East®SurvAdapt

Software for Adaptive Sample Size Re-estimation of Confirmatory Time to Event Trials

Cytel Webinar

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Outline of Presentation

- Motivating example: non-small-cell lung cancer trial with optimistic and pessimistic assumptions about HR
- Sample size requirements of pessimistic design too great for an up-front commitment
- Promising zone design: design optimistically and commit additional resources only if interim results are promising
- Software demonstration of design, simulation and interim monitoring with East®SurvAdapt
- Concluding remarks

Lung Cancer Example

- 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

Group Sequential Design

Plan ID	Plan1			Plan2		
Test Parameters						
1-Sided or 2-Sided Test	1-Sided			1-Sided		
Significance Level (Alpha)	0.025			0.025		
Power (1 - Beta)	0.9			0.9		
Assigned Fraction (Treatment)	0.5			0.5		
Boundary Parameters						
Planned Number of Looks	2			2		
Spacing of Looks	Equal			Equal		
Hypothesis to be Rejected	H0 or H1 (NB)			H0 or H1 (NB)		
Boundary Family	SpF (Pub)			SpF (Pub)		
Boundary to Reject H0	LD (OF)			LD (OF)		
Boundary to Reject H1	Gm (-5)			Gm (-5)		
Survival Parameters						
-Log-hazard Ratio	0.3567			0.2614		
Number of Hazard Pieces	1			1		
Number of Accrual Periods	1			1		
Variance of -Log-hazard Ratio	Null			Null		
Committed Accrual						
Committed Accrual (Duration)	24.0			24.0		
Committed Accrual (Subjects)	417			763		
Max. Duration and Events						
Maximum Study Duration	36.0			36.0		
Maximum Number of Events	333			620		
Expected Values under...	H0	H1	H ½	H0	H1	H ½
Expected Accrual (Subjects)	377	400	407	692	730	743
Expected Study Duration	26.348	31.852	31.981	26.949	31.821	32.5
Expected Number of Events	258	290	311	480	539	578

Adaptive Strategy

- Design optimistically (HR=0.7; 333 events; 417 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 equivalently in terms of conditional power, or HR, or Z-statistic

The Promising Zone Design

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

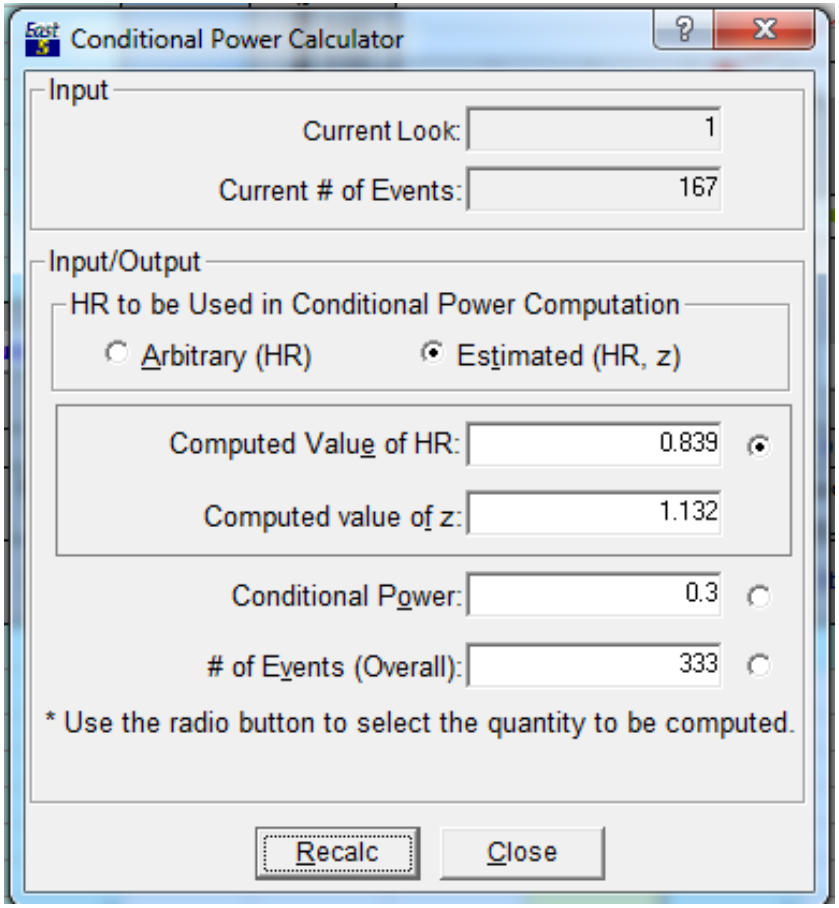
  Unfavorable: CP $< 30\%$; no change in design

  Promising: $30\% \leq$ 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) method or Chen, DeMets Lan (CDL) method to control type-1 error

Conditional Power Calculator



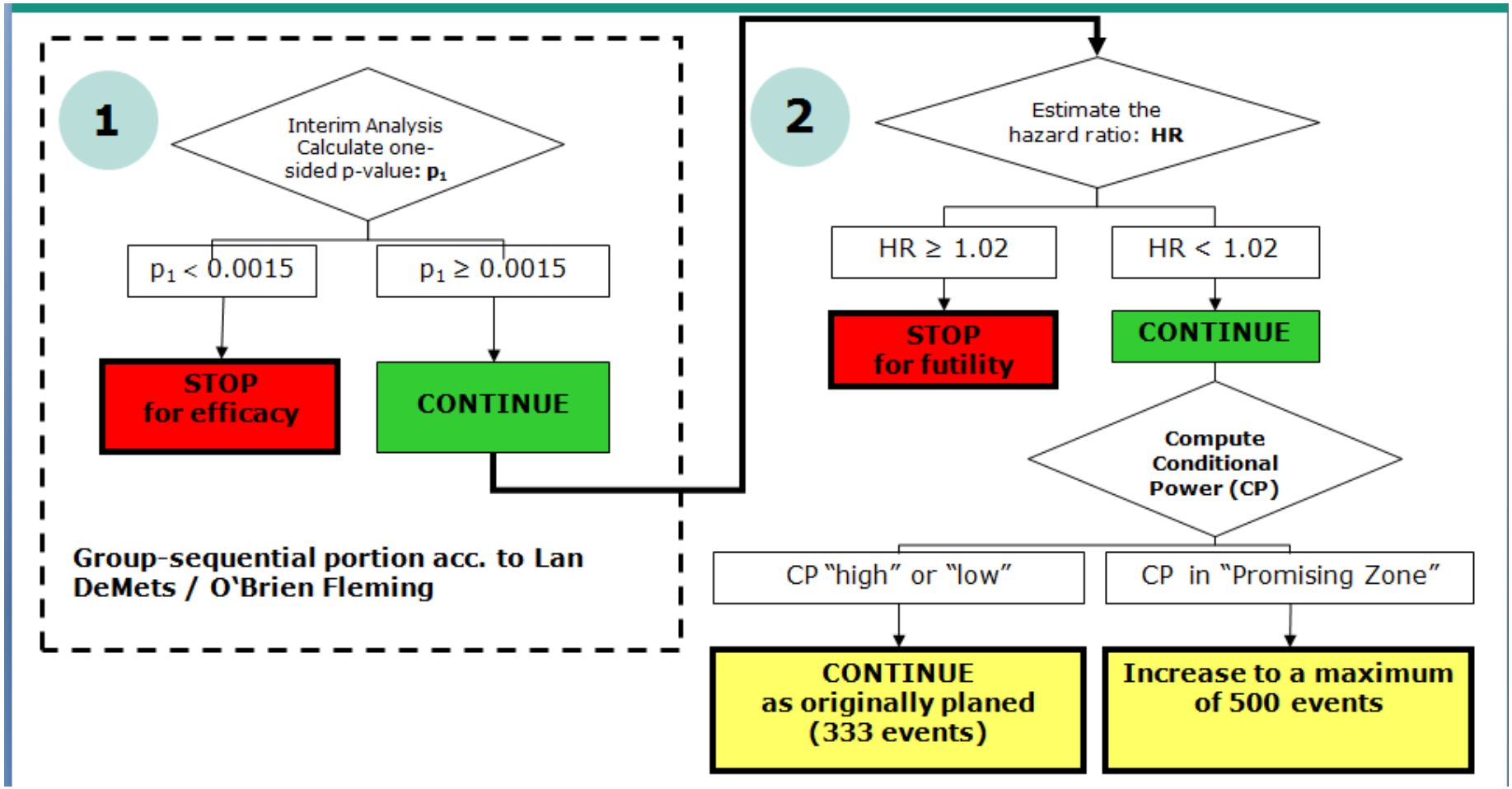
30% CP corresponds to $\widehat{HR} = 0.83$ at the interim analysis

On the $\ln(HR)$ scale this corresponds to observing $\hat{\delta} = 0.5\delta_1$

90% CP corresponds to $\widehat{HR} = 0.64$ at the interim analysis

On the $\ln(HR)$ scale this corresponds to obtaining $\hat{\delta} = 0.88\delta_1$

Schema of Adaptive Design



Adaptive Distribution Theory

- Let δ be the mean difference of two normal distributions with common variance σ^2
- Test H_0: $\delta = 0$ versus H_1: $\delta > 0$ with a K-look group sequential design
- For $j = 1, \ldots K$ define:
  - $b_j =$ level-α stopping boundaries for initial design
  - $n_j =$ cumulative sample sizes of initial design
  - $n_j^* =$ cumulative sample sizes after adaptation
  - $n^{(j)} = n_j - n_{j-1}$, $n^{*(j)} = n_j^* - n_{j-1}^*$; incremental data
  - $(\hat{\delta}^{(j)}, \hat{\delta}^{*(j)}) =$ estimates based on incremental data

Cui, Hung and Wang (CHW) Test

The CHW statistic is formed by combining the incremental Wald statistics

$$Z^{*(l)} = \frac{\hat{\delta}^{*(l)}}{\mathbf{se}(\hat{\delta}^{*(l)})} = \hat{\delta}^{*(l)}\sqrt{I^{*(l)}}, \quad l = 1, 2, \ldots j,$$

with the prespecified weights

$$w^{(l)} = \frac{n^{(l)}}{n_K} \quad l = 1, 2, \ldots j$$

so as to form the weighted statistic

$$Z^{*}_{j,\mathbf{chw}} = \frac{\sqrt{w^{(1)}}Z^{*(1)} + \sqrt{w^{(2)}}Z^{*(2)} + \ldots + \sqrt{w^{(j)}}Z^{*(j)}}{\sqrt{w^{(1)} + w^{(2)} + \ldots + w^{(j)}}}$$

CHW Test; continued

- This statistic is asymptotically normal with mean

$$E(Z^*_{j,\mathbf{chw}}) = \frac{\delta \sum_{l=1}^{j} \sqrt{w^{(l)} I^{*(l)}}}{\sqrt{\sum_{l=1}^{j} w^{(l)}}}$$

  and unit variance. Thus, under H_0, $Z^*_{j,\mathbf{chw}} \sim N(0,1)$

- As long as the weights $w^{(1)}, w^{(2)}, \ldots w^{(K)}$ are pre-specified,

$$\mathbf{corr}(Z^*_{j_1,\mathbf{chw}}, Z^*_{j_2,\mathbf{chw}}) = \sqrt{\frac{n^{(j_1)}}{n^{(j_2)}}}, \quad 1 \le j_1 < j_2 \le K$$

- It follows that, regardless of adaptive sample size change,

$$P_0\left(\bigcup_{j=1}^{K} Z^*_{j,\mathbf{chw}} \ge b_j\right) = \alpha$$

Repeated Confidence Intervals

We can show (Lehmacher and Wassmer, 1999) that the K repeated confidence intervals for δ are given by

$$\frac{(Z^*_{j,\mathbf{chw}} \pm b_j)\sqrt{s_j}}{\sum_{l=1}^{j}\sqrt{w^{(l)}I^{*(l)}}},\ j = 1, 2, \ldots K$$

where $s_j = n_{j/n_K}$ is the information fraction at look j based on the pre-specified sample sizes. Thus, if δ_0 is the true value of δ then, for all $j = 1, 2, \ldots K$,

$$P_{\delta_0}\left\{\bigcap_{i=1}^{j}\left(\frac{(Z^*_{i,\mathbf{chw}} - b_i)\sqrt{s_i}}{\sum_{l=1}^{i}\sqrt{w^{(l)}I^{*(l)}}} \le \delta_0 \le \frac{(Z^*_{i,\mathbf{chw}} + b_i)\sqrt{s_i}}{\sum_{l=1}^{i}\sqrt{w^{(l)}I^{*(l)}}}\right)\right\} \ge 1 - \alpha$$

Repeated p-values at each look are obtained by manipulating α such that the RCI just excludes $\delta = 0$

Conditional Power Calculation

- Sample size increase is based on CP (promising zone design)
- Suppose an interim look is taken at look $L < K$ and the observed value of the test statistic is $Z^*_{L,\textbf{chw}} = z_l$. Then

$$\textbf{CP}_\delta(z_L) = P_\delta\{\bigcup_{j=L+1}^{K}(Z^*_{j,\textbf{chw}} \geq b_j | z_L)\}$$

- East provides a CP calculator to perform this computation
- For the simulations, however, East ignores all intermediate looks between L and K. The approximate CP is given by

$$\textbf{CP}_\delta(z_L) \approx 1 - \Phi\left\{b_K\sqrt{1+\frac{n_L}{n_K-n_L}} - z_L\sqrt{\frac{n_L}{n_K-n_L}} - \frac{\delta\sqrt{n^*_K-n_L}}{2\sigma}\right\}$$

- Either the design δ or the estimated δ may be used for the CP calculations required by the simulations

Special Case of Survival Studies

- Let D_j (D_j^*) denote the number of events in the initial (adapted) design at look j
- Event driven trial; D_j plays the role of n_j and D_j^* plays the role of n_j^* for trial design
- Let LR_j^* be the logrank statistic based on cumulative data through look j and define

$$Z^{*(j)} = \frac{\sqrt{D_j^*}\,\text{LR}_j^* - \sqrt{D_{j-1}^*}\,\text{LR}_{j-1}^*}{\sqrt{D_j^* - D_{j-1}^*}}, \text{ for } j = 1, 2, \ldots K$$

- Alternatively let $\hat{\delta}_j^*$ be the Cox model estimate of $-\ln(\text{HR})$, $I_j^* = [\text{se}(\hat{\delta}_j^*)]^{-2}$ be the corresponding Fisher information through look j, and define

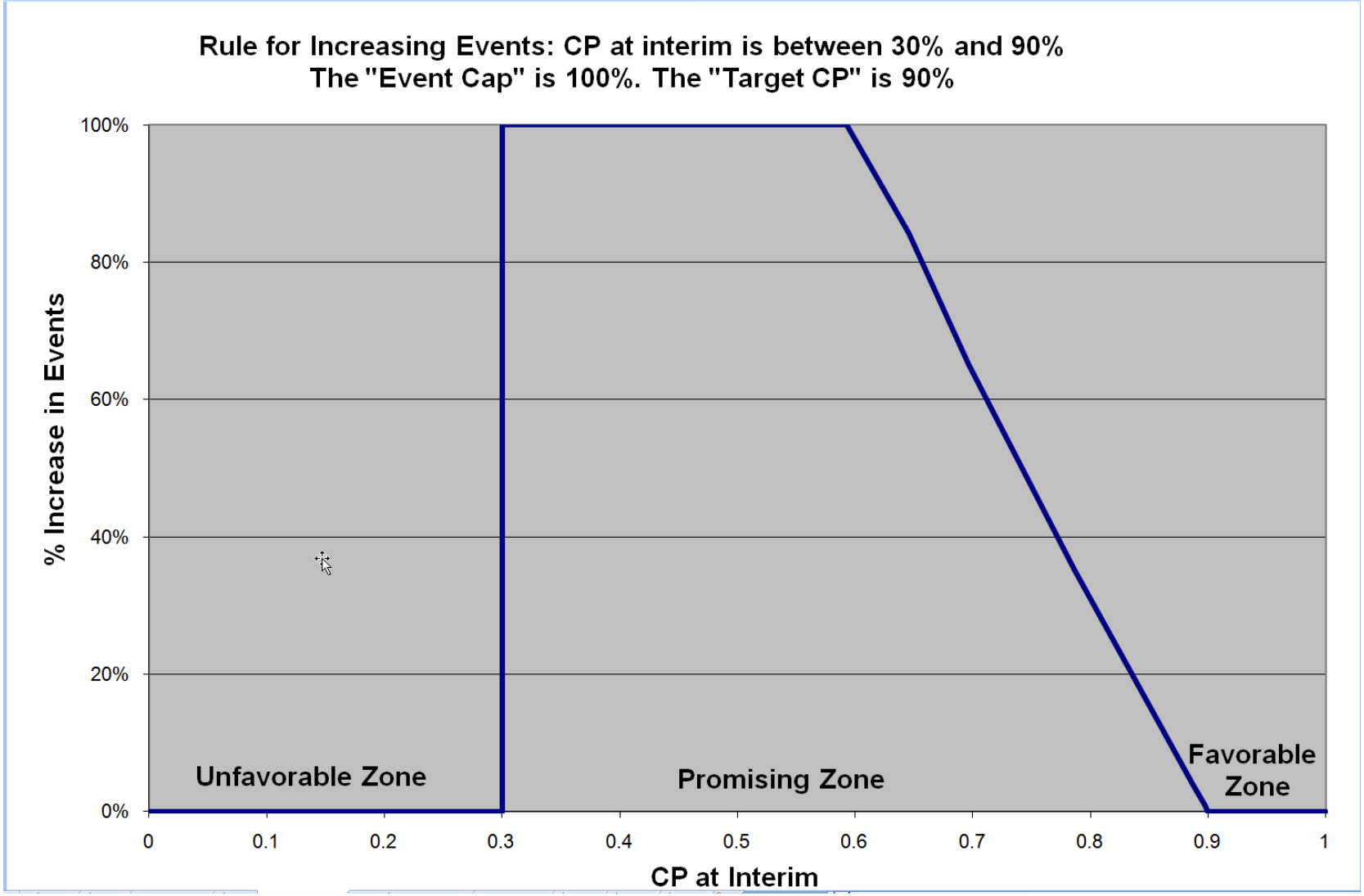
$$Z^{*(j)} = \frac{\sqrt{I_j^*}\,\hat{\delta}_j^* - \sqrt{I_{j-1}^*}\,\hat{\delta}_{j-1}^*}{\sqrt{I_j^* - I_{j-1}^*}}, \text{ for } j = 1, 2, \ldots K$$

- With the above substitutions all the previous results for normal and binomial endpoints carry over to the survival setting

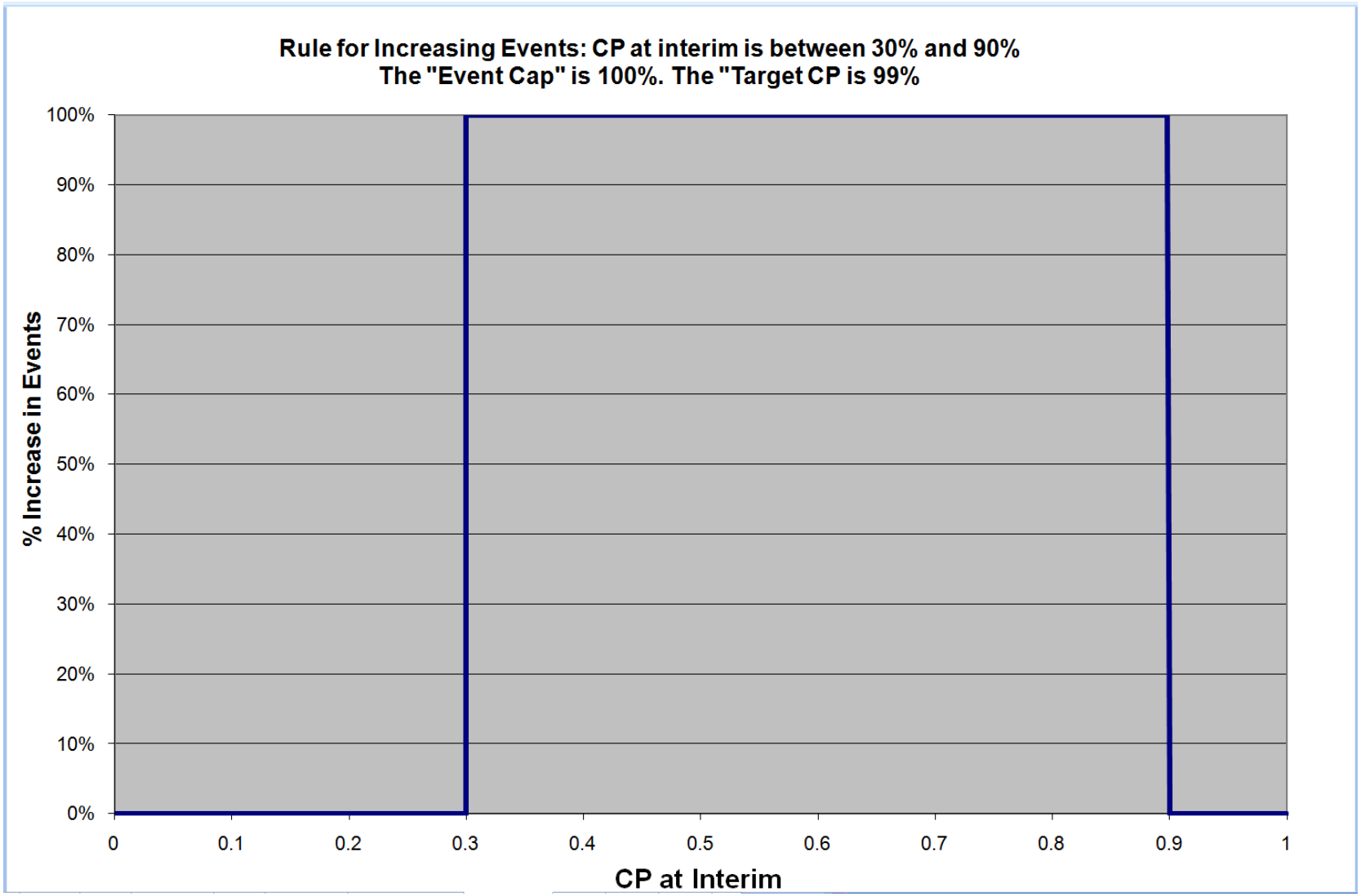
Adaptation Principles

- 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

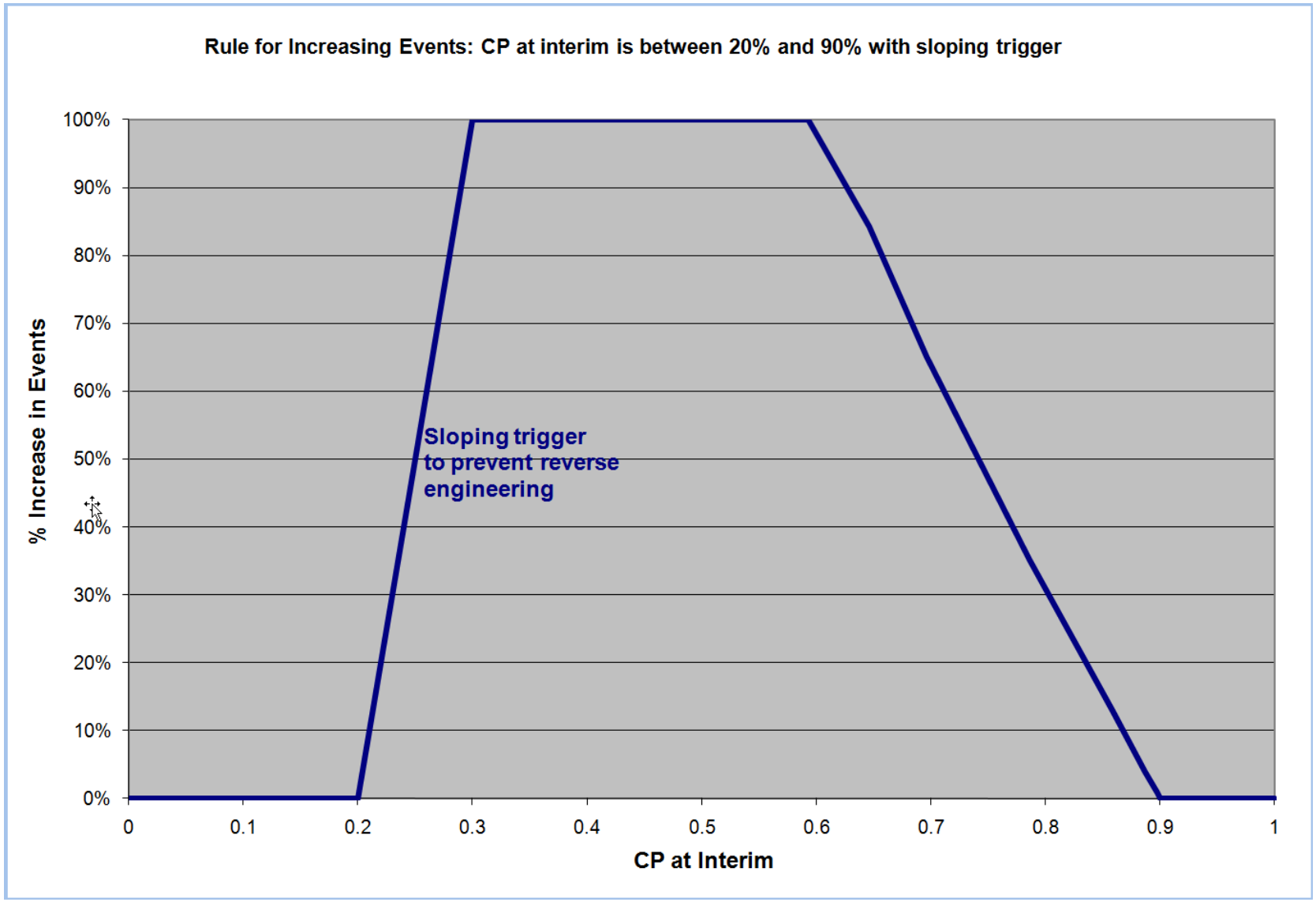
Increasing Number of Events: 1



Increasing Number of Events: 2



Increasing Number of Events: 3



Adaptive Simulation Worksheet

Survival Superiority Trials: Two Sample Test - Logrank Test: Given Accrual Duration and Study Duration (Survival CHW Simulation)

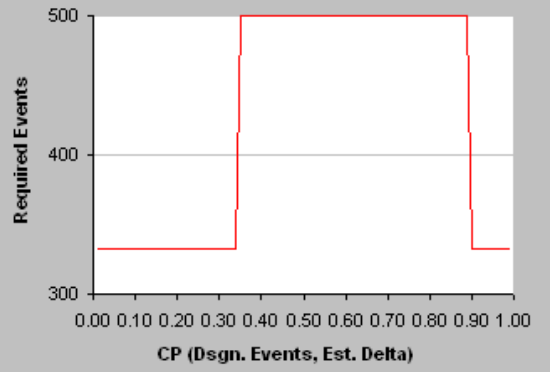
☑ Perform Adaptation if Necessary (During Simulations)

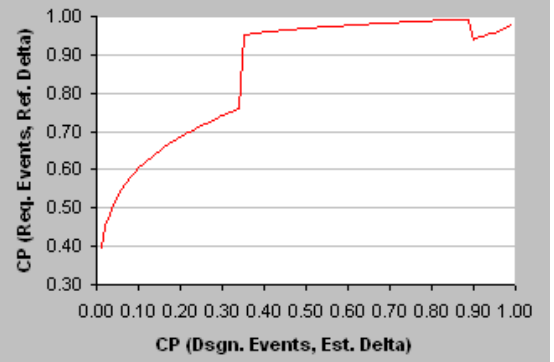
Input Parameters			
Adaptation at Look L		1	
Max. Events if Adapt (multiplier; total #)		1.50	500
Sample Size if Adapt (multiplier; total #)		1.50	627
Expected Study Duration if Adapt			
Upper Limit on Study Duration		108.00	
Shape Parameter for Re-estimating # of Events		0.99	
Promising Zone :	Min CP:	0.35	
	Max CP:	0.90	
Type of Adaptation	Increase Sample Size		
Accrual Rate After Adaptation	No Change		

Output for all Trials

Show Summary for: All Trials

Percentile	Study Duration	Number of Events	Accrual Duration	Number of Subjects
5%	19.6	167	19.5	341
25%	33.7	333	23.9	418
50%	35.3	333	24.0	418
75%	42.1	500	35.6	627
95%	44.0	500	36.4	627
Average	35.4	364	27.2	475





Run | Single Step | Reset | Stop

Simulation Results by Zone

Zone	Simulations Rejecting H0		Simulations Rejecting H1		Total Simulations		Avg. Study Duration	Avg. Number of Events	Avg. Accrual Duration	Avg. Number of Subjects
	Count	Row %	Count	Row %	Count	Column %				
Futility			330	100.0%	330	3.3%	19.7	167	19.7	344
Unfavorable: CP < 0.350	988	34.9%	1844	65.1%	2832	28.3%	34.7	333	23.9	418
Promising: 0.350 ≤ CP < 0.900	2843	89.0%	351	11.0%	3194	31.9%	42.9	500	35.9	627
Favorable: CP ≥ 0.900	2362	89.8%	269	10.2%	2631	26.3%	34.8	333	23.9	418
Efficacy	1013	100.0%			1013	10.1%	19.8	167	19.8	346
All Trials	7206	72.1%	2794	27.9%	10000	100.0%	35.4	364	27.2	475

Reference HR: 0.7000 | Refresh Charts

Simulation Inputs: Overall | Simulation Outputs: Overall | Simulation Inputs and Outputs: Adaptive | Exploration

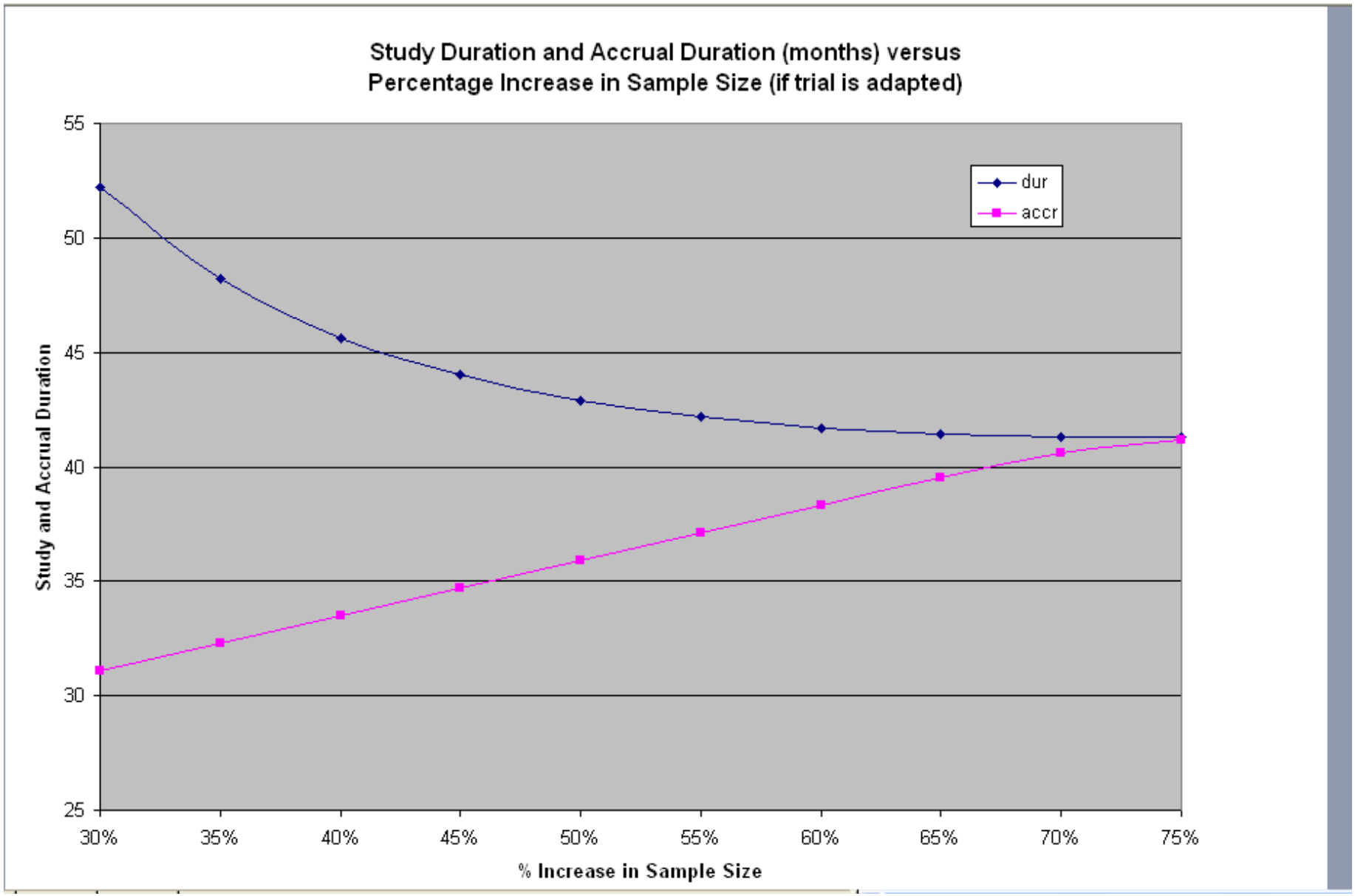
Design | Plan1_SurvivalCHW_Sim

Ready

Sample Size versus Study Duration Trade-Off

- Suppose you have entered the promising zone and the new number of events is $D^*_{\max}$
- How will you pick the new sample size, $N^*_{\max}$ to go along with the new number of events?
  - If $N^*_{\max}$ is too small, the trial will be excessively prolonged
  - If $N^*_{\max}$ is too large, the trial costs will be excessive while time savings might be marginal
- Obtain an accrual-duration chart by simulation and choose $N^*_{\max}$ by inspection

Show Summary for		Promising					
Type of Adaptation		Simulation Count	Power	Avg. Study Duration	Avg. Accrual Duration	Avg. Number of Events	Avg. Number of Subjects
Increase Sample Size							
Multiplier	Total						
1.30	543	3188	88.0%	52.2	31.1	500	543
1.35	564	3261	87.9%	48.2	32.3	500	564
1.40	585	3288	88.0%	45.6	33.5	500	585
1.45	606	3297	88.2%	44.0	34.7	500	606
1.50	627	3103	87.3%	42.9	35.9	500	627
1.55	648	3250	89.1%	42.2	37.1	500	648
1.60	669	3206	88.3%	41.7	38.3	500	669
1.65	690	3239	88.7%	41.4	39.5	500	690
1.70	711	3158	88.2%	41.3	40.6	500	709
1.75	732	3232	88.3%	41.3	41.2	500	719



Unnecessary to increase sample size by more than 50%

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

1. Simulations Under Pessimistic Scenario, HR = 0.77 (10,000 simulations)							
		Power		Duration (months)		SampSize	
Zone	P(Zone)	NonAdpt	Adapt	NonAdpt	Adapt	NonAdpt	Adapt
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	—	66%	72%	33	35	408	476

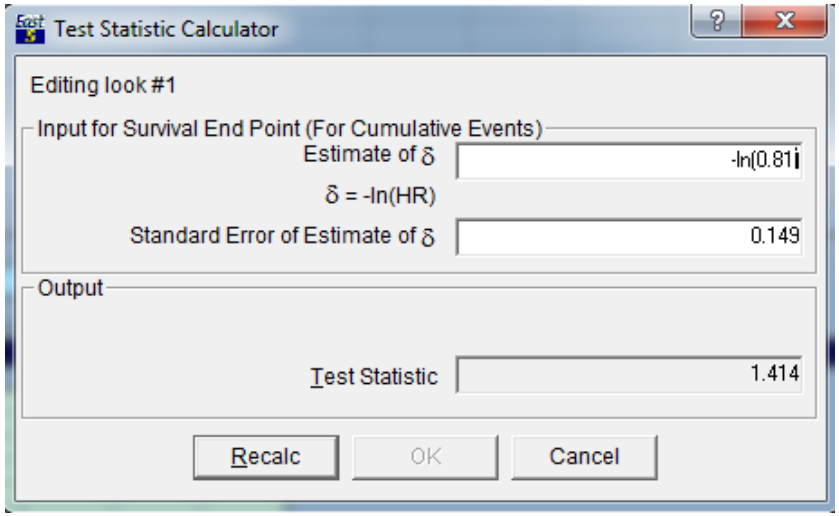
2. Simulations Under Optimistic Scenario, HR = 0.7 (10,000 simulations)							
		Power		Duration		SampSize	
Zone	P(Zone)	NonAdpt	Adapt	NonAdpt	Adapt	NonAdpt	Adapt
Unf	14%	57%	57%	35	35	414	414
Prom	26%	88%	98%	36	44	418	627
Fav	60%	98%	98%	29	29	390	390
Total	—	90%	93%	32	34	401	454

Interim Analysis: Look 1

- Suppose first look is taken after 180 events and $\widehat{\text{HR}} = 0.81$
- Thus the corresponding Wald statistic is

$$Z^{(1)} = \hat{\delta}^{(1)} / \text{SE}(\hat{\delta}^{(1)}) = -\ln(0.81) / (2/\sqrt{180}) = 0.211/0.149 = 1.414$$

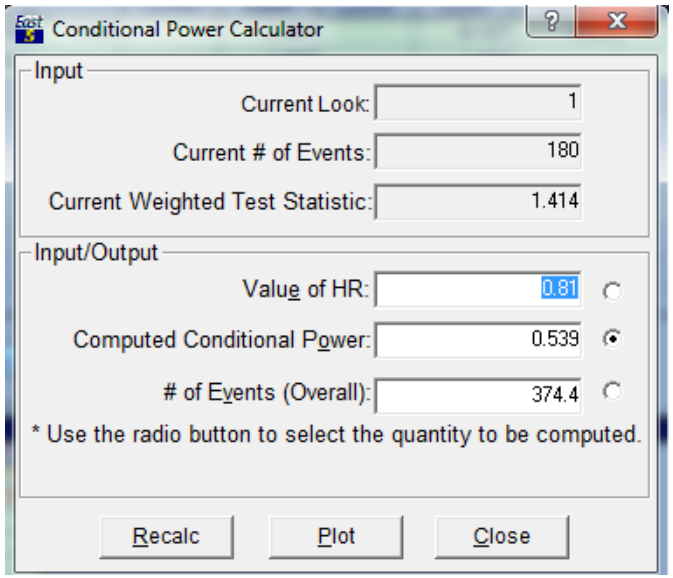
- Enter these values into the test statistic calculator of the CHW IM worksheet. Notice that $\text{SE}(\hat{\delta}^{(1)})$ was pre-computed



Two Sample Test - Logrank Test: Given Accrual Duration and Study Duration (Plan1) (C

Look #	Cumul. Events	Cumul. Statistic	Incr. Statistic	Prespec. Weights	Weighted Statistic	Prespecified Nominal Critical Points				Repeated 87.50% CI for HR		Repeated p-value
						Reject H0		Reject H1				
						Lower	Upper	Lower	Upper	Lower	Upper	
1	180	1.414	1.414	0.500	1.414		2.963		-0.127	0.568	1.260	0.214
2				0.500			1.969		1.969			
3												
4												

- **Cumulative, Incremental and Weighted Statistics are equal at look 1**
- **Conditional power if total events are unchanged is 0.539**

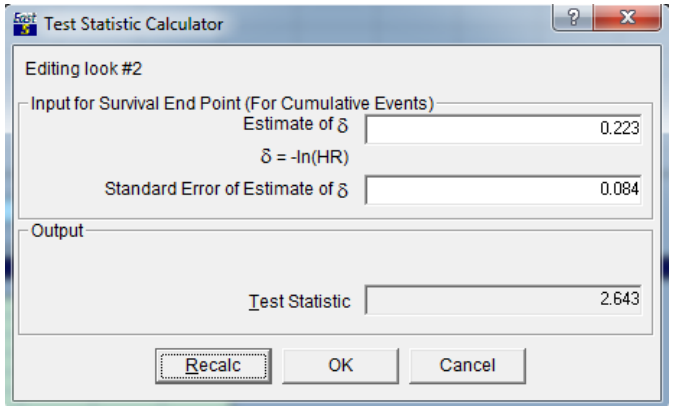


- **In Promising Zone; increase total events to 561**

Interim Analysis: Look 2

- Suppose look 2 is taken at 561 cumulative events and $\hat{HR} = 0.8$

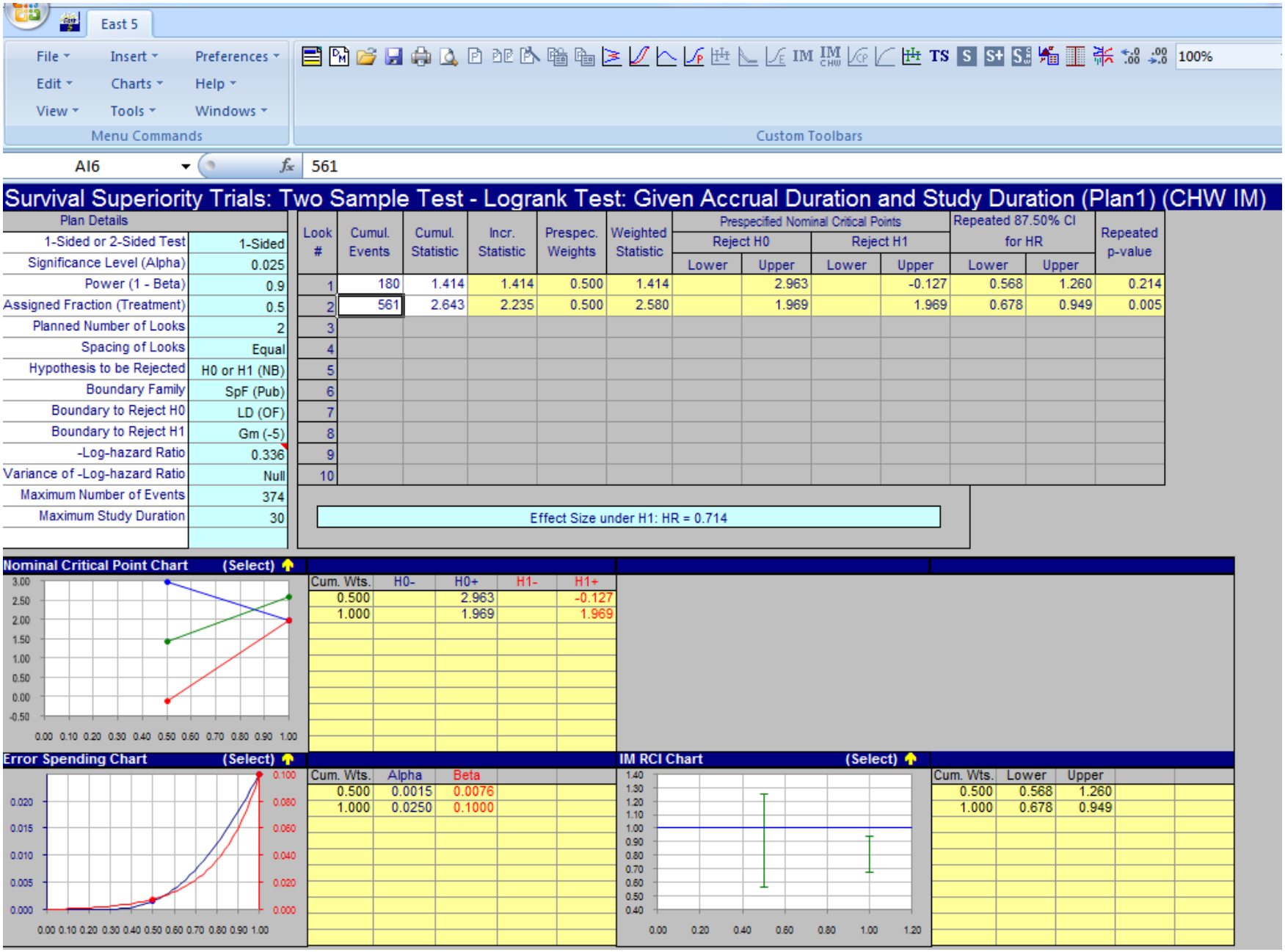
Cumulative: $Z_2^* = \hat{\delta}_2^* / \mathbf{SE}(\hat{\delta}_2^*) = -\ln(0.8)/(2/\sqrt{561}) = 0.223/0.084 = 2.643$



Incremental: $Z^{*(2)} = \dfrac{\sqrt{D_2^*}Z_2^* - \sqrt{D_1}Z_1}{\sqrt{D_2^* - D_1}} = \dfrac{\sqrt{581} \times 2.643 - \sqrt{180} \times 1.414}{\sqrt{561 - 180}} = 2.235$

Weightd: $Z_{2,\mathbf{chw}}^* = \dfrac{\sqrt{w^{(1)}}Z^{(1)} + \sqrt{w^{(2)}}Z^{*(2)}}{\sqrt{w^{(1)} + w^{(2)}}} = \dfrac{\sqrt{0.5} \times 1.414 + \sqrt{0.5} \times 2.235}{\sqrt{0.5 + 0.5}} = 2.58$

- The efficacy boundary is crossed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561
Survival Superiority Trials: Two Sample Test - Logrank Test: Given Accrual Duration and Study Duration (Plan1) (CHW IM)
Plan Details
1-Sided or 2-Sided Test 1-Sided
Significance Level (Alpha) 0.025
Power (1 - Beta) 0.9
Assigned Fraction (Treatment) 0.5
Planned Number of Looks 2
Spacing of Looks Equal
Hypothesis to be Rejected H0 or H1 (NB)
Boundary Family SpF (Pub)
Boundary to Reject H0 LD (OF)
Boundary to Reject H1 Gm (-5)
-Log-hazard Ratio 0.336
Variance of -Log-hazard Ratio Null
Maximum Number of Events 374
Maximum Study Duration 30
Look # | Cumul. Events | Cumul. Statistic | Incr. Statistic | Prespec. Weights | Weighted Statistic | Prespecified Nominal Critical Points: Reject H0 Lower | Reject H0 Upper | Reject H1 Lower | Reject H1 Upper | Repeated 87.50% CI for HR Lower | Repeated 87.50% CI for HR Upper | Repeated p-value
1 | 180 | 1.414 | 1.414 | 0.500 | 1.414 | | 2.963 | | -0.127 | 0.568 | 1.260 | 0.214
2 | 561 | 2.643 | 2.235 | 0.500 | 2.580 | | 1.969 | | 1.969 | 0.678 | 0.949 | 0.005
3
4
5
6
7
8
9
10
Effect Size under H1: HR = 0.714
Nominal Critical Point Chart (Select)
3.00 2.50 2.00 1.50 1.00 0.50 0.00 -0.50
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
Cum. Wts. | H0- | H0+ | H1- | H1+
0.500 | | 2.963 | | -0.127
1.000 | | 1.969 | | 1.969
Error Spending Chart (Select)
0.020 0.015 0.010 0.005 0.000
0.100 0.080 0.060 0.040 0.020 0.000
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
Cum. Wts. | Alpha | Beta
0.500 | 0.0015 | 0.0076
1.000 | 0.0250 | 0.1000
IM RCI Chart (Select)
1.40 1.30 1.20 1.10 1.00 0.90 0.80 0.70 0.60 0.50 0.40
0.00 0.20 0.40 0.60 0.80 1.00 1.20
Cum. Wts. | Lower | Upper
0.500 | 0.568 | 1.260
1.000 | 0.678 | 0.949

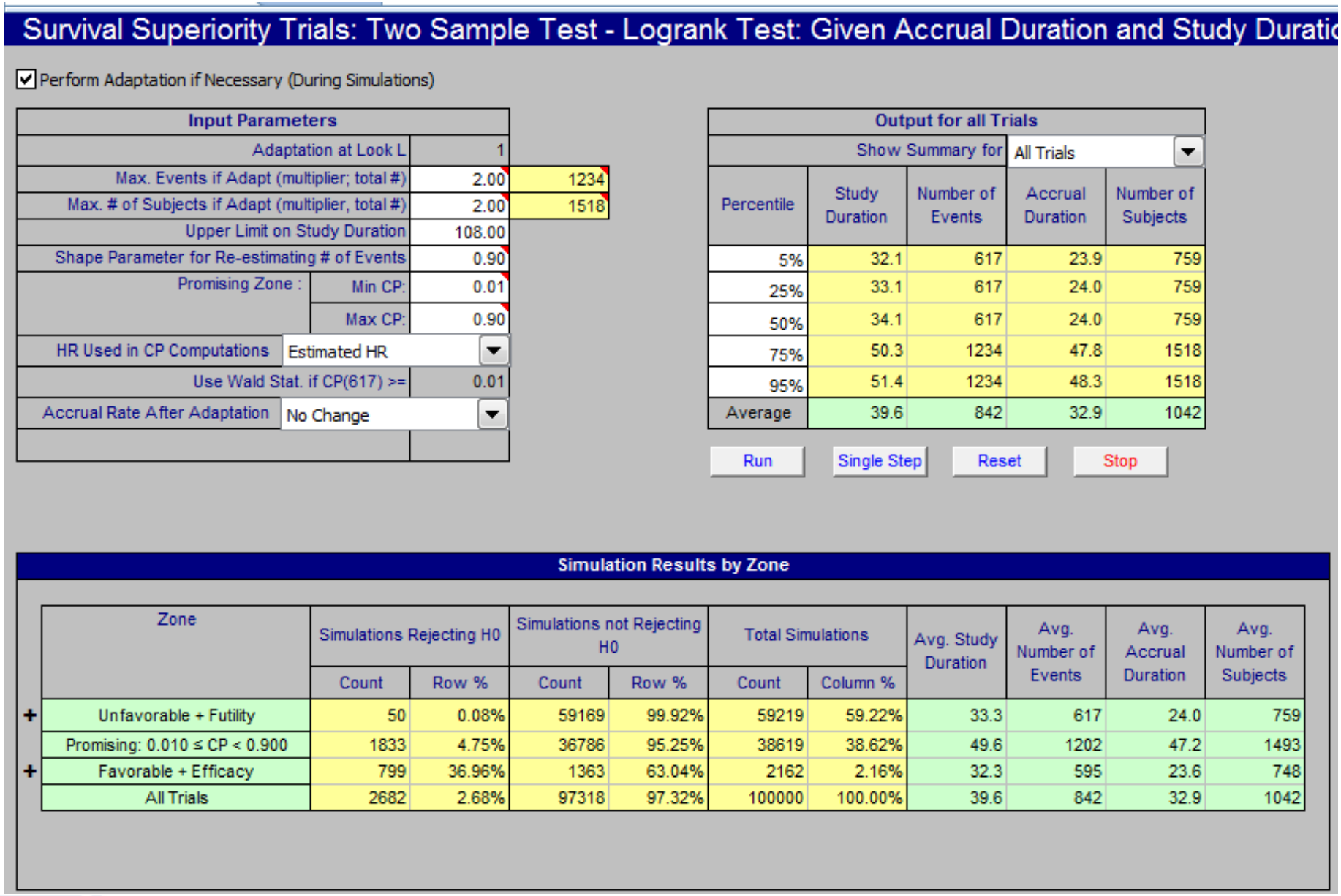
The CDL Method

- Some have objected to using the weighted statistic instead of the conventional statistic for performing the hypothesis test
- Chen, DeMets and Lan (2004) have shown that if promising zone starts at CP ≥ 0.5 it is ok to use the conventional statistic.
- Mehta and Pocock (2010) have extended this result
- Depending on event multiplier, target conditional power, and time of interim look, the promising zone can be widened as shown on the following table

CP_{min} for Various Design Options

Sample Size Ratios		CP_{min} Values for Targeted Conditional Powers	
Maximum Allowed (n_{max}/n_2)	At Interim Look (n_1/n_2)	80%	90%
1.5	0.25	0.42	0.42
1.5	0.5	0.41	0.41
1.5	0.75	0.38	0.38
2	0.25	0.37	0.37
2	0.5	0.36	0.36
2	0.75	0.33	0.33
3	0.25	0.32	0.32
3	0.5	0.31	0.31
3	0.75	0.30	0.27
∞	0.25	0.32	0.28
∞	0.5	0.31	0.27
∞	0.75	0.30	0.25

100,000 Wald Simulations: seed=66649



Survival Superiority Trials: Two Sample Test - Logrank Test: Given Accrual Duration and Study Duratic

☑ Perform Adaptation if Necessary (During Simulations)

Input Parameters			
Adaptation at Look L		1	
Max. Events if Adapt (multiplier; total #)		2.00	1234
Max. # of Subjects if Adapt (multiplier, total #)		2.00	1518
Upper Limit on Study Duration		108.00	
Shape Parameter for Re-estimating # of Events		0.90	
Promising Zone :	Min CP:	0.01	
	Max CP:	0.90	
HR Used in CP Computations		Estimated HR	
Use Wald Stat. if CP(617) >=		0.01	
Accrual Rate After Adaptation		No Change	

Output for all Trials

Show Summary for: All Trials

Percentile	Study Duration	Number of Events	Accrual Duration	Number of Subjects
5%	32.1	617	23.9	759
25%	33.1	617	24.0	759
50%	34.1	617	24.0	759
75%	50.3	1234	47.8	1518
95%	51.4	1234	48.3	1518
Average	39.6	842	32.9	1042

Run | Single Step | Reset | Stop

Simulation Results by Zone

Zone	Simulations Rejecting H0		Simulations not Rejecting H0		Total Simulations		Avg. Study Duration	Avg. Number of Events	Avg. Accrual Duration	Avg. Number of Subjects
	Count	Row %	Count	Row %	Count	Column %				
+ Unfavorable + Futility	50	0.08%	59169	99.92%	59219	59.22%	33.3	617	24.0	759
Promising: 0.010 ≤ CP < 0.900	1833	4.75%	36786	95.25%	38619	38.62%	49.6	1202	47.2	1493
+ Favorable + Efficacy	799	36.96%	1363	63.04%	2162	2.16%	32.3	595	23.6	748
All Trials	2682	2.68%	97318	97.32%	100000	100.00%	39.6	842	32.9	1042

100,000 CDL Simulations: seed=66649

Survival Superiority Trials: Two Sample Test - Logrank Test: Given Accrual Duration and Study Durati

☑ Perform Adaptation if Necessary (During Simulations)

Input Parameters			
Adaptation at Look L		1	
Max. Events if Adapt (multiplier; total #)		2.00	1234
Max. # of Subjects if Adapt (multiplier, total #)		2.00	1518
Upper Limit on Study Duration		108.00	
Shape Parameter for Re-estimating # of Events		0.90	
Promising Zone :	Min CP:	0.01	
	Max CP:	0.90	
HR Used in CP Computations		Estimated HR	
Use Wald Stat. if CP(617) >=		0.41	
Accrual Rate After Adaptation		No Change	

Output for all Trials

Show Summary for: All Trials

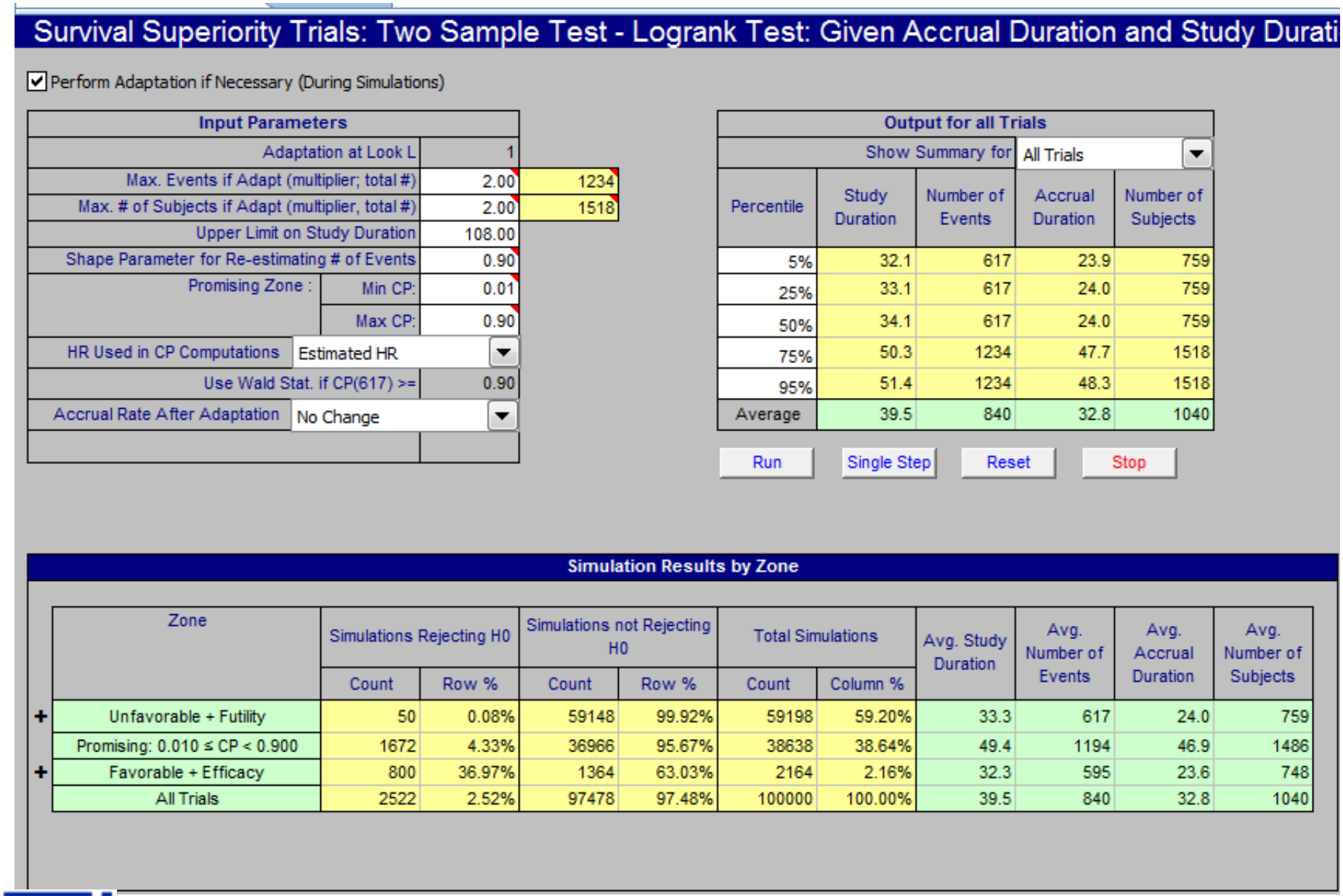
Percentile	Study Duration	Number of Events	Accrual Duration	Number of Subjects
5%	32.1	617	23.9	759
25%	33.1	617	24.0	759
50%	34.1	617	24.0	759
75%	50.3	1234	47.8	1518
95%	51.4	1234	48.3	1518
Average	39.6	842	32.9	1042

Run | Single Step | Reset | Stop

Simulation Results by Zone

Zone	Simulations Rejecting H0		Simulations not Rejecting H0		Total Simulations		Avg. Study Duration	Avg. Number of Events	Avg. Accrual Duration	Avg. Number of Subjects
	Count	Row %	Count	Row %	Count	Column %				
+ Unfavorable + Futility	50	0.08%	59169	99.92%	59219	59.22%	33.3	617	24.0	759
Promising: 0.010 ≤ CP < 0.900	1530	3.96%	37089	96.04%	38619	38.62%	49.6	1202	47.2	1493
+ Favorable + Efficacy	799	36.96%	1363	63.04%	2162	2.16%	32.3	595	23.6	748
All Trials	2379	2.38%	97621	97.62%	100000	100.00%	39.6	842	32.9	1042

100,000 CHW Simulations: seed=66649



Survival Superiority Trials: Two Sample Test - Logrank Test: Given Accrual Duration and Study Durati

☑ Perform Adaptation if Necessary (During Simulations)

Input Parameters			
Adaptation at Look L		1	
Max. Events if Adapt (multiplier; total #)		2.00	1234
Max. # of Subjects if Adapt (multiplier, total #)		2.00	1518
Upper Limit on Study Duration		108.00	
Shape Parameter for Re-estimating # of Events		0.90	
Promising Zone :	Min CP:	0.01	
	Max CP:	0.90	
HR Used in CP Computations		Estimated HR	
Use Wald Stat. if CP(617) >=		0.90	
Accrual Rate After Adaptation		No Change	

Output for all Trials

Show Summary for: All Trials

Percentile	Study Duration	Number of Events	Accrual Duration	Number of Subjects
5%	32.1	617	23.9	759
25%	33.1	617	24.0	759
50%	34.1	617	24.0	759
75%	50.3	1234	47.7	1518
95%	51.4	1234	48.3	1518
Average	39.5	840	32.8	1040

Run | Single Step | Reset | Stop

Simulation Results by Zone

Zone	Simulations Rejecting H0		Simulations not Rejecting H0		Total Simulations		Avg. Study Duration	Avg. Number of Events	Avg. Accrual Duration	Avg. Number of Subjects
	Count	Row %	Count	Row %	Count	Column %				
Unfavorable + Futility	50	0.08%	59148	99.92%	59198	59.20%	33.3	617	24.0	759
Promising: 0.010 ≤ CP < 0.900	1672	4.33%	36966	95.67%	38638	38.64%	49.4	1194	46.9	1486
Favorable + Efficacy	800	36.97%	1364	63.03%	2164	2.16%	32.3	595	23.6	748
All Trials	2522	2.52%	97478	97.48%	100000	100.00%	39.5	840	32.8	1040

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.

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

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