Natural History Studies

Form Follows Purpose

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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 difficultly 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

Natural History of Rare Diseases

- 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