# Cyte

#### Group Sequential and Adaptive Design for Confirmatory Trials using East

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# The design of a clinical trial is the **blueprint** for its eventual success







### Where are we today?







### **The Industry Standard**



### Quickly create multiple designs

					E	ast Archit	ect - [C	esign Input)	Output]									- 0 ×
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One Two Many Regression Mean Means Continuous	Single Two Proportion Proportions F	Many Regre Proportions	sion Agreement	Time to Event De Events Ge	Nther signs	Tables												
Library <del>4</del>					Desid	ın: Normal	Endpo	int: Test of a l	Difference of	Two Means for	Independ	ent Data						<b></b>
	Number of Loo	oks: 5 ▼			-	,											Ir	clude Options
	Design Paramet	ters Boundar	Info Accrual	/Dropout Ir	nfo													
Des 1	Trial Type:	Superiority	•	Input Meth Specify Me	od: Individ an Respons	ual Means		• [	)ist. of Test	Stat.: Normal								
<mark>1</mark> Des33 ⊖ <b>1</b> Des34 ■	Sidedness: Type I Error (α):	1-Sided 0.025	T	Mean Cont	rol (µ <sub>c</sub> ):			0	Std. Deviati	on (σ):	1, 1.2							
🎧 Sim1 IM Dashboard1	Power:	0.8, 0.9	~	Mean Trea	tment (µ <sub>t</sub> ):		0.3:1	.2:0.1										
🏠 Des35 🏠 Des36	Completers:	Computed	0															
1 Des37	Allocation Ratio: $(n_t/n_c)$	1																
Des39																		
Help 7																		
Power																		
(1-15) Description: The power of a statistical test is the probability																		Compute
hypothesis. The probability of failing to reject the null	vv v																	
hypothesis when it is false is referred to as Type II error and is denoted as ß. Hence, power	ID Trial	No. of Looks	Specified	Attained α	Specified Power	Attained Power	nt/nc	Spacing of Looks	Efficacy Boundary	Futility Boundary	Accrual Rate	Response Lag	Dropout Prob.	Study Duration	Total SS	Expected SS (H0)	Expected SS (H1)	Total ^ Completers
is equal to (1- ß).	Des36 Superiority	5 1-	ided 0.025	0.024	0.9	0.902	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	31	199	171.942	183.031	179
Usual choices of power are 0.9 and 0.8 (corresponding to	Des37 Superiority	5 1-	ided 0.025	0.024	0.9	0.9	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	24	146	130.34	141.241	131
10% and 20% type-2 error probabilities, respectively).	Des38 Superiority	5 1-	ided 0.025	0.024	0.9	0.902	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	20	113	105.167	112.83	101
Accentable Range:	Des39 Superiority	5 1-	ided 0.025	0.024	0.9	0.903	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	17	89	86.743	88.954	80
[0.0001, 0.999]	Des40 Superiority	5 1-	ided 0.025	0.024	0.9	0.904	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	15	73	72.795	72.998	65
< +	~			0.004				- 1	1.0 (00)	10 (05) (10)	0	-		10	50	50	50	F A
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### Preview, sort, and filter designs

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Home Data Editor Desi	gn Anal	ysis																		_ 8 ×
One Two Many Regression Mean Means Continuous	Single Proportio	Two n Proportions F	Many Proportions Discrete	Regression	K Agreement	Time to Event De Events Ge	Dther esigns eneral	Tables												
Library 🕂	1	. 🔄 X 💎	¢ 🏾								Οι	Itput Preview								
Q         III         Q         D         III         X         III           III         IIII         IIIII         IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	ID	Trial Type	No. of Looks	Sidedness	Specified α	Attained α	Specified Power	Attained Power	nt/nc	Spacing of Looks	Efficacy Boundary	Futility Boundary	Accrual Rate	Response Lag	Dropout Prob.	Study Duration	Total SS	Expected SS (H0)	Expected SS (H1)	Total Completers
🐪 Des 1	Des 11	Superiority	5	1-Sided	0.025	0.023	0.8	0.808	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	10	33	33	33	29
····· (1) Des2	Des12	Superiority	5	1-Sided	0.025	0.023	0.8	0.818	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	10	28	28	28	25
👘 Des33	Des 13	Superiority	5	1-Sided	0.025	0.023	0.8	0.801	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	83	616	513.116	539.54	554
🖻 🖓 Des34 📃	Des14	Superiority	5	1-Sided	0.025	0.023	0.8	0.801	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	49	347	289.201	309.685	312
····· 🎲 Sim1	Des 15	Superiority	5	1-Sided	0.025	0.023	0.8	0.802	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	34	223	187.161	204.575	200
👘 Des35	Des 16	Superiority	2	I-Sided	0.025	0.023	0.8	0.802	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	25	155	134.423	148.152	139
🙀 Des36	Des 18	Superiority	5	1-Sided	0.025	0.023	0.8	0.802	1	Equal			0	6	0.1	17	87	82 496	86 774	78
Des38	Des10	Superiority	5	1-Sided	0.025	0.023	0.0	0.804	1	Equal			8	6	0.1	17	69	68 454	68 977	62
🌇 Des39	Des20	Superiority	5	1-Sided	0.025	0.023	0.8	0.802	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	13	56	56	56	50
- 👘 Des40 👻	Des21	Superiority	5	1-Sided	0.025	0.023	0.8	0.81	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	12	47	47	47	42
Help 7	Des22	Superiority	5	1-Sided	0.025	0.023	0.8	0.806	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	11	39	39	39	35
•	Des23	Superiority	5	1-Sided	0.025	0.024	0.9	0.9	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	75	550	464.489	476.661	495
Boundary Family	Des24	Superiority	5	1-Sided	0.025	0.024	0.9	0.901	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	45	310	262.524	274.969	279
the generalization of the critical	Des25	Superiority	5	1-Sided	0.025	0.024	0.9	0.902	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	31	199	171.942	183.031	179
sequential methods, when the	Des26	Superiority	5	1-Sided	0.025	0.024	0.9	0.901	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	23	138	124.427	134.351	124
test statistic value crosses the boundaries, it is indicative of	Des27	Superiority	5	1-Sided	0.025	0.024	0.9	0.9	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	19	102	96.748	101.883	91
enough evidence to reject H0 or H1. There are various	Des28	Superiority	5	1-Sided	0.025	0.024	0.9	0.902	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	16	78	77.698	77.997	70
families of boundaries	Des29	Superiority	5	1-Sided	0.025	0.024	0.9	0.9	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	14	62	61.978	62	55
allow the user to specify how	Des 30	Superiority	5	1-Sided	0.025	0.024	0.9	0.903	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	12	50	50	50	45
tests are to be performed at	Des31	Superiority	5	1-Sided	0.025	0.024	0.9	0.902	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	11	42	42	42	37
each interim look and in the final analysis while preserving	Des32	Superiority	5	1-Sided	0.025	0.024	0.9	0.9	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	10	35	35	35	31
the type-1 error.	Des33	Superiority	5	1-Sided	0.025	0.024	0.9	0.9	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	105	793	669.582	681.678	713
Acceptable Range:	Des34	Superiority	5	1-Sided	0.025	0.024	0.9	0.9	1	Equal	LD (OF)	LD (OF) (NB)	8	6	0.1	62	446	376.015	389.512	401
Tsiatis, Published Spending	Des35 ∢	Superiority	5	1-Sided	0.025	0.024	<u> </u>	0 901	1	Foual	I.D. (OF)	LD (OF) (NR)	8	6	01	42	286	241 586	254 664	257 * +

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### Compare trials of different types and endpoints

		•								East	t Architect	- [Desi	ign Input	Output]								
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On Mea	e Two an Means C	Many Means Continuous	Si Proj	ingle portion Pro	Two Ma oportions Propo	any Regre	ssion Agre	ement Eve	to Other nt Design	Plots Ta	ables											
ΗL	library		<b>a</b> [	<b>V</b> - III	- N									Output	t Sumn	nary						
	۹ 📗	🖳 - 📰 - 🖸	;				[	Des 3	D	es 5	Des 7		Des4		D	es6	Des8					
	B- 🏠 P	Root			Test F	arameters	5															
		wbk1				Trial Type	sup	eriority	Supe	riority	Superiorit	y	Superiori	ity	Supe	eriority	Superiority					
	T				N	o. of Looks		1		1	1		3			3	3					
		Des2				Sidedness	2-	-Sided	2-9	Sided	2-Sided		2-Sideo	d	2-	Sided	2-Sided					
	÷	Wbk2				Attained or		0.05	0	.05	0.05		0.05		0	.05	0.05					
					Spec	ified Power	r v	0.9	(	.05	0.05		0.9		(	0.9	0.9					
	ģ	🗝 🎁 Des 34			Atta	ained Power	r	0.9	(	).9	0.9		0.9		(	0.9	0.9	Dif	foro	nce		
		🎁 Sim1			Model P	arameters	i												icici	ice		-
		IM Dashboard1		Propo	ortion under (	Control (πc)	)	0.1	(	), 1	0.1		0.1		(	0.1	0.1					=
		📊 Des35			Diff. in Pro	p. (πt – πc)	-	0.05				Line	-0.05									
		🎁 Des36		Ratio	of Proportio	variarice		eo Estimate	(	5		Unp	ooled Es	limale	(	15		Rai	tio			
		- 📶 Des37		Ratio	orrioportio	Variance	2		Unpoole	d Estimate				Ur	npoole	d Estimate	2					
		01 Des38		Odds F	Ratio of Prop	ortions (ψ1)	)		-		0.474	-					0.474					
	ľ	Des39			Allocation R	atio (nt/nc)	)	1		1	1		1			1	1					
		1 Des40			Boundary F	arameters	5													1:-		
		Ues41			Efficac	y Boundary	/						LD (OF)	)		(OF)	LD (OF)	Udd	IS Ra	llo		
					spacii Si	mole Size	) a						Equai		E	quai	Equal					
						Maximum	- 1 1	1156	1	225	1211		1170		1	240	1225					
					Expecte	d Under H0	)						1165.20	2	12	34.91	1219.972					
					Expecte	d Under H1							938.20	5	99	4.338	982.452					<b>T</b>
			Ī	U 🖪 🛛	<b>X</b> 🖗 ⊄	A									∘ Outpul	t Preview						
				ID	Trial Type	No. of Looks	dedness	Specified α	Attained α	Specified Power	Attained Power	nt/nc	Total SS (	Total Completers	πς	πt - πc	Variance	Spacing of Looks	Efficacy Boundary	Expected SS (H0)	Expected SS (H1)	Expected Completers (H0)
			7	Des 3	Superiority	1	2-Sided	0.05	0.05	0.9	0.9	1	1156	1156	6 0.1	-0.05	Unpooled Estimate					
			n	Des4	Superiority	3	2-Sided	0.05	0.05	0.9	0.9	1	1170	1170	0 0.1	-0.05	Unpooled Estimate	Equal	LD (OF)	1165.202	938.205	1165.202
			n	Des5	Superiority	1	2-Sided	0.05	0.05	0.9	0.9	1	1225	1225	5 0.1							
			n	Des6	Superiority	3	2-Sided	0.05	0.05	0.9	0.9	1	1240	1240	0 0.1			Equal	LD (OF)	1234.91	994.338	1234.91
			n	Des7	Superiority	1	2-Sided	0.05	0.05	0.9	0.9	1	1211	1211	1 0.1							
			7	Des8	Superiority	3	2-Sided	0.05	0.05	0.9	0.9	1	1225	1225	5 0.1			Equal	LD (OF)	1219.972	982.452	1219.972
				•								1										۲.

#### Visualize multiple designs on a single chart



ROeS 2013, Dornbirn

### Disable boundaries at selected interim looks

	Fast Architect - [Decige Input Output]											
	East Arcintect - [Design input Output]											
Home Data Editor Desi		_ 8 X										
One Two Many Regression Mean Means	Single Two Many Regression Agreement Time to Other Plots Tables											
Continuous	Discrete Events General Plots											
Library *	Design: Normal Endpoint: Test of a Difference of Two Means for Independent Data	Ø										
	Number of Looks: 5 •											
🖃 🏫 Root 📃	Design Parameters Boundary Info Accrual/Dropout Info											
🐪 Des1	Efficacy	*										
( <b>'))</b> Des2	Boundary Family: Spending Functions 🔻 Boundary Family: Spending Functions 👻											
WDKZ	Spending Function: Lan-DeMets  Spending Function: Lan-DeMets											
⊡ Han Des34	Spending runction. Lan-Demets V Spending runction. Lan-Demets V											
🐂 Sim1	Parameter: OF V Parameter: PK V O Binding											
IM Dashboard1	Type I Error (α):         0.025         Type II Error (β):         0.100											
	Spacing of Looks											
🔚 Des37	⊙ Equal O Unequal Boundary scale. Z Scale ♥ Ø 🖉 Recalc	Equal O Unequal Boundary Scale: Z Scale      Equal O Unequal Boundary      E										
	Info. Stop for Stop for Cum. α Cum. β Efficacy Futility											
	LOOK # Fraction Efficacy Futility Spent Spent Boundary Boundary											
Destu	1 0.200 🖸 📝 0.0295 NA -0.2820											
Help 4	₽         2         0.400         Image: Constraint of the second seco											
A	4 0.800 V 0.0122 2.2887 NA											
Boundary Family	5 1.000 V 0.0250 0.1000 2.0307 2.0307 -	-										
the generalization of the critical		Compute										
values of a test to group sequential methods, when the	Compute											
test statistic value crosses the boundaries, it is indicative of	III 🗈 🗟 X 🕅 🖉 🏄 Output Preview 🔳											
enough evidence to reject H0	Trial No of Specified Attained Specified Attained Specified of Efficacy Eutility Accrual Personal Dropout Study Tatal Expected Expected	Total										
families of boundaries	ID $\frac{1}{10}$ Type Looks $\frac{1}{10}$ Sidedness $\frac{1}{10}$ $\frac{1}{10$	Completers										
specified in the literature which allow the user to specify how	Des 36         Superiority         5         1-Sided         0.025         0.024         0.9         0.902         1         Enual         LD (OE) (NB)         8         6         0.1         31         199         171 042         183 031	179										
conservatively or aggressively	Des 37 Superiority 5 1-Sided 0.025 0.024 0.0 0.0 1 Equal LD (0F) LD (0F) (NB) 8 6 0.1 24 146 120 24 141 241	121										
each interim look and in the	Dec 38 Superiority 5 1_Sided 0.025 0.024 0.9 0.002 1 Equal LD (0F) LD (0F) (NR) 8 6 0.1 20 112 105 167 112 29	101										
final analysis while preserving the type-1 error.	Des 20 Superiority 5 1-Sided 0.025 0.024 0.0 0.002 1 Equal LD (01) LD (01) (10) 8 6 0.01 17 20 113 103.107 112.83	80										
Assessments big Demons	Des 35 Superiority 5 1-Sided 0.025 0.024 0.9 0.905 1 Equal ED (0F) (ED (0F)	65 E										
Acceptable Range: Haybittle-Peto (p-value), Wang-	Desito Superiority 5 1-Sided 0.025 0.024 0.9 0.904 1 Equal ED (OF) ED (OF) (WB) 8 6 0.1 15 /3 /2./95 /2.998	- 20										
Tsiatis, Published Spending 🔹		4										

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### A few new features

- 1. Response lag
- 2. Bayesian power
- 3. R functions
- 4. Stratification
- 5. Multiple endpoints

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Two arms: asenapine vs. olanzapine (control) Endpoint: negative symptoms assessment (NSA)

<u>Accrual / Dropout Info</u> Accrual 8 patients / week Response lag = 26 weeks Dropout = 8%

#### Example 2: Adaptive Re-estimation of Events in a CV Outcomes Trial



- New agents for type-2 diabetes must demonstrate safety to cardiovascular risk
- Primary outcome is major adverse cardiac event (MACE) -- death, MI, stroke
- Non-inferiority trial at one-sided  $\alpha$ =0.025. If upper bound of 95% CI for HR is:
  - $\leq 1.8 \text{file for provisional approval}$
  - $\leq 1.3 file for final approval$

#### **1.3 Non-Inferiority Design: Assumptions**



- Enroll 6500 patients over 3 years
- Complete the study within 5 years
- 90% power to reject  $H_0$ : HR  $\leq$  1.3 at  $H_1$ : HR = 1 with a 1-sided test at  $\alpha$  = 0.025
- 3% annualized event rate for control arm
- Interim analysis at 80% of information:

### **Options available at interim analysis**



- If upper 97.5% CI > 1.3, proceed to final analysis
- If upper 97.5% CI is between 1 and 1.3, either:
  - 1. Stop and file claim for non-inferiority
  - 2. Continue and test for superiority (HR = 1) at the planned final analysis
  - Adaptively extend number of events. Test for superiority (HR=1) at the extended final analysis
- If upper 95% CI <1, stop and claim superiority

### **Rationale for Adaptive Option**

- Easier to show that new anti-diabetic agents (e.g. the class of DPP4 inhibitors) do not increase CV outcomes than to show that they actually decrease CV outcomes relative to current standard of care (e.g. Insulin, Metformin, Sulfonylureas)
- CV outcome trials powered for superiority require more follow-up and/or more patients than CV outcome trials powered for NI
- Design up-front for NI. If interim results are promising, then extend follow-up to show Sup.

### **Design Tab for the NI Design**

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Design Type: No	ninferiority 🔹	Number of Looks: 2	•			
Design Parameter	s Boundary Info	Accrual/Dropout Info				
Test Type:	1-Sided	# of Hazard Pie	ces: 1 🔹	Input Met	hod: Cum.	% Survival 🔻
Type I Error (α):	0.025	✓ Hazard Ratio	(Optional)		Null	Alternative
Power:	0.9	Hazard Ratio		$(\lambda_t / \lambda_c)$		1.3 1
No. of Events:	623	○ Ratio of % Su	rvivals at Period	# 1 (S <sub>t</sub> /S <sub>c</sub> )	0.9	991 1
Allocation Ratio: (n,/n,)	1	Period At	Cum. % (Con	Survival Cum. trol) (Treatr	% Survival nent: Null)	Cum. % Survival (Treatment: Alt.)
		1 12.0	00 91	7 9	6.118	97.000
		-Variance of Log	Hazard Ratio –			
		⊙ Null	🔿 Alter	native		

### **Boundaries Tab for the NI Design**

Design Type: Noninferiority Design Parameters Boundary Info Ad Efficacy Boundary Family: Spending Functions Spending Function: Lan-DeMets Parameter: OF Type I Error (α): 0.025	umber of Looks: 2 crual/Dropout Info Futility Boundary Family: None	3
Spacing of Looks Ο Equal $\odot$ Un Look # Info. Cum. α Efficac	equal Efficacy Boundary: Z Scale	
LOOK # Fraction Spent Bounda	y Settings Print Conv. Zoom Save As	Hido Road offe
1         0.800         0.012         -2.250           2         1.000         0.025         -2.025	Stopping Boundaries	Hide Read-oils //
III 9 📥 X 🔬 🗮 🇞	-0.5 all block all block all block all block all block bloc	Ind. Fraction

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### **Accrual Tab for NI Design**

Design Type: Noninferiority   Number of Looks: 2 Design Parameters Boundary Info Accrual/Dropout Info	•
Subjects are followed: Until End of Study  Accrual Info # of Accrual Periods: 1	Piecewise Constant Dropout Rates # of Pieces: 0 • Input Method: Hazard Rates •
Period #     Starting At     Accrual Rate       1     0.000     180.556	Period # Starting At Hazard Rate (Control) (Treatment)
Accrual         Min.         Comtd.         Sugg. Max.           O Duration:         3.45         36         53.297           ③ Subjects:         623         6500         9623	

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### **Design Summary of NI Design**

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	NI-SUP:NI
Mnemonic	SU-2S-LRAR
Test Parameters	
Design Type	Noninferiority
No. of Looks	2
Test Type	1–Sided
Specified α	0.025
Power	0.9
Model Parameters	
Hazard Ratio (Null)	1.3
Hazard Ratio (Alt.)	1
Var (Log HR)	Null
Allocation Ratio (nt/nc)	1
Boundary Parameters	
Spacing of Looks	Unequal
Efficacy Boundary	LD (OF)
Accrual & Dropout Parameters	
Accrual Rate	180.556
Subjects are Followed	Until End of Study
No. of Accrual Periods	1
No. of Dropout Pieces	0
Sample Size	
Maximum	6500
Expected Under H0	6500
Expected Under H1	6500
Events	
Maximum	623
Expected Under H0	621.478
Expected Under H1	529.192
Accrual Duration	
Maximum	36
Expected Under H0	36
Expected Under H1	36
Study Duration	
Maximum	57.832
Expected Under H0	52.619
Expected Under H1	51.609

- 623 events
- 6500 patients
- 58 months max study duration

#### Design: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration

Test Parameters	
Design ID: Design Type: Number of Looks: Test Type: Specified α: Power:	NI Noninferiority 2 1-Sided 0.025 0.9
Model Parameters	
$\label{eq:HR} \begin{split} HR &= \lambda_t / \lambda_c \\ & Under H0: \\ & Under H1: \\ & Ratio of \% Surv. at Period \#1 \\ & Var (Log HR): \\ & Allocation Ratio (n_t / n_c): \end{split}$	1.3 1 :1 Null 1
Boundary Parameters	
Spacing of Looks: Efficacy Boundary:	Unequal LD (OF)
Accrual/Dropout Parameter	ers
Accrual Duration: Max Study Duration: Dropout:	36 57.832 No

#### Stopping Boundaries: Look by Look

Look	Info.	Events	Cumulative	Boundaries		
#	Fraction (s/s max)	(s)	α Spent	Efficacy Z		
1	0.799	498	0.012	-2.251		
2	1	623	0.025	-2.025		

#### Events, Sample Size, Pipeline and Analysis Times: Look by Look (Under H0)

Laste	Info.	0	Events (s)	Disalias	Amelia	Incr. Boundary Crossing Prob.
LOOK #	Fraction	Sample Size (n)		Pipeline (n-s)	Time	Under H0
	(s/s_max)					Efficacy
1	0.799	6500	498	6002	45.486	0.012
2	1	6500	623	5877	52.707	0.013

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

Lask	Info.	0	Et.	Disalias	America	Incr. Boundary Crossing Prob.
LOOK #	Fraction	Sample Size (n)	Events (s)	(n-s)	Analysis Time	Under H1
	(s/s_max)					Efficacy
1	0.799	6500	498	6002	49.54	0.75
2	1	6500	623	5877	57.832	0. <b>1</b> 5

#### Survival Info. : Cum. % Survival

Period #	At		Cum. % Surviv	Hazard Ratio		
		Control (Ac)	Treatment (λt0)	Treatment (λt1)	Null (λt0/λc)	Alt. (λt1/λc)
1	12	97	96.118	97	1.3	1



Create a superiority design in East so as to have:

- 623 events (like NI)
- 6500 patients enrolled over 36 months (like NI)
- 3% annualized event rate for control arm (like NI)
- Interim analysis at 80% of information (like NI)
- One-sided  $\alpha$ =0.025 to reject H<sub>0</sub>=1
- Powered at HR=0.8

(Decrease power by trial & error until 623 events)

### **Design Tab for Superiority Trial**

Design Parameters	Boundary Info	Accrual/Dropout	Info			
Test Type:	1-Sided		ard Pieces: [ d Ratio (Opti	1 V I	nput Method: Hazard F	Rates 🔹
Type T Error (α): Power: No. of Events:	0.025	⊙ Hazard ○ Log Ha	Ratio zard Ratio	$(\lambda_t / \lambda_c)$ ln $(\lambda_t / \lambda_c)$		0.8
Allocation Ratio: (n_/n_)	1	Period #	Starting At	Hazard Rate (Control)	Hazard Rate (Treatment: Alt.)	
		1	0.000	0.00254	0.002	
		Variance	of Log Haza	ard Ratio		
		⊙ Null		O Alternative		

#### 623 events, $\alpha$ = 0.025 and 3% annualized event rate -- just like NI design

### Boundary Tab for Superiority Design

Desigr	n Type: Supe	eriority	✓ Numb	nber of Looks: 2 👻
Design	n Parameters	Boundary	Info Accrua	ual/Dropout Info
Efficacy				Futility
Bounda	ary Family:	Spending	Functions	▼ Boundary Family: None ▼
Spendi	ng Function:	Lan-DeMe	ets 🔻	
Parame	ter:	OF	•	
Tune L	Fron (a):			
Type T	Error (α).	0.025		
- Spacin <u>c</u>	) of Looks	O Equal	⊙ Unequa	al Efficacy Boundary: Z Scale 🔹 📝
Leelu#	Info.	Cum. α	Efficacy	
LOOK #	Fraction	Spent	Boundary	
1	0.800	0.012	-2.250	
2	1.000	0.025	-2.025	

#### Interim analysis at 80% of information. Same as NI design

### **Accrual Tab for Superiority Design**

Design Type: Superiority   Number of Looks: 2	
Design Parameters Boundary Info Accrual/Dropout Info	
Subjects are followed: Until End of Study	
	Piecewise Constant Dropout Rates
# of Accrual Periods: 1	# of Pieces: 0  Input Method: Hazard Rates
Period # Starting At Accrual Rate	Poriod # Starting At Hazard Rate Hazard Rate
1 0.000 180.556	(Control) (Treatment)
Accrual	
Min. Comtd. Sugg. Max.	
O Duration: 3.45 36 56.116	
⊙ Subjects: 623 6500 10132	

#### 6500 patients enrolled over 3 years. Same as for NI design

### Summary Comparison of NI and Sup

	NI-SUP:NI	NI-SUP:SUP
Mnemonic	SU-2S-LRAR	SU-2S-LRAR
Test Parameters		
Design Type	Noninferiority	Superiority
No. of Looks	2	2
Test Type	1–Sided	1–Sided
Specified α	0.025	0.025
Power	0.9	0.787
Model Parameters		
Hazard Ratio (Null)	1.3	
Hazard Ratio (Alt.)	1	0.8
Var (Log HR)	Null	Null
Allocation Ratio (nt/nc)	1	1
Boundary Parameters		
Spacing of Looks	Unequal	Unequal
Efficacy Boundary	LD (OF)	LD (OF)
Accrual & Dropout Parameters		
Accrual Rate	180.556	180.556
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	6500	6500
Expected Under H0	6500	6500
Expected Under H1	6500	6500
Events		
Maximum	623	623
Expected Under H0	621.478	621.478
Expected Under H1	529.192	548.727
Accrual Duration		
Maximum	36	36
Expected Under H0	36	36
Expected Under H1	36	36
Study Duration		
Maximum	57.832	62.257
Expected Under H0	52.619	57.731
Expected Under H1	51.609	56.777

#### Comparison of Sup and NI

- Same number of events
- Same sample size
- Hence longer maximum and expected study durations for Sup
- Only 79% power at HR = 0.8 for Sup
  - Permit adaptive increase of events to boost power



- Perform interim analysis at 600 events
- Is 1 < (upper 97.5% confidence bound) < 1.3?
  - compute the conditional power for superiority at 650 events
  - if CP is in promising zone, permit a one-time increase in number of events
- Explore by simulation the impact on study duration of various decision rules

**Note:** Sample size increase is not an option

### Select a range of Adaptive Options

Number of Lo	oks: 2 💌				
Simulation Para	ameters Response Generation	Info Accrual/Dropo	out Info Samp	le Size Re-estimation	Simulation Control Info
Use Adaptation N ③ CHW (	1ethod ) CDL				
Adapt at:	Look #	1 •			
Max. # of Events i	f Adapt (multiplier; total #):	1:2:.1 Com	outed		
Max. Sample Size	if Adapt (multiplier; total #):	1	6500		
Upper Limit on Stu	udy Duration:	186.772			
Target CP for Re-e	estimating # of Events:	0.999			
Promising Zone So	cale:	Cond. Power 👻	CP		
Promising	Min. CP:	0.5			
Zone:	Max. CP:	0.9			
CP Computation B	ased on:	Estimated HR	•		
Accrual Rate After	Adaptation:	No Change	•		

Advantage: can submit multiple inputs as a single batch job (11 designs with 10,000 simulations/design took 15 minutes

### **Summary results from 11 trials**



	NI-SUP:SUP:CHWSim1	NI-SUP:SUP:CHWSim6	NI-SUP:SUP:CHWSim7	NI-SUP:SUP:CHWSim8	NI-SUP:SUP:CHWSim9
Mnemonic	SU-2S-LRAR	SU-2S-LRAR	SU-2S-LRAR	SU-2S-LRAR	SU-2S-LRAR
Test Parameters					
Design Type	Superiority	Superiority	Superiority	Superiority	Superiority
Test Type	1–Sided	1–Sided	1–Sided	1–Sided	1–Sided
Test Statistic	Logrank	Logrank	Logrank	Logrank	Logrank
Power	0.784	0.794	0.805	0.806	0.814
Power (Promising)	0.77	0.857	0.881	0.926	0.949
No. of Looks	2	2	2	2	2
Model Parameters					
No. of Hazard Pieces	1	1	1	1	1
Boundary Parameters					
Efficacy Boundary	User Specified				
Spacing of Looks	User Specified				
Accrual & Dropout Parameters					
Followup Duration	Until End of Study				
Accrual Rate	180.556	180.556	180.556	180.556	180.556
No. of Accrual Periods	1	1	1	1	1
Sample Size					
Maximum	6500	6500	6500	6500	6500
Events					
Maximum	623	623	623	623	623
Sample Size Re-estimation Parameters					
Method of Adaptation	Cui-Hung-Wang	Cui-Hung-Wang	Cui-Hung-Wang	Cui-Hung-Wang	Cui-Hung-Wang
Adaptation Stage	Look # : 1				
Max. # of Events if Adapt	623	685	747	809	872
Max. Sample Size if Adapt	6500	6500	6500	6500	6500
Upper Limit on Study Duration	186.772	186.772	186.772	186.772	186.772
Target CP	0.999	0.999	0.999	0.999	0.999
CP Computation Based on	Estimated HR				
Promising Zone	0.5 <= CP < 0.9				
Study Duration					
Maximum	56.811	57.58	58.266	59.091	59.704
Simulation Results (Promising)					
Average Study Duration	62.314	66.842	71.602	76.345	81.184
Average Sample Size	6500	6500	6500	6500	6500
Average Events	623	685	747	809	872

#### Details of CHWsim6 (increases events by 10% in the promising zone)

#### Simulation: Survival Endpoint: Two-Sample Test - Parallel Design - Logrank Given Accrual Duration and Accrual Rates (CHW Sim

Simulation Parameters	
Simulation ID:	CHWSim6
Design Type:	Superiority
Number of Looks:	2
Test Type:	1-Sided
Fix at Each Look:	Total No. of Events
Test Statistic:	Logrank
Average Events:	559.277
Total Accrual Duration:	36
Avg. Power at Termination:	0 794

Sample Size Re-estimation Parameters					
Method of Adaptation:	Cui-Hung-Wang				
Adapt At Look No.:	1				
Max. # of Events if Adapt:					
Multiplier:	1.1				
Total #:	685				
Max. Sample Size if Adapt:					
Multiplier:	1				
Total #:	6500				
Upper Limit on Study Duration	: 186.772				
Target CP:	0.999				
Promising Zone Scale:	Cond. Power				
Min. CP:	0.5				
Max. CP:	0.9				
CP Computation Based on:	Estimated HR				
Accrual Rate After Adaptation	: No Change				

Simulation Control Parameters				
Starting Seed:	Clock			
Number of Simulation	s: 10000			

#### Simulation Boundaries and Boundary Crossing Probabilities:

Look #	Events	Boundaries Efficacy	Early Stopping For	Tot Simula	al ations
		Lower	Efficacy	Count	%
1	498	-2.251	5880	5880	58.8
2	623	-2.025	2057	4120	41.2
Total			7937	10000	
%			79.37		

#### Average Sample Size and Look Times:

Look #	Average	Average	e Events	Average	Average
	Sample Size	Control	Treatment	Look Time	Follow up
1	6500	275.492	222.508	53.046	33.569
2	6500	347.613	299.118	64.035	43.583
Average	6500	309.358	249.919	57.58	37.702

#### Response Generation Parameters

No. of Hazard Pieces: 1

Input Method: Hazard Rates

Piece #	Starting At	Control	Treatment	Hazard Ratio
1	0	0.00254	0.00203	0.8

#### Simulation Results by Zone:

Zone	Simulation Rejecting H0		Simulation Not Rejecting H0		Total Simulations		Average Number	Average Sample Size	Average	Average Study Duration	
	Count	Row %	Count	Row %	Count	Column %	or Events	Sample Size	Accidal Duration	Study Duration	
Futility	0	0	0	0	0	0	0	0	0	0	
Unfavorable	706	27.762	1837	72.238	2543	25.43	623	6500	35.994	62.294	
Promising	1351	85.669	226	14.331	1577	15.77	685	6500	35.994	66.842	
Favorable	0	0	0	0	0	0	0	0	0	0	
Efficacy	5880	100	0	0	5880	58.8	498	6500	35.994	53.057	
All Trials	7937	79.37	2063	20.63	10000	100	559.277	6500	35.994	57.58	



- Adaptive change only affects the study duration, not the sample size
- Additional investment of study duration only made if entering the promising zone
- Probability enter promising zone is about 16%
- If entering the promising zone:
  - 6 month study prolongation (685 events) yields 86% power instead of 77% power in the PZ
  - 12 month study prolongation (747 events) yields 88% power instead of 77% power in the PZ

# Example 3: Impact of Stratification in a Lung Cancer Clinical Trial



- The base-case design has:
  - 2-sided level 0.05 logrank test
  - 90% power to detect HR = 0.447
  - Baseline hazard (control arm) = 0.009211 (corresponds to 9% five-year survival)
  - 3 equally spaced OBF stopping boundaries
  - Uniform enrollment at 12/week for 24 weeks
- Consider stratification by cell type (4), age (2) and performance status (2)

# Kalbfleisch and Prentice (2002) Data



Cell type	Proportion	Hazard Ratio
Small cell	0.28	Baseline
Adenocarcinoma	0.13	2.127
Large cell	0.25	0.528
Squamous	0.34	<mark>0</mark> .413
Age Group	Proportion	Hazard Ratio
≤ 50	0.28	Baseline
> 50	0.72	0.438
Karnofsky P.S.	Proportion	Hazard Ratio
≤ 50	0.43	Baseline
50 to 70	0.37	0.164
>70	0.20	0.159

#### **Entering the Stratification Information**

				Sin	nulation: S	urvival E	ndpoint:	Two-Sa	mple Test - Pa	arallel Design - Logrank Given Ac	crual Duratio	n an	d Accrual Rates
Number	of Looks:	3 🔻											
Simulatio	n Paramet	ers Stra	tification I	nfo Res	ponse Gen	eration In	fo Ac	crual/D	ropout Info	Simulation Control Info			
Number of S Stratum Variable	tratum Va # of Levels	riables: 3 Marginal Distributi	➡ Al Stratum ion:	llocate Fra	actions to S	Strata: 💿	Marginal	lly O	Individually Total Numbe Stratum Spec	er of Strata: 24 cific Information:			
Cell Type	4 -	Cell	Cell Type Age				ofsky		Stratum ID Label Fraction 🔺				
Age	2 -	Level	Fraction	Level	Fraction	Level	Fraction	n	SID01	Small   Young   le. 50	0.034	=	
	<u> </u>	Small	0.28	Young	0.28	le. 50	0.43		51002	Small   Young   50-70	0.029		
Karpofeky		Adeno	0.13	Old	0.72	50-70	0.37		SID03	Small   Young   gt. 70	0.016		
Kathorsky	3 🔻	Large	0.25			at. 70	0.2		SID04	Small   Old   le. 50	0.087		
		Squam	0.34			9		_	SID05	Small   Old   50-70	0.075		
		Squam	0.01						SID06	Small   Old   gt. 70	0.040		
									SID07	Adeno   Young   le. 50	0.016		
									SID08	Adeno   Young   50–70	0.013		
									SID09	Adeno   Young   gt. 70	0.007	Ŧ	

- There are 24 strata: Cell(4) x Age(2) x Karnofsky(3)
- East provides two ways to enter the hazard rate for each stratum
  - enter individual hazard rates stratum by stratum
  - enter hazard rates implicitly through the Cox model

#### Entering Hazard Ratios through a Cox Model



Simulation Para	meters Str	atification I	nfo Response Ge	neration Info	Accrual/Drop	out Info S	imulation Control I	nfo
O User Specified	O User Specified Hazard Rates Model Based Hazard Rates				SID08:Ade	eno   Young	50-70 ▼	
<ul> <li>Model Based Hazard Rates</li> <li>Hazard Rate ~ (Treatment + Cell Type + Age + Karnofsky)</li> <li>Model Parameters</li> </ul>				⊙ Using ⊖ Using	Hazard Rates Cum. % Survival			
				Diana	Charting At	Ha	zard Rates	Useend Datis
	0	.009211		Piece	Starting At	Control	ntrol Treatment	Hazard Katio
				1	0.000	0.00321	0.00144	0.447
Treatment		Cell Type						
Cell Type	Level	Fraction	Hazard Ratio					
Karnofsky	Small	0.280	Baseline					
	Adeno	0.130	2.127					
	Large	0.250	0.528					
	Squam 0.340 0.413							

#### Comparing Stratified and Unstratified Analyses



	Stratification:no strat:Sim1	Stratification:no strat:Sim2	Stratification:no strat:Sim3
Mnemonic	SU-2S-LRAR	SU-2S-LRAR	SU-2S-LRAR
Test Parameters			
Design Type	Superiority	Superiority	Superiority
Test Type	2-Sided	2-Sided	2-Sided
Test Statistic	Logrank	Stratified Logrank	Logrank
Power	0.887	0.849	0.771
No. of Looks	3	3	3
Model Parameters			
No. of Hazard Pieces	1		
Boundary Parameters			
Efficacy Boundary	User Specified	User Specified	User Specified
Spacing of Looks	User Specified	User Specified	User Specified
Accrual & Dropout Parameters			
Followup Duration	Until End of Study	Until End of Study	Until End of Study
Accrual Rate	12	12	12
No. of Accrual Periods	1	1	1
Sample Size			
Maximum	289	289	289
Events			
Maximum	66	66	66
Study Duration			
Maximum	43.9	171.115	177.394
Stratum Information			
No. of Stratum Variables		3	3
No. of Strata		24	24
Allocate Fractions to Strata		Marginally	Marginally
Specification of Hazard Rates		Model based	Model based

#### Example 4: Alzheimer's Disease Trial with Multiple Endpoints



- There are four efficacy variables measuring change from baseline
  - CS: Clinician's Score
  - ADAS-cog: Alzheimer's disease assessment scale of cognitive function
  - SIB: Severe Impairment Battery
  - MMSE: Mini-Mental State Examination
- Must win on **both** CS and ADAS-cog in order to claim efficacy
- SIB and MMSE are secondary endpoints. Can be included in claim if strong control of type-1 error



#### Require strong control of the FWER at one-sided level $\alpha = 0.025$

#### Means and Covariances from Historical Data



#### Week 28 change from baseline in control arm and targeted change in treatment arm

	<b>Control Mean</b>	Treatment Mean
CS	2.3	2.6
ADAS-cog	-4.5	-2.5
SIB	-10	-6.5
MMSE	-1.2	-0.4

#### Variance Covariance matrix for the four endpoints

CS	ADAS-cog	SIB	MMSE
1.2	3.6	6.8	1.6
3.6	42	38	9.3
6.8	38	145	17
1.6	9.3	17	8

### Enter the design parameters in East



Number of Endpoints:	4
Simulation Parameters	Response Generation Info Simulation Control Info
Test Type: 1-Side Rejection Region: Right- Type I Error (α): ( Sample Size (n): 0:1000	d  Multiple Comparisons Procedures Serial Gatekeeping For Last Family Bonferroni Sidak Weighted Bonferroni Holm's step down Hochberg's step up Hommel's step up Fixed Sequence Fallback

Number of E	ndpoints:	4							
Simulation Parameters Response Generation Info				on Info	Simulation Control Info				
Endpoint Infor	Endpoint Information:				Cova	riance M	Aatrix:		
EndPoint ID	Family	Mean	Mean			CS	ADAScog	SIB	MMSE
	Rank	Ctrl	Trmt			1.2	3.6	6.8	1.6
CS	1	2.3	2.6			3.6	42	38	9.3
ADAScog	1	-4.5	-2.5			6.8	38	145	17
SIB	2	-10	-6.5			1.6	9.3	17	8
MMSE	2	-1.2	-0.4						

### Simulation based Sample Size Assessment Cuto

Vii 🗐 🍬 🚔			Output Summary						
	Sim1	Sim2	Sim3	Sim4	Sim5	Sim6			
Mnemonic	MN-2S-ME	MN-2S-ME	MN-2S-ME	MN-2S-ME	MN-2S-ME	MN-2S-ME			
Test Parameters									
Multiple Comparisons Procedure	Hochberg's step up	H							
Test Type	1–Sided	1–Sided	1–Sided	1–Sided	1–Sided	1–Sided			
Design Type	Serial	Serial	Serial	Serial	Serial	Serial			
Specified α	0.025	0.025	0.025	0.025	0.025	0.025			
No. of Endpoints	4	4	4	4	4	4			
No. of Families	2	2	2	2	2	2			
Rejection Region	Right-Tail	Right-Tail	Right-Tail	Right-Tail	Right-Tail	Right-Tail			
MCP Results									
Conjunctive Power First Family	0.151	0.366	0.567	0.717	0.826	0.899			
Conjunctive Power Last Family	0.066	0.218	0.411	0.588	0.726	0.83			
Disjunctive Power Last Family	0.106	0.303	0.515	0.677	0.801	0.886			
Overall FWER	0	0	0	0	0	0			
Sample Size									
Maximum	100	200	300	400	500	600			

- Conjunctive Power is power to reject every false null hypothesis
- Disjunctive Power is power to reject at least one false null hypothesis
- 600 patients are needed for 90% conjunctive power for first family

Next investigate by simulation: how many patients do we need for 90% conjunctive power for last family?

# Maximize conjunctive power of last family by choice of test

# Cytel

Number of Endpoints: 4					
Simulation Parameters Response Generation Info Simulation Control Info					
Test Type:1-SidedRejection Region:Right-TailType I Error (α):0.0Sample Size (n):6	Multi	iple Comparisons Procedu Serial Gatekeeping r Last Family Bonferroni Sidak Weighted Bonferroni Holm's step down Hochberg's step up Hommel's step up Fixed Sequence Fallback	For Hor mo for	a 600 pati mmel's tes st conjunc last family	ient trial, it has the tive power y, 0.835

	Sim11	Sim12	Sim13	Sim14	Sim15
Mnemonic	MN-2S-ME	MN-2S-ME	MN-2S-ME	MN-2S-ME	MN-2S-ME
Test Parameters					
Multiple Comparisons Procedure	Bonferroni	Holm's step down	Hochberg's step up	Hommel's step up	Fixed Sequence
Test Type	1–Sided	1–Sided	1–Sided	1–Sided	1–Sided
Design Type	Serial	Serial	Serial	Serial	Serial
Specified α	0.025	0.025	0.025	0.025	0.025
No. of Endpoints	4	4	4	4	4
No. of Families	2	2	2	2	2
Rejection Region	Right-Tail	Right-Tail	Right-Tail	Right-Tail	Right-Tail
MCP Results					
Conjunctive Power First Family	0.896	0.896	0.895	0.895	0.897
Conjunctive Power Last Family	0.78	0.83	0.827	0.835	0.829
Disjunctive Power Last Family	0.88	0.883	0.881	0.882	0.865
Overall FWER	0	0	0	0	0
Sample Size					
Maximum	600	600	600	600	600

#### Increase Sample Size to Boost Hommel's Test to 90% Conjunctive Power for Second Family

# Cytel

	Sim18
Mnemonic	MN-2S-ME
Test Parameters	
Multiple Comparisons Procedure	Hommel's step up
Test Type	1–Sided
Design Type	Serial
Specified α	0.025
No. of Endpoints	4
No. of Families	2
Rejection Region	Right-Tail
MCP Results	
Conjunctive Power First Family	0.942
Conjunctive Power Last Family	0.902
Disjunctive Power Last Family	0.935
Overall FWER	0
Sample Size	
Maximum	700

- 700 patients needed to obtain 90% conjunctive power for last family
- At this sample size, conjunctive power of first family is 94%

## Coming soon...in 6.3



- 1. Adaptive dose selection with SSR
- 2. Interim simulations
- 3. More MCP options

### **Thank you!**

et





#### **Backup slides**

#### **Bayesian Probability of Success (Assurance)**

Assign a prior distribution to  $\delta$  to capture the uncertainty associated with it

✓ Assurance (Probability of Success):       0.685         Prior Distribution for: δ Distribution:       Normal         Input Method:       User Specified E(δ) and SD(δ ▼)         User Specified       2         E(δ):       2         SD(δ):       1	The "Assurarce" of success is only 0.685 due to uncertainty about $\delta$
Assurance (Probability of Success):0.798Prior Distribution for: $\delta$ Distribution:NormalInput Method:User Specified E( $\delta$ ) and SD( $\delta$ User SpecifiedE( $\delta$ ):2SD( $\delta$ ):0.1	In this case the "Assurance is 0.798 due to less uncertainty about $\boldsymbol{\delta}$