Multiplicity Issues in FDA-Reviewed Clinical Trials

EMA Workshop on Multiplicity Issues
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Note

A regulatory FDA guidance is under preparation on the topic of Multiple Endpoints in Clinical Trials. The draft guidance has not yet been released for public comment.
Key Multiplicity Issue: Defining ‘Claim’

• Ensure that all important ‘claims’ have overall Type I error rate control

• Regulators are charged with making two types of decisions:
  – Should this drug be approved?
  – If so, what information should be included in labeling?

• What constitutes a claim?
  – Indication only? (approval decision)
  – Any primary or secondary endpoint?
  – Any statement that appears in labeling?
How Far Should Error Rate Control Extend?

Continuum for Type I Error Control

→ To all primary and secondary endpoints
→ Overall error rate should not exceed $\alpha$
Endpoint Families

- **Primary Endpoints**
  - Endpoint(s) necessary and/or sufficient to establish efficacy (define a successful trial)

- **Secondary Endpoints**
  - Not sufficient to establish efficacy in the absence of an effect on the primary endpoints; not required for establishing efficacy
  - Potentially could lead to additional labeling claims

- **Exploratory Endpoints**
  - Hypothesis generating endpoints (clinical utility unknown)
  - Variations on primary or secondary endpoints (alternate ‘responder’ definitions, alternate timepoints)
Challenging Cases – Which Family?

• (Possibly underpowered) mortality endpoint
  – Primary or secondary?
  – Ideally, primary (if sufficient to determine efficacy), however may not always be feasible

• Minor variations in endpoints (alternate responder definitions, alternate timepoints)
  – Secondary or exploratory?
  – Do these represent ‘new claims’?
  – Many may not need to be under Type I error control
What is Permissible for Labeling?

• Primary endpoints (multiplicity controlled)

• Secondary endpoints that provide clinically meaningful information (multiplicity controlled)
  – Not all may qualify—being multiplicity-controlled not a guarantee that the endpoint belongs in labeling
  – Role for non-significant secondary endpoints? May provide useful information on endpoints that characterize the indication

• Descriptive or graphical extensions of endpoints that established efficacy (not new claims)
  – time course trends
  – full distribution (histogram or cumulative distribution graph)
  – descriptive subgroups
  – components of composite endpoint
Targeted Subgroups

• Want approval for the most general population for which the drug product is efficacious (target subgroup or whole population)

• Not the same as the most general population for which the hypothesis test is statistically significant (‘average effect’ may be significant, but comes from averaging a large effect and no effect)

• Challenging area – needs careful thought on defining the hypotheses and how best to characterize the effect on the non-target subgroup
Additional Multiplicity Challenges

• How to handle situations where different regulatory bodies request different primary endpoints?
  – Is a ‘within-regulatory-body’ multiplicity plan sufficient?

• Are methods that pass $\alpha$ from secondary endpoints back to primary endpoints permissible?

• When are procedures that rely on additional assumptions (e.g. Hochberg’s) permissible? How much justification is needed?
Mismatch of Study Goals and Procedures

- Overuse of sequential methods
  - Multiple dose studies (natural ordering, but might regret consequences)
  - Secondary endpoints (usually not naturally ordered)

- For complex designs, how can we ensure that sponsors and reviewers can determine whether the multiplicity is controlled?
  - Intuition is often not sufficient
  - Literature findings misused or not trickling down to users
Key Message

• Carefully select the most appropriate hypotheses
  – Choose ‘need to have’ endpoints, but don’t pile on ‘nice to have’ endpoints
  – Put the endpoints in the right families
  – Carefully consider which hypotheses represent distinct claims, and ensure all ‘claims’ are covered under the multiplicity control structure

• Ensure a good match between the study objectives and the multiplicity control methods
  – Utilize natural hierarchies (but avoid arbitrary ones)
  – Take the time to understand complex structures to ensure overall control