Motivating example: the VALOR trial

Sponsor’s dilemma with conventional design

Promising zone design as an alternative

Benefits: staged investment versus large upfront investment

Avoidance of operational bias: interacting with regulators, investors, and investigators
VALOR

Vosaroxin and Ara-C combination evaluating overall survival in relapsed/refractory AML
Design Objectives

- Primary endpoint is overall survival (OS)
- Design for 90% power at 5% significance level
- Complete the trial in 30 months
  - Enroll for 24 months
  - Follow for 6 additional months
Prior Phase 2 Data

- Median OS 5 months for Cytarabine, from meta-analysis of prior studies and consultation with KOLs
- Hazard ratio estimated to be 0.71 amidst considerable uncertainty

![Graph showing overall survival over time with median OS 7.1 (4.6 – 10.1) months]
Sponsor’s Dilemma

- 375 Deaths
- 450 Patients
  - 5 vs. 7 months Median OS

- 619 Deaths
- 732 Patients
  - 5 vs. 6.5 months Median OS
Sponsor adopts a strategy of staged investment

- Design realistically up-front. Power study to detect HR=0.71 (requires 375 events; 450 subjects @ 19/month)

- One interim analysis after 50% information (187 events)
  - Stop early if overwhelming evidence of efficacy
  - Stop early for futility if low conditional power
  - Increase number of events, sample size and (if possible) rate of recruitment at the interim if results are promising

Key idea: invest additional resources and re-power the study to detect HR=0.77 only after seeing interim results
The Promising Zone Design

- Partition the interim outcome into three zones based on the interim estimate of conditional power, or equivalently the observed hazard ratio
  - **Unfavorable:** Obs. HR ≥ 0.86; no change to design
  - **Promising:** 0.74 ≤ Obs. HR < 0.86; increase resources
  - **Favorable:** Obs. HR ≤ 0.74; no change to design

- Control type-1 error by using Cui, Hung and Wang (1999) weighted statistic modified for survival data
- Evaluate operating characteristics of design by simulation

**Note:** The cutoffs specified above for the three zones are not the actual cut-offs used in the trial. The actual cut-offs are confidential information.
Adaptive decision rule

- Favorable Zone: (P-value < 0.03)
- Promising Zone: (P-value between 0.03 and 0.12)
- Unfavorable Zone: (P-value > 0.12)
Adaptation principles

• Primary driver of power is number of events
• FDA guidance recommends increase only, not decrease
• Increase events by amount needed to achieve some target conditional power, subject to a cap
• Compute sample size increase necessary to achieve the desired increase in events without undue prolongation of the trial
• Complex relationship exists between increase in events, increase in sample size and study duration. Best evaluated by simulation
## Operating characteristics

<table>
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<tr>
<th>Zone</th>
<th>P(Zone)</th>
<th>Power</th>
<th>Duration (months)</th>
<th>SampSize</th>
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<tr>
<td></td>
<td></td>
<td>NonAdpt</td>
<td>Adapt</td>
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<tr>
<td>Fav</td>
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<td>95%</td>
<td>95%</td>
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</table>

Under Pessimistic Scenario, HR = 0.77 (10,000 simulations)
Briefing document with SAP is crucially important

• Justify why adaptive approach is necessary

• Describe the statistical methodology and details for control of type-1 error

• Describe the promising zone decision algorithm

• Provide simulation results under various scenarios

• Provide the Data Monitoring Committee (DMC) charter
Operational considerations

• Establish excellent SOPs:
  • Document “who saw what and when”
  • Document who has had full access to details of the adaptive algorithm
  • Document all data and programs used for the interim analysis

• Appoint a Data Monitoring Committee
• Appoint an Independent Statistical Center to perform the interim analysis for the DMC
• Educate investigators, analysts and investors
Avoidance of Operational Bias

• Guidance documents by FDA and EMA for DMC and Adaptive Trial Design:
  • Reference the importance of confidentiality of interim results
  • Require that well-trusted firewalls are established for trial conduct to provide assurance that operational biases have not been introduced.
  • Request an accurate recording of trial conduct and documentation – who saw what and when
Access Control Execution System (ACES)

- ACES is a secure, web-based system that streamlines the interim analysis process

- **DMC Portal**
  - Secure centralized storage of documents (interim analysis reports, meeting agendas and minutes, DMC decisions)
  - Customized access for DMC, ISC, and Sponsor

- **ACES engine generates interim reports**
  - Analysis programs pre-tested and loaded to ACES
  - Blinded dataset uploaded to ACES

- **Non-invasive audit trail**
  - Who see what and when is time stamped
  - Dataset and analysis program available for review
Traditional Process

1. **Sponsor**
   - Create Documents (Protocol, SAP, DMC Charter)

2. **ISC**
   - Store/Archive Documents
   - Enroll Subjects & Collect Responses
   - Send Response Data to ISC
   - Request additional information

3. **DMC**
   - Send Analysis to DMC
   - Perform Analysis and Create Reports
   - Create and Test Analysis Programs
   - Make Recommendation
   - Send Recommendation to Sponsor/Steering Committee

4. **Steering Committee**
   - Make Decision About Trial
   - After decision:
     1. DMC notified
     2. Drug Supply notified
     3. IVRS notified
ACES Process

Sponsor

Create Documents (Protocol, SAP, DMC Charter) → Store/Archive Documents in ACES → Enroll Subjects & Collect Responses → Send Response Data to ISC with ACES

ISC

Request additional information → Send Analysis to DMC in ACES → Perform Analysis and Create Reports in ACES

DMC

Send Recommendation to Sponsor/Steering Committee → Make Recommendation → Load Final Analysis Programs into ACES

Steering Committee

Make Decision about Trial → After decision... 1. DMC notified 2. Drug Supply notified 3. IVRS notified

Make Recommendation

Create and Test Analysis Programs
Summary: Design

• The adaptive design mitigates risk of initial over-investment, and risk of failing to detect a relevant survival benefit

• Statistical rigor: theoretical and simulation-based guarantee that Type-I Error is controlled

• DMC may call for sample size increase only if interim result falls into Promising Zone

• Study design prevents from back-calculation of treatment effect

• This design satisfies both statistical and operational requirements stipulated in FDA Draft Guidance and in EMA Reflection Paper on Adaptive Design Clinical Trials
Summary: Process

- **Integrated Systems** can increase efficiency in the flow of data and information, and how groups communicate.
- **Operational Bias** is greatly reduced by using secure systems, and by limiting access to unblinded data.
- **Trial Integrity** is protected by documenting the conduct, logistics, and operation of the trial through security and audit trails.
- **Regulatory Confidence** in the consistent execution of adaptive trials by implementing systems that enforce ‘best practice’ processes.