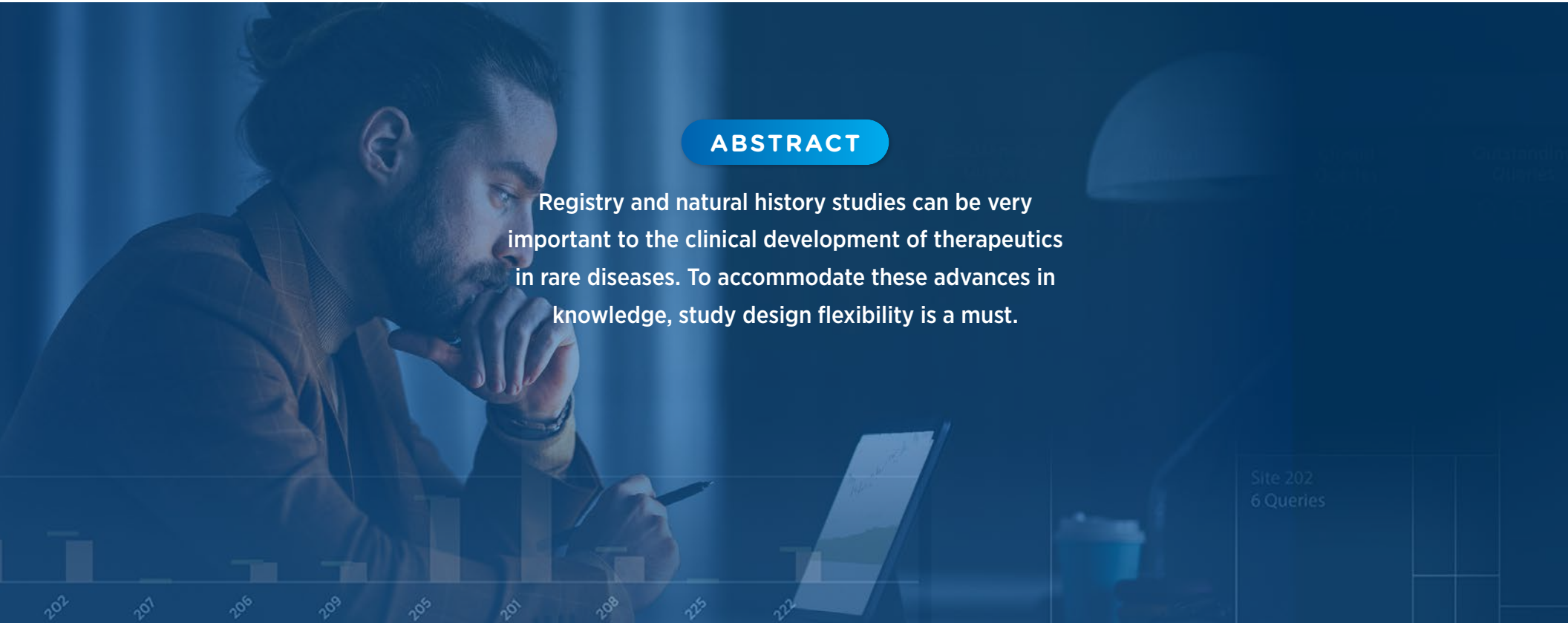
WHITE PAPER

premier research
Built for Biotech℠

RARE DISEASE

Natural History Studies: Understanding and Enhancing Their Value in Rare Diseases



ABSTRACT

Registry and natural history studies can be very important to the clinical development of therapeutics in rare diseases. To accommodate these advances in knowledge, study design flexibility is a must.

Observational studies, encompassing both registry and natural history studies, play important roles in rare disease research.

Introduction

Successful drug development requires a comprehensive understanding of the underlying disease. To design reliable clinical trials with meaningful, measurable outcome measures, sponsors must apply thorough knowledge of disease presentation, manifestations, and progression, which may be challenging in rare diseases where this information is minimal. Thus, observational studies, encompassing both registry and natural history studies, play important roles in rare disease research. In fact, the value of prospectively designed, protocol-driven natural history studies initiated in the earliest stages of drug development planning cannot be overemphasized.

In this white paper, we discuss the challenges of rare disease development and explore the role of observational studies in informing clinical development, with an emphasis on natural history studies.

Rare disease development

Sponsors who are developing in rare diseases face several hurdles, including:

- **Scarce and incomplete data.** Data collection is not harmonized, especially when the disease is not widely known or has not yet been identified as a specific condition. It may take time for physicians to identify what is going on as delays in diagnosis are common.
- **Small populations.** By definition, rare and ultra-rare diseases have low incidence and prevalence. When recruiting for clinical trials, sponsors need to actively find eligible patients through engagement with advocacy groups and other outreach strategies.

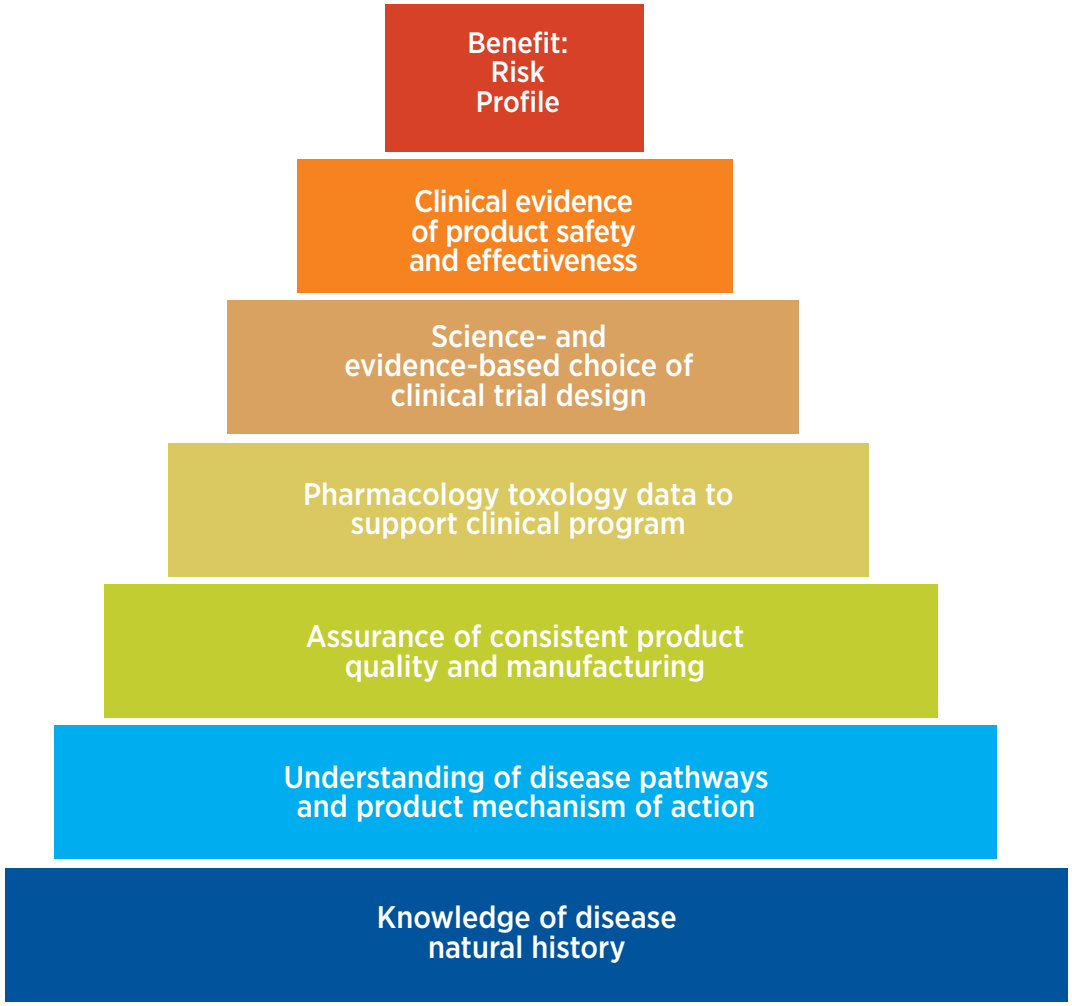


Figure 1. Building blocks of a product development program[1]

- **Disease heterogeneity.** Rare and ultra-rare diseases are unlikely to have a single presentation. Instead, they typically comprise a highly heterogeneous group of disorders, with a series of complex and overlapping individual diseases or phenotypes, each of which is defined by unique interactions among genetic and environmental factors. This heterogeneity – and the diverse presentations that accompany it – further complicates diagnosis, categorization, and consistent data collection.
- **Lack of precedents.** Given the lack of precedents for drug development, there is no consistent way of gathering or generating information that can be used to support regulatory submissions. As small patient populations preclude the possibility of running large Phase 3 trials, sponsors need to think outside the box to design trials that still yield meaningful data for demonstrating clinical endpoints or other outcomes.

Taken together, these hurdles mean that development in rare diseases may require more careful planning. Sponsors need to cast a wide net when thinking about the "what ifs" and anticipate questions that might arise over the course of development to ensure that they collect the data necessary to answer those questions.

In a 2018 article in Translational Science of Rare Diseases, Larissa Lapteva, M.D., MHS, and colleagues outlined the building blocks of every product development program, with an emphasis on their applicability in rare diseases (see Figure 1).[1] The foundation of this pyramid is knowledge of the disease and its natural history, and its apex is a Benefit:Risk profile, derived from the clinical study of a product's safety and efficacy.

Role of registries and natural history studies in rare disease research

Clinical research can be categorized into two broad categories: clinical trials and observational studies. Clinical trials are studies where participants receive specific interventions according to a research plan or protocol, usually in a randomized fashion with a required schedule of assessments, with the goal of assessing certain objectives. Observational studies, on the other hand, are those where participants may receive diagnostic, therapeutic, or other types of interventions but the protocol does not assign them to specific interventions. Of note, in the EU, Directive 2001/20/EC dictates that no additional diagnostic or monitoring procedures shall be applied patients in observational studies. However, EudraLex Volume 9A clarifies that interviews, questionnaires, and blood sampling may be considered as normal clinical practice in such studies.

Observational studies may be either retrospective or prospective and may be either registry or natural history studies. Most prospective observational studies with human participants will require informed consent, and sponsors should seek formal Institutional Review Board (IRB) exemptions before proceeding with any observational study that does not require consent. For registry studies, drug products must be approved, commercially available, and used in accordance with product approval. For natural history studies, no drug is required as the focus is on gaining insight into the disease and its progression in a real-world setting.

Purpose of registry studies

Importantly, registry studies are not the same as natural history studies, and both differ from randomized clinical trials. In rare diseases, natural history studies typically come first and their objective is to collect information about the natural history of a disease in the absence of intervention, from the time of onset until either resolution or death. Registry studies generally follow randomized clinical trials and can be quite large. Patient registries are organized systems that use observational study methods to collect, store, retrieve, analyze, and disseminate information on individuals who have either a particular disease, a condition, or risk factor that predisposes them to the occurrence of a health-related event, or prior exposure to substances known or suspected to cause adverse health effects. As such, registries can be used to:

- Advance research hypotheses
- Observe population behavior patterns
- Recruit participants for future clinical trials, not just for the indication that enrolled them in the registry but also for secondary health conditions

Registries can also be used to monitor healthcare and outcomes, allowing researchers to study or identify best practices in care or treatment. For example, one registry study involving approximately 6,000 individuals enabled the identification of optimal treatment regimens for patients with HIV based on their CD4 count and viral load.[2]

Observational studies may be either retrospective or prospective and may be either registry or natural history studies.

Purpose of natural history studies

Natural history studies play an essential role in enhancing research and moving forward the development of drugs for rare diseases. These studies are extremely useful for identifying and differentiating among disease subtypes, as variances among these subtypes may be key to understanding the most effective approaches to treatment. Moreover, natural history studies can help shape the design of clinical trials by providing insight into:

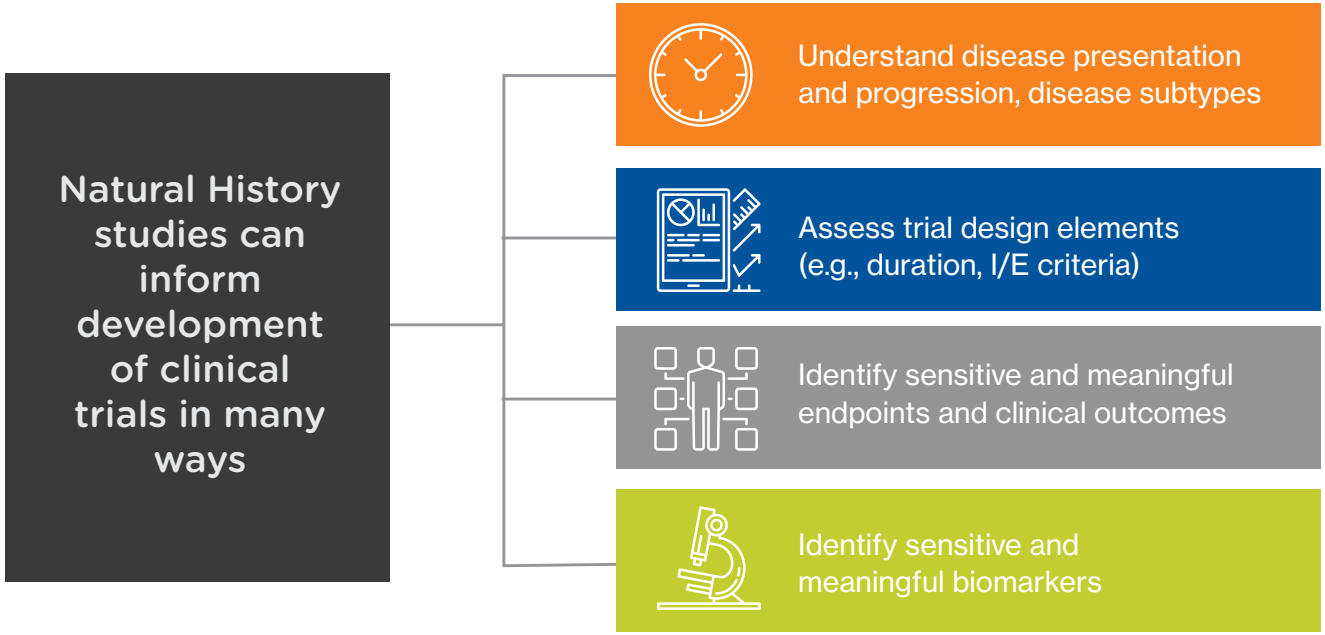
- Study duration
- Inclusion and exclusion criteria
- Meaningful endpoints and clinical outcomes
- Appropriate biomarkers

Designing and operationalizing natural history studies

Executing a meaningful natural history study that provides data which can be used to design a clinical trial requires careful consideration and planning. Types of natural history study designs include:

- **Medical literature reviews**, which are collections of data limited to information reported in published literature. Oftentimes, this data is presented with limited information from the author's viewpoint. There is no opportunity to address any mission information related to the patient's medical records or to know if it was even available at the time of the writing of the article. While this approach to natural history studies is the least expensive and least resource-intensive, it is also difficult to standardize data collected from a variety of articles as each author has a different objective and viewpoint. Moreover, these studies may not meet natural history study objectives.
- **Retrospective chart reviews,** which involve review of existing medical records of patients with the condition of interest. These studies are relatively inexpensive and require limited resources but may be hampered by missing data or lack of data standardization.
- **Cross-sectional studies,** which involve collection of predefined data elements from a variety of patients at a single point in time. While these studies may provide insight into the generalities of a disease, they do not provide information on patient experience or disease progression.
- **Prospective longitudinal studies,** which involve collection of predefined data elements from a variety of patients over a prospectively defined time period. These studies can be lengthy, and therefore costly, but can enable researchers to assess progression of a disease over time. Given the potential duration of the study, sponsors need to plan for possible changes in measurement and standard of care (SOC), which may vary among countries and even sites.

Figure 2. Value of natural history studies



	Retrospective Chart Review	Cross-Sectional Studies	Prospective Longitudinal
Description	Review of existing medical charts of patients with the condition	Collection of data from a variety of patients at one point in time	Collection of data from a variety of patients over a prospectively defined period of time
Pros	▪ May be more timely to complete ▪ Relatively inexpensive ▪ Limited resources required	▪ Limited duration of study ▪ Predefined data elements ▪ May provide insight into generalities about disease	▪ Predefined data elements ▪ Able to assess disease progression over time
Cons	▪ Limited to available data: likely missing data; no way to correct or question data ▪ Lack of standardization: data elements can vary from site to site and can vary over time ▪ Requires prospective rules about how to address missing data ▪ May require consent to perform chart review	▪ Doesn't collect patient experience in time; data is a 'snapshot' ▪ Doesn't provide robust data on the pace of progression of a disease state ▪ Difficult to extrapolate from 'snapshot' to make assumptions about disease progression on a per-patient basis	▪ Can be quite lengthy to complete, especially in diseases that progress slowly ▪ Can be expensive ▪ Need to plan for changes in measurements and SOC over time ▪ May require amendments to adjust for additional assessments or biomarkers over time

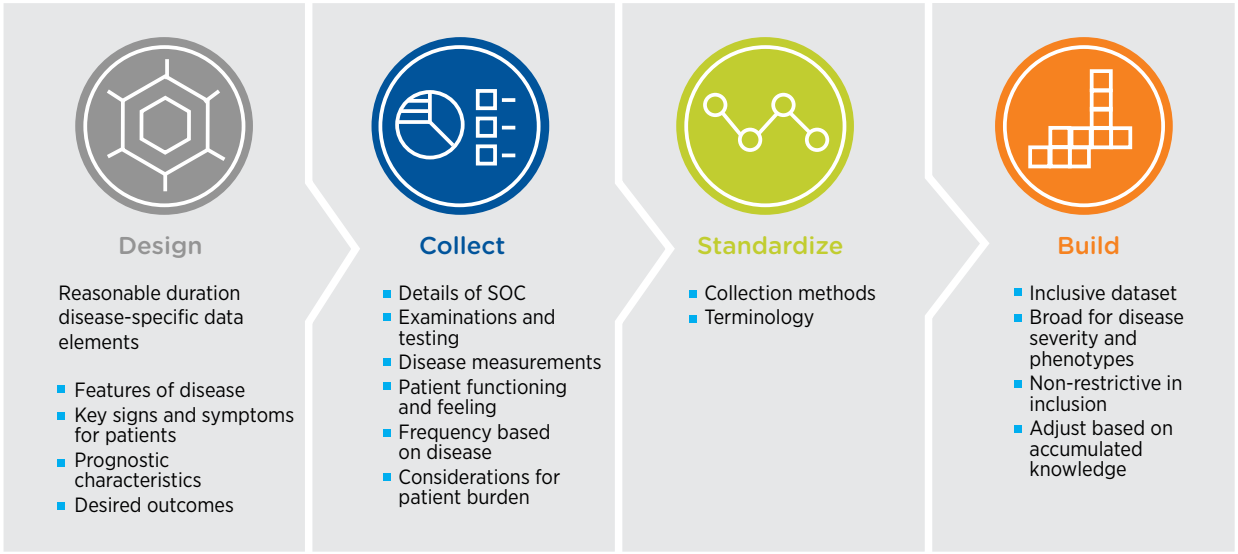
Figure 3. Comparison of natural history study designs

Key design considerations

Natural history studies focus on the disease, not the treatment. Thus, though these studies collect information on therapeutic interventions, it is important to ensure that data collection parameters include measures that assess all aspects of the underlying disease. Ideally, the data collected from a natural history study should be robust enough to support the development of multiple therapeutic options.

Though natural history studies are likely to be most useful if they are completed prior to the start of clinical development, these studies are sometimes performed in concert with clinical trials. Natural history studies contribute to the design of clinical trials through validation of outcome measures and biomarkers. Another key consideration is data quality and monitoring. Even if these studies will not be included in regulatory submissions, it is critical to ensure high-quality data, as this data may be required to support questions asked by regulatory authorities throughout the development process.

Figure 4. Enhancing the usefulness of natural history studies



To enhance the usefulness of a natural history study, sponsors should consider the following four elements (see Figure 4):

- **Design.** Select a reasonable study duration, identify disease-specific data elements to be collected, and determine the desired outcomes. Developing a deep understanding of disease presentation, manifestations, morbidity, and progression can help sponsors determine the size and duration of the study. It also informs both endpoint selection and statistical considerations such as effect size.
- **Collect.** Ensure that data collection requirements, assessment type, and assessment frequency encompass and align with differences in standard of care, and how standard of care may change over time. It is important to clarify the effect of standard of care on site feasibility, patient selection, study endpoints, study duration, and inclusion or exclusion criteria. It is also essential to identify sensitive and meaningful endpoints that can be measured. Determining which assessments most accurately reflect progression of the disease informs selection of the most appropriate clinical efficacy endpoints for future studies and provides the opportunity to validate potential measurement tools and biomarkers prior to inclusion in a clinical trial.
- **Standardize.** Standardization of collection methods and terminology ensures universal usage, especially in global settings. If the study includes questionnaire elements, sponsors should also think about how to ensure consistency and continuity in administration of those questionnaires as variances can impact outcomes data.
- **Build.** Ensure the study database is inclusive of a broad range of data points that encompass disease severity, nuances, and phenotype variances. It is also important to build a database that can be adjusted on an ongoing basis as new knowledge emerges.

Key operational considerations

As with interventional studies, sponsors of natural history studies will need to determine whether to use local sites, central sites, or a combination thereof. With local sites, data is collected by each patient's existing healthcare provider and then submitted to central data collection. This approach limits patient burden but may introduce variability and data inconsistency. With central sites, all assessments are performed at a limited number of highly experienced sites. Though this increases consistency and reduces the potential for missing data or protocol violations, it may increase patient burden and dropout rate. In a combination model, which is most common, certain assessments are performed at local sites, while complex assessments are reserved for central sites.

Quality is also key for operationalizing natural history studies. While 100 percent source data verification is not required, some level of monitoring is recommended for ensuring quality and avoiding violations. If the study is collecting prospective data, it is important to define critical data elements, reporting standards, and methods for handling missing data or data variations.

Other operational considerations include:

- **Project design.** Identifying the specific data points needed and reviewing sample patient charts prior to study start helps ensure that sites have the data, capabilities, and training necessary to support study success.
- **Site selection and management**. Conducting site-level feasibility and developing site-specific plans helps ensure that study operations run smoothly.
- **Informed consent.** Requirements for informed consent may vary or even conflict across sites and regions. Understanding local regulations and site-specific requirements will facilitate compliance.
- **Data management.** As natural history studies may need to capture historical data and the data strategy is subject to change as more data becomes available, it is crucial to design a flexible database with options for unknown data. It is also important to distinguish among required and optional data and to define the scope of data cleaning.
- **Biostatistics.** Given the potential for collection of unexpected – and possibly meaningful – data, the statistical analysis plan should allow for flexibility and amendments.

Regulatory considerations

From a regulatory perspective, when the criteria for observational studies are clearly met, such studies only require IRB and ethics committee review at the site level. Regulatory agency and competent authority review are not necessary. There are, however, grey areas regarding the inclusion of additional diagnostic interventions.

The FDA has not implemented any strict rules regarding natural history studies. The agency did, however, publish draft guidance in March 2019 noting, "This draft guidance, when finalized, will represent 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." This guidance document is intended to help inform the design and implementation of natural history studies and support the development of rare diseases from study planning through execution. In the conclusion of the guidance document, the FDA encourages sponsors to meet with appropriate divisions at the agency regarding the use of natural history studies in the development of targeted studies that advance rare disease drug development.[3]

In Europe, EU member states may differ in their interpretations of the distinction between interventional and non-interventional assessments, though diagnostic interventions are generally allowed provided they meet the criteria for minimal risk. Minimal risk indicates that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Broadly, the standard is that data from natural history studies are intended to inform interventional studies. Treatment approval is not dependent on natural history data. While full good clinical practice documentation is generally not required, quality is essential and some level of data and conduct quality assurance should be incorporated into study design.

Key Takeaways

Both registry and natural history studies can be very important to the clinical development of therapeutics in rare diseases. These studies require careful planning that incorporates key objectives, as well as design and operational considerations. The timing of these studies may vary depending on purpose, though the optimal time for natural history studies is prior to undertaking clinical development. While natural history data may not be incorporated into regulatory submissions, they are nevertheless important to regulators. To that end, sponsors must design studies that are both well-defined and flexible enough to accommodate ongoing advances in disease knowledge and treatment.

Both registry and natural history studies can be very important to the clinical development of therapeutics in rare diseases. These studies require careful planning that incorporates key objectives, as well as design and operational considerations.

References

1. Lapteva L, Vatsan R, Purohit-Sheth t. Regenerative medicine therapies for rare diseases. Trans Sci Rare Dis. 2018;3(3-4):121-132.
2. Becker S. The CHORUS database on patient clinical care--and interview with Stephen Becker, M.D. Interview by John S. James. AIDS Treat News. 1998;301:1-5.
3. U.S. Food and Drug Administration. Rare Diseases: Natural History Studies for Drug Development – Guidance for Industry, March 2019. Available at https://www.fda.gov/media/122425/download.

Kris O'Brien | Executive Director, Program Strategy, Rare Disease and Pediatrics

Kris O'Brien has been in the clinical research industry for over 35 years and has functioned in a variety of roles during that time. Her expertise in operations positions her well to provide well rounded expertise in all areas of study execution which is supported by her knowledge in a multitude of therapeutic areas with a depth of knowledge in rare diseases. With past roles that range from Study Coordinator at the site level to roles at CROS, academia, and pharmaceuticals such as: Data Editor, CRA, Project Manager, Director of Training, Client Manager, Head of Project Management, Project Director, VP of Operations, and VP of Client Strategy and Development, she has gained real-world experiences that allow her to understand practical application of strategy and what is likely to be successful when applied. This type of knowledge adds real value to our customers when executing study designs from phase natural history studies to phase 1-3 to post-marketing studies.

Kris currently supports the business development and operations departments at Premier Research with strategic planning, coordination, and subject matter expertise for new and existing client projects and consultant services. She holds an executive sponsor role for current projects and also advises, directs, and provides input on strategy for project execution including regulatory, medical/scientific, and operational knowledge. For proposal documents, she ensures that timelines and costing for each project are in alignment with the project goals, the customer's considerations and expectations, as well as the industry feedback to ensure optimal execution for all RFPs.

premier research

Built for Biotech℠

About Premier Research

Premier Research, a clinical research company, is dedicated to helping biotech, specialty pharma, and device innovators transform life-changing ideas and breakthrough science into new medical treatments. As a global company, Premier specializes in the use of innovative technologies for smart study design and trial management to deliver clean, conclusive data to sponsors. Whether it's developing product lifecycle strategies, reducing clinical development cycle times, securing access to patients, navigating global regulations, maximizing the impact of limited rare disease data, or providing expertise in specific therapeutic areas, Premier is committed to helping its customers answer the unmet needs of patients across a broad range of medical conditions.

Visit premier-research.com

North America: +1 919 627 9100 | Europe: +44 118 936 4000 | info@premier-research.com | premier-research.com