Multiplicity Issues in FDA-Reviewed Clinical Trials

EMA Workshop on Multiplicity Issues

Kathleen Fritsch, Ph.D.
FDA/CDER/OTS/DBIII

November 16, 2012

Note

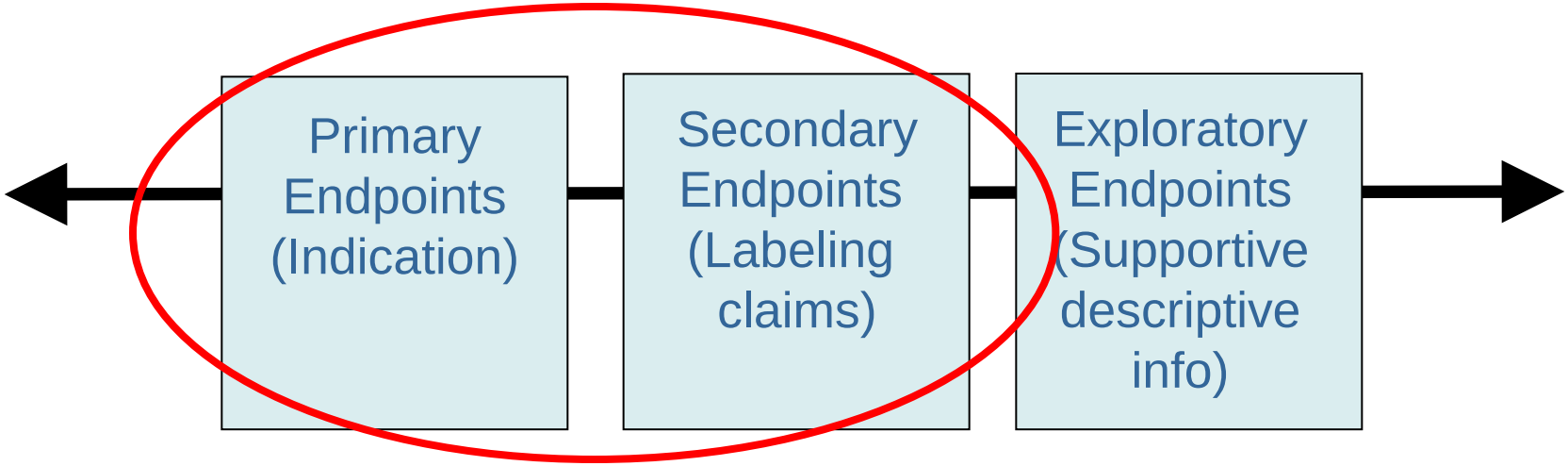
A regulatory FDA guidance is under preparation on the topic of Multiple Endpoints in Clinical Trials. The draft guidance has not yet been released for public comment.

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 α

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 α 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