A Mathematical Comparison of a "Randomized-Withdrawal" Clinical Trial Design and a Parallel-Groups Design to Demonstrate Disease Modification in Alzheimer's Disease (AD)

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Background

- Demonstration of Disease Modification in AD is a complicated methodological and regulatory issue that has been approached in several ways
- Among the strategies proposed are those based on measuring clinical outcomes in cross-over type studies:
  - "Randomized Withdrawal" design
  - "Staggered Start" design

  These two designs are complicated by ethical issues and long study durations leading to unbalanced dropout rates introducing bias
- A suggested alternative is a parallel-groups design assessing DM and symptomatic effects after adjusting for differences due to severity of disease at baseline
  - This analysis may be used to characterize a drug treatment that confers both disease modification and symptomatic benefit

Definitions

Disease-Modifying Effects ("Slope Effects")

- Clinical effects observed result from affecting the underlying disease process (pathology) in a way that does not depend on the continued presence of the drug
- Can be referred to as a "slope" effect, proportional to time, since the clinical benefit accumulates as drug continues to be given

Symptomatic Effects ("Shift Effects")

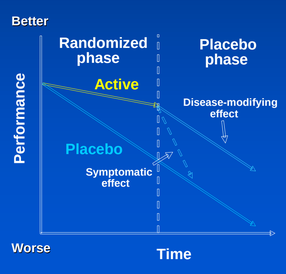
- Clinical effects observed result from affecting disease symptoms and not the underlying disease process (pathology)
- Can be referred to as a "shift" effect since the clinical outcomes are temporarily shifted while on drug

Refs: Leber 1997, Velas et al 2007, Mani 2004, Cummings 2007, Whitehouse et al 1998

Traditional Leber Designs*

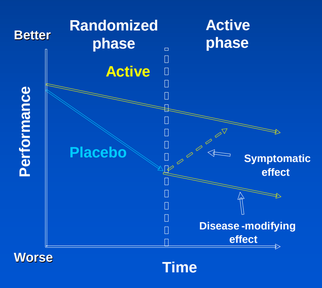
Randomized Withdrawal

- Are any treatments effects maintained over placebo when active treatment is stopped?



Staggered Start

- Do patients treated for a longer time maintain some benefit over newly treated patients?



*Leber 1997

Notation

- i=0 placebo in phase 1
  i=1 treatment in phase 1
- j=0, same treatment in phase 2 as phase 1
  j=1, different treatment in phase 2 – active
  j=-1, different treatment in phase 2 – placebo
- β = slope in phase 1
  φ = additional slope on drug if started later
  α = time 0 shift (beginning of phase 1)
  γ = time T1 shift (beginning of phase 2)

Model

$$\mu_{ij}(t) = \alpha_i + \beta_i(\min(t,T_1)) + jI_{t>T1}\,[\gamma_j + \varphi_j(t-T_1)] + \beta_i(\max(0,t-T_1))$$

$$\mu_{ij}(t) = \alpha_i + \beta_i(t) + jI_{t>T1}\,[\gamma_j + \varphi_j(t-T_1)]$$

$$Y_{ijk}(t) = \alpha_i + \beta_i(t) + jI_{t>T1}\,[\gamma_j + \varphi_j(t-T_1)] + \varepsilon_{ijk}$$

- 4 treatment arms:
  Group 1: i=0, j=0: Placebo group
  Group 2: i=0, j=1: Delayed active (Placebo -> Active)
  Group 3: i=1, j=0: Active group
  Group 4: i=1 j=-1: Active removed (Active -> Placebo)

Hypotheses

Null Hypothesis H_o is a Symptomatic Effect
Alternative Hypothesis H_a is a Disease-Modifying Effect

- Randomized Withdrawal

H_o: $\mu_{00}(T_2) = \mu_{1\text{-}1}(T_2)$: The mean for patients who were on placebo for both phases is equal at the end of the second phase to the mean for patients who were on drug for the first phase and on placebo for the second phase (i.e. patients removed from drug lose all drug effect)

H_a: $\mu_{00}(T_2) < \mu_{1\text{-}1}(T_2)$

- Staggered Start

H_o: $\mu_{01}(T_2) = \mu_{10}(T_2)$: The mean for patients who were on placebo for the first phase and drug for the second phase is equal at the end of the second phase to the mean for patients who were on drug for both phases (i.e. patients with delayed treatment "catch up" to patients with immediate treatment)

H_a: $\mu_{01}(T_2) < \mu_{10}(T_2)$

Simplification of Model for Randomized Withdrawal

H_o: $\mu_{00}(T_2) = \mu_{1\text{-}1}(T_2)$

$$\mu_{00}(t=T_2) = \alpha_0 + \beta_0 T_2 + 0*I_{T2>T1}\,[\gamma_0 + \varphi_0(T_2-T_1)] = \alpha_0 + \beta_0 T_2$$

$$\mu_{1\text{-}1}(t=T_2) = \alpha_1 + \beta_1 T_2 + -1*I_{T2>T1}\,[\gamma_{-1} + \varphi_{-1}(T_2-T_1)] = \alpha_1 + \beta_1 T_2 + -[\gamma_{-1} + \varphi_{-1}(T_2-T_1)]$$

So, H_o: $\alpha_0 + \beta_0 T_2 = \alpha_1 + \beta_1 T_2 + -[\gamma_{-1} + \varphi_{-1}(T_2-T_1)]$
H_o: $\alpha_0 + \beta_0 T_2 + \gamma_{-1} + \varphi_{-1}(T_2-T_1) = \alpha_1 + \beta_1 T_2$

And H_a: $\alpha_0 + \beta_0 T_2 + \gamma_{-1} + \varphi_{-1}(T_2-T_1) < \alpha_1 + \beta_1 T_2$

Simplification of Model for Staggered Start

H_o: $\mu_{01}(T_2) = \mu_{10}(T_2)$

$$\mu_{01}(t=T_2) = \alpha_0 + \beta_0 T_2 + 1*I_{T2>T1}\,[\gamma_1 + \varphi_1(T_2-T_1)] = \alpha_0 + \beta_0 T_2 + \gamma_1 + \varphi_1(T_2-T_1)$$

$$\mu_{10}(t=T_2) = \alpha_1 + \beta_1 T_2 + 0*I_{T2>T1}\,[\gamma_0 + \varphi_0(T_2-T_1)] = \alpha_1 + \beta_1 T_2$$

So H_o: $\alpha_0 + \beta_0 T_2 + \gamma_1 + \varphi_1(T_2-T_1) = \alpha_1 + \beta_1 T_2$

and H_a: $\alpha_0 + \beta_0 T_2 + \gamma_1 + \varphi_1(T_2-T_1) < \alpha_1 + \beta_1 T_2$

Proof of Equivalence for Randomized Withdrawal and Staggered Start Hypotheses

- For a staggered start, the hypotheses being tested are:
  H_o: $\alpha_1 + \beta_1 T_2 = \alpha_0 + \beta_0 T_2 + \gamma_1 + \varphi_1(T_2-T_1)$
  H_a: $\alpha_1 + \beta_1 T_2 > \alpha_0 + \beta_0 T_2 + \gamma_1 + \varphi_1(T_2-T_1)$
- For a randomized withdrawal, the hypotheses being tested are:
  H_o: $\alpha_1 + \beta_1 T_2 = \alpha_0 + \beta_0 T_2 + \gamma_{-1} + \varphi_{-1}(T_2-T_1)$
  H_a: $\alpha_1 + \beta_1 T_2 > \alpha_0 + \beta_0 T_2 + \gamma_{-1} + \varphi_{-1}(T_2-T_1)$

So if $\gamma_1 = \gamma_{-1}$ and $\varphi_{-1} = \varphi_1$, then the hypotheses are equivalent

- The effect gained by going onto drug from placebo is equal to the effect that would be lost by going off of drug at that same point, so $\gamma_1 = \gamma_{-1}$. Also, any additional slope effect that could be gained by going onto drug will be lost by going off of drug, so $\varphi_1 = \varphi_{-1}$

Natural History Staggered Start

- Theorem: The hypothesis that is tested by the Staggered Start and Randomized Withdrawal designs can also be tested in a study with a parallel-groups design
- Let ω_i represent the slope of the response with respect to baseline severity, or in other words, the coefficient of the interaction term between treatment and severity. This represents how much the shift effect varies over different baseline disease severities. Let ψi represent the slope of the response over time with respect to baseline severity or in other words, the coefficient of the interaction term between treatment, severity and time. This represents how much the slope effect varies over different baseline disease severities

Natural History Staggered Start (cont.)

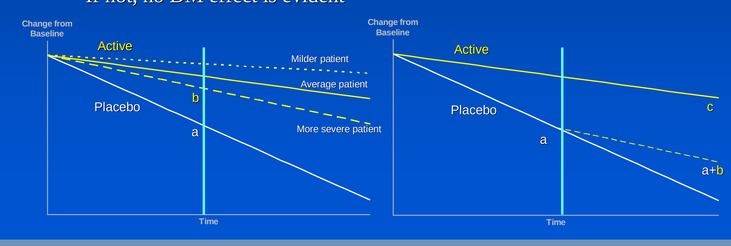
- The additional shift effect at the start of active drug (time T_1) is the difference between the treatment effect for the active drug and placebo ($\gamma_1 = (\omega_1 - \omega_0)$) at the point where baseline severity is equal to the average severity in the placebo group at time T_1 (at the point $\alpha_0 + \beta_0$). The additional slope at the start of active drug is the difference between the slope of the active group against baseline severity and the slope of the placebo group against baseline severity multiplied by the slope of the placebo group from time T_0 to time T_1 ($\varphi_1 = (\psi_1 - \psi_0)*\beta_0$)
- These values can be estimated by using the coefficients from the model fitting data to the first phase of the study if terms are included in the model for baseline severity, baseline severity by treatment group interaction and the baseline severity by treatment group by time interaction. Because these estimates rely on data from the first phase of the model, one assumption that is necessary is that the average severity of the placebo group after the first phase of the study is within the range of the original data values of baseline severity. The estimates of these coefficients will be extrapolations if the value $\alpha_0 + \beta_0$ is less than the minimum baseline severity

Natural History Staggered Start Analysis

1. Use primary model to estimate the placebo mean at an interim timepoint, for example halfway through the study (a)
2. Take the estimate from #1 (a) and add the estimated decline over the first half of the study for a treated patient of the same disease severity at treatment initiation (b)
3. Compare this new estimate (a+b) to the mean of the active group at the end of the study (c)

⇨ If the active group estimate (c) differs significantly from the estimated placebo + active group (a+b), then a DM effect has been demonstrated

If not, no DM effect is evident



Natural History Staggered Start Assumptions

- Requirements:
  - The range of disease severity of the patient population at entry into the study must include the expected mean severity of the placebo group at the end of the study or at the end of the time representing the first phase
  - Only data collected after shift effects are fully evident should be used to calculate slopes
  - The study duration must be long enough and sample size large enough to provide appropriate slope estimates
- There is an implicit assumption that the patients who are more severe at baseline are similar to placebo-treated patients who achieve that same severity after some time on placebo
- Although examples have been linear over time and over severity, these same principles and methods apply to non-linear patterns over time

Conclusions

- The Staggered Start and Randomized Withdrawal designs are mathematically equivalent (i.e. test equivalent hypotheses)
  - However, designs are impractical to demonstrate disease modification and have ethical concerns
- A novel and practical parallel-groups analysis – the Natural History Staggered Start – allows the same hypotheses to be tested without the complications of the cross-over designs
- Correcting for severity effects allows estimation of the true slope (disease modification) effect
- This analysis method is not limited to AD but is generally applicable to measuring disease modification in any chronic degenerative disease

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