Clinical Trial Methods Course 2017
Trials in Rare Diseases

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Overview

Challenges in studying rare diseases

Strategies for trial design

Legislation and funding
Rare Diseases
More Common Than You Think

What is a rare disease?

In the US, a disease is defined as rare when it affects fewer than 200,000 Americans at any given time.¹

In Europe, a disease is defined as rare when it affects less than 1 in 2,000 people.²

7,000 = 300 million
In the US alone, about **1 in 10 people** suffers from a rare disease.³

- **95 PERCENT** of rare diseases do not have an FDA-approved treatment.³
- **80 PERCENT** of rare diseases are genetic.³
- **50 PERCENT** of the people affected by rare diseases are children.³
- **ABOUT 50 PERCENT** of rare diseases do not have a dedicated organization.
Key Concepts

Scientific Question
Right Outcome Measures
Participant Selection
Sound Trial Design
Effective recruitment strategies
Gain and Disseminate Knowledge
Key Concepts

Scientific Question
Right Outcome Measures
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Rare Diseases: Preclinical Challenges

• Animal models
• Drug readiness
• Understanding of regulatory requirements
Rare Diseases: **Design Challenges**

- Unknown etiology
- Lack of natural history data
- Heterogeneous population
- Chronic diseases
- Multi-symptomatic
- No validated outcome measures, surrogate endpoints, biomarkers
- Small sample sizes

*Cartoon:*

**Patient:** Does it work?

**Doctor:** That depends on what you mean by “does,” “it” and “work.”

**Footnote:** Things got really interesting when the statistician started doing ward rounds.
Rare Diseases: Recruitment and Implementation Challenges

- Number of patients
- Geographic dispersion, travel burden
- Clinical research workforce
- Trial infrastructure
- Understanding of regulatory requirements
- Competing trials and off-label use of drugs
- Pediatric diseases
Challenges in CNS Therapeutic Development

Success rates from first-in-man to registration

Higher Success Rates for Rare Disease

General Design Considerations

• Understand natural history!

• Adapt outcome measures, biomarkers, or surrogate endpoints from common diseases

• Continuous measures, repeated measures

• Extend treatment period

• Sample selection

• $\alpha$-level
Alternatives to the RCT

- Open-label
- Factorial designs
- N-of-1 studies
- Crossover studies
- Randomized withdrawal
- Adaptive designs
Small, uncontrolled trials

• Disease follows a homogenous clinical course

• Anticipated effect size is large
Recombinant human acid α-glucosidase

Major clinical benefits in infantile-onset Pompe disease

P.S. Kishnani, MD*; D. Cerzo, MD*; M. Nicolino, MD, PhD; B. Byrne, MD, PhD; H. Mandel, MD;
W.L. Hwu, MD, PhD; N. Leslie, MD; J. Levine, MD; C. Spencer, MD; M. McDonald, MD; J. Li, MD;
J. Dumontier, MD; M. Halberthal, MD; Y.H. Chien, MD; R. Hopkin, MD; S. Vijayaraghavan, MD;
D. Gruskin, MD, PhD; D. Bartholomew, MD; A. van der Ploeg, MD, PhD; J.P. Clancy, MD; R. Parini, MD;
G. Morin, MD; M. Beck, MD, PhD; G.S. De la Gastine, MD; M. Jokic, MD; B. Thurberg, MD, PhD;
S. Richards, PhD; D. Bali, PhD; M. Davison, MD; M.A. Worden, BS; Y.T. Chen, MD, PhD; and J.E. Wraith, MD
Table 3: Proportion of Matched Symptomatic Pediatric Patients with CLN2 Disease without Decline* in the Brineura Single-Arm Clinical Study with Extension and in the Natural History Cohort assessed at Weeks 48, 72, and 96

<table>
<thead>
<tr>
<th>Time Point/Period</th>
<th>Natural History Cohort (N=17)</th>
<th>Brineura-Treated (N=17)</th>
<th>Difference % (95% CI**)</th>
<th>Odds Ratio** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up through Week 48</td>
<td>13 (76)</td>
<td>16 (94)</td>
<td>18% (-19, 51)</td>
<td>4 (0.4, 200)</td>
</tr>
<tr>
<td>Follow-up through Week 72</td>
<td>11 (65)</td>
<td>16 (94)</td>
<td>29% (-7, 61)</td>
<td>5.9 (0.7, 250)</td>
</tr>
<tr>
<td>Follow-up through Week 96</td>
<td>6 (35)</td>
<td>16 (94)</td>
<td>59% (24, 83)</td>
<td>11 (1.6, 500)</td>
</tr>
</tbody>
</table>

*Decline is defined as an unreversed (sustained) 2-category decline or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale.

![Graph showing Proportion of Matched Patients without Decline in Motor Function](image)

*94% of Brineura-treated patients (16/17) had no decline in motor function from week 48 through 96.†
Crossover Studies

- Each participant serves as own control
- Symptomatic relief
- Limited carry-over effect
N-of-1 Design

- Specialized crossover study
- Single patient
- Symptomatic treatments
### 2×2 Factorial design

<table>
<thead>
<tr>
<th></th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug A+B</th>
<th>Neither Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Image]</td>
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</tbody>
</table>

- Used when it is desired to study the influence of a number of factors on the treatments compared as well as their interaction with different treatments.
Randomized start

Randomized withdrawal

McQuay et. al., 2008
Recruitment Challenges

- Complex diseases
- Physical impairments
- Poor QoL
- Clinical heterogeneity
- Fragmentation of patient-related information

- Multiple specialists
- Numerous visits
- Lack of services
- Travel distance
- Need for family care
- Lost time from work

- Access to research
- Recruitment and retention
- Ascertainment bias
Everyone with the Disease

Everyone with the Diagnosis

Accessible patients

Suitable patients

Recruited to Trial

Close to 80% of clinical trials fail to meet milestones
The process of translating lab research into potentially life-saving treatments is often severely delayed
Patient enrollment challenge is the leading cause of missed clinical trial deadlines
Recruitment strategies

• Patient Groups
• Disease networks
• International
• Multi-media
• Build relationships through continued engagement
• Registries
• Share information
• Plan for extended accrual
Legislation and Funding
The Orphan Drug Act (ODA)

- Decade prior to 1983 – only ~1 drug/year independently developed by pharmaceutical sponsors

- Legislation needed to promote rare disease drug development

- The Orphan Drug Act signed into law on Jan. 4, 1983
Basic Definitions

• What is an orphan drug?
  – Drug (or biological product) used for the prevention, diagnosis or treatment of a rare disease in the US; OR
  – Drug that will not be profitable within 7 years following approval by the FDA

• What is a rare disease?
  – Disease/condition that affects <200K people in the US

• Incentives
  – Tax Credits – 50% of clinical trials costs
  – Waiver of User Fees - $1.9 M
  – 7-year Marketing Exclusivity
Review of a Designation Request

1. What is the disease/condition?
2. Is the disease rare (prevalence)?
3. Is there sufficient scientific rationale that demonstrates “promise” that the drug/biologic will treat, diagnose or prevent the disease/condition at issue?

- Once designated, sponsor is required to submit annual reports until drug is approved
The Orphan Drug Act has had strong impact and rare disease approvals are on the rise

Source: FDA Law Blog
# FDA Expedited Programs for Serious Conditions

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>Serious condition</td>
<td>Serious condition</td>
<td>Serious condition</td>
<td>Serious condition</td>
</tr>
<tr>
<td>Non-clinical or clinical data show potential to address unmet need</td>
<td>Preliminary clinical evidence shows potential for substantial improvement over current therapies</td>
<td>Meaningful advantage over available therapies AND effect on surrogate endpoint</td>
<td>Significant improvement in safety or effectiveness</td>
<td></td>
</tr>
<tr>
<td>Program</td>
<td>Designation</td>
<td>Designation</td>
<td>Approval Pathway</td>
<td>Designation</td>
</tr>
<tr>
<td>Features</td>
<td>Rolling review</td>
<td>Rolling review</td>
<td>Approval based on surrogate endpoint</td>
<td>Shorter clock for review of marketing application</td>
</tr>
<tr>
<td>Actions to expedite development and review</td>
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<td>Approval based on surrogate endpoint</td>
<td>\</td>
<td>Intensive guidance on efficient development</td>
</tr>
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Funding Sources

- Federal
- Industry – Orphan designation & incentives
- Foundation
- Multiple Sources
FDA Orphan Products Grant Program (R01)

- Phase 1 $250,000/year up to 3 years
- Phase 2 or 3 $500,000/year up to 4 years
- Must be conducted under an active IND
- Annual February deadline

http://www.fda.gov/forIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/default.htm
FDA Orphan Products Natural History Program (R01)

- Prospective natural history studies
  - up to $400,000/year for 5 years
- Retrospective natural history or survey studies
  - up to $150,000/year for 2 years
- October 15, 2018 deadline

http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/OrphanProductsNaturalHistoryGrantsProgram/default.htm
Validation of tools for outcomes assessment
• Maximum 5 years, no specific budgetary limit
• August 2017, February 2018 deadlines

NINDS Child Neurologist Career Development Program (K12)

• $85k Salary support, $38k research & travel support, 3 years
• Letter of intent deadline summer, annually
• Submission deadline August, annually

CNCDP Minority Research Scholars Program
Deadline, August 15, 2017

http://cncdp-k12.org/
References

