Randomized Withdrawal and Delayed Start Design in Rare Disease Clinical Trials

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United Therapeutics is a biotech company in Rare Disease Arena

**Pulmonary arterial hypertension:** Approximately 500-1000 new cases each year and total 50,000 patients in US

**Neuroblastoma:** Approximately 700 new patients each year in US
Challenges in Clinical Trial Design In Rare Diseases

- Small number of patients affected
- Small number of patients for clinical trials
- Limited understanding of the disease’s natural history
- Lack of well-defined study endpoints
- Limited early phase clinical trial data

Design a study to extract the most amount of knowledge from the limited number of participants.
• Enrichment design / Randomized withdrawal design

• Delayed start design / Delayed start analysis
Enrichment Design

- Selecting a study population more likely to show the treatment effect

- Pretty much all clinical trials have some sort of enrichment (inclusion/exclusion criteria)
- Select a study population that is
  - more homogeneous
  - more likely to show the treatment effect
  - more likely to tolerate the treatment

This is even more important in rare disease clinical trials
Enriched population -> with larger treatment effect -> smaller sample size needed

The downside: more difficult for patient enrollment

FDA (2012) Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products
Randomized Withdrawal Design

Run-in x weeks

Subjects who can tolerate the active treatment

Responders

Active Drug → R → Active Drug → R

Active

Placebo

Superiority

R – randomize
Delayed-Start Design

• One group receives active treatment and another group receives placebo during the first stage of the trial.
• Both groups receive active treatment during the second stage of the trial.
• The results in the second stage may show whether an effect is long term / disease modifying or short term / symptomatic.
• The positive results at the end of both stages provide strong evidence of efficacy.
Delayed-Start Analysis

- Two trials: First trial as typical RCT
  Followed by an OLE (open label extension) study
- Data from two studies are pooled for analysis – delayed start analysis

- Good results from delayed-start analysis can strengthen the efficacy evidence in rare disease clinical trials
Randomized Withdrawal versus Delayed Start Design

Randomized Withdrawal Design:
All patients receive active drug, then randomized to continue the active drug or placebo (withdrawal of the active drug)

Delayed Start Design:
Patients are randomized to receive active drug or placebo, then all patients receive active drug

Maximize the amount of information from the fewest patients
Randomized Withdraw Design

- Droxidopa in Symptomatic Neurogenic Orthostatic Hypotension

Biaggioni (2015) Randomized Withdrawal Study of Patients With Symptomatic Neurogenic Orthostatic Hypotension Responsive to Droxidopa
Randomized Withdraw Design

- Droxidopa in Symptomatic Neurogenic Orthostatic Hypotension

• 181 subjects participated in OL phase,
• Responders from OL phase are eligible for randomization
  Determined by improvement of at least one point on a symptom question (Orthostatic Hypotension Symptom Assessment (OHSA) Item 1) and an improvement in SBP of at least 10 mmHg at 3 minutes post-standing
• 101 responders are randomized in the double-blind phase (51 to placebo group)

• Despite its enrichment design, Study failed on its primary efficacy endpoint - the change from baseline in OHSA Item 1.

• Second study used a different endpoint show positive results – eventually resulted in FDA approval.
Randomized Withdrawal Design – ICE Study Example
- Immunoglobulin (IGIV) in CIDP (Chronic Inflammatory Demyelinating Polyneuropathy)

CIDP is debilitating chronic disorder caused by the damaged myelin sheaths in peripheral nervous system affecting both motor and sensory nerves in both legs and arms.

Patients have weakness, numbness, tingling, pain and difficulty in walking.

40,000 patients in the US
Randomized Withdrawal Design
- Immunoglobulin in CIDP (Chronic Inflammatory Demyelinating Polyneuropathy)

Hughes RAC et al Lancet Neurology 2008
Randomized Withdrawal Design
- Immunoglobulin in CIDP (Chronic Inflammatory Demyelinating Polyneuropathy)

Hughes RAC et al Lancet Neurology 2008
ICE Study: first randomized portion

<table>
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<th>IGIV</th>
<th>Placebo</th>
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<tr>
<td>n</td>
<td>59</td>
<td>58</td>
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<tr>
<td>Responder</td>
<td>32 (54%)</td>
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<td>Difference (95% CI)</td>
<td>33.5% (14.4% - 51.75)</td>
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<td>p-value</td>
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Hughes RAC et al Lancet Neurology 2008
ICE Study: re-randomized portion

Hughes RAC et al Lancet Neurology 2008
ICE Study Design: Advantages and Disadvantages

Disadvantages:
- Lengthy trial
- Loss some efficiency

Advantages:
- Two studies in one including randomized withdrawal
- Multiple endpoints (responder rate and time to relapse)

Drug (Gamunex-C) was approved in 2008 for CIDP (Chronic Inflammatory Demyelinating Polyneuropathy)
Delayed-Start Analysis

- Two trials: First trial as typical RCT
  Followed by an OLE (open label extension) study
- Data from two studies are pooled for analysis – delayed start analysis

- Good results from delayed-start analysis can strengthen the efficacy evidence in orphan drug trials
Delayed-Start Analysis
– RAPID study of A1PI augmentation therapy in Alpha-1 Antitrypsin Deficiency

Delayed-Start Design

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Delayed-Start Design
– ADAGIO study of Rasagiline in Idiopathic Parkinson’s Disease

Olanow et al (2009) NEJM
Delayed-Start Design
– ADAGIO study for Rasagiline in Idiopathic Parkinson’s Disease

Olanow et al (2009) NEJM
Delayed-Start Design
– ADAGIO study for Rasagiline in Idiopathic Parkinson’s Disease

Slope(rasagiline) – slope(placebo) = -0.05, p=0.0133; 95% CI: -0.08, -0.01
Curves are divergent

Week 72(early-start) – Week 72(delayed-start) = -1.7, p=0.025; 95% CI: -3.15, -0.21
UPDRS changes are different

Slope(early-start) – slope(delayed-start) = -0.0, 90% CI: -0.04, 0.04
Curves are non-convergent


Schematic illustration
Delayed-Start Design

– ADAGIO study for Rasagiline in Idiopathic Parkinson’s Disease

$slope_{\text{rasagiline}} - slope_{\text{placebo}} = -0.07, p<0.001; 95\% \text{ CI: } -0.11, -0.04$

Curves are divergent

$Week_{72(\text{early-start})} - Week_{72(\text{delayed-start})} = 0.36, p=0.603$

Changes are not different

Schematic illustration

Delayed-Start Design
– ADAGIO study for Rasagiline in Idiopathic Parkinson’s Disease

1 mg versus placebo: all three hypothesis tests are met
2 mg versus placebo: only the first hypothesis testing criterion met

FDA declined to grant the Rasagiline as a disease modifier therapy

Olanow et al (2009) NEJM
October 17, 2011 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee
Conclusion

Randomized Withdrawal Design and Delayed Start Design are useful in extracting the most amount of knowledge from the limited number of participants.

Randomized withdrawal design and delayed start design are especially useful in rare disease clinical trials.