Considerations for Natural History Studies

One of the cornerstones of developing therapies for rare diseases is the use of natural history (or non-interventional) data to help inform the clinical development process. Though you may think natural history studies aren't relevant or valuable to your clinical program, they may be worth keeping under consideration. Natural history data can play a surprisingly helpful role in the clinical development process, with many potential uses and benefits for drug developers.

WHAT ARE NATURAL HISTORY STUDIES?

Defining statements excerpted from the FDA Draft Guidance, *Rare Diseases: Natural History Studies for Drug Development,* March 2019:

- *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.*
- *A natural history study is a preplanned observational study intended to track the course of the disease. Its purpose is to identify demographic, genetic, environmental, and other variables 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.*

Types of natural history studies, with their benefits and drawbacks

	PROS	CONS
Retrospective Studies In retrospective studies, the patient evaluations have already occurred, and data is drawn from existing medical records compiled for patient care.	May be performed more quickly than prospective studies, since the data are already available. Can collect and organize important information about a disease and identify gaps to be addressed in prospective data collection and analysis. Adjudication committees are key to reducing bias.	May be limited by such factors as incomplete data, variability and inconsistency in collection, length-biased sampling, and other potential selection bias.
Prospective Studies In prospective studies, new evaluations are conducted according to a prespecified data collection plan that may reflect current data standards.	Can address many of the limitations encountered in the retrospective approach (e.g. by following standard operating procedures and a consistent patient examination schedule).	Generally require more time than retrospective studies, depending on needed duration of observation – particularly for longitudinal studies.
Cross-Sectional Studies In cross-sectional studies, data are collected from across a cohort of patients during a specified, limited time period. May be either retrospective or prospective.	Can be of value in drug development for a rare disease because they can indicate the general course of the disease through various stages.	The data may not fully characterize the disease course and identify subtypes that may be less well characterized because of length-biased sampling.
Longitudinal Studies In longitudinal studies, data are collected from patients at several points over time. May be either retrospective or prospective.	Typically yield more comprehensive information about disease onset and progression over time than cross-sectional studies, so they tend to be more useful as a source of natural history information.	Generally require more time to conduct than cross-sectional studies and are more resource intensive.

WHEN ARE NATURAL HISTORY STUDIES MOST USEFUL?

To identify the patient population

- May uncover important predictors of disease progression.
- May provide evidence for which patient subgroup(s) may benefit from a particular drug trial.

To identify or develop clinical outcome assessments

- 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.
- Can be used to evaluate the performance and reproducibility of a clinical outcome assessment for use in a clinical investigation.

To identify or develop biomarkers

- Can help identify or develop biomarkers that can be diagnostic, prognostic, predictive of treatment response, or useful in guiding patient selection and dose selection in drug development.
- Can provide an opportunity to collect specimens and images for use in an analytical validation program.

To serve as a comparator in designing externally controlled studies

- Data and information from a natural history study can provide an untreated, external control group for use as the comparator to the treatment group(s) in an investigational drug trial.
- Natural history studies can act as a comparator dataset in marketing authorization applications, particularly in rare or orphan diseases where patient populations are small.

Figures adapted from the FDA Draft Guidance, *Rare Diseases: Natural History Studies for Drug Development*, March 2019.

Having completed many full-service natural history studies, Veristat's global team is able to leverage lessons learned from the course of our work. Based on experience, we believe these studies are most useful in the following circumstances:

- When it would not be ethical or possible to give a control group a placebo – such as with extremely rare diseases or very small patient populations.
- As a means to identify the right patient population(s), including subgroups that may benefit from a therapy.
- When sponsors are considering the use of validated biomarkers as endpoints to help in clinical trial design.
- To open new communication pathways to relevant study sites, centers that specialize in the treatment of rare diseases, and patient advocacy groups.
- As valuable data to strengthen the understanding of the disease pathway and progression in preparation for Marketing Application for a rare disease.

Meet Veristat – Getting It Right, the First Time

Learn more about Veristat and how we can assist you with the planning and execution of retrospective or prospective natural history studies as starting points or additions to your clinical trial program.

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