

Statistical Design Strategies for De-Risking Oncology Drug Development

Promising Zone Designs

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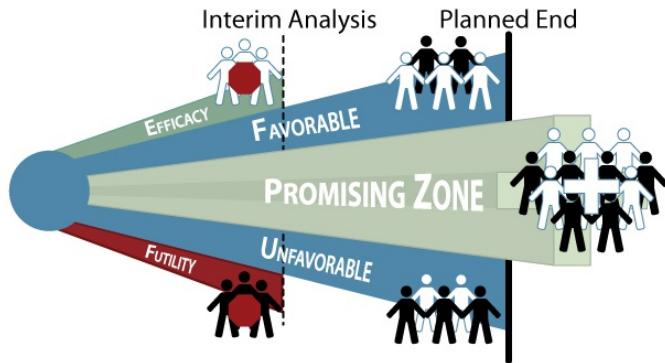
Design Difficulties in Phase 3

Typically in a phase 3 trial of an oncology drug development program:

- Primary endpoint is overall survival (OS), which has not been studied in the exploratory part of the program
- Produces great uncertainty in treatment effect size to be targeted, i.e. uncertainty in required sample size
- Small gains in OS (e.g. hazard ratios between 0.75 and 0.8) may nevertheless be clinically meaningful
- Sample size requirements for such small gains are consequently large and pose a major design challenge
- The risk of improperly powering the trial is great

Promising Zone Designs

- **Promising Zone Designs** resolve this difficulty and **de-risk** a study by requiring a smaller up-front sample size commitment, to be followed up by a larger commitment only if interim results are **promising**



Advantages of Promising Zone Designs

- **Early intimation of efficacy**: option to either terminate or prepare for an early regulatory submission
- **Early intimation of inefficacy or harm**: option to either terminate for futility, drop the ineffective arm, or divert key resources to more promising studies
- **Verify design assumptions** (variance, effect size, covariates, etc.) from accumulating data: option to revise the sample size adaptively to avoid an underpowered study

Case study in NSCLC

- Two arm double-blind multicenter trial with second line therapy for metastatic non-small cell lung cancer
- Primary endpoint is overall survival (OS)
- Median OS for control arm is 8 months
- Require 90% power to detect $HR = 0.7$ (median OS = 11.4 months on treatment arm)
- One-sided level 0.025 test with one interim look for early efficacy or futility stopping
- Design for 24 months accrual and 12 additional months of follow-up

Uncertainty about Treatment Effect

- If $HR = 0.7$ we need 333 events for 90% power and must enroll 417 subjects over 24 months to complete study in 3 years
- Could easily have underestimated hazard ratio due to improved standard of care or weaker than optimistic treatment effect
- If $HR = 0.77$ we need 620 events for 90% power
 - enroll 763 subjects over 24 months and follow for 12 additional months
 - or enroll 672 subjects over 24 months and follow for 24 additional months
- Sponsor cannot make such large up-front commitments

Sponsor is Resource and Time Constrained

- Unable to invest up-front to protect power in case of pessimistic scenario
- But willing to invest additional resources if interim results are **promising**

True HR	Power of Optimistic Design (design for HR = 0.7)	Power of Pessimistic Design (design for HR = 0.77)
0.7	90%	99%
0.75	74%	95%
0.77	66%	90%

Sponsor Adopts a De-Risking Strategy

- Design optimistically (HR = 0.7; 333 events; 417 subjects)
- One interim analysis after 50% information (167 events)
 - Stop early if overwhelming evidence of efficacy
 - Stop early for futility if low conditional power
 - Increase number of events, sample size at the interim if interim results fall in a promising zone
- Can define promising zone equivalently in terms of conditional power, or HR, or Z-statistic
- More generally, the promising zone is defined by any measure of success probability (e.g. Bayesian predictive power)

The Promising Zone Design

- Estimate the conditional power at the interim look

Unfavorable: $CP < 35\%$; no change in design

Promising: $35\% \leq CP < 90\%$; increase resources

Favorable: $CP \geq 90\%$; no change in design

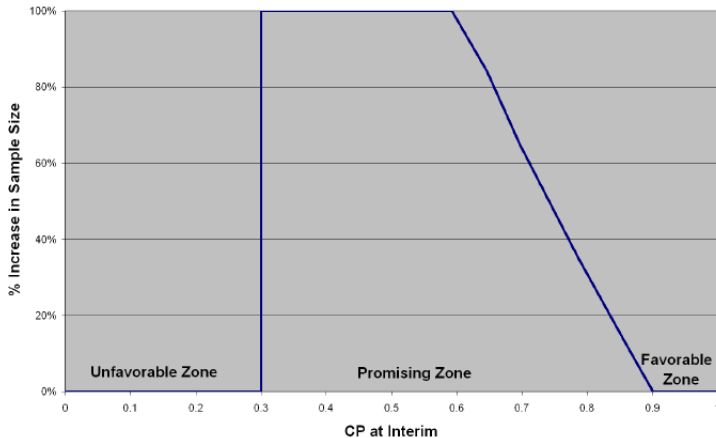
- Sponsor willing to invest more resources at the interim look, if results fall in the promising zone ($0.35 \leq CP \leq 0.9$) because then the chances of success would increase dramatically
- Simulations guide the definition of promising zones, of sample size re-estimation rules, and provide final operating characteristics of the design
- Use of Cui, Hung, and Wang (CHW, 1999) method guarantees strong control of type-1 error

Principles for Interim Decision Rules

- Primary driver of power is number of events
- FDA guidance recommends increases only, no decreases in sample size
- 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

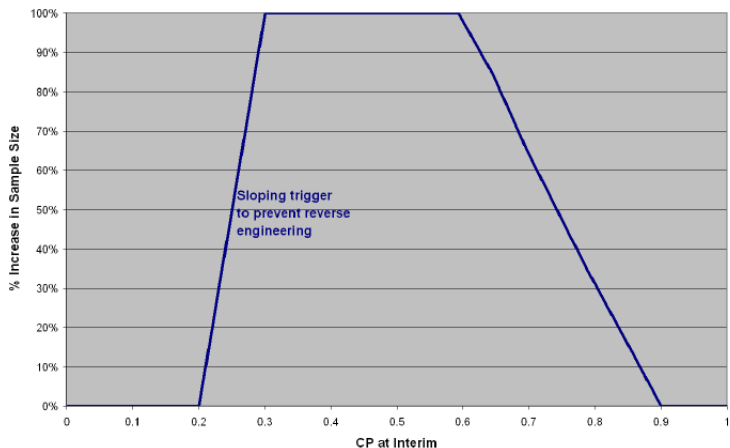
Increase Number of Events 1

Rule for Increasing Sample Size: CP at interim is between 30% and 90%
The "Cap" is 100%. The "Target CP" is 90%



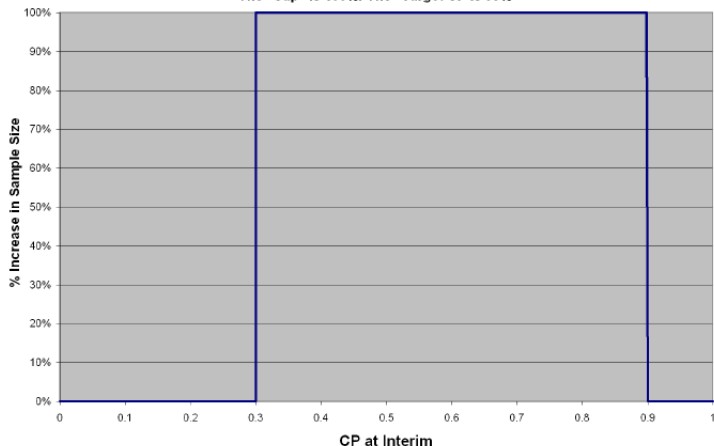
Increase Number of Events 2

Rule for Increasing Sample Size: CP at Interim is between 20% and 90% with sloping trigger

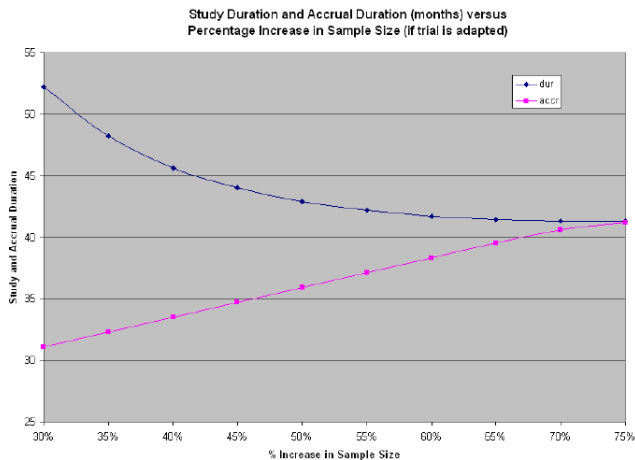


Increase Number of Events 3

Rule for Increasing Sample Size: CP at interim is between 30% and 90%
The "Cap" is 100%. The "Target CP is 99%



Accrual vs Study Duration



- Unnecessary to increase sample size by more than 50%

Operating Characteristics of Optimistic Design (Powered to Detect HR = 0.7)

1. Simulation under Pessimistic Scenario HR = 0.77 (10,000 simulations)

Zone	P(Zone)	Power		Duration (months)		Sample Size	
		Trad	PZD	Trad	PZD	Trad	PZD
Unf	32%	31%	31%	33	33	409	409
Prom	32%	69%	88%	35	43	418	627
Fav	36%	93%	93%	31	31	398	398
Total	100%	66%	72%	33	35	408	476

2. Simulation under Optimistic Scenario HR = 0.7 (10,000 simulations)

Zone	P(Zone)	Power		Duration (months)		Sample Size	
		Trad	PZD	Trad	PZD	Trad	PZD
Unf	14%	57%	57%	35	35	414	414
Prom	26%	88%	98%	36	44	418	627
Fav	60%	98%	98%	29	29	390	390
Total	100%	90%	93%	32	34	401	454

Observations

- It is believed that true HR is between 0.7 and 0.77
- Option 1: Power the trial for HR=0.77 with aggressive early stopping boundaries
 - Large up-front commitment is often an obstacle
 - Aggressive stopping boundaries require spending more alpha at the interim
 - Stopping a trial prematurely with aggressive boundaries is unlikely to alter medical practice
 - Overruns can be problematic
- Option 2: Power the trial for HR=0.7 and increase resources in promising zone
 - Requires a lower up-front commitment
 - Additional commitment only called forth if it is needed
 - Compromise design: Better than traditional trial powered at HR=0.7 but not as powerful (unconditionally) as the traditional design powered at HR=0.77

Operational and Regulatory Issues

- The protocol should only describe the design in general terms
- Detailed decision rules and statistical methods should be in the DMC charter
- Restrict access to the DMC charter
- Submit the design for regulatory review along with charter, simulation results and software
- Implement internal processes to prevent sponsor organization and investigators from reverse-engineering interim results
- Create an auditable DMC portal for storage of charter, decision rules and interim results

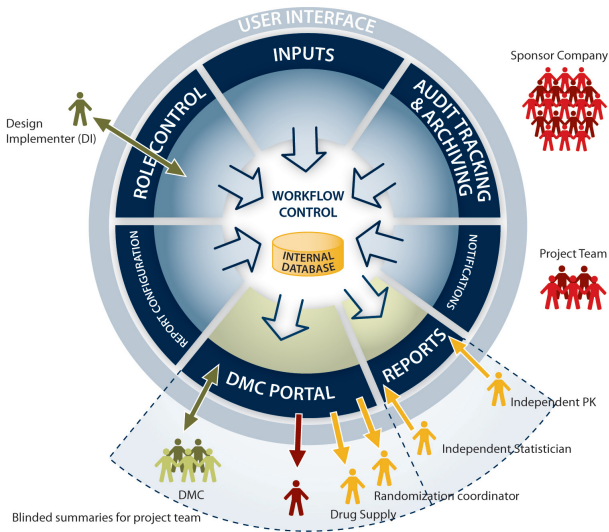
What are the Logistical Problems?

- Timely access to accurate interim data is essential. Data management processes must be streamlined. EDC technology can be valuable
- Access to the interim efficacy results must be restricted. Their availability to trial investigators could bias the future conduct of the study. The potential for bias can be controlled through:
 - An external Data Monitoring Committee
 - An external statistical center preparing the reports
 - Documentation and Processes; SOPs
 - Creative use of technology (including Cytel's [ACES™](#) environment)

What is ACES™?

ACES™ streamlines the Interim Analyses Workflow process and provides full audit tracking

- Standalone web based system
- Controlled access
- Independent of the study design
- Provides security & protection within a controlled environment (automatic or manual) for the management of the interim analysis workflow process
- Available as software hosted by Cytel or an enterprise package for internal deployment by a sponsor.



Conclusion

- Promising Zone Designs provide opportunity to stage risk and investment in a clinical trial or even in a drug development program
- Statistical, operational, and regulatory issues can be addressed with careful planning and as industry gains experience
- Technology in the form of simulation software and secure and controlled execution environments is extremely helpful in gaining the trust and buy-in of regulatory and scientific bodies