VERISTAT

Natural History Studies in Rare Disease Drug Development

Critical Tools for Defining Populations, Endpoints, and Regulatory Strategy

One of the cornerstones of developing therapies for rare diseases is the use of natural history (or noninterventional) data to inform the clinical development process. Though you may think natural history studies aren't relevant or valuable to your clinical program, their real utility deserves consideration. The value of natural history data is driven by the type of study in which it was generated. When thoughtfully applied, natural history data can play a surprisingly helpful role in the clinical development process, offering 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Defining statements excerpted from the FDA Draft Guidance, *Rare Diseases: Natural History Studies for Drug Development*, March 2019: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.

Their purpose is to identify **demographic, genetic, environmental**, and other variables that correlate with the disease's development and outcomes.

Types of Natural History Studies—Benefits and Drawbacks

Retrospective Studies

Use existing medical records.

- \+ Faster, cost-effective
- \- May suffer from incomplete or inconsistent data

Prospective Studies

Follow a prespecified data plan.

- \+ Standardized, reliable
- \- More time- and resource-intensive

Cross-Sectional Studies

Single timepoint across a cohort.

- \+ Captures disease stage variation
- \- Cannot track progression over time

Longitudinal Studies

Track patients over time.

- \+ Most complete picture of progression
- \- Longer and more complex to run

When to Use Natural History Studies

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.

For comparison when 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 serve as comparators and, under updated FDA guidance, may also provide confirmatory evidence supporting approval when aligned with clinical trial data.

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 identify or develop clinical outcome measures for trials

- Detect changes in disease-related outcomes.
- Determine the magnitude of a clinically meaningful change.
- Create a valid, untreated, nonconcurrent control group for trial analysis.

Figures adapted from the FDA Draft Guidance, Rare Diseases: Natural History Studies for Drug Development, March 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-one-adequate-and-well-controlled-clinical

Maximizing the Value of Natural History Studies

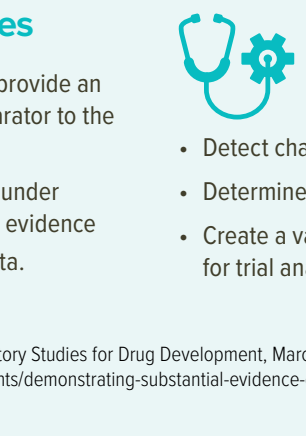
Having completed many full-service natural history studies, Veristat's global team is able to leverage lessons learned from the course of our work. Based on experience, we believe these studies are most useful in the following circumstances:

- 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.

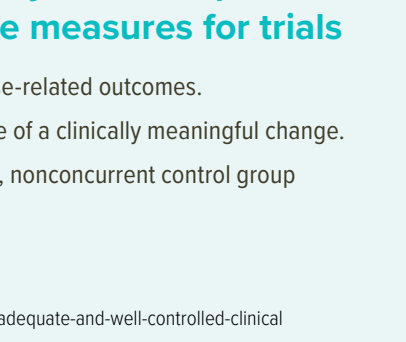
Resources

Blog

Case Study



Presentation



Explore Veristat's Expertise

Discover how Veristat helps sponsors design and execute impactful natural history studies.

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