Cytel
Shaping the Future of Drug Development

East® Orientation Webinar Series:

Conducting Sample Size Reassessment with Time-to-event Endpoints

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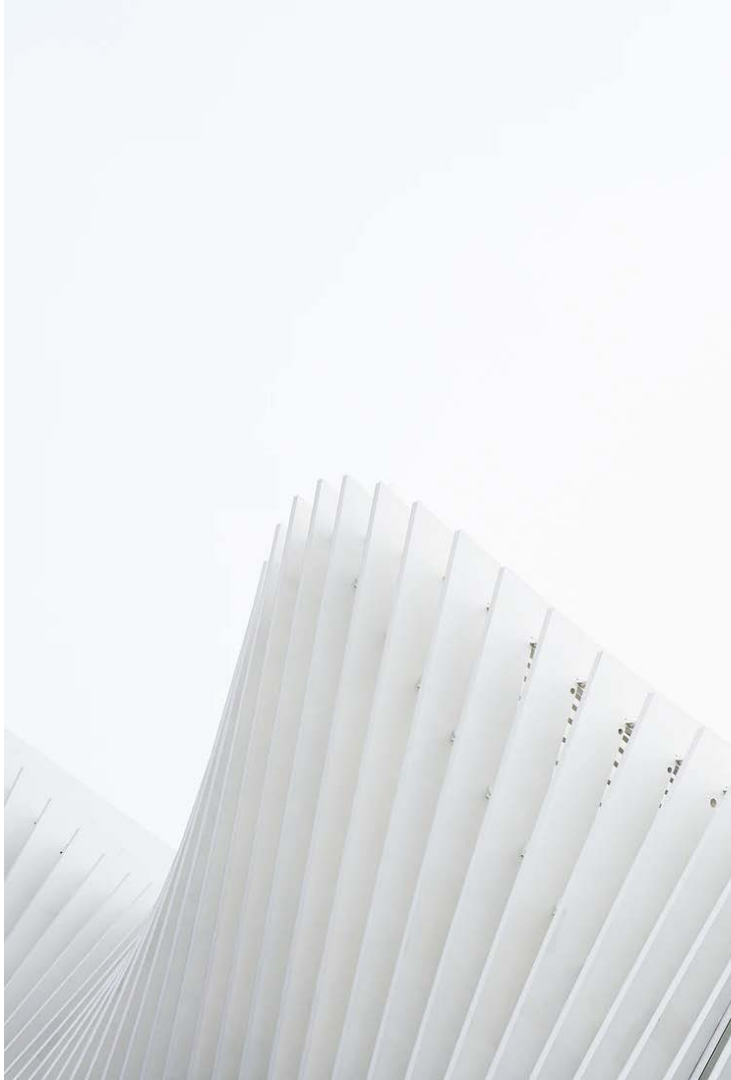
Agenda

- Methodology
- Case study
- Q/A
- Conclusion



East gives you easy access to the adaptive designs that matter

Popular tools for fixed-sample clinical trials.

Wide selection of model-based adaptive designs for Phase 1 dose escalation studies.

Multiple Comparison Procedure Modeling for Phase 2 dose-finding studies.

Strategic testing of multiple endpoints.

Tools for small sample clinical trials with binomial endpoints.

Tools for multi-arm fixed-sample clinical trials.

Tools for group sequential clinical trials with normal or binomial endpoints.

Multi-arm multi-stage clinical trials.

Allow for sample size re-estimation in trials with normal and binomial endpoints.

Tools for group sequential clinical trials with survival endpoints.

Allow for sample size re-estimation in trials with survival endpoints.

Allow for population enrichment in trials with survival endpoints.

Predict future course of trial at outset and interim analyses.

Design through simulation.

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Today's presentation

BASE

Popular tools for fixed-sample clinical trials.

ESCALATE

Wide selection of model-based adaptive designs for Phase 1 dose escalation studies.

MCPmod

Multiple Comparison Procedure Modeling for Phase 2 dose-finding studies.

ENDPOINT

Strategic testing of multiple endpoints.

EXACT

Tools for small sample clinical trials with binomial endpoints.

MULTIARM

Tools for multi-arm fixed-sample clinical trials.

SEQUENTIAL

Tools for group sequential clinical trials with normal or binomial endpoints.

MAMS

Multi-arm multi-stage clinical trials.

ADAPT

Allow for sample size re-estimation in trials with normal and binomial endpoints.

SURVIVAL

Tools for group sequential clinical trials with survival endpoints.

SURVADAPT

Allow for sample size re-estimation in trials with survival endpoints.

ENRICH

Allow for population enrichment in trials with survival endpoints.

PREDICT

Predict future course of trial at outset and interim analyses.

PROGRAM

Design through simulation.

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East SURVIVAL

Test survival endpoints in superiority and non-inferiority studies

SUCCESSFUL OUTCOME:	**Compute events, sample size, study duration, for complex survival designs**
Pre-Requisites:	East SEQUENTIAL
Functions:	• Variable and fixed subject follow-up • Piecewise hazard rates, accruals, and dropouts • Charts for predicting events/sample size, accrual and study duration • Simulate non-proportional hazards
New in 6.5:	• Go-No-Go Based on Surrogate Endpoints
Note:	•Cytel also offers Proc East MONITOR as a SAS PROC to facilitate your usage of SAS to monitor trials designed using East SURVIVAL.

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East ADAPT / SURVADAPT

Incorporate unblinded sample size re-estimation rules

SUCCESSFUL OUTCOME:	**Improve statistical power when results are 'promising'**
ADAPT Pre-Requisites:	East SEQUENTIAL
SURVADAPT Pre-Requisites:	East SURVIVAL
Functions:	• Adaptive rules for increasing sample size, or other possibilities • Methods include CHW, CDL, Müller-Schäfer • Specific adaptive tools for survival (eg., adapt sample size and events) • Müller-Schäfer Method for Interim Monitoring ***Unique to East:*** • Promising Zone Design based on unblinded interim data • Adjusted unbiased point estimates, confidence Intervals, and p-values
New in 6.5:	• SSR for Non-Inferiority designs
Note:	•Cytel also offers Proc East MONITOR as a SAS PROC to facilitate your usage of SAS to monitor trials designed using East ADAPT and SURVADAPT.

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Methodology

Traditional vs Adaptive for Confirmatory Trials

- **Traditional Design**:
  - Fix total sample size in advance
  - Monitoring accruing data for safety only
  - **One** final efficacy analysis at study end
- **Adaptive Design:**
  - Monitor accruing data for efficacy and safety
  - Possibly alter future course of study
  - Design changes can utilize unblinded data

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Types of Design Changes

- Stop early due to overwhelming efficacy
  - Group sequential efficacy boundaries
- Stop early due to inefficacy or harm
  - Group sequential futility boundaries
- Mid-course corrections to design assumptions
  - Unblinded sample size re-estimation
  - Dropping ineffective doses in multi-arm trials
- Changing goals
  - Biomarker-based population enrichment
  - Switching endpoints from non-inferiority to superiority

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Motivation for Mid-Course Sample Size Correction in Pivotal Trials

We don't know what δ and σ to power the study for

- Prior experience limited to small pilot studies
- Improved standard of care dilutes treatment effect
- Powering for **smallest clinically important** effect expensive
- Better safety profile at interim might justify smaller δ
- Opportunity to combine internal and external data

If only σ is unknown, blinded SSR is recommended by FDA

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Why not design for the smallest clinically meaningful treatment effect?

Large effects are uncommon, but designing for very small clinically meaningful effects requires huge up-front investments that management will not approve. A strategy of staged investment is more practical

- Unreliability of Pilot Studies: Most large treatment effects emerge from small studies, and when additional trials are performed, the effect sizes typically become much smaller. Well-validated large eff ects are uncommon and pertain to nonfatal outcomes. *Pereira et. al., JAMA. 2012; 308(16): 1676-1684*
- Milestone-Driven Investment: Sunesis Pharmaceuticals to Implement One-Time Sample Size Increase to Phase 3 VALOR Trial in AML. DSMB Recommends Increase Following Single, Pre-Planned Interim Efficacy and Safety Analysis of VALOR; DSMB Recommendation Triggers $25.0 Million Investment in Sunesis from Royalty Pharma. *Press Release, September 11, 2012. Sunesis Pharma, South San Francisco*

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Featured Article

Statistics in Medicine

Received 12 December 2009, Accepted 8 September 2010 Published online 30 November 2010 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.4102

Adaptive increase in sample size when interim results are promising: A practical guide with examples

Cyrus R. Mehta[a,b*†] and Stuart J. Pocock[c]

This paper discusses the benefits and limitations of adaptive sample size re-estimation for phase 3 confirmatory clinical trials. Comparisons are made with more traditional fixed sample and group sequential designs. It is seen that the real benefit of the adaptive approach arises through the ability to invest sample size resources into the trial in stages. The trial starts with a small up-front sample size commitment. Additional sample size resources are committed to the trial only if promising results are obtained at an interim analysis. This strategy is shown through examples of actual trials, one in neurology and one in cardiology, to be more advantageous than the fixed sample or group sequential approaches in certain settings. A major factor that has generated controversy and inhibited more widespread use of these methods has been their reliance on non-standard tests and p-values for preserving the type-1 error. If, however, the sample size is only increased when interim results are promising, one can dispense with these non-standard methods of inference. Therefore, in the spirit of making adaptive increases in trial size more widely appealing and readily implementable we here define those promising circumstances in which a conventional final inference can be performed while preserving the overall type-1 error. Methodological, regulatory and operational issues are examined. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: sample size re-estimation; two-stage designs; flexible clinical trials; conditional power; adaptive design; real examples

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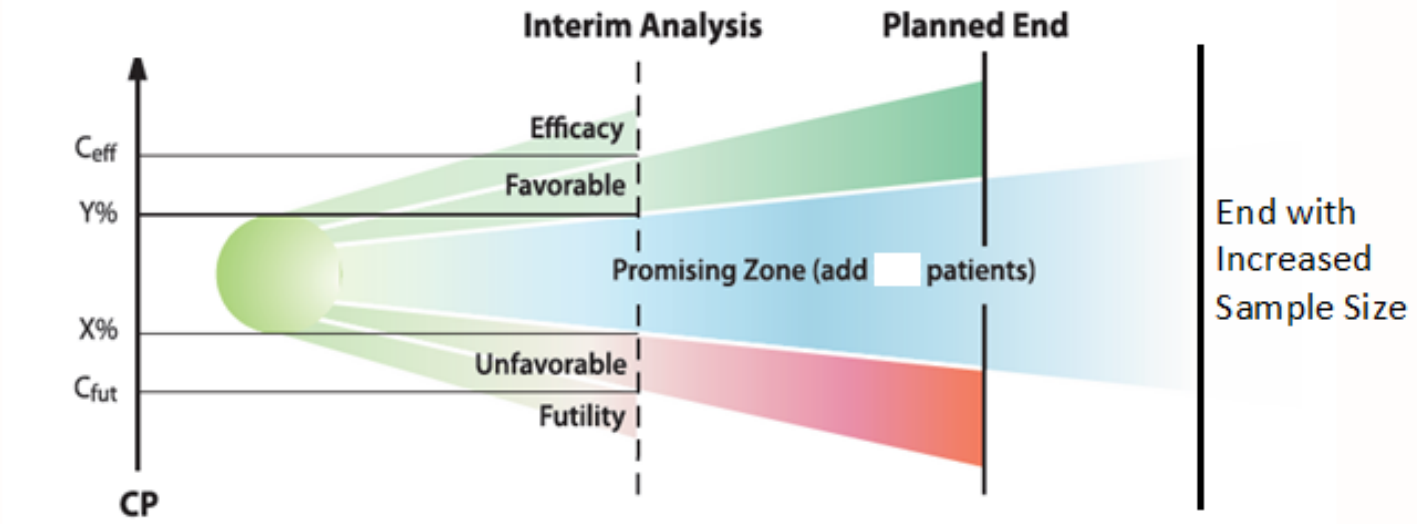
ADAPT / SURVAdapt: Adaptive Sample Size Re-estimation



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

Transparent, pre-specified plan to increase sample size only if interim analysis was in "promising zone"

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Case Study

Case Study: Metastatic Lung Cancer

Two arm, multicenter trial with second line therapy for metastatic non-small cell lung cancer

Primary endpoint is overall survival (OS)

Median for control arm is 8 months

Require 90% power to detect HR = 0.7 (median = 11.4 months on experimental arm)

One-sided level 0.025 test with one interim look for early efficacy or futility stopping

Design 24 month enrollment and 12 months additional follow-up

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Group Sequential Design

	Wbk2:Des2	Wbk2:Des3
Mnemonic	SU-2S-LRSD	SU-2S-LRSD
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	2	2
Test Type	1-Sided	1-Sided
Specified α	0.025	0.025
Power	0.9	0.9
Model Parameters		
Allocation Ratio (nt/nc)	1	1
Hazard Ratio (Alt.)	0.7	0.77
Var (Log HR)	Null	Null
Boundary Parameters		
Spacing of Looks	Equal	Equal
Efficacy Boundary	LD (OF)	LD (OF)
Accrual & Dropout Parameters		
Subjects are Followed	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
No. of Dropout Pieces	0	0
Sample Size		
Maximum	416	760
Expected Under H0	415.864	759.763
Expected Under H1	399.146	728.269
Events		
Maximum	332	618
Expected Under H0	331.747	617.529
Expected Under H1	289.991	539.855
Study Duration		
Maximum	36	36
Expected Under H0	32.453	33.348
Expected Under H1	31.973	31.936
Accrual Duration		
Maximum	24	24
Expected Under H0	23.992	23.993
Expected Under H1	23.028	22.998

- Uncertainty about HR=0.7;
- HR = 0.77 is still clinically meaningful but requires 760 patients and 618 events.
- Up-front commitment is impossible

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Adaptive Strategy

Design optimistically (HR=0.7; 332 events; 416 subjects)

One interim analysis after 50% information

- Stop if overwhelming evidence of efficacy ($\widehat{HR} \leq 0.63$)
- Stop if overwhelming evidence of futility ($\widehat{HR} > 1.02$)
- Increase number of events and sample size at the interim if interim results fall in a promising zone

Can define promising zone in terms of conditional power, or HR, or Z-statistic

Special CP calculator available in East

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The Promising Zone Design

Partition the interim outcome into three zones based on the estimated conditional power. For example:

- Unfavorable: $CP < 35\%$; no change in design
- Promising: $35\% \leq CP < 90\%$; increase resources
- Favorable: $CP \geq 90\%$; no change in design

Use simulation to experiment with promising zones

Use simulation to experiment with sample size re-estimation rules

Use Cui, Hung, Wang (CHW), Chen, DeMets & Lan (CDL) or Mueller and Shaeffer (MS) methods to control type-1 error

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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

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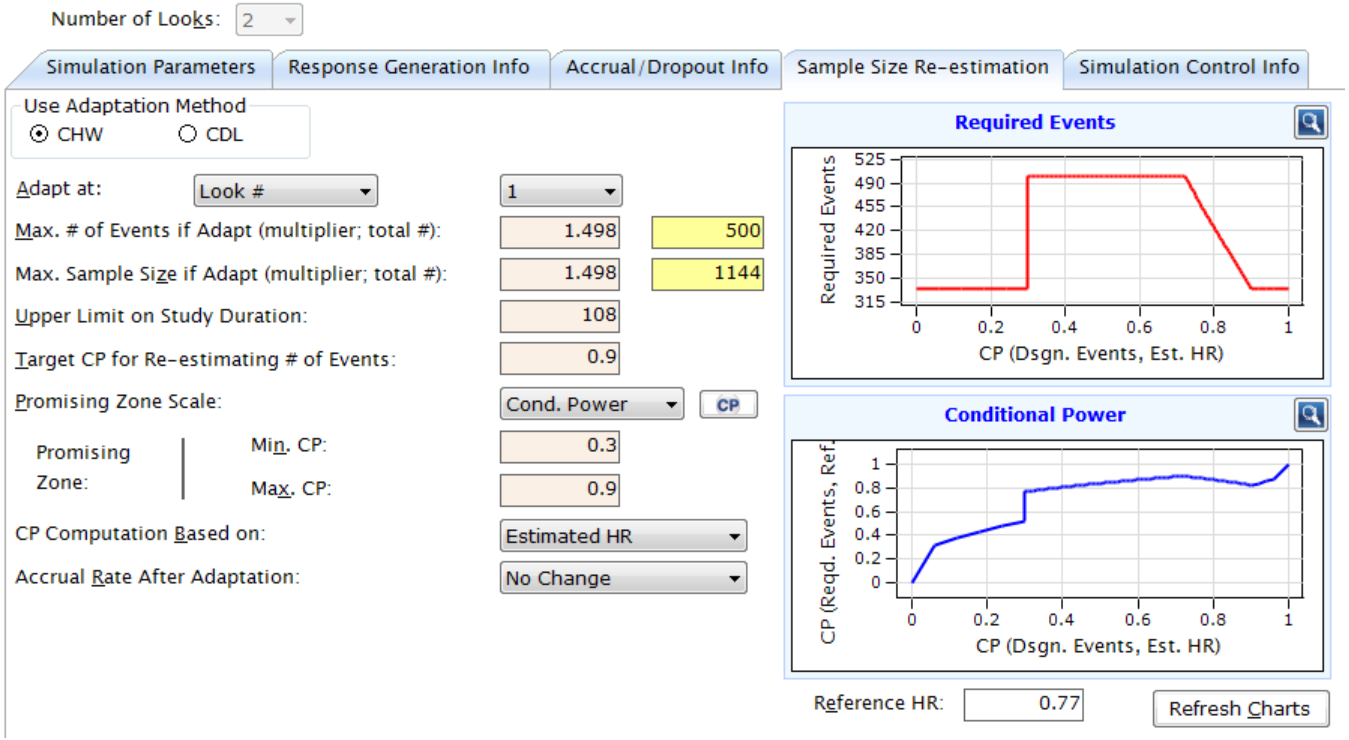
Adaptive Simulation Worksheet



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Operating Characteristics

1. Simulations Under Pessimistic Scenario, HR = 0.77 (10,000 simulations)

Zone	P(Zone)	Power		Duration (months)		SampSize	
		NonAdpt	Adapt	NonAdpt	Adapt	NonAdpt	Adapt
Unf	28%	34%	35%	35	35	419	419
Prom	32%	70%	85%	35	40	419	616
Fav	40%	91%	90%	35	35	419	419
Total	—	66%	71%	33	34	408	472

2. Simulations Under Optimistic Scenario, HR = 0.7 (10,000 simulations)

Zone	P(Zone)	Power		Duration		SampSize	
		NonAdpt	Adapt	NonAdpt	Adapt	NonAdpt	Adapt
Unf	13%	62%	61%	36	35	419	419
Prom	27%	87%	97%	36	40	419	616
Fav	60%	97%	98%	36	35	419	419
Total	—	90%	92%	32	33	402	454

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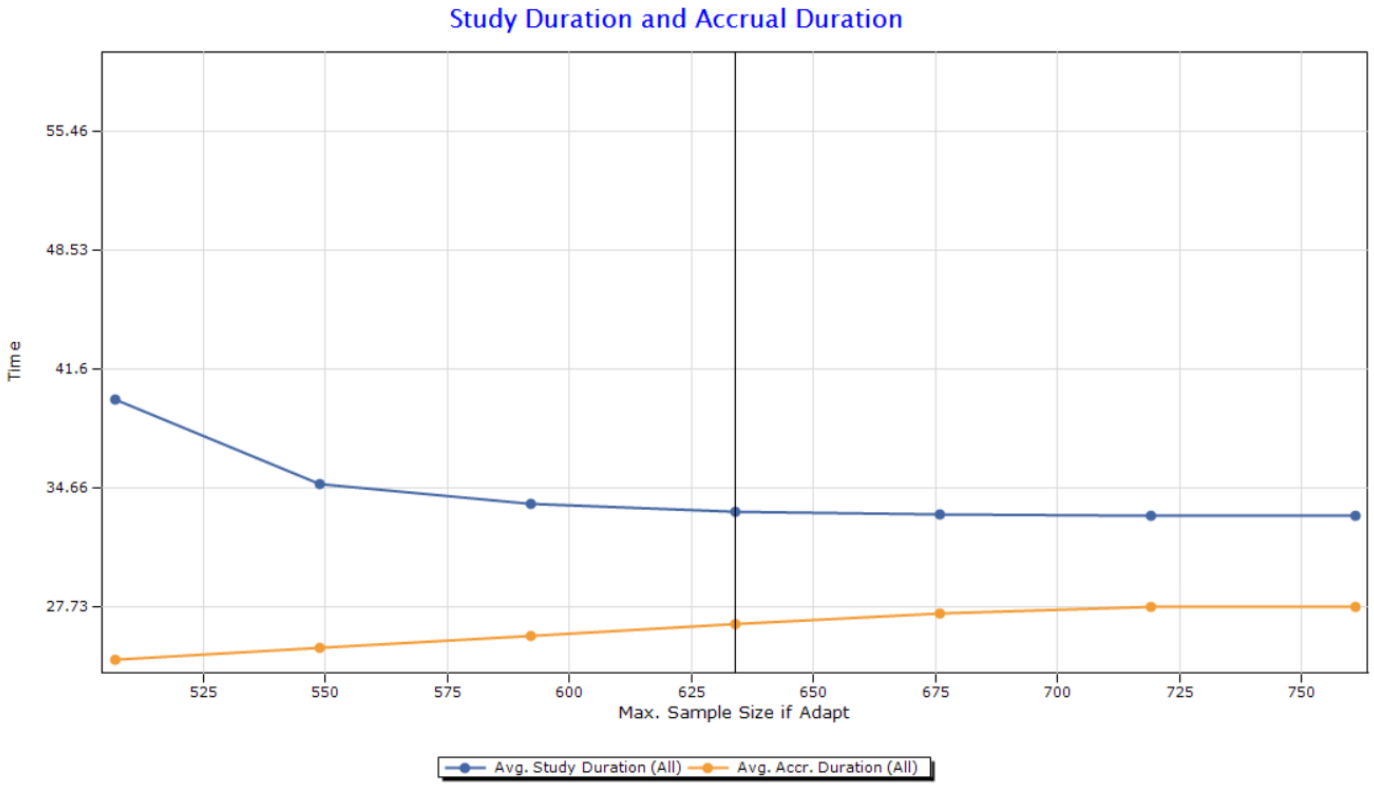
Trade-off between Study duration and *n*



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Concluding 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 non-adaptive trial powered at HR=0.7 but not as powerful (unconditionally) as the non-adaptive design powered at HR=0.77.

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- Mueller HH, and Schafer H. Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and classical group sequential approaches. Biometrics 2001; 57: 886-891.

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Easy Access to the Adaptive Designs That Matter

Delivered by the Thought Leaders Behind the Methods

Software that is Faster & Easier to Use

Popular Fixed and Adaptive Designs at your Fingertips

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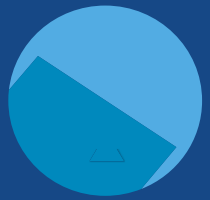
Global Products and Services



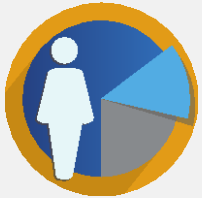
Statistical Software

Industry standard for trial design, including CID adaptive (East, EOD)

Leader in exact statistical solutions (Xact: StatXact, LogXact, Procs)

Operations software (e.g. ACES, EnForeSys, FlexRandomizer)

All 25 top biopharma companies, the FDA, EMA & PMDA use our software



Strategic Consulting

PhD statisticians expert in innovative design & complex statistical questions

Experts in Data Science, PK/PD, Enrolment & Event Forecasting, Portfolio/Program Optimization (NPV)

Project-Based Services

Reliable Biometrics service provider delivering high quality, on time

Lead staff with over 15 years industry experience on average

Including biostatistics & programming, ISC, data management, PK/PD analysis, medical writing

Functional Services Provision (FSP)

Creation of dedicated teams operating within/as an extension of the client's own biostatistics & programming, data management and PK/PD teams

Leader in offshoring of Biometrics competencies

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Q&A Session

Conclusion

Final Remarks

- The statistical methodology for adaptive designs is well established
- Operational and regulatory concerns are a greater barrier to implementation
  - Auditable processes for documenting who saw what documentation and when
  - How will knowledge of interim decision affect the investigator behavior?
  - Will FDA/EMEA approve the design?
- Gradually these concerns are being resolved

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Upcoming Webinars

Topic	Date	Time	
Adaptive Umbrella Trial Using MAMS Module	Tuesday, April 14, 2020	11:00AM EDT | 16:00 GMT	✓
Phase 1 dose escalation trials with ESCALATE	Wednesday, April 22, 2020	11:00AM EDT | 16:00 GMT	✓
Phase 2 Dose-finding Studies with MCP and Modelling Techniques	Wednesday, April 29, 2020	11:00AM EDT | 16:00 GMT	✓
Conducting Sample Size Reassessment with Time-to-event Endpoints	Wednesday, May 6, 2020	11:00AM EDT | 16:00 GMT	✓
Refocus your Enrollment to the Subpopulation of Interest with ENRICH	Wednesday, May 13, 2020	11:00AM EDT | 16:00 GMT	

Respond to survey in post-webinar thank you email to request certificate of attendance for today's webinar.
Recordings will be posted to www.cytel.com.

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Thank you

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Thank you!