Multi-Stage Enrollment in Clinical Trials

Benefits vs. Potential Costs

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General Design Issue

- Multiple stage studies
  - Different objectives for each stage
- Subjects initially enroll into Stage 1
- Design calls for roll over into Stage 2
- Stage 1 results limit rollover to Stage 2
  - Stage 1 failures off study or are not eligible
  - This has potential effects on Stage 2 results

Examples

- PROMISE
  - Stage 1 = Antepartum (AP)
  - Stage 2 = Postpartum (PP) – re-randomized
  - AP results limit who can proceed to PP
- IMPAACT 2017
  - Stage 1 = One of the 2 study products
  - Stage 2 = Both products
    - Stage 1 subjects roll into Stage 2
    - Stage 1 results can limit who rolls over

Benefits of Multiple Stage

- Accrual
  - Often difficult in pediatrics
- Longitudinal data
  - Combined data across the two stages might be of interest
- Regulatory Sample Size
  - Rollover subjects contribute to total number exposed to study drug

Costs: Selection Issue

- Stage 1 results select subjects for Stage 2
  - Failures selected out
    - Safety failures
    - Efficacy failures
    - PK problems/indication of non-adherence
  - Eligibility for Stage 2 influenced by Stage 1 Tx effects
  - Lost to follow-up in Stage 1 /Unwilling to roll into Stage 2
    - Possibly due to Stage 1 treatment effect
- Stage 2 gets subjects most likely to succeed

Costs: Bias

- Stage 1 successes are the sample for Stage 2
- Results in Stage 2 may be different than they would be with a random sample
  - Potential positive bias
    - Strongest subjects survive Stage 1, roll over into Stage 2 - increased chance of good outcomes
  - Potential negative bias
    - Stage 1 successes who roll over might have little room for improvement on a Stage 2 outcome
      - Treatment effect reduced: so less power

Costs: Generalizability

- Results of Stage 2 generalize only to population represented by Stage 2 sample
  - These Stage 2 patients:
    - Initially receive Stage 1 regimen
    - Are relatively successful on Stage 1 regimen
- Is this the patient population whose treatment will be determined by Stage 2 results?
  - Or will Stage 2 results be applied to a wider group?

Example: PROMISE Study
Benefits of Sequential Enrollment

- Accrual
  - Separate accrual to AP and PP difficult
- Get data on combined effects of AP+PP interventions
- Ability to track maternal health through both AP and PP interventions

Example: PROMISE Study
Costs of Sequential Enrollment Design

- PP sample selected by AP results
  - AP efficacy failures cannot proceed to PP
  - Early infant death/Stillbirths/Spontaneous Abortions also lost to PP
- AP treatment effects influence failures and rollover into PP
  - Significant effects on MTCT, Infant death, Prematurity, Low Birthweight, etc.
- Effect on generalization?
  - Same PP results without selective dropout related to AP Treatment?
- Longitudinal study of combination AP/PP regimen becomes complex
  - Can’t assume sample participating in both is random

AP to PP transitions

- 70% (2,282/3,259) transitioned from AP to PP
  - Lower than the assumed 90% rate
  - Population represented by this 70%?
  - Dropout not random
- Major reasons for non-enrollment:
  - Mothers
    - 7% required ARVs for their own health
    - 3% had a CD4 count < 350 cells/mm^3
    - 8% decided not to breastfeed
  - Infants (AP treatment related to the most common reasons)
    - 9% infant deaths
    - 7% infant birth weight < 2 kg
    - 3% HIV MTCT
    - 1% infant life-threatening illness

Attempts to Address These Issues
Design/Analysis

- Design: Participants not progressing to PP enrolled in observational follow-up
  - We can examine differences in outcomes between this group and those progressing to PP
- Analysis depends on research question
  - ITT may be appropriate in some cases
    - e.g. Those not progressing to PP classified as failures
  - Epidemiological techniques will help in some cases
    - e.g. Marginal Structural Models
- Sensitivity analyses
  - e.g. Rollover and Tx effects consistent across sites/countries?

Example: IMPAACT Study 2017

- Combination CABO and RLP
  - Dose finding is primary objective
  - Depends on PK and Safety
- Multi-stage design
  - Cohort 1 subjects get either CABO or RLP
    - Design calls for them to roll over into Cohort 2
  - Cohort 2 gets combination of both drugs
  - Cohort 2 is regimen intended to generalize to clinical use

Example: IMPAACT Study 2017

Total Sample = 2 Subsamples

- One subsample rolls over from Cohort 1 to Cohort 2
  - Those failing in Cohort 1 will not roll over
    - Screens out most vulnerable subjects
    - Creates a potential bias
  - Sequential regimen will not generalize to intended use

Example: IMPAACT Study 2017

- Another subsample are enrolled directly into Cohort 2 – no Cohort 1 participation
  - N is smaller than the Total sample
  - Results generalize to intended use
  - Primary group for testing scientific objectives
- Total N may be used for some analyses
  - Sensitivity analyses needed to test whether results differ when rollovers are included

Example: IMPAACT Study 2017

- Total sample in Cohort 2:
  - Cohort 1 Rollovers + Subjects accrued to Stage 2
  - Total N meets FDA requirement for N exposed
  - Effects of Rollover selection bias?
    - Do analyses including rollovers lead to same conclusions as primary analyses restricted to those accrued only to Stage 2?
    - Sensitivity analyses needed to test this
      - Results will be part of the regulatory submission

IMPAACT 2017 Design Meets Primary Objectives

- Dose finding
  - Dose determined for each product in Stage 1, where rollover is not an issue
- Primary final analyses
  - Restricted to subjects enrolled only in Stage 2
  - Limited to those taking the final recommended dose of each product

Summary

- Multi-stage studies can be attractive
  - Accrual
  - Science
- Various types of designs can be multi-stage
  - PROMISE – Phase III
  - IMPAACT 2017 – Phase I/II dose finding
- Potential problems include: Bias / Generalizability
  - Techniques to address problems depend on:
    - Study design
    - Study objectives / research question

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