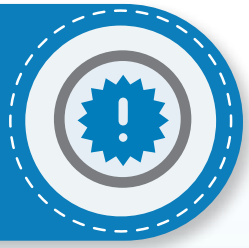
U.S. FOOD & DRUG ADMINISTRATION

Multiple Endpoints in Clinical Trials
Guidance for Industry

What Is Covered in This Guidance?

This guidance reflects FDA's thinking about analysis, interpretation, and management of issues related to the use of multiple endpoints in clinical trials. Strategies for grouping and ordering endpoints for analysis of a drug's effects and statistical methods to control the chance of making erroneous conclusions about drug effects are discussed.



Why is this guidance important?

Most clinical trials in drug development contain multiple endpoints to document the ability of the drug to affect one or more disease characteristics. When more than one endpoint is analyzed in a clinical trial without appropriate adjustment, the likelihood of making false conclusions about a drug's effects may be increased. This guidance recommends strategies that will allow for appropriate assessments of drug effects when multiple endpoints are used.

The Hierarchy of Families of Endpoints

Because diseases may have multiple clinical manifestations, studies may sometimes use multiple endpoints or endpoints that incorporate multiple aspects of the disease to establish efficacy.

Endpoints in adequate and well-controlled drug trials are usually grouped hierarchically in the following categories according to their clinical importance. Each category in the hierarchy may contain a single endpoint or a family of endpoints.

What is multiplicity?

Multiplicity is the existence of many comparisons in a clinical trial which, without appropriate statistical adjustments, can lead to a higher-than-intended rate of making false conclusions about a drug's effect. A focus of this guidance is the appropriate planning of primary and secondary endpoints of a clinical trial to ensure that the major findings of a clinical trial are well supported.

PRIMARY ENDPOINTS

- Establish the effect(s) of the drug
- Are the basis for concluding that the study meets its objectives

SECONDARY ENDPOINTS

- May extend understanding of an effect related to the primary endpoint or provide evidence of a distinct clinical benefit
- Should be included in the prospective statistical analysis plan if they provide evidence of additional effects of the drug

EXPLORATORY ENDPOINTS

- Generally not used to support definitive conclusions, so multiplicity adjustment not needed

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. **To learn more about the multiple endpoints in clinical trials, read the guidance:**

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry

Circumstances for Using Different Types of Multiple Primary Endpoints

CO-PRIMARY ENDPOINTS

Used when a treatment effect on all of two or more clinical features is critically important to demonstrate efficacy

- The chance of making an erroneous conclusion of efficacy based on co-primary endpoints is reduced compared to the use of any single endpoint.
- The chance of failing to detect beneficial effects may be increased

MULTIPLE PRIMARY ENDPOINTS

Multiple Primary Endpoints where a treatment effect on any one of these endpoints is sufficient to support a conclusion of effectiveness

- It is critical to develop a prospective plan to address the chance of erroneously detecting an effect that is not present.
- A variety of approaches to address multiplicity are described in the guidance

COMPOSITE ENDPOINTS

Important clinical outcomes are combined into a single primary endpoint

- When a single statistical test is performed on the composite endpoint, there is no multiplicity problem
- Choice of, and effects on, the components should be examined with care
  - » Clinical importance of components may be substantially different
  - » There is a possibility that there can be an effect on a composite endpoint when there is no effect on the most important components but there is a large effect on less important components
  - » Overall outcome may have a favorable result even with adverse effects on an important component
  - » Assessment of clinical meaningfulness may be important
  - » Pre-specification and multiplicity adjustment is important to support conclusions about treatment effect on specific components

MULTI-COMPONENT ENDPOINTS

Within-patient combination of two or more components

- Each patient gets an overall rating based on observation of all specified components according to specified rules
- May be efficient if within-subject component effects generally trend in the same direction
- The chance of detecting a beneficial effect may be adversely affected if there is limited concordance among component endpoints
- Evaluation of components involves similar considerations as for composite endpoints

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Background About the Guidance

The ICH guidance for industry E9 Statistical Principles for Clinical Trials (September 1998) is a broad guidance that includes discussion of multiple endpoints. This guidance provides greater detail on this topic and corresponds with an FDA commitment under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

Guidance Recommendations Apply Throughout the Drug Development Timeline

During Clinical Development: FDA recommends that sponsors considering the use of multiple endpoints should prospectively specify all planned endpoints, time points, analysis populations, and analyses in the study protocol or statistical analysis plan. Sponsors should consider the variety of methods available to control the likelihood of making false conclusions about drug effects and in the prospective analysis plan select the most powerful method that is suitable for the design and objective of the study.

Guidance Recap Podcast – Hear Highlights Straight From FDA Staff

Speaker: John Lawrence, PhD, statistician in CDER's Office of Biostatistics

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