Harvard Catalyst
Adaptive Clinical Trials
Design and Implementation

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Overview of Novel Adaptive Designs
Definition of an Adaptive Design

- A study design is called "Adaptive" if it allows modification of an essential design feature (e.g., sample size, randomization ratio, number of treatment arms), based on accruing data from *within that* clinical trial
  - Should be carried out without compromising the integrity of the trial
  - For confirmatory trials full details of adaptations need to be pre-specified
Novel Adaptive Designs

• Also known as “Less-Well Understood” Adaptive Designs (Draft FDA AD Guidance):
  • Phase 2
    – Adaptive Dose Selection Studies
  • Phase 3
    – Unblinded Sample Size Re-Assessment
    – Confirmatory Trials with Dose Selection (Seamless Phase 2b/3)
    – Confirmatory Trials with Sub-Population selection (Adaptive Enrichment Design)
When applicable: entering Phase 3 there is still residual uncertainty regarding the treatment effect

GSD vs. Unblined SSR:
1. Both address the same problem
2. With GSD one commits to a larger study initially, can stop early if efficacy better than assumed, or for futility
3. With USSR one initially assumes a more optimistic effect, increases the sample size at the interim as needed.
When applicable: entering Phase 3 there isn’t enough evidence that Biomarker subpopulation would perform (substantially) better than complementary (or full) population.

Randomization stratified by the Biomarker status. At the interim the enrolment in the complementary sub-population may be stopped as guided by the data.
When applicable: after completion of Phase 2, there is still residual uncertainty regarding the best dose.

Formerly known as “Seamless Phase 2b/3, and has caused some controversy. Now actually recommended in the guidance.

Preferably initiated as a follow-up to Phase 2b, although many sponsors still use it as a replacement for (or skipping) Phase 2b.
Implementation
Key Considerations when Planning Adaptive Studies

- Required expertise
  - Statistical methodology
  - Independent data monitoring committee (IDMC) involving both clinicians and statisticians
  - Experienced operational team to manage the logistical complexities and firewalls to limit potential operational biases

- Adequate planning time
  - Pre-study simulations
  - Early communication with the regulators for confirmatory trials (e.g. SPA, Parallel Scientific Advice - FDA/EMA)
  - Document preparation (DMC Charter and SAP submission) and operational setup

- Choosing the right technology
  - IVRS and/or IWRS: Drug logistic management and randomization
  - EDC: Real-time access to high-quality data
  - Endpoint Adjudication: Centralized processing and independent review
  - Integrated Workflow Management System: Strict security levels (firewalls) to ensure data and trial integrity in compliance with regulatory guidance
Data monitoring of Adaptive Clinical Trials

• Key issues:
  – Who knows what and when?
  – Access control and verification
  – Firewalls
  – Storage of DMC materials
  – Communication of Results and Recommendations
Improving the Process

EDC  IRT  CTMS

DMC

ISC  Sponsor

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DMC Issues
DMC Role

• The FDA Adaptive Design Guidance: “Because the DMC is unblinded to interim study results it can help implement the adaptation decision according to the prospective adaptation algorithm, but it should not be in a position to otherwise change the study design except for serious safety-related concerns that are the usual responsibility of a DMC”
Unblinded Sample Size Reassessment

• Similarities with GSD:
  - The adaptation algorithm can be pre-specified in a relatively straightforward manner
  - Both based on the unblinded results of the treatment effect
  - The pre-specified statistical algorithm can be compromised by safety findings for both of these designs

• Differences:
  - GSD; concerns re overflow
  - SSR; design carefully not to reveal treatment effect
Complex Adaptive Designs at Confirmatory Stage

• Decisions involve parameters beyond just ethical considerations.
• Include decisions that traditionally have been sponsor responsibilities.
• May have major commercial implications, for example dose selection or sub-population selection.
• Complex algorithms
• DMC may desire to consult with the steering committee that includes a sponsor representative not involved in trial management.
Adaptive Designs in Exploratory Studies

- Not intended to demonstrate confirmatory evidence; less rigor in restricting knowledge of interim results
- Lesser regulatory implications, though avoiding operational bias should be recommended in any trial
- May require frequent updates based on interim data
- Adaptations are often driven by a pre-specified algorithm automated through an integrated response system
- Therefore, it may be preferable that recommendations are endorsed by an Internal Review Committee
References

Back-up Slides
Phase 2b Dose Finding Studies

Value of Design
- Easily under-appreciated, trial designs have a major impact on the value of a pharmaceutical product

Adaptive Phase 2 Designs
- The FDA AD Guidance recommends use of AD in Phase 2
- AD is the most efficient approach for this stage of development

Development Program Optimization
- Phase 2 most critical for optimal drug development

Development Scenario Simulation
- Comparison of relative efficiency of various development options can be accomplished only with simulations
Case Study

Scenarios

– (7) different statistical approaches
– (2) Phase 2 strategies
– (3) Phase 3 strategies
– For a total of 42 scenarios. Same assumptions for safety and efficacy used for all scenarios
– Cost and development time calculated using real data from existing databases

Results

– The expected NPV for different scenarios ranged from $0.5B to $1.2B
– Adaptive Designs far outperformed traditional approaches
Expected NPV

Method:
- LOCFIT
- BMA
- MTT
- MCPMod
- GADA
- Dopt
- ANOVA

N = 250

1 dose
2 doses, fast
2 doses, normal

N = 150

Average NPV (millions)