

# Role of Natural History Data in Clinical Trial Design

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# Role of NH data in trial design

- NH data to design a clinical trial
  - NH data to serve as the control
  - NH data to guide the trial design
- FDA experience using NH data to design a clinical trial
- Design of a NH study to obtain data to support a future trial

# NH data to serve as the control

## Phase 1 and Phase 2 Studies

- NH controls generally acceptable, because only qualitative conclusions sought (i.e., no definitive conclusions)
- Problem – These studies tend to have shorter time-lines, whereas NH studies may not provide short-term data.

# NH data to serve as the control

## Phase 3 Studies

- Regulatory requirement for marketing approval – well-controlled trials; historically-controlled (i.e., NH control) may be, in select situations, well-controlled

# NH data to serve as the control

## Phase 3 Studies

- NH controls generally not acceptable, except for select situations, such as:
  - Dramatic efficacy
  - Usual course of disease is highly predictable
  - Objective endpoints, not susceptible to bias
  - Impact of baseline and treatment variables on the endpoint is well-characterized
  - Ethical issues

# NH data to serve as the control

## Other issues

- Comparability between NH control group and new clinical trial group
- Safety database
- Alternative trial designs

## Comparability between NH control group and new clinical trial group

### Study population

- Lack of randomization yields lack of (or great concern about) comparability of study groups (often unable to prove non-comparability, but difficult to provide strong evidence of comparability)

# Comparability between NH control group and new clinical trial group

## Study population

- Subjects in clinical trials generally do better than subjects outside of a trial; factors (which are difficult to quantitate) include patient selection (different eligibility criteria, in addition to self-selection by subjects)
- Diagnostic criteria change over time
- Prognostic factors to be recognized, (may require/benefit from stratification)

# Comparability between NH control group and new clinical trial group

## Clinical Management

- Increased medical care
  - Due to trial participation
  - Change in medical practice / standard of care during the time between collection of NH data and the time of the clinical trial

# Comparability between NH control group and new clinical trial group

## Outcome Assessment

- Lack of blinding produces potential for biased assessment; placebo effect (expectation of benefit) in an open-label study
- Exaggeration of how bad things are/were (including publication bias, if using literature reports as evidence of NH)

# Comparability between NH control group and new clinical trial group

## Safety Database

- Control database must control for safety as well as efficacy
- What adverse events, and when do they occur

# Comparability between NH control group and new clinical trial group

## Alternative Trial Designs using NH

- NH control in Phase 1; Randomized withdrawal in Phase 3
- “Short” placebo-controlled period followed by NH control period (e.g., placebo-controlled for 1 year, followed by NH control for second year)

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# NH data to guide the trial design

- Selecting the study population
- Sample size
- Randomization procedures

# NH data to guide the trial design

- **Selecting the study population**
- For genetic disorders, connect genetic mutation to clinical course (e.g., dystrophinopathy)
- NH study population is likely to be different than population in a clinical trial; we need to understand what the differences are, and the clinical consequences of those differences
- Need shape of the curve for the outcome measure vs. time (avoid ceiling and floor effects)

# NH data to guide the trial design

## 2. Sample size

- Know variability of disease with regard to outcome measures
- Intra-rater and inter-rater reliability for outcomes of interest

# NH data to guide the trial design

## 3. Randomization and analysis

procedures: Prognostic factors may be important for stratification of randomization (or to include in analysis model)

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# FDA experience using NH data to design a clinical trial

- Indication: Fabry's disease (alpha-galactosidase deficiency)
- Proposed treatment: alpha-galactosidase, Genzyme
- Approximately 4000 patients in United States
- Major academic centers with clinics for Fabry's disease patients
- Trial design to focus on renal impairment as an outcome measure
- NH data available with regard to renal function

# FDA experience using NH data to design a clinical trial

## NH data available regarding renal function

- Not all centers with interest in disorder may choose to participate: 27 participated of 51 identified centers
- Not all patients at participating sites can be located and provide consent to have their data used: Of 742 patients, 447 consented
- Not all patients may be suitable to include: Methods of diagnosis and criteria for diagnosis need to be comparable between NH data and prospective study
- Not all patients in clinic records at a stage of interest for the drug development program

# FDA experience using NH data to design a clinical trial

For Fabry disease with interest solely on renal function as assessed by serum creatinine

- Required accurate, documented diagnosis
- Evidence of renal impairment at some time during period of follow-up
- Of 447 potential patients, only 115 met criteria

# FDA experience using NH data to design a clinical trial

Value of Natural History database related  
to repeated evaluations: The more  
frequent, and longer the total duration  
of follow-up, the more valuable

## Conclusion

The strength of the data may not be as  
great as expected, and revealed only  
by explicitly evaluating the dataset.

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Design of a NH study to obtain  
data to support a future trial

Predicting the future ...

(i.e., What should NH studies  
provide?)

# What should NH studies provide?

## Study population

- Look at full spectrum (e.g., age groups and severity of disease) of population
- Intervention may only be effective with earlier disease (perhaps even preclinical)
- Informed consent an issue in children; therefore, early phase studies of an intervention may enroll only adults

# What should NH studies provide?

Regular, comprehensive assessments,  
including adverse events

- Don't assume that you know what aspect of the disease the future trialist will want to study
- Be open-minded; look at as many outcome measures as feasible
- Assess reliability of outcome measures in the population, including standardized methods across all collaborating centers

# What should NH studies provide?

## Long-term NH study

- Is the NH evolving as the standard of care changes?
- Ideal is the NH study that continues until the disease is cured.

# What should NH studies provide?

## Hereditary disorders

- Genetic information as part of dataset
- DNA samples tied to data

# What should NH studies provide?

## Preserve raw data from NH studies

- Information in a manuscript is seldom (never) sufficient
- Need ability to look at outcomes in population subsets that are comparable to the population for the proposed clinical trial

What should NH studies provide?

Warning: NH is seldom what you expect: for example, progression (or lack of progression) of weakness in spinal muscular atrophy (DCN group)

# Elements of an optimal NH study

- Study population
  - Well-specified diagnostic criteria
  - Full spectrum of disease status (baseline characteristics)
  - Full spectrum of subject demographics (e.g., all ages, regions)

## 2. Hereditary Disorders

- Genetic information
- DNA database

## 3. Characterization of Standard of Care

- Concomitant interventions

# Elements of an optimal NH study

## 4. Outcome measures

- Capture all aspects of disease
- Measures with a variety of advantages (e.g., feasibility, sensitivity, resistance to bias, clinical meaningfulness)
  - Use different outcome measures for early development (Phase 1-2) and later development (Phase 3)
  - Measures that are less likely to evolve
- Measures (or combinations of measures) that are informative throughout the course of the disease

## Elements of an optimal NH study

4. Regular (e.g., monthly, q 3 months, annual) data collection
5. Long-term studies (to track changes in NH), until there is a cure
6. Preserve the data

# Contributors

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