Introduction to Interim Analysis for Behavioral Studies

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The primary reason why interim analyses are needed

- To monitor the progress of a study

Need for Monitoring a Trial

Need for Monitoring a Trial

- Ethical concerns
  - Subjects already on trial
    - Avoid continued administration of harmful treatments
    - Maintain validity of informed consent

Need for Monitoring a Trial

- Ethical concerns (cont.)
  - Subjects not yet on trial
    - Start treatment with best therapy
    - Ensure informed consent valid

Need for Monitoring a Trial

- Ethical concerns (cont.)
  - Subjects never on trial
    - Facilitate rapid introduction of beneficial treatments
    - Warn about risks of existing treatments

Need for Monitoring a Trial

- Efficacy considerations
  - Fewer subjects may be needed on average
    - Decrease costs associated with number of subjects
  - Time savings
    - Decrease costs associated with monitoring subjects

Need for Monitoring a Trial

- Futility considerations: Efficacy and Ethics
  - Efficiency
    - Stop a study when it is known (or reasonably certain) that no effect will be demonstrated
    - Can perform more studies with limited resources
  - Ethics
    - Is it ever ethical to expose subjects to experimental treatments when no meaningful information will be gained?
    - Can devote resources to study of more promising treatments

Criteria for Stopping a Trial

Criteria for Stopping a Trial

- Sufficient evidence available to be confident of rejecting specific hypotheses
  - Stopping early for
    - Efficacy (superiority)
    - Equivalence
    - Harm (inferiority)

Criteria for Stopping a Trial

- Test of a two-sided alternative ($\theta_+ > \theta_0 > \theta_-$)
  - Upper alternative: $H_+ : \theta \geq \theta_+$
  - Null: $H_0 : \theta = \theta_+$
  - Lower alternative: $H_- : \theta \leq \theta_-$
- Decisions
  - Reject H_0, H_- (for H_+) $\longleftrightarrow$ $T \geq c_U$
  - Reject H_+, H_- (for H_0) $\longleftrightarrow$ $c_L \leq T \leq c_U$
  - Reject H_+, H_0 (for H_-) $\longleftrightarrow$ $T \leq c_L$

Criteria for Stopping a Trial

- Futility of demonstrating effect that would change behavior
  - Stopping early for futility
    - Not sufficiently superior
    - Not dangerously harmful

Criteria for Stopping a Trial

- And there is no advantage of continuing
  - Even if confident of ultimate decision about primary endpoint, may want to continue trial to gain more information on
    - Safety
    - Longer term follow up
    - Gather additional data on secondary outcomes

Criteria for Stopping a Trial

- Statistical basis for stopping criteria
  - Group sequential test
    - Sufficient evidence to make decision in classical frequentist framework.
    - Type I and II errors controlled at desired levels.

Criteria for Stopping a Trial

- Sequential monitoring of a trial
  - Data are analyzed after accrual of each observation
    - (Group sequential monitoring: Analysis after groups of observations accrued)
    - Analyses must take into account the repeated analyses of the same data
      - Sampling distributions of the test statistic is altered.
      - Frequentist properties are altered.

Criteria for Stopping a Trial

- Repeated significance testing
  - Continuous monitoring:
    - Reject H_0 the first time

$$\overline{X_{Nj}} > \mu_0 + Z_{1-\alpha}\frac{\sigma}{\sqrt{N_j}}$$

$$\overline{X_{Nj}} < \mu_0 - Z_{1-\alpha}\frac{\sigma}{\sqrt{N_j}}$$

Criteria for Stopping a Trial

- Repeated significance testing
  - Monitoring after each of J groups of observations:
    - Analyses at N_1, N_2, …., N_J
    - Reject H_0 the first time

$$\overline{X_j} > \mu_0 + Z_{1-\alpha}\frac{\sigma}{\sqrt{j}}$$

$$\overline{X_j} < \mu_0 - Z_{1-\alpha}\frac{\sigma}{\sqrt{j}}$$

Stopping Rules

Stopping Rules

- Basic Strategy
  - Find stopping boundaries at each analysis such that desired operating characteristics (e.g., type I and type II statistical errors) are attained.

Stopping Rules

- Issues
  - Conditions under which the trial might be stopped early
  - When to perform analyses
  - Test Statistics
  - Relative position of boundaries at successive analyses
  - Desired operating characteristics

Stopping Rules

- Choice of Test Statistic
  - Let $T_n (X_1, \ldots, X_n)$ be any test statistic such that Tn tends to be larger for larger values of θ.

Stopping Rules

- Choice of Test Statistic T_n
  - Sum of observations
  - Point estimate of treatment effect
  - Normalized (Z) statistic
  - Fixed sample P value
  - Error predicting function
  - Conditional probability
  - Predictive probability
  - Bayesian posterior probability

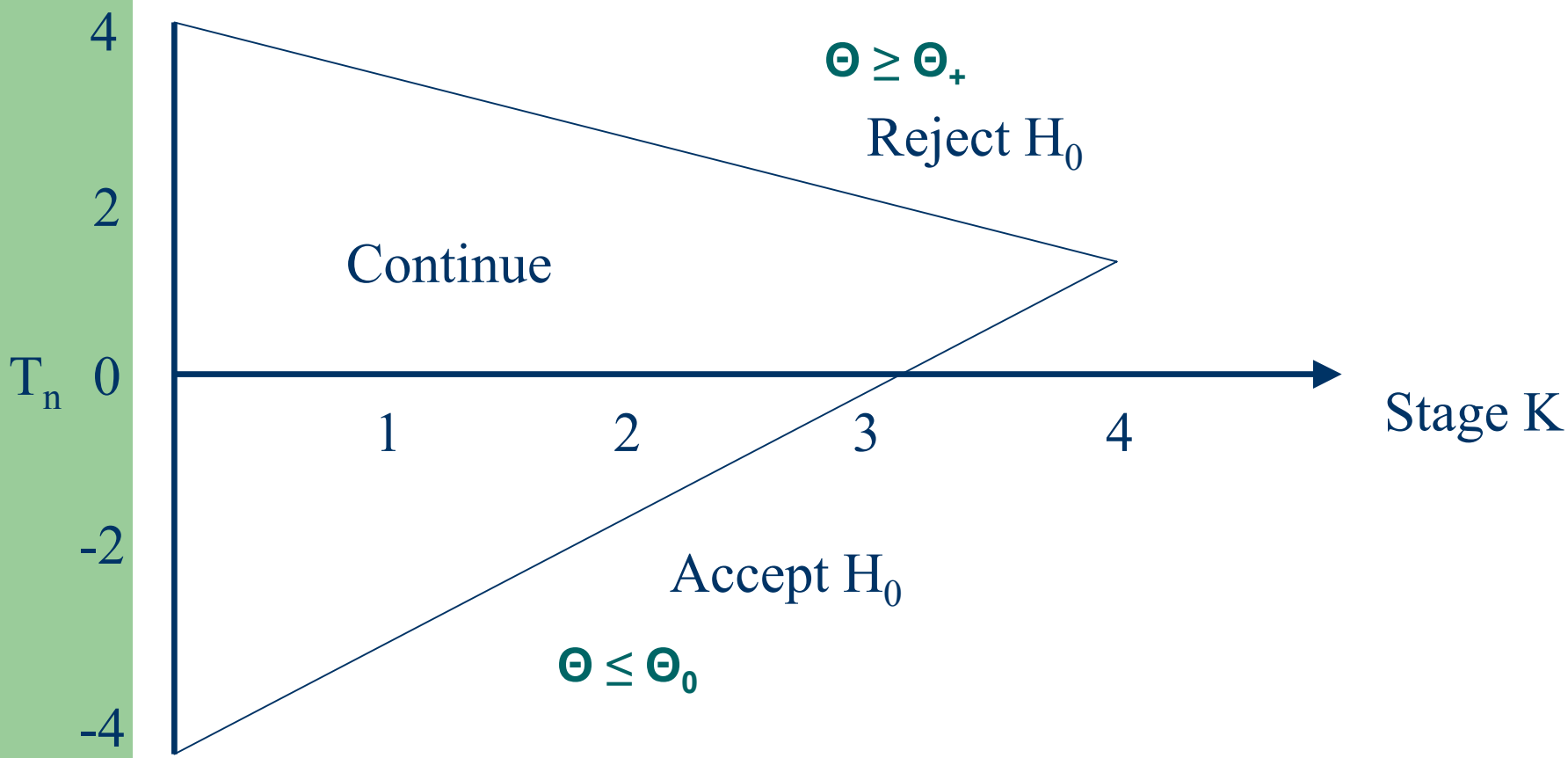
Stopping Rules

- Choice of Test Statistic T_n
  - All of those choices for test statistics can be shown to be transformations of each other
  - Hence, a stopping rule for one statistic is easily transformed to a stopping rule for a different statistic
  - We regard these statistics as representing different scales for expressing the boundaries.

Stopping Rules

- Conditions for early stopping: One-sided tests
  - Test of a greater alternative ($\Theta_+ \geq \Theta_0$)
    - Null: $H_0: \Theta \leq \Theta_0$
    - Alternative: $H_1: \Theta \geq \Theta_+$
  - Possibilities for early stopping:
    - Stop only for the null (when T_n is small)
    - Stop only for the alternative (when T_n is large)
    - Stop either for the null or for the alternative

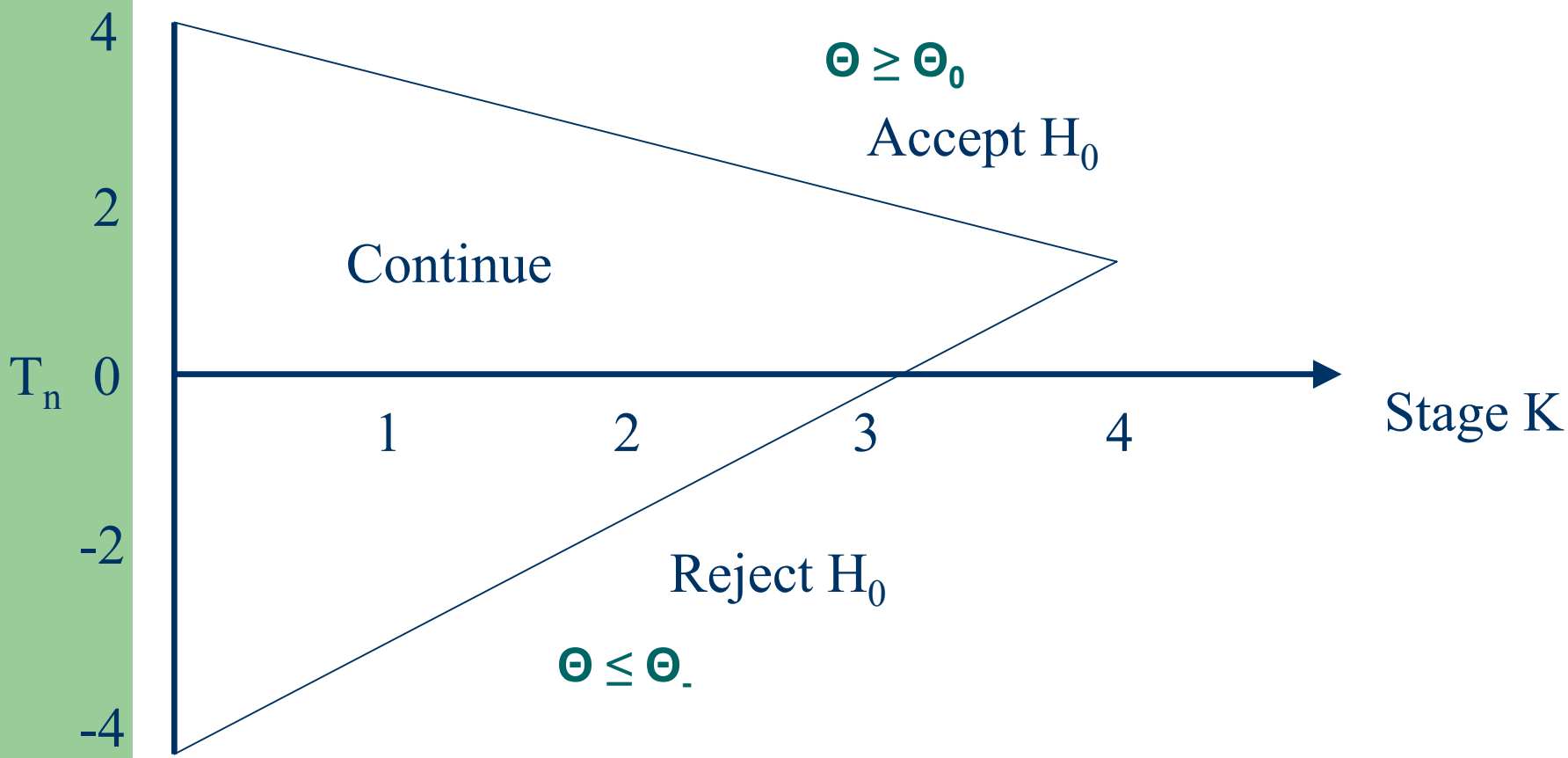
One-sided Test of a Greater Alternative with Four Groups of Observations.



Stopping Rules

- Conditions for early stopping: One-sided tests
  - Test of a lesser alternative ($\Theta_+ \geq \Theta_0$)
    - Null: H_0: $\Theta \geq \Theta_0$
    - Alternative: H_1: $\Theta \leq \Theta_-$
  - Possibilities for early stopping:
    - Stop only for the null (when T_n is small)
    - Stop only for the alternative (when T_n is large)
    - Stop either for the null or for the alternative

One-sided Test of a Lesser Alternative with Four Groups of Observations.



Stopping Rules

- Conditions for early stopping: Two-sided tests
  - Test of a two-sided alternative ($\Theta_+ \geq \Theta_0 \geq \Theta_-$)
    - Upper Alternative H_+: $\Theta \geq \Theta_+$
    - Null: H_0: $\Theta = \Theta_0$
    - Lower Alternative: H_-: $\Theta \leq \Theta_-$
  - Possibilities for early stopping:
    - Stop only for the null (when T_n intermediate)
    - Stop only for the alternative (when T_n small or large)
    - Stop either for the null or for the alternative

Two-sided Test with Four Groups