Natural History Studies

*Form Follows Purpose*

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The views expressed are those of the author, and do not necessarily represent an official FDA position.
Outline

• Why and Where Apply NH knowledge
• Design Principle – Objectives Drive Content
• NH Study Type Overview
• Design Principle – Planned Evolution
• Communal Endeavor
• Operational Design Concepts
Rare Disease

• Orphan disease
  ➢ Less than 200,000 patients in U.S.

• Rare – *for purposes of this presentation*
  ➢ Qualitative rather than quantitative term
  ➢ Subset of orphan diseases
  ➢ Increased difficulty of therapy development
  ➢ Therapy development for large population
  orphan disease much like for common diseases
Natural History Knowledge

• Important source of critical knowledge to advance therapy development
• Guides selection of design features for Tx studies
  ➢ Patient population to study
  ➢ Outcome assessments
  ➢ Duration of study
  ➢ Biomarker usage
• Guides choice of objectives for therapy benefit
• Drug development program can fail if wrong choices
Critical knowledge not known for many rare diseases

- Successful therapy development may require substantial new natural history knowledge

- NH studies are not part of drug treatment studies
  - NH knowledge needs to be applied in Tx development program
  - NH studies most useful if conducted and data available prior to Tx development program

- NH studies contribute to therapy development along with interventional trials
NH Knowledge in Therapy Development

• NH knowledge is disease specific
  ➢ Not Tx specific

• Appropriate to be done outside of any specific drug development program
  ➢ Shared knowledge for community to use
  ➢ Greatest value of NH knowledge if:
    ➢ Widespread origination of information
    ➢ Widely available to apply
  ➢ Applicable to multiple potential Tx development programs
Time Period of NH Knowledge Use

- Chief use of NH knowledge is during the drug development (IND) period
  - Not the Application for Marketing Approval period (NDA / BLA)
  - NH study data usually not significant part of NDA / BLA review
  - IND studies will have succeeded (or failed) prior to submission of NDA / BLA
  - Avoiding study failure is value of NH study
Study Conduct and NH Data Quality

• Value of NH knowledge is mainly in designing clinical trials (IND period)
  - Critical regulatory decision (Tx approval) does not depend on the NH data
  - Data does not need to be verifiable GCP quality
  - Full GCP documentation usually not essential
  - Good quality data is important
    - Poor quality data may mislead the decision-making during the Tx development program

• Some data quality and conduct quality monitoring should be included to ensure quality is adequate
NH Study Design Principle

• Careful, prospective planning essential to success
  ➢ Just as for any clinical study
  ➢ Plan with objectives in mind
  ➢ Objectives drive study design and operational choices

• Consider broad range of possible therapies
  ➢ What knowledge will those Tx development programs need – not all the same
  ➢ Enables the NH data to support advancement of multiple different therapeutic possibilities
Objectives Determine Design Content

• Identify and state all objectives for the study
  ➢ All purposes study data are intended to serve
  ❖ Explicitly and comprehensively
  ❖ What specific questions arise during a drug development program that will need to be answered based on NH knowledge
  ❖ Determines what data are needed to answer questions

• Experienced drug development perspective in NH study design stage important to this step
Questions During Tx Development

Examples:

• Who to enroll in studies?
• How to determine what doses to test?
• How to determine what dosing schedule to test?
• What intermediate assessments are useful?
• What is the clinical efficacy endpoint?
• How is the endpoint measured?
• What is the duration of the study?
• How large is the study?
Aspects of NH Knowledge

• Define the disease
  ➢ Disorders that are poorly understood syndromes may have multiple different etiologies, with similar end-stage
  ➢ Ill-defined collection of pathophysiologies may be resistant to any single therapy
  ➢ Solidify diagnostic criteria
Aspects of NH Knowledge

• Identify distinct clinical phenotypes
• Identify distinct pathophysiology subsets
  ➢ Including genetic subsets
    ❖ Causative gene or modulating gene
• Standard of care
  ➢ Potential that supportive care or unproven Tx have effects on disease course
  ➢ Care of patients at time of measurements
  ➢ Historical may be different from current
• Biomarkers correlating with disease course
• Biomarkers for MoA pharmacologic responses
Aspects of NH Knowledge

• Comprehensive identification of disease features
  ➢ Major and minor
  ➢ Survival
  ➢ Physical function abilities
  ➢ Sensory function abilities
  ➢ Neuropsychological function abilities
    ❖ Cognitive
    ❖ Psychiatric
Aspects of NH Knowledge

- Full range of severity of manifestations
- Pace of development of manifestations
- Frequency each manifestation occurs
- Method to reliably measure the manifestations
- Intra-patient variability
  - Day to day severity
- Inter-patient variability
  - Which manifestations present
  - Relative severity of different manifestations
  - Time course of manifestation progression
NH Knowledge: Tx Study Outcome Comparator?

• Historical control concept
  ➢ Suitable only in very special cases

• Most rare disorders not amenable to defining a highly homogenous subset with uniform, reliable outcome, rigorously recorded

• Some cases may be suitable to consider
  ➢ Highly homogenous disorder or phenotype
  ➢ Patient evaluation(s) highly uniform across multiple sites in NH study
  ➢ Pt evaluation rigorously recorded at all sites in NH study
  ➢ Pt evaluation not easily influenced by variations in patient care
General Design Types of NH Study

• Published medical literature review
• Retrospective chart review
• Prospective cross-sectional
• Prospective longitudinal

• View NH knowledge as a knowledge development program
  ➢ May have multiple parts or stages
Retrospective Chart Review

• Often a starting place for a NH knowledge program
• Usually not sufficient for all objectives
• Guide to designing a prospective longitudinal study
• Limitations
  ➢ Often because clinical care chart records were for purposes of clinical care, not objectives of NH study
Retrospective Chart Review

- Data often not comprehensive
  - Determined by utility for clinical care at that time

- Variability in what was evaluated and how it was recorded
  - Often varies from site to site
  - May vary within site over time
  - Quality of data may vary
    - Erroneous data not corrected (e.g., lab values)
    - Particularly when not important for clinical care
  - Even if intended to be same aspect of disease
Prospective Cross-Sectional

• May be efficient method to get moderately detailed understanding of disease
• Usually cannot provide knowledge about pace of disease
  ➢ Exception for very uniform disease with reliably identifiable moment of onset
    ➢ Uncommon
• Can be strong guide to designing a prospective longitudinal study
• Valuable for outcome tool development
Prospective Longitudinal

• Most comprehensive understanding of disease
  ➢ Greatest depth
  ➢ Greatest richness

• Most detailed source of knowledge on pace and sequential course of disease

• Sustained commitment from patients and investigators essential
  ➢ Longitudinal defined in context of the disease

• Most valuable design for depth and strength of knowledge to apply to clinical trial issues
Design Principle – NH Study as an Evolving Protocol

• Some NH objectives may require multi-step approach to achieve
  ➢ May not know at outset exactly what, when, or how to measure to achieve an objective
  ➢ e.g., New endpoint development

• Analyze accumulating data periodically
• Plan to refine questions the study is addressing, and revise data collection design to progressively advance to ultimate objective
Protocol Evolution Example

- **Biomarkers**
  - Initial measurements may indicate biomarkers that appear promising vs those that do not
    - Eliminate unpromising biomarkers
    - Increase data on promising biomarkers
  - May need to refine assay for more precision
  - May need to add other biomarkers physiologically related
  - May need to revise sampling frequency plan, or synchronize sampling with clinical events
Protocol Evolution Example

• Clinical trial outcome measures
  ➢ What manifestations can be measured?
  ➢ What ones have stability over time if intending to show restoration of function?
  ➢ What ones have uniform worsening if intending to show slowing of progression?
  ➢ What methods are available to measure the manifestation? Are they reliable?
    ❖ Suitable to this patient population and the severity of the manifestation
  ➢ Are new measurement methods needed?
    ❖ Devise, try out, analyze, revise
    ❖ Interactive process with study design, evaluation
Learn and Confirm Within NH Study

- Initial ‘hypothesis’ allows identifying data to obtain
- Utilize data of early period of study to refine the measurement or hypothesis
- Subsequent data used to prove ‘hypothesis’ that states a reliable choice or conclusion
- Interim analyses may indicate data that would be useful to collect but was not apparent initially
- NH Study is not a fixed protocol study methodology
Community Endeavor

• Successful NH study for rare diseases most likely to succeed if it is a unified community-wide endeavor
  ➢ Multiple separate efforts lead to incompatibility of data and incompleteness of data
  ➢ Rarity of patients prevents individual site from succeeding alone

• Value of NH knowledge maximal when data is shared widely
  ➢ Data shared with other investigators
    ➢ Including those not in same specialty
  ➢ Absence of access to data can impair progress as much as absence of data
Community Endeavor

- Multiple investigators
  - Multiple sites
  - Common accepted protocol
- NIH role
  - Direct investigators
  - Support of studies; ensuring commonality of effort
- Industry role
  - Need to initiate study before Tx candidate in hand
  - May need to initiate before decision to attempt Tx in the disorder
  - May be difficult to justify resources for a private endeavor
Community Endeavor

- **Patient groups**
  - Can identify patients
  - Educate patients and families on NH value
    - What it will produce and what it will not, how it is valuable, importance of consistent commitment
  - Help sustain involvement
  - Might help in data collection, management

- **FDA**
  - Experience in rare disease Tx development programs; perspective on distant objectives for the NH study to build in from outset
  - Advisory role
Study Operational Structure Concepts

• How is study conduct organized
  ➢ Many choices influenced by specifics of disease and study objectives

• Centralized vs. dispersed data management
  ➢ Centralized quality checking
  ➢ Ongoing analyses of full existing database support study design evolution concept
Study Structure Concepts

- Pure widely dispersed model
  - Many local clinics with few patients or
  - Patient’s individual physician conducts protocol
    - Collects and reports data
  - Convenience for patients
  - Infrequent use of protocol at each site
    - Risks variability between sites in how evaluations performed, data quality, data quantity (patient call back)
Study Structure Concepts

• Pure central clinical site model
 ➢ Patients travel to single, highly experienced site
 ➢ Inconvenient for patients
 ➢ Investigator and staff experienced and effective
    ✷ All data collected in consistent manner
    ✷ Good accounting for all patient follow up and timing
    ✷ Complex evaluations can be reliably performed
    ✷ Specialized skills or infrastructure can be available
Study Structure Concepts

• Mixture clinic model
  ➢ Dispersed clinics for easy to perform evaluations that occur on more frequent basis
  ➢ Central site for less frequent but more intensive evaluations

• In home model
  ➢ Visiting health care provider or other trained persons
  ➢ Most convenient for patients
  ➢ For less intensive evaluations or sample collection that is obtained on frequent basis
  ➢ Sufficient training to perform on reliable manner
Study Structure Concepts

• Patient reported model
  ➢ Especially attractive as internet collection
  ➢ Reliability of measurements must be considered
  ➢ Chiefly for less quantitative evaluations
    ❖ Training of patients (families) on how to report
    ❖ Reporting tool tested for reliability across range of patients and families
  ➢ Easiest model for high frequency reporting
Study Structure Concepts

• Much work still needed to assess
  ➢ Efficiency
  ➢ Effectiveness
  ➢ How to match structure design to study design
  ➢ Quality, and training for quality

• Suitability of approaches likely to vary for different rare diseases
Closing Points

• NH knowledge can be essential to Tx development
  ➢ Extensive NH knowledge can make the disorder attractive to undertake Tx development
  ➢ NH knowledge enables many Tx development program options to be understood

• Good NH knowledge comes from soundly planned and conducted studies

• Planning requires identifying objectives
  ➢ In detail
  ➢ For near term and later uses of data

• NH study design can evolve as knowledge grows

• Importance of community-wide effort