Endpoints, Secondary Endpoints, Alpha-spending, Ranking

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Composite of multiple clinical events

e.g., death or heart failure hospitalization, death or ICD event

Time to first occurrence of the event

This only applies to the treatment effect in an overall sense.

What about multiple non-fatal events in patients?

In some scenarios, recurrent events signify disease progression, whereas in others may not.

Recurrent events may constitute a “storm” that may or may not signify worsening health status or equivalence to a reversible outcome or death.

Poor health status after a single event or a series of multiple events may be relevant for consideration in analysis.

Ranking in statistical analysis

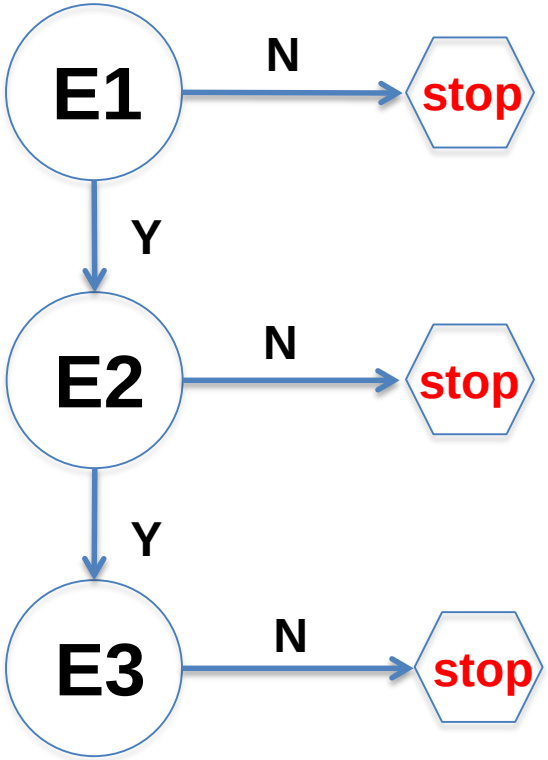
Patient is assigned a rank (a score) based on their health condition resulting from their total events. Compare each patient with all other patients based on a rank, then perform Wilcoxon rank analysis.

What is the best way to describe treatment effect on each component endpoint after the composite endpoint shows a significant treatment effect?

What is a secondary end point?

- May be part of a formal analysis plan, but not get (all of its) alpha initially allocated
  - Implications for claim reasonably understood.
- May not be part of a formal alpha-conserving plan at all
  - Implications for claim are less clear.

Hierarchical Testing of Endpoints



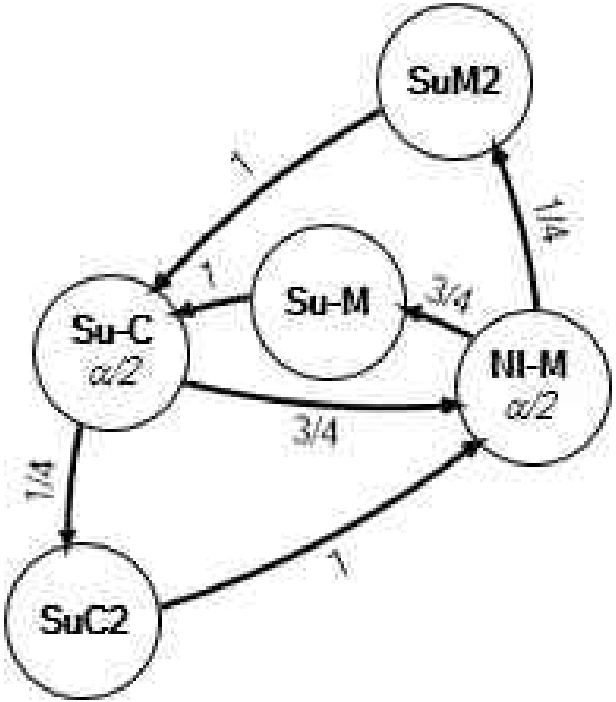
Statistical power of each endpoint can be grossly misunderstood

Suppose the desired power for testing each end point is 90%. If the three endpoints are at most mildly correlated, then actual statistical power for E2 is 81% and for E3 is 73%.

A potentially smarter method for testing multiple endpoints: alpha-passing concept

When a null hypothesis is rejected, its alpha can be reused for testing other null hypotheses for testing in a *pre-specified* algorithm (e.g., Bretz et al.).

Bretz diagram for a study of Aliskiren±Enalapril vs Enalapril



- Two “primary” hypotheses
- Depending on what nulls get rejected, alpha can go…
  - To 3 “secondary” hypotheses
  - Back to re-test a “primary”

- Even in a formal alpha-conserving plan, it may not be clear what “secondary” means

Relationship to claims (1)

- Win as part of formal analysis plan considered as valid as rejection of the primary null.
- If the primary claim is more important, we might take a win at non-extreme p-value for the secondary.
- In general, should not include things in the formal analysis plan that aren’t likely to get a claim.

End points not part of formal alpha-conserving analysis plan

- Mortality
- Variations on another (possibly sustained) end point
  - Components of a composite end point
  - Subgroups (±prespecified)
  - Temporal features
- Mechanistic

Relationship to claims (2)

- Win not part of formal analysis plan might yield a claim.
- It is not entirely clear when a data presentation or verbal description in a label is a “claim”.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