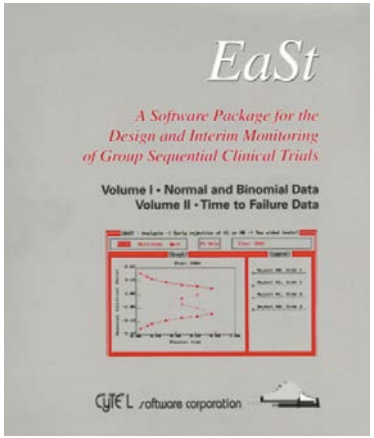
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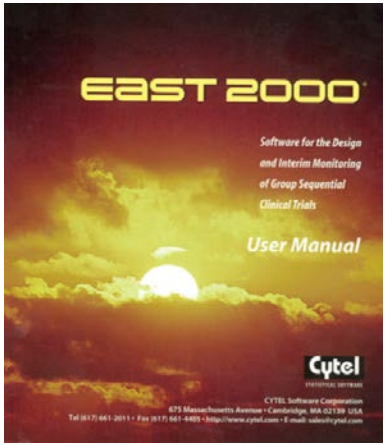
Introduction to East

Pantelis Vlachos

Pantelis.Vlachos@cytel.com

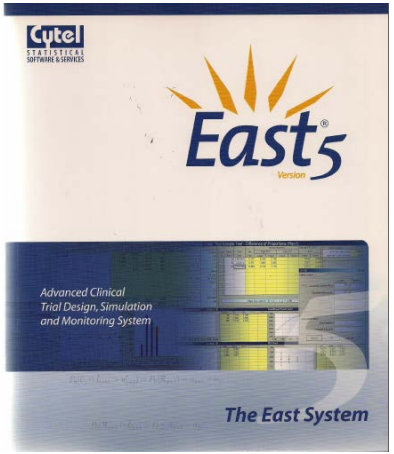


1994



2000





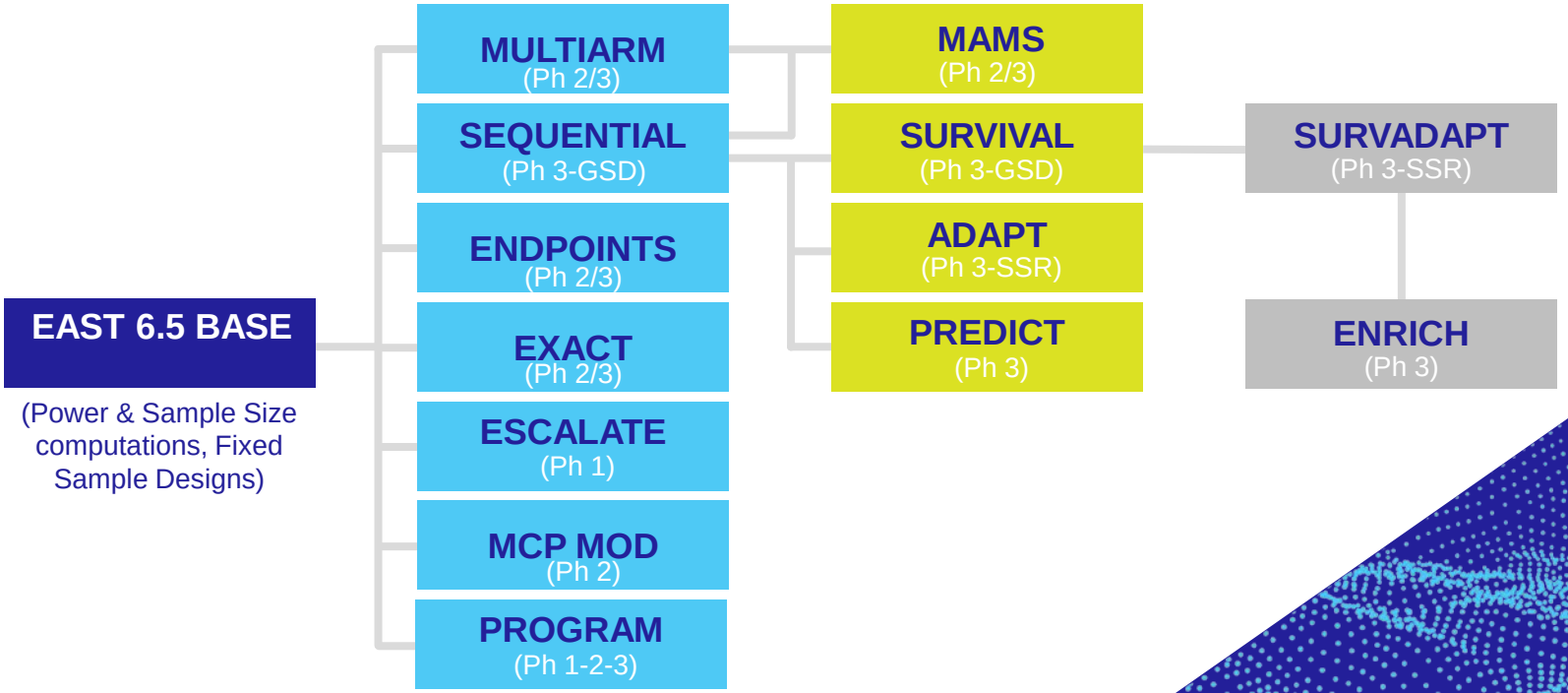
2010

What is special about the new East®?

Broad coverage of designs for biostatisticians
One integrated tool for all types of designs: fixed sample, group sequential or adaptive
Superior User Interface
- Multiple windows with graphs and tables
- Organized storage of designs in workbooks

Rapid creation, viewing and filtering of multiple scenarios for design parameters
Commitment to continuous improvement and expansion of features

East Modules and Dependencies



Cytel

East gives you easy access to the adaptive designs that matter

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.

East SEQUENTIAL

SUCCESSFUL OUTCOME:	**Compare operating characteristics of group sequential designs**
Pre-Requisites:	East BASE
Functions:	• Extensive selection families of stopping rules for efficacy and futility • Display boundaries on multiple scales. • Optimize trial design for savings in sample size, study duration, and cost • Conditional and Predictive Power calculations for interim decisions
New in 6.5:	• Equivalence Group Sequential Designs
Note:	•Cytel also offers Proc East MONITOR as a SAS PROC to facilitate your usage of SAS to monitor trials designed using East SEQUENTIAL.

East SURVIVAL

Test survival endpoints in superiority and non-inferiority studies

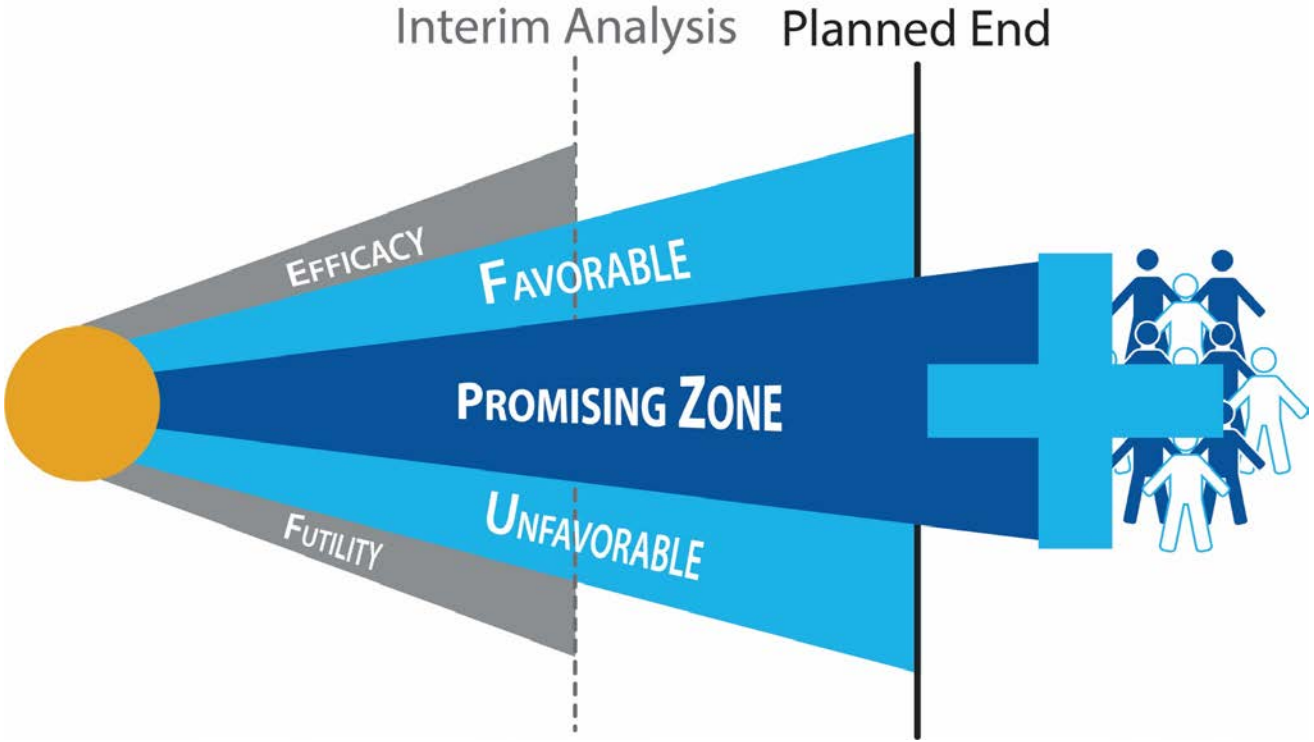
SUCCESSFUL OUTCOME:	**Compute events, sample size, study duration, for complex survival designs**
Pre-Requisites:	East SEQUENTIAL
Functions:	• Variable and fixed subject follow-up • Piecewise hazard rates, accruals, and dropouts • Charts for predicting events/sample size, accrual and study duration • 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.

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.

ADAPT / SURVAdapt: Adaptive Sample Size Re-estimation



East ESCALATE

ADAPTIVE PHASE 1 DOSE-ESCALATION STUDIES

SUCCESSFUL OUTCOME:	IDENTIFICATION OF THE MAXIMUM TOLERATED DOSE (MTD)
Pre-Requisites:	East BASE
Description:	• Simulate dose-toxicity profiles and designs • Dose recommendations for next cohort of patients • Methods include: 3+3, Continual Reassessment Method, Bayesian Logistic Regression Model, and modified Toxicity Probability Interval • Dual-agent dose combination designs (BLRM, PIPE)
Benefits:	• Better characterization of the MTD • Clearly communicate critical information to clinicians • Improve screening and selection of active agents to carry forward
New in 6.5:	• mTPI-2

East MULTIARM

SUCCESSFUL OUTCOME:	**Strong Error Control for Multiplicity in Multi-arm Trials**
Pre-Requisites:	East BASE
Functions:	• Continuous, Binomial endpoints and Survival • Establish strong control of the family-wise error rate. • Fast design by batch simulation • Types of power: global, disjunctive, conjunctive, marginal • Tests include: Dunnett, Bonferroni, Sidak, Holm, Hochberg, Hommel, Fixed Sequence, Fallback

East MAMS

MULTI-STAGE MULTI ARM DESIGNS

SUCCESSFUL OUTCOME:	**Compare operating characteristics of multi-arm group sequential designs**
Pre-Requisites:	East MULTIARM, East SEQUENTIAL
Functions:	• 2-stage “Treatment Selection” design using p-value combination approach by Posch et. al. (Statistics in Medicine, 2005) • MAMS design – Extension of GSD to more than 2 arms
Benefits:	• Identification of promising therapies and inference on selected treatments performed in two or more stages • Multiple treatments to be compared with a control • Allows several primary research questions to be answered in a single trial with increased efficiency compared to separate trials
New in 6.5:	• Binomial multi-stage; Survival p-value combination

East MCPMod

MULTIPLE COMPARISON AND MODELING APPROACHES FOR DOSE FINDING

SUCCESSFUL OUTCOME:	**Improve efficiency of identifying a more effective dose**
Pre-Requisites:	East BASE
Functions:	• MCPMod design: design dose-finding clinical trials • MCPMod Analysis: analyze continuous, discrete or count data using the MCPMod methodology
Benefits:	• Combination of MCP (Multiple comparison procedures) and Mod (modeling) approaches (Bornkamp et al., 2009) for fitting a dose-response •East accepts raw subject data, summarized data or data with a covariance matrix for discrete and count data and raw data for continuous endpoints. • Perform multiple contrast tests to control Type I error, adjusting for the fact that multiple candidate dose-response models are being considered.
Note:	•Note: Cytel also offers Proc MCPMod as a SAS PROC to facilitate your usage of SAS to analyze your data using the modern MCPMod method.

East Exact

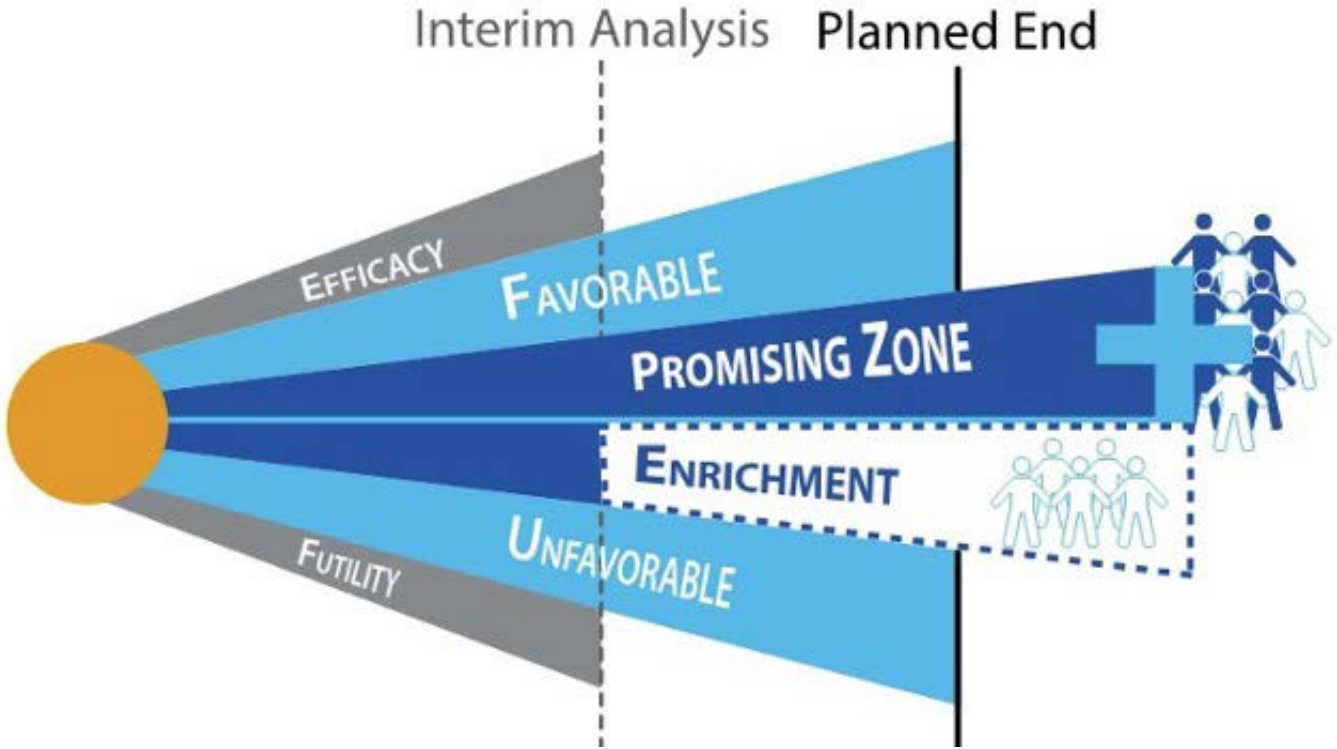
SUCCESSFUL OUTCOME:	**Design and monitor trials using exact binomial distributions**
Pre-Requisites:	East BASE
Functions:	• Ideal for small-sample trials, or Phase 2 single-arm screening trials • Includes: Exact single-stage, optimal and mini-max two-stage, group sequential designs for single-arm studies

East ENRICH

ADAPTIVE POPULATION ENRICHMENT

SUCCESSFUL OUTCOME:	**Prospective use of patient characteristics to obtain study population in which detection is more likely than in unselected population**
Pre-Requisites:	East SURVAdapt
Functions:	• Simulation of a population enrichment design with a time-to-event endpoint •Adaptive rules for increasing sample size in full of sub-populations, or other possibilities
Benefits:	•Design starts out by enrolling subjects from a full population, consisting of a subpopulation of interest and its complement. •East user to perform an interim analysis and decide whether to continue enrollment in both subpopulations with or without sample size re-estimation, only continue enrollment from the subpopulation of interest, or terminate the trial for futility.

ENRICH: Extending SURVAdapt

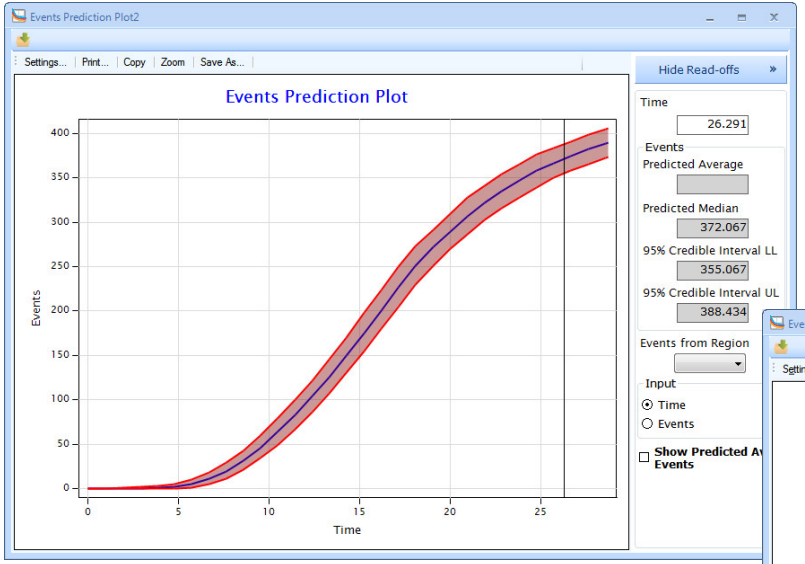


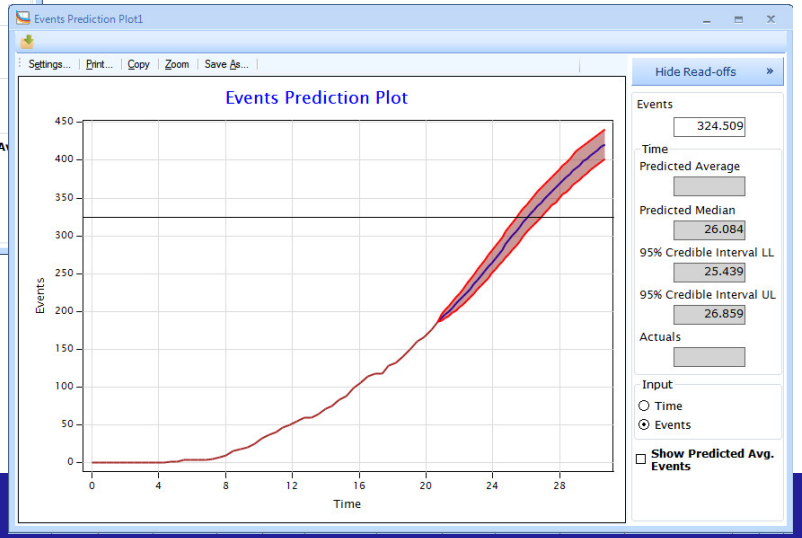
East PREDICT

FORECASTING TRIAL SUCCESS AND TIMELINES

SUCCESSFUL OUTCOME:	PREDICTION OF THE FUTURE COURSE OF THE TRIAL
Pre-Requisites:	East SURVAdapt
Functions:	• Include Region/Site Information: Simulate enrollment and trial duration • Conditional Simulations at Interim: Probabilistic statements about accruals/events/duration • Predicted Interval Plots: expected treatment effects and confidence intervals at future looks • Blinded and unblinded prediction
Benefits:	• Improve Planning and Decision-making • Timing of major milestones • Probability of success for your trial
New in 6.5:	• Weibull distribution

PREDICT: Visualize uncertainty in enrollment timelines and trial duration





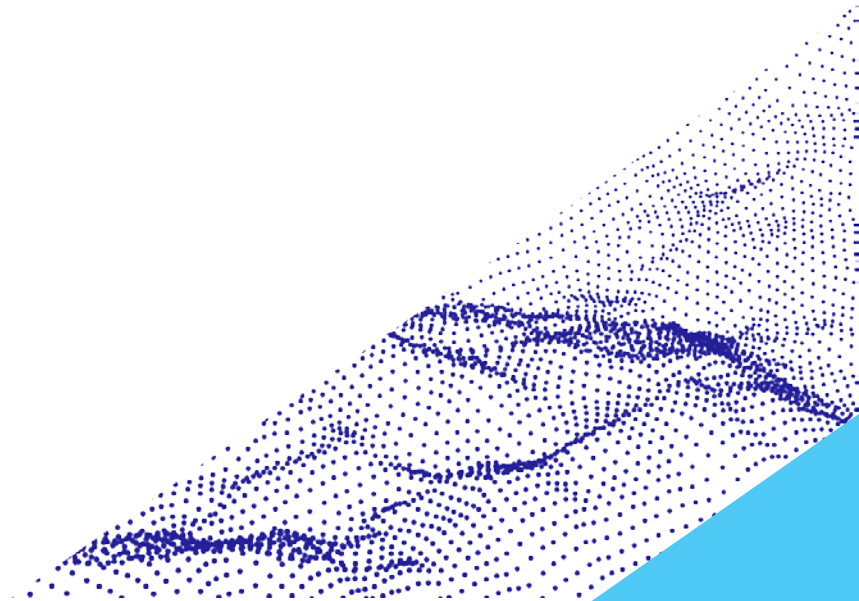
East PROGRAM

PROGRAM DESIGN THROUGH SIMULATION

SUCCESSFUL OUTCOME:	**Simulate a clinical development program consisting of a sequence of two studies**
Pre-Requisites:	East BASE
Functions:	• Dose escalation followed by cohort expansion. In the dose escalation phase, the goal is to determine the maximum tolerated dose. In the cohort expansion phase, go no-go decisions are taken based on pre-specified criteria for efficacy •Combination of multiple trials: single- or multi-look single proportion design, Simon's two stage design or a single- or multi-look logrank test followed by multi-look logrank test given accrual duration and study duration design for survival endpoint
Benefits:	• Bayesian or frequentist go no-go criteria for single mean or single proportion or single survival endpoint • Specification of the time duration between the end of the first trial and the beginning of the second trial. • Computation of operating characteristics for the entire program after simulating both trials.

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East Demo

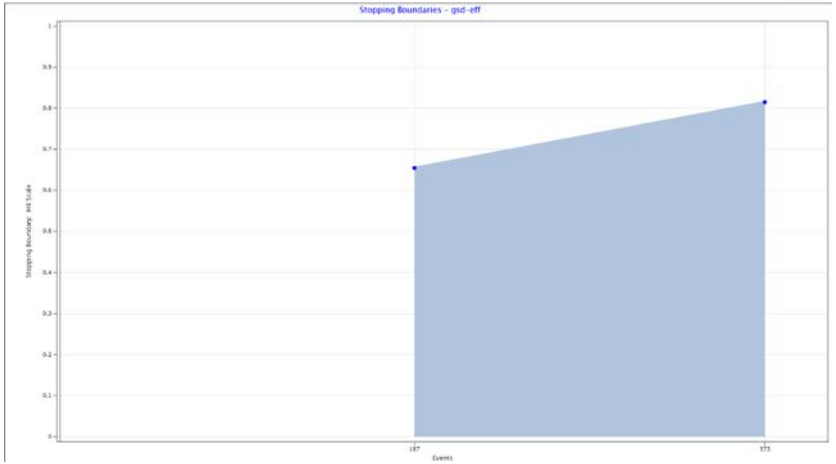


Design Of A Non Small Cell Lung Cancer Clinical Trial

Design Parameter	Value
Primary Endpoint	OS
α	0.025 1-sided
Power	90%
Interim Analysis	To be explored
Median (Control Arm)	5 months
Median (Experimental Arm)	7 months
Hazard Ratio	0.714
Sample Size	~460
Events	~375
Plan to enroll for 24 months and follow for 6 more months	

Design Summary

	webinar:fixed	webinar:gsd-eff
Mnemonic	SU-2S-LRSD	SU-2S-LRSD
Test Parameters		
Design Type	Superiority	Superiority
No. of Looks	1	2
Test Type	1-Sided	1-Sided
Specified α	0.025	0.025
Power	0.901	0.9
Model Parameters		
Allocation Ratio (nt/nc)	1	1
Hazard Ratio (Alt.)	0.714	0.714
Var (Log HR)	Null	Null
Boundary Parameters		
Info. Fraction at Interim Look		0.5
Efficacy Boundary		Gm (-5)
Accrual & Dropout Parameters		
Subjects are Followed	Until End of Study	Until End of Study
No. of Accrual Periods	1	1
No. of Dropout Pieces	1	1
Sample Size		
Maximum	457	458
Expected Under H0	457	457.723
Expected Under H1	457	422.92
Events		
Maximum	372	373
Expected Under H0	372	372.645
Expected Under H1	372	321.492
Study Duration		
Maximum	30	30
Expected Under H0	27.771	27.767
Expected Under H1	29.94	26.472
Accrual Duration		
Maximum	24	24
Expected Under H0	24	23.985
Expected Under H1	24	22.162



This Design Has No Futility Boundary

Design Details

Test Parameters	
Design ID	gsd-eff
Design Type	Superiority
Number of Looks	2
Test Type	1-Sided
Specified α	0.025
Power	0.9
Model Parameters	
HR = λ_t/λ_c	
Under H0	1
Under H1	0.714
Ratio of Medians:	1.4
Med. Surv. Time Control (m_c)	5
Med. Surv. Time Treatment (m_t)	7
Var (Log HR)	Null
Allocation Ratio (n_t/n_c)	1
Boundary Parameters	
Efficacy Boundary	Gm (-5)
Accrual / Dropouts Parameters	
Cum % Accrued	100
Accrual Duration	24
Max Study Duration	30
Dropout	Yes
Prob. of Dropout by Time =	12
Control	0.04
Treatment	0.04

Sample Size Information

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum	228	230	458
Expected H1	211.46	211.46	422.92
Expected H0	228.861	228.861	457.723
Events (s)			
Maximum	196	177	373
Expected H1	178.888	157.462	321.492
Expected H0	186.385	186.385	372.645
Dropouts (d)			
Maximum	4	7	11
Expected H1	3.723	5.892	9.615
Expected H0	4.994	4.996	9.99
Maximum Information (I):			93.25

Accrual and Study Duration

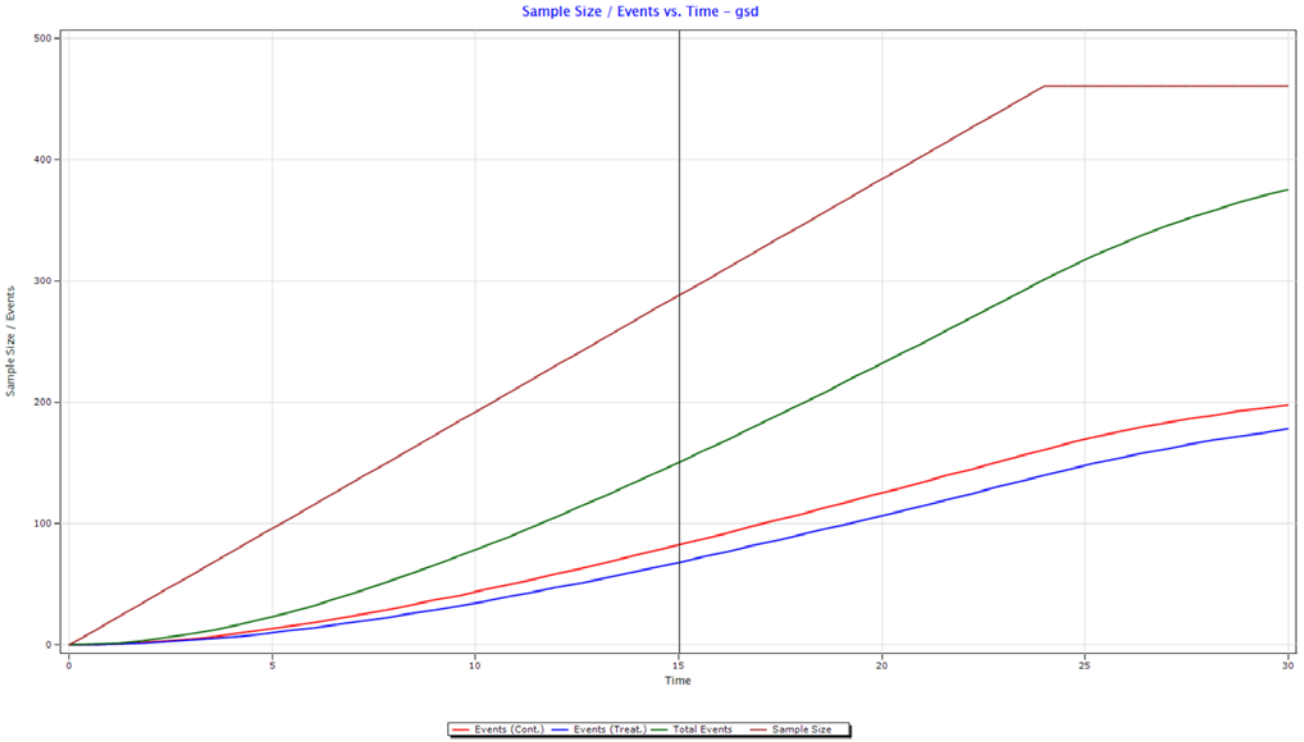
	Accrual Duration	Study Duration
Maximum	24	29.962
Expected H1	22.162	26.472
Expected H0	23.985	27.767

This Design Will Enroll 458 Patients & Wait For The Arrival Of 373 Events.

Events, Sample Size, Dropouts, Pipeline and Analysis Times: Look by Look (Under H1)

Look #	Info. Fraction (s/s_max)	Sample Size (n)	Events (s)	Dropouts (d)	Pipeline (n-s-d)	Analysis Time	Boundary Crossing Probability (Incremental)
							Efficacy
1	0.501	332	187	6	139	17.362	0.2769
2	1	458	373	11	74	29.962	0.6231

Events Accumulation (Ignores Site Level Data)



Assumes Constant Enrollment For 24 Months & 6 More Months For Follow-up

Thank you

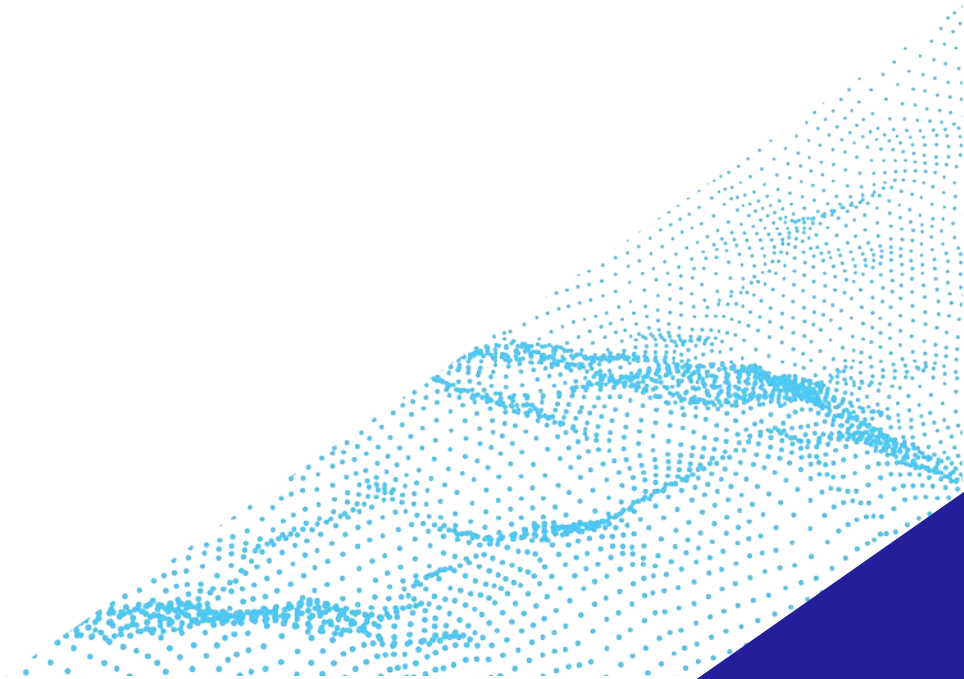


Pantelis Vlachos, Ph.D.
Pantelis.Vlachos@cytel.com
Cytel Inc. | Geneva

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Introduction to Survival trials



Introduction to Survival Designs in Clinical Trials

Survival trial:

Primary endpoint is time from entry of a patient into the study until a specific event of interest. Survival endpoints are often used as primary endpoints in various therapeutic areas like oncology, cardiovascular, and immunology.

Example:

- Death
- Tumor Recurrence
- Heart Attack

Survival Trial also known as:

- Time-to-event trial
- Time-to-failure trial

Example1: JUPITER trial

Objective: Justification for the Use of Statins in Prevention of cardiovascular event: An Intervention Trial Evaluating Rosuvastatin (**JUPITER**) examined the question of whether treatment with 20 mg of rosuvastatin daily, as compared with placebo, would reduce the rate of first major cardiovascular events *(Ridker et al., 2008)*

Primary Endpoint: Occurrence of a first major cardiovascular event as defined by principal investigator.

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Example2: Advanced Colorectal Carcinoma with AMT2003 trial

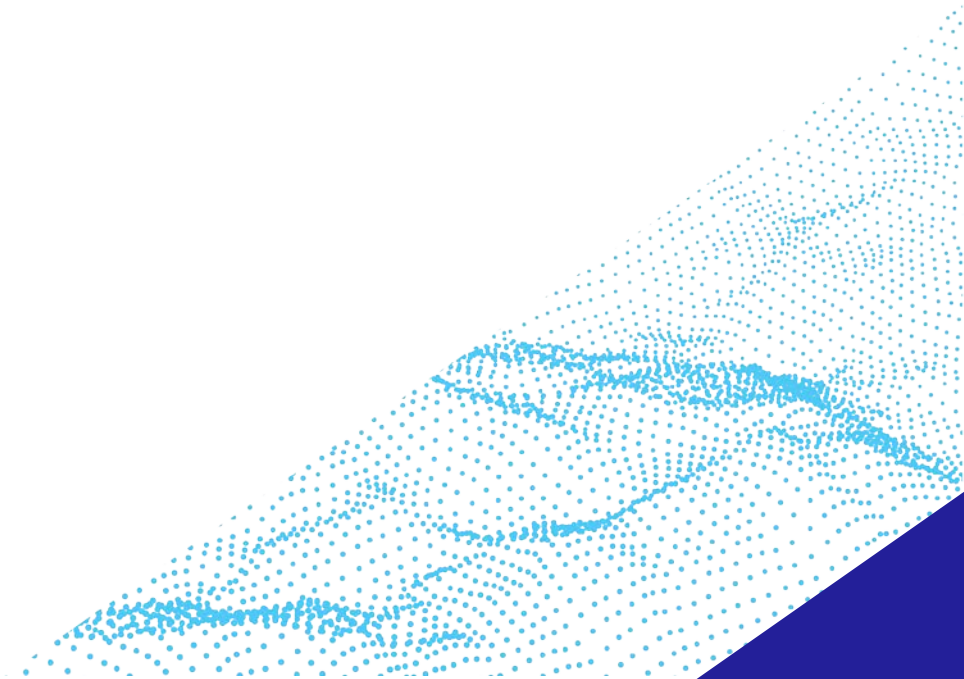
Objective: Study to Evaluate Progression Free Survival in Cancer Patients With Advanced Colorectal Carcinoma With ***AMT2003.***

Primary Endpoint: Progression free survival at 18 weeks after registration.

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Survival trials - Basic concepts



Events, Dropouts and Censoring

At the end of the study each patient can be categorized into one of the following:

- Resulted in an Event
- Dropped out
- Censored

Note: What contributes to deciding the effectiveness of the treatment is time spent by the patient in the study regardless of event or dropout.

OS and PFS

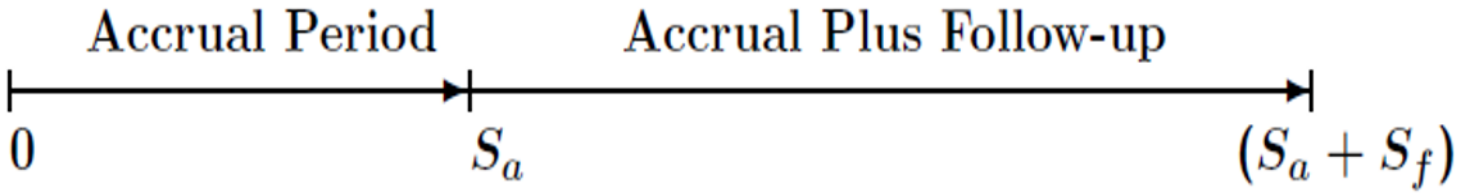
Overall Survival (OS): Duration of time from the date of diagnosis or commencement of treatment of a particular disease that a patient is still alive. It is usually employed to assess how a novel treatment works.

Progression Free Survival (PFS): Duration of time of a disease state, in which a patient lives with the disease condition showing no signs of exacerbating or growing worse.

Accrual and Study Duration

Accrual Duration (Sa): Accrual duration is the time required to achieve the number of patients entering the study.

Study Duration (Sa + Sf): Accrual duration plus the additional follow up time.



Effectiveness of Treatment

- Effectiveness of a treatment is often characterized by following Measures:
  - Hazard Rate (λ): Instantaneous failure rate. Lower the hazard rate better is the chance of survival.
  - Median Survival Time (M): Average survival time. Higher the median survival time, better is the chance of survival.
  - Cum. % Survival Time (S): Proportion of subjects survived at a given time. Higher the Cum. % Survival time, better is the chance of survival

Hypotheses To be Tested

Null Hypothesis of No Difference

$H_0 : \lambda(t) = \lambda(c)$
$H_0 : S(t) = S(c)$
$H_0 : M(t) = M(c)$

Typically,
$H_0 : HR = 1$
$H_0 : \delta = 0$

Alternative Hypothesis

$H_1 : \lambda(t) < \lambda(c)$
$H_1 : S(t) > S(c)$
$H_1 : M(t) > M(c)$

Typically,
$H_1 : HR < 1$
(like 0.7 or 0.6)
$H_1 : \delta < 0$

Design Computations

What do we need?

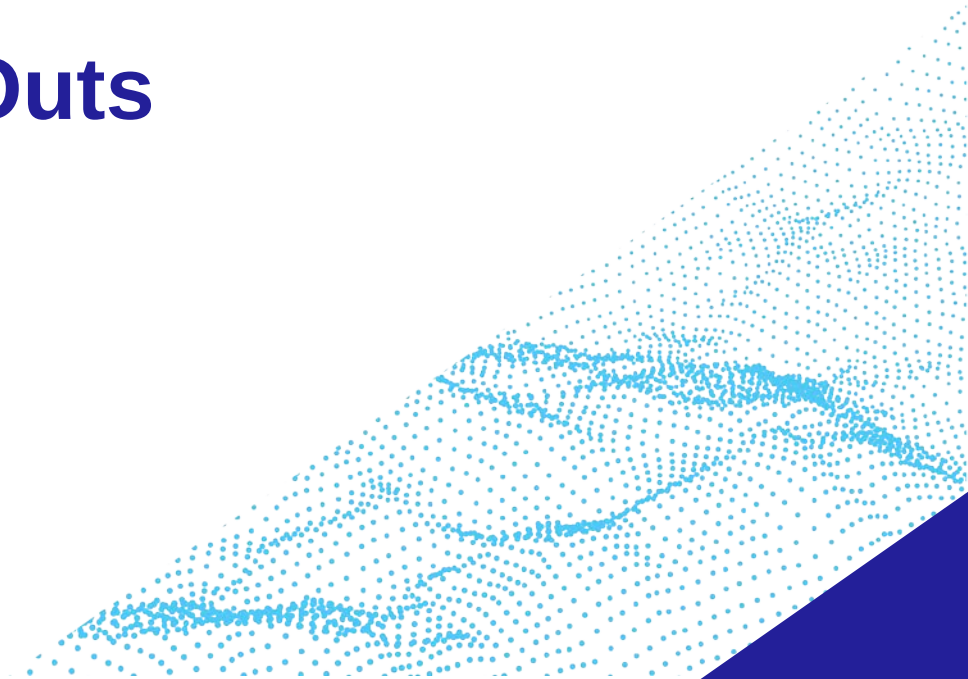
- Max. Events (Dmax)
- Max. Sample Size (Nmax)
- Study duration

In design phase, it may often be necessary to perform design computations for optimistic as well as pessimistic scenarios in terms of sample size, accrual process as well as study duration.

East allows you to perform these computations seamlessly and compare operating characteristics of various designs.

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Incorporating Drop-Outs

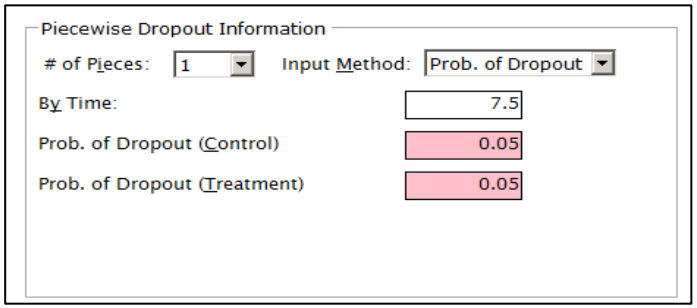


Adding Dropout Information

- Suppose, investigators expect 5% of the patients to drop out in each of the treatment and the control groups.
- Problem is how to translate this estimate to either a hazard rate or a probability of dropout in a specific period, in the light of the facts that subjects accrue over a time period and the risk set for dropouts will be diminishing due to subjects leaving the study because of events.
- This happens since both events and dropouts follows exponential distribution and dropouts compete with events.
- One way to find the right specification for dropout rate is by trial-and-error method.

JUPITER Design Dropouts

- Dropouts: 5% per year in both the treatment and placebo arms.



- Dropouts assumed exponential distribution, with corresponding hazard rates
- Prob. of dropout calculated for patient time (from study entry), not calendar time (from study start)

Trial and Error method

All the subjects are not accrued at the beginning of this 7.5 years duration study.

Specifying a subject's probability of dropping out as 0.05 within 7.5 years may not be appropriate.

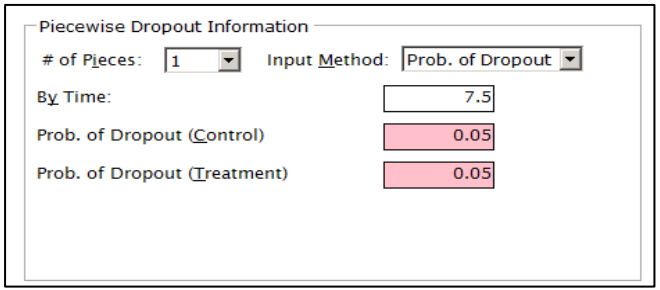
Assume that the average accrual duration of the subjects is 2 years for 4 years of accrual duration.

Each subject may be in the study on the average for a maximum of 5.5 years (Study Duration-Average accrual duration).

May not work in non-constant accruals study.

Adjustments

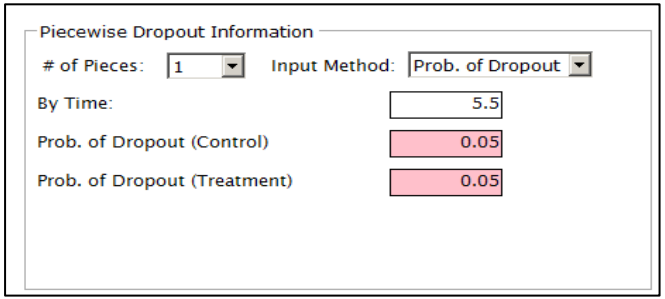
Dropout probability:
557/15378*100=3.6%



Sample Size Information

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum	7688	7690	15378
Expected H1	7689	7689	15378
Expected H0	7529.647	7529.647	15059.294
Events (s)			
Maximum	312	236	548
Expected H1	242.244	182.469	424.177
Expected H0	175.322	175.322	350.118
Dropouts (d)			
Maximum	277	280	557
Expected H1	214.884	216.485	431.368
Expected H0	155.554	155.989	311.544
Maximum Information (I):			137

Dropout probability:
759/15486*100=4.9%



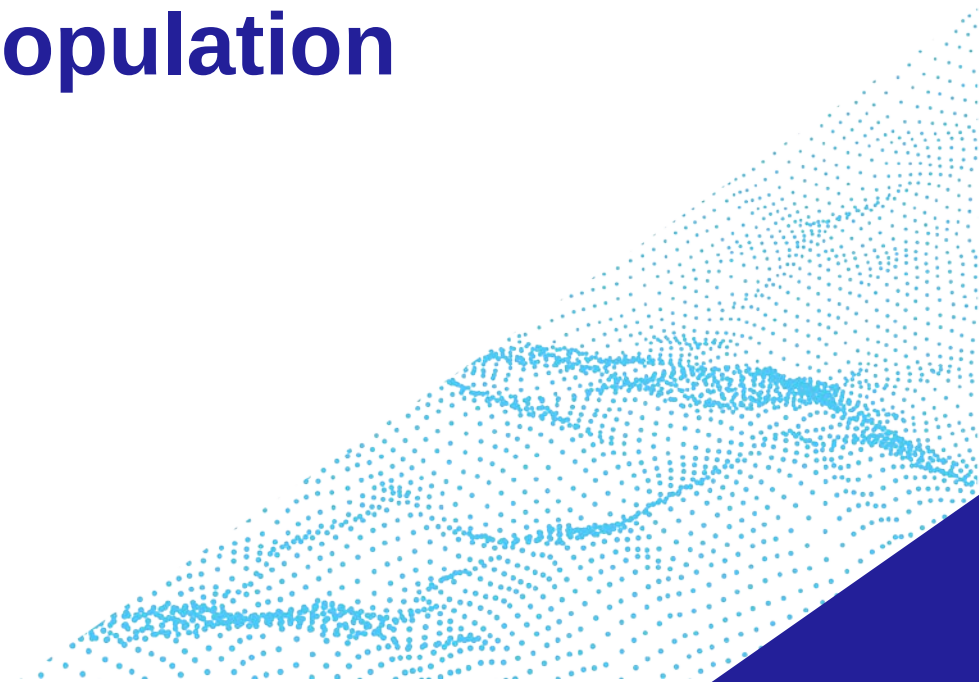
Sample Size Information

	Control Arm	Treatment Arm	Total
Sample Size (n)			
Maximum	7742	7744	15486
Expected H1	7743	7743	15486
Expected H0	7577.463	7577.463	15154.927
Events (s)			
Maximum	312	236	548
Expected H1	242.302	182.51	424.177
Expected H0	175.381	175.381	350.118
Dropouts (d)			
Maximum	378	381	759
Expected H1	293.011	295.064	588.075
Expected H0	212.184	212.184	424.369
Maximum Information (I):			137

Questions?

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Phase III: Adaptive Population Enrichment

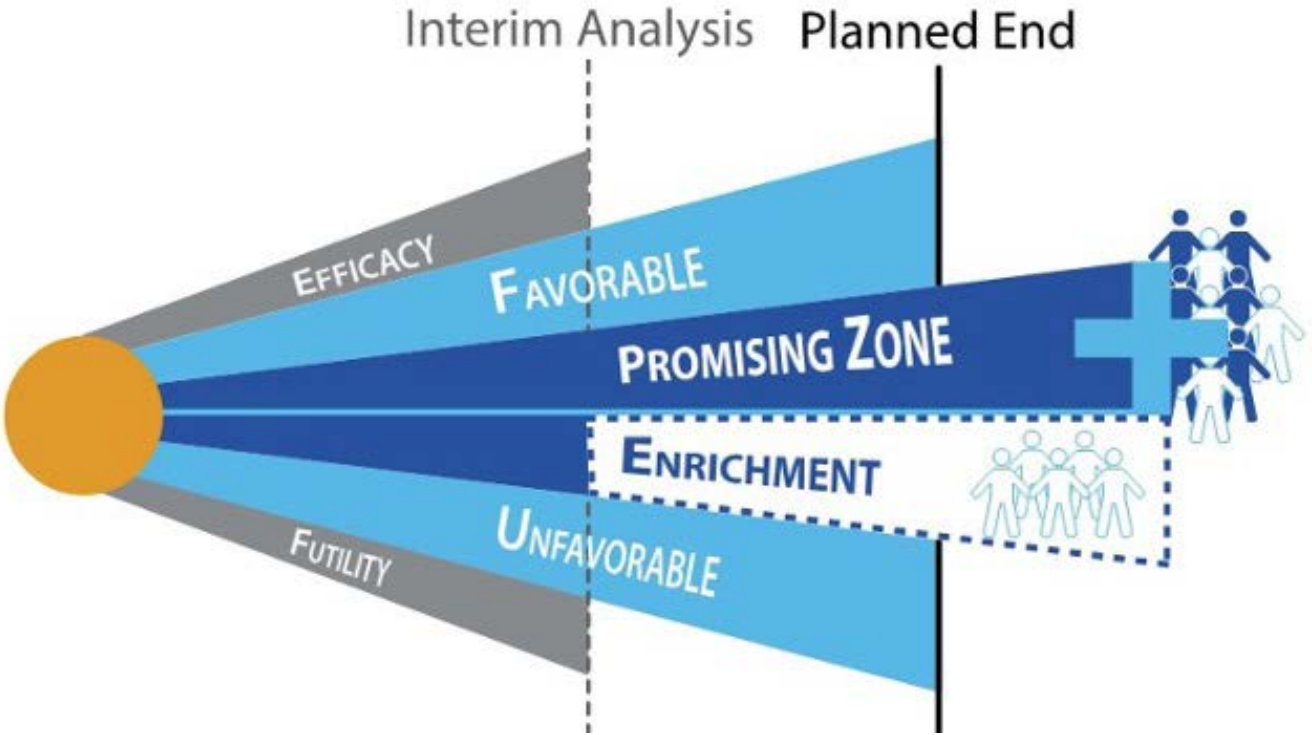


East ENRICH

ADAPTIVE POPULATION ENRICHMENT

SUCCESSFUL OUTCOME:	**Prospective use of patient characteristics to obtain study population in which detection is more likely than in unselected population**
Pre-Requisites:	East SURVAdapt
Functions:	• Simulation of a population enrichment design with a time-to-event endpoint •Adaptive rules for increasing sample size in full of sub-populations, or other possibilities
Benefits:	•Design starts out by enrolling subjects from a full population, consisting of a subpopulation of interest and its complement. •East user to perform an interim analysis and decide whether to continue enrollment in both subpopulations with or without sample size re-estimation, only continue enrollment from the subpopulation of interest, or terminate the trial for futility.

Extending SURVAdapt



Overview

- Background
- Method and Assumptions
- Software
- Case study in Angiosarcoma
- Q&A

Background

Population Enrichment (PE): *prospective use of any patient characteristic to obtain a study population in which detection is more likely than in unselected population*

Types of PE:

- Prognostic: identify high risk patients based on biomarkers
- Predictive: identify patients more likely to respond

Issues:

- Cost of clinical trials increasing
- Discovery of blockbuster drugs on the decline; move away from “one size-fits-all idea”

Background (cont)

Importance:

- Help identify high responsive group, detect treatment effect with smaller sample size
- Failed molecules from one study, may succeed in a different group

Examples:

- BMS immunotherapy Opdivo failed in lung cancer study whereas Merck competitor Keytruda succeeded: In later case study population was enriched by including only subjects with high level of PD-L1
- ISPY2 identifies different combination therapies across different biomarker subgroups

Method & Assumptions

Based on **Predictive Enrichment**

Study population: divided in two groups based on a predefined biomarker

Study will materialize into two independent cohorts

- First cohort recruits from full population
- Second cohort recruitment depends on an interim analysis based on the first cohort data only

At interim:

- Continue with full population
- Continue with sub-population
- Stop the trial for futility

Subpopulation prevalence will be user-specified

Case study: The TAPPAS trial

Angiosarcoma is an ultraorphan disease

Poorly addressed by current treatments

- Pazopanib a VEGF inhibitor shows modest benefit
- TRC105 can compliment Pazopanib by inhibiting endoglin, a different angiogenic target

Adaptive trial considered optimal due to:

- Small population (1800 cases/year)
- Limited prior data
- Subgroup interaction. Greater benefit possible with TRC105 for cutaneous vs visceral tumors

The TAPPAS Trial: Objective

Demonstrate superior PFS of the combination of TRC105 + pazopanib vs single agent pazopanib

Eligibility

Advanced cutaneous and non-cutaneous AS not amenable to curative intent surgery

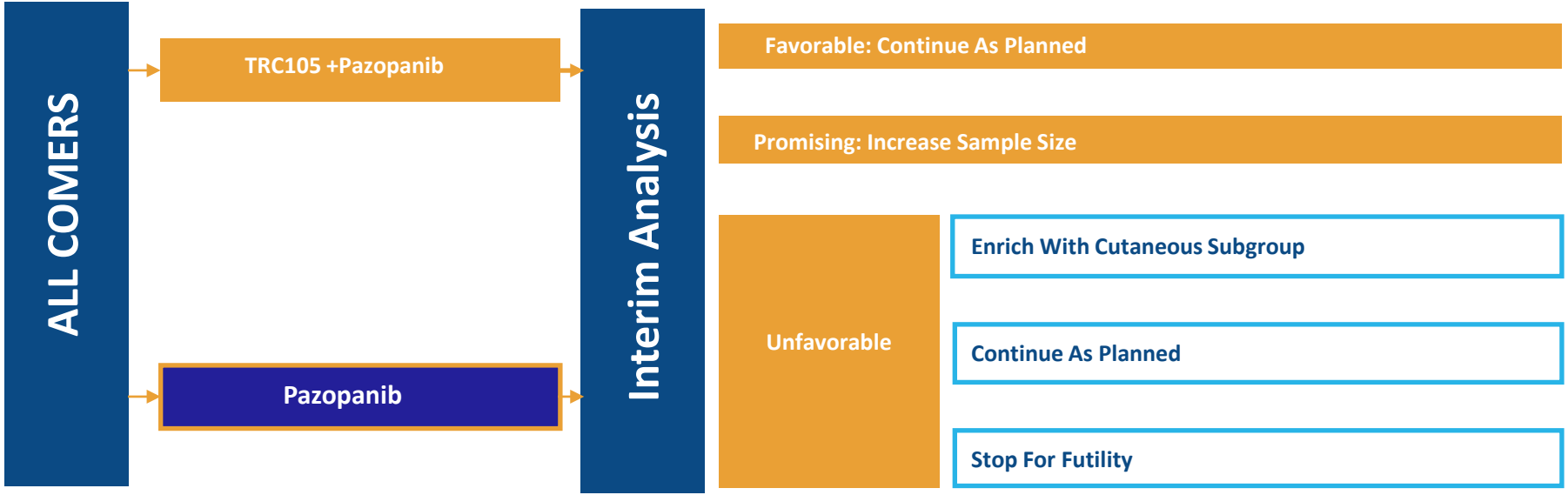
Measurable disease by RECIST 1.1

No prior treatment with a VEGF inhibitor

0,1 or 2 prior lines of therapy

ECOG ≤ 1

2-Stage Design with SSR & Enrichment



p_1: p-value for data from cohort 1
p_2: p-value for data from cohort 2

Preserving type I error

Let H_0^F and H_0^S denote the null hypotheses for the full population and the cutaneous group respectively

Let $H_0^{FS} = H_0^F \cap H_0^S$ denote the global null hypothesis

Closed testing principle states that type I error is strongly controlled as long as

- Each of the hypotheses in the closed family is tested at local level-α
- H_0^F significant only if both tests for H_0^F and H_0^{FS} are significant at local level-α
- H_0^S significant only if both tests for H_0^S and H_0^{FS} are significant at local level-α

Closed Testing With Combination Of P-values

In case of no enrichment, declare significance on Full population if

$$w_1\Phi^{-1}\left(p_1^{FS}\right) + w_2\Phi^{-1}\left(p_2^{FS}\right) > z_\alpha$$
$$w_1\Phi^{-1}\left(p_1^{F}\right) + w_2\Phi^{-1}\left(p_2^{F}\right) > z_\alpha$$

In case of enrichment, declare significance on cutaneous subgroup if

$$w_1\Phi^{-1}\left(p_1^{FS}\right) + w_2\Phi^{-1}\left(p_2^{S}\right) > z_\alpha$$
$$w_1\Phi^{-1}\left(p_1^{S}\right) + w_2\Phi^{-1}\left(p_2^{S}\right) > z_\alpha$$

Special Considerations for Event-Driven Trials

Independence of p_1 and p_2 essential for valid level-a test

Use of auxiliary data in the censored observations of cohort 1 that become completers in cohort 2 **is forbidden**

- ORR data, lab values, toxicities of patients censored for PFS in cohort 1 can provide insights about their eventual PFS result in cohort 2. Type I error could be inflated

Use of auxiliary data to decide on enrichment destroys independence of p_1 and p_2

(Jenkins, Stone and Jennison, Pharmaceutical Statistics, 2011)

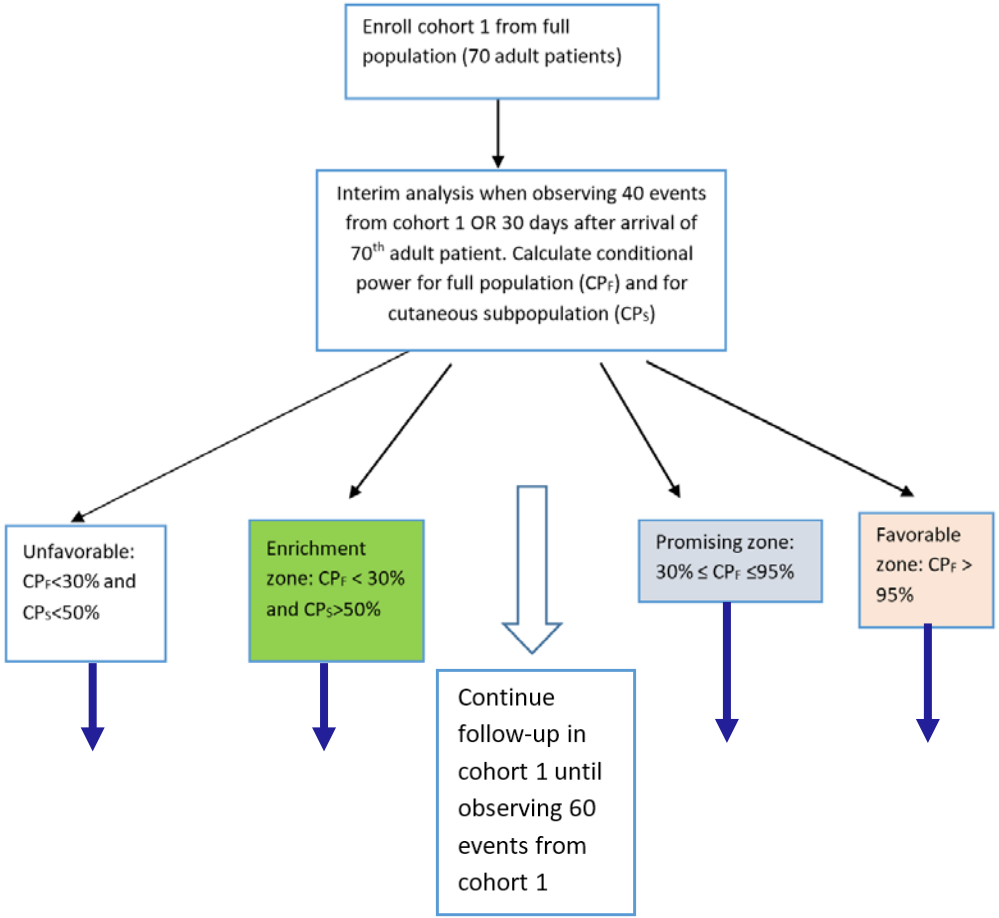
How to permit use of auxiliary data

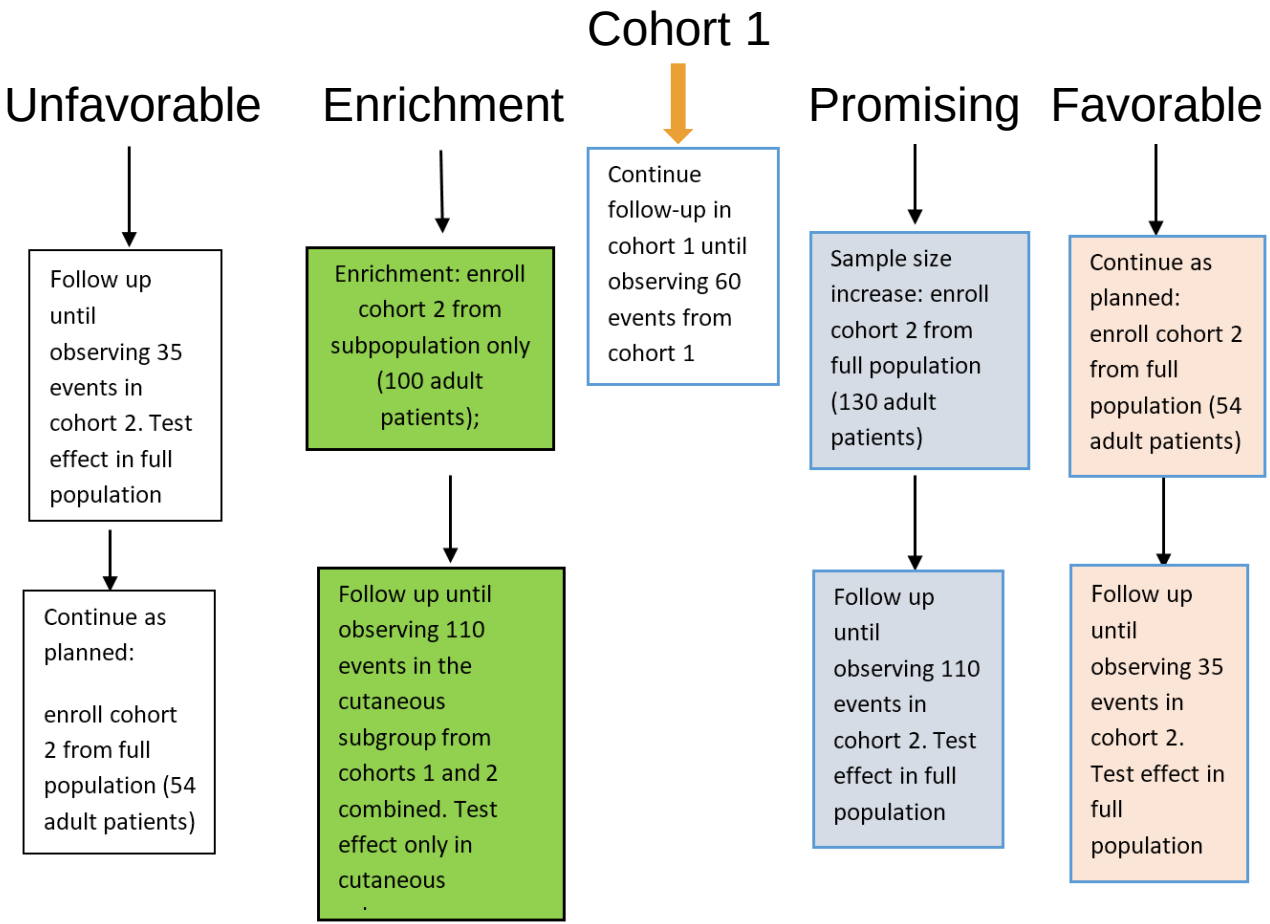
Do not choose the **interim analysis time point** to split data into cohort 1 and cohort 2

Instead, pre-specify allocation of events and sample size to each cohort
before taking the interim analysis

- 70 patients and 60 events for cohort 1
- 54 patients and 35 events for cohort 2
- Interim analysis after 40 events have arrived

That will permit full inspection of all cohort 1 data at interim analysis, including censored data


Enroll cohort 1 from full population (70 adult patients)
Interim analysis when observing 40 events from cohort 1 OR 30 days after arrival of 70th adult patient. Calculate conditional power for full population (CPF) and for cutaneous subpopulation (CPS)
Unfavorable: CPF<30% and CPS<50%
Enrichment zone: CPF < 30% and CPS>50%
Continue follow-up in cohort 1 until observing 60 events from cohort 1
Promising zone: 30% ≤ CPF ≤95%
Favorable zone: CPF > 95%


Cohort 1
Unfavorable
Enrichment
Promising
Favorable
Continue follow-up in cohort 1 until observing 60 events from cohort 1
Follow up until observing 35 events in cohort 2. Test effect in full population
Enrichment: enroll cohort 2 from subpopulation only (100 adult patients);
Sample size increase: enroll cohort 2 from full population (130 adult patients)
Continue as planned: enroll cohort 2 from full population (54 adult patients)
Continue as planned:
enroll cohort 2 from full population (54 adult patients)
Follow up until observing 110 events in the cutaneous subgroup from cohorts 1 and 2 combined. Test effect only in cutaneous
Follow up until observing 110 events in cohort 2. Test effect in full population
Follow up until observing 35 events in cohort 2. Test effect in full population

The TAPPAS trial: non-adaptive case

Control arm (Pazopanib): median time to progression = 4 months

HR expected to be 0.55

Accruals: 8 pts/month

Power: 83%

Test Parameters	
Design ID	fixed
Design Type	Superiority
Number of Looks	1
Test Type	1-Sided
Specified α	0.025
Power	0.834
Model Parameters	
HR = λ_t/λ_c	
Under H0	1
Under H1	0.55
Med. Surv. Time Control (m_c)	4
Med. Surv. Time Treatment (m_t)	7.273
Var (Log HR)	Null
Allocation Ratio (n_t/n_c)	1
Accrual / Dropouts Parameters	
Accrual Rate	8
Dropout	No

Sample Size Information

Sample Size (n)	124
Treatment (n_t)	63
Control (n_c)	61
Events (s)	96
Treatment (s_t)	43
Control (s_c)	53
Information (I)	24

Accrual and Study Duration

Accrual Duration	15.5
Max. Study Duration	20.839

Critical Points

Critical Point	-1.96

The TAPPAS trial: Design parameters

Type I Error (α): 0.025

Rejection Region: Left-Tail

Subpopulation Prevalence: 0.5

Allocation Ratio (n_t/n_c): 1

Subjects are followed: Until End of Study

Initial Sample Size

Cohort #	Sample Size	# of Events	
		Total	At IA
Cohort 1	62	48	40
Cohort 2	62	48	

# of Accrual Periods: 1

Accrual Rate: 8

Time Lag: Coh1 and Coh2: 0

Prevalence Drives Subpopulation Accrual

Survival Information

Input Method: Hazard Rates

Subpopulation

☐ Use Piecewise Hazard Rates

Piece #	Hazard Rates		Hazard Ratio
	Control	Treatment	
1	0.173	0.095	0.55

Complement

☐ Use Piecewise Hazard Rates

Piece #	Hazard Rates		Hazard Ratio
	Control	Treatment	
1	0.173	0.095	0.55

Full Population

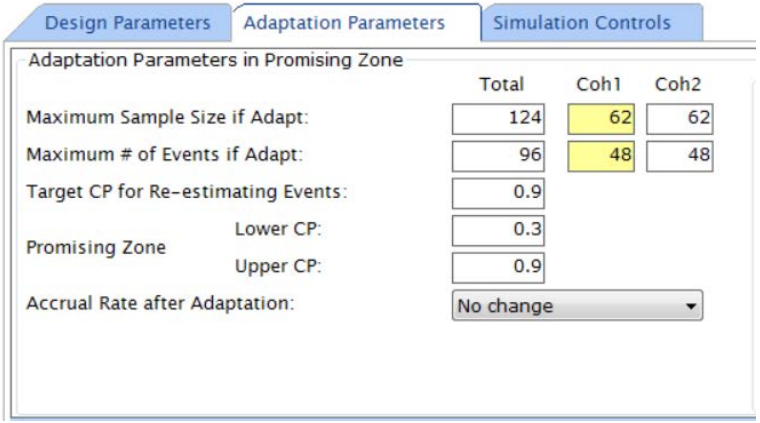
Control	Treatment	Hazard Ratio
0.173	0.095	0.550

Note: Full Population parameters are approximate.

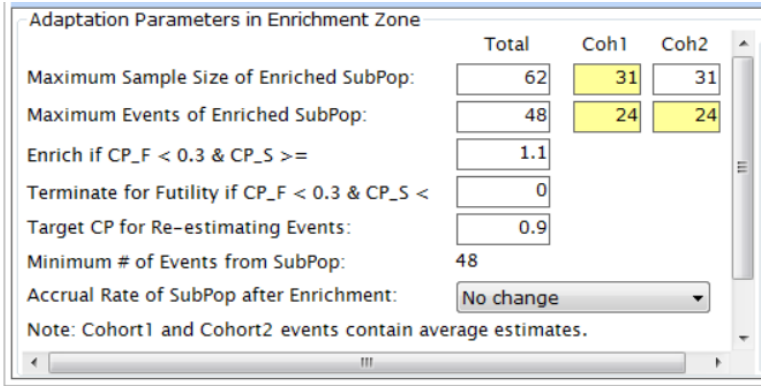
The TAPPAS Trial: Adaptation Parameters Tab

(No Adaptation)

No sample size increase in full population

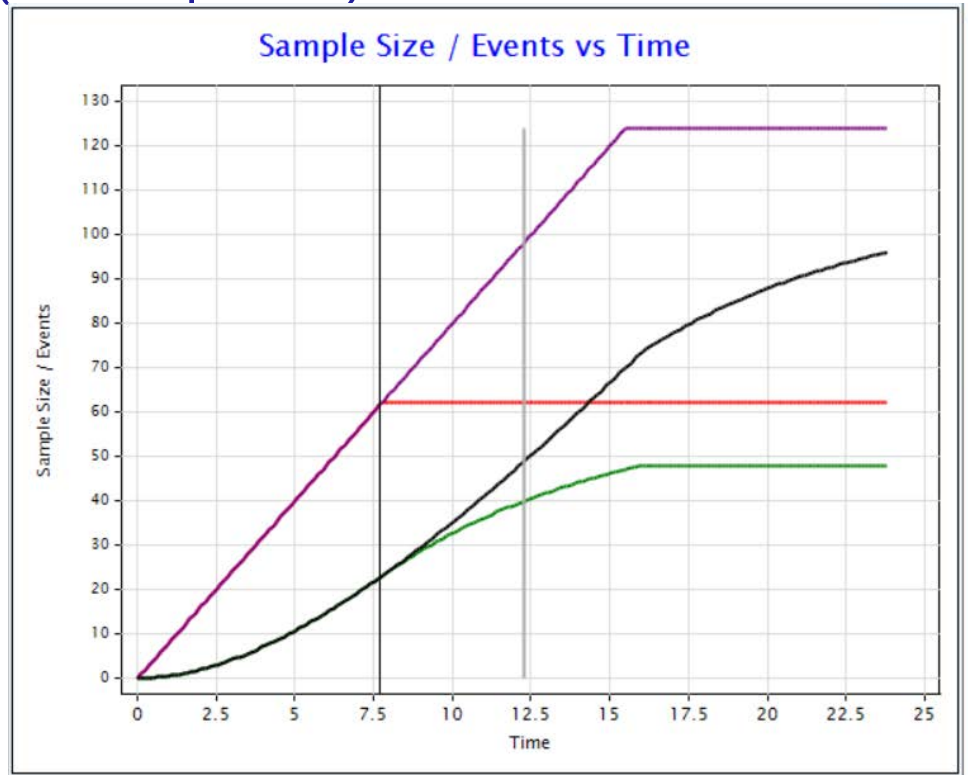


Disable Enrichment and Futility stopping



The TAPPAS Trial: Adaptation Parameters Tab

(No Adaptation)



Time: 7.696 ☑ Display IA Line

	Series	Y
☑	Coh1 Sample Size	62
☑	Coh1 Events	23
☐	Coh1 SubPop Events	
☐	Coh2 Sample Size	
☐	Coh2 Events	
☐	Coh2 SubPop Events	
☑	Coh1&2 Sample Size	62
☑	Coh1&2 Events	23
☐	Coh1&2 SubPop Events	

The TAPPAS Trial: Simulation Results (No Adaptation)

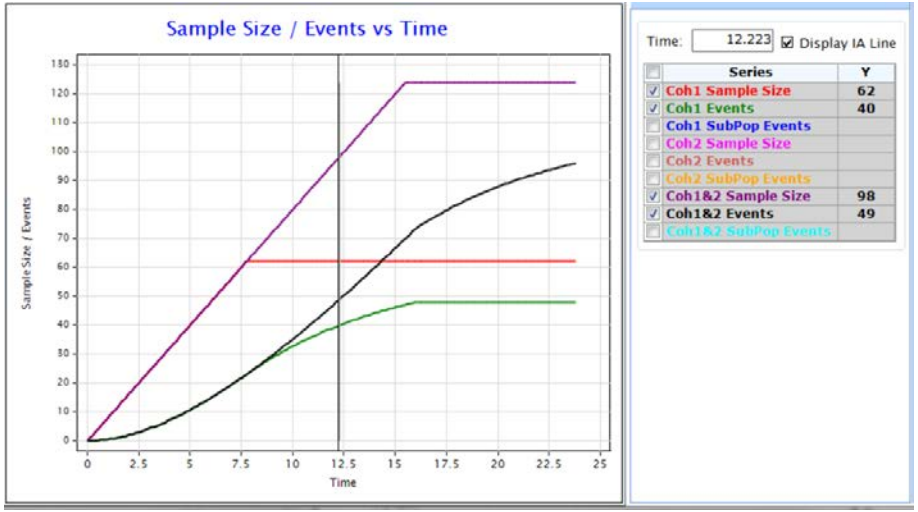
Simulation Summary

Zone		# Simulations	Reject H0_F Only	Reject H0_S Only	Reject Both	Conditional Power	Average Patients	Average Events	Average Study Duration
Unfavourable	(CP_F < 0.3)	19.300%	15.078%	1.969%	22.228%	39.275%	124	96	23.499
Promising	(0.3 <= CP_F < 0.9)	31.190%	25.136%	1.667%	43.027%	69.830%	124	96	23.482
Favourable	(CP_F >= 0.9)	49.510%	22.541%	0.364%	67.905%	90.810%	124	96	23.413
	Overall	100.000%	21.910%	1.080%	51.330%	74.320%	124	96	23.451

Design has 74% power (compared to 83% for fixed design)

An adaptive population enrichment should only be considered if there is a possibility that there is a strong treatment effect in the subpopulation, but NOT its complement

The TAPPAS trial: Design Parameters



When 40 events have arrived, cohort 1 will have met its sample size quota (62 pts) while the total sample size from cohort 1 plus cohort 2 will be 98 patients.

Data from half of these extra 36 pts assigned to cohort 2 will NOT be used if there is enrichment

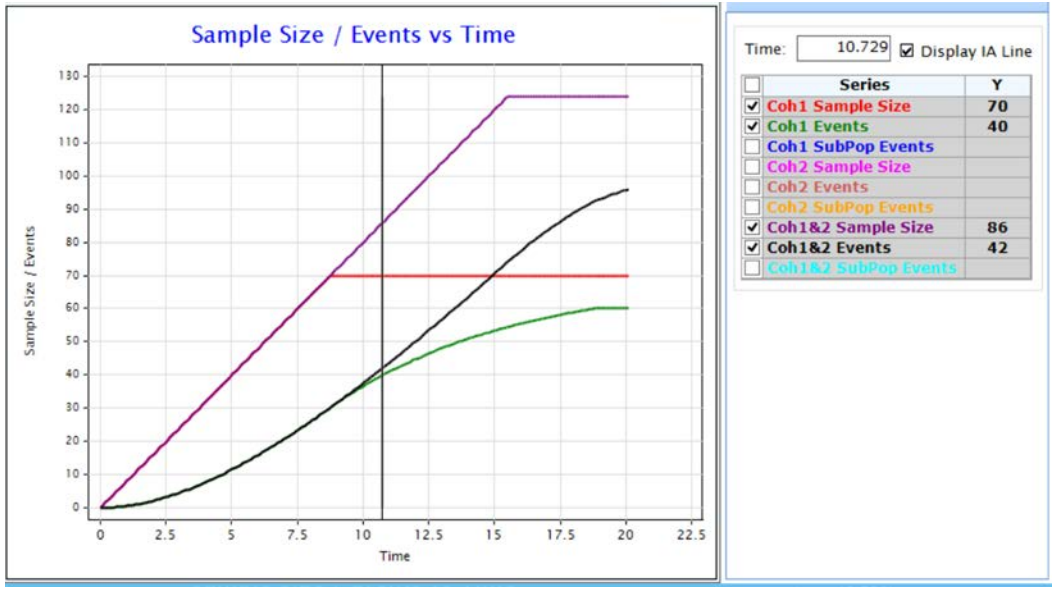
Should increase n and events for cohort 1

The TAPPAS Trial: Design Parameters

Type I Error (α):	0.025
Rejection Region	Left-Tail
Subpopulation Prevalence:	0.5
Allocation Ratio (n_t/n_c):	1
Subjects are followed:	Until End of Study

Initial Sample Size

Cohort #	Sample Size	# of Events	
		Total	At IA
Cohort 1	70	60	40
Cohort 2	54	36	



16 pts have been assigned to cohort 2 at the time of the interim analysis

If interim results fall in the enrichment zone, data from at most 8 cohort 2 patients will be useable

The TAPPAS trial: Adaptation Parameters

Survival Information

Input Method: Hazard Rates

Subpopulation

☐ Use Piecewise Hazard Rates

Piece #	Hazard Rates		Hazard Ratio
	Control	Treatment	
1	0.173	0.095	0.55

Complement

☐ Use Piecewise Hazard Rates

Piece #	Hazard Rates		Hazard Ratio
	Control	Treatment	
1	0.173	0.147	0.85

Full Population

Control	Treatment	Hazard Ratio
0.173	0.119	0.686

Note: Full Population parameters are approximate.

Adaptation Parameters in Promising Zone

		Total	Coh1	Coh2
Maximum Sample Size if Adapt:		200	70	130
Maximum # of Events if Adapt:		170	60	110
Target CP for Re-estimating Events:		0.999		
Promising Zone	Lower CP:	0.3		
	Upper CP:	0.95		
Accrual Rate after Adaptation:		No change		

Adaptation Parameters in Enrichment Zone

	Total	Coh1	Coh2
Maximum Sample Size of Enriched SubPop:	135	35	100
Maximum Events of Enriched SubPop:	110	29	81
Enrich if CP_F < 0.3 & CP_S >=	0.5		
Terminate for Futility if CP_F < 0.3 & CP_S <	0		
Target CP for Re-estimating Events:	0.9		
Minimum # of Events from SubPop:	46		
Accrual Rate of SubPop after Enrichment:	No change		

Note: Cohort1 and Cohort2 events contain average estimates.

The TAPPAS trial: Simulation results (with adaptation)

Zone		# Simulations	Reject H0_F Only	Reject H0_S Only	Reject Both	Conditional Power	Average Patients	Average Events	Average Study Duration
Unfavourable	Stop for Futility (CP_F < 0.3, CP_S < 0)	0.000%	0.000%	0.000%	0.000%	0.000%	0	0	0
	Continue without Enrichment (CP_F < 0.3, 0 <= CP_S < .5)	24.760%	2.625%	4.039%	8.966%	15.630%	124	96	20.212
	Continue with Enrichment (CP_F < 0.3, CP_S >= .5)	18.740%	0.000%	80.843%	0.000%	80.843%	166.655	136.655	36.064
Promising	(0.3 <= CP_F < .95)	37.660%	5.204%	5.762%	69.623%	80.589%	200	170	31.524
Favourable	(CP_F >= .95)	18.840%	8.758%	3.715%	70.276%	82.749%	124	96	20.46
	Overall	100.000%	4.260%	19.020%	41.680%	64.960%	160.615	131.487	27.489

Power conditional on falling in Enrichment zone is 81%

Power conditional on falling in promising zone is 81%

Power conditional on falling in favourable zone is 83%

Simulation Outputs

HR(C,NC)	Zone	P(Zone)	Power	E(Dur)	E(N)
0.55,0.55	Unfavorable	14	33	21	124
	Enrich	5	83	36	169
	Promising	38	94	33	200
	Favorable	43	93	22	124
	Total	100	85(97)	26(25)	155(200)
0.55,0.70	Unfavorable	20	22	21	124
	Enrich	12	83	36	168
	Promising	40	87	32	200
	Favorable	28	86	21	124
	Total	100	73(86)	27(25)	151(200)
0.55,0.85	Unfavorable	25	16	20	124
	Enrich	19	81	36	167
	Promising	37	81	31	200
	Favorable	19	83	20	124
	Total	100	65(66)	27(25)	150(200)
0.55,1.00	Unfavorable	27	12	20	124
	Enrich	27	80	36	166
	Promising	34	79	31	200
	Favorable	12	80	20	124
	Total	100	61643)	28(25)	160(200)

Results

Compared to fix design of n=200, adaptive design provides

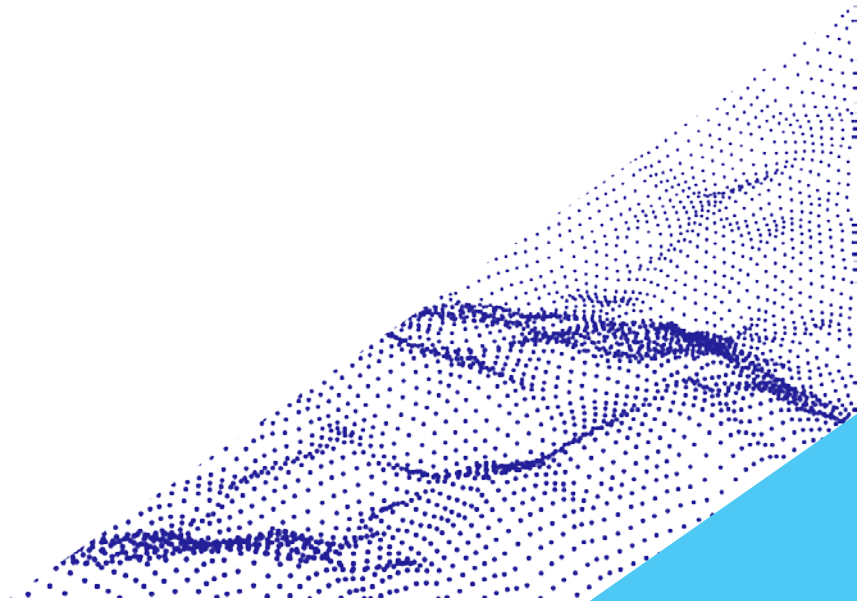
- Greater power
- Smaller sample size
- Shorter duration

Adaptive design maintains 80% power in favorable, promising and enrichment zones for HR=0.55 (cutaneous) even with larger HRs in the non-cutaneous subgroup

Cytel

EnForeSys

Recruitment Prediction



Traditional Forecasting is Prone to Error

Patient recruitment is widely recognized as a key determinant of success. Yet a substantial number of clinical trials fail to reach recruitment goals – a situation that has important scientific, financial, ethical, and policy implications. [1]

86%

As much as **86%** of clinical trials do not reach recruitment targets within their specified time.[2]

Sources [1]Huang et al, 2018. [2]Tufts CSDD (2013),

Cost of forecast inaccuracy is high

Duration Doubled

Study durations need to be **doubled** to meet target enrollments.[1]

19% Closed

19% of registered trials were closed or terminated early because they couldn't accrue enough patients.[2]

Costs Soar, Revenue Falls, Patients Suffer



Drug supply/demand mismatch at sites.[3]



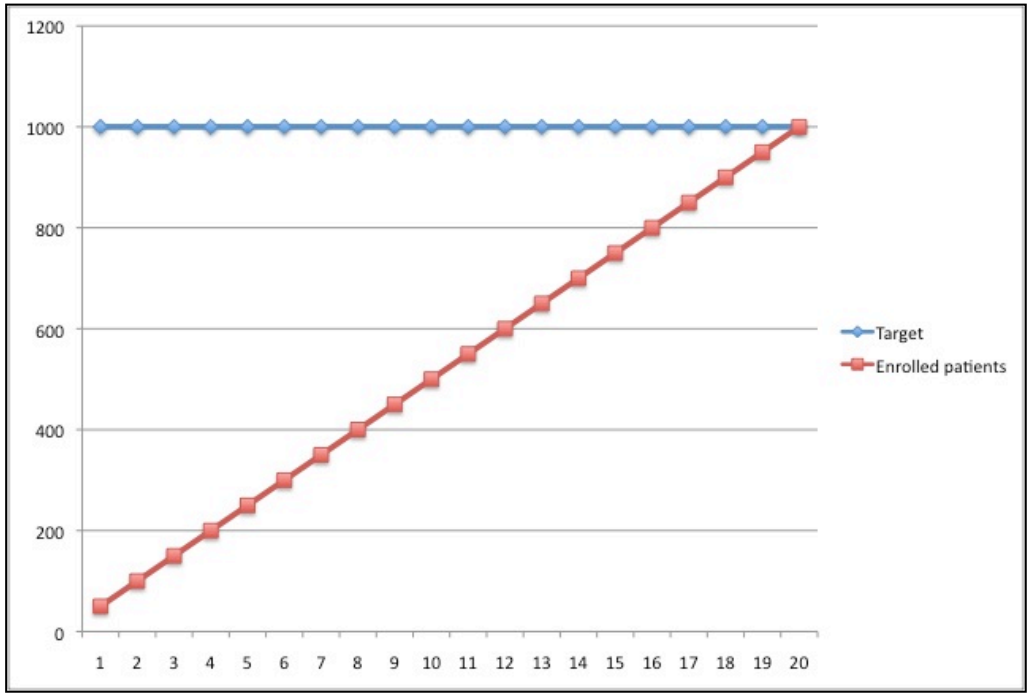
Site-related cost overruns.
$0.4M to $3.0M per study[4]
~$194k per additional site[5]



2-3 years of lost revenue, delayed treatments.[6]

Sources: [1] Tufts CSDD (2013), [2] Carlisle et al, 2015. [3] Interview with Jannsen 19Feb2020, [4] Cytel Analysis based on Eastern Research Group Report to HSS, Examination of Clinical Trial Costs and Barriers for Drug Development (2014), [5] Case study, 2019. [5] Cytel analysis based on Getz / Tufts CSDD (2015).

Traditional Models Oversimplify Enrollment Curve



Reality is more complicated

Study startup can differ by country

Pre-screening period & rates

Holiday effects & Seasonal variations

Mid-trial changes in enrollment rates (e.g., "site fatigue")

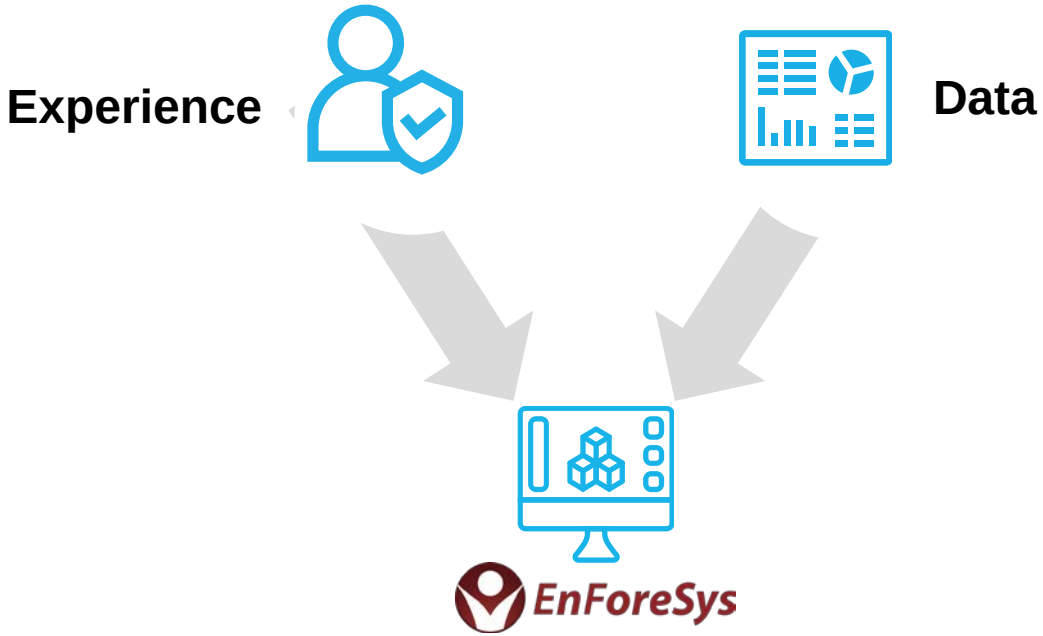
Regulators require "minimum patients" by country

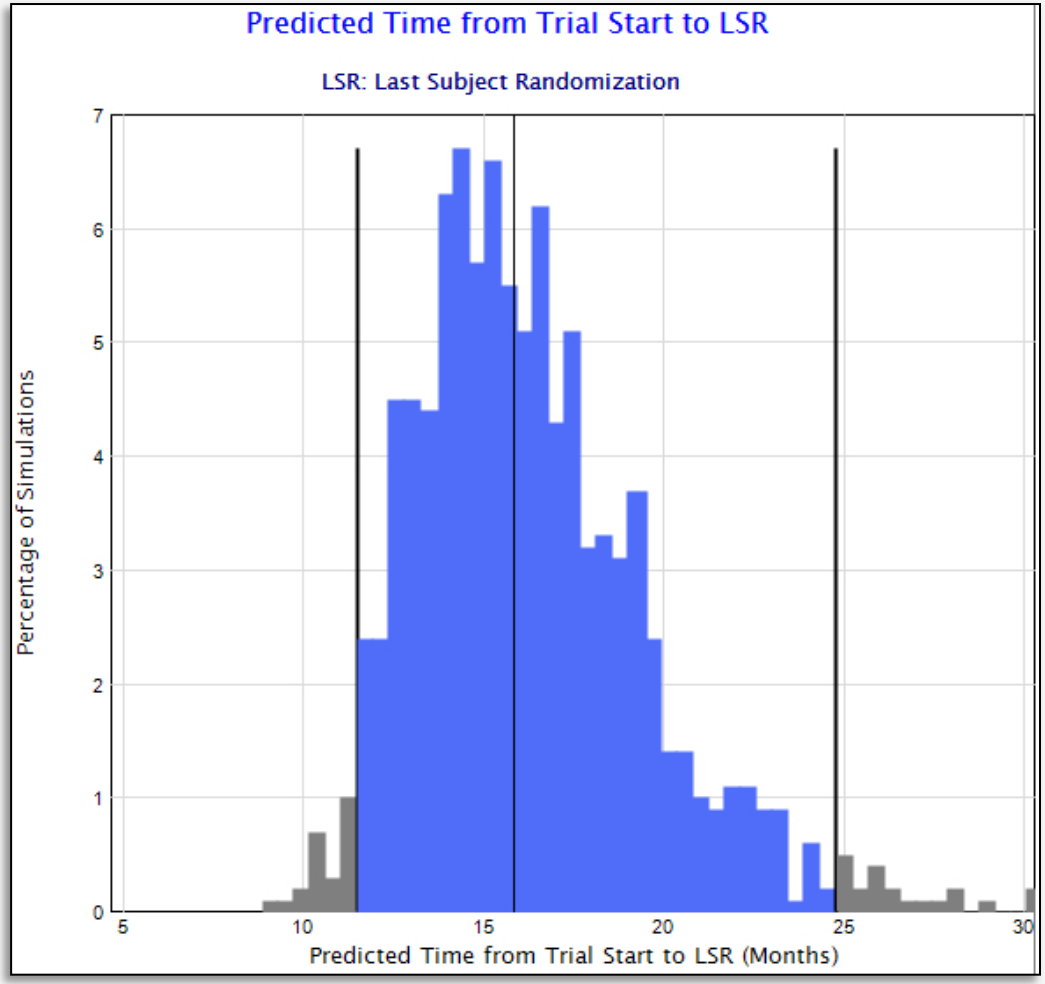


Unrealistic assumptions:

- All sites ready from start date
- No sites will fail to recruit
- Patients arrive in early
- No pauses in enrollment

Cytel Alternative





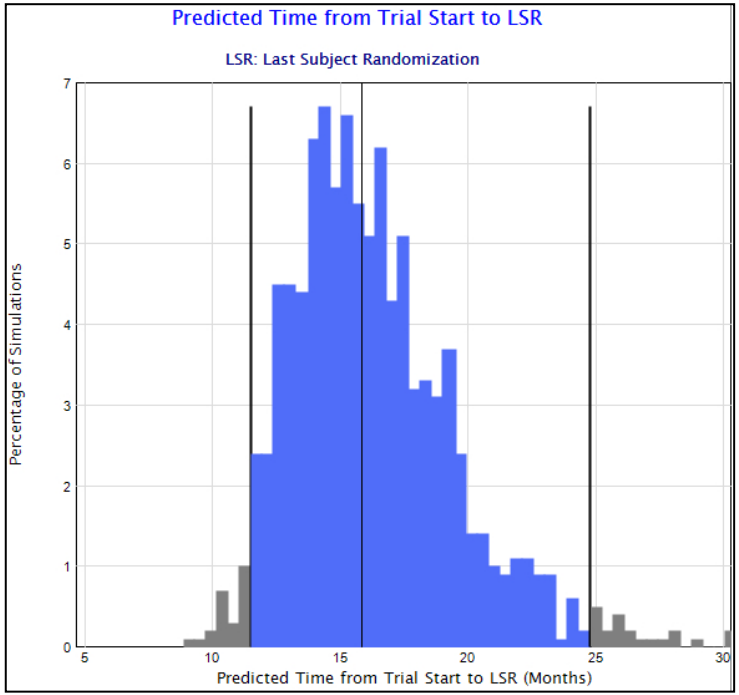
Forecast enrollment with confidence

EnForeSys

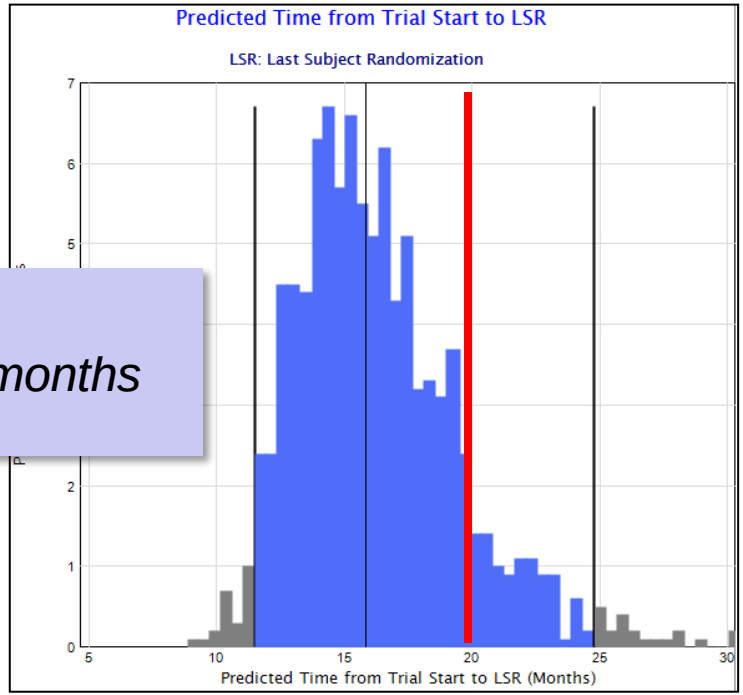
- More accurately set expectations around your recruitment deadlines
- Incorporate realistic assumptions with sophisticated modeling
- Leverage thousands of simulations to drive insights from your prior data

Cytel

Probability of Success



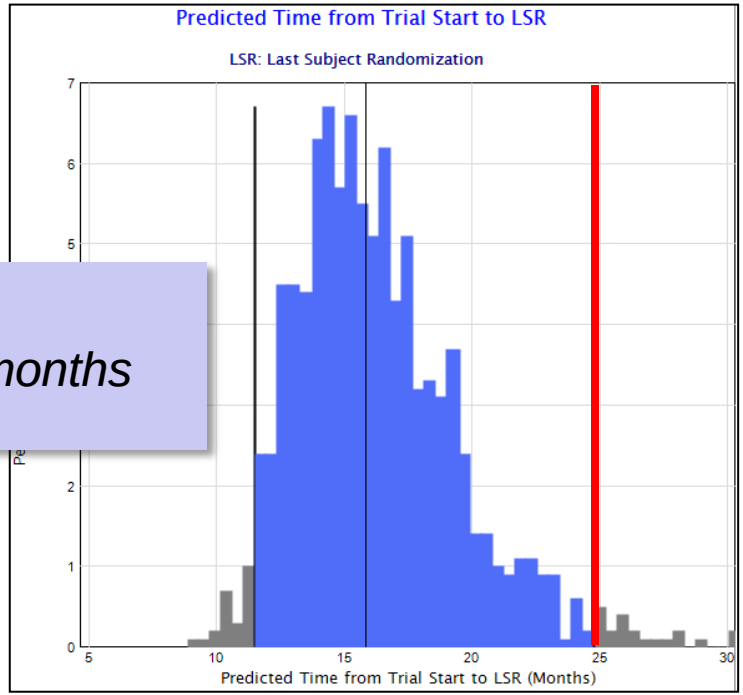
Probability of Success



Realistic Target

- *80% that LSR < 20 months*

Probability of Success



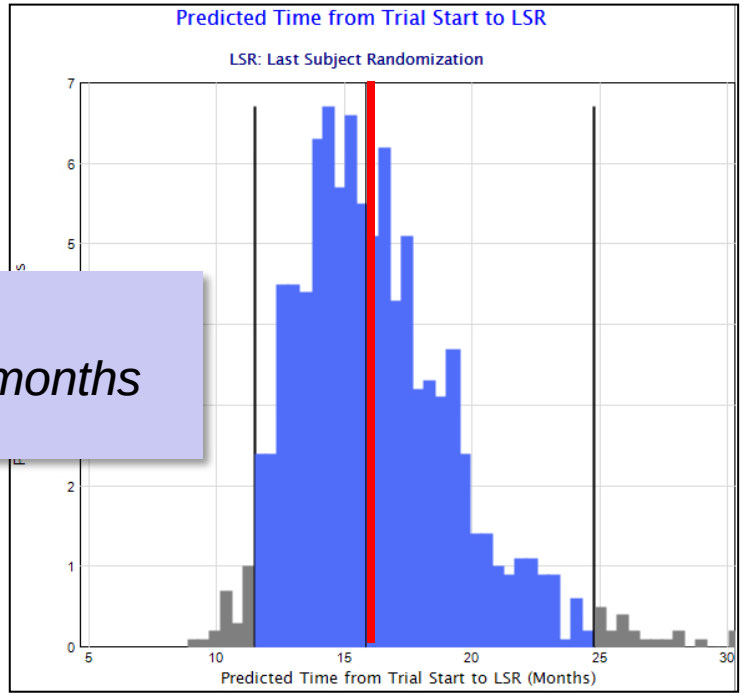
Safe Target

- *97% that LSR< 25 months*

Probability of Success

Aggressive Target

- *50% that LSR < 16 months*



Why EnForeSys?



Simulate across a range of input parameters as opposed to a linear approach

Account for uncertainty to support more realistic stakeholder expectations



Provides a thorough understanding of which inputs are impacting the outcome the most

Focus resources, plan mitigations



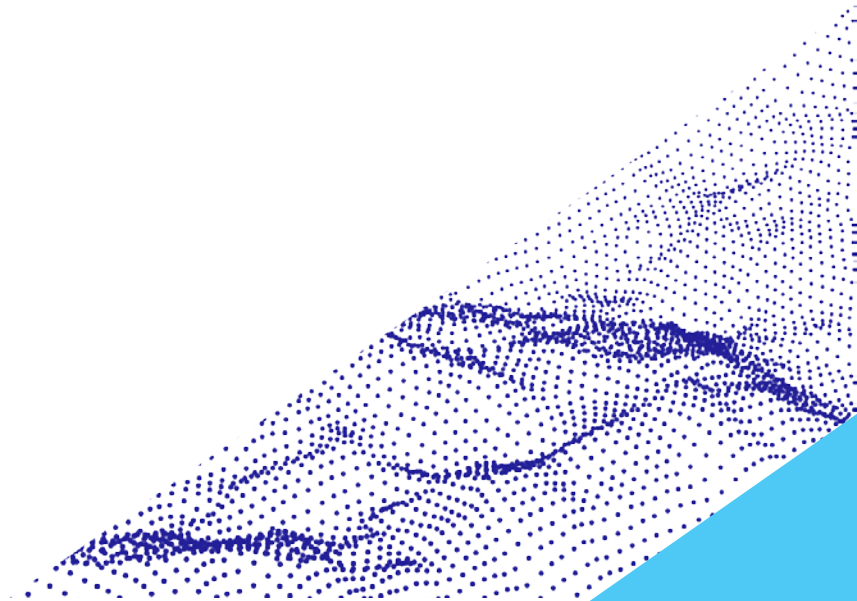
Assess target enrollment duration based on your risk tolerance

Outcomes are expressed in probabilistic terms

Cytel

EnForeSys

EnForeSys Demo



Acute Myeloid Leukemia

A phase III double-blind multicenter placebo-controlled trial to assess the efficacy of a treatment for acute myeloid leukemia

Group Sequential Design	Inputs
Planned Sample Size	450
Planned Number of Events	375
Treatment Effect (Hazard ratio)	0.71
Control median survival time	5.5 months
Type-1 error (1-sided)	0.025
Target average power	85% or above
Number of Interim Analyses	1
Timing of Interim Analysis	50%
Alpha spending function	Gamma -4
Beta Spending Function	None

Primary Outcome:

Overall Survival (OS)

Optimization Aim:

Reduce overall trial duration while maintaining power at or above 85%

Questions of interest:

- What is the optimal spacing of the interim analysis to achieve the aim?
- Should early stopping for efficacy/futility be considered?
- What are the tradeoffs between sample size and duration?
- How will enrollment and treatment effect variations affect the trial?

AML Trial

- Multi-country, multicenter randomized pbo-controlled trial
  - 14 countries in Europe, NA and Oceania
- 450 subjects to be enrolled
- Questions:
  - How long it is expected to take based on current enrollment plan?
  - How long to open all sites?
  - Site performance?

AML Trial Inputs

- 121 sites in 14 countries
- Average site randomization rate ~0.3/month
- Typical site initiation duration >1 and <11 months

Region	# of Sites	Site Activation Time (Months)		Randomization Rate (Subjects/Site/Month)	Max. Randomizations
		Minimum	Maximum		
Austria	4	3	6	0.384	64
Belgium	6	5	6	0.319	72
CZ	3	4	6	0.247	36
France	9	4	5	0.449	168
Germany	10	4	5	0.397	164
Hungary	4	6	8	0.176	28
ITALY	7	5	7	0.267	73
Poland	4	4	5	0.481	65
Spain	7	4	6	0.176	47
UK	8	4	6	0.28	92
Australia	11	4	6	0.299	181
NewZealand	4	5	6	0.254	55
Canada	5	6	7	0.234	64
US	39	0	11	0.254	544

Output Details

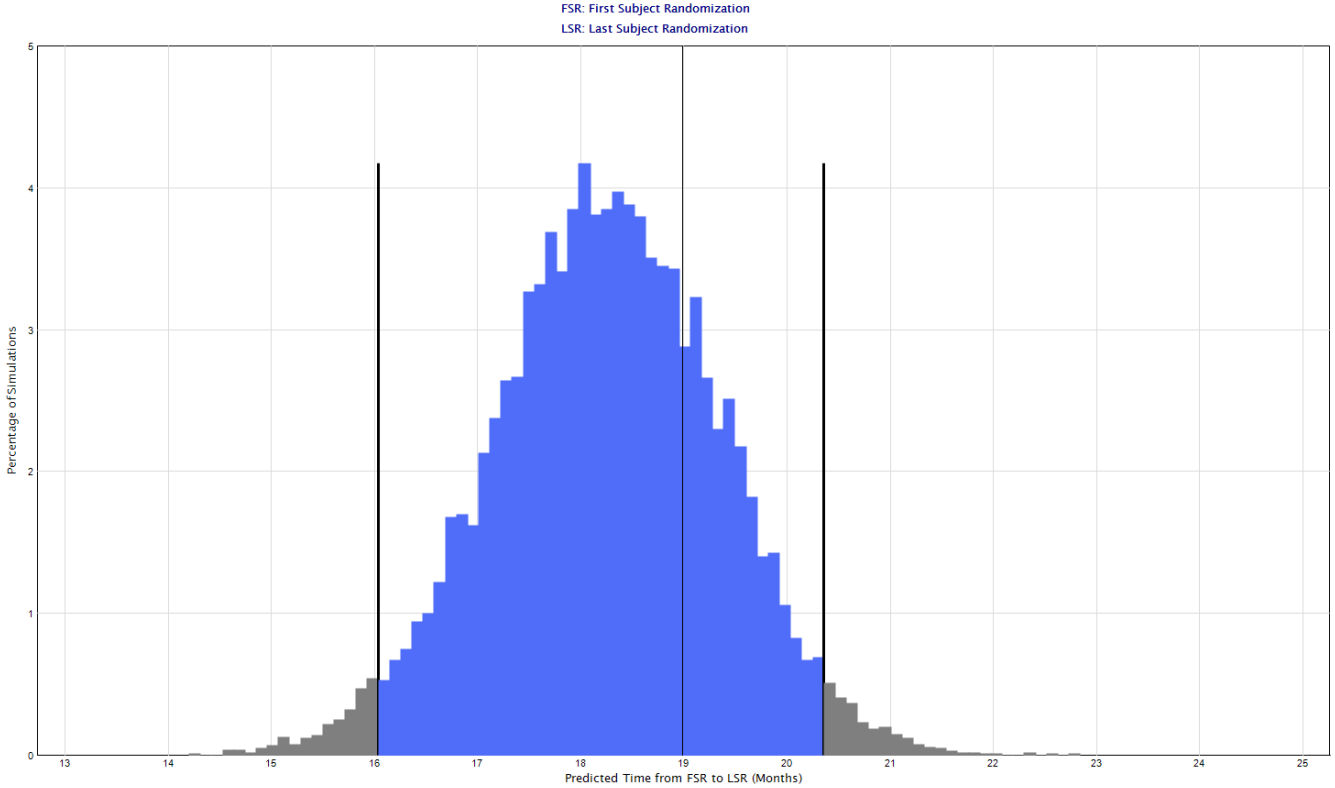
Parameter	Minimum	Maximum	Mean	Median	95% Prediction Interval	
					LL	UL
Time from Trial Start to FSA (Months)	4.30E-05	2.6	0.3	0.2	7.50E-03	1
Time from Trial Start to First Screening (Months)	2.30E-03	4.3	1.4	1.3	0.2	3.2
Time from Trial Start to FSR (Months)	3.00E-03	4.7	1.5	1.4	0.3	3.3
Time from FSR to LSR (Months)	14.2	22.8	18.2	18.3	16	20.4
Time from Trial Start to LSR (Months)	16.7	23	19.7	19.7	18.2	21.4
Overall Randomization Rate (Subjects/Month)	19.719	28.926	23.184	23.172	21.216	25.216
Arrival Rate (Subjects/Site/Month)	0.267	0.375	0.319	0.318	0.292	0.347
Randomization Rate (Subjects/Site/Month)	0.239	0.346	0.287	0.287	0.261	0.314
# of Subjects Arrived/Site	3.926	4.43	4.132	4.132	4.017	4.256
# of Subjects Randomized/Site	3.719	3.719	3.719	3.719	3.719	3.719
# of Screen Failures	25	86	50.022	50	36	65
# of Sites Opened	121	121	121	121	121	121
# of Sites with at least 1 Subject Arrived	91	118	106.488	107	100	113
# of Sites with No Subject Arrived	3	30	14.512	14	8	21

- Time from Trial Start to SIV Summary (Months)
- Site Performance Summary
- Country Wise Recruitment Summary (Mean)
- Monitor Interim Analyses
- Monitor by # of Subjects Randomized
- Monitor by Dates

Output Summary

	OncoX:Normal
Trial Details	
Trial Name	OncoX
Phase	3
Therapeutic Area	Oncology
Group Sites By	Region
# of Regions/Groups	14
Total # of Sites	121
Plan	
Target Randomization	450
# of Interim Analyses	1
IA Defined by	Proportion of Target
Ramp Up Factor	1
Site Information	
Distribution of SA Time	Uniform
SA Time Unit	Months
Distribution of Site Failure	Fixed (10)
Recruitment Information	
Distribution of Max. Randomizations	Fixed
Recruitment Model	Poisson
Distribution of Randomization Rate	Fixed
Randomization Rate Time Unit	Months
Distribution of Screening Failure Rate	Fixed (10)
Screening Period	0
Screening Period Time Unit	Weeks
Results	
Output Time Unit	Months
Median Time from Trial Start to LSR	19.7
Median Time from FSR to LSR	18.3
Mean Time from Trial Start to FSR	1.5
Mean Time from Trial Start to FSA	0.3
Mean Time from Trial Start to LSR	19.7
Mean # of Sites Opened	121
Mean # of Subjects Arrived/Site	4.13
Mean # of Screen Failures	50.022
Mean # of Sites with at least 1 Subject Arrived	106.488
Mean Randomization Rate/Site	0.287

Time from FSR to LSR



Output Time Unit

Months

FSR-LSR

Minimum

14.2

Maximum

22.8

Mean

18.2

Median

18.3

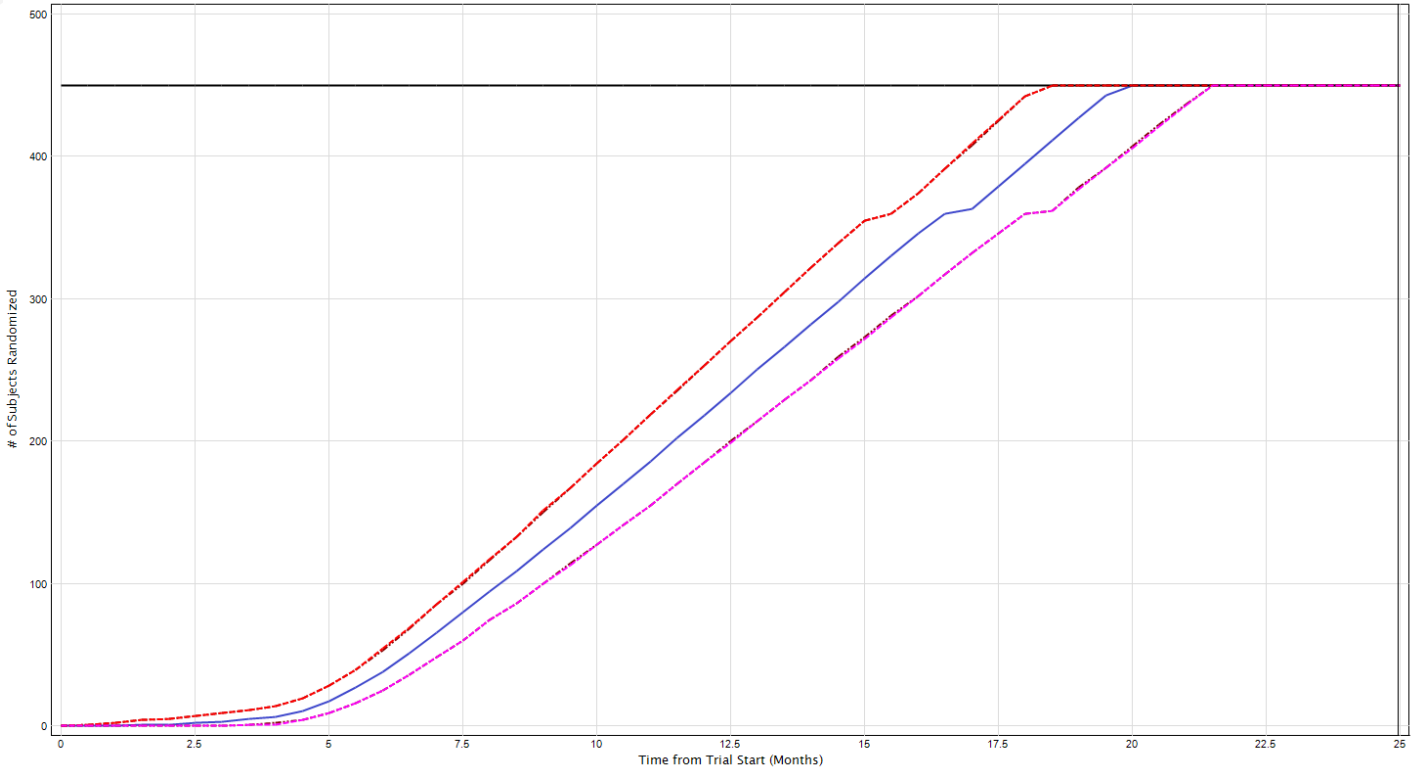
95% Prediction Interval LL

16

95% Prediction Interval UL

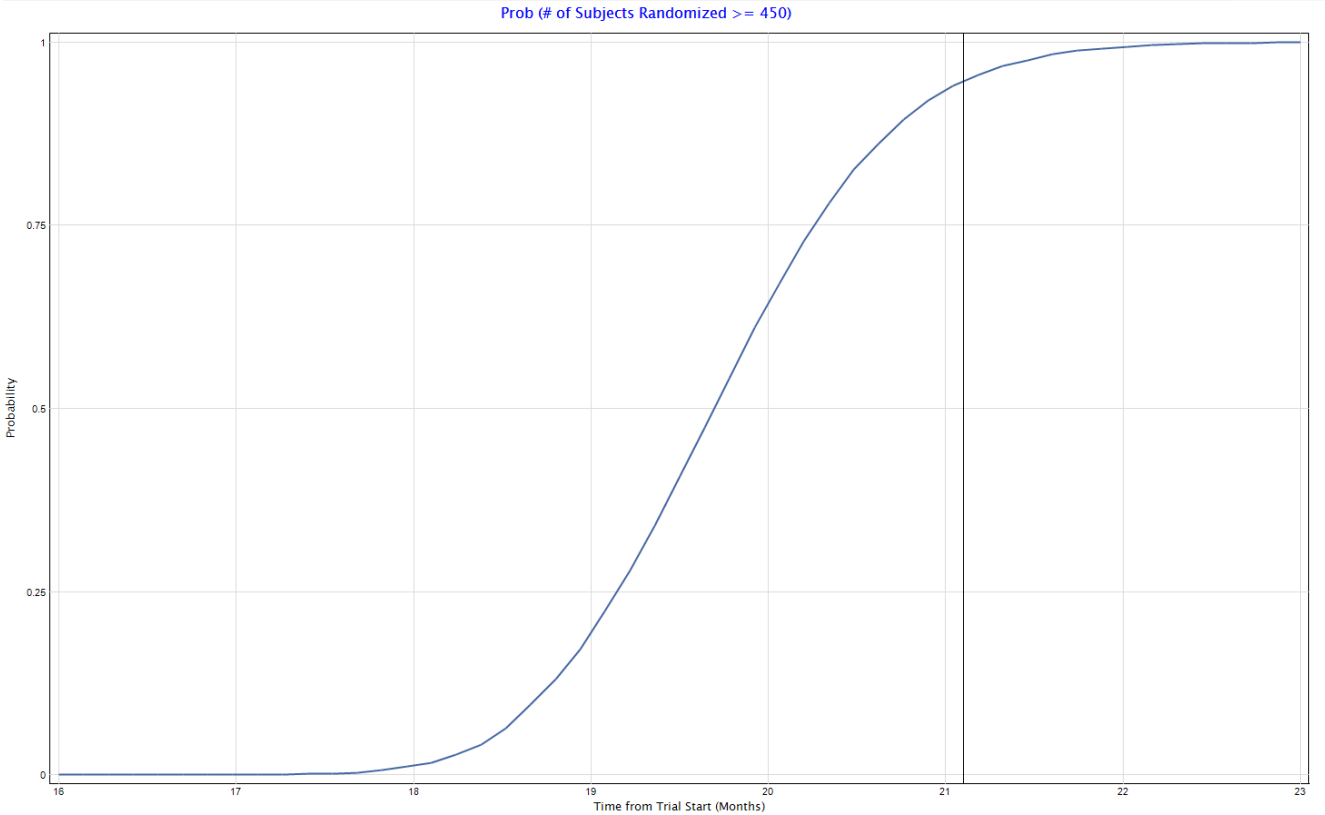
20.4

Subjects Randomized vs Time



Cytel

Milestone Probability



Compare Slow to Faster Enrollment

