Harvard Catalyst
Adaptive Clinical Trials
Case Study
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Acknowledgements

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Presentation Contents

• Study Design Overview
• Operational Challenges with Adaptive Trials
The VALOR Trial for AML

• Vosaroxin and Cytarabine combination evaluating Overall Survival in relapsed/refractory Acute Myeloid Leukemia (AML)
• Phase 3, double-blind, placebo-controlled, multinational trial
• Design for 90% power at 5% significance level
Sponsor’s Dilemma

• Based on phase 2 data (N=69):
  – Assume 5/7 month median on Ctrl/Trtm (HR=0.71)
  – Require 375 events and 450 subjects @ 19/month

• But phase 2 estimates are subject to uncertainty:
  – What if 5/6.5 month median on Ctrl/Trtm (HR=0.77)?
  – HR = 0.77 is still clinically meaningful
  – Require 616 events and 732 subjects @ 31/month
  – Not a feasible option for sponsor
Sponsor Adopts a Strategy of Staged Investment

• Power study to detect HR=0.71 up-front
• One interim analysis after 50% information
  – Stop early if overwhelming evidence of efficacy
  – Stop early for futility if low conditional power
  – Increase number of events and sample size if results are promising
The Promising Zone Design

• Partition the interim outcome into three zones based on the interim estimate of conditional power.
  – Favorable: CP ≥ Y%; no change to design
  – Promising: X% ≤ CP < Y%; increase resources
  – Unfavorable: CP ≤ X%; no change to design

• Control type-1 error by using Cui, Hung and Wang (1999) weighted statistic modified for survival data
Adaptive Decision Rule

Interim analysis at ~187 events:

Efficacy

Promising Zone (add 225 patients)

Futility

Unfavorable

Favorable

CP = Conditional power
The probability of success (statistical significance) at the end of the trial given current data trend

Interim outcome partitioned into unfavorable, promising, and favorable zones
Data Monitoring Committee

• DMC responsible for monitoring both, safety and efficacy
• DMC may call for sample size increase only if interim result falls into Promising Zone
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.
  – Requests an accurate recording of trial conduct and documentation – who saw what and when
Avoidance of Operational Bias

• Must provide auditable evidence that GSD/SSR was strictly followed and based only on the pre-specified decision rule
• Ensure that firewalls were in place to protect unblinded analyses
• Show evidence that Sponsor was not involved in ISC and DMC interactions and was not exposed to unblinded IA results
Access Control Execution System (ACES)

• ACES is a secure, web-based system used during the interim analysis to:
  – Centrally store interim analysis reports, meeting agendas and minutes, and DMC recommendations
  – Assign team members to specific roles and grant explicit privileges to securely access data and information
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

- Use of technology to control flow of information between sponsor, independent statistical center and DMC
  - DMC portal for storage of sensitive documents
  - Interim analysis report generated and stored in DMC portal without possibility of external intervention
  - Audit trail of access to all reports stored in the DMC portal to track "who saw what and when"