Bayesian Goldilocks Designs: Getting the Sample Size *Just Right*

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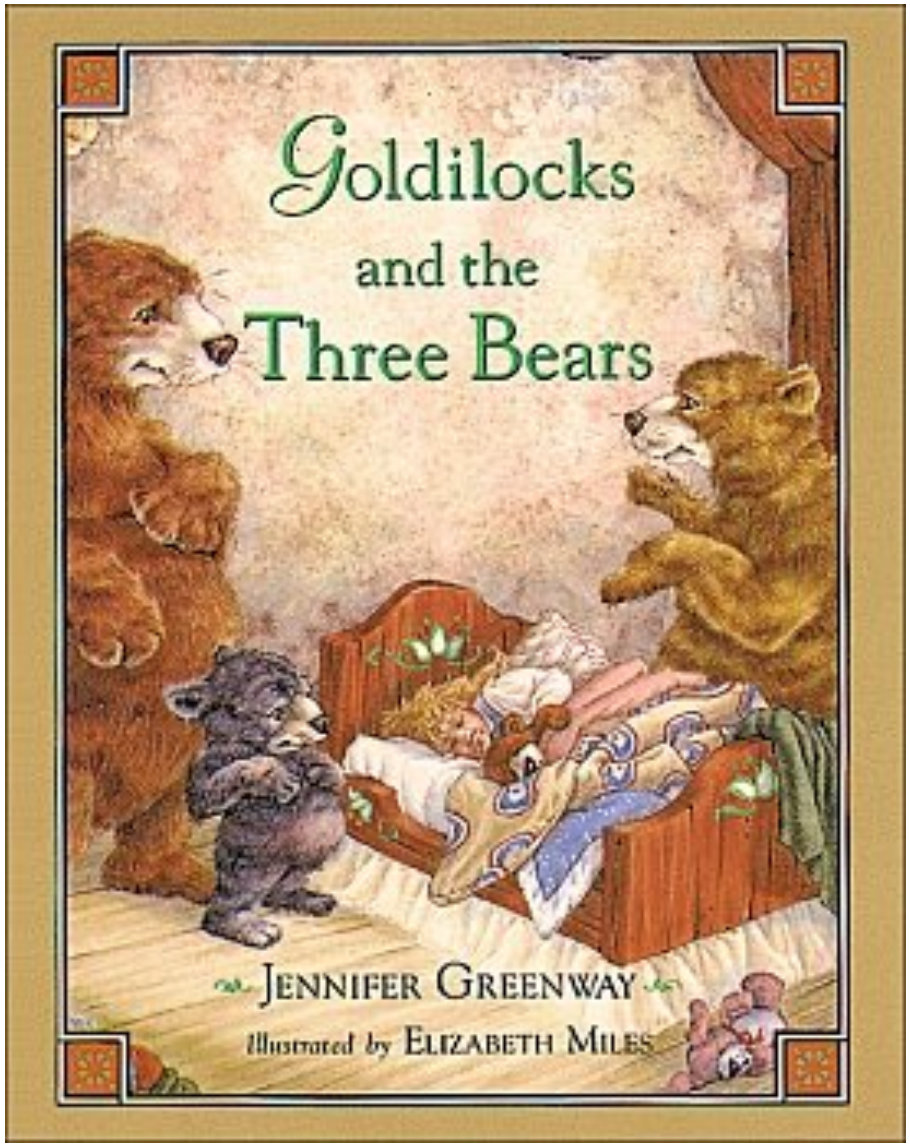
Statistical Innovation

Porridge: Not too hot,
or too cold,
but *just right*

Trial: Not too big,
too small,
But *just right*



Outline

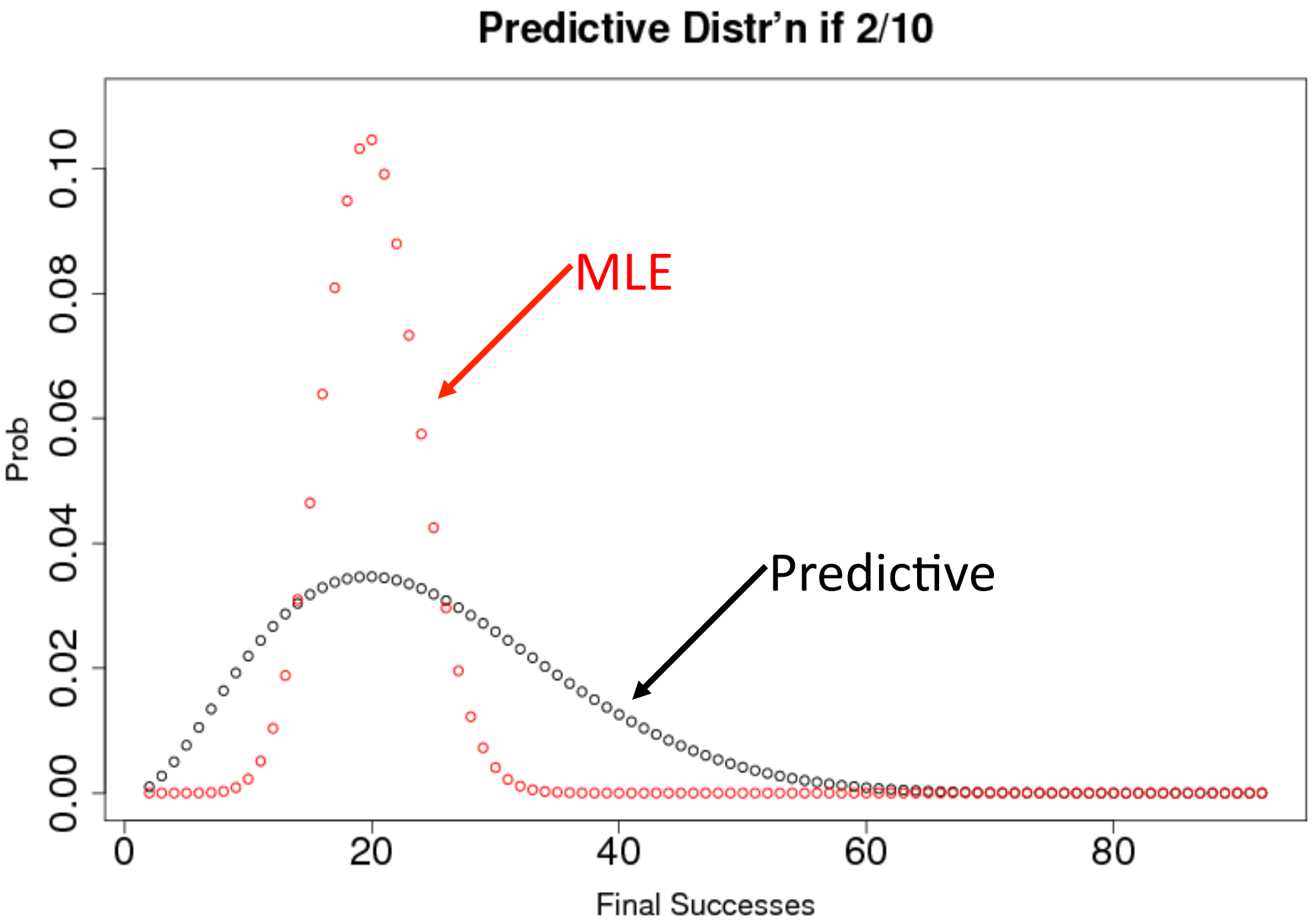
- Bayesian Predictive Probabilities
- Confirmatory Trials Issues
- Example 1: Generic Phase III Cancer Trial
- Example 2: ThermoCool® Catheter
- Example 3: Libigel® for HSDD
- Discussion

Posterior and Predictive…same?

- Clinical Trial, 100 subjects. H_A: p > 0.25? FDA will approve if # success ≥ 33 [post > 0.95, beta(1,1)]
- See 99 subjects, 32 successes
- Pr[p > 0.25 | data] = 0.955
- Predictive prob trial success = 0.327

Example of Predictive Prob

- Same Trial, 33+ out of 100 is a SUCCESS
- Look at data at n=10
- Predict remainder of 90 subjects
- Predictive Prob accounts for uncertainty and “only” 10% of data observed


Predictive Distr'n if 2/10
Prob
0.00
0.02
0.04
0.06
0.08
0.10
0
20
40
60
80
Final Successes
MLE
Predictive

Possible Calculation

$$\int \binom{90}{x} p^x (1-p)^{90-x} \frac{\Gamma(3)\Gamma(9)}{\Gamma(12)} p^2 (1-p)^8 \, dp$$

- Simulate a *p* from the beta(3,9)
- Simulate an *x* from binomial(90, *p*)
- Distribution of *x*'s is beta-binomial--the predictive distribution

Predictive, Posterior, MLE Project

S@10	Post Prob >0.25	Pred Prob 33+	MLE Proj Prob 33+
0	.042	.0096	0
1	.197	.070	6.6×10^{-11}
2	.455	.234	.00097
3	.713	.487	.279
4	.885	.737	.948
5	.966	.900	.99991
6	.992	.973	1
7	.9988	.995	1

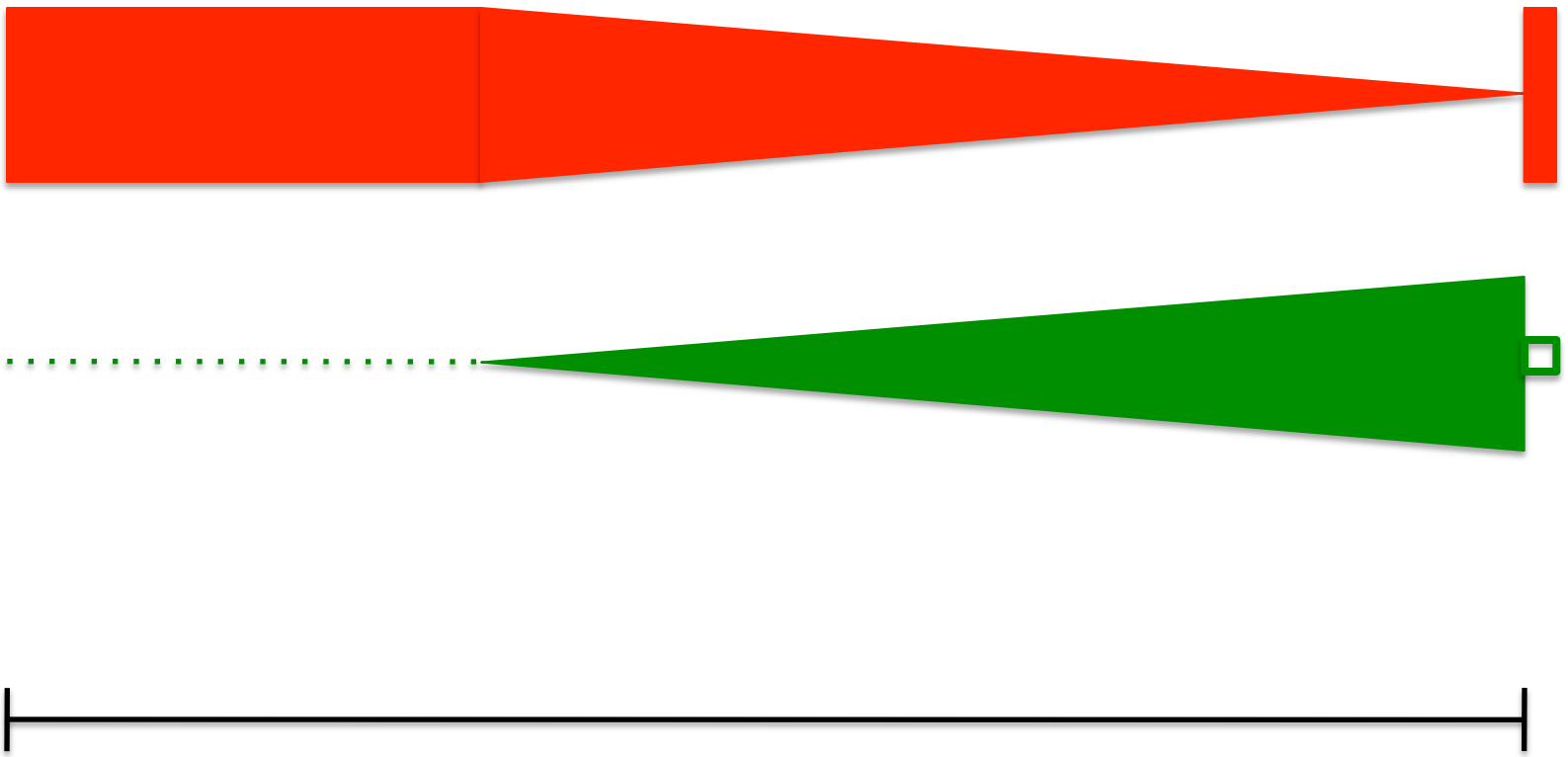
Interpretation

- Predictive is VERY different than posterior probability
- If you were using frequentist MLE to project you need to have constraints on # subjects before method “kinda works”
- Predictive distribution handles uncertainty of future and current and does not need “constraints”

What is Different About Confirmatory Trials?

- Type I error is a dominant factor
- Adjusting the design (goal) in order to accommodate adaptive aspects—control type I error
- Predictive probabilities much more relevant than posterior probabilities!
- Very well-defined goal. A "game"—sport!

Posterior/Predictive



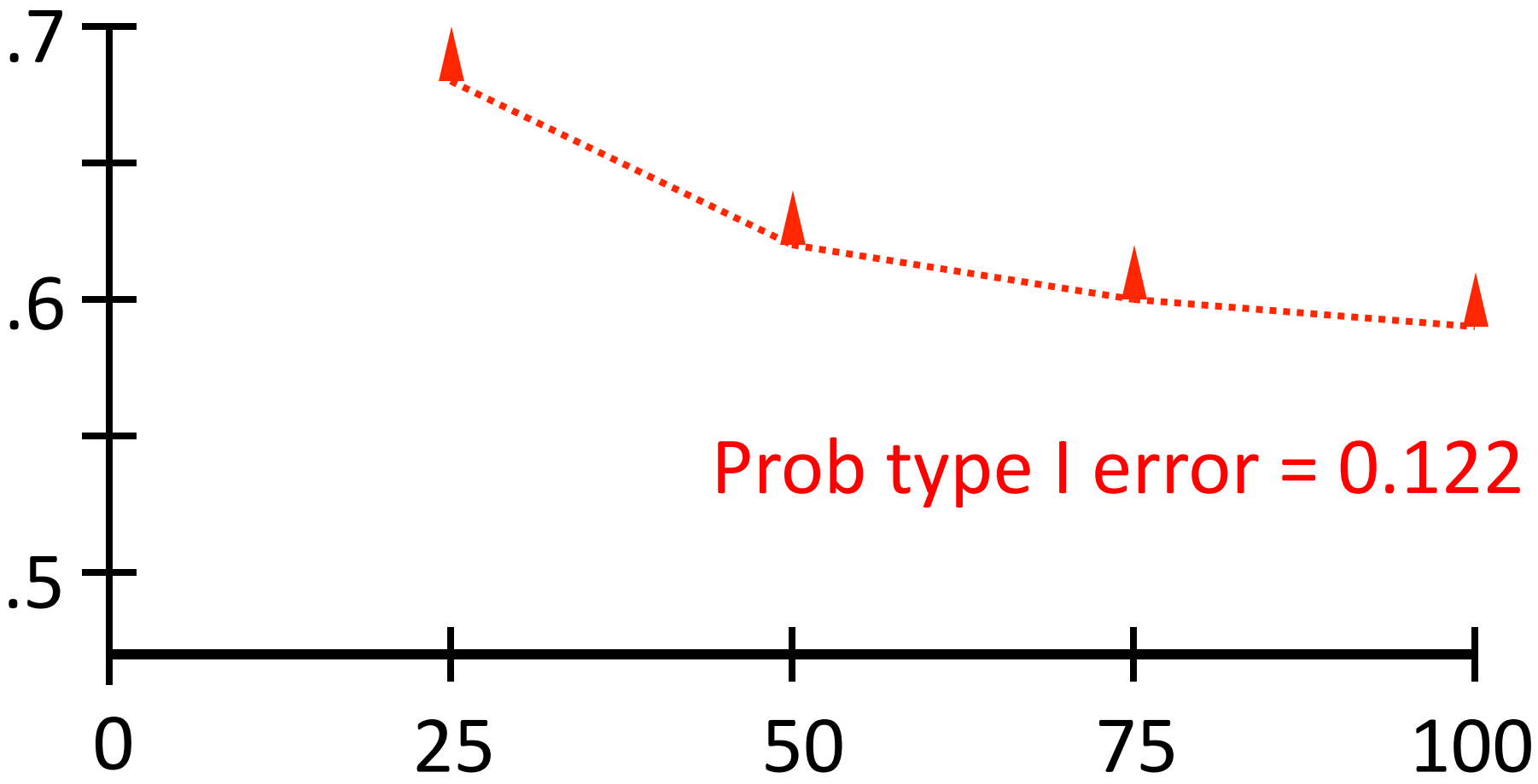
Simple Bayesian Trial

- Single-arm trial, n=100 maximum trial size.
- X ~ Binomial(n,*p*)
- If Pr[π > 0.5 | data] ≥ 0.95 then trial success

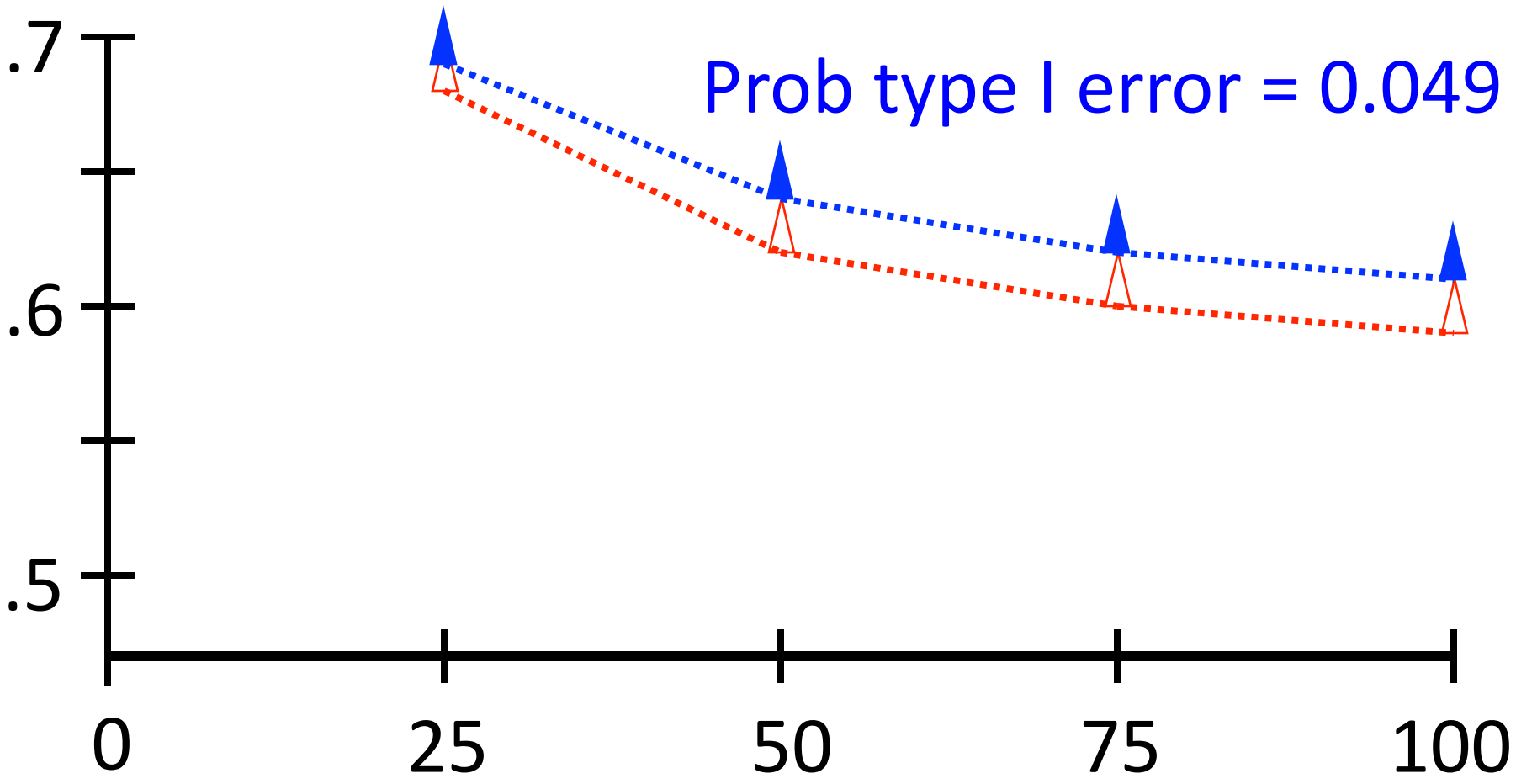
$$\pi \sim \text{Beta}(1,1)$$

- At n=100, if there are 59 or more successes then trial success
- Type I error is 0.044

- Add in looks at n=25, 50, 75.
- If Pr[π > 0.5] ≥ 0.95 at any look then stop for success (17,31,45,59)



- If Pr[π > 0.5] ≥ 0.98 at any look then stop for success (18,33,47,61)



Likelihood Principle

- In phase III/Confirmatory trials,
- This controlling of type I error is inherently "frequentist."
- Violates likelihood principle
  - Trial 1: no looks, get 16, 30, 44, 59: SUCCESS
  - Trial 2: adaptive, get 16, 30, 44, 59: FAILURE
- Building "frequentist" design using Bayesian methods
- Can add multiple arms, delay in observations, more flexible n, … and control same way

Operating Characteristics

π	Pr(Win)	Mean N	SD N	50	75	100
0.50	0.0421	98.9	6.9	0.017	0.011	0.972
0.55	0.217	94.7	14.2	0.077	0.058	0.864
0.60	0.578	84.1	21.0	0.237	0.162	0.601
0.65	0.889*	69.0	21.1	0.504	0.229	0.266
0.70	0.989	57.0	14.2	0.780	0.160	0.060
0.75	0.999	51.5	6.5	0.944	0.051	0.005

*A fixed trial with 69 subjects, in the 0.65 case, has power 0.802

Adding Futility

- Futility is set up to stop the trial when the "value" of the study is in doubt or there is evidence there is harm
- Futility is not a determination that the experimental is "worse" than the control (or nothing)
- We utilize predictive probabilities

Example Interim

- Suppose there are 25 successes and 25 failures at the 50 subject analysis
  - Posterior is a Beta(26,26)
  - 50% posterior prob π is greater than 0.5
  - Relevance of posterior?
- What is the likelihood of trial success?

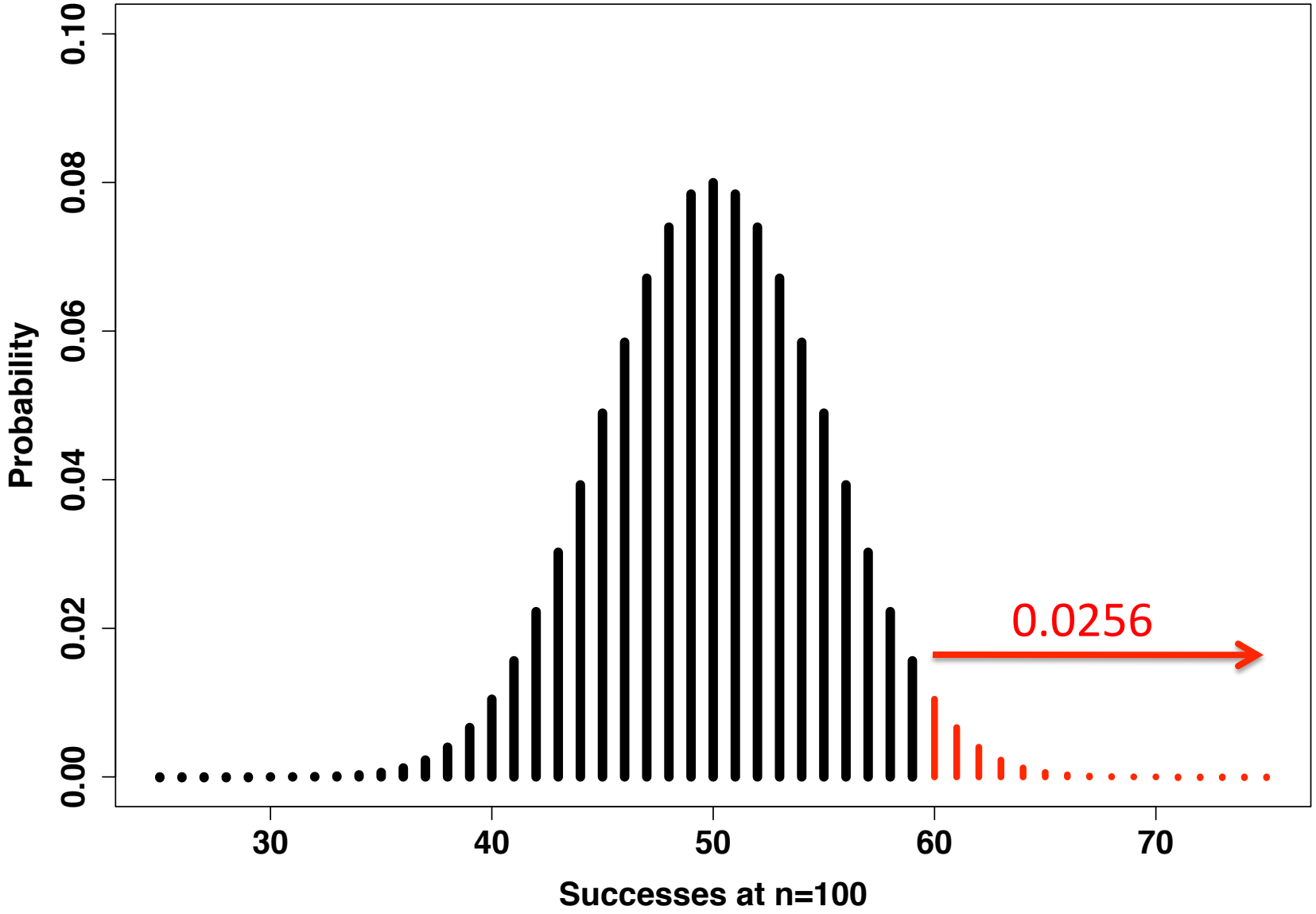
Predictive Distribution

- In this case the predictive distribution of *k* successes in the next *n* subjects is a beta-binomial (current Beta(α,β)):

$$f(k) = \frac{\Gamma(\alpha+\beta)\Gamma(n+1)\Gamma(k+\alpha)\Gamma(n-k+\alpha)}{\Gamma(\alpha)\Gamma(\beta)\Gamma(n-k+1)\Gamma(n+\alpha+\beta)}$$

$$= \int \binom{n}{k} p^k (1-p)^{n-k} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} p^{\alpha-1}(1-p)^{\beta-1}\, dp$$

  - Simulate a *p* from the beta(α,β)
  - Simulate an *k* from binomial(n, *p*)
  - Distribution of *k*'s is beta-binomial--the predictive distribution


Predictive Distribution at n=100
Probability
0.00
0.02
0.04
0.06
0.08
0.10
30
40
50
60
70
Successes at n=100
0.0256

Add Futility to the Design

- If the predictive probability < 0.05 @ 50, 75

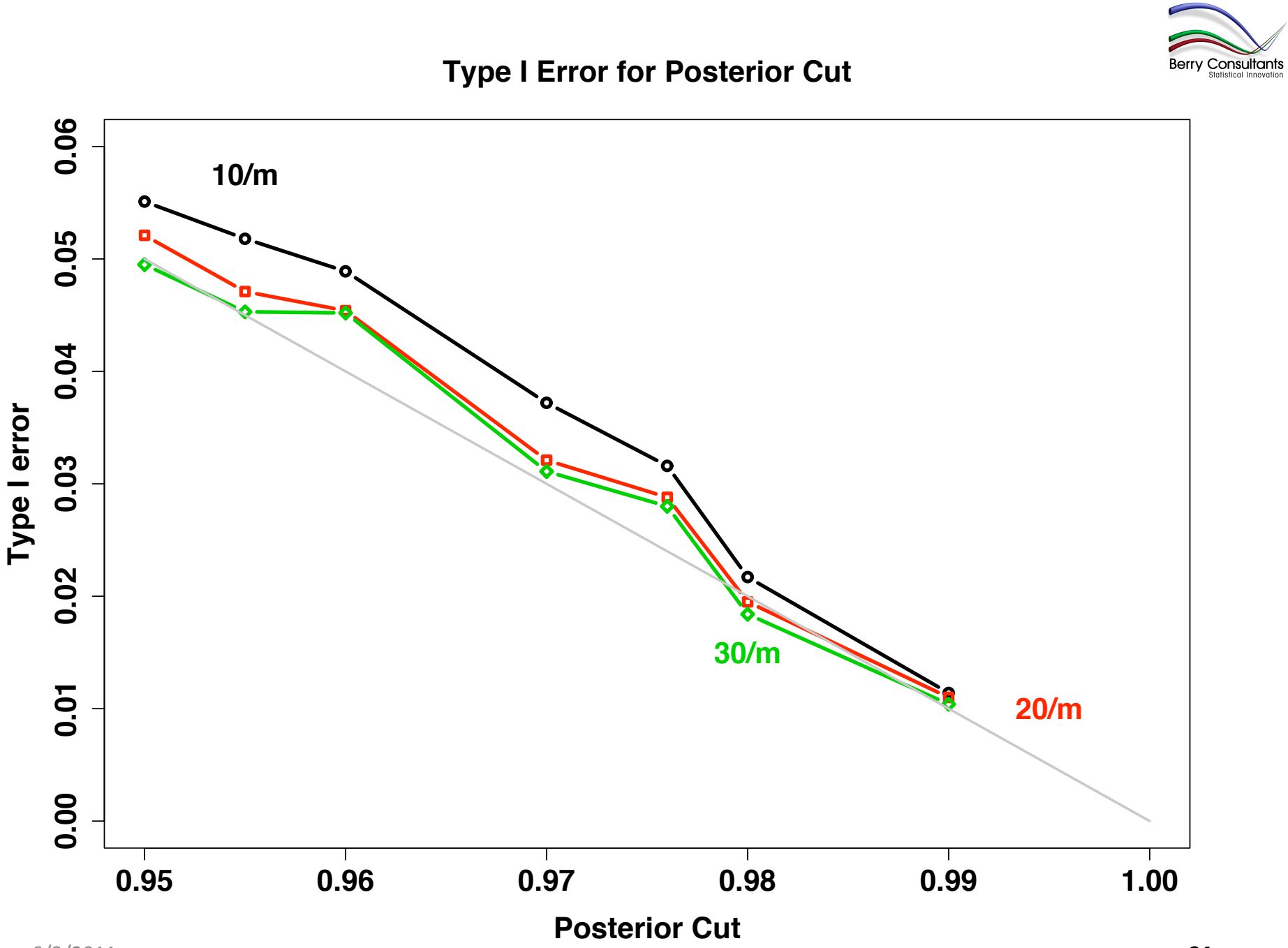
π	Pr(Win)	Mean N	SD N	50	75	100
0.50	0.0407	64.3	18.2	0.016 0.555	0.011 0.275	0.014 0.129
0.55	0.215	74.1	20.7	0.078 0.283	0.059 0.253	0.078 0.248
0.60	0.569	76.1	21.1	0.238 0.099	0.161 0.122	0.170 0.210
0.65	0.882	67.3	20.1	0.506 0.021	0.227 0.028	0.148 0.069
0.70	0.987	56.8	13.9	0.782 0.003	0.158 0.003	0.048 0.008
0.75	0.999	51.5	6.4	0.945 0.000	0.050 0.000	0.005 0.000

Delayed Observations

- Very common that the endpoint is longer term
- Decisions made about sample size are incomplete
- Assume “no” information learned earlier than observing the endpoint—say one month
- Make decisions about success based on predictive probabilities
- Stopping for “expected success” if pred prob is greater than 0.90 at the 50 or 75 look

Accrual Rate

- Accrual rate becomes a critical aspect of the adaptive design
- 100/month or 1/month is a very different design
- Assume a default 20/month
- Need to find the P_{cut} to meet type I error restrictions
- Use P_{cut}= 0.96


Type I Error for Posterior Cut
Type I error
0.00
0.01
0.02
0.03
0.04
0.05
0.06
10/m
30/m
20/m
0.95
0.96
0.97
0.98
0.99
1.00
Posterior Cut

OC's

π	Pr(Win)	Mean N	SD N	50	75	100
0.50	0.0454	76.3	20.2	0.005 0.296	0.008 0.337	0.032 0.322
0.55	0.235	85.1	18.9	0.025 0.141	0.047 0.214	0.163 0.409
0.60	0.602	86.7	18.3	0.086 0.056	0.158 0.088	0.358 0.254
0.65	0.891	79.5	19.7	0.218 0.019	0.322 0.023	0.352 0.066
0.70	0.986	68.5	18.4	0.430 0.005	0.387 0.003	0.169 0.005
0.75	0.999	59.1	13.8	0.673 0.001	0.288 0.000	0.037 0.000

Early Endpoints or "Biomarkers"

- Suppose an early endpoint that may be related to the final endpoint is observed
- Assume a 1-week value of the same endpoint is observed (S or F). May or not be a good predictor of final one month value
- Could be a biomarker – or predictor
- CA125, FBG, Tumor size, TTP→ OS,…
- NOT a surrogate marker!

Example #1:
Generic Time-to-Event

Example 1: Time-To-Event Final Analysis

- Time-to-event endpoint
- 2 arms, treatment, control
- Superiority trial
- Final analysis is a Log-rank test, one-sided 0.025

Adaptive design

- Most sponsor can go to is 360 subjects.
  - Consistent with classical power calculations (more on this)
- Deemed "minimum" acceptable by agency is 100 subjects, total
- Interim looks, how often, what is done?
- At any interim analysis have partial information on some subjects
  - Hard to do "final analysis" at interim—like O'Brien-Fleming
- Pausing or interfering with natural trial process is discouraged (other than accrual!)
- Estimated accrual is 1, 2, 3, 3, 4, 4, 5, … /week

Design

- "Sample Size Looks" at 100, 120, 140, …, 360
  - Stop for expected success if predictive probability of success with current sample size is > 0.99
  - Stop for futility if predictive probability of success at cap n is < 0.01
  - Stop at 360
- If non-futility stop, follow all subjects for 26 weeks, then do THE final analysis
  - Log-rank test with α=?

Mathematical Modeling

- Time-to-event model (exponential):

$$f(t) = \lambda_d e^{-\lambda_d t}$$

- Easy to do "any" model.
  - We commonly use piecewise exponential (as we'll see in a different example)
  - Common to observe "early information" on a subject
    - Such as TTP when endpoint is OS
    - Maybe a continuous measure of something correlated to time of event (when a continuous measure becomes unacceptable?)

Priors

$$f(t) = \lambda_d e^{-\lambda_d t}$$

$$\lambda_d \sim Gamma(\alpha = 1.0, \beta = 1/10) \text{ for } d = 0,1$$

- This prior is for the adaptive design "working model" not the "final analysis"
- Mostly a sponsor dependent prior

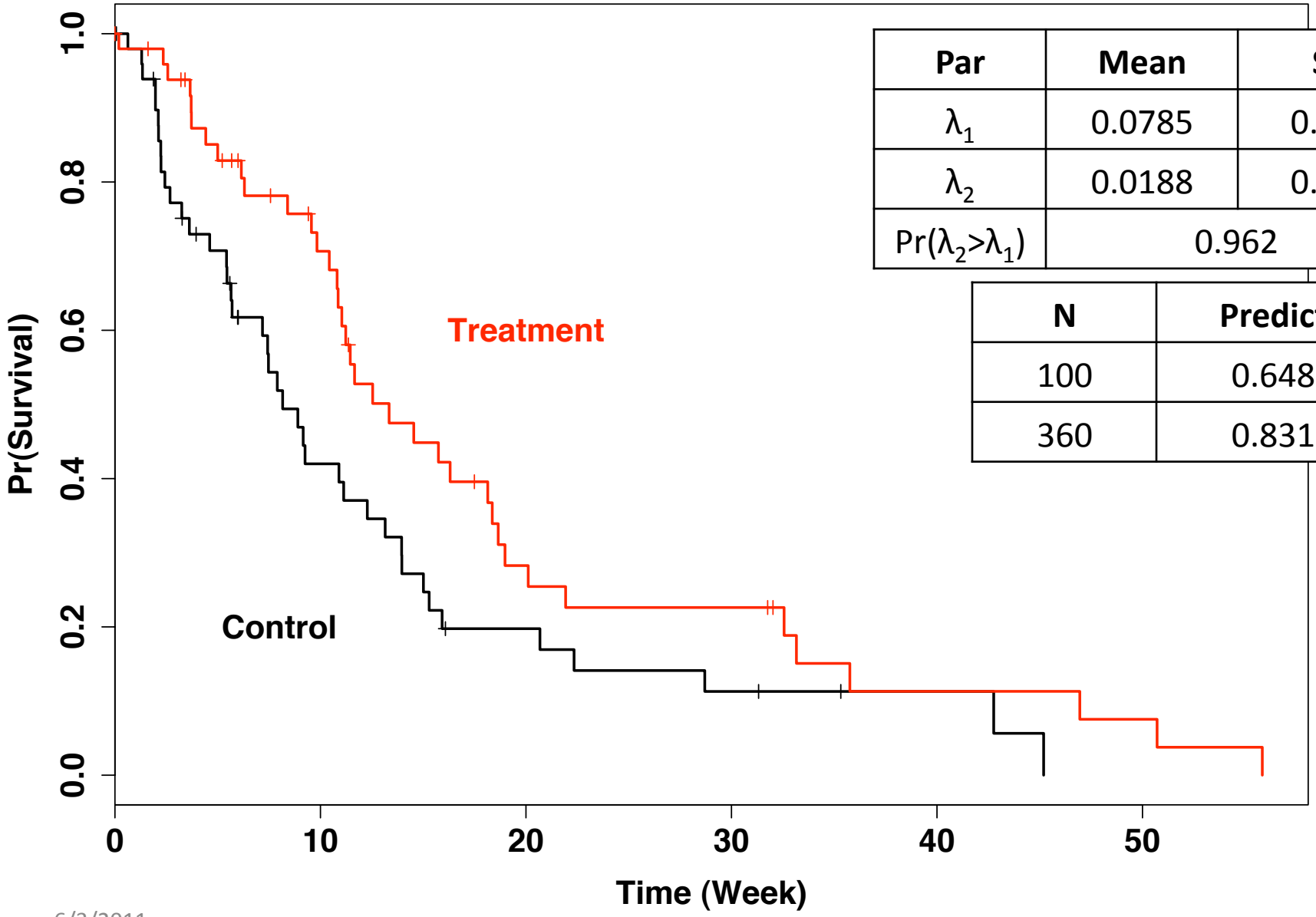
Calculation

- At "Analysis" data X, future data Y
  - Simulate $\lambda \sim [\lambda \mid X]$
  - Simulate $Y \sim [y \mid \lambda]$
  - Evaluate $\log\text{rank}(Y)$
  - Repeat

If this itself is a Bayesian analysis using MCMC then this becomes extremely slow to simulate!! Too slow for R or Winbugs. Use C or Fortran

- The frequency of Y_n or Y_{cap} "successful" is the predictive probability of success at the future time

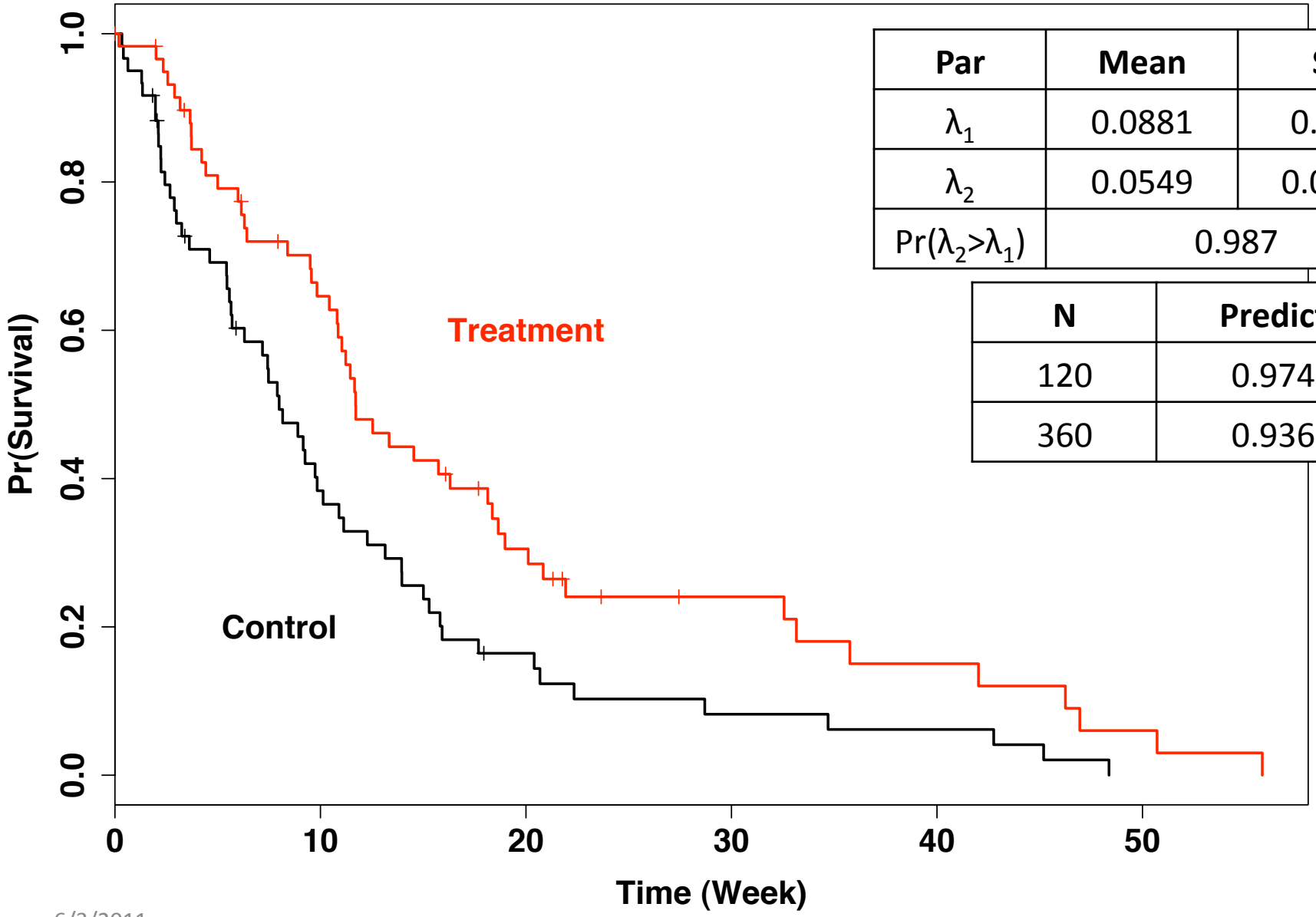
Example Look @ 100



Par	Mean	SD
λ_1	0.0785	0.012
λ_2	0.0188	0.027
$Pr(\lambda_2>\lambda_1)$	0.962	

N	Predict
100	0.648
360	0.831

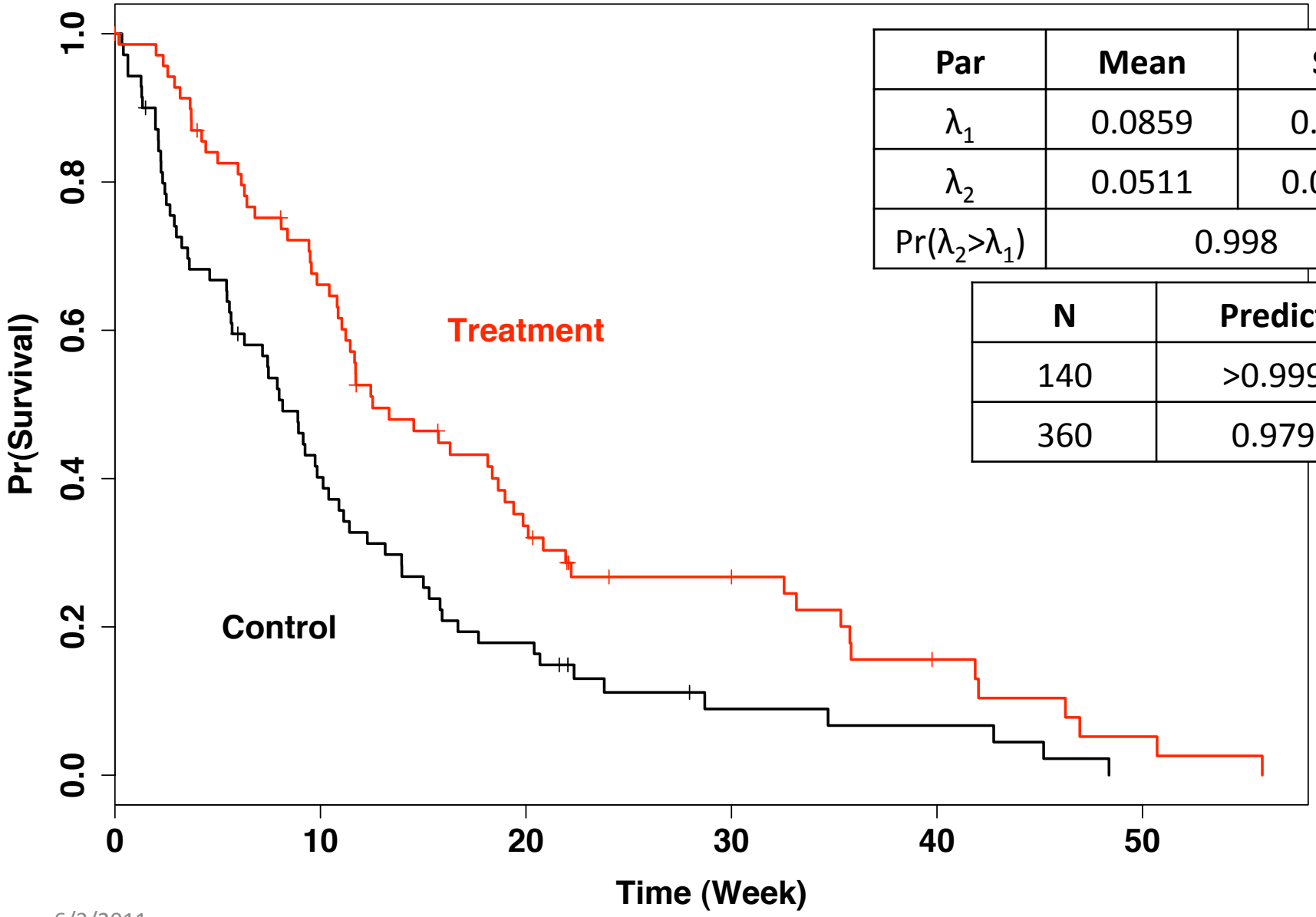
Example Look @ 120



Par	Mean	SD
λ_1	0.0881	0.012
λ_2	0.0549	0.0077
$Pr(\lambda_2>\lambda_1)$	0.987	

N	Predict
120	0.974
360	0.936

Example Look @ 140



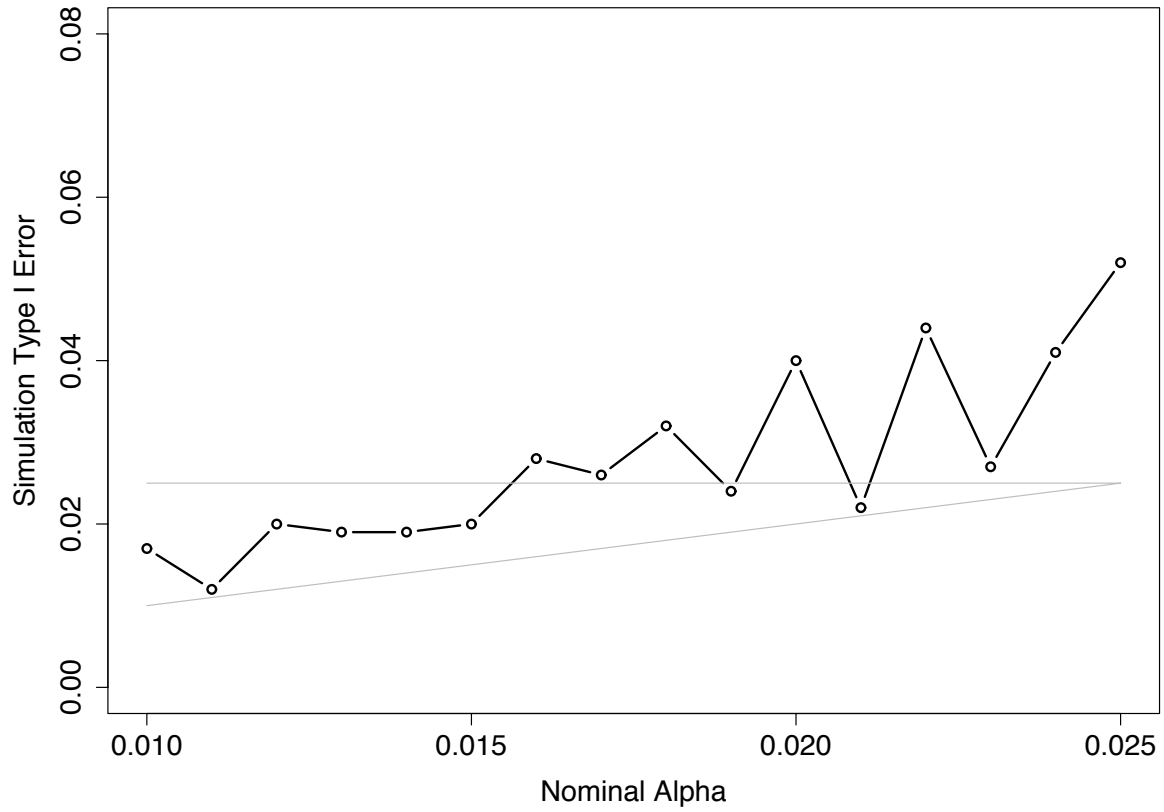
Par	Mean	SD
λ_1	0.0859	0.010
λ_2	0.0511	0.0067
$Pr(\lambda_2>\lambda_1)$	0.998	

N	Predict
140	>0.999
360	0.979

Simulations

- Set up simulations with full subject accrual and these analyses EXACTLY as described.
- Repeat trials with an assumed effect—true simulation values to assess
  - Effects from sponsor priors to assess the value of the trial—or to do decision analysis for sponsor
- A set of "null scenarios" are set up – multiple accruals, nulls, underlying model of data, etc. Simulate with different α and evaluate type I error
  - Select α to satisfy any type I error constraints
  - Obviously these nulls must satisfy the rules of the game (regulatory enforced)

- Here is the type I error for 1000 simulated trials for each value of α. Typically do this, then crank up null simulation size numbers to 10K or 100K to validate



- α=0.015 is used

OC's from 14/10

Prob win 0.819

	Mean	SD
Sample Size	247.800	89.008

	Lose	Win
Success	0.001	0.717
Cap	0.069	0.102
Futility	0.111	0.000

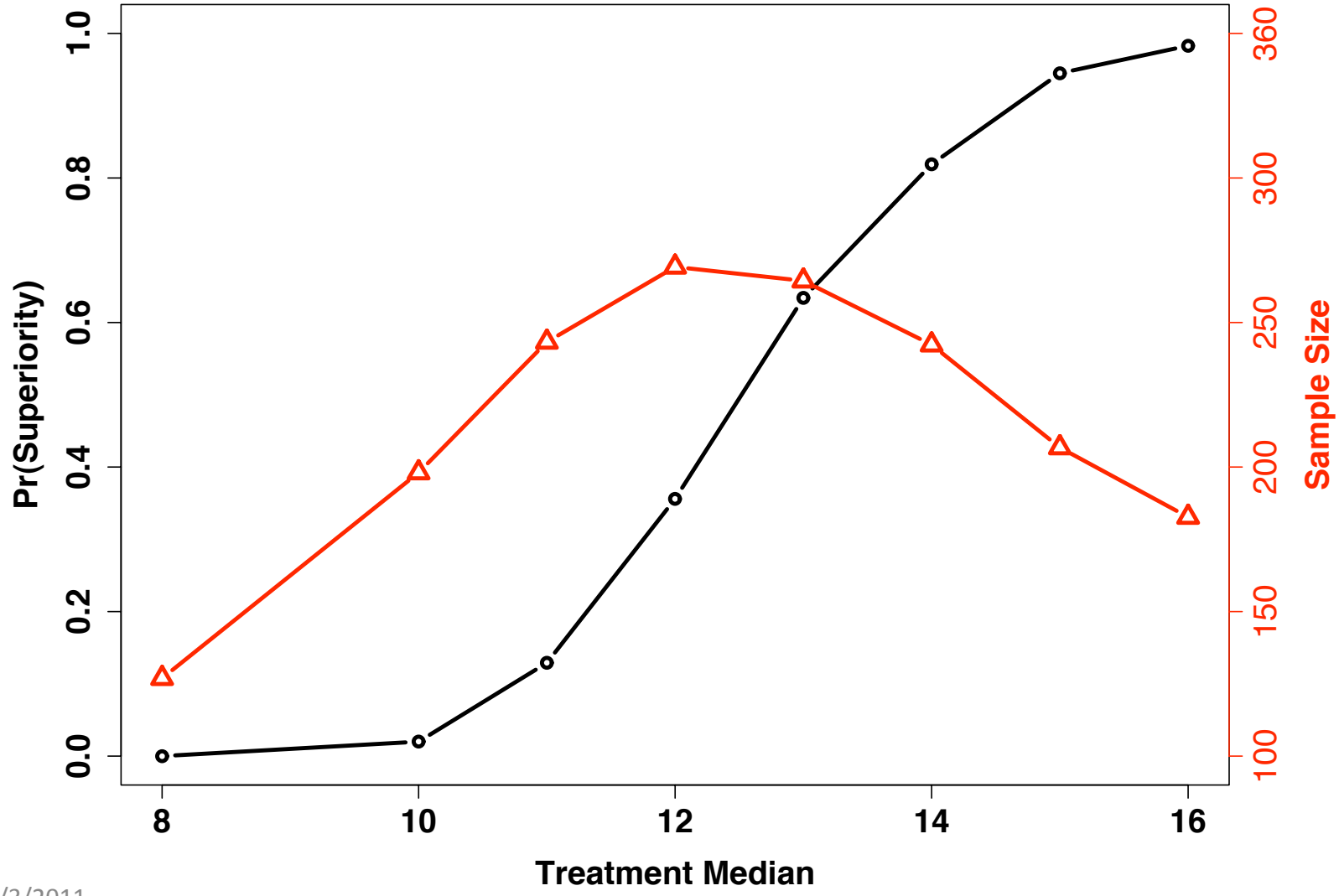
Look	Lose	Win	Total
100	0.006	0.063	0.069
120	0.006	0.057	0.063
140	0.004	0.054	0.058
160	0.006	0.053	0.059
180	0.002	0.060	0.062
200	0.004	0.054	0.058
220	0.004	0.068	0.072
240	0.008	0.054	0.062
260	0.006	0.055	0.061
280	0.005	0.056	0.061
300	0.010	0.033	0.043
320	0.013	0.033	0.046
340	0.015	0.046	0.061
360	0.092	0.133	0.225

OC's

TRT Median	Sup	N	Max	Expect Success		Cap		Futility	
				Sup	No	Sup	No	Sup	No
8	.000	128	.00	.00	.00	.00	.00	.00	1
10	.020	202	.07	.02	.00	.01	.03	.00	.95
11	.129	249	.19	.09	.00	.04	.08	.00	.79
12	.356	276	.34	.25	.00	.11	.14	.00	.50
13	.634	271	.33	.50	.00	.13	.12	.00	.24
14	.819	248	.23	.72	.00	.10	.07	.00	.11
15	.945	211	.11	.90	.00	.04	.03	.00	.03
16	.983	186	.04	.96	.00	.02	.01	.00	.01

Assume control median time is 10 weeks

Operating Characteristics



Adaptive Design

TRT	P(Sup)	N
8	0.000	128
10	0.020	202
11	0.129	249
12	0.356	276
13	0.634	271
14	0.819	248
15	0.945	211
16	0.983	186

Fixed Designs

TRT	P(Sup)	N
8	0.000	360
10	0.025	360
11	0.143	360
12	0.401	360
13	0.694	360
14	0.888	360
15	0.968	360
16	0.994	360

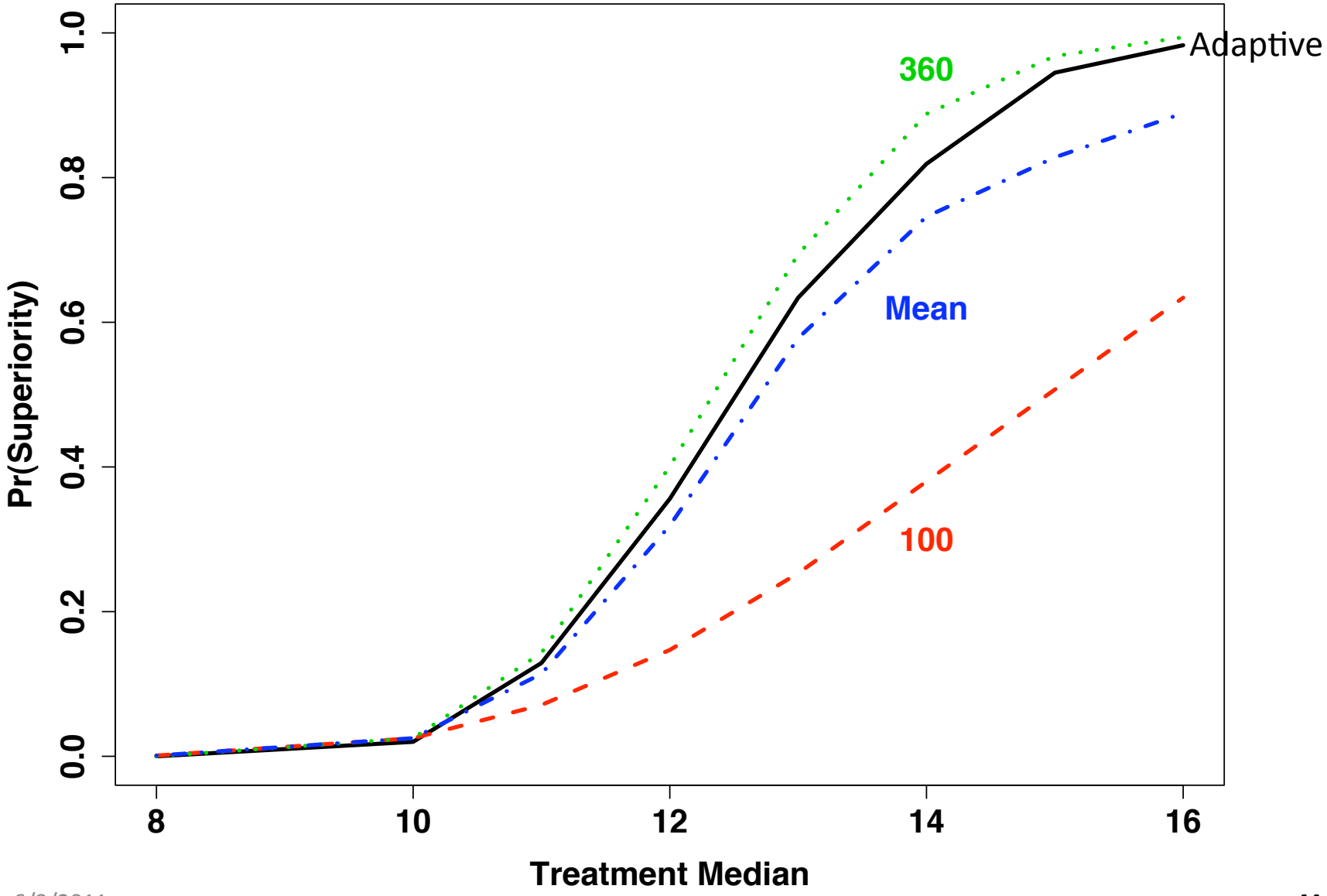
Adaptive Design

TRT	P(Sup)	N
8	0.000	128
10	0.020	202
11	0.129	249
12	0.356	276
13	0.634	271
14	0.819	248
15	0.945	211
16	0.983	186

Fixed Designs

TRT	P(Sup)	N
8	0.001	128
10	0.025	202
11	0.114	249
12	0.319	276
13	0.578	271
14	0.746	248
15	0.828	211
16	0.889	186

Comparison to Fixed Designs



Example #2: ThermoCool Catheter

ThermoCool® Catheter

- 2:1 randomized trial to compare to drug therapy
- 9-Month failure-free
- Composite endpoint of AF or need for change in drug therapy (protocol failure)
- Superiority:
  - $\Pr(P_{TC} > P_{DRUG} | \text{Data}) > 0.98$
- Independent Beta(1,1) priors for each *P*

Adaptive Design

- Look when 150, 175, 200 are enrolled or go to cap of 230.
- If Predictive Probability of trial success is
  - ≥0.90 then stop accrual for *expected success*
  - ≥0.99 then *submit early for success*
  - <0.05--for 230-- stop for *futility*

Adaptive "Working" Model

- Model Time to Failure:
  - Piecewise exponential

$$H_T(t) = \begin{cases} \theta_{T,1} & 0 < t \le \frac{1}{2} \\ \theta_{T,2} & \frac{1}{2} < t \le 2 \\ \theta_{T,3} & 2 < t \le 9 \end{cases}$$

$$\theta_{T,1};\theta_{T,2};\theta_{T,3} \sim Gamma(\alpha_T, \beta_T)$$

$$\alpha_T \sim Exp(1) \qquad \beta_T \sim Exp(1)$$

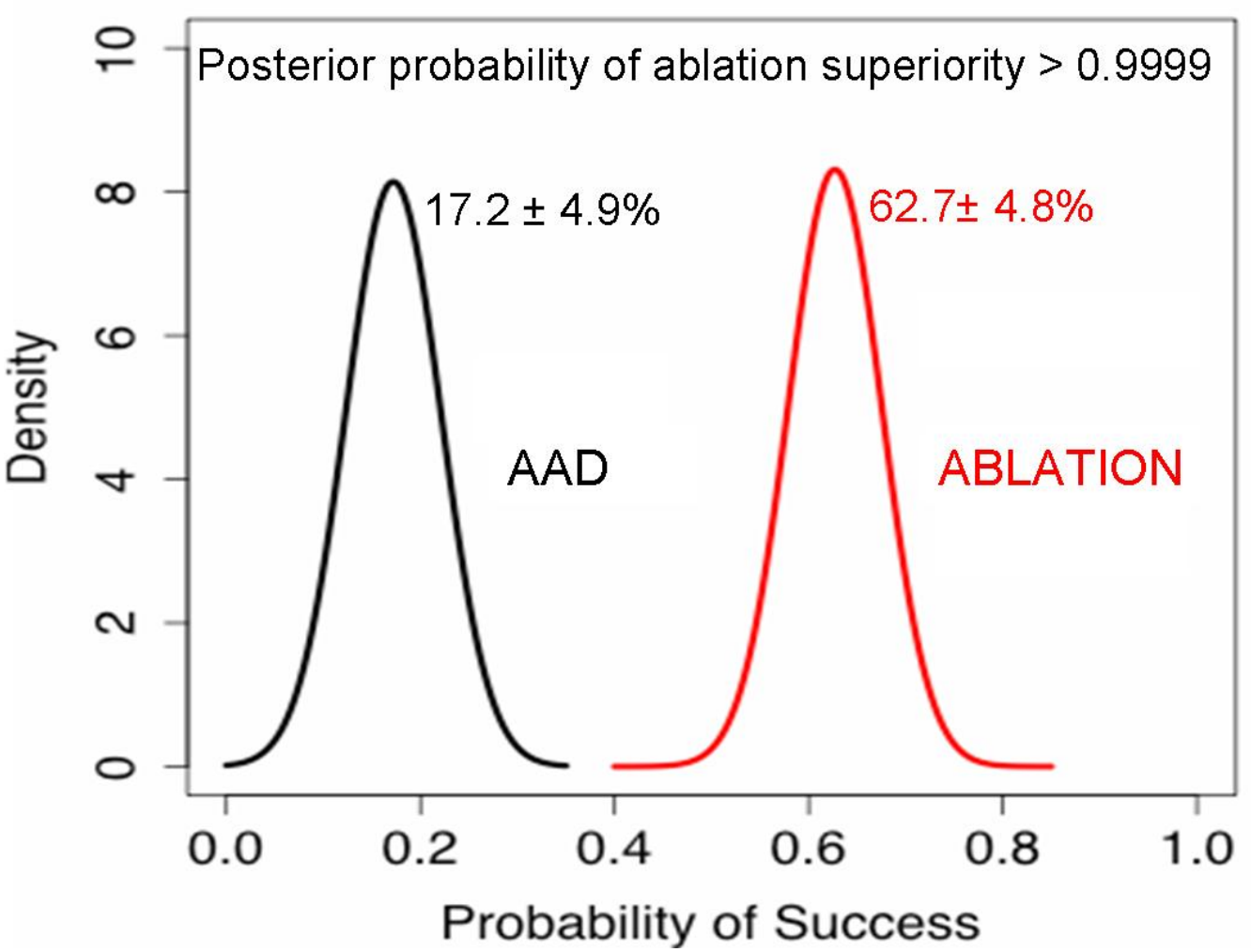
Example Operating Characteristics

P_C	P_T	P(S)	P(F)	SS	Time	P(Early)	Sample Size			
							150	175	200	230
0.20	0.20	0.019	0.92	158.1 21.5	35.4 7.2	.001	.85 .84	.06 .05	.03 .03	.07
0.20	0.30	0.316	0.46	182.3 34.6	44.7 12.0	.090	.46 .34	.15 .07	.10 .05	.30
0.20	0.40	0.845	0.06	175.9 31.6	44.1 10.6	.401	.51 .03	.18 .01	.10 .01	.20
0.20	0.45	0.959	0.01	164.2 25.2	39.9 9.1	.791	.70 .01	.14 .00	.07 .00	.09
0.20	0.50	0.993	0.00	155.9 16.2	36.4 6.5	.880	.85 .00	.09 .00	.03 .00	.03

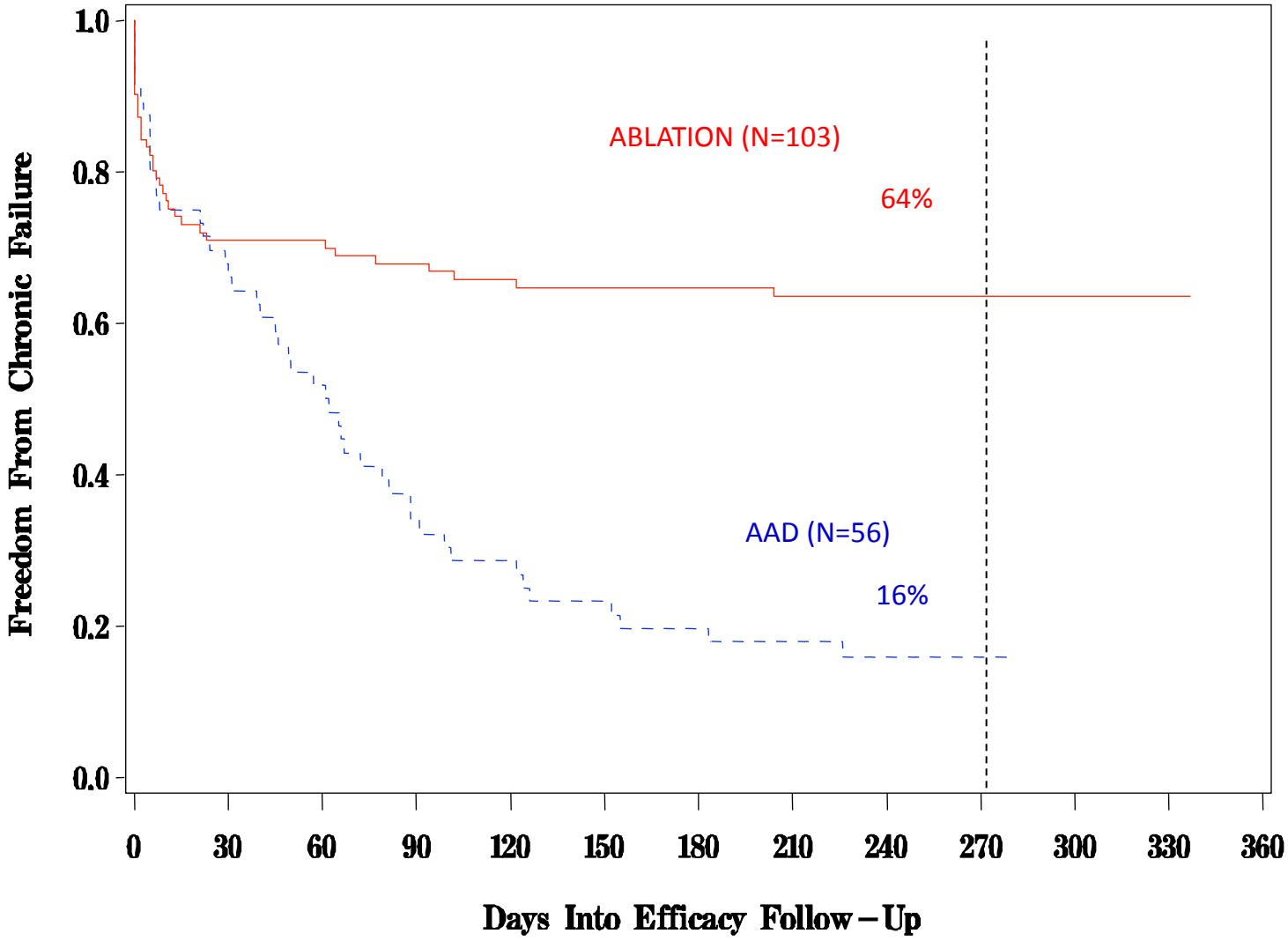
Results Announced at Panel (11/08)

- In July, 2007, first analysis was done for the 150-look
  - Predictive probability of success ≥ 0.9999
  - Trial accrual stopped
  - Immediate success claimed and PMA filed

Final Bayesian Results…



Final KM's


1.0
0.8
0.6
0.4
0.2
0.0
Freedom From Chronic Failure
ABLATION (N=103)
64%
AAD (N=56)
16%
0
30
60
90
120
150
180
210
240
270
300
330
360
Days Into Efficacy Follow–Up

FDA Approves First Ablation Catheters for the Treatment of Atrial Fibrillation (FDA Press Release) February 6, 2009 -

The U.S. Food and Drug Administration today approved the first ablation catheters for the treatment of atrial fibrillation (uncoordinated contractions of the upper heart chambers), one of the most common types of arrhythmias—or abnormal heart rhythms--affecting more than two million Americans.The devices approved today, the NaviStar ThermoCool saline irrigated radio-frequency ablation catheter and the EZ Steer ThermoCool Nav, can be used to create small, strategically placed scars in heart tissue to block irregular electrical waves that cause atrial fibrillation. … Both catheters are manufactured by BioSense Webster of Diamond Bar, Calif.

No mention of Bayesian or adaptive

Example #3:
LibiGel Safety Study

CV Event study

- Testosterone gel for treatment of hypoactive sexual desire disorder (HSDD)
  - Efficacy is a different study
- Study to determine if no elevated CV risk
- Non-inferiority: $p_L - p_C < 0.01$ or $p_L / p_C < 2$
  - Posterior probability ≥ 0.986
- Adaptive sample size 2500 to 4000
  - "Analysis" every 2 events
    - "Stop accrual" and follow last subject 12 months
    - "Stop for futility"

Bayesian Model

- Assumes exponential event rates
  - Separate prior for 'sample size looks' and final analysis
  - Predicts events over 12 months and for possibly newly accrued subjects
  - Predicts drop outs– *final data*
- Over 100 scenarios simulated for the control of type I error

BioSante Pharmaceuticals Completes Enrollment in LibiGel® Phase III Safety Study

LINCOLNSHIRE, Illinois (May 31, 2011) – BioSante Pharmaceuticals, Inc. (NASDAQ: BPAX), today announced completion of enrollment in its ongoing LibiGel (testosterone gel) Phase III cardiovascular and breast cancer safety study. LibiGel is in development for the treatment of female sexual dysfunction (FSD), specifically, hypoactive sexual desire disorder (HSDD) in menopausal women, for which there is no FDA-approved product.

BioSante has been informed by the LibiGel safety study independent Executive Committee regarding the outcome of the sample size analysis that determines the number of subjects to be enrolled in the LibiGel Phase III safety study. The FDA-agreed sample size analysis indicates that enrollment should stop, based on meeting a minimum 90 percent predictive probability of success of the safety study to show the safety of LibiGel at the primary data analysis. As per the protocol, the safety study will continue for 12 months of therapy from the last subject enrolled before the primary analysis will be conducted by BioSante, which will provide the data for BioSante's new drug application (NDA) submission anticipated to be made in 2012. The study will continue for five years.

BioSante reported that the independent Data Monitoring Committee (DMC) reviewed unblinded data in over 3,250 women enrolled and over 3,450 women-years of exposure in its LibiGel Phase III cardiovascular and breast cancer safety study including 22 adjudicated cardiovascular (CV) events. To date, the cardiovascular event rate is lower than anticipated at approximately 0.58 percent. There have been nine breast cancers reported; also a lower than anticipated rate of approximately 0.24 percent.

Although enrollment is complete, the Phase III LibiGel safety study will continue as per the FDA-agreed protocol, without modification, after the sixth unblinded review of study safety data by the DMC, during which no safety issues were identified to BioSante. BioSante remains blinded as to which events fall into the LibiGel arm or the placebo arm of the study.

"Formal completion of enrollment in the LibiGel safety study is based on the third sample size re-estimation analysis, and the first time that BioSante has been informed that the analysis indicates that enrollment should stop. We are very encouraged that after six reviews of all unblinded safety data, no safety issues have been raised to us by the independent DMC," stated Michael Snabes, M.D., Ph.D., senior vice president of medical affairs for BioSante. "The LibiGel safety study will continue as per protocol and the DMC will continue to take its periodic unblinded looks at all safety data. BioSante will remain blinded until the primary data analysis which, as per protocol, will occur after the last subject enrolled has been in the study for 12 months of therapy."

The sample size analysis was conducted, by the DMC's unblinded statistician, based on 3,307 subjects enrolled at the time of the analysis and on 22 adjudicated CV events. Since the analysis, an additional 250 subjects have been enrolled. The sample size analysis requires BioSante to stop enrollment of subjects when there is at least a 90% chance of meeting one or both of the following criteria one year after enrollment is completed: the ratio of the rate of CV events on LibiGel compared to placebo has an upper bound of the 97.2% confidence interval ≤ 2, or the 97.2% confidence interval for the risk difference is ≤ 1% (and less than twice the observed CV events in the LibiGel group vs. placebo group).

Subjects have been enrolled in this study for an average of 12.8 months. More than 1,500 subjects have been enrolled in the study for more than a year and over 700 subjects for more than two years. The periodic reviews by the DMC are based on the DMC's protocol-defined mandate in accordance with FDA Guidance on study oversight. BioSante's objective is to submit the LibiGel NDA by the end of 2012.

"LibiGel remains the only product in the world in Phase III clinical development for the treatment of HSDD," said Stephen M. Simes, BioSante's president & CEO. "The ability to stop enrollment as per the sample size analysis that indicates a 90 percent predictive probability of success is very encouraging for the outcome of our LibiGel Phase III clinical development program. With this most recent development, we continue to believe that LibiGel will be the first product approved by the FDA to treat HSDD, also referred to as FSD, in menopausal women."

May 31, 2011

Tuesday!!!!!!

BioSante Pharmaceuticals Completes Enrollment in LibiGel® Phase III Safety Study

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Discussion

- Ideal for scenarios with good deal of uncertainty
  - Even beneficial when not a lot of uncertainty
- Ideal for scenarios with "early markers" and prediction and longer term follow-up
- Not Group Sequential Method
  - Can create *immediate* success