

Seamless Phase 2/3 Designs

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Outline

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- Design Issues
- Analytical Issues
- Monitoring Issues
- Logistical Issues

Introduction

Classical Phase 2 and 3

- Phase 2 - Does the drug work, and if so at what dose?
 - Generally several hundred patients, parallel designs, selected population
 - Write protocols, find sites, submit to IRB's, ethics committees, regulatory agencies, ramp up enrollment
 - Results must be analyzed, reported, presented to management and regulatory agencies
- Phase 3 – Confirmation of safety and efficacy.
 - Parallel designs, perhaps more comprehensive population
 - Write new protocols
 - Again - Find sites, submit to IRB's, ethics committees, regulatory agencies, ramp up enrollment

Introduction

Seamless Phase 2 and 3

- Time saved
 - Reporting phase 2 data and presenting to management, regulatory agencies, preparing new protocols for phase 3, find new sites, submit to IRB's, ethics committees, regulatory agencies, ramp up enrollment
- Greater efficiency in trial design
 - More patients funneled to effective doses earlier?
 - Robust safety database with fewer patients overall?

Definitions

- Adaptive seamless Phase 2/3 design:
Learning and confirmatory phase in a single trial
 - Analyzed together as one trial
- Operationally seamless Phase 2/3 design:
Continuous in enrollment, instantaneous transition from phase 2 to phase 3
 - Analyzed separately and independently

Design Issues

Choice between combination and nonstop designs

- Applicability, advantages, and disadvantages of each, one or two concrete examples of seamless and/or combination designs

Discussion of endpoints

- What type of endpoints are most appropriate for trials employing an adaptive design? The goal would be to define some general principles that would apply across multiple therapeutic areas.

Design Issues

Feasibility

- Fast enrollment and long follow-up, biomarker vs. clinical endpoint, intent-to-treat analysis
- Short-term endpoints or time-to-event (survival) endpoints

Types of Modifications

- How should characterization of patient populations be handled in trials employing an adaptive design in order to make changes in inclusion/exclusion criteria and retain trial interpretability?
- What kind of modifications can be made in an adaptively designed trial that will retain trial interpretability?

Implementation

- Who does the analysis and modification, DSMB or sponsor?
Variability over time?
- Regulatory interactions during the trial?
- How to blind patients, investigators, and trial sponsor staff to avoid additional operational bias

Analytical Issues

Criteria for validity

- How to control type I error rates while allowing **the totality of efficacy and safety data** and ethical considerations to be taken into account in decision making

Specified Rules versus Guidelines

- Rules are meant to be followed to control type I error rates
- Guidelines permit unexpected modifications while still controlling type I error rates
- Traditional phase 2 and 3 paradigm does not require pre-specified rules

Combining Information

- Combination tests (e.g., p-values combination and normal inverse combination) control type I error rates but contradict scientific rationale
- Sufficient test statistics require rules to be followed
- Bayesian inference requires rules that are calibrated by computer simulations

Monitoring Issues

Roles of DSMB

- Patient safety, scientific rigor
- Elimination of ineffective study arms to ensure adequate information for optimal benefit-to-risk evaluations
- Totality of data

Considerations of Sponsor's Concerns

- Probability of technical and regulatory success
- Development costs and time-to-market
- Financial planning, e.g., additional funding, sites etc due to sample size increase

Communications

- DSMB and Sponsor
- Sponsor and investigators

Logistical Issues

- Drug supply
- Change in randomization
- Fast delivery of interim analyses