**Background**

Characterization of Disease Modification (DM) in AD is AD is a complicated task that has been approached in many ways.

- Among the many approaches proposed are those based on measuring clinical outcomes in a cross-over type study.
  - Randomized Withdrawal design
  - "Staggered Start" design

These two designs are complimentary for different issues and long study durations leading to long dropout rates confounding bias.

A suggested alternative is a parallel groups design assuming DM and symptomatic effects after adjusting for differences due to severity of disease at baseline.

This analysis may be useful in determining if the treatment is better than discounting in both disease modification and symptomatic benefit.

**Disease Modifying Effects ("Slope Effects")**

- One of the benefits of the random withdrawal is offering the underlying disease pathology (i.e. that does not depend on the continued presence of the drug).
- Can be converted to a "slope" effect proportional to the length of the treatment period. The slope effect is significant if the clinical outcomes are expanding from placebo at the initial point.

**Symptomatic Effects ("Shift Effects")**

- Clinical effects observed usually reflecting disease symptoms at the time of treatment effects.
- Can be converted to a "shift" effect proportional to the length of the treatment period. The clinical effect is significant if the clinical outcomes are improving from placebo at the initial point.

**Model**

- \( y(i, j, t) = \beta_i(T2) + \gamma_j(T1) + \phi_{ij}(t) \)
- \( \beta_i(T2) \) = the slope of the response with respect to baseline severity
- \( \gamma_j(T1) \) = the slope of the response with respect to treatment
- \( \phi_{ij}(t) \) = the interaction term between treatment, severity and time.

**Simplification of Model for Randomized Withdrawal**

- \( H_0: \beta_i(T2) = \gamma_j(T1) \)
- \( H_a: \beta_i(T2) > \gamma_j(T1) \)

**Simplification of Model for Staggered Start**

- \( H_0: \beta_i(T2) = \gamma_j(T1) \)
- \( H_a: \beta_i(T2) > \gamma_j(T1) \)

**Conclusions**

The Staggered Start and Randomized Withdrawal designs can also be tested in a study with a parallel groups design.

- Let \( \gamma \) represent the slope of the response with respect to baseline severity, at regular intervals, the coefficient of the interaction term between treatment and severity. This represents how much the treatment effect varies over different baseline disease severities.

**Notation**

- \( p \): placebo in phase 1
- \( a \): treatment in phase 1
- \( p \): placebo in phase 2
- \( a \): treatment in phase 2
- \( p \): placebo in phase 3
- \( a \): treatment in phase 3

**Hypotheses**

- **Randomized Withdrawal**
  - \( H_0: \gamma = 0 \)
  - \( H_a: \gamma > 0 \)

- **Staggered Start**
  - \( H_0: \gamma = 0 \)
  - \( H_a: \gamma > 0 \)

**Proof of Equivalence for Randomized Withdrawal and Staggered Start Hypotheses**

- For a staggered start, the hypothesis being tested are:
  - \( H_0: \gamma = 0 \)
  - \( H_a: \gamma > 0 \)

- For a random withdrawal, the hypothesis being tested are:
  - \( H_0: \gamma = 0 \)
  - \( H_a: \gamma > 0 \)

**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.

**Natural History Start at Phase 1 (cont.)**

- \( H_0: \gamma = 0 \)
- \( H_a: \gamma > 0 \)

**Assumptions**

- The range of disease severity of the patient population at entry into the study must include the expected mean severity of the placebo group.
- The study duration must be long enough and sample size large enough to calculate slopes.
- These values can be estimated by using the coefficients from the model fitting data to these same principles and methods apply to nonlinear patterns.

**Randomized Withdrawal**

- Take every patient for treatment and see if any effects are treatment or placebo.

**Staggered Start**

- Take every patient for a longer time (minimum 6 months) and then place them in placebo.

**References:**


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