Clinical Trial Primer

Objectives

• Review basics of clinical trial design/implementation

• Highlight difficulties and controversial issues related to clinical trials

• Give examples of illustrative past clinical trials

• Serve as set up man for panel discussants & questions
Learning About Clinical Trials

A Guide for Individuals and Families Affected by Spinal Muscular Atrophy (SMA)

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Clinical Trials Definition

- Per World Health Organization
  - “For the purposes of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.”

- Does not always involve drug or medicine
- Procedure (surgery) or medical device (brace)
- Can also include natural history studies!
  - Usually (NOT always) to get FDA approval
Clinical Trials
Purpose

• Get FDA approval for new drug/procedure/intervention
  – OR new indication for established drug/procedure
• Compare two treatments/procedures (e.g. cancer trials)
• Evaluate supportive treatments/standard of care
• Evaluate biomarkers as surrogate markers for disease
• Determine natural history of disease
• Understand pathophysiology of disease better
  – How do we get from gene defect to muscle weakness?
  – Other organ involvement (e.g. GI tract)
• CLINICAL TRIALS ARE INVESTIGATIONS!
Phases of Clinical Trials

• Phase 1 - small # subjects looking at SAFETY, side effects, and dose. Often NOT placebo controlled! (1-2 years)

• Phase 2 - larger # subjects; safety & early look at efficacy; usually placebo controlled (1-2 years)

• Phase 3 - larger # to confirm effectiveness, monitor side effects, almost always placebo controlled (3-5 years)

• Phase 4 - after FDA approval; data collected on long term efficacy and side effects; effects in specific populations – Felbamate experience in 1993; 33 cases of aplastic anemia!
**SMA Drug Pipeline: June 2015**

This year, we are funding research with more breadth, depth, and diversity than ever before. This chart shows the drugs and therapies that are currently in the pipeline for SMA, including a few that are just steps away from potential FDA approval.

<table>
<thead>
<tr>
<th>BASIC RESEARCH SEED IDEAS</th>
<th>PRECLINICAL: DISCOVERY</th>
<th>CLINICAL DEVELOPMENT</th>
<th>FDA APPROVAL</th>
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<td><strong>IND</strong></td>
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<td>AurimMed Pharma/Small Molecule</td>
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<td>Harvard/Small Molecule</td>
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**IND** = Investigational New Drug  **NDA** = New Drug Application
Clinical Trials
Sobering Facts

• Researchers must prove scientifically that an investigational drug is safe AND effective in to submit it for approval.
• Only 1/1000 investigational drugs make it to human trials
• Only 10-15% of clinical trial drugs get eventual approval (.01%)
  – Lack of efficacy
  – Safety issues
  – Practical/manufacturing/strategy issues (e.g. cost, other drugs)
• Multistep process with “go-no go” decisions at each step
  – $$$$$$$$$$$$$$$
• Process takes 10-15 years or more for most drugs
Success Rate by Phase
Hey et al, 2014

NDA = New drug application
Reasons for Failures
Arrowsmith & Miller 2013

Causes of failure:
- Efficacy: 56%
- Safety: 28%
- Strategic: 5%
- Commercial: 5%
- Operational: 7%

Failure by therapeutic area:
- Oncology: 30%
- Central nervous system: 29.5%
- Musculoskeletal: 14%
- Infectious disease: 8.5%
- Cardiovascular: 8.5%
- Other: 9.5%

Phase II failures:
- 2008-2010: 51%
- 2011-2012: 35%

Phase III and submission failures:
- 2007-2010: 66%
- 2011-2012: 52%
Clinical Trials

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BUT

- Even a negative trial is valuable and informative
  - Eliminates drug/intervention from consideration
  - Provides information to better the next trial & get it right!
  - Improves SOC for studies AND for patients
- Don’t throw out baby with bath water!
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Selection & Outcome Criteria
Where the Rubber Meets the Road

• Inclusion criteria – what you need to get IN
  – Exclusion criteria – what you can’t have and still get in!
• Make sure trial hits target but representative population!
  – Reduce variables that can affect outcome!
  – Reduces time to recruit sufficient subjects
  – Make sure you can recruit enough patients for trial!
• Outcome criteria
  – Patient reported – how do they feel/look?
  – Strength related – is he/she getting stronger
  – Functional scales – which one and how does scale translate to everyday “real life”
• Do we need placebo?
Common SMA Study Criteria

- Age at SMA diagnosis or age at onset of symptoms
- Number of copies of the SMN2 gene
- Motor function
- Respiratory function
- Current health status and other medical conditions (not related to SMA)
- Surgical history, including prior or planned surgeries
- Current treatment or therapies for SMA
- Previous exposure to the investigational drug
- Previous exposure to other investigational drugs for SMA
- Recent participation in a clinical trial
- Distance from a participating clinical trial site
Cautionary Tale #1 Laetrile

- Amygdalin, vit B17
  - Apricots and almond pits
- Labeled “quackery” by ACS in 1972
- Taken by 50,000 cancer patients in 1970s
- Proven worthless by FDA & NIH
  - Possibly even toxic due to cyanide poisoning!
Cautionary Tale #2 - MT

- Cell Therapy Research Foundation (Memphis, TN)
  - “Refinements” to MT
- $150,000 per course
- $18 million pt. expenses
- ?? millions in donations
- Dateline NBC 1998!
- 6 independent scientific studies showed no effect in the 1990s

Myoblast Transferf in DMD
Peter Law, PhD
Cautionary Tale #2- MT

• FDAs inspection of your establishment from July 12 - September 15, 1999, disclosed serious deficiencies in quality control and product manufacturing …the clinical use of cells of questionable sterility or viability. …failure to conduct studies according to the study protocols and regulations for protecting the rights and safety of human subjects…..

• Still doing myoblast transfers in Singapore and recruiting via website!
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Clinical Trial Stakeholders

• Patients and families – ALWAYS most important
• Investigators – often multiple at multiple sites
• Academic centers – where studies occur with alphabet soup
  – IRB, EC, HIPPA, CTSA, GCRC
• Study sponsor – usually pharma or government agency ($)
  – Biotech companies with or without big pharma
• Lay organizations – both for funding and recruitment
• Regulatory agencies!