Elements of a Phase 3 IND Study Protocol

An FDA Statistical Perspective

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Disclaimer

The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

Outline

- FDA CBER structure
- Product review process
- Motivation for checklist
- Protocol components
- Summary

Center for Biologics Evaluation and Research (CBER)

- CBER's mission

  to protect and enhance the public health through the regulation of biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies.

- 3 product offices
  - Vaccines
  - Cell, Tissue and Gene Therapy
  - Blood

Review Teams

- Multidisciplinary
  - Biologist
  - Pharmacologist/Toxicologist
  - Clinician
  - Biostatistician
- Primary review discipline changes depending on product review stage

Product Review Process

- Pre-IND* meeting (at sponsor request)
- Phase 1 IND study
- Phase 2 IND study
- End-of-Phase 2 meeting (at sponsor request)
- Phase 3 IND study
- Marketing application
- Post-marketing study

*IND = Investigational New Drug

Motivation for List of Protocol Elements

- Developed for Phase 3 studies
- Improve efficiency and consistency
- May lead to less correspondence with the sponsor
- Aid to statistical reviewers
  - Not a formal review document
  - Not prescriptive or a guidance

Clinical Trial Protocol

Primary regulatory concerns

- Study design and statistical analysis methods are appropriate for objectives
- Sample size provides adequate power to detect treatment effect

Protocol Elements

- Categories
  - Background of the product
  - Objectives and endpoints
  - Study subjects
  - Study design
  - Statistical analysis
  - Study conduct
- Check off item if:
  - Sponsor addressed item
  - Reviewed item

Objectives and Endpoints

- Primary and secondary objectives
- Primary and secondary endpoints
- Consistency between endpoints and objectives

Study Design (1)

- Treatment arms
  - parallel, single arm, crossover …
- Control group(s)
  - usually placebo or active control for pivotal trials
  - historical or self-control acceptable under specific circumstances

Study Design (2)

- Randomization
  - ratio
  - stratification variables
- Blinding
  - single, double, open-label
  - justification

Study Design (3)

- Hypotheses
  - superiority, non-inferiority, equivalence
  - appropriate for study objectives
- Sample size
  - assumptions used and justifications
  - consistent with primary endpoint and analysis method
  - adequate power to reject the null hypothesis at the pre-determined significance level

Study Design (4)

- Complex design (adaptive, Bayesian…)
- Interim analyses
  - purpose (efficacy, safety, futility)
  - stopping rules
  - schedule for interim looks
  - access to unblinded results

Statistical Analysis (1)

- Approach
  - hypothesis testing
  - p-value
  - confidence intervals
- Success criterion specified

Statistical Analysis (2)

- Statistical method
  - Consistent with objective, hypothesis, endpoint
  - Data dependent
    - Demographic (*descriptive*)
    - Continuous (*t-test, ANOVA)*)
    - Proportion (*Chi-square, Fisher's exact*)
    - Count (*Poisson*)
    - Time-to-event (*log-rank, hazard ratio*)
  - Include stratification variables?
  - Other covariates (baseline,…)?

Statistical Analysis (3)

- Analysis population
  - intent-to-treat (ITT)
  - per protocol (PP)
  - subgroups (age, gender, race, site, …)
- Control of type 1 error rate
  - multiple primary endpoints
  - multiple comparisons
  - interim analysis

Statistical Analysis (4)

- Missing Data
  - addressed?
  - justification for procedure
  - sensitivity analyses
- Analysis plan for safety
  - usually descriptive

Study Conduct

- Data Monitoring Committee (DMC)
- Safety stopping rules
- Monitoring
  - study
  - data
  - site performance
- Protocol deviations

Main Points

Objectives and endpoints: Need consistency between them

Study design: Need to have the correct study design for the endpoints of interest

Statistical analysis: Method is tailored to the study design

Study conduct: Be vigilant to ensure the integrity of the trial execution so that the data presented in the marketing application can support licensure for the intended use