FSH Society's 2014 Biennial "FSHD Connect" Meeting: Natural History Studies

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Overview of FSHD: We Need to Understand More

Current State of Affairs

- Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal-dominant disorder localized to 4q35. Neither the gene nor gene product has been identified.
- FSHD clinical research faces several hurdles, delaying a cure:
  - Molecular basis for FHSD is still not completely worked out
  - Difficulty in defining and measuring the rate of change in this slowly progressing disease
  - Variability in disease progression
  - Differences in the genetic mode of transmission (e.g., autosomal dominant inheritance, autosomal recessive inheritance, germline mosaic, *de novo* mutations, etc.)
  - Existence of various forms of FSHD (FSHD1 and FSHD2)
  - Differing phenotypes for each form of FSHD with varying treatment goals at each stage
  - Few patients available or eligible for clinical trials
  - Variability between males and females
  - Preclinical animal models are not yet predictive of FSHD disease in humans, though significant progress has been made.

FSHD Research, Clinical Trials & Tissue Donation[1]

- Continued advances in basic mechanistic, translational and clinical research and understanding of FSHD depend greatly on patient involvement.
- Some research that requires medical information and biomaterials, such as blood and tissue donations, from people with FSHD.
  - › Tissue samples are used to create cell lines and cell systems to study therapies, and to help understand how FSHD cells progress from a healthy to an unhealthy state.
- **Some studies do not require blood or tissue samples but are 'natural history' studies that monitor a person's FSHD over time to understand how the disease progresses.**
- In other studies, volunteers might be interviewed or asked to complete surveys about the quality of life, pain, wellness and living with FSHD, or have a non-invasive medical procedure such as an eye exam or a magnetic resonance imaging (MRI) scan.
- All of these studies and others will eventually help doctors better understand, treat and cure FSHD.

1. http://www.fshsociety.org/pages/patStudies.html

Natural History Studies

- Natural History studies do not raise ethical concerns when there is no adequate treatment and the purpose is to try to gather information so that treatments may be developed.
- Definitions of natural history studies (*National Cancer Institute,* August 2014):
  - A study that follows a group of people over time who have, or are at risk of developing, a specific medical condition or disease.
  - A study that collects health information to understand how the medical condition or disease develops and how to treat it.
- Definition of natural history:
  - The natural course of a disease from the time immediately prior to its inception, progressing through its presymptomatic phase and different clinical stages to the point where it has ended and the patient is either cured, chronically disabled or dead without external intervention."[1]
- Natural history studies:
  - Track course of disease over time
  - Identify demographic, genetic, environmental and other variables that correlate with disease and outcomes in the absence of treatment.

1: Posada de la Paz M and Groft SC (Eds). 2010. *Rare Diseases Epidemiology*. Vol. 6862010, XXII, 542.

Examples of Natural History Studies in MD

- Currently underway:
  - A Multicenter Collaborative Study on the Clinical Features, Expression Profiling, and Quality of Life of Infantile Onset Facioscapulohumeral Muscular Dystrophy (FSHD) (2014, in conjunction with Duke University (see *clinicaltrials.gov*)
  - A Prospective Natural History Study of Progression of Subjects With Duchenne MD
    - Primary Outcome measure: 6 minute walk distance
    - Time Frame: Change from visit 1 walking distance
    - Participants are asked to walk at their own preferred speed on a fixed distance for 6 minutes.
    - Subjects are warned of the time and that they may stop earlier if they feel unable to continue. Total distance walked within 6 minutes (or until stopping) is recorded.
- Older NH studies with FSHD:
  - A prospective, quantitative study of the natural history of facioscapulohumeral muscular dystrophy (FSHD): implications for therapeutic trials. The FSH-DY Group. (Neurology.1997 Jan;48(1):38-46).
  - Facioscapulohumeral muscular dystrophy (FSHD): design of natural history study and results of baseline testing. FSH-DY Group (Neurology.1994 Mar;44(3 Pt 1):442-6).

FSH-DY Group 1997

Historical Precedent

- Prospective data on the natural history of this disorder are essential for the effective design of therapeutic trials.
- The FSH-DY Group systematically followed 81 well defined FSHD patients for up to 3 years using a standardized protocol that included manual muscle testing (MMT), maximum voluntary isometric contraction testing (MVICT), and functional testing.
- Muscle strength was strongly associated with measures of muscle mass, age at onset, and duration of disease.
- Decline in strength over time was slow but detectable with both MVICT and MMT. The magnitude of decline was not associated with either age, gender, age at onset, or duration of disease.
- This study establishes reliable and valid measures of disease state and progression for use as outcome variables in clinical trials in FSHD, and also **provides guidelines for determining sample size and duration of follow-up**.
  - A two-armed clinical trial involving 160 patients per group and 1 year of follow-up would provide 80% power to detect complete arrest of the progression of the disease. Trials with fewer patients would thus have adequate power to detect only improvements in strength, unless follow-up duration were extended well beyond 1 year.

Registry Study vs. Natural History Study

- A registry study is not the same as a natural history study
- **Registries**:
  - Can include communications to participants
  - Can meet post-marketing commitments/requirements (e.g., Intervention assessment)
  - Compile safety data
  - Quintiles was awarded the national registry for MD studies from the MDA (though focus has not yet been on FSHD)

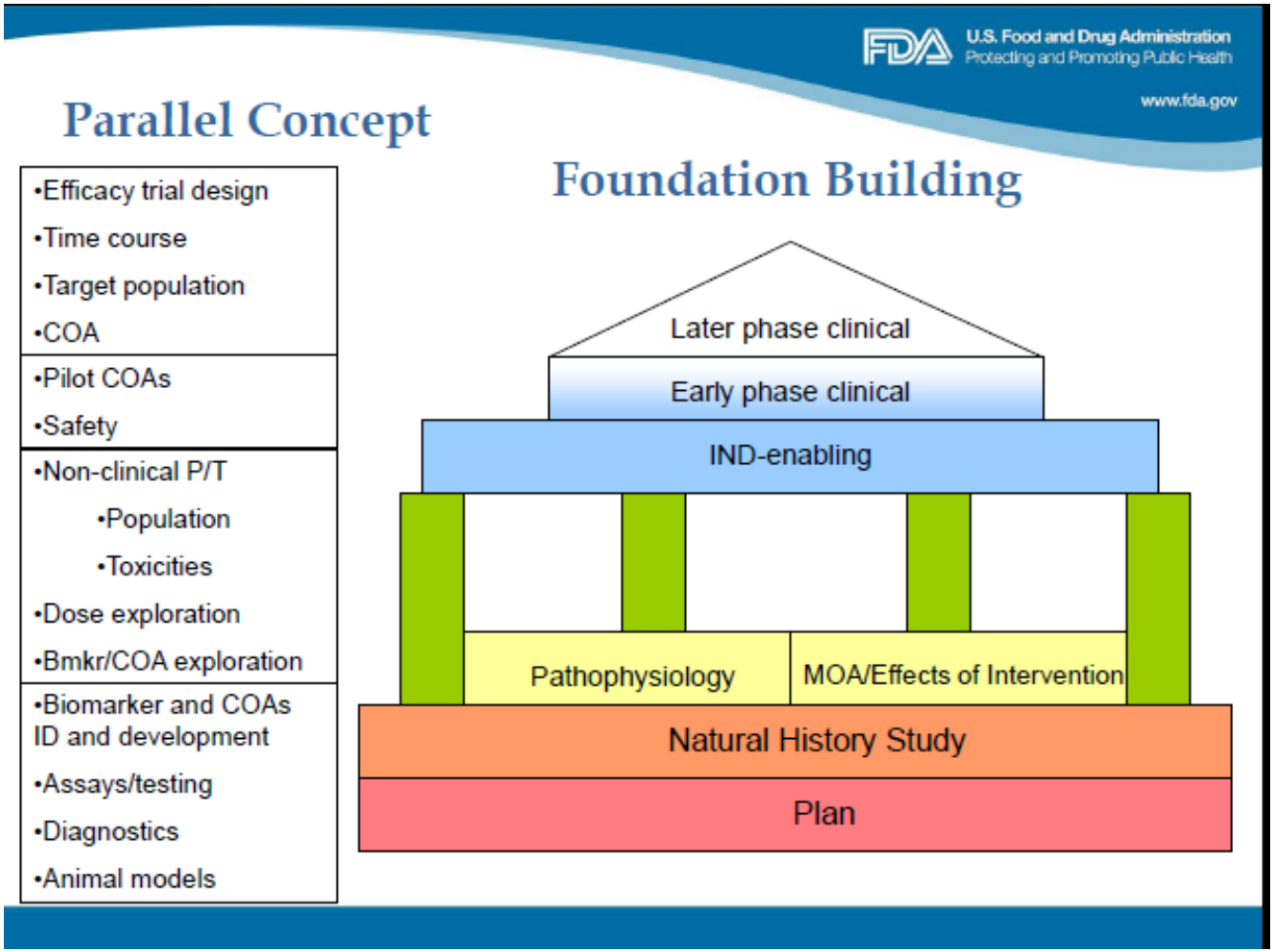
- **Natural History Studies**:
  - Specific purpose, with the intention of describing the disease
  - Intended to be comprehensive and provide granular information.

Natural History Studies: The FDA Perspective

- Purpose: To inform drug development
  - › Marketing approvals require design and conduct of adequate and well-controlled studies, based on a scientific foundation, including knowledge of the natural history of the disease
  - › Rare diseases, in general, are poorly understood
  - › Important and essential role for NH studies in rare disease drug development (IND phase) to facilitate efficient clinical development

- *Pariser AR. FDA's Associate Director for Rare Diseases, Office of New Drugs, CDER*

FDA : Natural History Studies Provide a Foundation



Adequate and Well Controlled Studies

Adequate and well controlled studies require:[1]

- A research goal and/or objective
- A valid comparison with a control – concurrent (strongest) or historical
- An appropriate selection of subjects
- A method of assignment to treatment and control
- The employment of measures to minimize bias
- Well-defined and reliable methods of assessing response
- An adequate analysis of the results (generally based on statistical powering).

1. Code of Federal Regulations (21CFR314.126)

State of the Union: MD Regulatory Guidance for Industry

- No regulatory guidance exists for the study of FSHD in patients.
- Draft guidance for Duchenne Muscular Dystrophy (DMD) and Becker's Muscular Dystrophy (BMD) is available in Europe (A concept paper was issued June 2011; draft guidance has been available since February 2013)
- Parent Project Muscular Dystrophy (PPMD) Guidance available in US (June 2014).
  - Titled, *"Guidance for Industry: Duchenne Muscular Dystrophy: Developing Drugs for Treatment over the Spectrum of Disease"*
  - The section on natural history characterizes the clinical course of DMD, including details of scientific consensus on tools, instruments and outcome measures
  - Note that this patient advocacy issued guidance, while requested and acknowledged by the FDA, has not yet been formally adopted.

Summary

- Natural history studies are needed to enhance our understanding of FSHD and its progression.
- NH studies are part of the study continuum that will ultimately lead to the conduct of clinical trials.
- NH studies may involve sample taking (e.g., blood, tissue, urine) or undergoing diagnostic procedures (e.g., MRI, CT, ultrasound, etc).
- A registry is NOT a natural history study.
- A natural history study is NOT a clinical trial investigation.
- The FSH Society can be a key resource to identify ongoing NH studies; other studies can be found at *clinicaltrials.gov* (which provide an overview of acceptability for enrollment) or elsewhere online.
- The FDA has not yet issued formal guidance for industry, but has received (though not yet adopted) draft guidance from patient advocacy groups like PPMD which advocate on behalf of patients with DMD (June 2014).