Overview of the Clinical Trials Process

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Drug: A substance intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.
Drug development is long, costly, inefficient

It takes ~10-15 years to develop a new drug

It costs ~$2,600 million (50-70% for rare diseases) to develop a new drug

55%-90% of drugs entering phase 1 clinical trial will fail*

*DiMasi et al., J. Health Econ, 2016; Hwang et al, JAMA, 2016
Lack of efficacy is the main reason for clinical failures

Hwang et al, JAMA, 2016
Clinical trial concepts: definition

<table>
<thead>
<tr>
<th>CONCEPTS</th>
<th>DEFINITION</th>
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<tbody>
<tr>
<td>Randomized placebo-controlled clinical trial</td>
<td>Trial has been designed well enough so as to be able “to distinguish the effect of a drug from other influences,” such as spontaneous change..., placebo effect, or biased observation&quot;</td>
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<tr>
<td>Placebo</td>
<td>A placebo is an inactive drug or treatment used in a clinical trial.</td>
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<tr>
<td>Open label</td>
<td>A trial in which no blinding is used and all parties are aware of the treatment groups is called open label or unblinded.</td>
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<tr>
<td>Primary endpoint</td>
<td>Primary outcome measured by a clinical trial to assess the effect of a drug. Primary endpoints are required for approval by regulatory agency.</td>
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<tr>
<td>Secondary endpoint(s)</td>
<td>Secondary endpoints are measures that may support the primary endpoints or demonstrate additional clinical effects.</td>
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Why placebo-controlled trials are important?

Hyperphagia change from baseline at 13 weeks
Why placebo-controlled trials are important?

Hyperphagia change from baseline at 13 weeks

Not statistically different
Why placebo-controlled trials are important?

Hyperphagia

No effect

Hyperphagia

Week 0  Week 2  Week 4  Week 6  Week 8
Why placebo-controlled trials are important?

Diagram showing the comparison between Placebo and Drug groups over 8 weeks.
The critical role of patients and caregivers in clinical trials

- Patient-centric design of clinical trials
- Representativity (age, symptoms, ethnicity, socio-economic) of the community in trials
- Design of meaningful clinical trial endpoints
- Gather evidence-based data on what matters to the community
- Involvement in the post-marketing period
Thank you!

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Additional Slides
## Clinical trials phases for new drugs

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
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<tbody>
<tr>
<td><strong>SAFETY and DOSE SELECTION</strong></td>
<td><strong>SAFETY/ EFFICACY</strong></td>
<td><strong>EFFICACY/ SAFETY</strong></td>
<td><strong>REAL-WORLD EVIDENCE</strong></td>
</tr>
<tr>
<td>10-20 patients</td>
<td>10-50 patients</td>
<td>100-300 patients</td>
<td>up to thousands patients</td>
</tr>
<tr>
<td>Short exposure</td>
<td>Short exposure</td>
<td>Longer exposure (2 months-1 year)</td>
<td>&gt;1 year</td>
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<tr>
<td><strong>First study in humans</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Multiple doses are tested</strong></td>
<td><strong>Efficacy</strong>: How well drug works?</td>
<td><strong>Efficacy</strong>: is the drug effective in comparison to placebo, do clinical benefits outweigh the risk?</td>
<td><strong>Long term effectiveness</strong>: how well the medicine works when used in the real-world</td>
</tr>
<tr>
<td>What is the dose where you see an effect, and where side effects appear?</td>
<td>Safety: How well is the drug tolerate? Does it distribute to the body? How long does the drug stay in the body?</td>
<td>Safety: expand safety assessments on the highest dose tolerated</td>
<td>Collect additional information about side-effects and safety, long-term risks and benefits</td>
</tr>
<tr>
<td><strong>Safety</strong>: How well is the drug tolerate? Does it distribute to the body? How long does the drug stay in the body?</td>
<td><strong>Must reach predetermined &quot;endpoints&quot;</strong></td>
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Regulatory incentives for orphan drug development

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<thead>
<tr>
<th></th>
<th>United States</th>
<th>Japan</th>
<th>Australia</th>
<th>European Union</th>
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<tbody>
<tr>
<td>Prevalence*</td>
<td>Fewer than 200,000 (6.25 per 10,000)</td>
<td>Fewer than 50,000 (4 per 10,000)</td>
<td>Fewer than 2,000 (1.1 per 10,000)</td>
<td>Fewer than 5 per 10,000</td>
</tr>
<tr>
<td>Market exclusivity</td>
<td>7 years</td>
<td>Re-examination period extended from 4 to 10 years</td>
<td>None</td>
<td>10 years</td>
</tr>
<tr>
<td>Fee waiver</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>At least partial</td>
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Protocol assistance
Tax credits
Accelerated approval strategies
(Priority Review, Breakthrough Therapy, Accelerated Approval, Fast Track)

Number of FDA approved orphan products by year
## Roadmap to Patient-Focused Outcome Measurement in Clinical Trials

### Understanding the Disease or Condition

1. **A. Natural history of the disease or condition**
   - Onset/Duration/Resolution
   - Diagnosis
   - Pathophysiology
   - Range of manifestations

2. **B. Patient subpopulations**
   - By severity
   - By onset
   - By comorbidities
   - By phenotype

3. **C. Health care environment**
   - Treatment alternatives
   - Clinical care standards
   - Health care system perspective

4. **D. Patient/caregiver perspectives**
   - Definition of treatment benefit
   - Benefit-risk tradeoffs
   - Impact of disease

### Conceptualizing Treatment Benefit

1. **A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:**
   - Survives
   - Feels (e.g., symptoms)
   - Functions

2. **B. Define context of use (COU) for clinical trial:**
   - Disease/Condition entry criteria
   - Clinical trial design
   - Endpoint positioning

3. **C. Select clinical outcome assessment (COA) type:**
   - Patient-Reported Outcome (PRO)
   - Observer-Reported Outcome (ObsRO)
   - Clinician-Reported Outcome (ClinRO)
   - Performance Outcome (motor, sensory, cognition)

### Selecting/Developing the Outcome Measure

1. **A. Search for existing COA measuring COI in COU:**
   - Measure exists
   - Measure exists but needs to be modified
   - No measure exists
   - Measure under development

2. **B. Begin COA development**
   - Document content validity (qualitative or mixed methods research)
   - Evaluate cross-sectional measurement properties (reliability and construct validity)
   - Create user manual
   - Consider submitting to FDA for COA qualification for use in exploratory studies

3. **C. Complete COA development:**
   - Document longitudinal measurement properties (construct validity, ability to detect change)
   - Document guidelines for interpretation of treatment benefit and relationship to claim
   - Update user manual
   - Submit to FDA for COA qualification as effectiveness endpoint to support claims