Earning Regulatory Approval for a Phase II/III Design: a Case Study from Start to Finish

Adam Hamm

JSM 2017

Agenda

- Introduction
- Target Audience
- Background on my Experience
- Case Studies
- Common Statistical Themes
- Regulatory Interaction/Lessons Learned
- Summary

Introduction

- The purpose of this presentation is to give the audience an overview of:
  - My experiences with the FDA in the development of Phase 2/3 Studies with dose selection
  - Lessons learned, including suggestions for dealing with regulatory agencies with respect to adaptive designs

Target Audience

- Statisticians
- Data Management
- Clinical Personnel

Experience in Adaptive Designs

- Early Phase Oncology
  - CRM Modeling
  - mTPI
- Phase 1|2
  - Normal Dynamic Linear Model (Bayesian)
- Phase 2
  - Sample Size Re-estimation/Promising Zone
  - Superiority/Non-Inferiority
- Phase 2/3
  - Dose selection at interim
  - Dose selection and possible SS re-estimation (Promising Zone)

Case Studies – Phase 2/3 Seamless Design

- Phase 2/3 Two-Stage Design with Dose Selection
  - Neuromuscular agent to treat muscular condition in upper-limbs in adult population
  - Need to fill a Post-Marketing requirement
  - Client pursued a separate indication in parallel
  - Client desired a single study to address the PMR and provide a pivotal study for submission
  - Start with 2 active doses and placebo
    - Reduce to one active dose and placebo after stage 1
    - Only interest was in getting minimum number of subjects in the study to meet PMR AND meet statistical requirements on co-primary endpoints
  - Expected a large difference in co-primary endpoints between selected dose and placebo

Phase 2/3 Seamless with Dose Selection

- Preparation for Original Design and Submission
  - Programmatic Simulation of Design (SAS)
  - Selection of One Dose based on effect threshold
  - Small sample size in phase 2 (stage 1) with expected increase in phase 3 (stage 2)
  - Analysis plan for final analysis consisting of tests of intersection hypotheses and inverse normal p-value combination
  - Protocol submitted to FDA

Phase 2/3 Seamless with Dose Selection

- Modifications after FDA Response
  - Increased sample size in phase 2 part of study
  - Simulated Type I error
  - Provided full statistical analysis plan with second submission
- Second FDA response
  - Type I error control established
    - Must control for potential operational bias and subjective decision-making during the course of study
  - Effect Size threshold at end of stage I may be overly optimistic and could falsely decide to end the study early for futility
    - Should use a different stopping criteria such as OBF boundary

Phase 2/3 Seamless with Dose Selection

- Final Design Submitted
  - EAST used for simulations
  - Phase 2/3 Two-Stage Design
  - One of Two Active Doses selected to advance to Phase 3 part of study
    - Futility determined by conditional power criteria rather than threshold
  - Appropriate statistical methods employed for dealing with two-stage design with adaptive hypotheses and combination of data from two stages
  - Minimization of operational bias detailed, including plans and timing for unblinding of data
  - Study Approved under SPA

Phase 2/3 Seamless with Dose Selection and Promising Zone

- Phase 2/3 Two-Stage Design with Dose Selection and possible sample size re-estimation
  - Same client and indication as in the first study
    - Agent being tested in lower limbs
  - Start with 2 active doses and placebo
    - Reduce to one active dose and placebo after stage 1
    - Interest in trying to detect a moderate response
      - Historically not seen with other treatments
  - Expected a small to moderate difference in primary endpoint between selected dose and placebo
    - Client wanted options for what to do between stages depending on the results at the interim

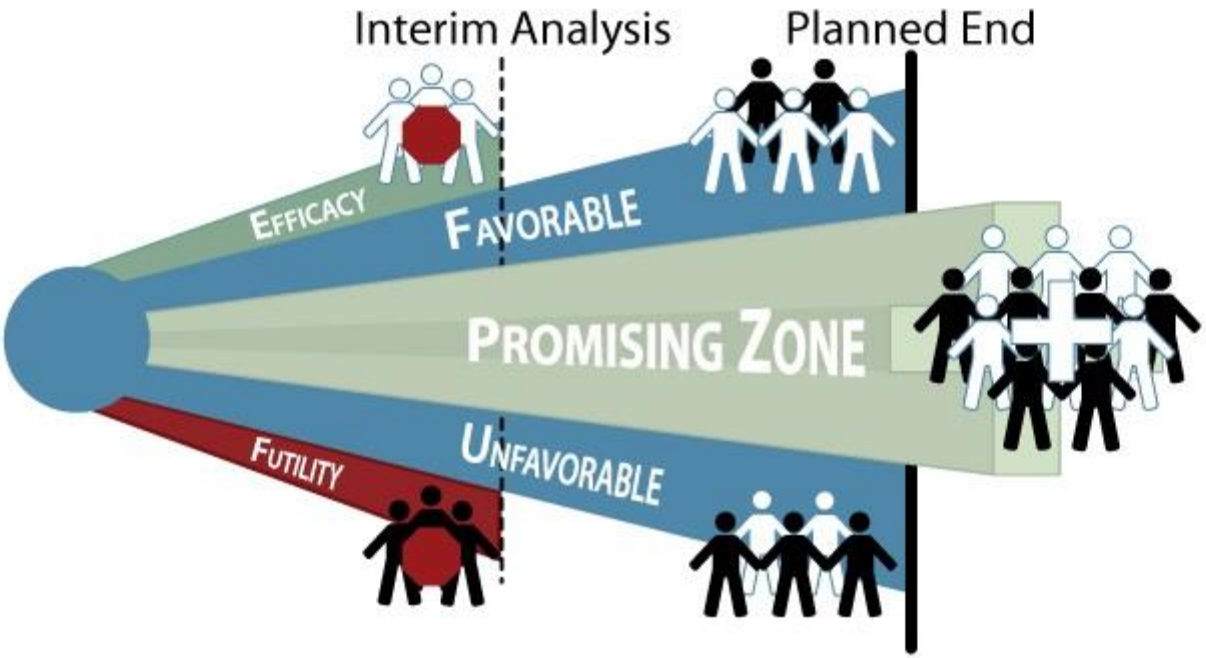
Phase 2/3 Seamless with Dose Selection and Promising Zone

- Timing and Highlights of Design
  - Client considered this design AFTER first submission of upper limb study and FDA comments received
  - Programmatic Simulation of Design (SAS)
  - Selection of One Dose based on **conditional power with possible sample size re-estimation**
  - Because of uncertainty in response, client set the initial sample size at 100
    - Comfort zone for the client in the event that the results at interim were exceedingly positive or negative
  - Analysis plan for final analysis consisting of tests of intersection hypotheses and inverse normal p-value combination
  - Protocol submitted to FDA

Phase 2/3 Seamless with Dose Selection and Promising Zone

- Important statistical considerations
  - Promising zone design based on Mehta, Pocock paper
    - Boundaries defined by conditional power and allowable increase after stage 1
    - Depending on conditional power results, sample size could increase to a pre-set amount after stage 1
    - Could also consider futility
  - Simulations performed to account for dose selection at end of first stage
  - Simulated Type I error (common theme)
- FDA acceptance on first submission!

Promising Zone



Common Statistical Themes: Two Stage Designs

- Dose selection at interim
  - Definition of futility boundaries for decision making is key
  - Usually other factors involved (ex. Safety considerations) in making dose selection
    - Essential to have experienced DMC, including **statisticians** to understand decision ramifications
- Sample size re-estimation
  - Conditional power boundaries for decision making
  - How much sample size increase is acceptable?
- Final analysis
  - Adaptive hypotheses
  - Intersection tests
  - P-value combination (stages)
- All must be accounted for given nature of adaptive designs
- TYPE I ERROR CONTROL

Regulatory Interactions/ Lessons Learned

- Must submit a statistical analysis plan or adaptive design plan with protocol
- Careful consideration of boundaries used for decision making at interim analysis
  - “May erroneously conclude futility at interim”
  - “have not demonstrated strict type I error control”
- Phase 2 sample size should be sufficiently large to make correct decisions at interim analysis
- Appropriate firewalls must be in place to ensure data integrity and appropriate communication of results

Summary

- Key to include clinical and data management personnel from the start
- Regulatory interaction is important
  - Be prepared to present a statistical analysis plan and results of simulations
- Appropriate DMC selection is important
  - Require understanding of design, decision making at interim analysis, and statistical methods being used
- Simulations usually required as support for type I error control and support for other statistical assumptions
  - Software can be key
- Be prepared to present a summary of how you plan to ensure data integrity
  - Could involve a detailed unblinding plan at interim analysis including documentation of unblinding personnel