Importance of Natural History Studies for the Biotechnology Industry

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Reasons to Develop a Natural History Study in a Rare Disease

- Determine the true incidence of the disease
- Understand the phenotypic variability of the disease
- Understand the genotypic variability
- Understand the geographical variability
- Identify the cause of morbidity/mortality
- Determine if lifespan is affected
Duchenne Muscular Dystrophy: Prevalence of a Devastating Rare Disease

- Most common and severe muscular dystrophy
  - Incidence: 1 in 4,000 live male births
- Caused by mutation that prevents dystrophin expression, a key protein for muscle function
- Symptoms at 3-5 years old, wheelchair as early as age 9
- Patients typically live into 20s
- High yearly cost of care, increasing with disease progression

Source: 1 E. Emery: Neuromuscular Disorders, 1991
Natural History Data can Inform the Clinical Trial Design

- What is the correct population to study?
- What is the natural progression of the disease?
  - Example: Spinal Muscular Atrophy
    - Type I - severe phenotype with rapid progression
    - Type II – more prevalent, less severe but may not be very progressive and may plateau
    - Type III – milder disease phenotype but may not demonstrate a decline in the controls
Natural History Studies for Endpoint Selection

- Natural history studies can be used to assess the ability of a particular endpoint to be used in a rare disease trial
  - Is it practical?
  - Does it monitor change?
  - Is it relevant to all of the sub-populations?
Natural History of 6 MWT in Duchenne Muscular Dystrophy

- 6 MWT distance has become the de-facto standard for clinical trials in Duchene muscular dystrophy but what is the natural history?
6MWT: Natural course of DMD

(McDonald et al Muscle & Nerve 42:966-974, 2010)

- Healthy (N=22)
  Mean change = +13 m (+2.1%)

- DMD (N=18)
  Mean change = -57 m (-15.9%)

p = 0.037*
Natural History as a Precompetitive Space

- The non-competitive nature of obtaining natural history information allows for the possibility of competitors and Foundations working together
  - Example: Does 2 or 4 minute walk test distance correlate with 6 MWT distance?
  - How well does the 10 meter walk/run correlate to the 6MWT distance?
Can natural history data be collected in a rigorous manner that would allow for a regulatory filing?

- Example: Infantile Pompe Disease
Data Collection in Natural History Studies

- Source verification challenging
- Data from different centers may not be comparable (different normative values, different machines, etc)
- Has the standard of medical care changed over the years? Example-steroids in DMD
- Is the time of the event knowable? Example-age at ventilation
How much Data is Enough

- Natural history studies are voluntary and cannot have the rigor of a clinical trial
  - Collect only the data that is required
  - The physicians and patients have limited time and many demands
  - Thoughtful discussion on data collection must occur with medical experts, families, and patients to understand the importance and burden of the data collection
Informing a Clinical Trial

- The focus of data collection should be to give insight into the clinical trial design

Questions:
- What are the endpoints?
- What is the natural history?
- How many patients are required to power the study?
- What sites are likely to have enough patients for a study?
Practical Considerations

- Data collection should be web-based and easy to use
- Adequate geographic representation is critical
- Are the sites able to enter the data in an accurate and timely manner?
Learn from the Mistakes of Others

- It is important to understand previous natural history studies
  - Why did they fail
  - Are there adequate resources
  - What about the competition?
  - Numbers of patients are important?
  - Is it practical?
Natural History Registries: Size matters

- One large and diverse registry is worth much more than several small registries.
- Individual country, center, or group registries are much less useful than a single powerful registry.