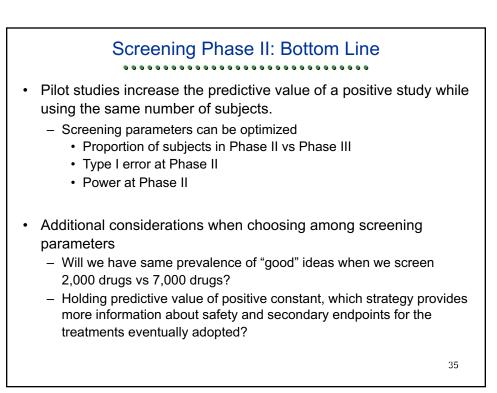


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		Sum	mary	
		Scenario 1	Scenario 2a	• • Scenario 2b
Phase	Number RCT N per RCT	2,000 (10% eff) 0	7,000 (10% eff) 100	2,047 (10% eff) 342
ie 2	Type 1 err; Pwr		0.025; 24%	0.100; 85%
	"Positive" RCT		168 eff; 158 not	173 eff; 184 not
Confirmtaory Phase	Number RCT N per RCT	2,000 (10% eff) 500	326 (52% eff) 921	357 (49% eff) 839
itaory	Type 1 err, Pwr	0.025; 80%	0.025; 97%	0.025; 95%
Pha	# Effctve Adopt	160	162	165
se 3	# Ineff Adopt	45	4	5
	Pred Val Pos	78%	98%	97%
	N per Adopt	500	1,021	1,181

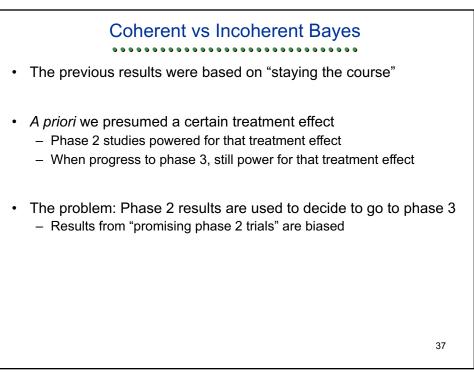
	••	Summary	: Phase 2	••
		Scenario 1	Scenario 2a	Scenario 2b
Phase	Number RCT N per RCT	2,000 (10% eff) 0	7,000 (10% eff) 100	2,047 (10% eff) 342
se 2	Type 1 err; Pwr		0.025; 24%	0.100; 85%
	"Positive" RCT		168 eff; 158 not	173 eff; 184 not
Confirmtaory Phase	Number RCT N per RCT	2,000 (10% eff) 500	326 (52% eff) 921	357 (49% eff) 839
Itaory	Type 1 err, Pwr	0.025; 80%	0.025; 97%	0.025; 95%
' Pha	# Effctve Adopt	160	162	165
se 3	# Ineff Adopt	45	4	5
	Pred Val Pos	78%	98%	97%
	N per Adopt	500	1,021	1,181

		Summary	: Phase 3	
	••	Scenario 1	Scenario 2a	Scenario 2b
Phase	Number RCT N per RCT	2,000 (10% eff) 0	7,000 (10% eff) 100	2,047 (10% eff) 342
se 2	Type 1 err; Pwr		0.025; 24%	0.100; 85%
	"Positive" RCT		168 eff; 158 not	173 eff; 184 not
Confirmtaory Phase	Number RCT N per RCT	2,000 (10% eff) 500	326 (52% eff) 921	357 (49% eff) 839
Itaory	Type 1 err, Pwr	0.025; 80%	0.025; 97%	0.025; 95%
' Pha	# Effctve Adopt	160	162	165
Ise 3	# Ineff Adopt	45	4	5
	Pred Val Pos	78%	98%	97%
	N per Adopt	500	1,021	1,181



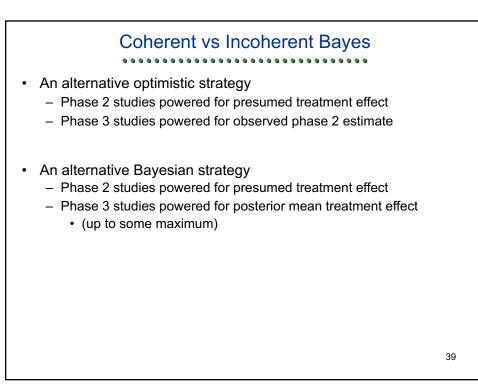
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	S	Summary: "Dr	ug Discovery	,11
	••	Scenario 1	Scenario 2a	Scenario 2b
Phase	Number RCT N per RCT	2,000 (10% eff) 0	7,000 (10% eff) 100	2,047 (10% eff) 342
se 2	Type 1 err; Pwr		0.025; 24%	0.100; 85%
	"Positive" RCT		168 eff; 158 not	173 eff; 184 not
Confirmtaory Phase	Number RCT N per RCT	2,000 (10% eff) 500	326 (52% eff) 921	357 (49% eff) 839
ntaor	Type 1 err, Pwr	0.025; 80%	0.025; 97%	0.025; 95%
y Pha	# Effctve Adopt	160	162	165
tse 3	# Ineff Adopt	45	4	5
	Pred Val Pos N per Adopt	78% 500	98% 1,021	97% 1,181



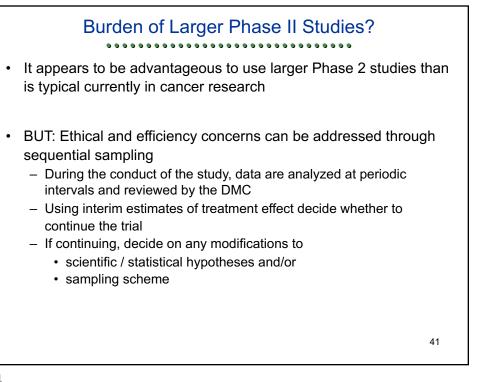
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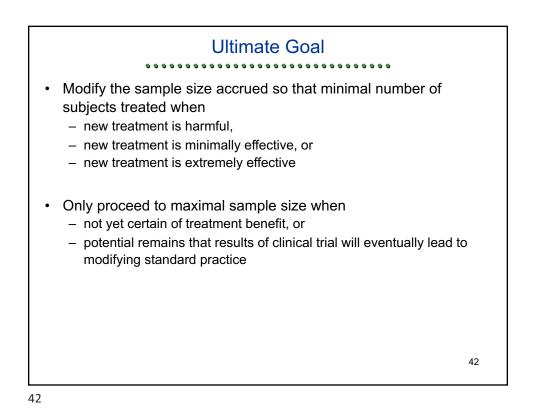
	-	,000 pat ample siz		g bias of	"positive" s	tudies		
				Null: ∆	=0		Alt: Δ= .:	125
N per RCT	RCTs	Crit Value	Prob Sig	N Sig RCT	Expected Estimate	Prob Sig	N Sig RCT	Expected Estimate
7000	100	0.0234	0.025	2	0.028	1.000	100	0.125
3500	200	0.0331	0.025	5	0.039	1.000	200	0.125
700	1000	0.0741	0.025	25	0.089	0.912	912	0.132
350	2000	0.1048	0.025	50	0.125	0.649	1,298	0.156
70	10000	0.2343	0.025	250	0.280	0.180	1,801	0.299
35	20000	0.3313	0.025	500	0.390	0.114	2,271	0.407

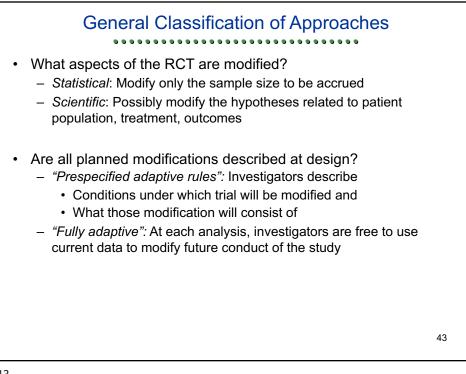


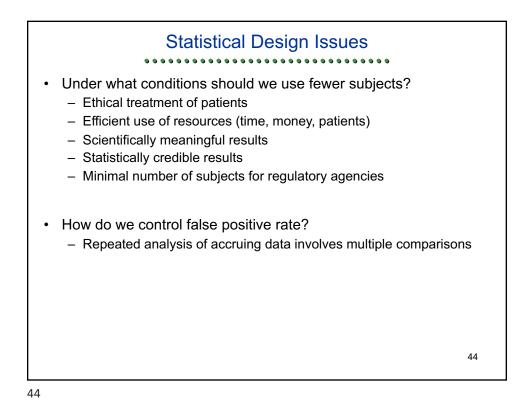
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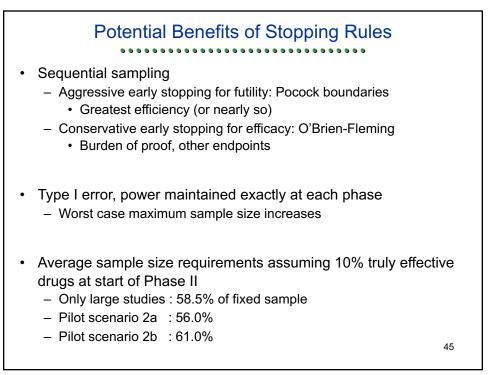
		Sum	mary	
		Scenario 2b	Optimistic	Mod. Bayes
Phase 2	Number RCT	2,047 (10% eff)	1,759 (10% eff)	1,959 (10% eff)
	N per RCT	342	342	342
	Type 1 err; Pwr	0.100; 85%	0.100; 85%	0.100; 85%
	"Positive" RCT	173 eff; 184 not	150 eff; 159 not	163 eff; 176 not
Confirmtaory Phase 3	Number RCT	357 (49% eff)	309 (49% eff)	339(48% eff)
	N per RCT	839	894 vs 1665	941 vs 998
	Type 1 err, Pwr	0.025; 95%	0.025; 95 vs 86%	0.025; 95%
	# Effctve Adopt	165	129	156
	# Ineff Adopt	5	4	4
	Pred Val Pos	97%	97%	97%
	N per Adopt	1,181	1,259	1,285

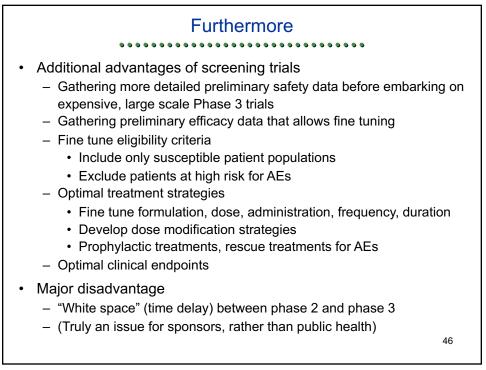


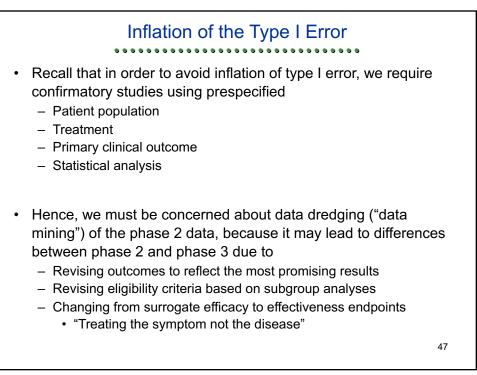


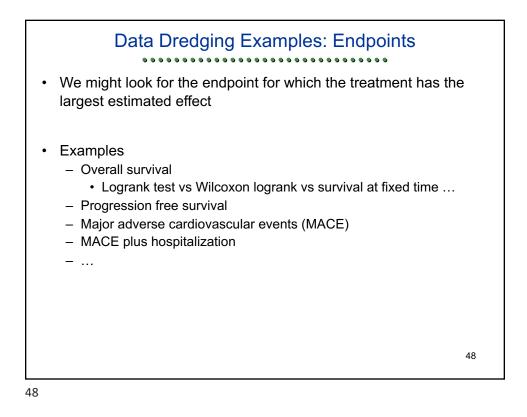


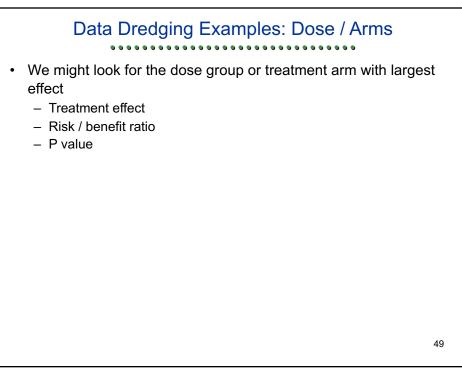


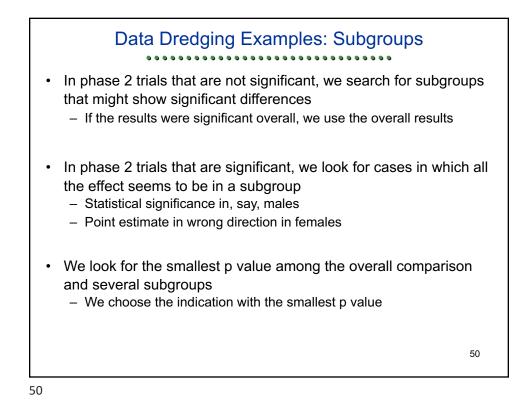








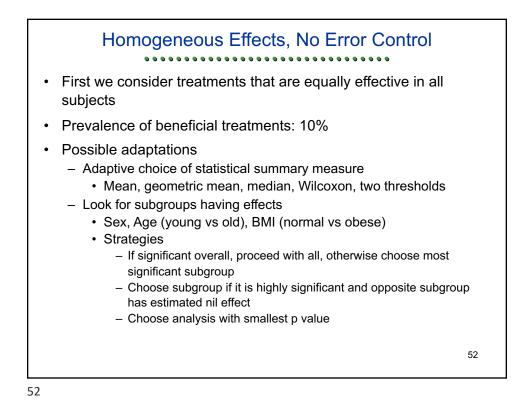




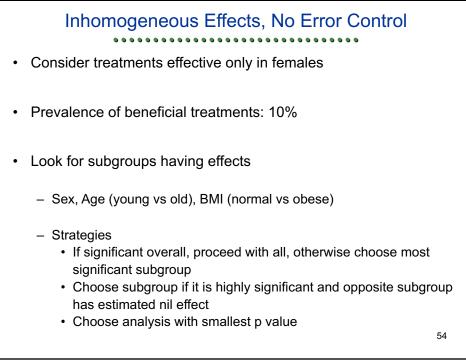


We can explore the impact of adaptive changes in RCT in several examples

- Consideration of multiple summary measures
 - Mean, geometric mean, Wilcoxon, median, two proportions
- Consideration of subgroups
 - Overall sample
 - Plus equal sized subgroups defined by three variables
- Consideration of change of endpoint between phase 2 and 3
 - Phase 2: potential surrogate
 - Phase 3: clinical outcome
- · We consider
 - Adaptations that do or do not control type I error
 - Treatment effect in all groups or only in one subgroup
 - Surrogates that do or do not always predict outcome

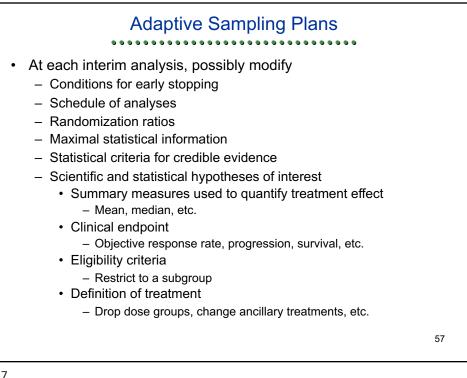


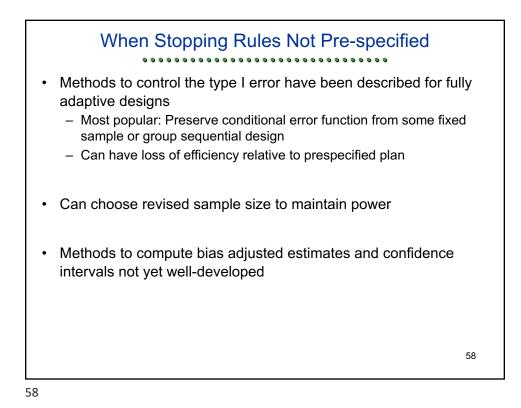
	Summary (Homogeneous Effects)							
		Scenario 2b	Alt Smry Meas	Subgroups				
	Number RCT	2,047 (10% eff)	1,695 (10% eff)	1,485 (10% eff)				
Phase	N per RCT	342	342	342				
se 2	Type 1 err; Pwr	0.100; 85%	0.227; 92%	0.334; 95%				
	"Positive" RCT	173 eff; 184 not	155 eff; 346 not	141 eff; 446 not				
Cor	Number RCT	357 (49% eff)	501 (31% eff)	587 (24% eff)				
ıfirm	N per RCT	839	839	839				
Confirmtaory Phase	Type 1 err, Pwr	0.025; 95%	0.025; 94%	0.025; 95%				
Pha	# Effctve Adopt	165	147	134				
se 3	# Ineff Adopt	5	9	11				
	Pred Val Pos	97%	94%	92%				
	N per Adopt	1,181	1,181	1,181				

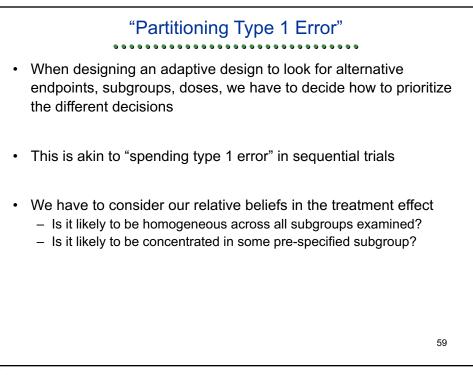


Impact of Strategies for Subgroups						
<u>Analysis</u>		<u>Sig</u>	Pref All	<u>Choice</u>	<u>Min P</u>	
All		.64	.64	.40	.07	
Females		.85	.20	.40	.60	
Males		.10	.00	.00	.00	
Young		.45	.02	.03	.06	
Old		.45	.02	.03	.06	
Norm Wt		.45	.02	.03	.06	
Obese		.45	.02	.03	.06	
						55

	Sum	mary (Inhomo	ogeneous Eff	ects)
	•••		Duefen All	
		Scenario 2b	Prefer All	Choose Subgrp
	Number RCT	2,123 (10% eff)	1,490 (10% eff)	1,490 (10% eff)
Phase	N per RCT	342	342	342
se 2	Type 1 err; Pwr	0.100; 64%	0.334; 92%	0.334; 92%
	"Positive" RCT	136 eff; 191 not	137 eff; 448 not	137 eff; 448 not
Con	Number RCT	327 (42% eff)	584 (23% eff)	584 (23% eff)
firm	N per RCT	839	839	839
Confirmtaory Phase	Type 1 err, Pwr	0.025; 73%	0.025; 75%	0.025; 80%
Pha	# Effctve Adopt	99	103	109
se 3	# Ineff Adopt	5	11	11
	Pred Val Pos	95%	90%	91%
	N per Adopt	1,181	1,181	1,181

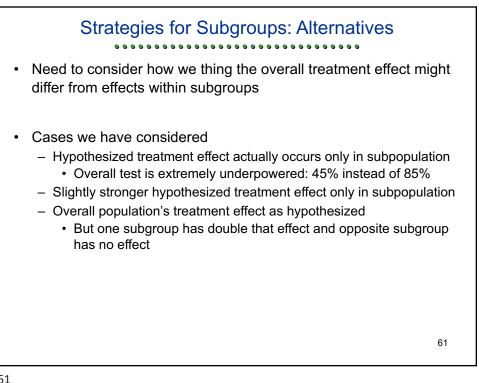


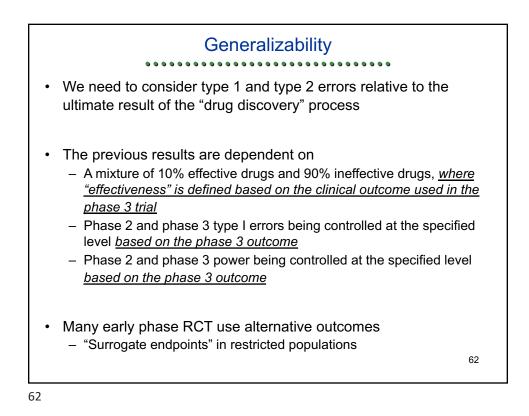


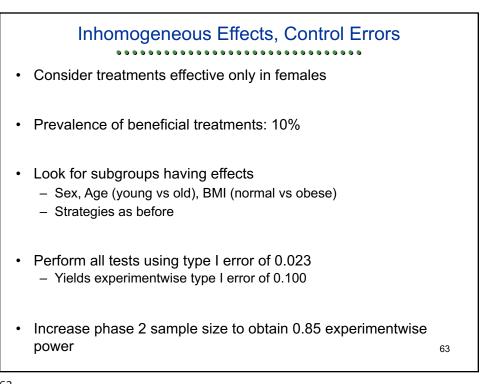


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Strategies for Subgroups: Type 1 Error Example: Assuming independent covariates with 50-50 split					
<u>Analysis</u>	<u>Sig</u>	Pref All	<u>Choice</u>	<u>Min P</u>	
All	.023	.022	.021	.007	
Females	.023	.013	.013	.015	
Males	.023	.013	.013	.015	
Young	.023	.013	.013	.015	
Old	.023	.013	.013	.015	
Norm Wt	.023	.013	.013	.015	
Obese	.023	.013	.013	.015	
					60

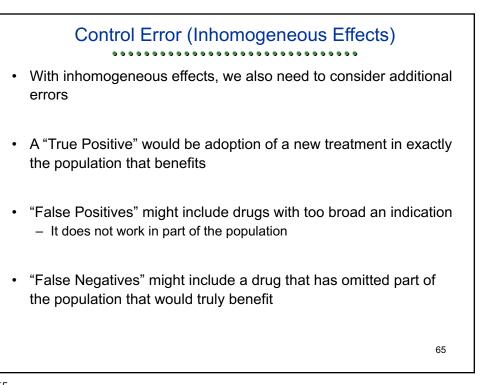


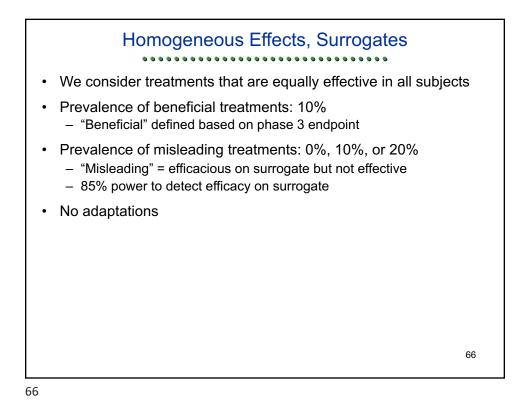




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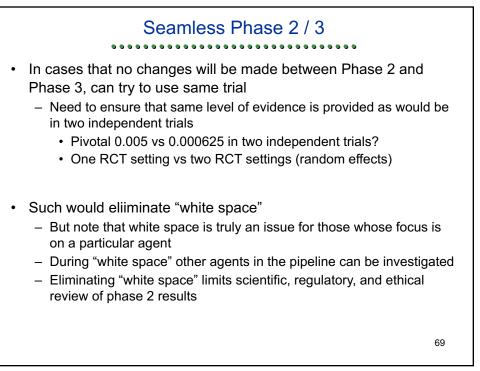
	Contro	l Error (Inhon	nogeneous E	ffects)
		Scenario 2b	Inflate Error	Control Error
Phase	Number RCT N per RCT	2,123 (10% eff) 342	1,490 (10% eff) 342	1,720 (10% eff) 438
ie 2	Type 1 err; Pwr	0.100; 64%	0.334; 92%	0.100; 80%
	"Positive" RCT	136 eff; 191 not	137 eff; 448 not	138 eff; 156 not
Confirmtaory Phase	Number RCT N per RCT	327 (42% eff) 839	584 (23% eff) 839	294 (47% eff) 839
taory	Type 1 err, Pwr	0.025; 73%	0.025; 80%	0.025; 76%
Pha	# Effctve Adopt	99	109	105
se 3	# Ineff Adopt	5	11	4
	Pred Val Pos	95%	91%	96%
	N per Adopt	1,181	1,181	1,277

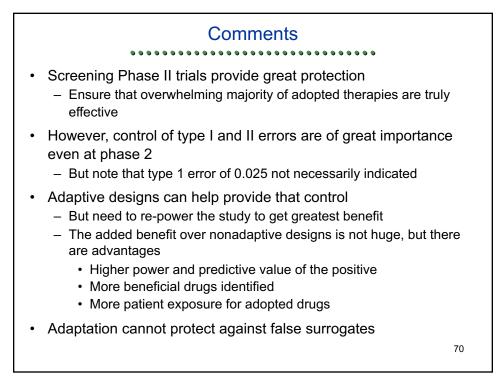


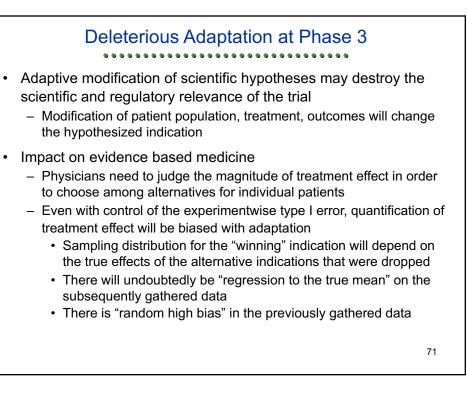


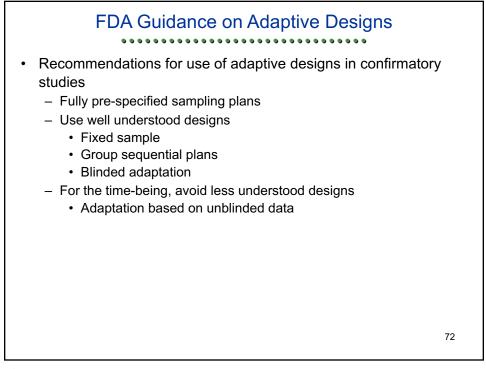
	Surrogates (Homogeneous Effects)						
		0% Misleading	10% Misleading	20% Misleading			
Phase	Number RCT N per RCT	2,046 (10% eff) 342	1,812 (10% eff) 342	1,627 (10% eff) 342			
e 2	Type 1 err; Pwr	0.100; 85%	0.100; 85%	0.100; 85%			
	"Positive" RCT	174 eff; 184 not	154 eff; 337 not	138 eff; 494 not			
Confirmtaory Phase	Number RCT N per RCT	358 (49% eff) 839	491 (31% eff) 839	632 (22% eff) 839			
taory	Type 1 err, Pwr	0.025; 95%	0.025; 95%	0.025; 95%			
Pha	# Effctve Adopt	166	147	132			
se 3	# Ineff Adopt	5	8	12			
	Pred Val Pos	97%	95%	91%			
	N per Adopt	1,181	1,181	1,181			

Comparisons				
••••••				
	RCT	Eff (TP)	Not(FF	P) n
Nonadaptive				
Homogeneous effect	2,040	165(165)	5	1,181
Homogeneous,10% misleading	1,812	147 (147)	8	1,181
Homogeneous,20% misleading	1,627	132 (132)	12	1,181
Inhomogeneous effect	2,123	99(0)	5	1,181
Adaptive subgroups: inflate error				
Homogeneous effect	1,488	134(43)	11	1,181
Inhomogeneous effect	1,493	122(88)	11	1,181
Adaptive subgroups: control error				
Homogeneous effect	2,040	153(56)	4	1,277
Inhomogeneous effect	2,067	135 (103)	4	1,277











• In a large, expensive study, it is well worth our time to carefully examine the ways we can best protect

- Patients on the study
- Patients who might be on the study
- Patients who will not be on the study, but will benefit from new knowledge
- Sponsor's economic interests in cost of trial
- Eventual benefit to health care costs
- Adaptation to interim trial results introduces complications, but they can often be surmounted using methods that are currently well understood
 - It is not immediately clear how close we already are to optimality
 - (Multiple 0.023 tests yielded experimentwise 0.10)
- To get good results, we need to learn to take "NO" for an answer

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