Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

July 2024
Real-World Data/Real-World Evidence (RWD/RWE)

Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

July 2024
Real-World Data/Real-World Evidence (RWD/RWE)

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION AND SCOPE

The 21st Century Cures Act (Cures Act),[2] signed into law on December 13, 2016, is intended to accelerate medical product development and bring innovations faster and more efficiently to the patients who need them. Among other provisions, the Cures Act added section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355g). Pursuant to this section, FDA created a framework for a program to evaluate the potential use of real-world evidence (RWE) to help support the approval of a new indication for a drug[3] already approved under section 505(c) of the FD&C Act or help support or satisfy postapproval study requirements.

FDA is issuing this guidance as part of its RWE Program[4] and to satisfy, in part, the mandate under section 505F of the FD&C Act to issue guidance about the use of RWE in regulatory decision-making.[5] The RWE Program will cover clinical studies that use real-world data (RWD) sources, such as information from routine clinical practice, to derive RWE.

---

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and Oncology Center for Excellence (OCE) at the Food and Drug Administration.

[2] Public Law 114-255.

[3] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products. This guidance does not apply to medical devices. For information on medical devices, see the guidance for industry and FDA staff *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (August 2017). We update guidances periodically. For the most recent version of the guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See *Framework for FDA's Real-World Evidence Program*, available at https://www.fda.gov/media/120060/download. The framework and RWE Program also cover biological products licensed under the Public Health Service Act.

[5] See section 505F(e) of the FD&C Act.

This guidance is intended to provide sponsors and other interested parties with considerations when proposing to use electronic health records (EHRs) or medical claims data[6] in clinical studies[7] to support a regulatory decision on effectiveness or safety of a drug.

For the purposes of this guidance, FDA defines RWD and RWE as follows:[8]

- RWD are data relating to patient health status or the delivery of health care routinely collected from a variety of sources.

- RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Examples of RWD include data derived from EHRs, medical claims data, data from product and disease registries,[9] patient-generated data including from in-home use settings, and data gathered from other sources that can inform on health status, such as digital health technologies.[10] This guidance focuses on health-related data recorded by providers that can be extracted from two sources: EHRs and medical claims data. EHRs and medical claims data are types of electronic health care data that contain patient health information, and these data are widely used in safety studies and increasingly being proposed for use in effectiveness studies. EHRs and medical claims data can be considered as data sources in various clinical study designs.

This guidance discusses the following topics related to the potential use of EHR and medical claims data in clinical studies to support regulatory decisions:

(1) Selection of data sources that appropriately address the study question and sufficiently characterize study populations, exposure(s), outcome(s) of interest, and key covariates.

(2) Development and validation of definitions for study design elements (e.g., exposures, outcomes, covariates).

---

[6] For purposes of this guidance, the term *medical claims data* (sometimes referred to as *administrative healthcare claims data*) refers to information submitted to insurers to receive payment for treatments (e.g., pharmacy claims data) and other interventions.

[7] For the purposes of this guidance, the term *clinical studies* refers to all study designs, including, but not limited to, interventional studies where the treatment is assigned by a protocol (e.g., randomized or single-arm trials, including those that use RWD as an external control arm) and non-interventional (observational) studies where treatment is determined in the course of routine clinical care (e.g., case-control or cohort studies). Throughout the guidance, FDA uses the terms *clinical studies*, *studies*, and *study* interchangeably.

[8] See *Framework for FDA's Real-World Evidence Program*, available at https://www.fda.gov/media/120060/download.

[9] For additional discussion, see the guidance for industry *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (December 2023).

[10] For additional discussion, see the guidance for industry, investigators, and other stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2023).

(3) Data traceability[11] and quality during data accrual, data curation, and incorporation into the final study-specific dataset.

This guidance does not provide recommendations on choice of study design or type of statistical analysis, and it does not endorse any type of data source or study methodology. For all study designs, it is important to ensure the reliability and relevance of the data used to help support a regulatory decision. For the purposes of this guidance, the term *reliability* includes accuracy, completeness, and traceability. The term *relevance* includes the availability of data for key study variables (exposures, outcomes, covariates) and sufficient numbers of representative patients for the study.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The FDA guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013) focuses on the use of electronic health care data in pharmacoepidemiologic safety studies. The 2013 guidance includes recommendations for documenting the design, analysis, and results of pharmacoepidemiologic safety studies to optimize FDA's review of protocols and study reports that are submitted to FDA.

This guidance complements the 2013 guidance by expanding on certain aspects of that guidance relating to the selection of data sources, and provides additional guidance for evaluating the relevance and reliability of both EHRs and medical claims data for use in a clinical study. This guidance also provides a broader overview of considerations relating to the use of EHRs and medical claims data in clinical studies more generally, including studies intended to inform FDA's evaluation of product effectiveness.

III. GENERAL CONSIDERATIONS

For all studies using EHRs or medical claims data that will be submitted to FDA to support a regulatory decision, sponsors should submit protocols and statistical analysis plans before conducting the study. Sponsors seeking FDA input before conducting the study should request comments or a meeting to discuss the study with the relevant FDA review division. All essential elements of study design, analysis, conduct, and reporting should be predefined, and, for each study element, the protocol and final study report should describe how that element was

[11] For the purposes of this guidance, traceability is the method (e.g., audit trail) that allows for knowledge of data provenance (i.e., the origin of a piece of data and how it got to the electronic health record or medical claim).

ascertained from the selected RWD source, including applicable validation studies. More information about study elements is provided in section V, Study Design Elements.

This guidance provides recommendations on selecting data sources to maximize the completeness and accuracy of the data derived from EHRs and medical claims for clinical studies. The use of certain study design features or specific analyses to address misclassified or missing information, as well as methods to achieve covariate balance are out of scope of this guidance. Instead, this guidance addresses issues that are essential to determining the reliability and relevance of the data and that should be addressed in the protocol, including:

(1) The appropriateness and potential limitations of the data source for the study question and to support key study elements.

(2) Time periods for ascertainment of study design elements.

(3) Conceptual definitions and operational definitions for study design elements (e.g., inclusion/exclusion criteria for study population, exposures, outcomes, covariates) and the results of validation studies. See section V, Study Design Elements, for examples of conceptual and operational definitions for study design elements.

(4) Quality assurance and quality control (QA/QC) procedures for data accrual, curation, and incorporation into the final study-specific dataset.

IV. DATA SOURCES

Protocols submitted to FDA should identify all data sources proposed for the study, as well as other relevant descriptive information (discussed below). FDA does not endorse one data source over another or seek to limit the possible sources of data that may be relevant to answering study questions.

Each data source should be evaluated to determine whether the available information is appropriate for addressing a specific study question. Given that existing electronic health care data were not developed for research purposes or to support regulatory submissions to FDA, it is important to understand their potential limitations when they are used for that purpose. Examples of potential limitations include:

(1) The purpose of medical claims data is to support payment for care; claims may not accurately reflect a particular disease or the comprehensive management of a disease (e.g., the transcription and classification practices of clinical coders may differ), or a patient may have a particular disease or condition that is not reflected or well-reflected in claims data. In addition, medical claims data can change during the run-off period and claims adjudication process, as initial submissions may be adjusted or corrected, leading to variations in reported diagnoses and procedures over time.

(2) EHR data are generated for use in clinical care and may also serve as a basis for billing and for auditing of practice quality measures. Structured and unstructured data recorded in an EHR system depend on each health care system's practices for patient care, the clinical and documentation practices of its providers, and the functionality and configuration of the EHR system. In addition, data collection is limited to the data captured within an EHR system or network, and may not represent comprehensive care (e.g., care obtained in different facilities in the same or outside of the health care system). Similar to claims data, EHR data may not accurately reflect the presence, characteristics, or severity of a particular disease.

(3) For prospective clinical studies proposing to use EHRs, it may be possible to modify the EHR system for the purpose of collecting additional patient data during routine care through an add-on module to the EHR system. However, given the limited ability to add modules to collect extensive additional information, EHR-based data collection may still not be comprehensive.

(4) Information regarding continuity of care depends on patients remaining within the specific health care system and engaging with the health care system for continuing care.

Prior use of the selected data source for research purposes (e.g., previous submissions to FDA by the sponsor or relevant examples in the published literature) should be described in the protocol. This description should include how well the selected data source has been shown to capture study variables (e.g., inclusion and exclusion criteria, exposures, outcomes, key covariates) and how the study variables can be validated for a particular research activity.

A. Relevance of the Data Source

There are differences in the practice of medicine around the world and between health care systems that may affect the relevance of the data source to the study question. Patients in different types of commercial or government health care payment programs can differ in a range of characteristics, such as age, socioeconomic status, health conditions, risk factors, and other potential confounders. Various factors in health care systems and insurance programs, such as patient out-of-pocket expenses, formulary decisions, and patient coverage, can influence the degree to which patients on a given therapy in one health care system might differ in disease severity, or other disease characteristics, from patients on the same therapy in another health care system. It is also important to identify whether the data sources cover all populations relevant to the study if those sources are to be used to address the study question. Differences in terminology and coding systems used in different health care systems should also be considered.

FDA recommends including the following in the protocol:

(1) The reason for selecting the particular data sources, and the time frame of data that are available, to address the specific study question.

(2) Relevant background information about the health care system(s), including (if available) any specified method of diagnosis and preferred treatments for the disease of interest, and

the degree to which such information is collected and validated in the proposed data sources.

(3) A description of any available information on prescribing and utilization practices (e.g., stepped therapy, prior authorizations, formulary restrictions) that may impact feasibility of the study in the data source or interpretation of study findings.

(4) A discussion on how factors relating to the health care system, including its practices, might affect the generalizability of the study findings from the selected data sources. When non-U.S. data sources are proposed, additional explanation (e.g., demographic factors, standard of care) should be provided to support the generalizability to the U.S. population.

B. Data Capture: General Discussion

A record in EHR systems or medical claims databases is generated only if there is an interaction of the patient with the health care system. Because EHRs and medical claims data are collected during routine care and not according to a prespecified research protocol, information needed to address certain questions in a proposed study may not be present in EHRs and medical claims data sources. Sponsors should demonstrate that the proposed data source(s) contain the detail and completeness needed to capture the study populations, exposures, key covariates, outcomes of interest, and other important parameters (e.g., time periods) that are relevant to the study question and design.

1. Enrollment and Comprehensive Capture of Care

The capture of patients' health care information in a medical claim or EHR data source depends on *continuity of coverage* (i.e., enrollment and disenrollment from the health insurance plan) and *continuity of care* (i.e., continuous interaction with the health care system). When using medical claims data sources, continuity of coverage should be addressed, given that patients often enroll and disenroll in different health plans when they experience changes in employment, or other life circumstances. When using EHR data sources, continuity of care should be discussed**,** specifically, whether patients receive all types of health care services within the same health system or network of facilities that contribute to the same EHR data source. The validity of findings from a study using these data depends in part on the documentation of the migration of patients into and out of health plans and health care systems. Such documentation allows for the identification of time periods during which data are and are not available on the patients of interest. Definitions of continuity of coverage and continuity of care should be developed and documented in the protocol. Of note, information on continuity of care may be difficult to accurately capture (e.g., data do not differentiate discontinuation of care and lack of encounters due to worsening or resolution of existing health conditions) and might need to be approximated in an EHR data source.

FDA recommends addressing the comprehensiveness of the data sources in capturing aspects of care and outcomes that are relevant to the study question. This information will help evaluate the likelihood that all exposures and outcomes of interest will be captured for

regulatory decision-making. For example, outpatient data sources that do not include hospitalization data would generally not be appropriate for studying outcomes likely to result in hospitalization. A second example is a study where an outcome is dependent on a specific frequency of laboratory tests, and clinicians do not typically order those tests at such a frequency.

FDA recommends specifying how all relevant populations, exposures, outcomes, and covariates will be captured during the study period, particularly in situations where data availability varies greatly over time. The data sources should contain adequate numbers of patients with adequate length of continuous follow-up to ascertain outcomes of interest based on the biologically plausible time frame when the outcome, if associated with the exposure, might be expected to occur. Information should be provided about the distribution of length of follow-up for patients in the data sources because the length of follow-up may inform whether the selected data sources are adequate or whether additional supportive data are needed to ascertain long latency outcomes.

In general, EHRs and medical claims data may not systematically capture the use of nonprescription drugs or drugs that are not reimbursed under health plans, episodes of medical tourism outside the U.S., or immunizations offered in the workplace, at pharmacies or public health clinics, or through government immunization programs. If these exposures are particularly relevant to the study question, the data source may not be suitable, or the protocol should describe how this information gap will be addressed (e.g., by building additional modules into the EHR system, linking, or collecting additional data).

Obtaining comprehensive drug coverage and medical care data on patients with certain types of privacy concerns (e.g., sexually transmitted infection, substance abuse, mental health conditions) can be challenging and failure to do so can result in incomplete or erroneous information. Patients with these conditions may receive treatment in federally qualified health centers, or in private clinics where an insurance claim may not be generated if self-payment is used. In addition, certain populations (e.g., patients with rare cancers) more often enroll in experimental clinical trials. In such cases, patients' health data may not be fully captured in electronic health care data. If these issues are relevant to the study question of interest, the protocol should describe how the issues will be addressed.

2. Data Linkage and Synthesis

Data linkages can be used to increase the amount of data available to capture the longitudinal patient journey, increase the amount of data available on individual patients, and provide additional data for validation purposes. If the study involves establishing new data linkages within the same data sources (e.g., mother-infant linkages) or across different data sources (e.g., vital records, disease and product registries, biobank data), the protocol should describe each data source, the information that will be obtained, linkage methods, and the accuracy and completeness of data linkages over time. Probabilistic and deterministic approaches to data linkage may result in different linkage quality, albeit both approaches can have value depending on the scenario. The deterministic approach for data linkage uses records that have an exact match to a unique or set of common identifiers. The probabilistic approach for data linkage uses less restrictive steps in which the linkage can be established by exact matching of

fewer identifiers or matching part of the information on the identifiers (e.g., the first several letters of a name) (Carreras et al., 2018). When a probabilistic approach is used, the analysis plan should include testing the impact of the degree of match and robustness of findings. In addition, if the study involves generating additional data (e.g., interviews, mail surveys, computerized or mobile-application questionnaires, measurements through digital health technologies), the protocol should describe the methods of data collection and the methods of integrating the collected data with the proposed EHRs or medical claims data.

For studies that require combining data from multiple data sources or study sites, FDA recommends demonstrating whether and how data from different sources can be obtained and integrated with acceptable sample size and quality, given the potential for heterogeneity in clinical and coding practices across data sources or systems.

Because patients typically visit multiple health care sites, especially in geographically contiguous areas, the inclusion of de-identified data from many sites creates the possibility that there will be multiple records from different health care sites for a single individual. The existence of multiple records of the same person in different sites can result in overcounts of a particular data measure or, alternatively, if some site records are not available, can result in a collection of patient histories that reflect only a fraction of the patient's total health care history. Specific attention to data curation[12] including individual level and population level linkages and understanding of many-to-one and 1:1 linkage is fundamental to assessing the appropriateness of a new data linkage. Even where multiple data sources are linked by a unique patient identifier or where the patient information is coming from only one data source, there still can be an issue with multiple records or duplicate records. FDA recommends considering and documenting the type of curation performed to address duplication or fragmentation issues and documenting approaches taken to address issues that cannot be fully rectified by curation. See section VI, Data Quality During Data Accrual, Curation, and Transformation into the Final Study-Specific Dataset.

3. Distributed Data Networks

Distributed data networks (or systems) of EHRs and medical claims data systems, often combined with the use of common data models (CDM), have been increasingly used for medical product safety surveillance and research purposes. A CDM standardizes a variety of electronic health care data sources into a common format to ensure interoperability across all sites providing data. The primary benefit of using a distributed network in which data from multiple sites are transformed into a single CDM, is the ability to execute an identical query (without any or substantial modifications) on multiple datasets. In some distributed data networks, queries can be run simultaneously at all network sites or at each site asynchronously, with results combined at a coordinating center for return to the end user. There are a number of the commonly used operational models employed by distributed data networks. Some networks are managed by a single business entity using a consistent EHR system or medical claims database structure and while data are maintained at many locations, they are structured and managed in a consistent manner (e.g., the U.S. Department of Veterans Affairs Veterans Health

[12] For the purposes of this guidance, data curation is the processing of source data through the application of standards for exchange, integration, sharing, and retrieval.

Administration). Another approach is a hybrid distributed model in which a subset of data from many remote sites is sent to a centralized repository that allows for research to be conducted on a combined dataset (e.g., U.S. Centers for Disease Control and Prevention's National Syndromic Surveillance System). A third commonly used approach is seen in networks of data systems with multiple owners and database structures, with data structured and managed differently from location to location (e.g., the member sites of FDA's Sentinel system). In this model, research queries are sent to the various network member sites and results returned to a central location for collation and reporting.

The latter type of networks, comprised of disparate data systems such as the Sentinel system, are facilitated by the use of CDMs. Networks using CDMs also typically provide tools and methodologies for analysis, a consistent level of data curation, unified QA/QC procedures, and periodic revision of the data model to incorporate new data concepts as needed. Additionally, methodologies have been developed that allow the ability to translate data from one CDM to another, however these involve additional data transformations,[13] which present added quality considerations. Data curation and transformation into a CDM, as well as general QA/QC procedures, are discussed in section VI, Data Quality During Data Accrual, Curation, and Transformation into the Final Study-Specific Dataset.

Distributed data networks are typically comprised of EHR, medical claim, or registry data. Nevertheless, combining many data sources, especially with the addition of data transformation into a CDM, adds a layer of complexity that should be considered. Because there are many different configurations of distributed health data networks, the configurations discussed in this guidance should not be considered comprehensive.

Transforming disparate database structures into a common health network with a CDM allows research across health care sites that would otherwise be more complex and costly. However, CDMs can introduce additional challenges to consider. Many CDMs, including those developed for FDA's Sentinel system, Biologics Effectiveness and Safety Initiative, and the National Patient-Centered Clinical Research Network, were created to satisfy a specific set of research purposes; the choice of data captured in a CDM is optimized for the types of data measures and detail needed for the intended use (e.g., Sentinel system for postmarket safety surveillance to inform regulatory decision-making, the National Patient-Centered Clinical Research Network for patient-centered outcomes research). Therefore, data in CDM-driven networks rarely contain all the source information present at the individual health care sites, and the data elements chosen for a given CDM network may not be sufficient for all research purposes or questions. Furthermore, CDMs often have many data elements within the model that are optional—that is, although the model has such data elements available to be filled with data, the individual sites can choose whether to put their original data into the optional fields.

Before using a CDM-driven network, data elements collected by the CDM should be considered—including whether needed data elements exist in the model and, if so, whether they are required or optional elements—to determine suitability for the study and whether identified deficiencies can be addressed by supplementing with customized study-specific data elements,

[13] For the purposes of this guidance, data transformation is the process of converting data from one format or structure into another format or structure.

collecting additional data, or using other data elements present in the dataset that are reasonable proxies for the missing information. It should be noted, however, that such workarounds involve additional considerations by the sponsor such as the work involved with validating proxy endpoints or any human subject research considerations that involve additional data. Suitability may also be improved with more flexible CDMs that are frequently expanded for new uses. For information on proxy variables, see section IV.C, Missing Data: General Considerations.

4. Computable Phenotypes

A computable phenotype identifies a clinical condition or characteristic using a computerized query to an EHR system or clinical data repository (including disease registries, claims data) using a defined set of data elements and logical expressions. Standardized computable phenotypes enable efficient selection of study populations and ascertainment of outcomes of interest or other study variables for large-scale clinical studies across multiple health care systems. A computable phenotype definition should include metadata and supporting information about the definition, its intended use, the clinical rationale or research justification for the definition, and data assessing validation in various health care settings (Richesson et al. 2016). The computable phenotype definition, composed of standardized and mapped data elements and phenotype algorithm, if applicable, should be described in the protocol and study report and should also be available in a computer-processable format. Clinical validation of the computable phenotype definition should be described in the protocol and study report. For additional information on validation, see section IV.D, Validation: General Considerations.

5. Unstructured Data

Although medical claims data are typically in structured fields, large amounts of key clinical data are unstructured data within EHRs, either as free text data fields (such as physician notes) or as other non-standardized information in computer documents (such as PDF-based radiology reports). To enhance the efficiency of data abstraction, a range of approaches, including both existing and emerging technologies and strategies, are increasingly being used to convert unstructured data into a computable format. More recent innovations include technology-enabled abstraction whereby software provides a mechanism for human data abstractors (e.g., tumor registrars) to do their work in a consistent and scalable fashion.

Technological advances in the field of artificial intelligence (AI) may permit more rapid processing of unstructured electronic health care data. AI is a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions, and making predictions.[14] Advances include natural language processing, machine learning, and particularly deep learning to: (1) extract data elements from unstructured text in EHRs; (2) develop computer algorithms that identify outcomes; or (3) evaluate images or laboratory results. FDA does not endorse any specific AI technology.

[14] See IMDRF/AIMD WG/N67 Machine Learning-enabled Medical Devices: Key Terms and Definitions, May 6, 2022.

All these methods are computer-assisted to various levels but require a significant amount of human-aided curation and decision-making, injecting an additional level of data variability and quality considerations into the final study-specific dataset. If the protocol proposes to use AI or other derivation methods, the protocol should specify the assumptions and parameters of the computer algorithms used, the data source from which the information was used to build the algorithm, whether the algorithm was supervised (i.e., using input and review by experts) or unsupervised, and the metrics associated with validation of the methods. Relevant impacts on data quality from use of AI or other computerized extraction methods should be documented in the protocol and analysis plan.

C. Missing Data: General Considerations

There are two broad scenarios in which information may be absent from data sources. The first scenario is when the information was intended to be collected (e.g., structured field present in EHRs), but is absent from the data sources. This is an example of traditional missing data.[15] The second case is when the information was not intended to be collected in EHRs and medical claims data and is therefore absent. The second scenario affects the relevance of the data source. Although both can have an impact on study validity, it is helpful to distinguish between these two scenarios and understand the reasons why information is present or absent in EHRs and medical claims. For example, lack of information about the result of a laboratory test could be caused by different circumstances: (1) the test might not have been ordered by the health care provider; (2) the test might have been ordered but not conducted; (3) the test might have been performed, but the result was not stored or captured in the data source; or (4) the test might have been performed and the result was stored in the data source, but data were not in an accessible format, or lost in the transformation and curation process when the final study-specific dataset was generated. Because providers might order a laboratory test based on a patient's characteristics, the decision not to order the test or a patient's decision to forgo the test may have implications on the data's fitness for use in a proposed study. An understanding of the reasons for missing data may help assess the impact of missing data on study findings.

As discussed above, data linkage is one way to address certain types of missing data. It may also be possible to identify a variable that is a proxy for the missing data. An example of a potential proxy variable includes maternal education as a proxy for socioeconomic status that often is an important confounder when evaluating child-health outcomes.

The protocol and the statistical analysis plan should be developed and based on an understanding of reasons for the presence and absence of information. Descriptive analyses should be included to characterize the missing data. Assumptions regarding the missing data (e.g., missing at random, missing not at random) underlying the statistical analysis for study endpoints and important covariates should be supported and the implications of missing data considered in the design and analysis of the study. Sensitivity analysis should be conducted to evaluate the robustness of findings.

[15] For the purposes of this guidance, missing data are data that would have been used in the study analysis but were not observed, collected, or accessible. This refers to information that is intended to be collected but is absent and information that is not intended to be collected and is therefore absent.

D. Validation: General Considerations

1. Conceptual and Operational Definitions of Study Variables

Studies using EHRs and medical claims data sources should include conceptual definitions for important study variables, including study population inclusion and exclusion criteria, exposure, outcome, and covariates. A conceptual definition should reflect current medical and scientific thinking regarding the variable of interest, such as: (1) clinical criteria to define a condition for population selection or as an outcome of interest or a covariate; or (2) measurement of drug intake to define an exposure of interest.

An operational definition should be developed based on the conceptual definition to extract the most complete and accurate data from the data source. In many studies using EHRs or medical claims data, the operational definition will be a code-based electronic algorithm using structured data elements. In other studies, the operational definition may be derived from extracting relevant information from unstructured data or constructing an algorithm that combines structured and unstructured data elements. Operational definitions can also specify additional data collection, such as a patient survey, when appropriate.

2. Selection of Study Variables for Validation

Given that operational definitions are usually imperfect and cannot accurately classify the variable of interest for every subject, a resulting misclassification can lead to false positives and false negatives (Table 1) and may bias the association between exposure and outcome in a certain direction and degree.[16] Misclassification may occur in any study variable (e.g., exposure, outcome, covariate). Understanding the implications of potential misclassification for study internal validity and study inference is the key step in determining what variables of interest might require validation and to what extent, based on the necessary level of certainty. For example, in a study to quantify a drug effect, internal validity should be optimized, and misclassification of key study variables should be minimized to accurately measure the association. Some misclassification might be tolerable in some studies when the presence of misclassification is not expected to change the interpretation of results (e.g., for signal detection, or when the hypothesized effect size is large and the impact of misclassification on the measure of association is deemed minimal).

To understand how potential misclassification of a variable of interest (e.g., exposure, outcome, covariate) might impact the measure of association and the interpretation of results, sponsors should consider: (1) the degree of misclassification; (2) differential versus non-differential misclassification (e.g., whether the degree of misclassification of an outcome may differ across treatment groups being compared); (3) dependent versus independent misclassification (e.g., correlated misclassifications of exposure and outcome when both are self-reported in the same

[16] For categorical variables, the performance of operational definitions can be measured by indices such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). For continuous variables, indices may be based on the correlation with, or the pairwise comparison to, the reference standard. These measures inform the presence and degree of misclassification or measurement error of a variable that may in turn bias the study findings from the truth.

survey); and (4) the direction toward which the association between exposure and outcome might be biased.

3. Validation Approaches

Validation refers to the process of determining if a study variable (e.g., exposure, outcome, covariate) is correctly measured, usually according to a reference standard (Porta, 2014). Examples of validation approaches include: (1) complete verification[17] of a key study variable for all subjects; (2) verification of a study variable for all those identified by an operational definition as positive (e.g., all those identified as exposed for exposure status, or all those identified as a case for outcome status), or as negative (e.g., all those identified as unexposed for exposure status, or all those identified as a non-case for outcome status, but not necessarily all subjects; or (3) assessing the performance of an operational definition (e.g., internally in a sample of the study population for the proposed study, or externally in a prior study). The extent of effort required for validation depends on the necessary level of certainty and the implication of potential misclassification on study inference. Although complete verification of a study variable is considered the most rigorous approach, there are scenarios where verifying a key study variable for every subject might not be feasible (e.g., a very large study population, lack of reference standard[18] data for all study subjects) and assessing the performance of the variable's operational definition might suffice. Based on the performance measures described in Table 1, sponsors should consider whether validating the variable to a greater extent (e.g., all positives classified by the operational definition) is necessary and discuss options with the relevant review division.

Because the performance of an operational definition is dependent on various factors, such as data source, study population, study time frame, and choice of reference standard, FDA recommends assessing the performance of operational definitions in an adequately large and representative sample of the study population as part of the proposed study, using justified sampling methods (e.g., random sampling, stratified sampling). If sponsors propose to use an operational definition that has been assessed in a prior study, ideally, those definitions should have been assessed using the same data source and in a similar study population as the proposed study. In addition, secular trends in disease, diagnosis, and coding may necessitate assessment of the operational definition using more recent data. The quality of prior studies used to establish sensitivity, specificity, and predictive values should always be evaluated.

Choice of a reference standard may vary by study design and question, variable of interest, and the necessary level of certainty. For example, subject matter experts' review of medical records (including structured and unstructured data) may be a preferred reference standard for validation of clinical events identified by diagnosis codes or automated algorithms, or drug intake diary may be

[17] For the purposes of this guidance, complete verification involves assigning an accurate value to the variable of interest for each study subject based on a reference standard of choice. For example, medical record review can be used in conjunction with a conceptual definition to determine whether a subject meets a critical inclusion criterion or has experienced the outcome event (adjudication may be involved in this process).

[18] For the purposes of this guidance, reference standard is the best available benchmark, also referred to as a *gold standard*. When a gold standard is not clearly identified, validation may indicate concordance between methods assessed by a Kappa statistic, precent agreement, or other indices.

used to assess the validity of medication exposures identified in pharmacy dispensing data. Other examples may include broadly accepted external reference data sources, such as national or state vital statistics data sources, if appropriate. Sometimes the reference standard of choice itself may have important limitations and not be entirely valid, in which case caution should be used when interpreting validation results.

The protocol should include a detailed description of the planned validation, including justification for the choice of a validation approach, reference standard, methods, processes, and sampling strategy (if applicable). If a previously assessed operational definition is proposed, additional information should be provided, including in what data source and study population and during what time frame the assessment was conducted, the value of the assessed performance measures, and a discussion of whether the performance measures are applicable to the proposed study. FDA also recommends using quantitative approaches, such as quantitative bias analyses, either *a priori* for feasibility assessment, or to facilitate interpretation of study results, or for both purposes, to demonstrate whether and how misclassification, if present, might impact study findings. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured during validation.

For further discussion about the validation of study design elements, see section V.C.5, Validation of Exposure; section V.D.3, Validation of Outcomes; and section V.E.3, Validation of Confounders and Effect Modifiers.

Table 1: Schematic Representation of the Calculation of Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for a Binary Variable

Condition based on proposed operational definition	Condition based on reference standard: Yes	Condition based on reference standard: No	Total	
Yes	a (true positive)	b (false positive)	a+b	PPV = a/(a+b)
No	c (false negative)	d (true negative)	c+d	NPV = d/(c+d)
Total	a+c	b+d	N	
	Sensitivity = a/(a+c)	Specificity = d/(b+d)		

V. STUDY DESIGN ELEMENTS

The ascertainment and validation of study design elements are discussed in detail below. The study questions of interest should be established first, and then the data source and study design most appropriate for addressing these questions should be determined. The study should not be

designed to fit a specific data source, because the limitations of a specific data source may restrict the options for study design and limit the inferences that can be drawn.

A. Definition of Time Periods

FDA recommends clearly defining the various time periods pertinent to the study design in the protocol (e.g., time periods for identifying study population, defining inclusion and exclusion criteria, assessing exposure, assessing outcome, assessing covariates, following up with patients, "washout" time period if applicable). The focus of the time scale (e.g., calendar time, age, time since exposure) should be explicitly described with adequate detail on data availability of the time unit (e.g., year, month, day, hour, minute) required to answer the study question.

The protocol should demonstrate the data availability, accuracy, and completeness for the proposed time periods and the potential impact on study validity. For example, justification should be provided regarding how data for the time period before exposure are adequate for identifying the study population and the important baseline covariates, or for the follow-up period to consider the biologically plausible time frame when the outcome (e.g., long latency events), if associated with the exposure, might be expected to occur. When the proposed outcome definition distinguishes disease onset (e.g., early symptoms) from a confirmed diagnosis, justification should be provided regarding whether the timing of disease onset can be accurately captured (e.g., for an insidious disease). In addition, when the study design involves time-varying covariates, description should be provided regarding the data availability of the time unit to capture the changes of the variable of interest (e.g., age in month as a time-varying covariate in a study among infants). The protocol should also address potential temporal changes in the standard of care, the availability of other treatments, diagnosis criteria, and any other relevant factors that are pertinent to the accuracy and completeness of data for study variables. For example, healthcare avoidance or limited access to healthcare during a pandemic may adversely impact the assessment of patients' underlying conditions for studies using RWD during or after the pandemic. Other relevant factors may include payer or provider policies (if known), such as formulary changes, step therapy, and laboratory assay changes. Before developing the study approach, sponsors should discuss with the relevant FDA review division the capability of data to capture such potential temporal changes and the impact of the potential temporal changes on internal validity.

B. Selection of Study Population

The protocol should include a detailed description of methods for determining how inclusion and exclusion criteria (e.g., demographic factors, medical condition, disease status, severity, biomarkers) will be implemented to identify appropriate patients meeting these criteria from the data source. The protocol should include a detailed description of operational definitions for inclusion and exclusion criteria to identify the eligible study population from the data source. The identification of the study population may rely on information recorded in multiple data fields such as diagnosis and procedure codes (e.g., International Classification of Diseases (ICD)-9-CM, ICD-10), laboratory tests (e.g., Logical Observation Identifier Names and Codes (LOINC)) and values, or unstructured data (e.g., physician's encounter notes, radiology and

pathology reports). The protocol should address the accuracy and completeness of the information collected in the proposed data source to fulfill the inclusion and exclusion criteria.

Operational definitions of key inclusion and exclusion criteria used to select the study population should be validated. As one example, to assess the drug effect in patients with immune thrombocytopenic purpura, the disorder ascertained by operational definition ICD-9-CM diagnosis code 287.31 or ICD-10 code D69.3 should be validated based on the conceptual definition of the disorder, which includes signs and symptoms, levels of platelets, and exclusion of other possible causes of thrombocytopenia.

In certain circumstances, key inclusion and exclusion criteria (e.g., gestational age for pregnancy studies) may be generated by the information recorded at the point of care by the health care providers. For example, health care providers may enter the calculated gestational age in EHRs based on patient self-reported last menstrual period, ultrasound dating, and other relevant information. If such data are used, the protocol should describe the source of information and the methods health care providers use to generate the data (if known).

FDA also recommends including quantitative approaches, such as quantitative bias analyses, in the protocol to demonstrate whether and how misclassification of inclusion and exclusion criteria, if present, might impact study findings. The approach can be applied *a priori* for feasibility assessment, to facilitate interpretation of study results, or for both purposes. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured in key inclusion/exclusion criteria validation.

C. Exposure Ascertainment and Validation

Considerations discussed in this section regarding exposure ascertainment in EHRs or medical claims data primarily apply to noninterventional studies, given that the assignment of exposure is documented in interventional studies.

1. Definition of Exposure

For the purposes of this guidance, the term *exposure* applies to the medical product or regimen of interest being evaluated in the proposed study. The product of interest is referred to as *the treatment*, and may be compared to no treatment, a placebo, standard of care, another treatment, or a combination of the above. Other variables that could affect the study outcome are considered covariates and are discussed in section V.E, Covariate Ascertainment and Validation. The exposure definition should include information about the drug dose, formulation, strength, route, timing, frequency, and duration of use for the product studied (if relevant). It may also be necessary to describe the specific manufacturer of a product (e.g., when a proper name for a vaccine is used by different manufacturers).

The description of exposure should include the intended or prescribed use of the product (e.g., the number, frequency, route of administration, and specific doses), the period between initiation of exposure and the earliest time one might reasonably expect to see an effect, and the expected duration of effect. This will usually require an understanding of the pharmacological properties

(e.g., half-life) and mechanism of action of the drug —for example, that a onetime infusion to prevent osteoporosis may have an effect for several months. See section V.C.3, Ascertainment of Exposure: Duration, and section V.C.4, Ascertainment of Exposure: Dose.

2. Ascertainment of Exposure: Data Source

Sponsors should be able to demonstrate an ability to identify the specific products of interest in the proposed data source, demonstrating that the data source contains data fields and codes that allow identification of the specific products of interest (e.g., through specific coding). For example, it is not always possible to infer a specific vaccine formulation from the billing or diagnostic code alone, such as in systems where a single billing code is used for multiple vaccines. The protocol should describe the coding system used, the level of granularity represented (e.g., using RxNorm concept unique identifiers (CUIs) mapped to the National Drug Code [NDC] codes), and the specificity attained by the coding system.

When relying on coded data, the operational exposure definitions should be based on the coding system of the selected data source and reflect an understanding of the prescription, delivery, and reimbursement characteristics of the drug (if applicable) in that data source over time. For example, in the United States, the operational definition should include the appropriate pharmacy codes (NDC or Healthcare Common Procedure Coding System (HCPCS) or other applicable codes) to capture the use of the drug in various settings. This approach is particularly important in the case of non-oral drugs that may be assigned different codes depending on how they are obtained. For example, patients using an injectable drug can obtain it from the pharmacy, in which case the NDC code would be recorded, or it can be administered by the provider, in which case the drug and its administration would be recorded using the HCPCS J code.[19]

It is also essential to report operational definitions and methods when combining information from unstructured and structured data. Emerging methods may involve review of unstructured information in medical records combined with pharmacy dispensing and physician prescribing data and notes to provide an assessment of whether a person was prescribed and received the medication of interest, as well as whether there are problems with the patient continuing the medication. An example of such methods is found in ascertainment of aspirin exposure in a retrospective cohort study of veterans undergoing usual care colonoscopy (Bustamante et al. 2019).

When using a medical claims data source, it is important to consider that there could be dispensed prescriptions that were not associated with insurance claims if these uncaptured prescriptions are relevant exposures for the study. Uncaptured prescriptions might include low-cost generic drugs, drugs obtained through discount programs, samples provided by pharmaceutical companies and dispensed by health care providers, and drugs sold via the internet or patient out-of-pocket purchases. An individual can seek care outside of the healthcare system(s), and exposure to medication prescribed by out-of-system providers would not be captured in the EHR. Lastly, nonprescription drugs and dietary supplements are not generally

[19] A drug's J code is a Healthcare Common Procedure Coding System (HCPCS) Level II code used in medical claims to report injectable drugs that ordinarily cannot be self-administered; chemotherapy, immunosuppressive drugs, and inhalation solutions; and some orally administered drugs.

captured, nor well-captured in electronic health care databases. It is important to address the likelihood of incomplete exposure ascertainment and its effect on study validity, see section V.C.5, Validation of Exposure.

3. Ascertainment of Exposure: Duration

The data source should capture the relevant exposure duration (anticipated use of a product over time). Given that some medical products are designed as onetime exposures (e.g., vaccines), and other products may be intended for use over extended periods of time, the suitability of a data source will vary with the specific medical product under investigation or the medical conditions the product is intended to treat (e.g., acute versus chronic conditions, treated daily versus as needed, or prophylaxis versus active treatment). FDA recommends describing the duration of exposure as well as the period during which the exposure is having its effect relative to the outcome of interest. Duration may refer to continuous exposure or cumulative exposure, depending on the study question. For some products, an immediate or near-immediate effect is expected; for other products, an effect is expected after a time interval (e.g., drugs that promote bone strength). FDA recommends considering the duration of continued drug effect after treatment discontinuation to include the entire period in which the drug effect may occur. For example, a vaccine effect may persist for years after vaccination, and persons might be considered exposed during that period. On the other hand, an anticoagulant's effects may not extend beyond several hours or days. FDA also recommends justifying the units (e.g., hours, days) selected for estimating the duration of exposure and ensuring the data are available in those units.

Because patients may not refill their prescriptions exactly on time or, alternatively, may refill their prescriptions early, gaps or stockpiling in therapy may exist and may be reflected in the dispensing medical claims data.[20] FDA recommends describing and justifying in the protocol how the study will measure use, address potential gaps in therapy in the data source, and handle refill stockpiling if there are early refills. Intermittent therapies (e.g., drugs used to treat pain on an as-needed basis) and therapies for which samples are often provided to patients (e.g., expensive drugs, drugs that are new to the market) present challenges in accurately assessing the actual exposure and duration of exposure, see section V.C.5, Validation of Exposure

4. Ascertainment of Exposure: Dose

Data about exposure should include information about dosing regimen (e.g., strength, dosing frequency, route of administration). Depending on the exposure and the question of interest in the study, it may be useful to describe the dose of each administration or a daily dose, as well as an estimated cumulative dose (i.e., the total amount of the drug of interest given to a patient over a specified period of time).

It is reasonable to begin with the dose information provided in the data source, and then discuss in the protocol or study report the specific assumptions made when estimating the dose of the exposures of interest, especially for pediatric patients. See section V.C.6, Dosing in Specific Populations. In addition to the dosing regimen, the data source should provide detailed and

[20] This guidance does not address issues related to medication adherence.

complete drug description information, including dosage formulation (e.g., oral solution versus injectable solution) to determine a patient's total daily dose, especially if the product has multiple formulations available.

5. Validation of Exposure

Other than for medications administered in hospital settings or infusion settings, electronic health care data capture prescriptions of drugs and the dispensing of drugs to patients, but generally do not capture actual patient drug exposure or dose consumption because this depends on patients obtaining and using the therapy as prescribed. Additionally, medical claims data do not capture dose adjustment of an existing treatment if the provider instructs patients in a clinic visit or by phone to adjust the dose without writing a new prescription. Dose adjustment for an existing treatment can be missed in the EHRs if the change was not noted in the patient's record.

Validation ideally involves a comparison of the exposure classification in the proposed data source with a reference data source,[21] and produces estimates of misclassification that can be used in qualitative or quantitative assessments of the impact on study validity. Validation might begin with defining the conceptual and operational definitions. For example, to define new use of drug X in a particular study, the conceptual definition may be "initiation of drug X and no exposure to drug X in the past 365 days," and the operational definition would be "at least one outpatient prescription claim for drug X (identified by NDC code xxx), and no claims for drug X in 365 days before the dispensing date of the prescription." For prescribed medications used in outpatient settings, dispensing or billing data would tend to be more accurate than most EHRs in reflecting exposure to a drug by documenting that the prescriptions were filled. In such cases, validation of EHRs prescribing data by examining medical claims data may be warranted. For drugs administered in the health care setting (e.g., vaccines, injectables, blood products), administration recorded in the EHRs may provide more complete information than is available in medical claims records. In these cases, it may be useful to validate medical claims data by examining the EHRs. In certain situations, when reference data sources are not available, additional studies conducted in the same population or published in the literature can provide estimates of potential misclassification of exposure status (e.g., survey of study participants to assess intake of drug, published reports of numbers of people obtaining vaccinations through pharmacies/workplaces/schools).

FDA recommends documenting the methods used to calculate and validate duration, dose, product switching, and other characteristics of exposure. Validation and misclassification issues should be addressed in appropriate study documents. FDA also recommends including in the protocol quantitative approaches, such as quantitative bias analyses, to demonstrate whether and how exposure misclassification, if present, might impact study findings. The approach can be applied *a priori* for feasibility assessment, to facilitate interpretation of study results, or for both purposes. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured in exposure validation.

[21] In certain cases, the RWD source may be the only reference. For example, if exposure is defined by whether the patient paid for the prescription, medical claims data may be used, and this information will be the reference source.

6. Dosing in Specific Populations

In addition to reporting validated information about the dose prescribed, dispensed, or administered, additional information may be necessary to permit an assessment of whether dosing was appropriate for specific populations (e.g., if there was significant underdosing or overdosing). For example, for patients with compromised renal function, it may be necessary to have access to measurements of serum creatinine, creatinine clearance, or estimated glomerular filtration rate to determine whether the recommended dose based on product labeling was used. Another example is when assessing exposure in pediatric populations where it may be necessary to obtain the patient's weight and describe the dose within weight categories. The need for additional data to permit appropriate assessment of dosing may occur more frequently with claims data, but can also occur when using EHRs, if necessary, data are absent.

7. Other Considerations

The patients providing comparator data should be defined clearly and with adequate detail in the protocol. The protocol should discuss the reasoning for selecting the: (1) source of comparator data; and (2) the time period (if the comparator group is not concurrent with the treatment group). Because a comparator agent may differ from the product of interest in specific indication within a disease, contraindication, safety profile, or user's disease severity or comorbidity, as well as other patient, physician, and healthcare system characteristics (e.g., timing of exposure relative to the onset of disease, disease status, prior treatment, patient's socioeconomic status, physician's prescribing behavior, drug availability and treatment guideline based upon particular healthcare system, etc.), it is important to ensure adequate data are available for FDA to assess the comparability of the exposed and comparator populations.

Relevant concomitant medication use (e.g., combination therapy components, standard of care therapy, etc.) should be described and ascertained from the data source. A study's definition of concomitant medication use should be described in detail. Definitions of concomitant medication use might include instances when drugs are dispensed on the same day, when drugs have overlapping days' supply, or when patients have filled prescriptions for two or more drugs during the study period. Limitations to ascertainment of concomitant drugs (e.g., nonprescription drugs) should also be described.

D. Outcome Ascertainment and Validation

A crucial step in selecting a data source is determining whether it captures the clinical outcome of interest. Because electronic health care data typically capture outcomes that are brought to the attention of a health care professional and documented in the medical record, outcomes representing mild symptoms or events occurring outside of medical care (e.g., out-of-hospital death) will not generally be well-captured. Conversely, discrete outcomes or acute events (e.g., stroke, myocardial infarction, new infection) are more likely to be captured than worsening of existing problems (e.g., depression, psoriasis, arthritis) that may not be discerned by a new diagnosis code. In general, the likelihood of capturing outcomes may vary by disease type and the extent to which the patient has ongoing encounters with health care professionals that could lead to additional information being documented in medical records. Unlike traditional clinical

trials, studies exclusively using electronic health care data to ascertain outcomes likely do not have protocol-defined follow-up visits and may not have monitoring of events at intervals necessary for outcome ascertainment; further, the severity of disease and responses to treatment may impact the frequency of follow-up visits, and hence the data available. In addition, the assessment of the outcome of interest is likely more standardized and comprehensive in traditional clinical trials. Therefore, the availability, accuracy, and completeness of data on the outcome of interest as well as the need for external data linkage should be carefully considered. Whether and to what degree a data source captures the outcome of interest should be assessed before study initiation and be independent of the exposure of interest.

1. Definition of Outcomes of Interest

Many outcomes involve diagnoses recorded by physicians as part of routine care. To minimize the effect of variability in practice by different physicians and over time (e.g., using different diagnosis and classification criteria, coding the same event in different ways), FDA recommends defining an outcome of interest based on the clinical, biological, psychological, and functional concepts of the condition, as appropriate. The conceptual definition for the outcome of interest (also referred to as the *case definition*) should reflect the medical and scientific understanding of the condition and might vary by study. For example, for anaphylaxis, the conceptual definition (or case definition) may include the following clinical criteria: sudden onset, rapid progression of signs and symptoms, ≥1 major dermatological criterion, and ≥ 1 major cardiovascular or respiratory criterion. The protocol should include a detailed description of the conceptual definition, including the signs, symptoms, and laboratory and radiology results that would confirm the outcome status.

Conceptual definitions should be able to be operationalized in RWD sources. For example, randomized controlled trials in oncology typically use tumor-based outcomes of interest in the setting of specific timing and frequency of follow-up assessment and often include molecular or other biomarker testing that may not be standard of care in all clinical practice settings. Since achievement of an objective response (tumor shrinkage), or the date of tumor progression based on standardized clinical trial criteria (e.g., RECIST 1.1) is not typically captured in RWD sources, proxy measures or multi-component definitions may need to be explored and their use justified. As mentioned above, it is more feasible to capture outcomes that have well-defined diagnostic criteria that are likely to be consistently captured in RWD. Sponsors should discuss the proposed outcomes definitions and the appropriateness of proxy measures with the FDA review division.

2. Ascertainment of Outcomes

To help identify potential cases in the selected data source and study population, operational definitions using diagnosis and procedure codes (e.g., ICD-9-CM, ICD-10), laboratory tests (e.g., LOINC) and values, or unstructured data (e.g., physician's encounter notes, radiology and pathology reports) should be developed based on the conceptual definition of the outcome of interest. If the operational definition includes information abstracted from unstructured data in the EHRs or another data source (e.g., mention of spina bifida in birth certificate records for the identification of neural tube defects in infants), the protocol should provide a detailed description

and rationale for the methods and tools used to process the unstructured data and the validation of those methods. See section IV.B.5, Unstructured Data, for additional information on unstructured data. When patient- or physician-generated data (e.g., data required for subjective end points) are proposed to assess the outcome of interest or to complement operational definitions, the protocol should specify how the outcome measure (e.g., sign score, severity index) will be defined and constructed and validated, if applicable, and how the data will be collected.

The sensitivity and specificity of an operational definition may both be reduced when there is outcome misclassification. Given that it is usually not possible for sensitivity and specificity to be perfect (i.e., 100%), outcome misclassification might result in both false positives and false negatives. FDA recommends considering the potential impact of outcome misclassification on study validity and inference when developing or selecting an operational definition for the proposed study. For example, when studying infrequently occurring outcomes in a cohort study, given the low prevalence of the outcome event, it is important to achieve high specificity to minimize false positive cases and high sensitivity so that more true cases can be captured. If the study is designed to estimate a risk ratio, selecting an operational definition with high specificity may be more important than high sensitivity, because imperfect sensitivity (some false negatives) may not bias the risk ratio, provided the outcome misclassification is non-differential and specificity is very high (almost no false positives), regardless of outcome prevalence. Thus, focusing on very high specificity in this scenario will help ensure the study result is correct even if data are imperfect, while high sensitivity is still important to ensure the precision of the estimates.

Operational definitions developed for one data source or study population might not perform as well in other sources or populations, due to database-specific sensitivity and specificity as well as variable disease prevalence. PPV and NPV are functions of sensitivity and specificity as well as prevalence of the outcome in the population in which the predictive values are measured. Therefore, PPV and NPV are variable by data source and study population characteristics (e.g., demographic factors, underlying diseases, comorbidities, clinical settings).

The protocol should include a detailed description of the operational definition, the coding system, the rationale, and associated limitations of information selected to construct the operational definition (e.g., selection of primary or secondary diagnosis codes for which the order may not correspond to their medical importance), and the potential impact on outcome misclassification. If the performance of the operational definition has been assessed in prior studies, the applicability to the proposed study should be discussed. Furthermore, because the case definition used in prior studies to establish sensitivity, specificity, and predictive values might include different diagnostic criteria from the conceptual definition developed for the proposed study, proper use of the performance measures assessed in prior studies should be carefully considered.

3. Validation of Outcomes

FDA expects validation of the outcome variable to address outcome misclassification. The extent of validation, such as complete verification of the outcome variable for all subjects, verification

of all potential cases (or non-cases) identified by an operational definition, or assessing the performance of an operational definition depends on the necessary level of certainty and the implication of potential misclassification on study inference.

Although complete verification of the outcome variable is considered the most rigorous approach, there are scenarios where verifying outcome for every subject might not be feasible and assessing the performance of the operational definition of the outcome might suffice. Outcome validation involves using a clinically appropriate conceptual outcome definition to determine whether a patient's status, classified by an operational definition, truly represents the outcome of interest, typically by reviewing clinical details recorded in the patient's medical records in either electronic or paper format.

FDA recommends using standardized medical record review processes, including the use of standardized tools, documentation of process, and training of personnel. A standard and reproducible process is critical for minimizing intra- and inter-rater variability, especially for multi-site studies in which medical records usually cannot be shared across systems and a centralized medical record review is not possible. Even with a centralized medical record review, a standardized process helps to ensure that the same criteria are applied by different adjudicators or a single adjudicator over time. Reporting of comparison metrics (e.g., kappa statistic) is useful to ensure replicability. An estimated medical record retrieval rate (e.g., when requesting medical records from health facilities for a study using claims-based databases) should be justified in the protocol, and the implications for internal and external validity should be discussed. In addition, because knowledge of a patient's exposure status may influence the observer and result in differential misclassification, blinding of the abstractor and adjudicator to exposure status should be considered by masking the study question or redacting the exposure information, especially when the abstractor or adjudicator may associate the exposure with the outcome of interest. The protocol should provide a description of how observer bias will be handled.

Ideally, through complete verification of the outcome variable, the outcome status is accurately classified for each subject to minimize outcome misclassification and improve study internal validity. In practice, a more commonly used approach is to assess the performance of an operational definition in validation studies. Performance measures, such as sensitivity, specificity, and predictive values, do not accurately classify cases and non-cases; rather, they inform the degree of outcome misclassification and facilitate the interpretation of results in the presence of misclassification.

PPV is often assessed in validation studies. PPV is the proportion of potential cases identified by an operational definition that are true positive cases. Therefore, PPV informs the degree to which false-positive cases are included among the identified cases. When the concern with false negative cases is negligible (e.g., when the sensitivity is deemed sufficiently high so that the number of false-negative cases is minimal), a high PPV might be adequate to provide confidence in the validity of the outcome variable, whereas a moderate-to-low PPV might warrant verification of the outcome variable for all potential cases. When the extent of false-positive cases and the extent of false-negative cases are both of concern, sponsors should consider assessing all performance measures needed for quantitative bias analysis to evaluate the impact of outcome misclassification on the measure of association or take a more rigorous

approach by validating the outcome variable for all potential cases and non-cases to accurately classify the outcome variable for each subject. Overall, the required extent of validation should be determined by the necessary level of certainty and the implication of potential misclassification on study inference.

In general, sponsors should consider the tradeoff between false-positive and false-negative cases when selecting an operational definition and identify the proper outcome validation approach to support internal validity. For example, to identify neural tube defects in infants, an operational definition that includes a spectrum of inpatient and outpatient diagnosis codes might have a high sensitivity, low specificity, and low PPV; restricting the operational definition to inpatient diagnosis codes only or a combination of diagnosis and procedure (e.g., surgical repair) codes might increase the PPV but miss a substantial proportion of true cases (low sensitivity). Because missing true cases is particularly a concern for infrequently reported outcomes, one approach is to select an operational definition of high sensitivity and perform verification of the outcome variable for all potential cases identified by the sensitive operational definition to maximize the likelihood that the true cases are all identified and that the false-positive cases are minimized through validation. Unlike rare disease outcomes, when an outcome of interest involves a more common event (e.g., disease-specific hospitalization) or improvement or worsening of a condition, the operational definitions for common diagnoses are likely to generate false-positive and false-negative cases to a considerable extent because both true cases and true non-cases are prevalent. Therefore, it might be difficult to obtain accurate and complete information (e.g., laboratory test results, functional measures) for the operational definition to accurately classify cases and non-cases. For such outcomes, measuring PPV alone will be inadequate to inform outcome misclassification.

In scenarios where complete verification of the outcome variable for each study subject is infeasible, the performance of an operational outcome definition should be assessed in the proposed study population using a justified sampling strategy. As stated earlier, use of an operational definition that has been assessed in a prior study should ideally be in the same data source and in a similar study population, because the performance of an operational definition may vary substantially by data source and study scenario, and more recent data may be needed if there are secular trends in disease, diagnosis, and coding. The quality of prior studies used to establish sensitivity, specificity, and predictive values should be evaluated. In particular, the case definition used in the prior study to establish these measures should be compatible with the conceptual outcome definition developed for the proposed study. The applicability of these measures to the proposed study should be justified, and sensitivity analyses can be considered.

Without complete patient information and complete verification of the outcome variable, outcome misclassification remains a threat to the study internal validity, and the impact on the measure of association between exposure and outcome varies depending on whether the degree of misclassification differs between the exposure groups. Differential misclassification involves a complex interplay of differences in sensitivity, specificity, and disease prevalence between the exposure groups, and thus may bias the association either toward or away from the null.[22] Because it is difficult to predict the direction of the bias, differential misclassification is a concern for both safety and effectiveness studies. Unlike differential misclassification, non-

[22] Null refers to no association between exposure and outcome of interest.

differential misclassification tends to bias the association toward the null; as a result, a true risk might be missed in safety studies, whereas a larger study population might be needed to demonstrate the drug effect in effectiveness studies.

Non-differential outcome misclassification might occur when the outcome definition is not adequately refined and includes conditions that have different magnitude of association with the exposure of interest. For example, neural tube defects include primary neurulation defects and post-neurulation defects. Primary neurulation defects are directly attributed to failure of primary neurulation (i.e., neural tube closure), which occurs between approximately 18 and 28 days after fertilization. The pathophysiology of post-neurulation defects is less understood. Therefore, drug exposure during the critical period for primary neurulation in gestation might not affect post-neurulation in the same manner. When the outcome definition includes both primary and post-neurulation defects, the risk of primary neurulation defects, if any, is likely not detected.

Differential outcome misclassification might be minimized in studies in which the exposure status is blinded. However, even when data collection methods seem to preclude the likelihood of differential outcome misclassification, it is not guaranteed that the only misclassification of the actual data will be non-differential outcome misclassification. For example, the physician who observed, diagnosed, and documented whether or not an outcome occurred could have been the same physician who made a decision as to which patients received the treatment meant to prevent that outcome, or the physician could have monitored disease progression or treatment side effects differently, given the knowledge as to which treatment they received. Therefore, the direction of the outcome misclassification might remain unpredictable when using RWD. In addition, when more than one misclassification exists in a study, sponsors should consider how they might be related to each other. For example, whereas non-differential exposure misclassification and non-differential outcome misclassification each might bias the association toward the null, when the two misclassifications are dependent, overall it can create a bias away from the null (Lash et al. 2009). Therefore, when evaluating the implication of potential misclassification on study inference, sponsors should consider how the individual non-differential misclassifications are interrelated, rather than assuming that the association is biased toward the null. Under such circumstances, assessing the performance of the operational outcome definition according to exposure status in the proposed study population might be necessary.

Regarding outcome validation, sponsors should justify the proposed validation approach, such as verifying the outcome variable for all potential cases or non-cases, versus assessing the performance of the proposed operational definition; if the latter will be done, justify what performance measures will be assessed. The protocol should include a detailed description of the outcome validation design, methods, and processes, as well as sampling strategy (if applicable). If a previously assessed operational definition is proposed, additional information should be provided, including: (1) data source and study population; (2) during what time frame validation was performed; (3) performance characteristics; (4) the reference standard against which the performance was assessed; and (5) a discussion of whether prior validation data are applicable to the proposed study.

FDA recommends including in the protocol quantitative approaches, such as quantitative bias analyses, to demonstrate whether and how outcome misclassification, if present, might impact study findings. The approach can be applied *a priori* for feasibility assessment, to facilitate interpretation of study results, or for both purposes. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured in outcome validation.

4. Mortality as an Outcome

In the United States, death and cause of death are generally not included in electronic health care data, with exceptions being made for death occurring while a patient is under medical care. Ascertainment of death (fact of death and cause of death) can be accomplished through linkage with public or commercial vital statistics data sources, to increase the completeness and recency of the death variables. The use of external mortality data, however, is subject to all of the limitations of such data and data linkage methods (Haynes 2019; Navar et al. 2019; Curtis et al. 2018). Careful documentation of mortality data quality and its implications should be included in the protocol.

If the death is not captured in the electronic health care data systems, patients who die after having been exposed to the study drug might be observed in electronic health care data as either not filing any further medical claims or not receiving any additional care past a particular date. For studies in which the outcome or outcomes of interest (e.g., myocardial infarction or stroke) include fatal outcomes, either excluding patients who appear to be lost to follow-up at any time following their exposure to the study drug or classifying patients who are lost to follow-up as deceased in the absence of data to the contrary, is likely to create bias. Searches of vital statistics systems may be considered to see whether their absence (disenrollment) from the system is because of death.

E. Covariate Ascertainment and Validation

For the purposes of this guidance, covariates in a particular study can include two types of elements: confounders and effect modifiers.

1. Confounders

Information on potential confounders is collected in a nonrandomized study to support appropriate efforts to balance treatment and comparator groups in the analysis.

After identifying the potential confounders in a study, the proposed data source should be evaluated to determine whether it is adequate to capture information on important factors which may contribute to confounding. These include confounders that are well-captured in the proposed data source (measured confounders) and those that are not well-captured (unmeasured or imperfectly measured confounders). Examples of confounders that can be unmeasured or imperfectly measured in electronic health care data, especially in claims data, include race/ethnicity, family history of disease, lifestyle factors (e.g., smoking, alcohol use, nutrition intake, physical activity), certain physical measurements (e.g., body mass index), drugs obtained

without insurance, and indication for drug use. FDA recommends considering potential linkages with other data sources or additional data collection to expand the capture of important confounders that are unmeasured or imperfectly measured in the original data source. The protocol should clearly disclose all known unmeasured confounders in the proposed data source(s), as well as approach(es) to supplement information on unmeasured confounders and justify the appropriateness of any proxy measure(s) for specific unmeasured confounder(s).

2. Effect Modifiers

Studies of drug effectiveness or safety usually report an average treatment effect, even though the same treatment can have different effects in different groups of people. Information on potential effect modifiers is used to better understand heterogeneity of treatment effect, the nonrandom, explainable variability in the direction and magnitude of treatment effects for individuals within a population (Velentgas et al. 2013). The potential for effect modification by demographic variables (e.g., age, sex, race, ethnicity) or pertinent comorbidities should be examined in the study, and relevant effect modifiers should be available in the chosen data source. The protocol should clearly disclose all known unmeasured effect modifiers, when relevant, in the proposed data source(s), as well as approach(es) to supplement information on unmeasured effect modifiers and justify the appropriateness of any proxy measure(s) for specific unmeasured effect modifier(s).

3. Validation of Confounders and Effect Modifiers

For all key covariates, including confounders and effect modifiers, FDA recommends providing and justifying the validity of operational definitions in the protocol and study report. Selection of such covariates depends on the study question, study design, and the impact of misclassification on study internal validity and study inference. For example, when a genetic factor is a key confounder for a study question, it may be implicitly adjusted as a time-fixed covariate in a self-controlled design, even if data are imperfect. If the measured covariates can change during a patient's follow-up period (time-varying covariates) and are important to the analysis, the protocol should describe whether and how frequently the information on time-varying covariates can be captured, particularly since capture of time-varying covariates in RWD can be differential by severity of illness (e.g., more testing in more seriously ill patients).

When evaluating the validity of covariate operational definitions, FDA recommends identifying the best reference data source based on the nature of the covariates. When validating operational definitions of covariates that are medical events or procedure utilizations (e.g., comorbidities, past medical history), the same principles apply as in section V.D.3, Validation of Outcomes. For discussion on validating operational definitions of covariates that are associated with drug uses, such as concurrent medications or past drug uses, see section V.C.5, Validation of Exposure. When assessing the validity of other covariate operational definitions, such as family history of disease, lifestyle factors, or indication for drug use, the appropriate reference may include a patient or provider survey or appropriate data linkages.

When supplemental information is needed to capture important covariates or is used for covariate validation, FDA recommends describing the likelihood of obtaining the supplemental

information for the overall study population. If this supplemental information is only available for part of the study population, FDA recommends discussing the potential effect on internal validity in relevant study documents.

Quantitative approaches, such as quantitative bias analyses, are encouraged to demonstrate whether and how misclassification of key covariate(s), if present, might impact study findings. The approach can be applied *a priori* for feasibility assessment, to facilitate interpretation of study results, or for both purposes. The protocol should pre-specify the indices (e.g., sensitivity, specificity) that will be used for quantifying bias and describe how the selected indices will be measured in key covariate(s) validation.

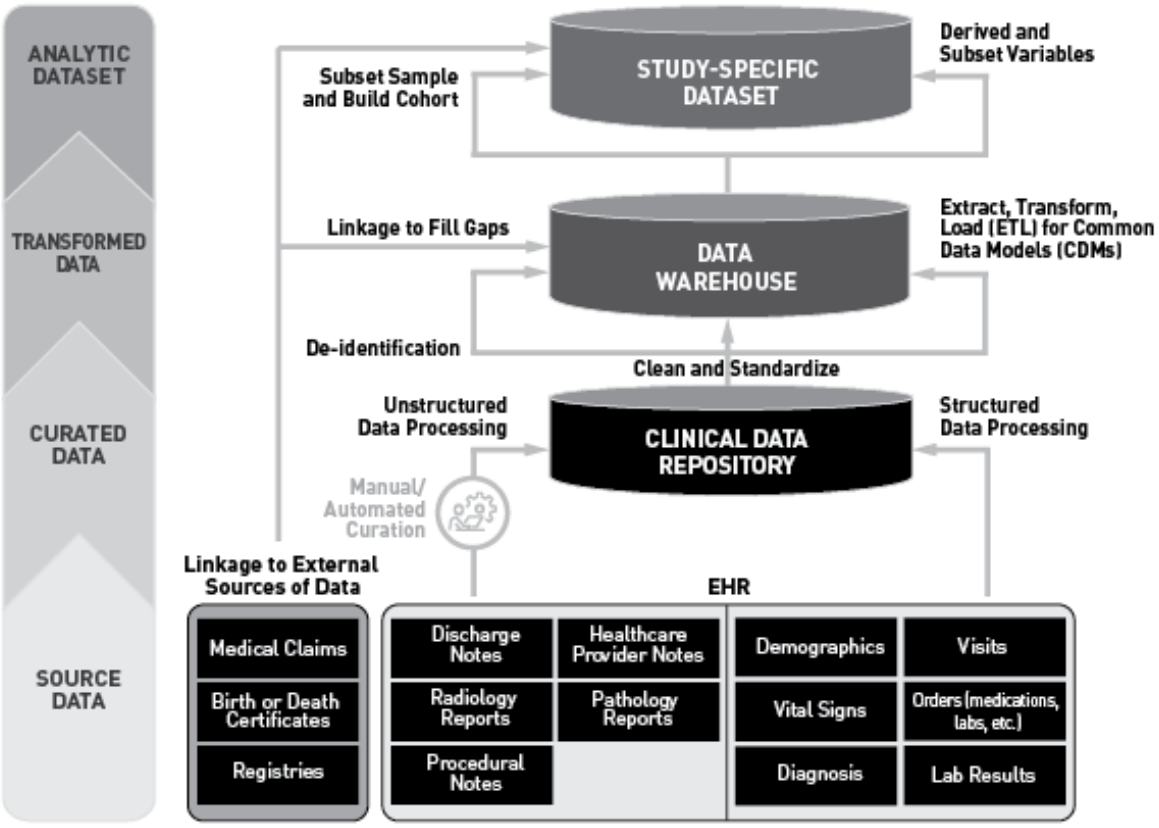
VI. DATA QUALITY DURING DATA ACCRUAL, CURATION, AND TRANSFORMATION INTO THE FINAL STUDY-SPECIFIC DATASET

This section discusses points for consideration when examining the quality of data over the course of the data life cycle. Although the data life cycle may vary depending on the type of data and setting (i.e., health care settings such as pharmacies, clinics, emergency departments and hospitals), in general, the life cycle involves multiple phases: data accrual from the original source data; curation of data to the clinical data repository; transformation and de-identification of data where necessary, creation of a data warehouse; and production of a study-specific dataset for analysis (see Figure 1).

The concept of the data life cycle illustrates the iterative nature of the process for examining the quality of data. The process is not a onetime assessment; rather, it is an ongoing process in which data quality checks, cleansing,[23] and monitoring occur at each phase in the cycle, and some checks may be repeated (i.e., occur in multiple phases of the cycle).

[23] Data cleansing (sometimes referred to as data scrubbing) is the process of correcting or removing inaccurate data (or improperly formatted, duplicate data or records) from a database. The data requiring correction/removal is sometimes referred to as "dirty data." Data cleansing is an essential task for preserving data quality.

Figure 1: Illustrative Example of the Life Cycle of EHR Data[24]



Guidelines that evaluate the quality of EHRs and medical claims data primarily focus on distributed data networks in which disparate data sources are aggregated, linked, and processed to create a comprehensive data warehouse (Miksad and Abernethy 2018; Girman et al. 2018; Daniel et al. 2018; Kahn et al. 2016; Wang et al. 2017; Mahendraratnam et al. 2019). Although FDA does not endorse any particular set of guidelines or checklists, sponsors should evaluate the completeness, accuracy, and plausibility of the data, including verifying data against its original source (e.g., discharge notes, pathology reports, registry records) and conforming to consensus-based data standards, where applicable. Sponsors should provide scientific justifications for choosing these standards and should articulate how these standards are adequate to ensure the completeness, accuracy, and plausibility of the relevant data source.

The study protocol and analysis plan should specify the traceability (curation and transformation procedures used throughout the data life cycle) and describe how these procedures could affect the integrity of the data and the overall validity of the study. Below are points for consideration when examining data at each step in the data life cycle, including (A) characterizing the data with respect to completeness, conformance, and plausibility of data values, (B) documenting the

[24] This figure illustrates some of the processes applied to EHR data to produce a dataset that may be appropriate for research use (i.e., steps from original source data through the final analytic dataset). This figure shows processes for EHR data; the process may differ for claims data. Quality checks for each process step are described in this section.

QA/QC plan that includes transformation processes; and (C) defining a set of procedures for ensuring integrity of the data.

A. Characterizing Data

The format and traceability of EHRs and medical claims data can vary significantly across health care entities (e.g., insurer, practice, provider, data vendor). In general, sponsors should address the procedures used to ensure completeness and accuracy of study data, as well as processes for data accrual, curation, and transformation over the data life cycle. The FDA recommends automated data quality reports that include the following characteristics and processes in a standardized way, when applicable to the chosen data source:

- Data accrual

  (1) Methods for data retrieval and processes to minimize missing data extraction, implausible values, and data quality checks in data captured at the point of care (e.g., during clinical practice for manual or automated health care data collection processes) to ensure accuracy and completeness of data elements.

  (2) Traceability of data elements to allow tracking of these elements back to their respective points of origin, with clear documentation of modifications that may have occurred.

  (3) Timeliness of data availability, data years spanned, and continuity of coverage (e.g., median duration of patient enrollment).

  (4) Handling data discrepancies and duplicate records. RWD may stem from multiple data streams, across various settings and platforms, which may present data discrepancies for the same variable (e.g., when the information for the same element is entered differently in different data sources) or even duplicate records for the same patient within the same data source.

  (5) The reason for and timing of data error corrections implemented by data holders during the relevant period of data collection.

  (6) The reason for and timing of changes in processes implemented by data holders during the relevant period of data collection that may impact data accrual and/or data quality checks.

  (7) Any updates or changes in coding practices and versioning (e.g., ICD diagnosis codes, Healthcare Common Procedure Coding System codes) across the study period that are relevant to variables of interest.

  (8) Any other changes in the data (e.g., collection, reporting, definitions) during the study period and their potential impact on the study results.

- Data curation

  (1) Routine migration of data from various sources over time.

  (2) QA testing and data quality checks employed across sites, as well as the criteria used in determining whether data quality techniques are appropriate for the intended purpose of the data.

  (3) Data elements that are well-defined with consistent and known clinical meaning and understanding of data traceability, as well as documentation of clinical definitions used.

  (4) Assessment of completeness of data elements including trends over time.

  (5) Unstructured and structured data processing (e.g., abstraction and conversion of unstructured data to structured data), including manual versus automated techniques.

  (6) Harmonization of structured data across systems.

  (7) Conformance to open, consensus-based data curation standards, when applicable.

  (8) Accuracy of mappings (e.g., in the presence of different coding systems, such as Systematized Nomenclature of Medicine—Clinical Terms [SNOMED CT] versus ICD-10-CM).

  (9) Additional harmonization and mapping considerations, if applicable (if data spans multiple countries—e.g., U.K. data used in addition to U.S. data).

- Data transformation[25]

  (1) Implementation of the extract, transform, and load process applied to the whole repository population as part of data warehouse creation.

  (2) De-identification of patient records and any process that could be used to re-identify unique patients in original source data without losing traceability (e.g., use of linkage tokens).

  (3) Algorithms used to transform and cleanse the data, as well as availability of standard operating procedures, including procedures for verifying the data against its original source.

  (4) Data standardization (e.g., data types, sizes, formats) for internal consistency of data elements and semantics, including semantics of local codes to a target terminology (e.g., for laboratory data).

[25] For purposes of this guidance, data transformation is the process of converting data from one format or structure into another format or structure.

(5) When converting multiple data sources into a CDM, processes used for data transformation into a CDM (e.g., common terminology and structure), the comprehensiveness of the CDM (e.g., does the CDM contain the key data elements), approaches (e.g., algorithms/methods) for identification and handling of duplicate records within and across data sources, and potential impact of restricting to CDM on sample size and duration of patient follow-up or duration of drug exposure. See section IV.B.3, Distributed Data Networks.

(6) Implementation of data checks pertaining to data model conformance errors.

(7) Data transformation processes used in preparation for data linkage. See section IV.B.2, Data Linkage and Synthesis.

(8) Quality of record linkage (i.e., linking records from multiple datasets) and deduplication (i.e., finding duplicate records in a dataset) process, which may vary depending on the accuracy of the data used to perform the matches and the accuracy of the linkage algorithm.

(9) Quantification of linkage errors (e.g., false matches, missed matches) that may lead to biased study findings. These are important when evaluating linkage quality (Harron et al. 2017). It is important to report details of the linkage algorithm and appropriate metrics (e.g., linkage error rates, match rates, comparison of characteristics of linked and unlinked data). Additional considerations include whether the error is random or nonrandom, potential bias, and impact on risk estimates and study findings.

(10) Procedures for adjudicating discrepancies in linked data as well as plans for handling linkage discrepancies (e.g., adjusting risk estimates for the linkage error).

Sponsors should also consider issues related to the study-specific analytic dataset:

(1) Adherence to data specifications outlined in the study protocol and statistical analysis plan when compiling the analytic dataset.

(2) Additional study-specific data transformations, such as data transformations that are only done for a subset of patients of interest and that are not applied to all patient records in the data warehouse (e.g., manual extraction of data from unstructured textual pathology reports).

(3) Data checks implemented on the final analytic dataset for implausible values for data elements (e.g., height, weight, blood pressure), how such values are addressed, and the completeness of data for key analytic variables.

(4) The extent, percentage, and pattern of missingness and implausible data. Depending on the analysis plan's proposed method for handling missing data, imputations may be performed and included in the final analytic dataset and the type of imputation described.

B. Documentation of the QA/QC Plan

A QA/QC plan for construction of analytical data, the planned approach for handling quality control issues during analysis, and contemplation of differing levels of data quality by data element (and the potential implications on study findings) should be described in the study protocol and analysis plan. In general, activities to ensure the quality of the data before data-related activities are developed during the design of the study, and such activities, which include standardizing procedures for how to collect the data, may be regarded as QA (Szklo and Nieto 2006). Quality control consists of the decisions and steps taken from data collection through compilation of the final analytic dataset to ensure it meets prespecified standards and to ensure the processes used are reproducible. A multidisciplinary approach that includes clinical input is necessary to ensure adequate capture and handling of data, particularly for electronic health care systems, which inherently incorporate nuances and intricacies of health care delivery.

C. Documentation of Data Management Process

All manual and automated data retrieval and transformation processes should be thoroughly assessed from data collection through writing of the final study report to ensure integrity of the data. Sponsors should ensure that curation and transformation processes do not alter the meaning of data or cause the loss of important contextual information. Descriptions of processes should include safeguards or checks to ensure that patient data are not duplicated or overrepresented. In addition, documentation of processes used to mine and evaluate unstructured data should describe the techniques employed (e.g., natural language processing) to abstract unstructured data (e.g., clinician notes) and supplement structured data (e.g., diagnostic codes).

Processes used for managing and preparing the final study-specific analytic dataset should be described in the study protocol or analysis plan. Analysts should have appropriate training or experience with the data and software used to compile the analytic datasets. To facilitate FDA review, all submitted programs (e.g., those written by analysts) should be thoroughly annotated with comments that describe the intent or purpose of each data management and analysis step written in the program (e.g., annotate each data step in a statistical analysis program).

REFERENCES

Bustamante, R, A Earles, JD Murphy, AK Bryant, OV Patterson, AJ Gawron, T Kaltenbach, MA Whooley, DA Fisher, SD Saini, S Gupta, and L Liu, 2019, Ascertainment of Aspirin Exposure Using Structured and Unstructured Large-scale Electronic Health Record Data, Med Care, 57:e60–e64.

Carreras, G, M Simonetti, C Cricelli, and F Lapi, 2018, Deterministic and Probabilistic Record Linkage: an Application to Primary Care Data, J Med Sys, 42(5):82.

Curtis, M, SD Griffith, M Tucker, MD Taylor, WB Capra, G Carrigan, B Holzman, AZ Torres, P You, B Arnieri, and AP Abernethy, 2018, Development and Validation of a High-Quality Composite Real-World Mortality Endpoint, Health Services Research, 53(6) Part I:4460-4476.

Daniel, G, C Silcox, J Bryan, M McClellan, M Romine, and K Frank, 2018, Characterizing RWD Quality and Relevancy for Regulatory Purposes, Duke Margolis Center for Health Policy, accessed January 9, 2019, https://healthpolicy.duke.edu/sites/default/files/2020-03/characterizing_rwd.pdf.

Girman, CJ, ME Ritchey, W Zhou, and NA Dreyer, 2019, Considerations in Characterizing Real-World Data Relevance and Quality for Regulatory Purposes: A Commentary, Pharmacoepidemiol Drug Saf, 28(4):439–442.

Harron, KL, JC Doidge, HE Knight, RE Gilbert, H Goldstein, DA Cromwell, and JH van der Meulen, 2017, A Guide to Evaluating Linkage Quality for the Analysis of Linked Data, Int J Epidemiol, 46(5):1699–1710.

Haynes, K, 2019, Mortality: The Final Outcome, Pharmacoepidemiol Drug Saf, epub ahead of print Jan 31, 2019, doi: 10.1002/pds.4715.

Kahn, MG, TJ Callahan, J Barnard, AE Bauck, J Brown, BN Davidson, H Estiri, C Goerg, E Holve, SG Johnson, ST Liaw, M Hamilton-Lopez, D Meeker, TC Ong, P Ryan, N Shang, NG Weiskopf, C Weng, MN Zozus, and L Schilling, 2016, A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data, EGEMS, 4(1):1244.

Lash, TL, MP Fox, and AK Fink, 2009, Applying Quantitative Bias Analysis to Epidemiologic Data, New York (NY): Springer.

Mahendraratnam, N, C Silcox, K Mercon, A Kroetsch, M Romine, N Harrison, A Aten, R Sherman, G Daniel and M McClellan, 2019, Determining Real-World Data's Fitness for Use and the Role of Reliability, Duke Margolis Center for Health Policy, accessed July 24, 2020 https://healthpolicy.duke.edu/sites/default/files/2019-11/rwd_reliability.pdf.

Miksad, RA, and AP Abernethy, 2018, Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality, Clin Pharmacol Ther, 103(2):202–205.

Navar, AM, ED Peterson, DL Steen, DM Wojdyla, RJ Sanchez, I Khan, X Song, ME Gold, and MJ Pencina, 2019, Evaluation of Mortality Data from the Social Security Administration Death Master File for Clinical Research, JAMA Cardiol, epub ahead of print Mar 6, 2019, doi: 10.1001/jamacardio.2019.0198.

Porta, M, 2014, A Dictionary of Epidemiology, Sixth Edition, New York (NY): Oxford University Press.

Richesson, RL, MM Smerek, and CC Blake, 2016, A Framework to Support the Sharing and Reuse of Computable Phenotype Definitions Across Health Care Delivery and Clinical Research Applications, EGEMS, 4(3):1232.

Szklo, M, and FJ Nieto, 2006, Epidemiology: Beyond the Basics, 2nd Edition, Burlington (MA): Jones & Bartlett Learning.

Velentgas, P, NA Dreyer, P Nourjah, SR Smith, and MM Torchia, editors, 2013, Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide, AHRQ Publication No. 12(13)–EHC099, accessed January 9, 2019, https://effectivehealthcare.ahrq.gov/sites/default/files/related_files/user-guide-observational-cer-130113.pdf.

Wang, SV, S Schneeweiss, ML Berger, J Brown, F de Vries, I Douglas, JJ Gagne, R Gini, O Klungel, CD Mullins, MD Nguyen, JA Rassen, L Smeeth, and M Sturkenboom, 2017, Reporting to Improve Reproducibility and Facilitate Validity Assessment in Healthcare Database Studies V1.0, Pharmacoepidemiol Drug Saf, 26(9):1018–1032.