Importance of Natural History Studies in Rare Disease Drug Development

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Outline

• Rare disease FAQs
• Why we need Natural History data for rare diseases
• Natural history study designs and considerations
• Natural history and clinical development
• Key points
Rare Disease FAQs

Rare (aka Orphan) diseases:
“…any disease or condition which affects less than 200,000 persons in the U.S…”\(^1\)

- In reality, most rare diseases are far less prevalent than this
- Individually rare, collectively--large public health problem
  - ~7,000 different rare diseases
  - Affect 25-30 million Americans (~1:10)
  - Most are serious, most have unmet medical needs

\(^1\)Orphan Drug Act, Public Law 97-414, as amended 1984
The Orphan Drug Challenge

• What is different about rare diseases and Orphan drugs?
  – Small populations
    • Limited opportunity for study and replication
    • Patients and treatment centers often geographically dispersed
  – Diseases are usually poorly or incompletely understood
    • Generally, the lower the prevalence, the less well we tend to understand them
  – Highly heterogeneous group of disorders
    • 7,000 different diseases
    • Often high phenotypic diversity within individual disorders
  – Usually little precedent for drug development within individual disorders
  – Often requires more (and more careful) planning than non-Orphan
    • Need a solid scientific base upon which to build an overall program
### Disease Precedent?

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| **2012 (as of Sept 4, 2012)** | Methotrexate toxicity  
Cystic Fibrosis G551D mutation |
| Respiratory Distress Syndrome in premature infants |  
Gaucher disease  
CML |
| **2011** | Advanced melanoma  
Melanoma  
BRAF mutation  
Medullary thyroid cancer  
Anaplastic systemic large cell lymphoma  
Alk+ non-small cell lung cancer  
Myelofibrosis |
| Organ rejection, kidney transplant  
Hodgkins lymphoma  
Hereditary Angioedema  
Acute lymphoblastic leukemia  
Transfusional iron overload  
Lennox-Gastaut |  |

• In same time period for non-rare disease indications: 36 NME/NBs, only 2 did not have disease precedent (6%)
Begin with the end in mind...
Natural History Studies

• Purpose: To inform drug development
  – Marketing approvals require demonstration of “substantial evidence of efficacy and safety”\(^2\)
    • Usually from design and conduct of adequate and well-controlled studies
    • Designing A & WC studies requires a scientific foundation upon which to build
      – Knowledge of disease NH is an essential element in the scientific foundation of any clinical development program
  – 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
    • Ideally, this knowledge will be available as early in the drug development process as possible

\(^2\)Code of Federal Regulations Title 21. Section 314.50
Adequate and Well-Controlled Studies

• A&WC studies require
  - Research goal/objective
  - Valid comparison with a control
    • Concurrent (strongest) or historical
  - Appropriate selection of subjects
  - Method of assignment to treatment and control
  - Measures to minimize bias
  - Well-defined and reliable methods of assessing response
  - Adequate analysis of results

321CFR 314.126 Adequate and well-controlled studies
Drug Development – Linear Concept

- Basic Science
  - Translational
  - Pre-IND
  - Clinical
  - Post-marketing

- NIH
  - NIH NCATS/Translational Science

- FDA
  - Critical Path
  - Interactions
  - NDA/BLA Review

- Drug Developers

Phases:
- Ph 1
- Ph 2
- Ph 3
- Ph 4
Parallel Concept -- Foundation Building

- Efficacy trial design
- Time course
- Target population
- COA

- Pilot endpoints
- Safety
- Dose exploration

- Non-clinical P/T
- Bmkr/endpt exploration

- Disease range
- Target ID
- Bmkr/endpt ID & develmt
- Assays/testing
- Diagnostics
- Animal models

Later phase clinical

Early phase clinical

IND-enabling

Pathophysiology
MOA/Effects of Intervention

Natural History Study

Plan
Natural History Studies
Definition
NH Study Versus Registry

- Registry ≠ NH Study
- Registries can include:
  - Communication
  - Post-marketing commitments/requirements e.g.,
    - Intervention assessment
    - Safety
  - NH Study
    - Specific purpose
    - Intended to be comprehensive, granular
    - Intended to describe the disease
Natural History of a Disease

“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”

Posada de la Paz M; Groft SC. 2010. Rare diseases epidemiology. Vol. 686
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
• “Pillar of epidemiologic research on rare conditions”\(^5\)
  - Many potential uses/functions of NH study data in addition to drug development, e.g.
    • Patient care, best practices
    • Research priorities identification
    • “centers of excellence” development, clinical trial readiness

\(^5\)Institute of Medicine. 2010. *Rare Disease and Orphan Products. Accelerating Research and Development*
NH Studies – Purpose and Goals

- Main purpose is to inform drug development
- Major goal is to assist with clinical trial design
  - Define the disease
  - Identify gaps, e.g.,
    - Improve diagnosis
    - Identify potential biomarkers and outcome measures
    - Biobanking (?)
  - Develop centers of excellence/expertise
  - Better estimates of prevalence, better understand patient community
- Infrequent and uncommon use of NH, may serve as historical control
  - “usually reserved for special circumstances”\(^6\), e.g.:
    - diseases with high and predictable mortality
    - Effects of drug self-evident

\(^6\)21CFR 314.126 Adequate and well-controlled studies
NH Studies and Clinical Research

Clinical Observations
- presentation
- course
- outcome measures

Biomarkers
- screening
- diagnostics
- outcome correlation/PD-PK effects

Pathophysiology

Prognosis
- genetic
- environmental

Therapies

Slide courtesy of Nuria Carrillo, M.D.
NIH NCATS, TRND
Natural History Studies – e.g., EoE

• For Eosinophilic Esophagitis, major concerns:
  – Endpoint identification and development
    • Consider disease characteristics, clinically important concerns of patients/caregivers
    • Design and acceptance of proposed measurement tools and outcome measures
    • Clinical meaningfulness of intervention(s) → interpretation of outcomes
  – Describe all phenotypes and full range of disease within phenotypes
  – Study timelines (e.g., disease chronicity)
  – Represent current practices (e.g., diet, PPI)
Designing an NH Study

• What already exists??
  – Registries
  – Literature
  – Expert opinion
  – *Talk to the patients and caregivers*

• What are the gaps?
  – Project forward to A&W trials – what will you need?

• 3 types
  – Retrospective chart review (≠literature review)
  – Prospective cross-sectional
  – Prospective longitudinal
# NH Study Design

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<th>Con</th>
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| Retrospective Chart Review | • Faster/cheaper  
• Data already collected | • Bias  
• Limited by available information |
| Prospective Longitudinal | • Objective  
• Comprehensive  
• Feedback/learning  
• Strong trial design support | • Time/cost  
• Scope  
• Long-term follow-up and participation |
| Prospective X-sectional | • Relatively faster  
• May combine existing + new info.  
• Endpoint selection | • Limited by available information/won’t “evolve”  
• Limited assessment |
Key Points

#1 NH data contribute to scientific foundation upon which drug development programs can be built
- Rational, scientifically-based drug development requires an understanding of the disease
- NH describes the disease - independent of individual investigational agents
- Most informative when NH study data are available early in development
  - Ideally before design of efficacy trials
- Support all phases of clinical development
  - E.g., endpoint identification and development, trial design, select patient (sub)populations for study inclusion

#2 Patient and caregiver involvement is important
- Engage all stakeholders early and on an ongoing basis

Key Point #3

- Monolith\(^8\) (mon\(\quad\)uh\(\quad\)lith)
  - an obelisk, column, large statue, etc., formed of a single block of stone
  - Something having a uniform, massive, redoubtable, or inflexible quality or character

\(^8\)dictionary.com

Rare diseases are a highly diverse collection of disorders
- Design and conduct of clinical development programs are highly individualized
- Dependant on disease and population under study, understanding of the intervention and its expected impact on the disease
Key Points #4

Drug development as a continuum
Efficiency ≠ corner-cutting

- Natural History
- Pathophysiology
- MOA/Effects of Intervention

- Efficacy Trials/Study Design
  - Earlier Phase Clinical Trials
  - IND-enabling
  - Endpoint Identification & Development
Questions?

If Train A leaves Boston at 9:27 PM heading west at 173 MPH and Train B leaves Milwaukee at 10:38 AM heading east at 123 MPH with a steady north wind blowing at 17 MPH,

which primary endpoint should be selected for an EOE clinical trial?