holder, DSP, MAH) • Data entry incentive can be done indirectly, for example, by reimbursing the involved organization for different coding, more data monitoring, data checks, etc.	• Incentivized data entry may lead to data that is more complete or inaccurate.
7	**Privacy:** • What process was used to protect patient privacy in the datasets utilized? • If consent was not obtained, is there another basis for use of the data? • For example, could data be reverse engineered to re-identify patients, was data deidentified or anonymized, can the original consent be verified…etc.?	• When using patient data, appropriate controls must be in place to assure that permission or consent is given when required and identifying characteristics of patients are adequately masked to maintain applicable human subject protections. • Sponsor organizations are responsible for their own privacy compliance.
8	**Patient population characteristics:** Be able to explain or describe the patient population characteristics. • What efforts were made to ensure a diverse population / well-characterized subgroup was included? • What methods were applied to minimize selection bias and loss to follow-up? • How are rare disease population / small patient population characterized? • How is lack of disease heterogeneity handled?	Clarifies how bias was handled and shows how the data may be "Fit-for-Purpose".

[iii] Stakeholders are best positioned to determine whether and to what extent these considerations may apply to a particular submission.

#	Accrual Considerations & Potential Supporting Documentation:	Purpose of Consideration
9	**Sensor/wearables data:** • Did the data come from a wearable and/or another similar device? If so what type of device or sensor? What documents can be provided to validate the device and the resulting data? • What controls were in place to assure data integrity from those devices?	The use of medical devices or sensors can be linked to the degree to which data are complete and reliable as well, use of devices may be subject to scrutiny in the validation of that device for the purpose of capturing specific data points, too.
10	**Patient recruitment:** How was patient recruitment/inclusion in the study accomplished? • How were the patient inclusion and exclusion criteria applied? • Was the process of collecting consent documented and supplied as part of the provision of data and is there evidence the process has been followed?	Defining measures taken to assure the recruitment of relevant patient populations will help underscore that data collection will be fit for purpose.
11	**Data storage:** How data are stored, secured, retrieved and timely should be made available, to the extent allowed under agreements • What is the process for storing, retrieving and securing data and how is this documented? • Can data be made available in case of need? • Is disaster recovery process in place?	In case of inspections, audits, questions from regulators or for traceability reasons it is important to understand how data are stored, retrieved and secured. The timeliness is crucial for responding to authority request.

Provenance Considerations

The following provenance considerations and potential supporting documentation may help demonstrate whether the data provides an audit trail that accounts for the origin(s) of data, sometimes including a chronological record of data custodians and transformations (sometimes referred to as "data lineage" or "data traceability").

#	Provenance Considerations & Potential Supporting Documentation	Purpose of Consideration
1	**Analytic data sets:** To enable readiness for an audit or inspection, consider describing how datapoints in the analytic dataset can be traced back to original (source) datasets and how regulator access to analytic datasets can be facilitated. See FDA guidance for detailed discussion of data submissions. For example: • Consider how to describe and list the datasets used to create the analytic dataset. • Consider developing methods to prove how data traceability can be demonstrated. Use of audit trails throughout the lifecycle of data collection and aggregation processes is encouraged. Auditors/inspectors may require access to and the ability to review all datasets and descriptive materials so that they can be assured of traceability. • It should be noted that not all regulators have specifically called out the need to access patient level data and the degree to which access is required may depend on the regulatory use of that data.	• FDA has highlighted the need to be able to trace data back to the original source; this is a fundamental concept for US submissions. • FDA has also specifically highlighted the requirement to be able to view and access all original data sources and patient-level data used in an analytic data set.[50] • Although Provenance is not specifically called out in the EU Heads of Medicine Data Quality Framework, the framework does allude to it: Access to the source system and processes is often required when improving coherence involves approximating or clarifying the meaning of data, (e.g., for clarifications). It should be noted that in some cases the ability to trace back to the original source may not be possible. We suggest that a risk-based approach be used to determine the impact of that situation on the overall reliability of the dataset. For example, if a source dataset is being used as evidence of a primary endpoint, traceability is critical to proving the quality of that endpoint. • The inability to trace data back to an original source may impact the reliability and ultimately the acceptability of the data. Consider using alternate data sources to support endpoints or support conclusions reached. [51]
2	**Data custodians:** Consider a method to list and/or describe data custodians that were used over the lifecycle of the data collection process. • Was the source data manipulated/managed by 3rd party or other organization prior to be integrated into program-level dataset? • If so, what controls/processes are in place to assure data integrity?	• Shows chain of custody and enables a reviewer to trace back to original data. • Shows that there is a process in place to document chain of custody – processes facilitate a clear understanding of what they did and how ALCOA+ was achieved.
3	**Data transformations:** Consider documentation to help explain any data transformations performed. Consider the following elements: • Details of the transformation formulae or algorithms (if applicable) and the timing of when each transformation was made to reflect whether data were stable or frequent changes were made over a short period of time. • Detailed documentation of transformation is especially critical for unstructured data. • Describe and show traceability of transformations made to the data. • How do modifications to data impact that traceability? • Is there a complete audit trail?	• Detailed documentation of transformation enables a reviewer to trace back to original data. NICE framework [10] recommends that data curation be well-described, such that auditors or inspectors can understand what was done and how it may impact results and should include any curation performed prior to the evidence developer accessing the data wherever possible. • Processes should be in place to document chain of custody, facilitate a clear understanding of what was done, and how ALCOA+ was achieved. • Although data transformations also fall under the Accuracy pillar (#11), transformations also heavily impact traceability.
4	**Data source identification:** Plan to identify the data source(s) utilized and indicate whether the data were derived from a single or multiple provider/health system. If different sources had different data management, how did this affect the interoperability of multiple RWD data sources and what processes were followed to document the reconciliation of the final data set?	• Help the user/reviewer understand if there is more than one original source. • Help user/reviewer understand how different data management processes were conducted and how the data were combined? (Related to Accuracy #14)
5	**Metadata and audit trail:** Consider a method to describe the source dataset metadata and audit trail system for each original data source: Was data collection done as a matter of routine practice or are the data captured as part of a "bespoke" program or process? • What type of system does the data originate from (e.g., EHR, administrative data, registry, primary data collection, chart review, etc.)? • What information was collected, how was information coded/recorded, who performed collection or how (e.g., digital health tech)? • Were there changes to data collection over time? • Are the audit trails/metadata complete? i.e., do they fulfill the minimum ALCOA+ criteria? • Are the audit trails/metadata viewable/accessible? • Can the information be changed?	• Shows how, why, when and by whom data may have been changed or updated and is thought to be a fundamental element of proving reliability. • The EMA Data Quality Framework discusses the Foundational determinants of data quality and states that for data to be used in a regulatory decision-making context, at a minimum the processes that pertain to data generation and manipulation should be documented, true and verifiable. [51]

#	Provenance Considerations & Potential Supporting Documentation	Purpose of Consideration
6	**Details of linked/merged data:** During dataset linkage/transformation, were all data able to be added to the analytical dataset? • Were there expected/unexpected complications in merging datasets and a list of variables for which merging was done? • What was the process for reconciling duplicate information? • What tactics/methods were used to overcome those issues? • Were those tactics pre-determined or developed post issue identification? Indicate whether this impacted the endpoint analysis. • Were any data from the original source lost during the merging process? If so, please indicate what type of data. • What processes were used to monitor for any loss of patient data during the linkage, and whether the data are tokenized and/or curated. • How is linkage being conducted and are there standard processes used? • How a data point can be traced back prior to transformation? • How can the Accuracy, Completeness and Provenance of any linked data be established? • Are there rules around excluding data?	Gives assurance that the process for merging of disparate datasets is robust and characterizes or minimizes data lost during that process.
7	**Unstructured data:** How were unstructured data handled? • For example, do the original datasets contain notes that needed to be read/ understood/reconfigured to expose outcomes in a way that enables analysis? • If done via a machine-based process, was a robust process used to aggregate or create data for the data set? (This may include availability of validation and reliability documentation and could be found in functional specifications, testing documents or validation routines as examples. • If done by humans, describe the certification/training/inter-assessor reliability methods used and associated metrics.	Standardized methods are more likely to be reproducible and transparency around data curation is important.[4]

Completeness Considerations

The following completeness considerations and potential supporting documentation may help demonstrate the presence of all needed and expected elements for a given percentage of data points of an individual variable.

#	Completeness Considerations & Potential Supporting Documentation	Purpose of Consideration
1	**Process of data collection:** What is the process for data collection in the original data sets? Consider documenting in the DMP to include information on the following: • Which data is structured vs. unstructured? • For what intent was the original data collected? • How was the original dataset accessed and managed? • How was completeness of the dataset assessed? • Was there adequate capture of population, intervention/treatment, comparator, outcomes, in the appropriate study setting and with the appropriate duration?	Showing how data was collected, handled, cleaned, and reported builds understanding and confidence in conclusions reached.
2	**Missing data:** How is missing data handled and what potential impact does it have on the usability of the data set and/or analyses? Which data are potentially missing and why. • Could a lack of data be interpreted as an intended absence of information (assessment was not intended to be done),as a function of non-responses (data should be collected but the assessment was not done for a particular subject thus truly missing), or a negative response (only the presence of a condition is routinely recorded, for example assessment revealed no adverse effects or no comorbidity)? • Can the data provider demonstrate defined processes for monitoring for missing data and show rationale for evaluating its impact? • Are the missing data structured vs unstructured?	Understanding how the missing values occurred can help to access limitations of the data and inform appropriate analytic approaches. As an example, out-of-network care may result in missing data, which could significantly impact interpretability if outcomes data are missing.
3	**Imputations:** What documentation to describe the imputation methodologies or variable derivations applied to data source, if any? • Is data missingness expected? If data is missing, does it impact the accuracy of the dataset, or the results derived therein? • How are missing data reflected and interpreted in the database? • This may be covered in a DMP/DHP, or the description of the datasets used. • Which variables were imputed and what percent were imputed versus total dataset?	Missing data can impact analysis, understanding how missing data was handled and how it may affect outcomes will inform analytic approaches and the interpretation of results.
4	**Source vs analytic data set:** What is the process to describe how the completeness/ accuracy of the data listed in the analytical dataset compares to source data? Consider documenting the following: • Were all data available used, if not why? • Are there potential impacts from the use of data/non-use of data? • If healthcare provider notes were used to assess outcomes, what were the processes for the validation of these data? • If the source data is not available how may this affect the completeness and accuracy?	An understanding of how the data was reviewed, monitored, and/or derived contributes to confidence in conclusions reached.
5	**Data management plans:** Is a Data Management Plan (DMP) and or Data Handling Plan (DHP) available? In most cases the DMP/DHP will describe in summary form many of the processes used to transform data from the original source datasets to the analytical dataset.	• The use and availability of a plan that describes the management and handling of data are thought to be a fundamental element of proving reliability. Though not formally required by regulators in most countries, a document containing similar information is still critical and highly recommended for demonstration of completeness and validity. • For example, a DMP IS required to be used by the Chinese agency for regulating drugs and medical devices National Medical Products Administration (NMPA) (formerly the China Food and Drug Administration or CFDA).

Accuracy Considerations

The following accuracy considerations and potential supporting documentation may help demonstrate whether data values stored for an object are correct values and stored in consistent and unambiguous form.

#	Accuracy Considerations & Potential Supporting Documentation	Purpose of Consideration
1	**Handling Outliers:** Documentation related to the handling of outliers in specific measures (e.g., laboratory or clinical) within the dataset. An outlier may be a value outside of an expected range (for example, a lab value), or any atypical case (case outlier), and may be context dependent. • Is there a process/policy whereby outliers are explored / handled / documented?	Provides confidence in the accuracy of variables within the dataset and integrity of data handling.
2	**Methodologies for data transformation:** Documentation related to methodologies or algorithms used for data transformation and verification/validation during data accrual and curation, including documentation of any internal published studies of the current database and documentation related to variable derivations applied to data source (e.g., Data Management Plan/Data Handling Plan (DHP)). • Can references be shared demonstrating algorithm use within the dataset (e.g., to define, transform or validate variables) in other settings? Documentation related to data transformations and assessments of the impact of these changes. • Were all data transformations documented so that auditors and inspectors can easily trace these changes? • What is being done to assess information loss due to transformations and whether transformations are impacting accuracy or introducing bias?	Allows traceability of data and provides evidence regarding how transformations were done and that they were done accurately. Auditors and inspectors will often check to see if data changes from source to final report and if so will want to be able to understand the rationale behind those changes and potential impact.
3	**Data Dictionary:** Availability of data dictionary (codebook) and documentation regarding data dictionary updates/maintenance and verification. • Is the dictionary available for review (as this is a critical to quality document)? • Does the data dictionary include information about variable names, character vs. numeric, format, labels, plausible values (e.g., range), and how variables were coded and transformed?	Data dictionary is a fundamental tool in building understandable datasets; shows how a variable is constructed and subsequently coded; helps to establish whether the data will be usable. Underscores data credibility.
4	**Incorrect/inaccurate data:** Documentation related to correcting or removing inaccurate data (or improperly formatted, inaccurate, or duplicate records) from a database (data cleaning procedures) and results (i.e., audit trail documenting issues identified and steps for resolution). A DHP/DMP may for example contain this process to illustrate how data changes are validated against transparent standards and how erroneous data are handled.	Showing how adequacy of the processes used to collect, handle, clean and report data builds understanding and confidence in conclusions reached.
5	**Data Standards:** Are the data compatible with recognized data standards? • If so, what internal, external, or industry-wide standards were followed with respect to organizing and formatting data to streamline processes in collection, management (data cleaning, and verification), analysis and reporting (e.g., CDISC standards)? • If data are not compatible, are there documented processes to make data compatible with recognized standards? How are structured data harmonized across systems? • Document technical details about data mapping to a standardized format, e.g., CDISC or OMOP-compliant.	• Standards around how data are collected, organized, and cleaned give confidence in the data, and enable rapid understanding of data parameter organization, alignment, and usability. • If a DSP uses a certain standard (ISO, USCDI, etc.) this should be listed and provided
6	**Laboratory data:** Determine and consider whether documentation may help address to describe the average level of precision applied to relevant laboratory and/or other biomarker measures collected in this database. Precision is the degree of approximation by which data represents reality. For example, age can be represented in years or months. Provide any documentation related to standardized methodologies related to precision assessment. • Was rounding used in any measures? • Is this consistent across the data? • Are there provider and institutional differences and how were these standardized? • Is the least precise measure good enough? • Is data coded using a standard method for evaluation of responses that allows direct comparisons? Provide coding systems used in your database. • Is the laboratory or method accredited to a recognized standard (ISO 17025, etc.)?	Helps assess potential usability of the data and whether it may be fit-for purpose.
7	**Data Coding:** Documentation related to guidelines for data coding (pharmacy, procedure, and disease classification codes) and any quality checks to show that guidelines are being followed. This will be data source dependent – Different datasets may require different handling; all of this should be documented (e.g., DMP/DHP). • Is information about specific laboratory tests documented?	Outlines applicability and robustness of dataset and reinforce that data are fit-for-purpose.

#	Accuracy Considerations & Potential Supporting Documentation	Purpose of Consideration
8	**Logic checks and data entry errors:** Documentation related to the process of data logic checks and identification/resolution of data entry errors. • Consider and determine what logic checks were applied and where in the data curation they were applied (e.g., at the analytic dataset stage or prior).	Showing how data were checked for plausibility as well as how data was curated/checked to assure that data are consistent with life, etc. shows overall reliability of the data.
9	**Trends in data**: Documentation explaining trends in the data and changes in healthcare practice over time. • How is the consistency of data elements evaluated and maintained across patients and within a patient? • Are the values plausible? • Have coding systems changed over time? • How are secular changes in healthcare practice monitored? How are these changes considered with respect to evaluation of database integrity and validity?	• Understanding trends in the evolution of treatment patterns speaks to the consistency of data captured over time periods. Though may be case specific, having this understanding and being able to explain how environmental factors changed patterns of treatment over time (Clinical guidance, med availability, lab test changes, etc.) will help to evaluate the usability of data.
10	**Data Linkage:** Documentation of the process for data linkage across multiple data sources and how are these linkages verified? For example: • Documentation on who performed linkages, how they were accomplished, what methods were used and what were the performance characteristics of the linkage. • Documentation including information characterizing the quality of the linkage, quantification of errors (e.g., false matches), procedures for identifying duplicates and for adjudicating discrepancies.	• Showing how data was collected, handled, cleaned, and reported builds understanding in how data was aggregated and confidence in conclusions reached. 22 • While using linked data, it is important to have a process that identifies and deals with duplicates
11	**Data Harmonization:** Document details on harmonization of the data. e.g., laboratory unit conversions and normal ranges	Allows traceability of data and provides evidence that transformations were done accurately.
12	**Accuracy of key variables**: Documentation/results of validation/verification studies that provide confidence in accuracy of variable measures.	Demonstrates that key variables were validated against gold or established standards or verified against relevant internal information within the database.

Other Considerations

The following "Other Considerations" relate to other fundamental compliance aspects and are dependent upon the use case.

#	Other Considerations & Potentially Supporting Documentation relating to other fundamental compliance aspects (depending on Use Case)	Purpose of Consideration
1	**Institutional Review Boards/Ethics Committee Reviews:** Consider what documentation may be appropriate to describe research governance for the protection of human subjects. • Did the ethics committee/Governance committee review the research project? • What documentation or information can be used to confirm the process for research project review/approval by IRB/IEC/governance committees as applicable?] • How was the program reviewed to ensure that the rights and wellbeing are maintained? Did you seek approval/review of the program from an IEC/IRB or similar committee? If not, why not?	• Ensures confidence that appropriate human subject protections are instituted. • Ensures consent was obtained appropriately based on the guiding regulation. • Assists in understanding how patient rights and well-being were maintained when applicable.
2	**Data Reuse:** • What is the legal basis for reuse of data if the data contains personal data? • If consent was obtained, describe and confirm the collection of patient informed consent and/or reselling of the data. • For data sources that patients do not actively provide consent how was a determination made that it was not needed? • Where consent is not used, what is the legal basis for sharing the data? (e.g., data was anonymized, public health emergency status, etc.) • Are patients given the opportunity to Opt-in or Opt-out of inclusion into data sets?	Ensure that appropriate measures were taken to ensure that applicable privacy laws were complied with in the data collection process.
3	**Training and experience:** Qualified people trained in procedures are essential from a quality management standpoint. • Do team members have appropriate background for tasks assigned? (CV on file) • What processes were used for training of people working with the data (for all data entry, including original data set if applicable as well as interpretation and entry of unstructured data elements later in the data handling lifecycle)? Important to describe processes. • Document the training process for employees entering/editing/reviewing data. • Provide copies of training materials or methods by which operators were taught to enter data, make interpretations, etc.	Shows how, why, when and by whom data may have been changed or updated and is thought to be a fundamental element of proving reliability.
4	**Maturity Levels:** • What level of "maturity" is the QA process? EMA has noted that "For data to be used in regulatory decision making, at a minimum, the processes that pertain to data generation and manipulation should be documented, true and verifiable (when relevant, this may extend to training procedures)."[51]	EMA and other regulators are starting to establish maturity levels for a DSP with the goal of improving quality processes and documentation over time.[50]

References

1. Berger ML, Daniel G, Frank K, hernandez A, McClellan M. A Framework for Regulatory Use of Real-World Evidence. Published online September 13, 2017. A Framework for Regulatory Use of Real-World Evidence

2. Daniel G, Silcox C, Bryan J, McClellan M, morgan R, Frank K. *Characterizing RWD Quality and Relevancy for Regulatory Purposes*. Accessed September 28, 2023. https://healthpolicy.duke.edu/sites/default/files/2020-03/characterizing_rwd.pdf

3. Mahendraaratnam N, Nirosha Mahendraratnam, Christina Silcox, et al. Determining Real-World Data's Fitness for Use and the Role of Reliability. Margolis Center for Health Policy. Accessed March 22, 2021. https://healthpolicy.duke.edu/publications/determining-real-world-datas-fitness-use-and-role-reliability

4. HMA-EMA Joint Big Data Taskforce. HMA-EMA Joint Big Data Taskforce Phase II report: Evolving Data-Driven Regulation.

5. National Institute for Health Care Excellence. Overview | NICE real-world evidence framework | Guidance | NICE. Published June 23, 2022. Accessed October 24, 2023. https://www.nice.org.uk/corporate/ecd9/chapter/overview

6. EMA. High-quality data to empower data-driven medicines regulation in the European Union. European Medicines Agency. Published October 10, 2022. Accessed October 24, 2023. https://www.ema.europa.eu/en/news/high-quality-data-empower-data-driven-medicines-regulation-european-union

7. Center for Drug Evaluation and Research. Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products. Published August 30, 2023. Accessed September 28, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug

8. Abernethy A. Time for real-world health data to become routine. *Nat Med*. 2023;29(6):1317. doi:10.1038/s41591-023-02337-0

9. Dreyer NA. Advancing a Framework for Regulatory Use of Real-World Evidence: When Real Is Reliable. *Ther Innov Regul Sci*. 2018;52(3):362-368. doi:10.1177/2168479018763591

10. Kahn MG, Callahan TJ, Barnard J, et al. A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data. *eGEMs*. 2016;4(1). doi:10.13063/2327-9214.1244

11. Liaw ST, Guo JGN, Ansari S, et al. Quality assessment of real-world data repositories across the data life cycle: A literature review. *J Am Med Inform Assoc*. 2021;28(7):1591-1599. doi:10.1093/jamia/ocaa340

12. Miksad RA, Abernethy AP. Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality. *Clin Pharmacol Ther*. 2018;103(2):202-205. doi:10.1002/cpt.946

13. Wang SV, Pinheiro S, Hua W, et al. STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies. :8.

14. Center for Devices and Radiological Health. *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*. FDA; 2023. Accessed September 15, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices

15. Franklin J, Glynn R, Martin D, Schneeweiss S. Evaluating the Use of Nonrandomized Real World Data Analyses for Regulatory Decision Making. *Clin Pharmacol Ther*. 2019;105. doi:10.1002/cpt.1351

16. US FDA. *Incorporating Real-Life Clinical Data into Drug Development: IMI1 Final Project Report Public Summary*. Accessed September 15, 2023. https://www.imi.europa.eu/sites/default/files/uploads/documents/115546_GetReal_Final_Report.pdf

17. Callahan TJ, Bauck AE, Bertoch D, et al. A Comparison of Data Quality Assessment Checks in Six Data Sharing Networks. *EGEMs Gener Evid Methods Improve Patient Outcomes*. 2017;5(1):8. doi:10.5334/egems.223

18. Center for Drug Evaluation and Research. *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets*. FDA; 2020. Accessed September 15, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic

19. Center for Drug Evaluation and Research. *E3 Structure and Content of Clinical Study Reports*. FDA; 2020. Accessed September 15, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e3-structure-and-content-clinical-study-reports

20. International Conference on Harmonization. *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)*. FDA; 2022. Accessed September 15, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1

21. Center for Drug Evaluation and Research. *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers*. FDA; 2023. Accessed September 15, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-systems-electronic-records-and-electronic-signatures-clinical-investigations-questions

22. O'Leary CP, Cavender MA. Emerging opportunities to harness real world data: An introduction to data sources, concepts, and applications. *Diabetes Obes Metab*. 2020;22(S3):3-12. doi:https://doi.org/10.1111/dom.13948

23. US FDA. Guidance for Industry - COMPUTERIZED SYSTEMS USED IN CLINICAL TRIALS. *FDA*. Published online November 3, 2018. Accessed March 24, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/guidance-industry-computerized-systems-used-clinical-trials

24. Orsini LS, Berger M, Crown W, et al. Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing—Why, What, and How: Recommendations and a Road Map from the Real-World Evidence Transparency Initiative. *Value Health*. 2020;23(9):1128-1136. doi:10.1016/j.jval.2020.04.002

25. Sobel R. ISPE's Position on Real-World Evidence (RWE) Feb 2020. :3.

26. Health Canada. *Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making*.; 2019. Accessed September 15, 2023. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html

27. PCORI. *PCORI-Guidance-Design-and-Conduct-of-Trials-Real-World-Settings-Factors-to-Consider-Pragmatic-PCOR.Pdf*. Accessed September 15, 2023. https://www.pcori.org/sites/default/files/PCORI-Guidance-Design-and-Conduct-of-Trials-Real-World-Settings-Factors-to-Consider-Pragmatic-PCOR.pdf

28. Gajra A, Marjorie E. Zettler, Ph.D., M.P.H., Bruce A. Feinberg, D.O. Randomization versus Real-World Evidence. *N Engl J Med*. 2020;383(4):e21. doi:10.1056/NEJMc2020020

29. Schneeweiss S, Eichler HG, Garcia-Altes A, et al. Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making. *Clin Pharmacol Ther*. 2016;100(6):633-646. doi:10.1002/cpt.512

30. Sherman, MD, MPH R, Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D. Real-World Evidence — What Is It and What Can It Tell Us? | NEJM. Accessed September 15, 2023. https://www.nejm.org/doi/full/10.1056/nejmsb1609216

31. Wang SV, Schneeweiss S, Berger ML, et al. Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0. *Value Health*. 2017;20(8):1009-1022. doi:10.1016/j.jval.2017.08.3018

32. Center for Drug Evaluation and Research. *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products*. FDA; 2023. Accessed September 15, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-

documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drug-and-biological-products

33. Collins R, Bowman L, Landray M, Peto R. The Magic of Randomization versus the Myth of Real-World Evidence. *N Engl J Med*. Published online February 12, 2020. doi:10.1056/NEJMsb1901642

34. Radawski CA, Hammad TA, Colilla S, et al. The utility of real-world evidence for benefit-risk assessment, communication, and evaluation of pharmaceuticals: Case studies. *Pharmacoepidemiol Drug Saf*. 2020;29(12):1532-1539. doi:https://doi.org/10.1002/pds.5167

35. Wang SV, Verpillat P, Rassen JA, Patrick A, Garry EM, Bartels DB. Transparency and Reproducibility of Observational Cohort Studies Using Large Healthcare Databases. *Clin Pharmacol Ther*. 2016;99(3):325-332. doi:https://doi.org/10.1002/cpt.329

36. Goodman SN, Fanelli D, Ioannidis JPA. What does research reproducibility mean? *Sci Transl Med*. 2016;8(341):341ps12. doi:10.1126/scitranslmed.aaf5027

37. US FDA. *FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM*. Accessed September 28, 2023. https://www.fda.gov/media/120060/download

38. EMA. *Data Quality Framework for EU Medicines Regulation*. Accessed September 28, 2023. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/data-quality-framework-eu-medicines-regulation_en.pdf

39. Minerva Consortium. *MINERVA: Metadata for Data DIscoverability aNd Study REplicability in ObseRVAtional Studies*. Accessed September 28, 2023. https://www.encepp.eu/encepp/openAttachment/studyResult/45315

40. Center for Drug Evaluation and Research. Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products. Published December 10, 2021. Accessed October 19, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory

41. ClinicalTrials.gov Glossary of Common Site Terms. Clinical study sponsor. In: *Toolkit*. Accessed September 28, 2023. https://toolkit.ncats.nih.gov/glossary/clinical-study-sponsor

42. AHRQ. Using the PICOTS Framework to Strengthen Evidence Gathered in Clinical Trials—Guidance from the AHRQ's Evidence-based Practice Centers Program. Accessed September 28, 2023. https://www.fda.gov/files/about%20fda/published/Using-the-PICOTS-Framework-to-Strengthen-Evidence-Gathered-in-Clinical-Trials---Guidance-from-the-AHRQ%27s-Evidence-based-Practice-Centers-Program.pdf

43. Hall GC, Sauer B, Bourke A, Brown JS, Reynolds MW, LoCasale R. Guidelines for good database selection and use in pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf*. 2012;21(1):1-10. doi:10.1002/pds.2229

44. Gatto NM, Campbell UB, Rubinstein E, et al. The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework. *Clin Pharmacol Ther*. 2022;111(1):122-134. doi:10.1002/cpt.2466

45. Center for Drug Evaluation and Research C for DE and. Providing Regulatory Submissions in Electronic Format -- Standardized Study Data. Published January 3, 2022. Accessed October 26, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-standardized-study-data