Decentralized Clinical Trials

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Disclosure

The views and opinions expressed in the following slides are those of the presenter and should not be constructed to represent the Food and Drug Administration view or policies.
Outline

Division of Dermatology and Dental Products

Drug Development and Approval Process

Decentralized Clinical Trials
Psoriasis patients have significantly higher values of Bleeding on Probing and Community Periodontal Index compared to matched controls. Psoriasis management should include regular dental exams.

Genetic factors, Pathophysiologic overlaps and Common risk factors

Woeste et al. The Journal of Investigative Dermatology, 2019
Our Team

- 21 physicians
  - 6 dermatologists, 1 pediatric dermatologist
  - IM, ID, nephrology, rheumatology, allergy/immunology, pediatrics, epidemiology
  - 1 dentist and 1 pediatric dentist
- 8 pharmacologists/toxicologists
- 5 project managers
- 2 administrative staff

Division of Dermatology and Dental Products
Review Team

- Medical Officer
- Chemist
- Pharmacologist/Toxicologist
- Clinical Pharmacologist
- Biostatistician
- Project Manager
- Others
2017 to present

- Approvals
  - 1 new drug applications (NDA)
  - 5 new biologic license application (BLA)
  - 12 supplemental applications
- > 130 meetings with industry

Division of Dermatology and Dental Products

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Drug Development and Approval Process

Decentralized Clinical Trials
Drug Development Process

De novo drug discovery and development  10-17 years

<10% overall probability of success

Ashburn and Thor Nature Reviews Drug Discovery, 2004
FDA CDER Mission

**PROMOTE PUBLIC HEALTH**
- Ensuring the availability of **safe and effective** drugs

**PROTECT PUBLIC HEALTH**
- Promoting the **safe use** of marketed drugs
- Ensuring the **quality and integrity** of marketed drugs
Ongoing FDA Support

- Pre-IND Meeting
- EOP1 Meeting
- EOP2 Meeting
- Pre-NDA/BLA Meeting
- Advisory Committee Meeting

- Preclinical
- Phase I
- Phase II
- Phase III
- Market Application Review
- Post-Action

- IND Submission
- Market Application Submission

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Drug Development and Approval Process

Decentralized Clinical Trials
Decentralized Clinical Trials

• Cost, Missed Opportunities and Barriers in Clinical Trials

• What are DCTs?
  – Potential Benefits
  – Challenges

• Case Studies: REMOTE trial
Transition and Approval Success

<table>
<thead>
<tr>
<th>Phase I - II</th>
<th>Phase II - III</th>
<th>Phase III - NDA/BLA Sub</th>
<th>NDA/BLA Sub - NDA/BLA App</th>
<th>Phase I - NDA/BLA App</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.5%</td>
<td>35.5%</td>
<td>62.0%</td>
<td>90.4%</td>
<td>11.8%</td>
</tr>
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</table>

Costs (2013 $, millions) per New Compound

NPR: Clinical Trials Still Don't Reflect The Diversity Of America

www.npr.org/sections/health-shots/2015/12/16/459666750/clinical-trials-still-dont-reflect-the-diversity-of-America
Diversity in Clinical Research

- Gender, race and ethnicity health disparities persist
- Physicians are informed by research in homogenous population - white and male
- Racial and ethnic minorities make 40% of the United States population
- Missed scientific opportunity
- Adequate representation - imperative as a matter of social justice, economics, and science

Oh et al. PLOS Medicine 2015
Diversity in Clinical Research

<table>
<thead>
<tr>
<th>Trait</th>
<th>Findings</th>
</tr>
</thead>
</table>

Oh *et al.* PLOS Medicine 2015
<table>
<thead>
<tr>
<th>Barriers to Participation</th>
<th>Number of studies pooled</th>
<th>n*</th>
<th>Proportion, % (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Dislike randomisation</td>
<td>5</td>
<td>719</td>
<td>38 (35-42)</td>
</tr>
<tr>
<td>Dislike possibility of placebo</td>
<td>3</td>
<td>1032</td>
<td>53 (50-56)</td>
</tr>
<tr>
<td>Inconvenience to everyday life</td>
<td>1</td>
<td>545</td>
<td>35 (31-39)</td>
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<tr>
<td>Potential side-effects</td>
<td>5</td>
<td>899</td>
<td>45 (37-55)</td>
</tr>
<tr>
<td>Trial not appropriate for diagnosis</td>
<td>1</td>
<td>246</td>
<td>24 (19-29)</td>
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<tr>
<td>Trial treatments not best option</td>
<td>2</td>
<td>791</td>
<td>44 (41-47)</td>
</tr>
<tr>
<td>Trial treatments offer no benefit</td>
<td>5</td>
<td>1016</td>
<td>24 (14-41)</td>
</tr>
<tr>
<td>Preference for other treatment</td>
<td>5</td>
<td>442</td>
<td>34 (20-58)</td>
</tr>
<tr>
<td>Not informed</td>
<td>4</td>
<td>662</td>
<td>23 (21-26)</td>
</tr>
<tr>
<td>Concern over cost or health insurance</td>
<td>2</td>
<td>255</td>
<td>17 (9-30)</td>
</tr>
<tr>
<td>Lack of family support</td>
<td>2</td>
<td>587</td>
<td>10 (3-30)</td>
</tr>
<tr>
<td>Dislike being experimented on</td>
<td>7</td>
<td>1851</td>
<td>19 (10-34)</td>
</tr>
<tr>
<td>Lose control over decision-making</td>
<td>5</td>
<td>650</td>
<td>23 (20-26)</td>
</tr>
<tr>
<td>Too uncertain</td>
<td>4</td>
<td>856</td>
<td>12 (10-14)</td>
</tr>
<tr>
<td>Quality of life might be reduced</td>
<td>2</td>
<td>590</td>
<td>55 (51-59)</td>
</tr>
<tr>
<td>Negative effect of physician-patient relationship</td>
<td>1</td>
<td>545</td>
<td>26 (22-29)</td>
</tr>
<tr>
<td>Physician should make decisions</td>
<td>4</td>
<td>435</td>
<td>38 (33-42)</td>
</tr>
<tr>
<td>Feels coerced to join</td>
<td>2</td>
<td>100</td>
<td>20 (10-29)</td>
</tr>
</tbody>
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Decentralized Clinical Trials

Not “All or Nothing”
Traditional Clinical Trials

Principal Investigator
Decentralized Clinical Trials

Principal Investigator
Clinical Trials Spectrum

Traditional  Hybrid  Decentralized
Decentralized Clinical Trials

- Highly Protocol Specific
- Fit for Purpose
- Patient-Reported Outcomes
- Adverse Event Reporting
- Technology and Limitations
Decentralized Clinical Trials

CTTI Recommendations: Decentralized Clinical Trials

September 2018
CTTI Potential Benefits of DCT

- Improved trial participant retention
- Greater control, convenience, and comfort for participants
- Faster trial participant recruitment
- Increased participant diversity
Decentralized Clinical Trials

• Demonstrate efficacy and safety
• Patient Focus
• Data management and integrity
• Regulatory Complexity
Roadmap to Demonstrating Efficacy
Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

1. Understanding the Disease or Condition
   - A. Natural history of the disease or condition
     - Onset/Duration/Resolution
     - Diagnosis
     - Pathophysiology
     - Range of manifestations
   - B. Patient subpopulations
     - By severity
     - By onset
     - By comorbidities
     - By phenotype
   - C. Health care environment
     - Treatment alternatives
     - Clinical care standards
     - Health care system perspective
   - D. Patient/caregiver perspectives
     - Definition of treatment benefit
     - Benefit-risk tradeoffs
     - Impact of disease
EXAMPLES
Tadalafil Interactive Clinical Trial

Eilenberg et al. Drug Information Journal 2004
Tolterodine REMOTE Trial

REMOTE - Research on Electronic Monitoring of OAB Treatment Experience

Orri et al. Contemp Clin Trials 2014
Tolterodine REMOTE Trial

**Participant**
- Web-based recruitment
- Web-based multi-media informed consent process
- Web-based screening

**Technology**
- Mobile communication device-based efficacy assessments (e.g., e-diary)
- Interactive remote data capture via secure participant portal
- Real-time data access for site, monitors, and auditors

**Investigator site**
- Coordinating function for virtual assessments: participant does not attend investigator site
- Study drug delivery to participants by overnight courier
- Study physician/call center available 24/7 by e-mail and phone
- Real-time processing of safety data
- Individual study data to each participant

Orri et al. Contemp Clin Trials 2014
Tolterodine REMOTE Trial Participants

Orri et al. Contemp Clin Trials 2014
Tolterodine REMOTE Trial

Baseline demographic and clinical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 6)</th>
<th>TOL ER (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6 (100)</td>
<td>12 (100)</td>
</tr>
<tr>
<td><strong>Mean (range) age, year</strong></td>
<td>46.2 (31–64)</td>
<td>48.4 (28–66)</td>
</tr>
<tr>
<td><strong>Race, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>OAB/UI diagnosis, n (%)</strong></td>
<td>6 (100)</td>
<td>12 (100)</td>
</tr>
<tr>
<td><strong>Mean (range) duration since diagnosis, year</strong></td>
<td>3.5 (1.2–15.7)</td>
<td>3.3 (1.3–30.3)</td>
</tr>
<tr>
<td><strong>Mean (SD) micturitions/24 hours</strong></td>
<td>9.9 (1.7)</td>
<td>11.5 (3.5)</td>
</tr>
</tbody>
</table>

OAB = overactive bladder, SD = standard deviation, TOL ER = tolterodine extended release, UUI = urge urinary incontinence.
59 novel drugs

- Rare Diseases
- Infectious Diseases
- Neurological Disorders
- Cancer and Blood Disorders
- Women’s Health
- Others
FDA Support

- Pre-IND Meeting
- EOP1 Meeting
- EOP2 Meeting
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Phases:
- Preclinical
- Phase I
- Phase II
- Phase III

Submissions:
- IND Submission
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