Rare Diseases: Natural History Studies for Drug Development

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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I. INTRODUCTION

This guidance is intended to help inform the design and implementation of natural history studies that can be used to support the development of safe and effective drugs and biological products for rare diseases.[2] Although existing FDA guidance considers common issues encountered in drug development for rare diseases,[3] this draft guidance expands on the subject of natural history studies specifically. The focus of this guidance is rare diseases; however, the recommendations in the guidance may be applicable to drug development for nonrare diseases. For applicability to nonrare diseases, discuss with the FDA review division or office responsible for the review of the drug.

This guidance describes the broad potential uses of a natural history study in all phases of drug development for rare diseases, the strengths and weaknesses of various types of natural history studies, data elements and research plans, and a practical framework for the conduct of a natural history study. This guidance also discusses some considerations for aligning the study design with study objectives and for enhancing the interpretability of study results; patient confidentiality and data protection issues in natural history studies; and potential interactions with FDA related to these studies.

[1] This guidance has been prepared by the Office of New Drugs, Rare Diseases Program, and the Office of Translational Sciences in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Office of Orphan Products Development, Office of the Commissioner, at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[3] See the draft guidance for industry *Rare Diseases: Common Issues in Drug Development* (January 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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II. BACKGROUND

Section 526(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a rare disease, in part, as a disease or condition that "affects less than 200,000 persons in the United States."[4] There are approximately 7,000 recognized rare diseases. Individually, each rare disease affects a small number of people, but cumulatively rare diseases affect about 1 in 10 people in the United States. Most rare diseases have no approved therapies, and thus, overall, this presents a significant unmet public health need.

The natural history of a disease is traditionally defined as the course a disease takes in the absence of intervention in individuals with the disease, from the disease's onset until either the disease's resolution or the individual's death. A *natural history study*[5] is a preplanned observational study intended to track the course of the disease. Its purpose is to identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease's development and outcomes. Natural history studies are likely to include patients receiving the current standard of care and/or emergent care, which may alter some manifestations of the disease. Disease registries are a frequent platform to acquire the data for natural history studies.

Knowledge of a disease's natural history is important for planning drug development; however, there is only limited information about the natural history of most rare diseases. In the following sections, this guidance describes major roles of natural history studies in planning controlled trials of investigational drugs to treat rare diseases. It also touches briefly on the potential use of natural history data as an external[6] control in a clinical trial, but not as the primary focus of this guidance.

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[4] In addition, section 526(a)(2)(B) of the FD&C Act also defines a rare disease as any disease or condition that "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

[5] See the National Cancer Institute Dictionary of Cancer Terms, available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/natural-history-study.

[6] The regulation at 21 CFR 314.126 uses the term *historical control*, which is a subset of *external control*. An externally controlled trial compares a group of subjects receiving the test treatment with a group of patients external to the trial, rather than to an internal control group consisting of patients from the same population assigned to a different treatment. The external control can be a group of patients treated at an earlier time (historical control) or a group treated during the same time period but in another setting. See the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001). This guidance uses the term *external control*, except when referring to section 314.126.

III. USES OF A NATURAL HISTORY STUDY

Information obtained from a natural history study can play an important role at every stage of drug development, from drug discovery to the design of clinical studies intended to support marketing approval of a drug and beyond into the postmarketing period.

A. Drug Development

Comprehensive knowledge of a disease can help sponsors design and conduct adequate and well-controlled clinical trials of adequate duration with clinically meaningful endpoints to support marketing applications for new drugs. The following sections highlight important contributions of a natural history study to the clinical development program.

1. Identifying the Patient Population

Some rare diseases have substantial genotypic and/or phenotypic heterogeneity, and the natural history of each subtype may be poorly understood or inadequately characterized. For example, different phenotypes may present with involvement of different organ systems, with different severity or rate of deterioration. A natural history study may uncover sentinel events or detectable physiologic changes that are important predictors of disease progression or that are clinically important in their own right. A well-designed natural history study may be useful in understanding which patient subgroup(s) may benefit from a particular drug trial. The information about subtype signs and symptoms and rates and patterns of progression are useful in deciding the inclusion criteria, the stage of disease to treat, the duration of a trial, the frequency of data collection, and the specific endpoints.

2. Identification or Development of Clinical Outcome Assessments

A clinical outcome assessment is an assessment that describes or reflects how an individual feels, functions, or survives. Clinical outcome assessments can be used during trials to assess the efficacy and safety of a drug. There are four types of clinical outcome assessments (FDA-NIH Biomarker 2017):

- Clinician-reported outcome
- Observer-reported outcome (e.g., reports by or from caregivers)
- Patient-reported outcome
- Performance outcome (e.g., tests of memory or walking ability)

A natural history study can help evaluate the ability of a new or existing clinical outcome assessment to detect change in a particular disease or a pattern of progression of a disease or symptoms of disease. Natural history studies also can be used to evaluate the performance and reproducibility of a clinical outcome assessment for use in a clinical investigation.

We recommend that input is obtained from clinicians with expertise in caring for patients with the target rare disease, patients, caregivers, regulatory agencies, and experts in clinical outcome

assessment measurement to ensure that the selected clinical outcome assessments are fit for regulatory use and are valid assessments of the important and relevant aspects of the disease.

3. Identification or Development of Biomarkers

In general, the term *biomarker* refers to a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathologic processes, or biological responses to a therapeutic intervention (see, for example, section 507(e)(1) of the FD&C Act, FDA-NIH Biomarker 2017). Biomarkers "include physiological measurements, blood tests and other chemical analyses of tissue or bodily fluids, genetic or metabolic data, and measurements from images" (Institute of Medicine Committee 2010). A natural history study can help identify or develop biomarkers that can be diagnostic of the disease, prognostic of the disease's course, predictive of treatment response, or useful in guiding patient selection and dose selection in drug development programs.[7]

Natural history studies provide an opportunity to collect specimens and images that can be used in an analytical validation program. When robustly validated, these biomarkers can serve as endpoints or surrogate endpoints in clinical trials.

4. Design of Externally Controlled Studies: Use of Natural History Study Data

To qualify for marketing approval, an application submitted under section 505(b) of FD&C Act must, among other things, be supported by investigations showing the drug to be safe and effective under the conditions prescribed, recommended, or suggested in the product labeling and demonstrate a favorable benefit-risk profile in the specified patient population.[8] To demonstrate effectiveness, sponsors must provide substantial evidence from adequate and well-controlled investigations, including clinical investigations,[9] that include (among other factors) a valid comparison to a control.[10] The sponsor uses data collected from an adequate control group to discriminate patient outcomes caused by the investigational drug from outcomes caused by other factors (i.e., what would have happened if similar patients had not received the investigational drug). FDA regulations recognize historical controls as a possible control group (usually reserved for special circumstances); however, inability to control for certain biases could limit

[7] See the guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (January 2014). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[8] Section 505(d) of the FD&C Act (21 U.S.C. 355).

[9] Section 505(d) of the FD&C Act (21 U.S.C. 355). FDA has also generally considered *substantial evidence* of effectiveness to be necessary to support licensure of a biological product under section 351 of the Public Health Service Act (PHS Act). For a biological product to be licensed under section 351 of the PHS Act, a sponsor must demonstrate that its product is safe, pure, and potent. Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)).

[10] The characteristics of an adequate and well-controlled investigation are detailed under FDA regulations at 21 CFR 314.126.

the ability of externally controlled trials to demonstrate substantial evidence of effectiveness.[11] However, bias may be mitigated in certain situations where the disease course is predictable and the treatment effect dramatic. In some cases where the natural history data exist and are part of the general medical knowledge of the disease course, a baseline control study design can be used because the pathophysiology is well understood (e.g., tumors do not shrink in the absence of treatment; tumors are known to have a high probability of progression in a defined time period). In other cases, data and information from a natural history study may provide an untreated, external control group for use as the comparator to the treatment group(s) in an investigational drug trial.

The use of external controls requires careful planning and assessment, including the following considerations:

- The external control group needs to be very similar to the treated group in all respects, including disease severity, duration of illness, prior treatments, and any other aspects of the disease that could affect outcomes and the timing of outcomes. The availability of patient level data[12] can help provide support for comparison between the control group and the group receiving the investigational drug.

- Use of valid epidemiological approaches can reduce selection bias (e.g., inclusion/exclusion criteria, prespecified statistical analysis plan) (Ellenberg 1994).[13] Selection bias is a major concern when using external controls because there is no randomization and unrecognized baseline differences can affect outcomes. Points to consider include the following:

  - Critical patient disease characteristics may not have been assessed or may have been assessed differently based on historical approaches, resulting in a lack of comparability (e.g., disease definitions, diagnostic techniques, and approaches to safety monitoring may have evolved).

  - Aspects of standard of care may have changed.

  - Data collection intervals and quality may lack consistency and not be comparable.

[11] See 21 CFR 314.126(b)(2)(v).

[12] Real-world data (i.e., data relating to patient health status and /or the delivery of health care that is routinely collected from a variety of sources) may be useful to collecting data for natural history studies. See Framework for FDA's Real-World Evidence Program available at https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf.

[13] See the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018). When final, this guidance will represent the FDA's current thinking on this topic.

- Use of an external control group is especially challenging if the outcome assessments used in the external control group are not well defined and reliable and, therefore, not suitable for regulatory use.

There are two types of external controls that provide varying strengths of evidence.[14] Nonconcurrent external controls[15] consider the subject-level data from a different group (external) of subjects followed in the past for whom the individual subject-level data are available for the same outcomes and same covariates as in the current trial. For example, subject-level data may be obtained from the comparator group from a prior clinical trial (e.g., placebo group) or a natural history study. The stronger concurrent[16] external control design considers subject-level data collected at the same time as the group being treated in the clinical trial. However, in contrast with a completed natural history study, a concurrent control arm may not provide timely advice for planning the clinical trials.

Regardless of external control type, even for diseases with relatively predictable progression, an external control is most interpretable when a treatment effect: (1) is large in comparison to potential biases and the known variability in progression,[17] (2) is not affected by patient or investigator motivation or choice of subjects for treatment,[18] (3) can be objectively measured, (4) is measured in a manner that reasonably manages and minimizes bias, (5) has a strong temporal association with administration of the investigational drug, and (6) is consistent with expected pharmacological activity based on the target and perhaps shown in animal models. The pros and cons of various controls are discussed at length in the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (ICH E10). While not discussed in ICH E10, a hybrid approach of using external control data to add to a concurrent randomized control arm in a clinical trial may sometimes be useful.

B. Other Uses

The benefits of planning, organizing, and implementing a natural history study may go beyond drug development. A natural history study may benefit patients with rare diseases by establishing communication pathways, identifying disease-specific centers of excellence, facilitating the understanding and evaluation of the current standard of care practices, and

[14] See ICH E10.

[15] For examples of nonconcurrent external control studies, see the Kanuma (sebelipase alfa) label (available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125561s000lbl.pdf) and the Brineura (cerliponase alfa) label (available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761052lbl.pdf).

[16] A *concurrent control group* is defined in ICH E10 as "one chosen from the same population as the test group and treated in a defined way as part of the same trial that studies the test treatment, and over the same period of time." The test and control groups should be "similar with regard to all baseline and on-treatment variables that could influence outcome, except for the study treatment."

[17] See ICH E10.

[18] A classic comparison of the results of randomized and externally controlled trials of a variety of treatments showed that externally controlled trials almost always showed a better effect, probably because the new treatment tended to be given to patients with a better prognosis (Sacks et al. 1982).

identifying ways to improve patient care. A natural history study may provide demographic data and epidemiologic estimates of the prevalence of the disease and disease characteristics and aid disease tracking.

IV. TYPES OF NATURAL HISTORY STUDIES

Natural history studies can be designed to collect data from case histories or ongoing clinical visits in a cross-sectional or longitudinal manner depending on the desired purpose.

A. Retrospective and Prospective Natural History Studies

Retrospective and prospective natural history studies differ in the time at which patients are evaluated relative to when the study is planned and initiated. In retrospective studies, the patient evaluations have already occurred. In prospective studies, the evaluations occur in the future according to a prespecified data collection plan that may reflect current data standards.

Retrospective studies are often used as first steps in collecting natural history information. This information is reviewed from existing medical records, such as patient charts, which were compiled for patient care rather than for use in a natural history study. Retrospective study designs are informed by reviews of the following: published scientific literature; the opinions and experience of disease experts; and other sources of information, such as data collected directly from patients (whether published or not). These studies can collect and organize important information about a disease and identify information gaps that may be addressed by prospective data collection and analysis. Because the data are already available, retrospective natural history studies may be performed more quickly than prospective natural history studies.

Retrospective natural history studies may be limited by several factors that affect their utility, including the following:

- Data elements may not have been collected in existing records.
- Data elements may lack comparability to more recently treated patients because the data elements were collected at variable time points or were obtained inconsistently.
- Medical terminology may have changed over time or have been used inconsistently among health care providers and data collection sites.
- Specialty clinics providing historical data may result in patient selection or referral bias (e.g., including only the most severely affected patients in a natural history study).
- The patient's medical record or longitudinal profile may not be sufficient to identify the onset of the disease or symptom.
- If current patients from a database are used to select for study, those patients who have been in the database the longest may be overrepresented and the study may

disproportionately fail to capture patients who enter and rapidly leave the database. This is often called length-biased sampling (Delgado and Llorca 2004).

- Natural history studies published in the medical literature may be biased toward reporting on patients with increased severity of illness or on successful outcomes. Thus, literature reviews may not be adequate substitutes for natural history studies because literature reviews often do not characterize the full spectrum of the disease.

- Retrospective natural history studies can be biased through patient selection criteria and through selection of dates of inception and cutoff.

These factors can result in variable and incomplete information about the disease and may limit the interpretability and generalizability of the available information. Importantly, these factors can render retrospective natural history studies susceptible to bias.

Prospective studies can address many of the limitations encountered in the retrospective approach by, for example, doing the following:

- Implementing standard, consistent, and up-to-date definitions of medical conditions and treatments. These elements employ uniform medical language and are typically provided in advance in study protocols and procedure manuals.

- Providing a consistent schedule of medical visits for the patient.

- Providing standard operating procedures for investigators, which provides for greater consistency in the information collected (e.g., using the same clinical outcome assessments with comparable instructions for use).

- Collecting additional data that may elucidate the pathogenesis and manifestations of a disease and the patient's concomitant treatments.

However, prospective natural history studies will generally require more time, depending on needed duration of observation, than the collection of existing data, particularly for longitudinal studies (see section IV.B., Cross-Sectional Studies and Longitudinal Natural History Studies).

B. Cross-Sectional Studies and Longitudinal Natural History Studies

In cross-sectional studies, data are collected from across a cohort of patients during a specified, limited time period, but in longitudinal studies, data are collected from patients at several points over time. Either of these studies may be retrospective or prospective. In general, data collection and analysis in a cross-sectional study take less time than a longitudinal study. Although data from cross-sectional studies may not be well suited to be used as an external control group in a clinical trial, the data may provide information that could be used to plan a future study.

1. Cross-Sectional Studies

Cross-sectional studies collect and analyze data from a specified, limited time period (i.e., a specific date range or often a single point in time). Cross-sectional data can be of value in drug development for a rare disease for reasons that include the following:

- The general course of a particular disease may be inferred by sampling a cohort of patients at various stages of the disease
- Studies can provide a description of the range and severity of manifestations of the disease and methods used to evaluate these manifestations
- Studies can provide information for therapies intended to provide largely immediate benefits when given to patients with an acute episode or flare of the disease (e.g., sickle cell crises, rare venomous snake bites).

Although cross-sectional studies offer a quick and effective way to survey a current patient population, data collected from a specified, limited time period may not fully characterize the disease course and identify subtypes, including rapidly progressive subtypes that may be less well characterized because of length-biased sampling.

2. Longitudinal Studies

Unlike cross-sectional studies that collect data at a specific time period, longitudinal studies collect data from all patients in a cohort over several time points. Longitudinal natural history studies typically yield more comprehensive information about disease onset and progression over time than cross-sectional studies, and therefore longitudinal studies tend to be more useful as a source of natural history information. In addition, longitudinal natural history studies are usually a better method to distinguish the variety of phenotypes and subgroups of a disease, especially in diseases with intermittent, variable, or unpredictable courses. Longitudinal studies may also be useful to identify prognostic factors (e.g., to distinguish slow progressors from fast progressors) for the rare disease, particularly when the onset of the disease is difficult to identify. The chief limitation of prospective longitudinal studies is that they typically require more time to conduct than cross-sectional studies and, therefore, are more resource intensive.

V. STUDY PROTOCOL, DATA ELEMENTS, AND RESEARCH PLANS

A. Study Protocol

Natural history studies should have well-defined, carefully documented protocols, completed before initiation of the study. These study protocols delineate who should be included in the study (inclusion and exclusion criteria), the information to be collected, how it is to be collected, the schedule for the data collections (if prospective), and the plan for analysis.

B. Data Elements

When collecting natural history information, all of the potential uses of the information should be considered, including those uses pertinent to drug development. FDA has specific data standards and terminology recommendations for marketing applications.[19] Therefore, natural history data that will be used to support a marketing application should be collected according to these data standards. Because rare disease drug development may take place in multiple countries, international data standards should also be considered.

C. Protocol Elements

A prespecified natural history study protocol should include the following:

- A description of methods for data collection.
- Disease definition and diagnostic criteria for entry into the study and rationale.
- List of demographic information to be collected.
- A list of disease related information to collect including:
  - Signs and symptoms.
  - Age at onset of symptoms, age at diagnosis, and age at development of important morbidities and mortality.
  - Measures that can assess the severity and nature of involvement of the disease for potentially affected body systems. The natural history study data should not be limited to the most severely affected body systems because treatment responses might be more reliably detected by evaluation of a less affected body system.
  - Documented genotypes and phenotypic features, which may be important in identifying disease subpopulations.
  - Clinically meaningful disease effects and outcomes including a focus on those important to patients and their families.
- A description of any regional treatment guidelines or algorithms, including any changes in standard of care over time, if applicable.
- Analytical plan.

[19] See the FDA's Study Data Standards Resources web page at https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm.

- A provision to record when protocol revisions are made and if that would alter the analysis.

- Study duration.

- Date of inception.

- Date of cutoff.

Prospective protocols may also include the following:

- Description of the data element to be collected, methods and procedures of measurement, and schedule of collection

- Standardized procedures for evaluating patients including procedures for those that leave prematurely

- Methods used for standardizing inter- and intra-rater reliability for clinical outcome assessments and performance requirements for biomarker measurement tests including reproducibility when multiple labs or testing sites are involved

- An analytical plan including a plan for how protocol deviations and drop-outs will be considered in the analysis

D. Statistical Analysis Plan

For natural history studies to be most informative, the Agency recommends that natural history studies have a prospectively defined statistical analysis plan (SAP).[20] The ICH guidance for industry *E9 Statistical Principles for Clinical Trials* (September 1998) was written for interventional trials, but many of the elements described are of use when considering the development and use of natural history studies. The Agency recommends the involvement of a statistician as part of the natural history study planning committee. The SAP elements should delineate the analysis population, definition of endpoints, descriptive objectives, testable hypotheses and statistical methods to be employed in analysis of the data including the timing of the data analyses conducted in the study. The SAP should include enough detail so that the analysis results can be replicated. The SAP can also increase the study's efficiency by focusing on the most relevant data to be collected without imposing excessive rigidity (Thomas and Peterson 2012). Preplanned interim analyses at certain intervals or milestones may suggest design changes to the protocol. Protocol elements may be modified or dropped for reasons of relevancy, feasibility, and reliability based on interim analyses, but any such changes should be

[20] In the ICH guidance for industry *E9 Statistical Principles for Clinical Trials* (September 1998), a *SAP* is defined as "a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data." See also ICH E10.

well documented as an amendment to the protocol, including the timing and rationale for the changes.

In any natural history study, consistency of procedures and data collection across data collection sites and across time is critical. The analysis model may also need to make adjustments for the effects of sites within the country or region. A natural history study that collects data in widely dispersed site locations needs to consider potential language and cultural differences in the patient perceptions, manifestations, and effects of a disease.[21] Evaluation of intra- and inter-rater reliability of clinical outcome assessments and performance requirements of the biomarker measurement assays/tests should be considered.

E. Practical Considerations for Study Design

1. Early Planning and Implementation

The starting point of a natural history study is the collection, organization, and analysis of all currently available data. These data may come from and be reviewed by a planning committee comprised of diverse stakeholder representatives such as patients and advocates, treating physicians, other health care providers, researchers, investigators, and drug developers. The planning committee can consider the data to be collected, the need for potential adjustments to the natural history study, and the potential uses of the information obtained from the natural history study. Natural history studies should include plans to formally monitor study conduct and approaches to make protocol adjustments when warranted.

2. When to Start a Natural History Study

For many rare diseases, early initiation of a natural history study (even before an investigational therapeutic drug has been identified) can provide benefit by allowing time to collect data including a longer duration and larger patient population. However, natural history studies need not delay drug development or delay approval of a needed treatment if drug development is already under way. For some diseases, there might be adequate information available for planning and initiation of a drug development program; however, data obtained from a natural history study may contribute additional information.

Because natural history studies often face an array of unknowns, a small pilot study may be valuable at any stage of the natural history study process. Pilot studies help clarify what data elements to collect, how to code the data, and how to standardize the information collection in a way to facilitate analysis (see section V.B., Data Elements). For prospective studies, a pilot study can refine study procedures, logistics, and data collection.

3. Finding Patients and Maintaining Their Involvement

For rare diseases, finding patients for inclusion in a natural history study can be a challenge and frequently requires participation of many sites across the United States or sites from multiple

[21] See the ICH guidances for industry *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data* (June 1998) and *E17 General Principles for Planning and Design of Multi-Regional Clinical Trials* (July 2018) (ICH E17).

countries. A retrospective literature review might identify referral centers or individual specialists that can help identify patients. Consideration should be given to enlisting the help of disease-specific support groups or patient advocacy groups because they are invaluable resources for identifying and helping to recruit patients. They also can contribute to study design and execution because of their unique perspectives. Natural history studies can be registered in https://wwww.ClinicalTrials.gov to also increase participation and recruitment.

Patients' continuing study participation ensures the robustness of follow-up data. Patient advocacy or support groups can make an important contribution in keeping the patient community interested and engaged and in providing valuable perspectives both on minimizing burdens to patients and families and on the acceptability of proposed investigations. Importantly, to minimize missing data and to enhance study quality and interpretability, the reasons participants drop out of the study or choose not to participate at all should be investigated and addressed. Approaches to increase patient participation may include providing support for travel and lodging expenses, issuing a study newsletter, and sharing the interim results of the study with the participants/community.

4. Study Site and Local Data Collection

Natural history study data may be collected by various means and in a variety of locations. Specialty medical centers may have expertise and testing equipment for making medical diagnoses and performing clinical and laboratory measurements. Data may be collected from patients or observers in the patients' homes or by the local health care provider in person or remotely. Remote data collection may be of special value for geographically dispersed patients with rare diseases. Local observations (e.g., lab test results) may be sent to a centralized study center. When multiple laboratories are used, each should be qualified for the study testing analysis and reporting; this is of particular importance for laboratory tests that are key to disease diagnosis or monitoring of disease manifestations. Alternatively, to decrease variability, a single central laboratory can analyze samples. Increased patient convenience leads to larger numbers of patients being able to participate in the study. In international studies, some countries may restrict sending samples outside their borders, so a determination should be made if this is an issue and, if so, plans to address this issue should be made.

The tradeoffs between (1) the less convenient location for patients (at centralized facilities) potentially offering better standardization of data collection and (2) the more convenient location for patients (e.g., local doctor's office, patient's homes) potentially offering less standardized data collection should be carefully explored. The particular approach used may need to be adjusted to collect data as understanding of the disease's natural history increases.

VI. DATA COLLECTION, STORAGE, AND DISSEMINATION

If the natural history study data are intended to provide essential support for a drug application (e.g., as a potential external control for comparison to patients treated with an investigational drug), FDA will likely find it necessary to have access to patient-level data and to evaluate the

natural history data in detail.[22] When the natural history data and information are used as an external control in a clinical trial, FDA's regulations covering investigational new drug applications under 21 CFR 312 may apply.[23] The ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018) may provide additional information about data collection standards.

Even if the data from a natural history study are not to be used as essential support for a marketing application, the quality and integrity of the data obtained in these studies will be important for effective use of the study results.

A. Data Collection[24]

Particularly for international studies, natural history studies should code data from patient experiences using a vocabulary that is internationally interpretable, is standardized for all participating health care providers, and is easily translatable to a database for analytical purposes. FDA encourages the use of available standardized data dictionaries, terminology, and common data elements (e.g., Medical Dictionary for Regulatory Activities (MedDRA)).[25] FDA encourages natural history study data to be coded using the same data standards they plan to use for the clinical trial data.

With the increasing use of electronic health records, standards development is evolving rapidly, and FDA encourages the use of data standards that are either government supported or produced by a standards developing organization (e.g., Systematized Nomenclature of Medicine — Clinical Terms (SNOMED CT),[26] Logical Observation Identifiers Names and Codes (LOINC),[27] Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC STDM)[28]).

[22] See 21 CFR 314.50(f).

[23] Researchers may discuss the applicability of these regulations to a specific natural history study with the appropriate review division.

[24] See the FDA Resources for Data Standards web page at https://www.fda.gov/forindustry/datastandards/default.htm.

[25] See also the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (April 2018).

[26] SNOMED CT is one of a suite of designated standards for use in U.S. federal government systems for the electronic exchange of clinical health information and is a required standard interoperability specification of the Healthcare Information Technology Standards Panel.

[27] LOINC is one of a suite of designated standards for use in U.S. federal government systems for the electronic exchange of clinical health information and has been identified by the Health Level Seven International standards development organization as a preferred code set for laboratory test names in health information transactions.

[28] CDISC defines STDM as a standard structure for human clinical trial study data tabulations.

B. Data Storage

For maximal usefulness of the data, it is important to ensure from the outset of the natural history study that the data are maintained securely and will be accessible and stable for the duration of the study and its analyses. A robust documentation and systematic auditing system to allow for traceability may be valuable for later regulatory purposes. FDA encourages adherence to current recommendations for data security and engagement of technical experts in the use and availability of hardware and software programs for storing and accessing natural history study data.[29]

C. Data Dissemination

Because of the general lack of clinical data available in rare diseases, FDA encourages dissemination of information as widely as possible (e.g., through peer-reviewed publications) on the methods used to conduct the natural history study, the practical aspects of conducting the study (including the study's limitations), and the results of the study in full consideration of any patient confidentiality and intellectual property rights issues. A dissemination plan should be considered at the beginning of the study and, as feasible, with the participation of all of the interest groups.

VII. HUMAN SUBJECT PROTECTION

For all research studies, adequate provisions should be in place to ensure the privacy of patients and to maintain the confidentiality of data. Those planning natural history studies should make detailed assessments of all regulatory requirements that may be applicable.

Natural history studies may be subject to several federal regulations designed to protect the rights, safety, and welfare of human subjects. The core of FDA's human subject protection regulations is found at 21 CFR part 50 (Protection of Human Subjects) and 21 CFR part 56 (Institutional Review Boards). The FDA regulations at 21 CFR part 50 outline the requirements related to informed consent, and the FDA regulations at 21 CFR part 56 outline the requirements related to institutional review board (IRB) operations.

Natural history studies may be subject to FDA regulations at 21 CFR parts 50 and 56 if they meet the definitions of *clinical investigation* and other applicable definitions under those parts.[30] Other regulations may also apply, particularly the regulations of the U.S. Department of Health and Human Services (HHS) governing the protection of human subjects found at 45 CFR part 46 (often referred to as the *Common Rule*). These regulations apply to all nonexempt research involving human subjects that is conducted, supported, or otherwise subject to regulation by

[29] Some current recommendations for data security are in the Health Insurance Portability and Accountability Act privacy and security rules (45 CFR part 160, subpart A and part 164, subpart C).

[30] See 21 CFR 50.3 and 21 CFR 56.102. Researchers may discuss the relevant regulatory requirements for a specific natural history study with the appropriate review division.

HHS.[31] The Common Rule is administered by the HHS Office for Human Research Protections (OHRP).

As with all research studies, natural history studies conducted in multiple regions may also be subject to different regulatory requirements.[32]

A. Confidentiality of Subjects and Data Protection

Protecting confidentiality is a critical human subject protection responsibility. Study planning should include addressing the applicable requirements of the HIPAA (Health Insurance Portability and Accountability Act)[33] Privacy, Security, and Breach Notification rules, which may include requirements to obtain authorization from study subjects for the use and disclosure of their health information or a waiver of authorization from an IRB or privacy board, as well as requirements to implement safeguards to protect that information.

Data protection and security are an important human subject right. The study organizers should consider all applicable local, state, national, and international privacy or security laws (to include tribal law passed by an official governing body of a Native American or Alaskan Native tribe) when planning the management of requests for access to the individual or aggregate data or data analyses by other researchers.

B. IRB Review[34]

IRB review is generally required for a natural history study that is subject to the Common Rule and may be subject to FDA regulations at 21 CFR part 56 as described above.[35] When multiple study sites participate in a natural history study, researchers should consider using a single IRB

[31] 45 CFR 46.101(a). Note that the Common Rule may also apply if the natural history study is conducted, supported, or otherwise subject to regulation by another federal department or agency that has adopted the Common Rule (45 CFR 46.103). Researchers should discuss the relevant regulatory requirements with the appropriate federal agency or department supporting the research.

[32] See ICH E17.

[33] Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191.

[34] The term *IRB* used here refers to organizations constituted to oversee human subject protections, such as IRBs in the United States or independent ethics committees (IECs) in the European Union.

[35] 45 CFR part 46; 21 CFR 56.102.

for most or all the study sites for the initial and any periodic continuing review.[36, 37] In many cases, natural history studies may be suitable for an IRB expedited review procedure.[38]

C. Informed Consent

Determining what information needs to be disclosed in an informed consent form will likely depend on the applicable law and regulations. FDA regulations at 21 CFR part 50 outline the informed consent process for applicable clinical investigations. If HHS supports or conducts the natural history study (to include studies funded by the FDA), then the requirements of the Common Rule must be met.[39] OHRP has published guidance addressing informed consent requirements under 45 CFR part 46.[40]

In designing a natural history study, the study organizer should consider the possibility that the data and biospecimens collected may be useful in addressing a research question not considered during the development of the original natural history study. In particular, biological samples and genetic testing results obtained during a natural history study might be of value in the future as biomedical knowledge about the disease increases (even though the specific future use of the data may not have been known). When planning a natural history study the study organizer may want to work with an IRB to determine the best approach to obtain consent, when appropriate, for the study as well as for any possible future secondary research use of the data and biospecimens collected.

VIII. INTERACTING WITH FDA

Because natural history studies can have broad applicability to different modes of treatment, discussions with FDA do not need to be related to a specific drug or conducted in the context of a regulatory submission or application. Discussions such as in a Critical Path Innovation Meeting with the Center for Drug Evaluation and Research or in presubmission discussions with the Center for Biologics Evaluation and Research may provide nonbinding, scientific, and medical advice on drug development issues.[41] For a sponsor with an investigational drug for a

[36] See the guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials* (March 2006).

[37] The Federal Policy for the Protection of Human Subjects (known as the Common Rule, 45 CFR part 46) requires cooperative research to rely on approval by a single IRB in certain circumstances (45 CFR 46.114(b)). This provision of the Common Rule is effective January 20, 2020 (see the revised final rule published June 19, 2018 (83 FR 28497 for details).

[38] 45 CFR 46.110.

[39] 45 CFR 46.

[40] See the OHRP Informed Consent web page at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/informed-consent/index.html.

[41] See the guidance for industry *Critical Path Innovation Meetings* (April 2015).

rare disease, FDA encourages the sponsor to meet with the relevant drug review division or office[42] about the use of natural history data to support development of a particular drug.

For those who plan to conduct natural history studies through the Office of Orphan Products Development (OOPD) Orphan Products Natural History Grants Program, the FDA encourages discussion with the OOPD program officers about proposals that support targeted studies that advance rare disease drug development through characterization of the natural history of rare diseases and conditions, identification of genotypic and phenotypic subpopulations, and development and/or validation of clinical outcome measures, biomarkers, and/or companion diagnostics.[43]

[42] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[43] For more information, see the Orphan Products Natural History Grants Program web page at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/OrphanProductsNaturalHistoryGrantsProgram/default.htm.

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