Bayesian Adaptive Clinical Trial Design

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Day 2

NOTE TO SELF:
START THE RECORDING

Phase 3 / Confirmatory Trials

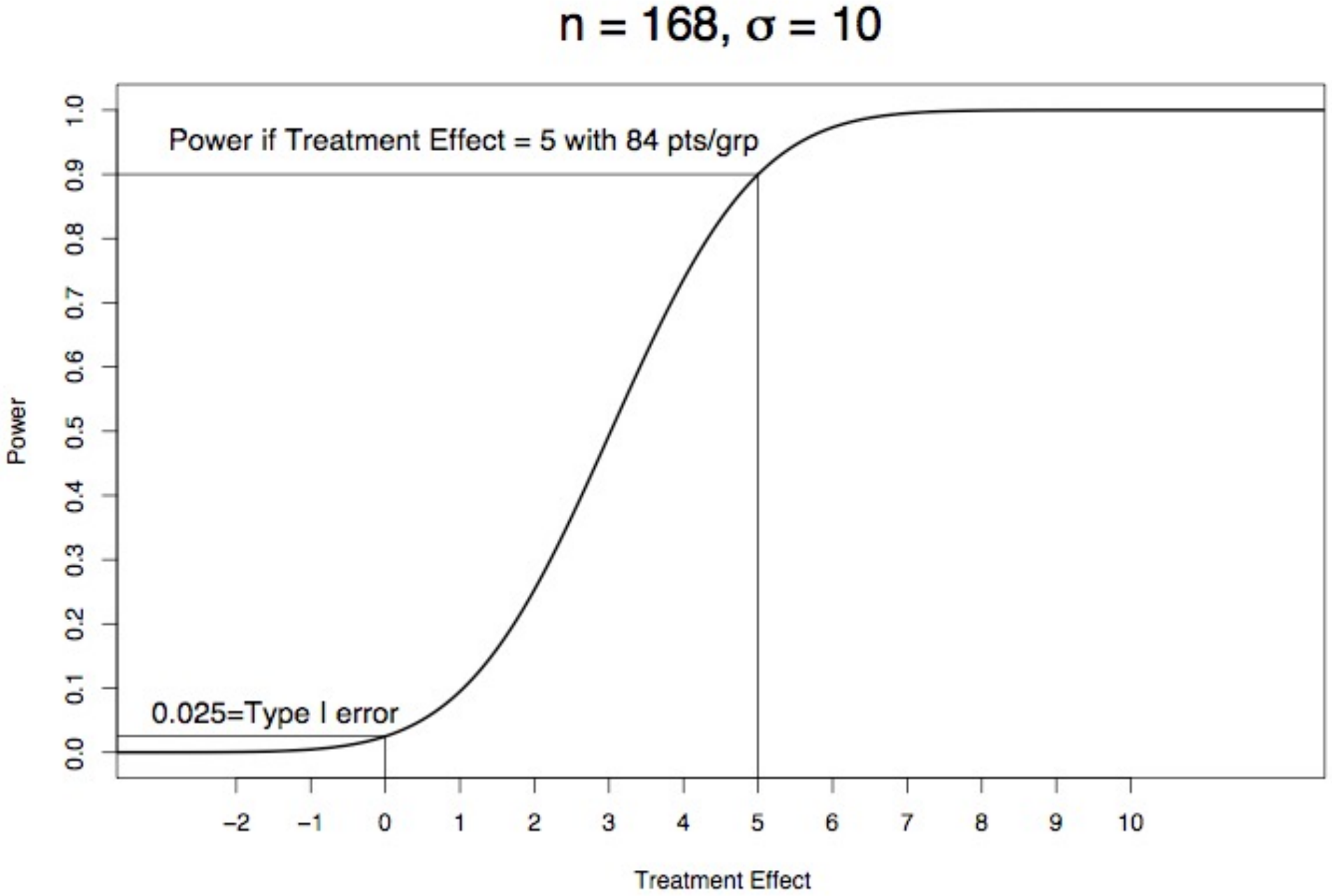
- CDER/CBER Phase 3
- CDRH Confirmatory
- The final test before market
- Control of Type I error rate very important
- Tend not to adaptively randomize
  - Fear of drift
  - Usually two arm
  - No power benefit with adaptive rand. in 2-arm trial

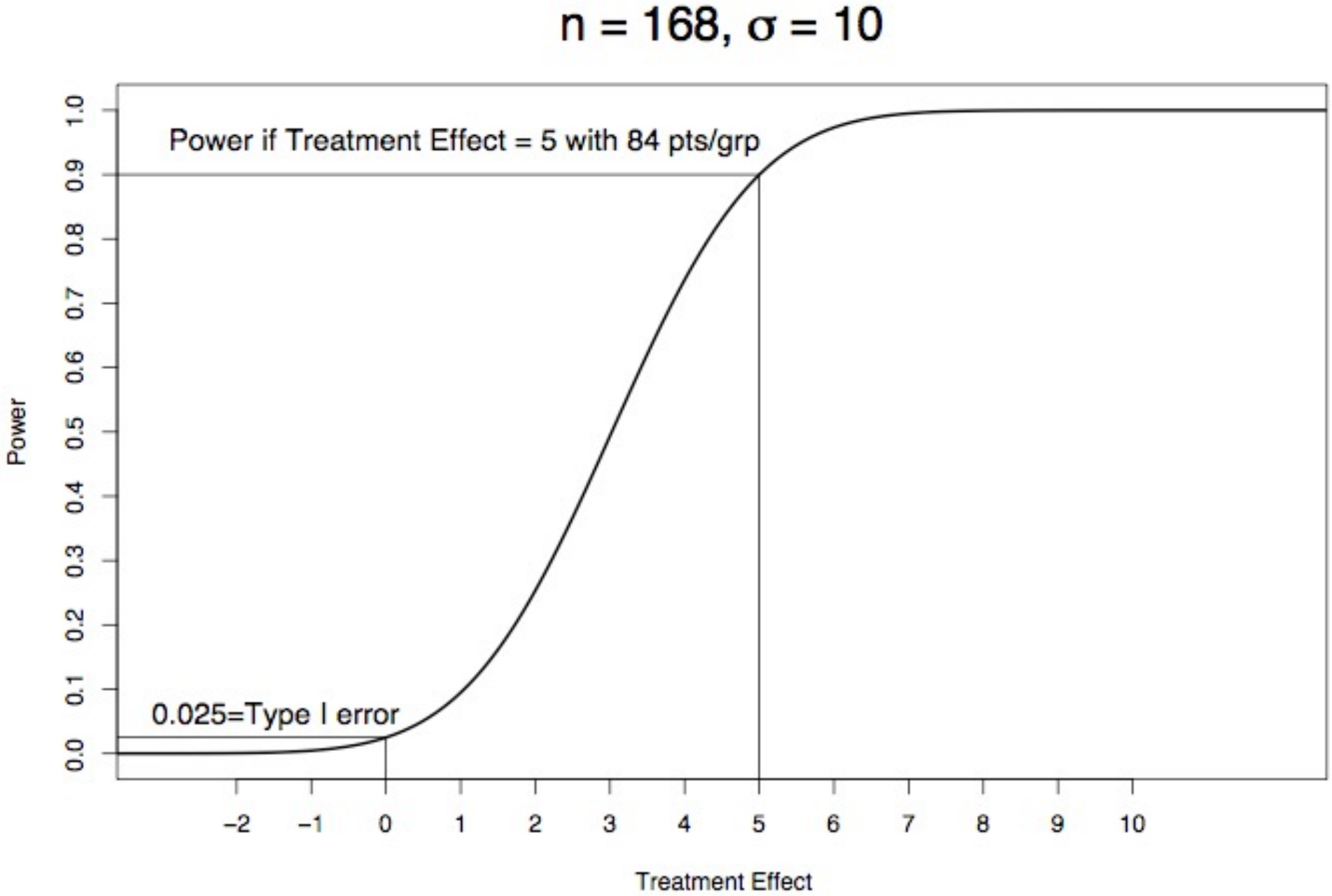
What is Different About Confirmatory Trials

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

Power vs. Prob of Success

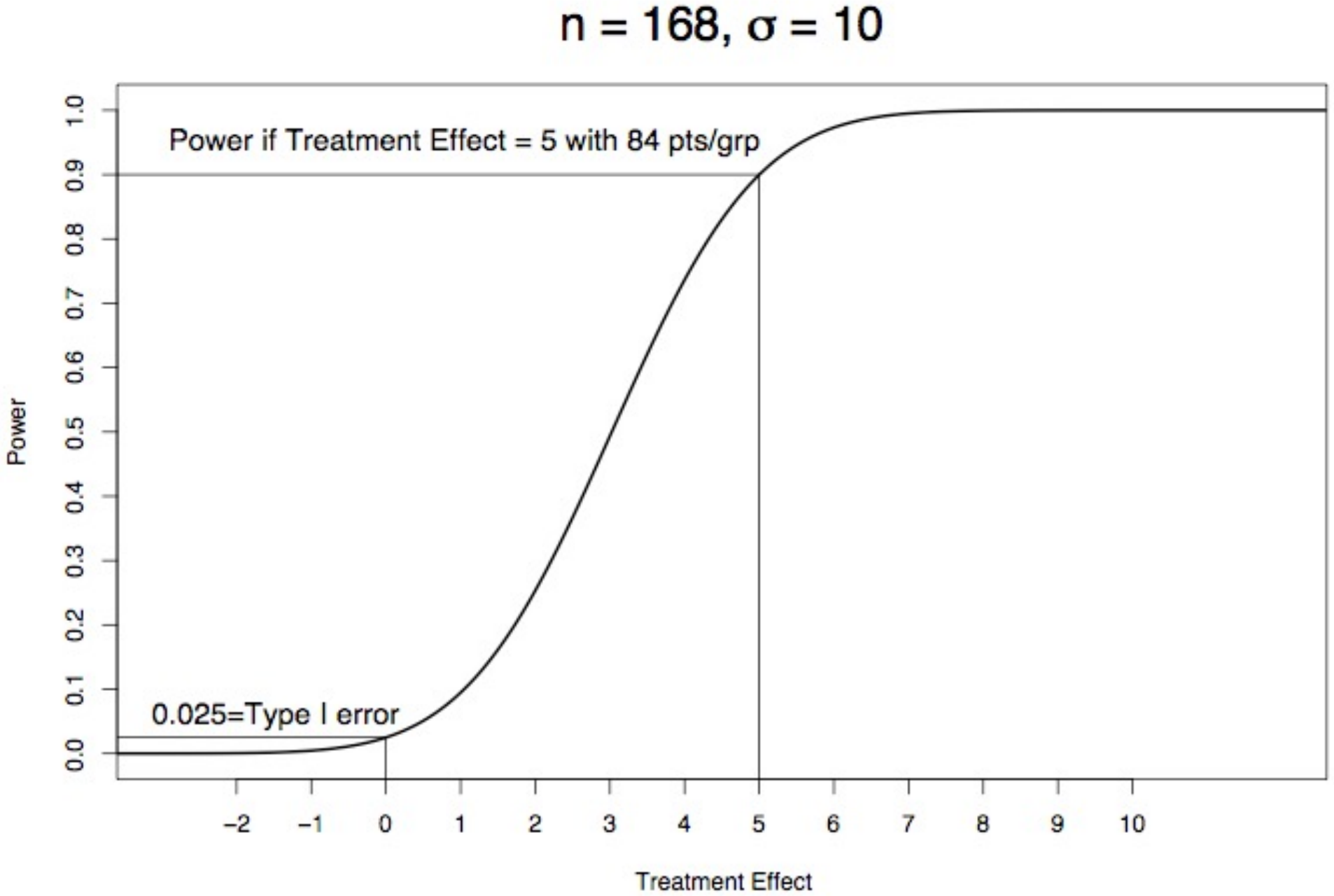
- Doctor comes to you.
- Claims her treatment increases IQ by 5 points
- SD = 10
- "How many patients do I need to have 90% power to demonstrate superiority?"


n = 168, σ = 10
Power if Treatment Effect = 5 with 84 pts/grp
0.025=Type I error
Power
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
−2
−1
0
1
2
3
4
5
6
7
8
9
10
Treatment Effect



$\Delta = 6 \rightarrow$ Power = 97% ($\uparrow$ 7%)

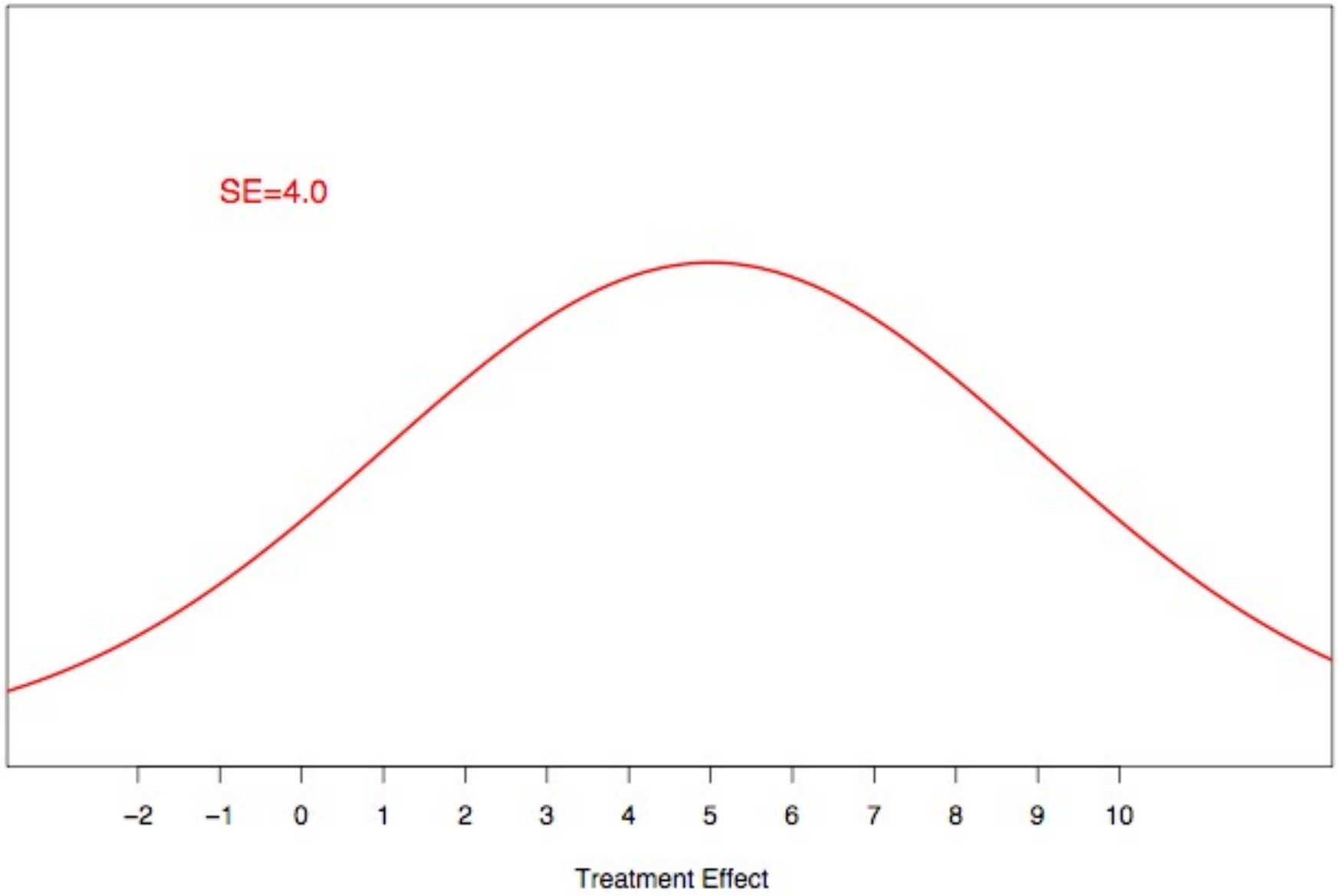
$\Delta = 4 \rightarrow$ Power = 73% ($\downarrow$ 17%)



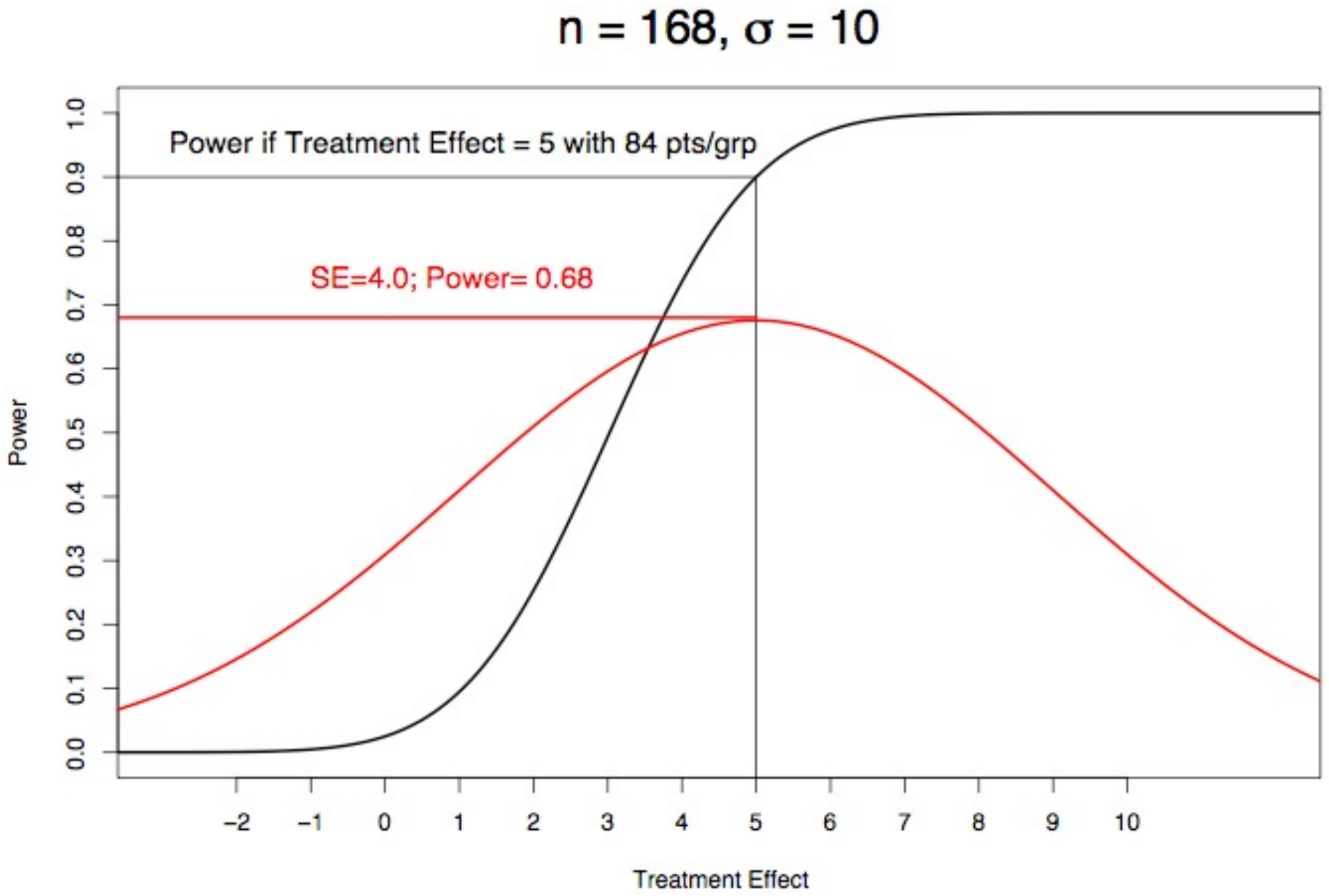
$\Delta = 7 \rightarrow$ Power = 99% ($\uparrow$ 9%)

$\Delta = 3 \rightarrow$ Power = 49% ($\downarrow$ 41%)

We've ignored the error in the pilot data



Estimate 5.0 (95% CI -3 to 13)



Probability of success < Power due to Jensen's inequality

Quick Bayesian Introduction

Three people get a positive pregnancy test

- My sister with 4 kids who I know wants more
- You or your wife/gf. Using oral contraception
- Me

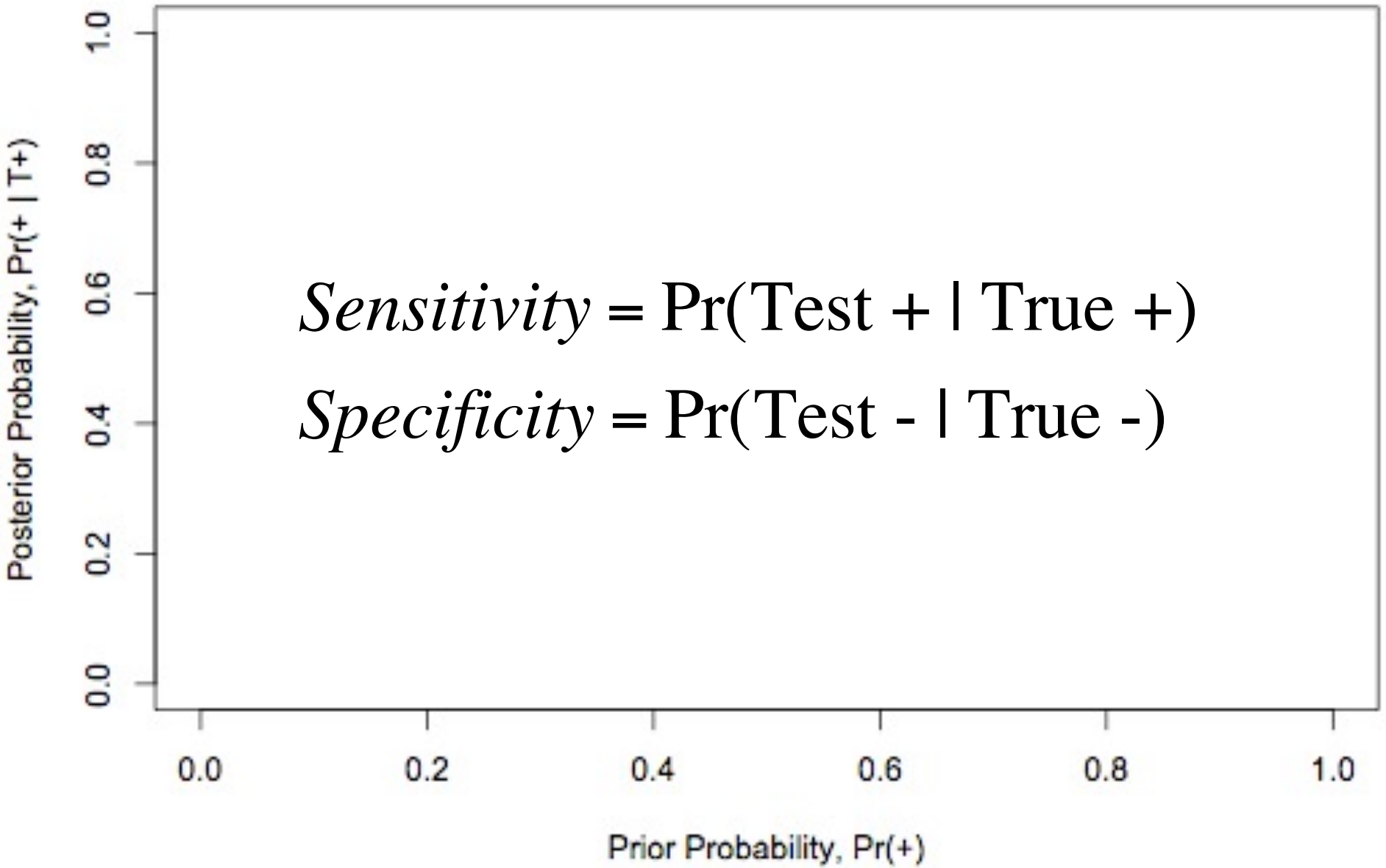
- What is the probability each person is pregnant?

Three people get a positive pregnancy test

- My sister with 4 kids who I know wants more
- You or your wife/gf. Using oral contraception
- Me
  - Sensitivity 100%, Specificity 95%

- What is the probability each person is pregnant?

$$Pr(+|T+) = Pr(T+|+)Pr(+) / \{Pr(T+|+)Pr(+) + Pr(T+|-)Pr(-)\}$$



Sensitivity = Pr(Test + | True +)

Specificity = Pr(Test - | True -)

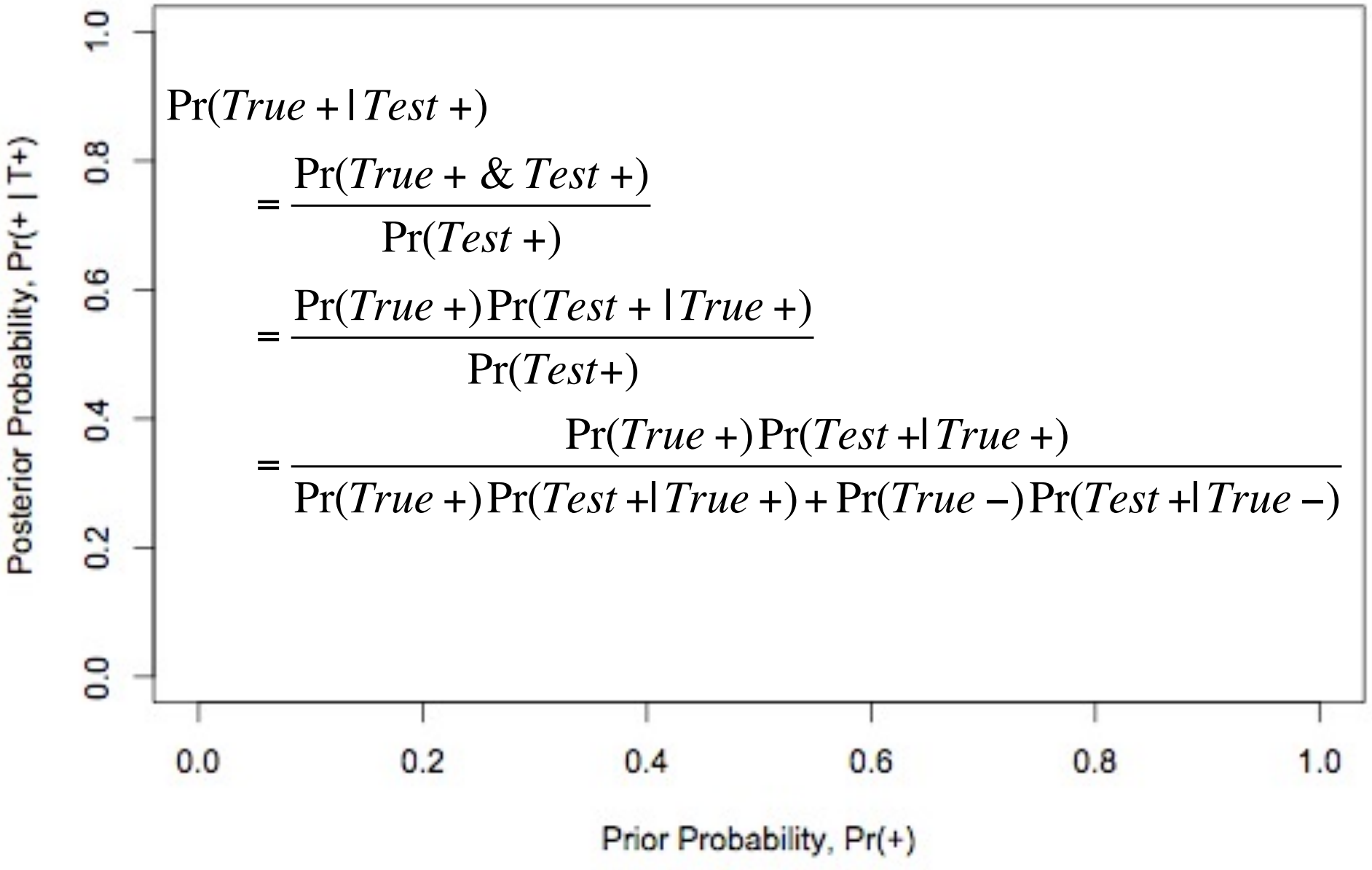
Pr(+|T+) = Pr(T+|+)Pr(+) / {Pr(T+|+)Pr(+) + Pr(T+|-)Pr(-)}

$$\Pr(True+ \mid Test+)$$

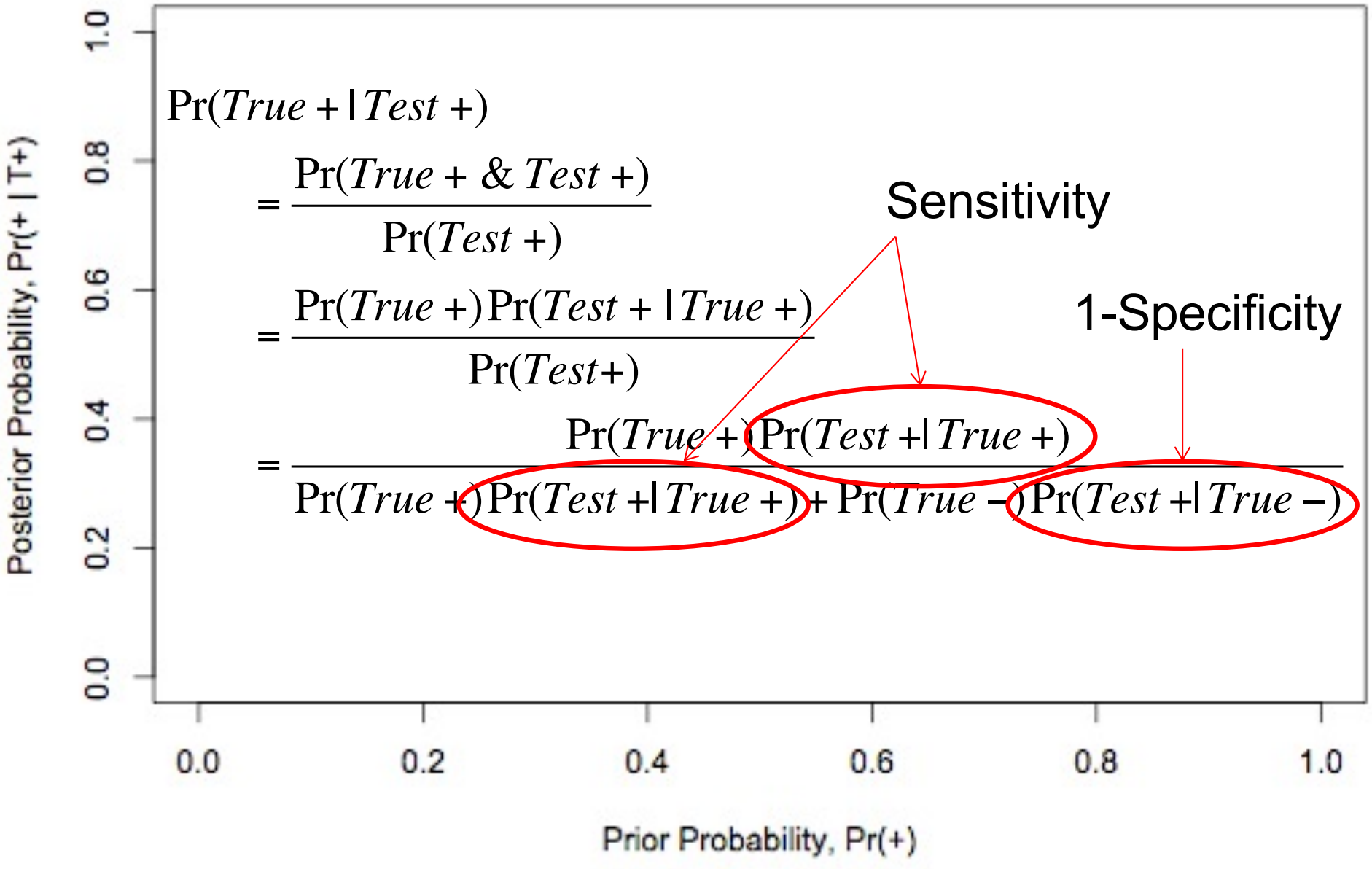
$$= \frac{\Pr(True+ \;\&\; Test+)}{\Pr(Test+)}$$

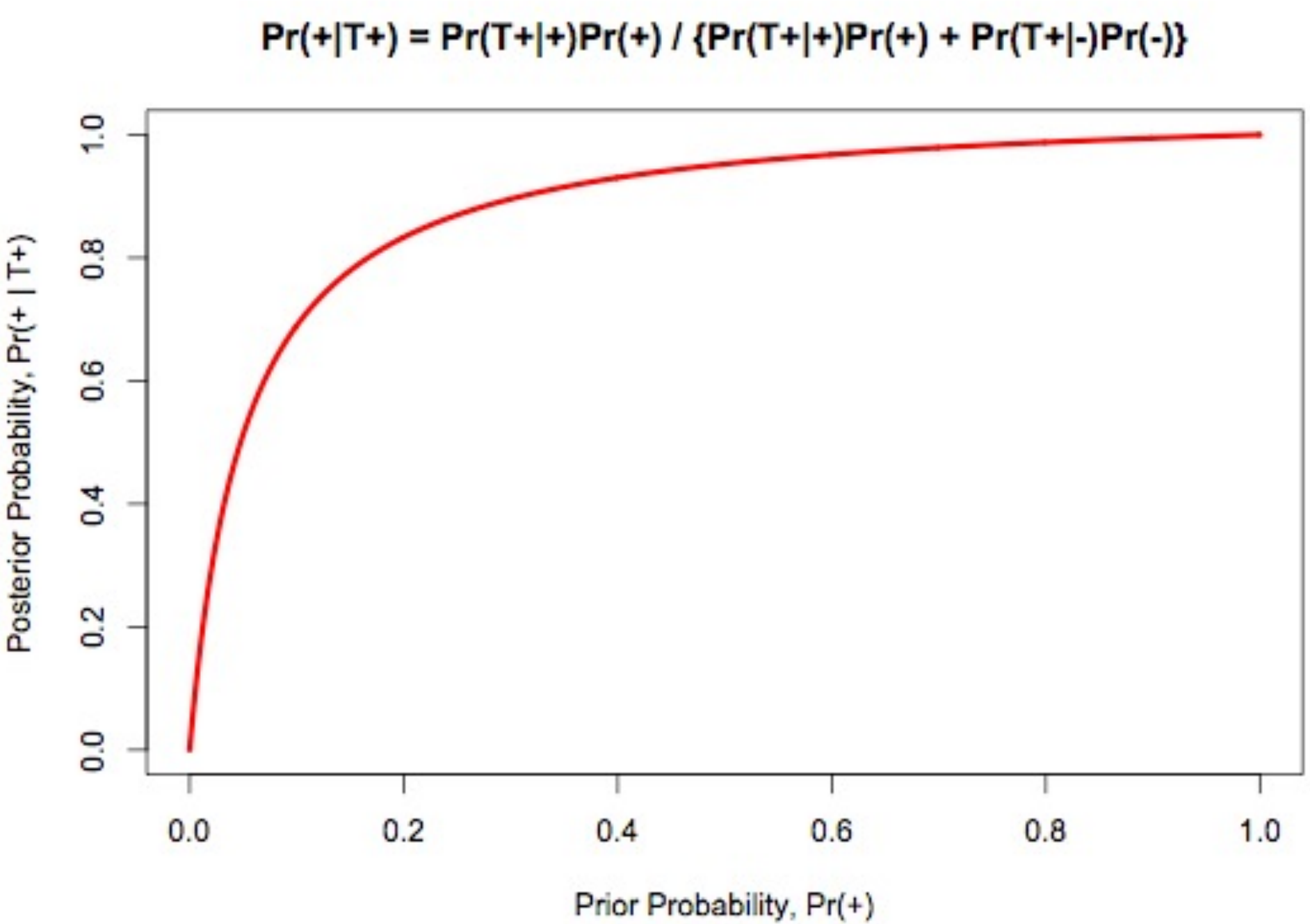
$$= \frac{\Pr(True+)\Pr(Test+ \mid True+)}{\Pr(Test+)}$$

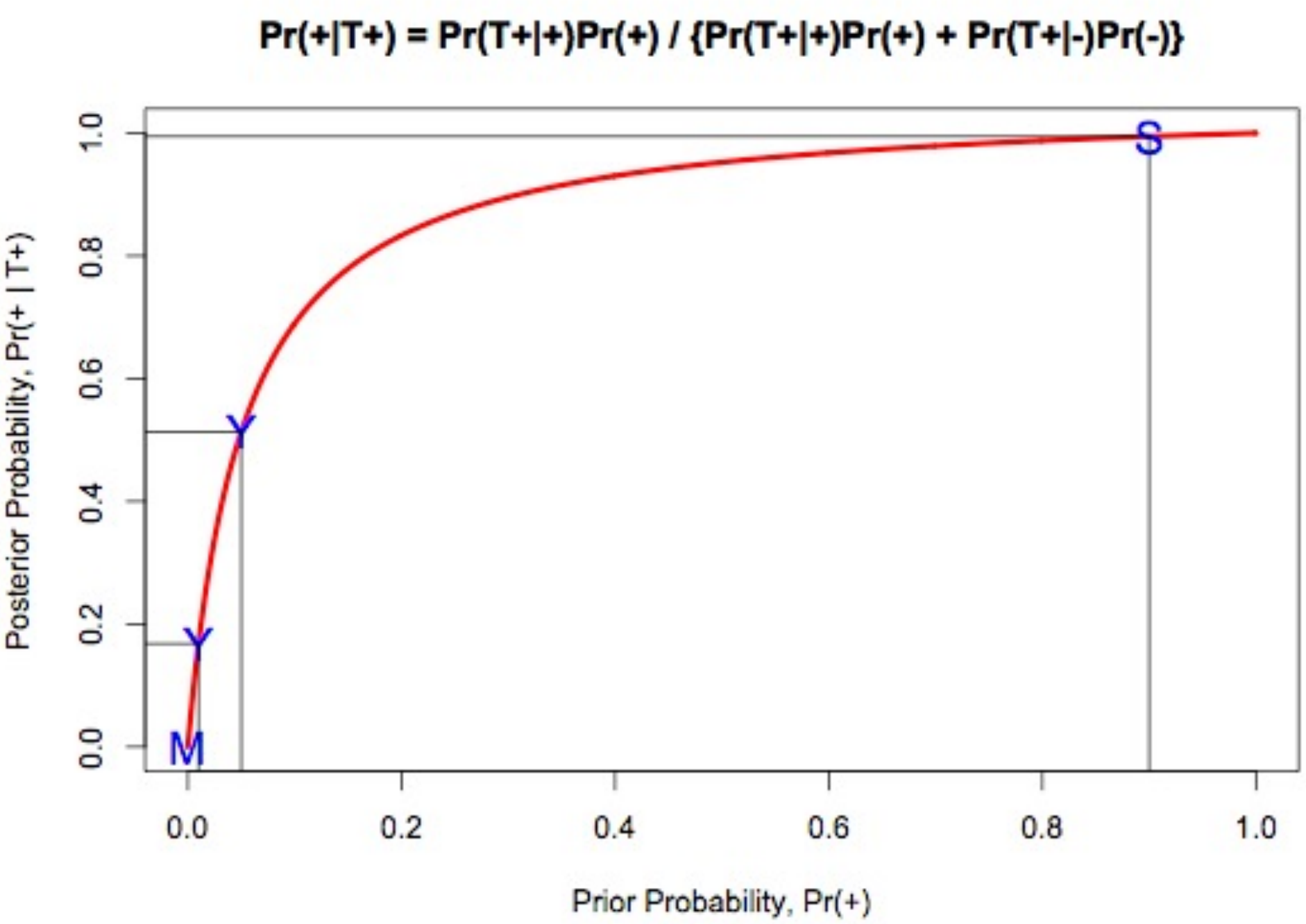
$$= \frac{\Pr(True+)\Pr(Test+ \mid True+)}{\Pr(True+)\Pr(Test+ \mid True+) + \Pr(True-)\Pr(Test+ \mid True-)}$$



Pr(+|T+) = Pr(T+|+)Pr(+) / {Pr(T+|+)Pr(+) + Pr(T+|-)Pr(-)}




Pr(+|T+) = Pr(T+|+)Pr(+) / {Pr(T+|+)Pr(+) + Pr(T+|-)Pr(-)}
Posterior Probability, Pr(+ | T+)
0.0
0.2
0.4
0.6
0.8
1.0
Prior Probability, Pr(+)


Pr(+|T+) = Pr(T+|+)Pr(+) / {Pr(T+|+)Pr(+) + Pr(T+|-)Pr(-)}
Posterior Probability, Pr(+ | T+)
0.0
0.2
0.4
0.6
0.8
1.0
M
Y
Y
S
0.0
0.2
0.4
0.6
0.8
1.0
Prior Probability, Pr(+)

Bayes Theorem

$$\Pr(A \mid B) = \frac{\Pr(B \mid A)\Pr(A)}{\Pr(B)}$$

$$= \frac{\Pr(B \mid A)\Pr(A)}{\Pr(B \mid A)\Pr(A) + \Pr(B \mid A^C)\Pr(A^C)}$$

$$\Pr(True+ \mid Test+) = \frac{\Pr(Test+ \mid True+)\Pr(True+)}{\Pr(Test+ \mid True+)\Pr(True+) + \Pr(Test+ \mid True-)\Pr(True-)}$$

$$PPV = \frac{Sensitivity \Pr(True+)}{Sensitivity \Pr(True+) + (1 - Specificity)\Pr(True-)}$$

Bayes Theorem

$$\Pr(A \mid B) = \frac{\Pr(B \mid A)\Pr(A)}{\Pr(B)}$$

$$= \frac{\Pr(B \mid A)\Pr(A)}{\Pr(B \mid A)\Pr(A) + \Pr(B \mid A^C)\Pr(A^C)}$$

$$\Pr(Hypothesis \mid Data) = \frac{\Pr(Data \mid Hypothesis)\Pr(Hypothesis)}{\Pr(Data)}$$

$$= \frac{\Pr(Data \mid Hypothesis)\Pr(Hypothesis)}{\int_{\substack{All\ possible \\ hypotheses}} \Pr(Data \mid Hypothesis)\Pr(Hypothesis)}$$

Bayes Theorem

$$\Pr(A \mid B) = \frac{\Pr(B \mid A)\Pr(A)}{\Pr(B)}$$

$$= \frac{\Pr(B \mid A)\Pr(A)}{\Pr(B \mid A)\Pr(A) + \Pr(B \mid A^C)\Pr(A^C)}$$

$$\Pr(Hypothesis \mid Data) = \frac{\Pr(Data \mid Hypothesis)\Pr(Hypothesis)}{\Pr(Data)}$$

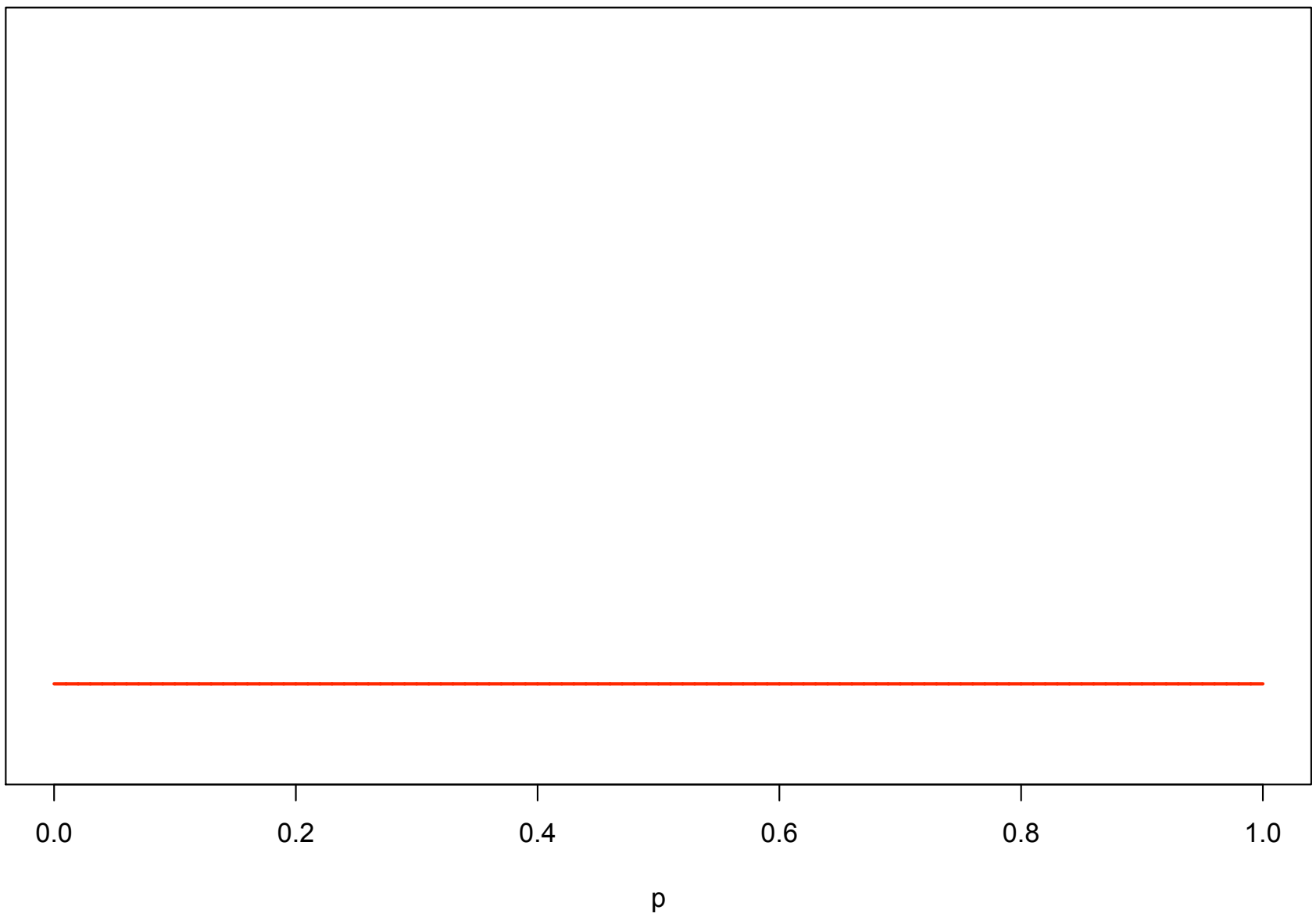
$$= \frac{\Pr(Data \mid Hypothesis)\Pr(Hypothesis)}{\int_{\substack{All\ possible \\ hypotheses}} \Pr(Data \mid Hypothesis)\Pr(Hypothesis)}$$

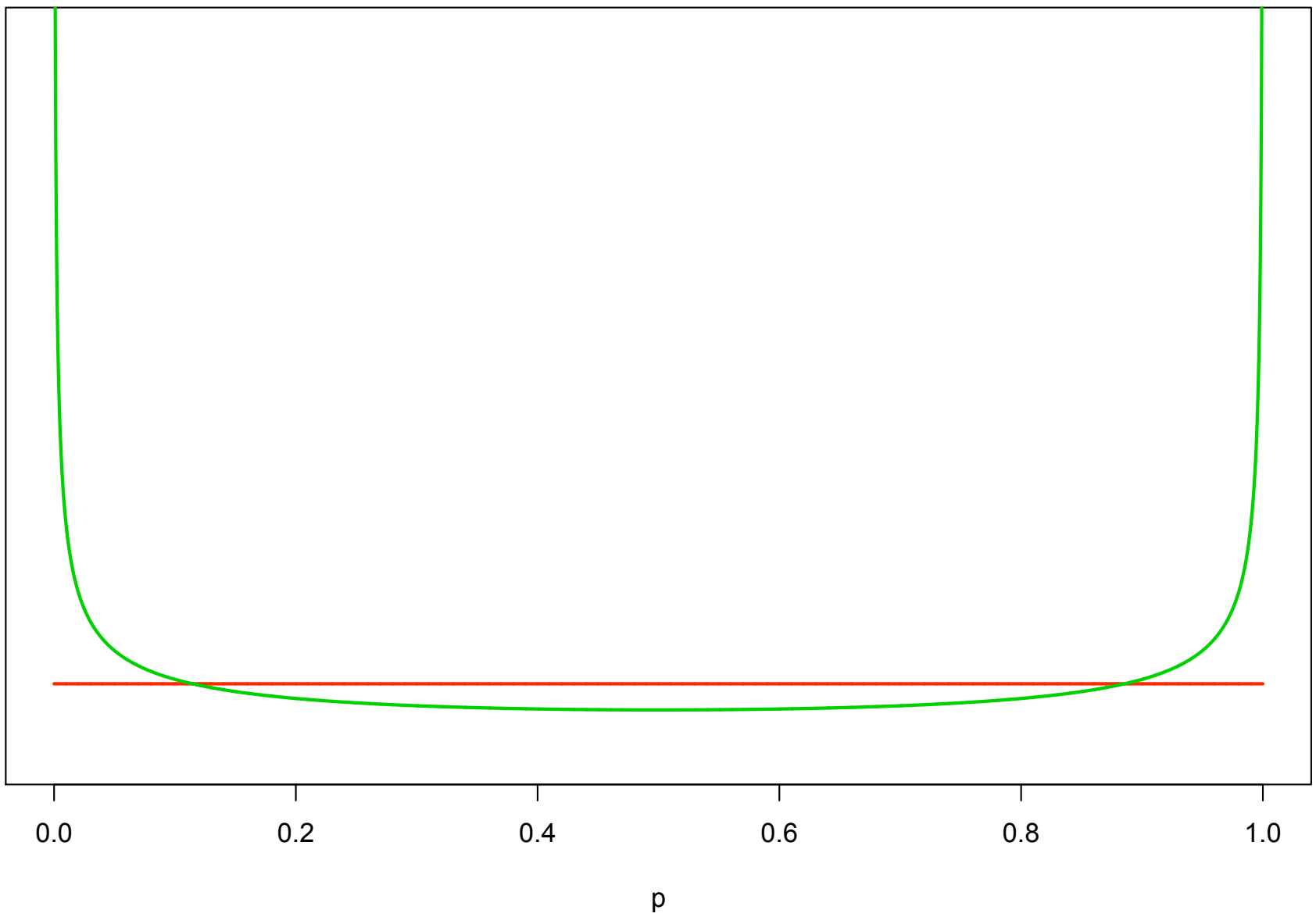
Common prior for Binomial Outcome

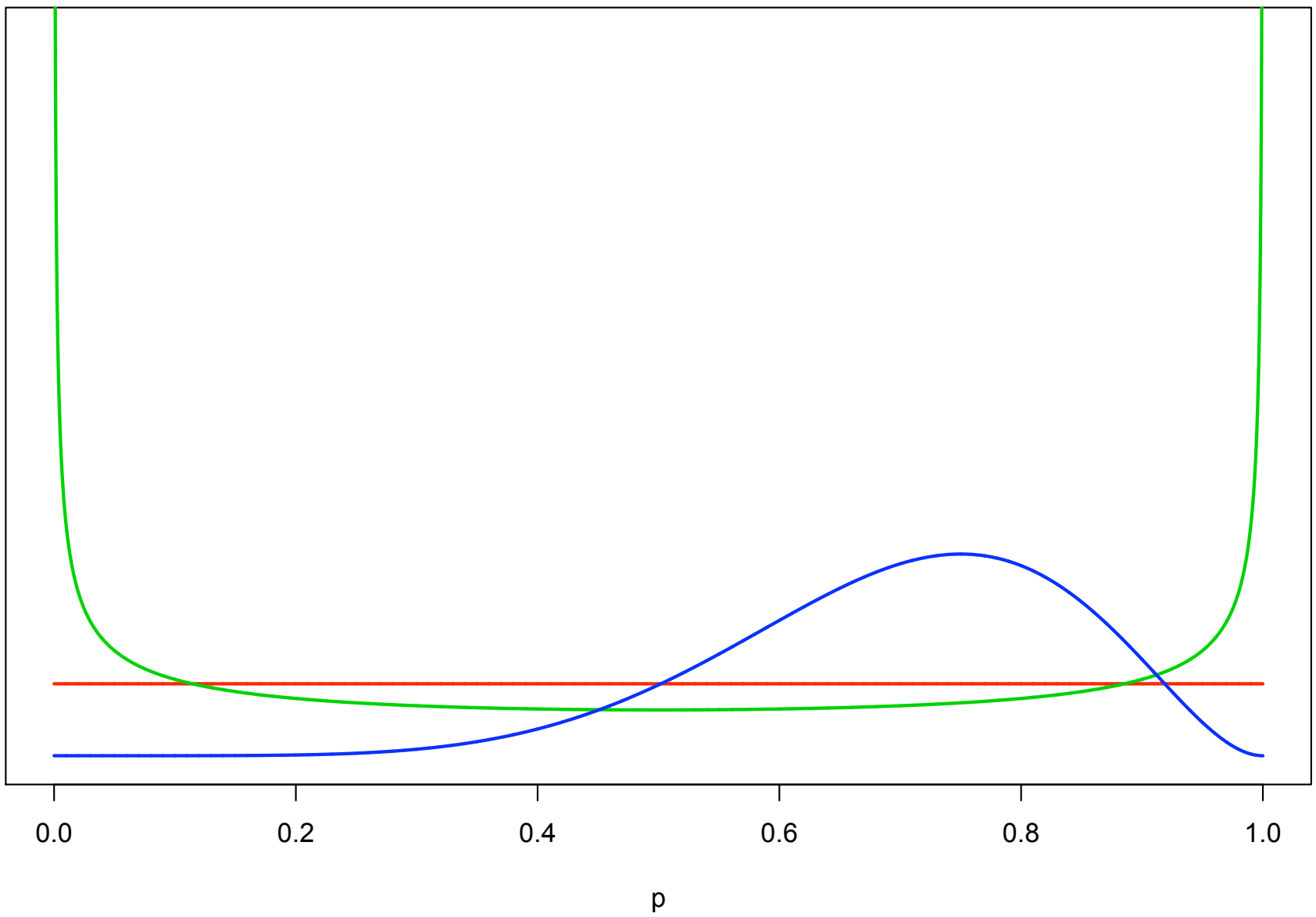
- Beta
  - used for event probabilities
  - conjugate with binomial
  - $x \sim$ Binomial(N, p)
  - $p \sim$ Beta(α,β), $p \in [0,1]$
  - $p \mid x \sim$ Beta(α+x, β+N-x)

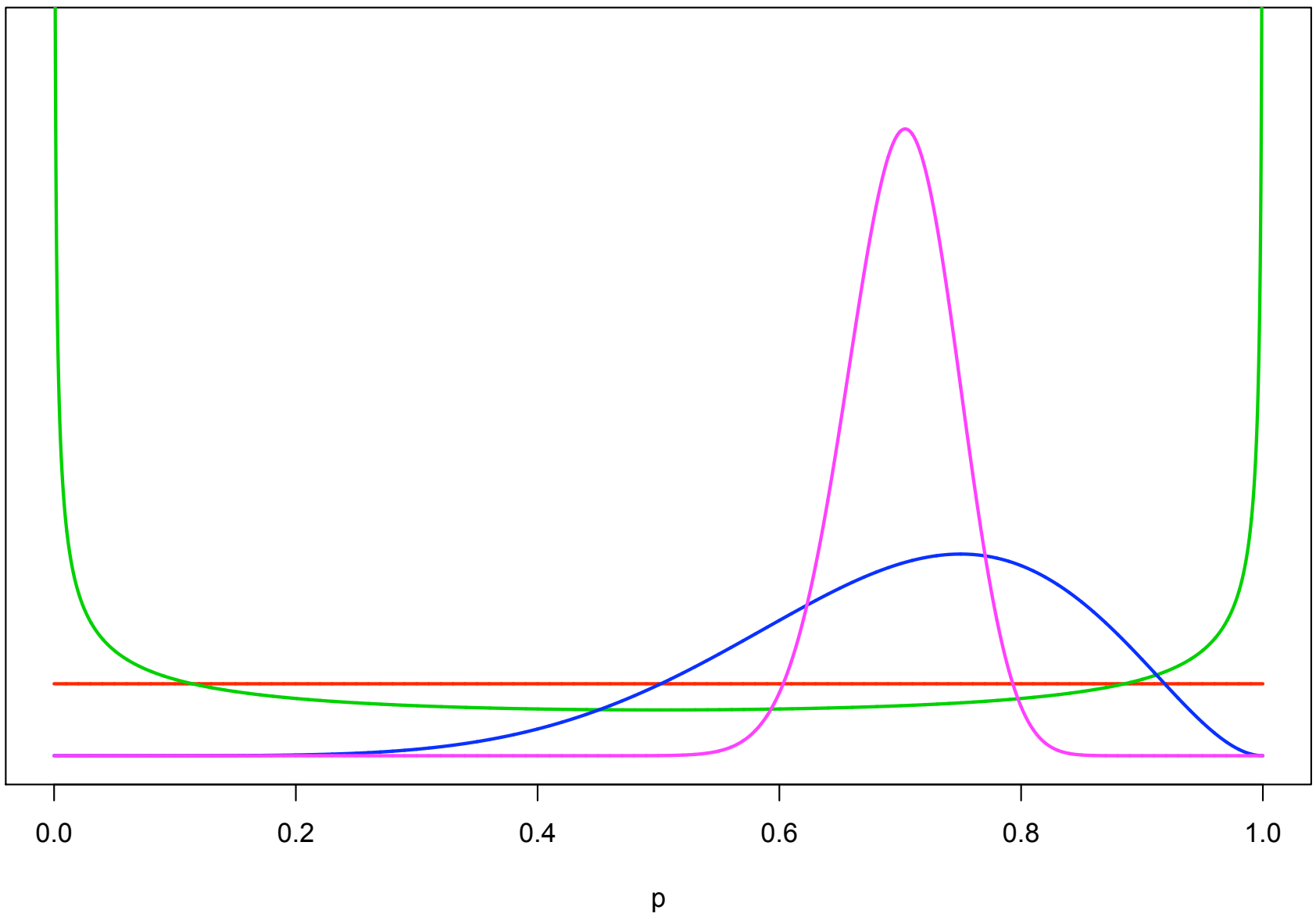
$$E(p) = \frac{\alpha}{\alpha+\beta}; \qquad V(p) = \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$$

$$E(p \mid x) = \frac{\alpha+x}{\alpha+\beta+N}; \qquad V(p) = \frac{(\alpha+x)(\beta+N-x)}{(\alpha+\beta+N)^2(\alpha+\beta+N+1)}$$


Beta(1,1)
0.0
0.2
0.4
0.6
0.8
1.0
p


Beta(.5,.5)
0.0
0.2
0.4
0.6
0.8
1.0
p


Beta(7,3)
0.0
0.2
0.4
0.6
0.8
1.0
p


Beta(70,30)
0.0
0.2
0.4
0.6
0.8
1.0
p

Beta Distribution

- $p \sim \text{Beta}(\alpha,\beta)$
  - α is like 'prior' number of successes
  - β is like 'prior' number of failures
  - $\alpha+\beta$ is the prior sample size (or amount of info)

- $p \mid N,x \sim \text{Beta}(\alpha+x, \beta+N-x)$
  - $\alpha+x$ is posterior number of successes
  - $\beta+N-x$ is posterior number of failures

- Posterior mean = $\alpha+x \,/\, (\alpha+\beta+N)$

Confirmatory Trials & Bayes

- You can't have an informative prior and control Type I error
  - Assuming the informative prior claims the treatment starts off better than the control

Simple Trial

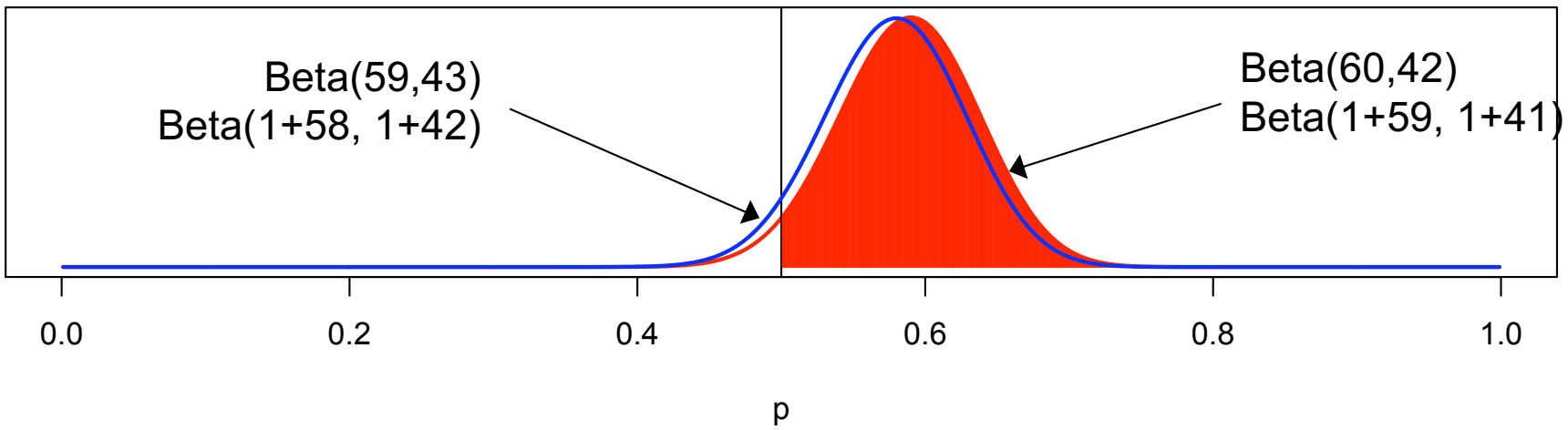
- Binomial data
- One-armed trial
- n = 100
- Need to show p > 0.5
- H_o: p ≤ 0.5
- H_a: p > 0.5

- FYI: 59/100 → Frequentist p-value = 0.044
  & 1-sided 95% CI (0.503 – 1.00)

Phase 3 & Priors

- Simple Trial:
  - Binary data. Observe x ~ Bin(100,p)
  - Need to show Pr(p > 0.5 | x out of 100) > 0.95
  - Assume p ~ Beta(1,1) prior
  - Pr(p > 0.5 | 59 out of 100) = 0.963
  - Pr(P > 0.5 | 58 out of 100) = 0.944

1-sided p-value < 0.05
approx posterior > 0.95



Phase 3 & Priors

- Simple Trial:
  - Binary data. Observe $x \sim Bin(100,p)$
  - Need to show $Pr(p > 0.5 \mid x \text{ out of } 100) > 0.95$
  - Assume $p \sim Beta(1,1)$ prior
  - $Pr(p > 0.5 \mid 59 \text{ out of } 100) = 0.963$
  - $Pr(P > 0.5 \mid 58 \text{ out of } 100) = 0.944$
- $Pr(X \geq 59 \mid p = 0.50) = 0.044$
  - Simple binomial calculation
  - This is Type I error and is < 5%
  - Bayesian trial
  - Good frequentist properties

Phase 3 & Priors

- Now we have "pure" information

  9 of 10 successes in European trial

- Instead of Beta(1,1) prior use Beta(1+9, 1+1)

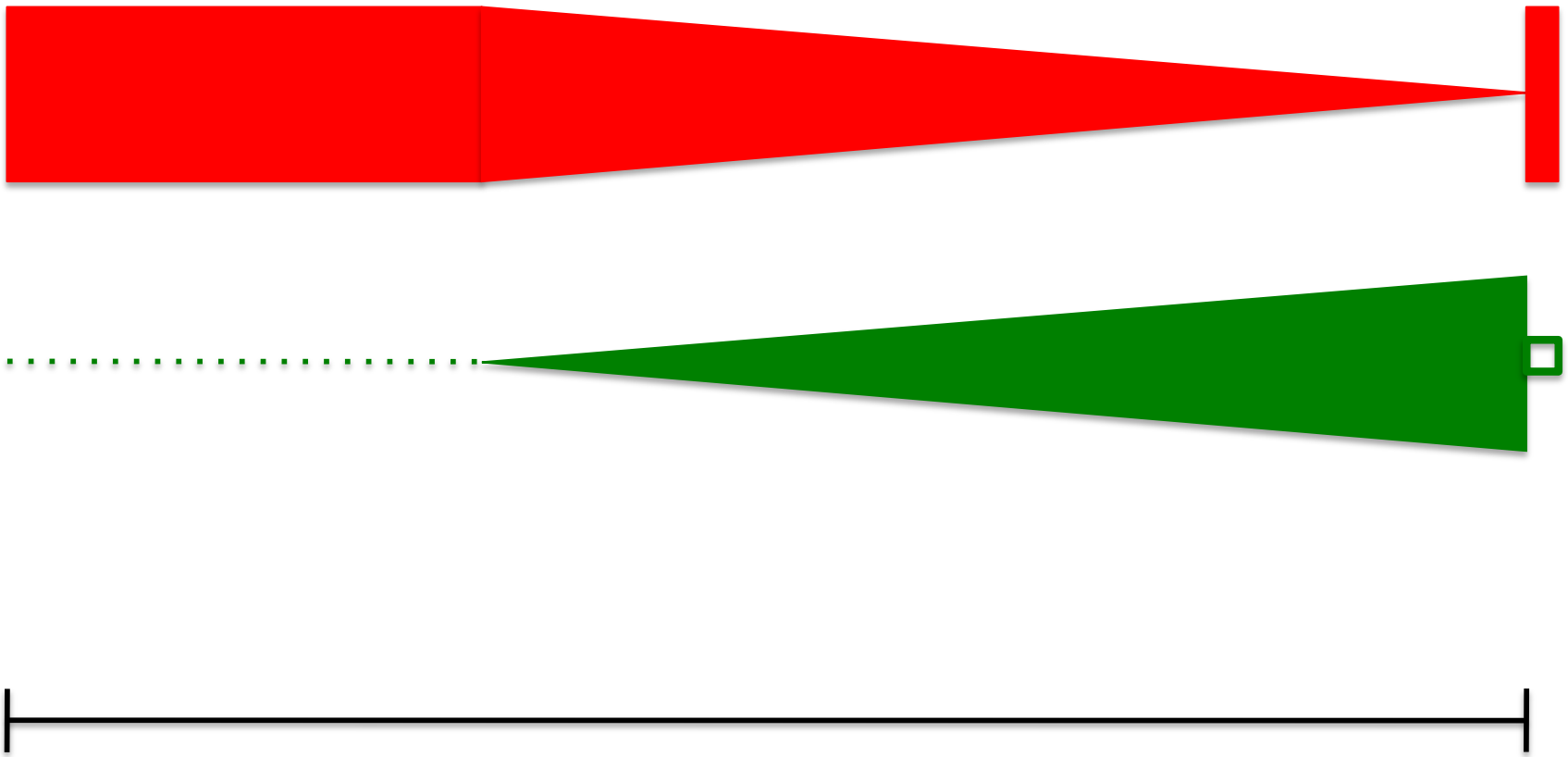
  = Beta(10,2) prior

- Regulatory agrees it is reasonable to use this as the prior
- Fixed design: for $Pr[p > 0.5 \mid data] \geq 0.95$
  - $Pr(p > 0.5 \mid 55 \text{ out of } 100, \alpha=10,\beta=2) = 0.956$
  - $Pr(P > 0.5 \mid 54 \text{ out of } 100, \alpha=10,\beta=2) = 0.936$
- $Pr(X \geq 55 \mid p = 0.50) = 0.184$
  - Type I error is inflated

Phase 3 & Priors

- Solution to control Type I error
  - Raise the post probability threshold from 0.95 bar to 0.99 (like decreasing critical level)
  - $\Pr(p > 0.5 \mid 59 \text{ out of } 100, \alpha=10, \beta=2) = 0.993$
  - $\Pr(P > 0.5 \mid 58 \text{ out of } 100, \alpha=10, \beta=2) = 0.989$
  - $\Pr(X \geq 59 \mid p = 0.50) = 0.044$
- Need a Beta(59+10,41+2) for a win…59 is back!!!
- The type I error "restriction" forces 59/100 regardless of prior…
- Can't allow beneficial priors AND force Type I of "new" experiment!

Posterior/Predictive

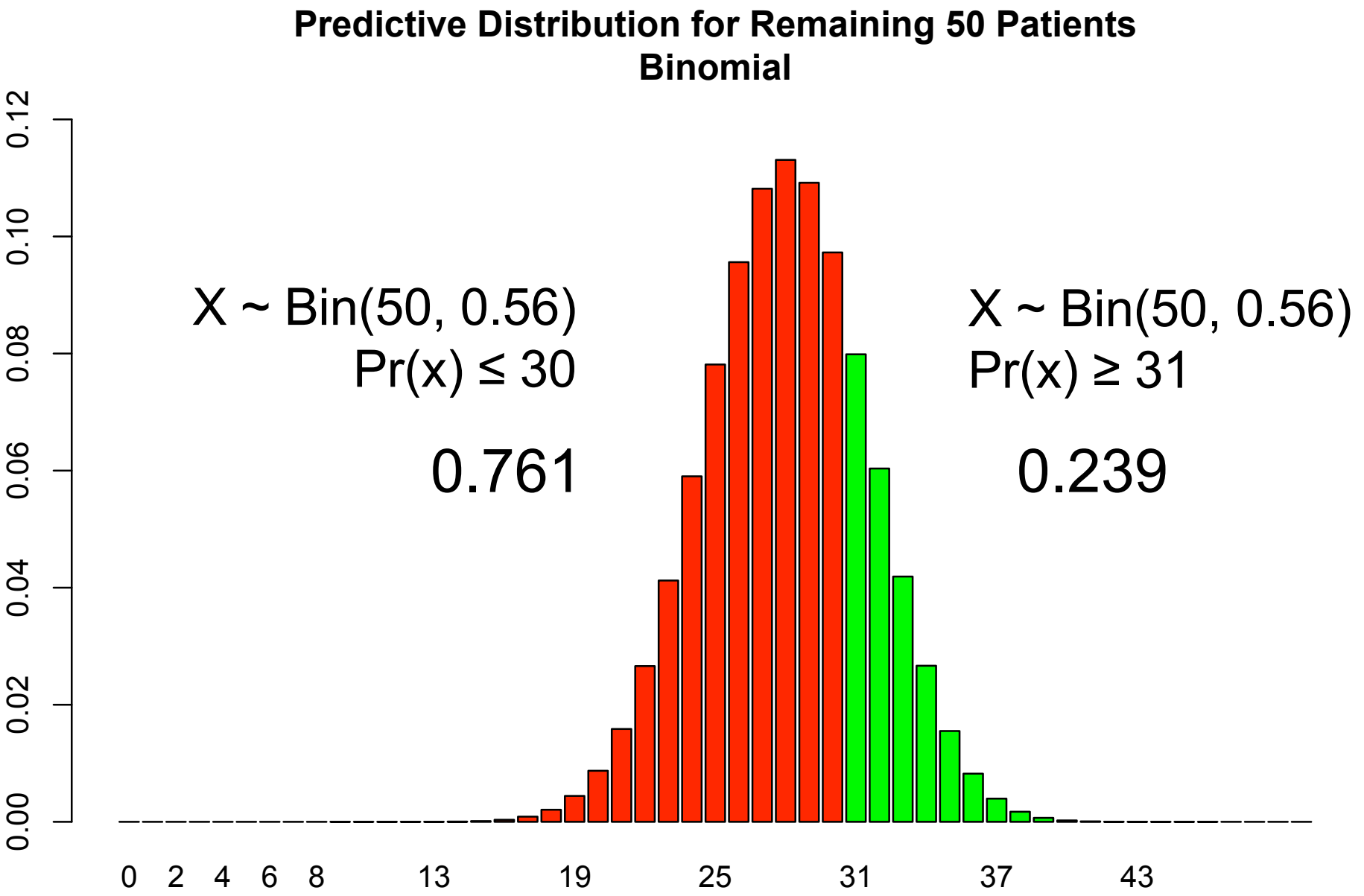


Predictive Probabilities

- Simple Trial:
  - Binary data. Observe $x \sim \text{Bin}(100, p)$
  - Need to show $\Pr(p > 0.5 \mid x \text{ out of } 100) > 0.95$
  - Assume $p \sim \text{Beta}(1,1)$ prior
  - $\Pr(p > 0.5 \mid 59 \text{ out of } 100) = 0.963$
  - $\Pr(p > 0.5 \mid 58 \text{ out of } 100) = 0.944$

Predictive Probabilities

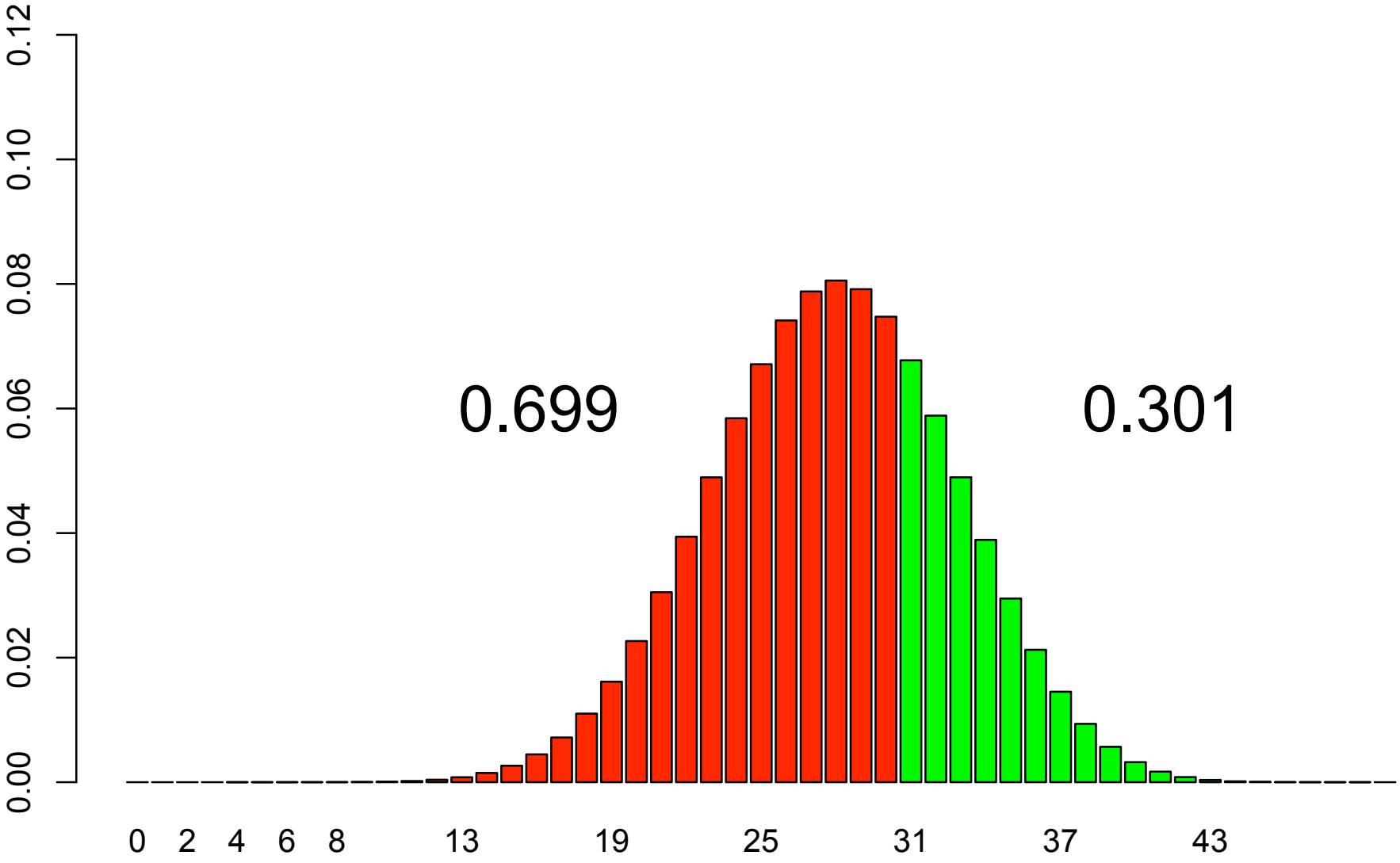
- Simple Trial:
  - Binary data. Observe $x \sim \text{Bin}(100, p)$
  - Need to show $\Pr(p > 0.5 \mid x \text{ out of } 100) > 0.95$
  - Assume $p \sim \text{Beta}(1,1)$ prior
  - $\Pr(p > 0.5 \mid 59 \text{ out of } 100) = 0.963$
  - $\Pr(p > 0.5 \mid 58 \text{ out of } 100) = 0.944$
- Observe data half way through
  - See 28/50 successes
  - Need to see 31/50 to meet threshold
  - What is predictive probability of trial success?

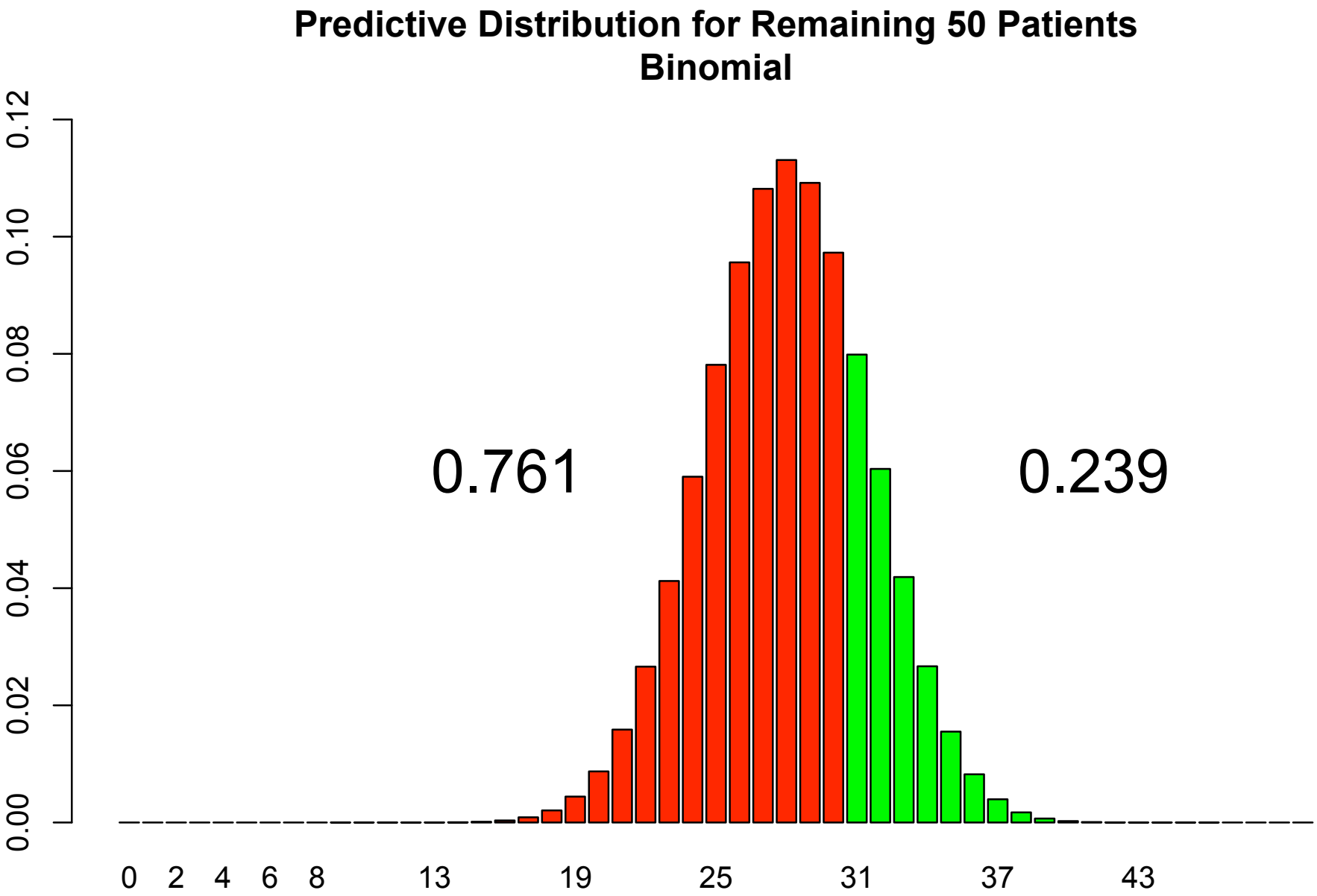

Predictive Distribution for Remaining 50 Patients
Binomial
X ~ Bin(50, 0.56)
Pr(x) ≤ 30
0.761
X ~ Bin(50, 0.56)
Pr(x) ≥ 31
0.239
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0
2
4
6
8
13
19
25
31
37
43

Predictive Probabilities

- Know we need $x \geq 59$ at trial's end
- Have $x_1 = 28$
- Need $x_2 \geq 31$
- $p \sim$ Beta(1+28, 1+22)
- $x_2 \sim$ Binomial(50, p)
- $x_2 \sim$ Beta-binomial(50, α=29, β=23)

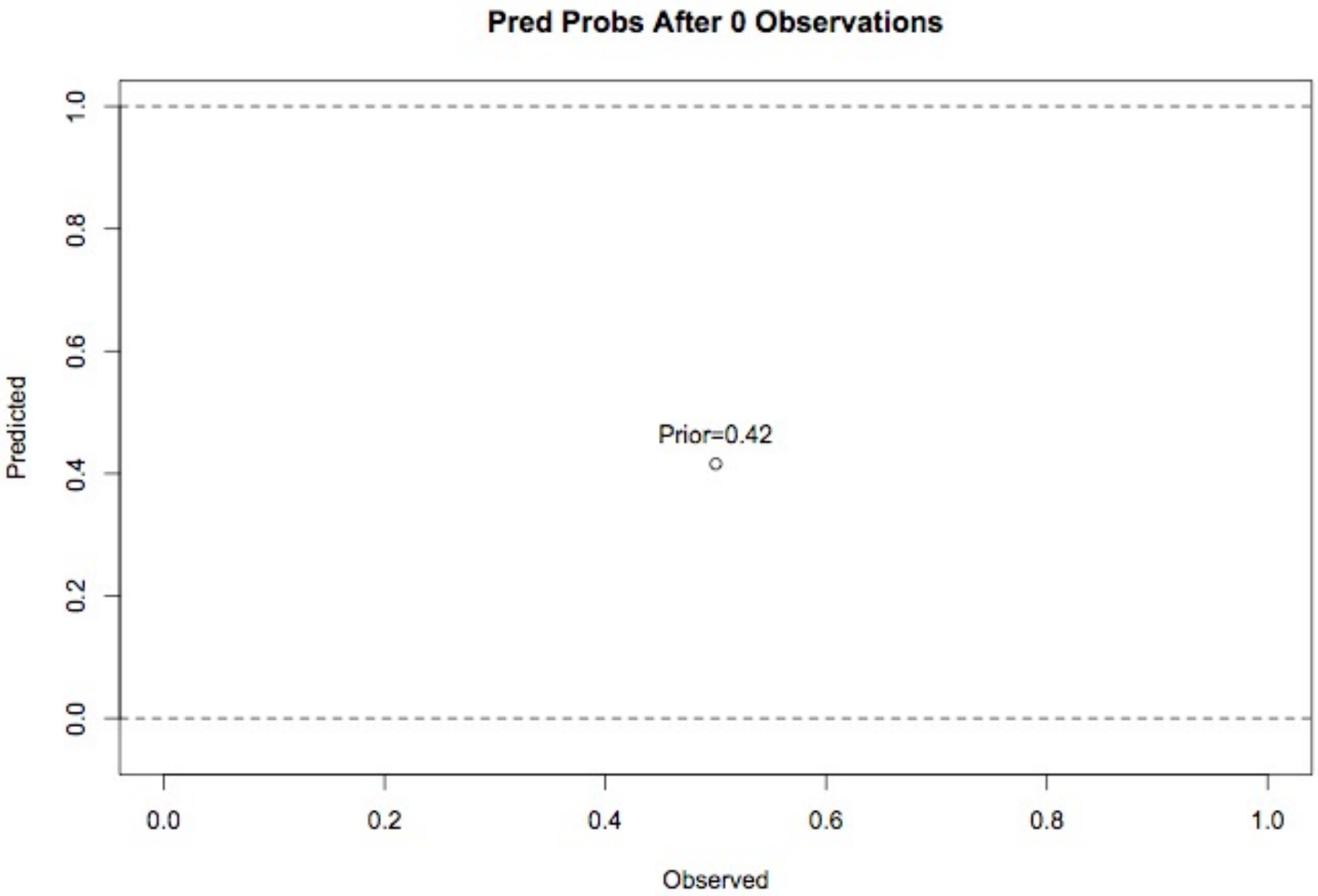
$$\Pr(\text{Win Trial}) = \sum_{x_2=31}^{50} \left\{ \binom{50}{x_2} \frac{B(x_2 + 29, 50 - x_2 + 23)}{B(29,22)} \right\} = 0.301$$

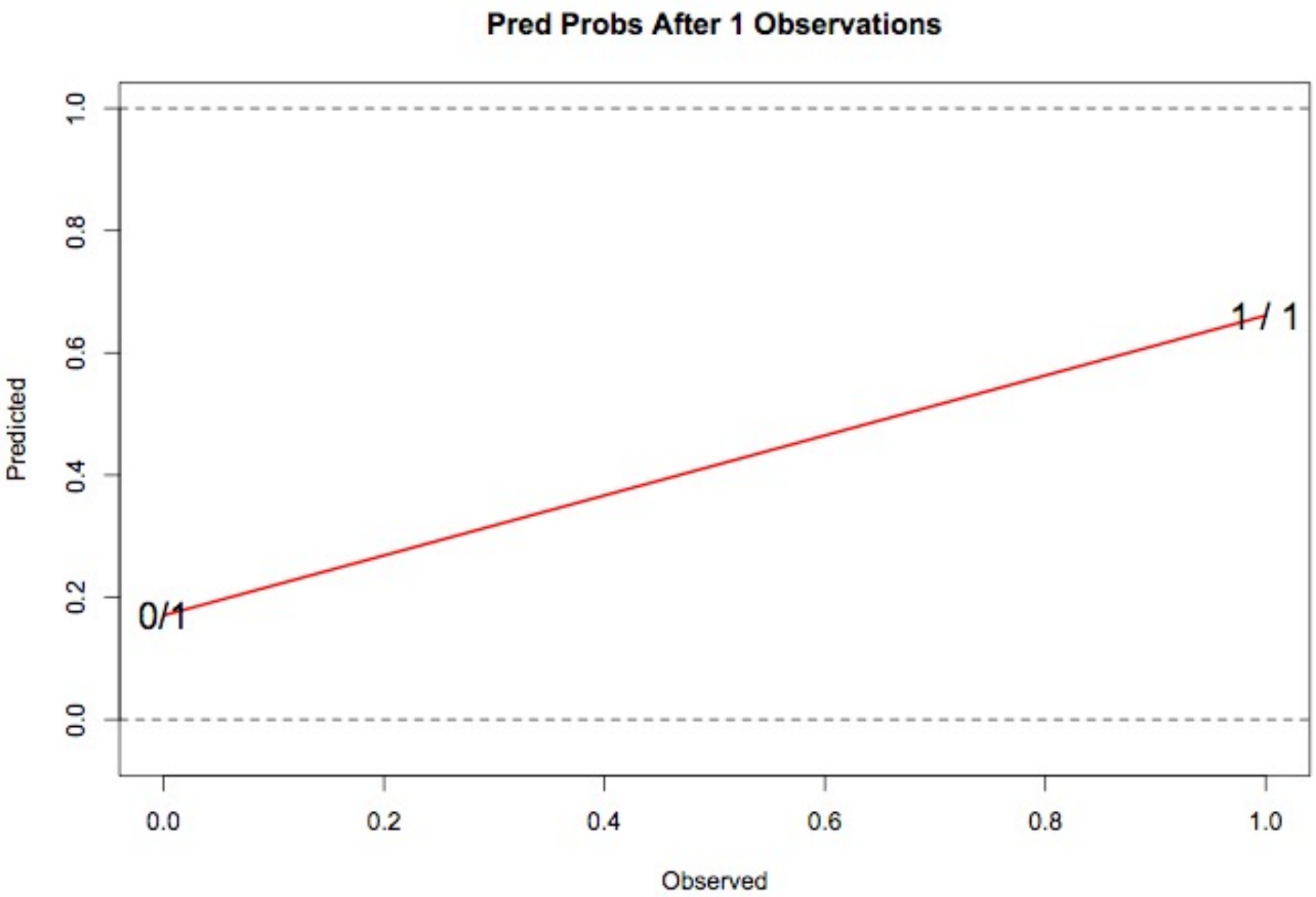

Predictive Distribution for Remaining 50 Patients
Beta-Binomial
0.699
0.301
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0
2
4
6
8
13
19
25
31
37
43

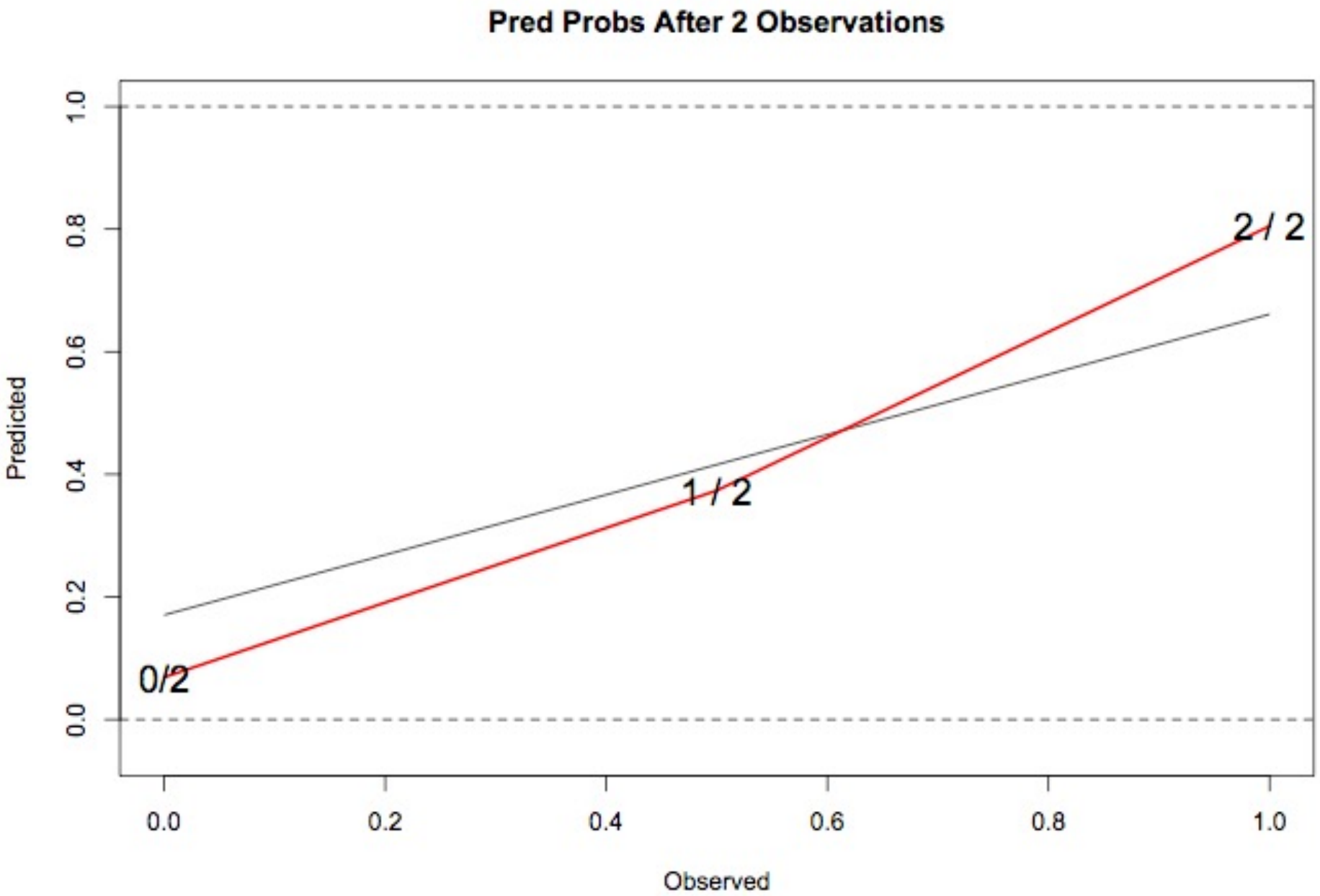

Predictive Distribution for Remaining 50 Patients
Binomial
0.761
0.239
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0
2
4
6
8
13
19
25
31
37
43

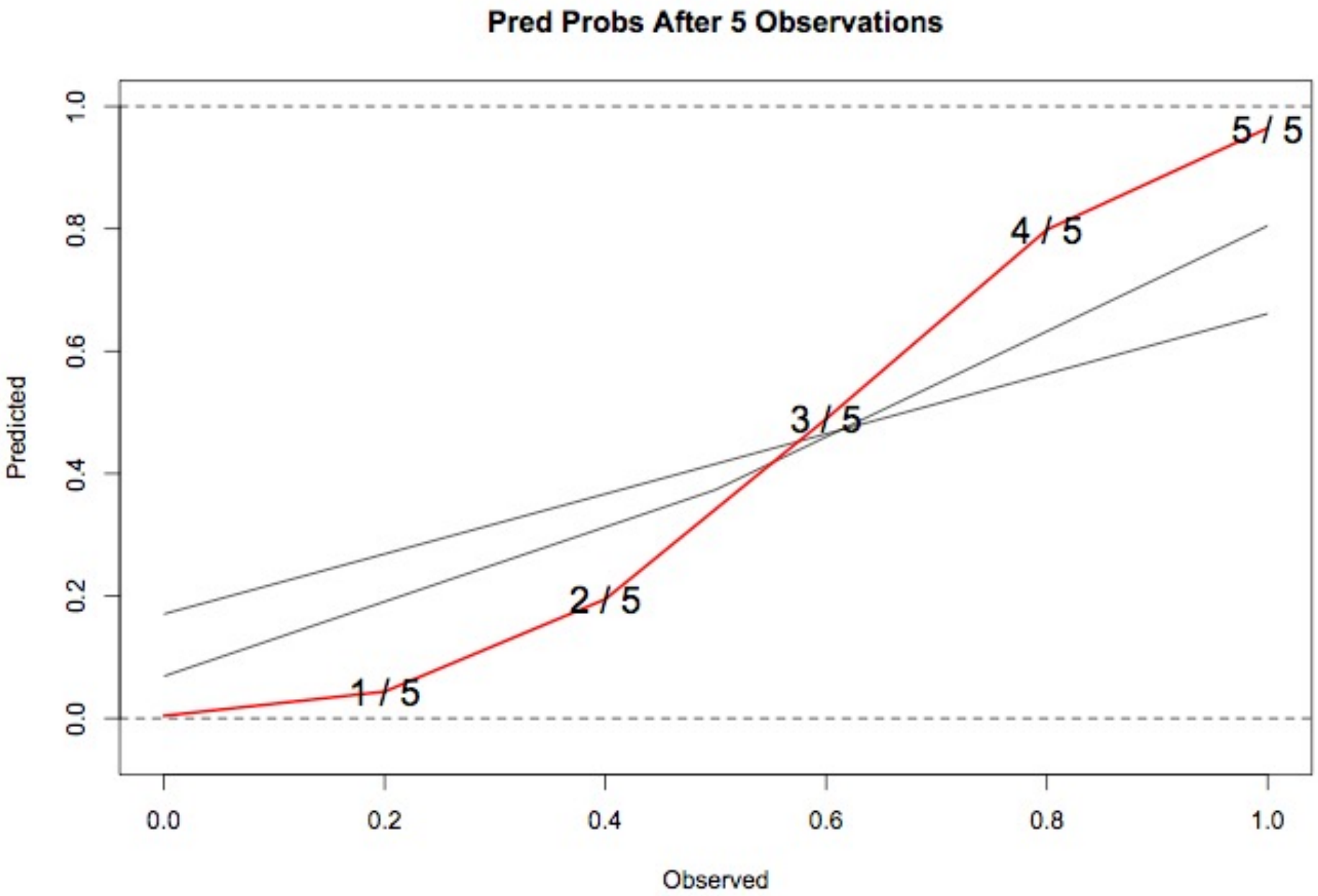
R code for predictive probability

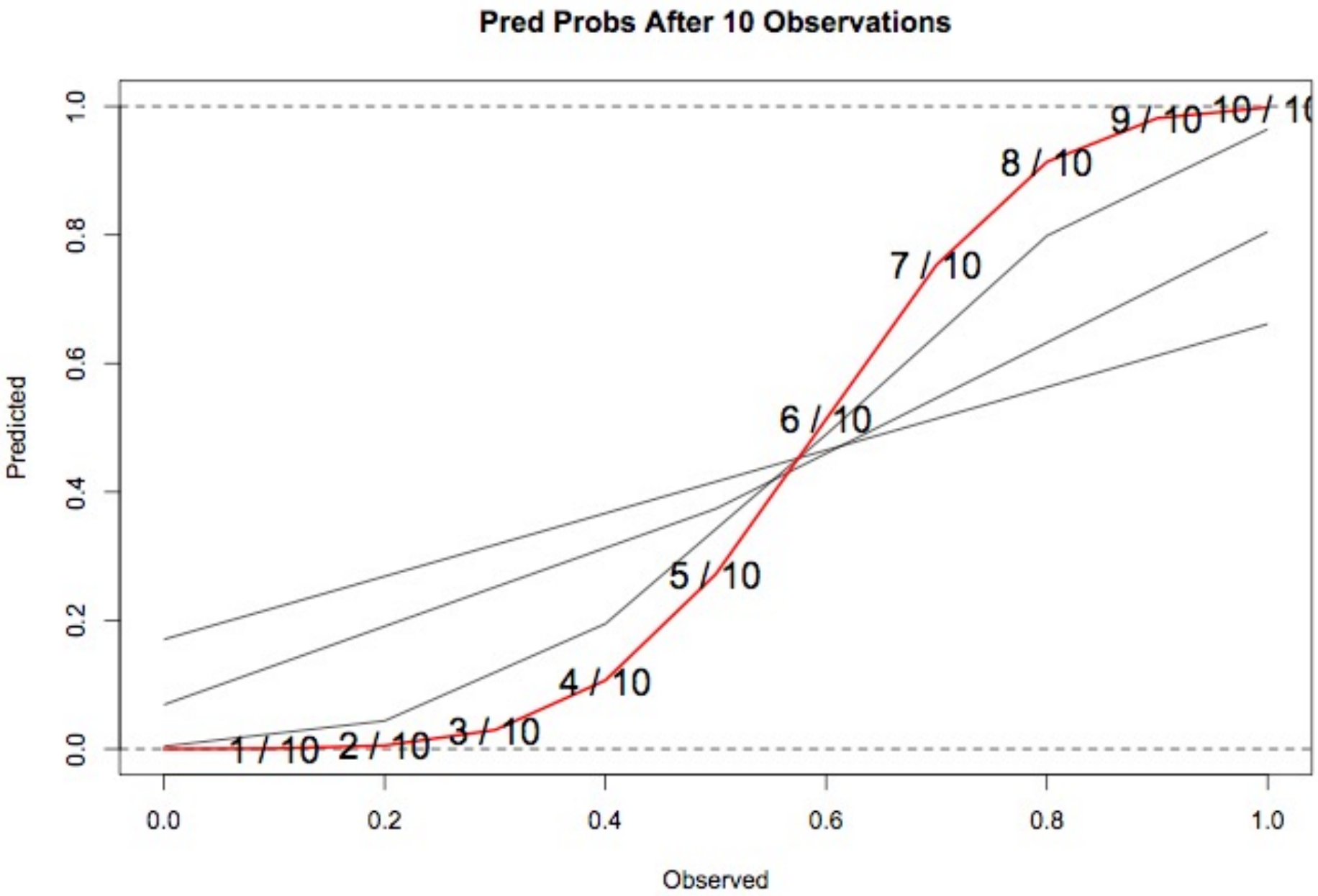
```
> ### VIA SIMULATION
> alpha <- 1; beta <- 1
> x <- 28; N <- 50
>
> p <- rbeta(1000000, alpha+x, beta+N-x)
> x.new <- rbinom(1000000, 50, p)
>
> mean(x.new >= 31)
[1] 0.301132
>
>
>
> ### VIA DIRECT CALCULATION
> N.new <- 50
> x.new <- 0:50
> prob <- choose(N.new,x.new) *
+       beta(alpha+x+x.new,(beta+N-x)+(N-x.new)) /
+          beta(alpha+x,       (beta+N-x))
> sum(prob)
[1] 1
> sum(prob[x.new >= 31])
[1] 0.3010906
> barplot(prob, names.arg=0:50, col=c(rep(2,31), rep(3,20)),
+        main="Predictive Distribution for Remaining 50 patients")
```

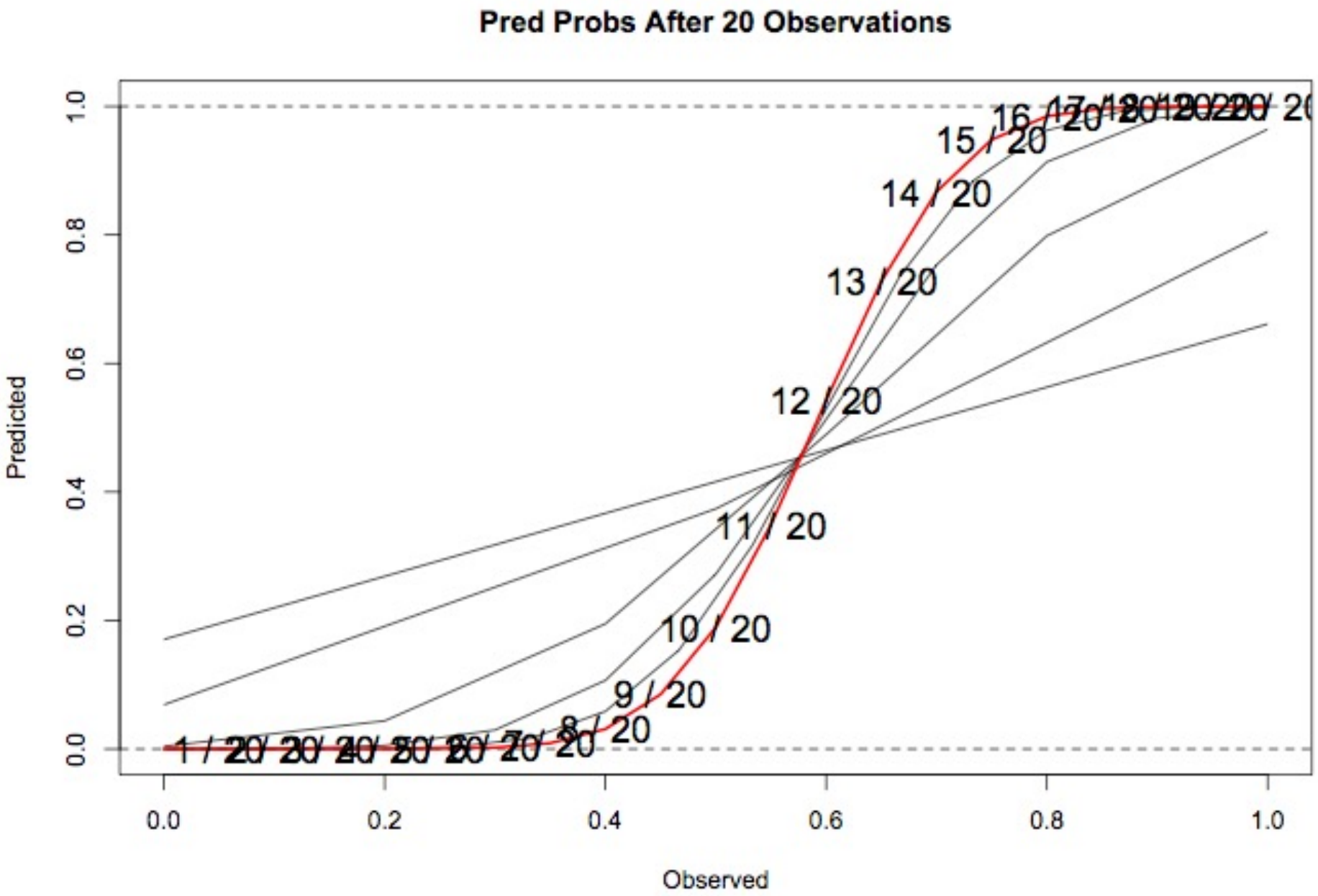

Pred Probs After 0 Observations
Predicted
1.0
0.8
0.6
0.4
0.2
0.0
Prior=0.42
0.0
0.2
0.4
0.6
0.8
1.0
Observed

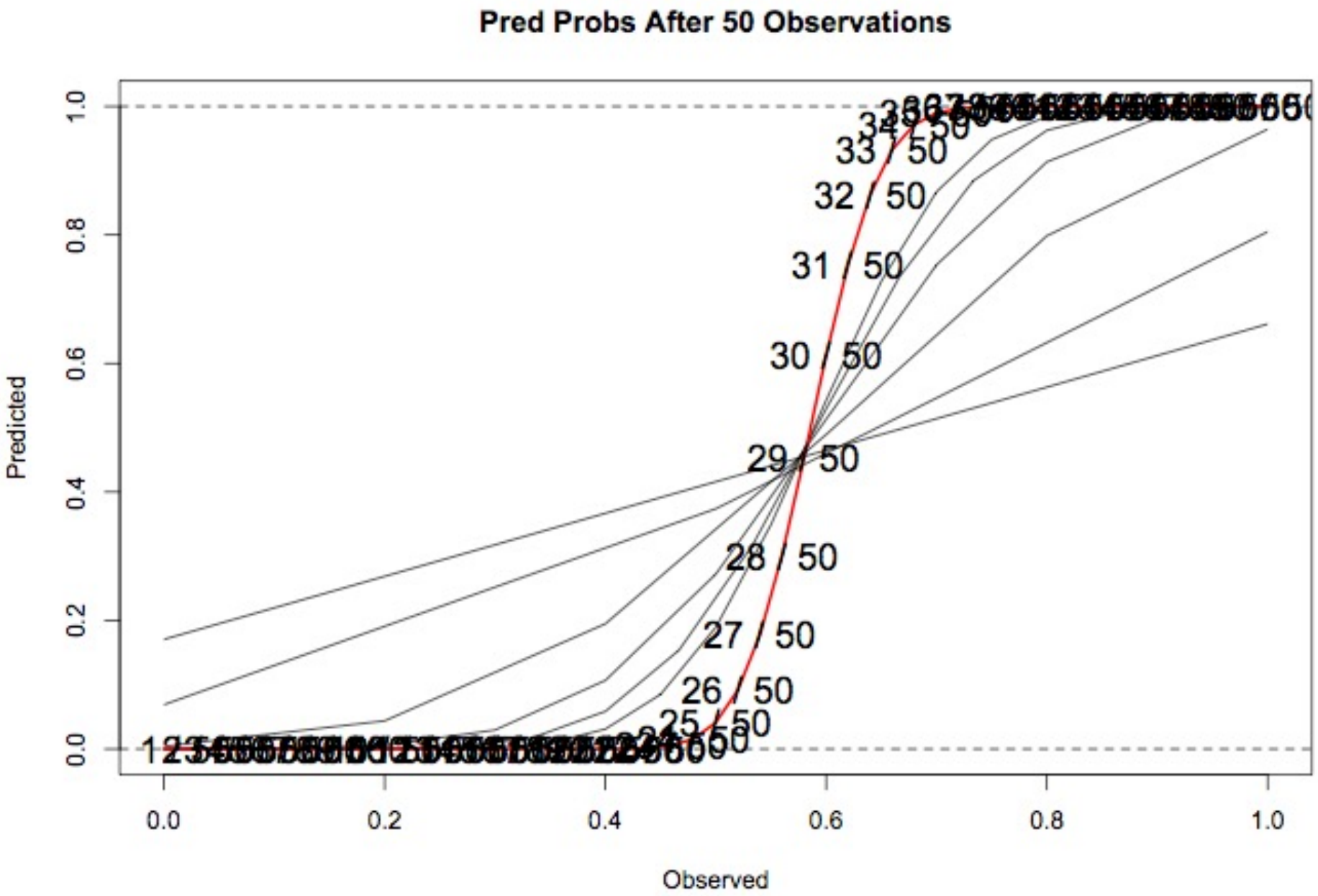

Pred Probs After 1 Observations
Predicted
Observed
0.0
0.2
0.4
0.6
0.8
1.0
0/1
1 / 1

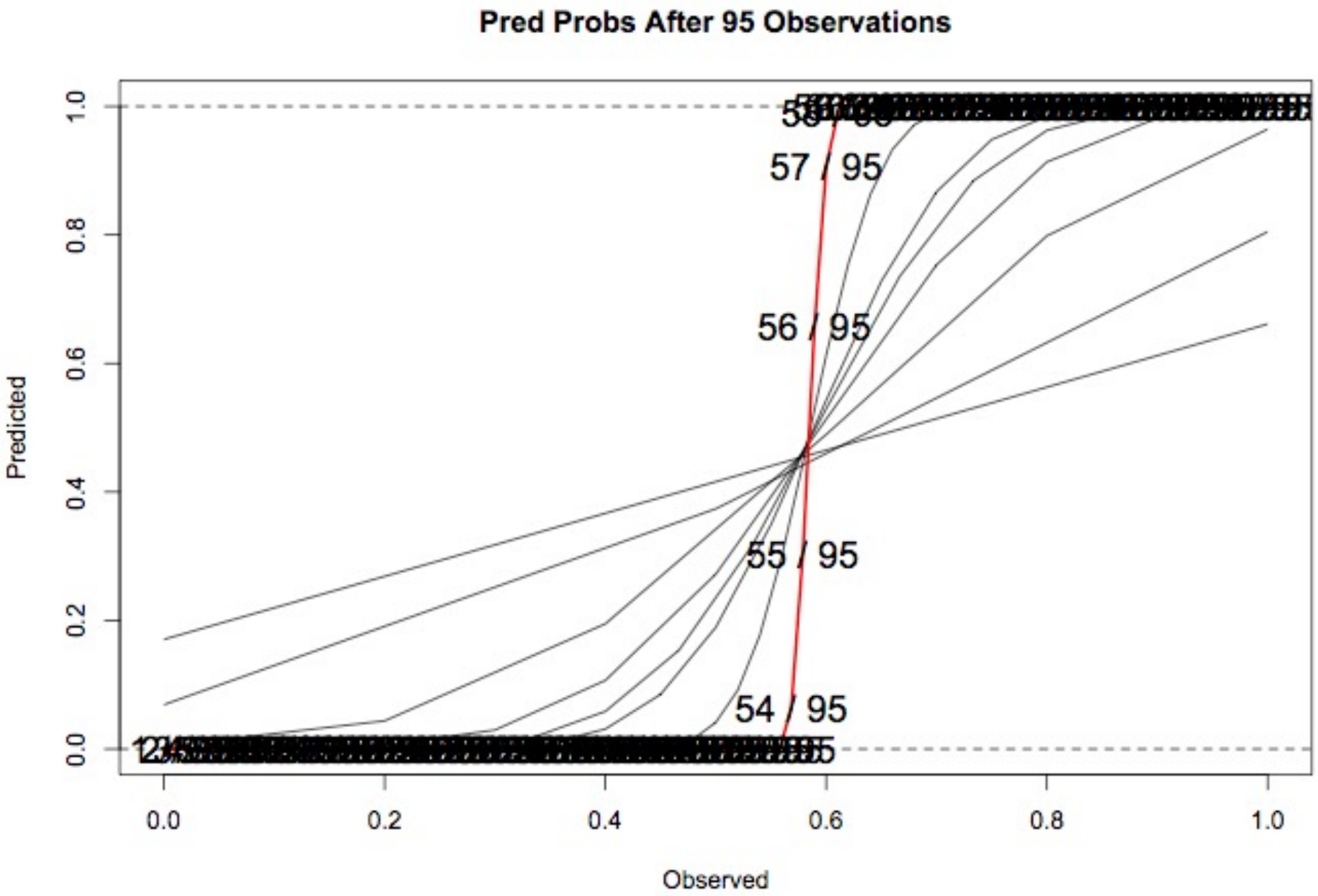

Pred Probs After 2 Observations
Predicted
Observed
0.0
0.2
0.4
0.6
0.8
1.0
0/2
1 / 2
2 / 2

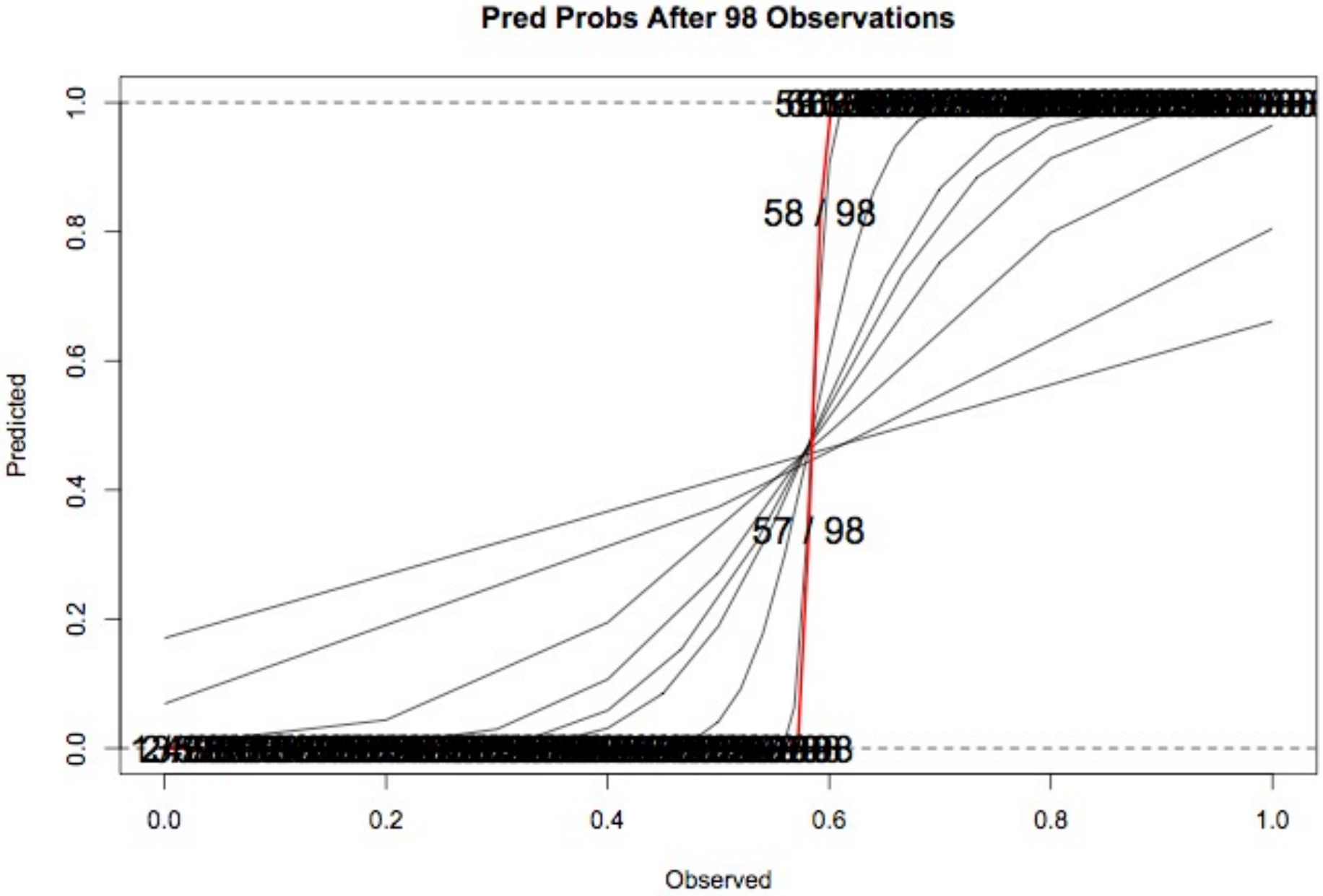

Pred Probs After 5 Observations
Predicted
Observed
0.0
0.2
0.4
0.6
0.8
1.0
1 / 5
2 / 5
3 / 5
4 / 5
5 / 5

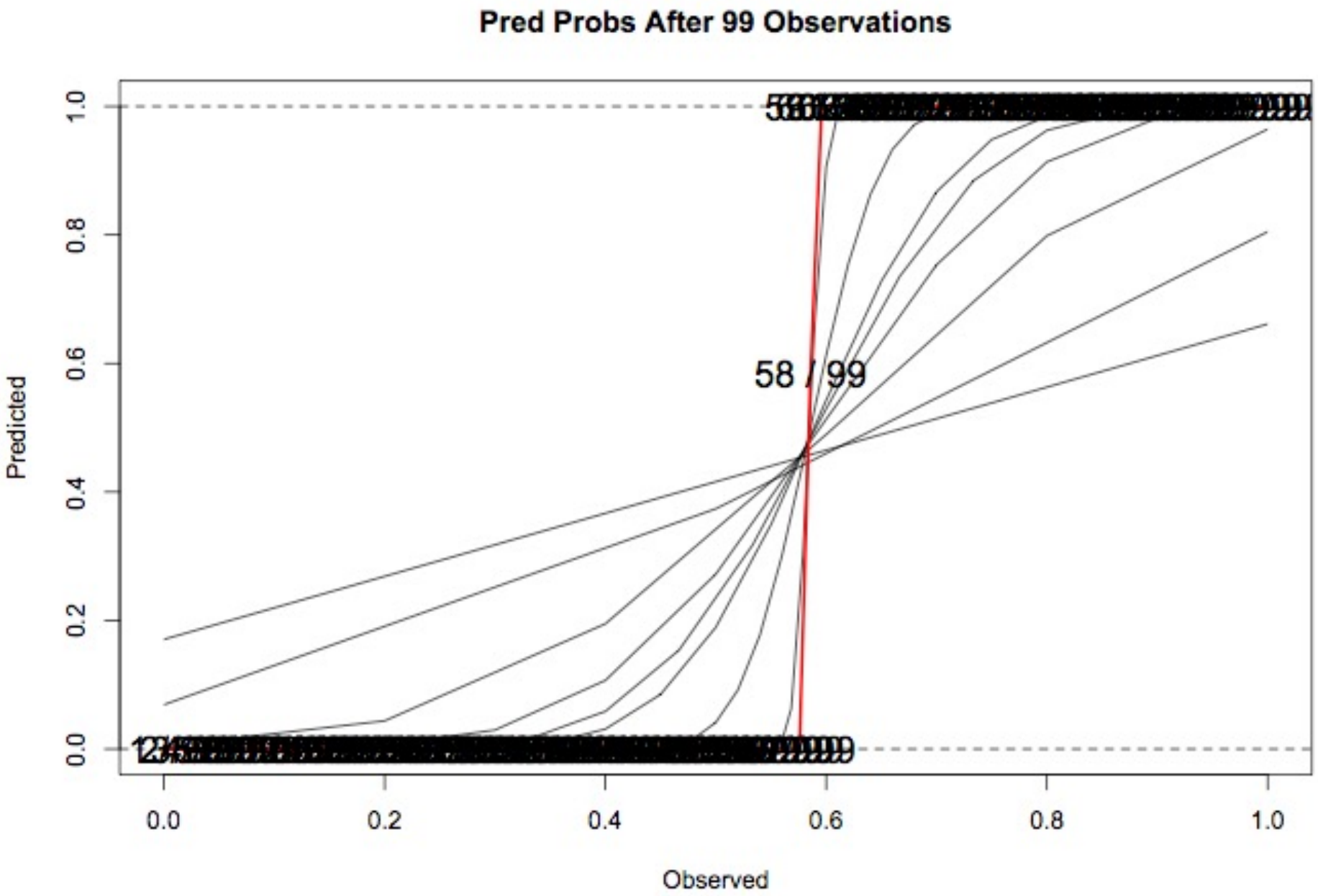

Pred Probs After 10 Observations
Predicted
Observed
0.0
0.2
0.4
0.6
0.8
1.0
1 / 10
2 / 10
3 / 10
4 / 10
5 / 10
6 / 10
7 / 10
8 / 10
9 / 10
10 / 10


Pred Probs After 20 Observations
Predicted
Observed
0.0
0.2
0.4
0.6
0.8
1.0
16 / 20
15 / 20
14 / 20
13 / 20
12 / 20
11 / 20
10 / 20
9 / 20
8 / 20


Pred Probs After 50 Observations
Predicted
Observed
0.0
0.2
0.4
0.6
0.8
1.0
34 / 50
33 / 50
32 / 50
31 / 50
30 / 50
29 / 50
28 / 50
27 / 50
26 / 50
25 / 50


Pred Probs After 95 Observations
57 / 95
56 / 95
55 / 95
54 / 95
Predicted
Observed
0.0
0.2
0.4
0.6
0.8
1.0


Pred Probs After 98 Observations
58 / 98
57 / 98
Predicted
Observed
0.0
0.2
0.4
0.6
0.8
1.0


Pred Probs After 99 Observations
58 / 99
Predicted
Observed
0.0
0.2
0.4
0.6
0.8
1.0

Predictive Probabilities

- Observe 12 / 20 (60%)
  - Need 47 / 80 successes; 59% or better rest of way
  - *p-value* = 0.25, Pr(p>0.5) = 0.81
  - Predictive probability of success @ 100 = 0.54

Predictive Probabilities

- Observe 12 / 20 (60%)
  - Need 47 / 80 successes; 59% or better rest of way
  - *p-value* = 0.25, Pr(p>0.5) = 0.81
  - Predictive probability of success @ 100 = 0.54
- Observe 28 / 50 (56%)
  - Need 31/50 successes; 62% or better rest of way
  - *p-value* = 0.24, Pr(p>0.5) = 0.80
  - Predictive probability of success @ 100 = 0.30

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  - Predictive probability of success @ 100 = 0.54
- Observe 28 / 50 (56%)
  - Need 31/50 successes; 62% or better rest of way
  - *p-value* = 0.24, Pr(p>0.5) = 0.80
  - Predictive probability of success @ 100 = 0.30
- Observe 41 / 75 (54.7%)
  - Need 18/25 successes; 72% or better rest of way
  - *p-value* = 0.24, Pr(p>0.5) = 0.79
  - Predictive probability of success @ 100 = 0.086

Predictive Probabilities

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  - Need 18/25 successes; 72% or better rest of way
  - *p-value* = 0.24, Pr(p>0.5) = 0.79
  - Predictive probability of success @ 100 = 0.086

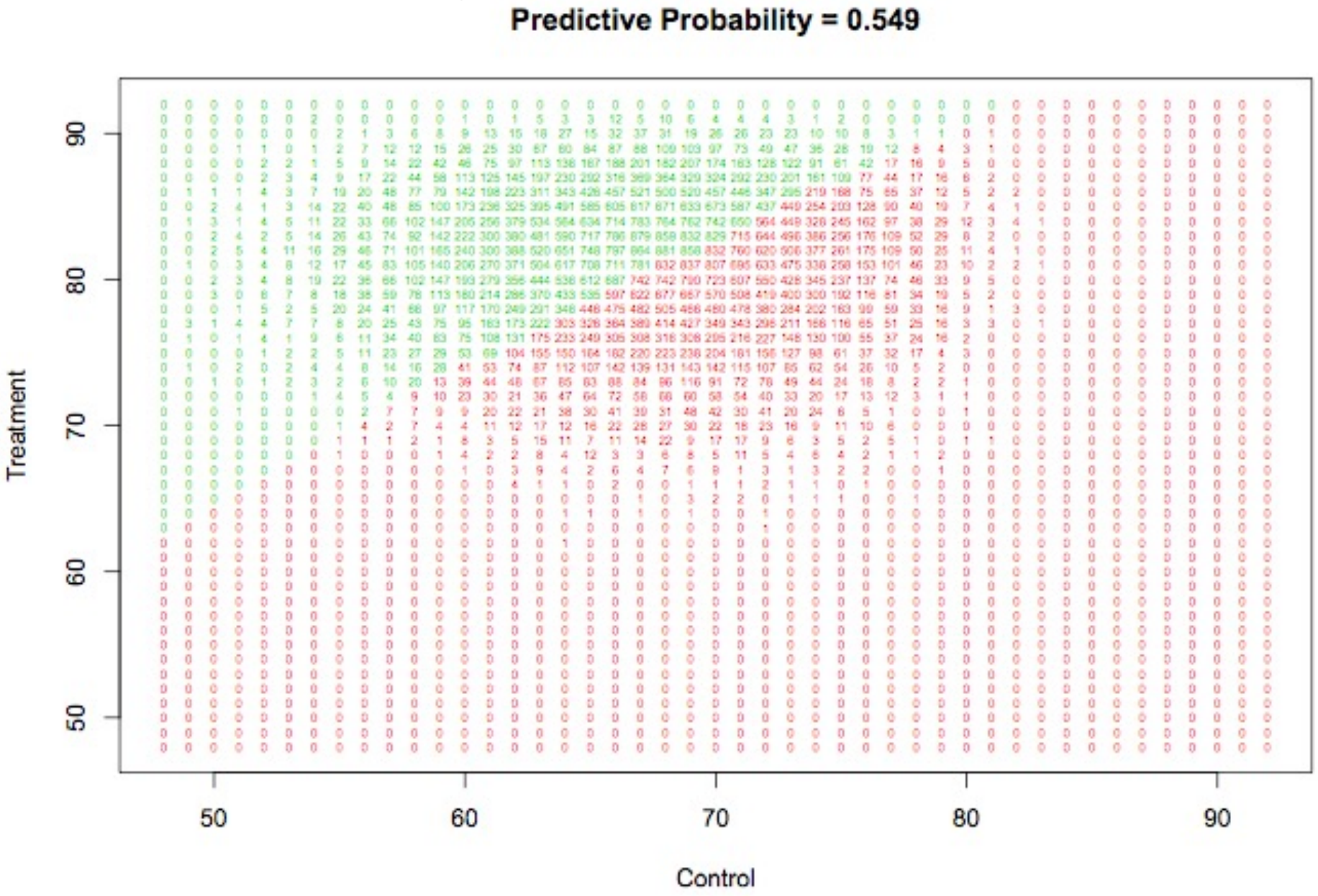
Another trial

- $N_G = 100$ in Treatment & Control Group
- Testing $p_t > p_c$ using Fisher's Exact Test @ 0.025
- Observe
  - 34/50 in Control Group
  - 41/50 in Treatment Group
- What is predictive probability of success?

Predictive Probability

```
alpha <- 1; beta <- 1
xc <- 34; nc <- 50
xt <- 41; nt <- 50

pc <- rbeta(100000, alpha+xc, beta+nc-xc)
pt <- rbeta(100000, alpha+xt, beta+nt-xt)

xc.total <- xc + rbinom(100000, 50, pc)
xt.total <- xt + rbinom(100000, 50, pt)

p.values <- rep(NA,100000)
for(i in 1:100000){
  p.values[i] <- fisher.test(
      matrix(c(xc.total[i], 100-xc.total[i],
               xt.total[i], 100-xt.total[i]),nrow=2),
               alternative="less")$p.value
}

> mean(p.value<0.025)
[1] 0.549
```

GREEN numbers are when it's statistically superior
RED are cases not significant



But what if we have historical data

- Well known historical data, $p_c = 60\% \pm 5\%$

- Expected from pilot studies, $p_t = 80\% \pm 15\%$

But what if we have historical data

- Well known historical data, $p_c = 60\% \pm 5\%$
- Expected from pilot studies, $p_t = 80\% \pm 15\%$
- Beta distribution defined by p~Beta(α,β) has mean & variance

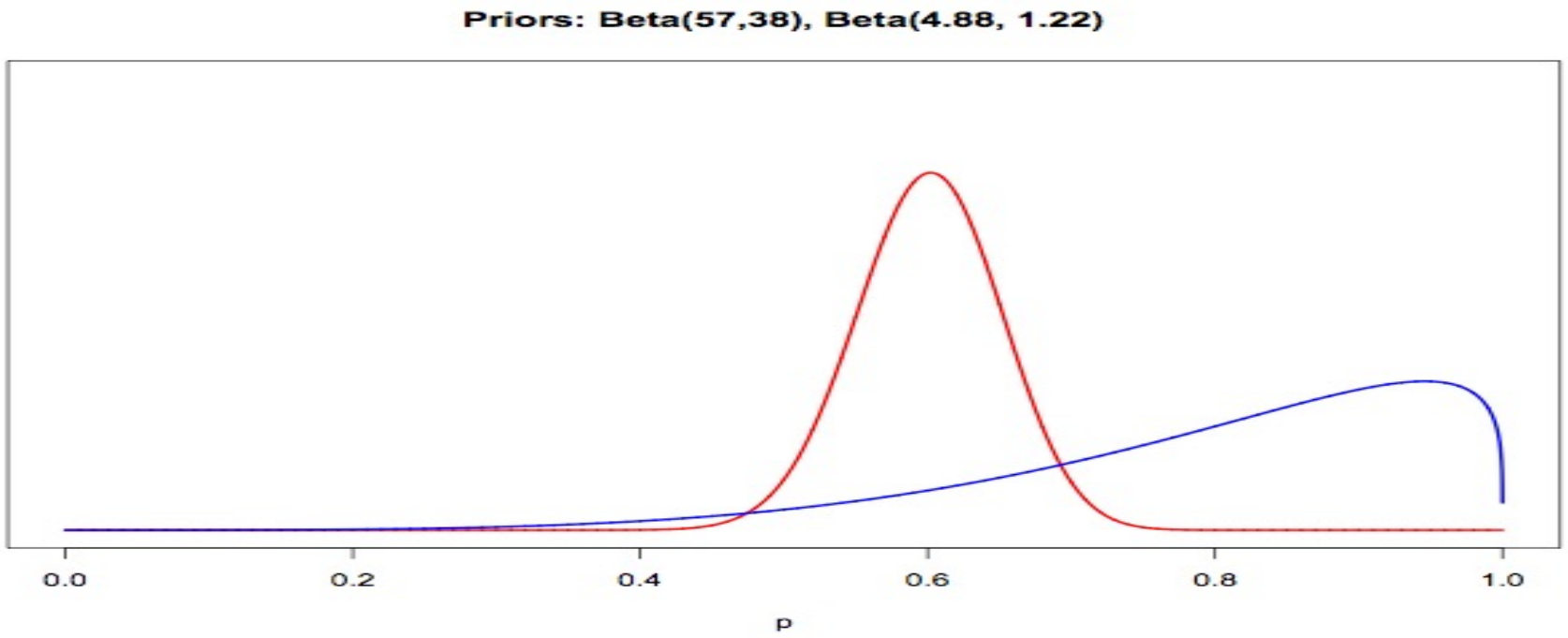
$$E(p) = \frac{\alpha}{\alpha + \beta} \qquad V(p) = \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$$

- Solve for α & β

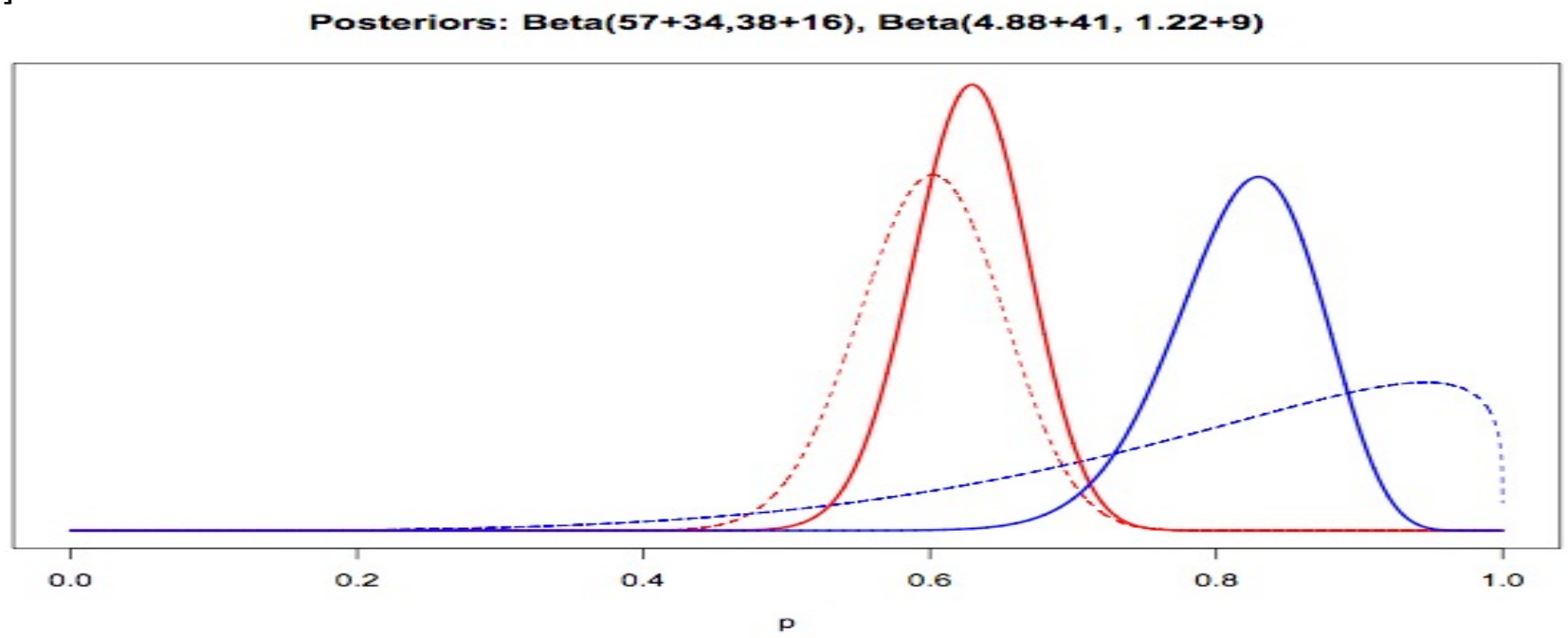
$$\frac{\alpha}{\alpha + \beta} = 0.6 \qquad \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)} = 0.05^2$$

But what if we have historical data

- Well known historical data, $p_c = 60\% \pm 5\%$
  - $\alpha_c = 57$, $\beta_c = 38$
- Expected from pilot studies, $p_t = 80\% \pm 15\%$
  - $\alpha_t = 4.8888$, $\beta_t = 1.2222$

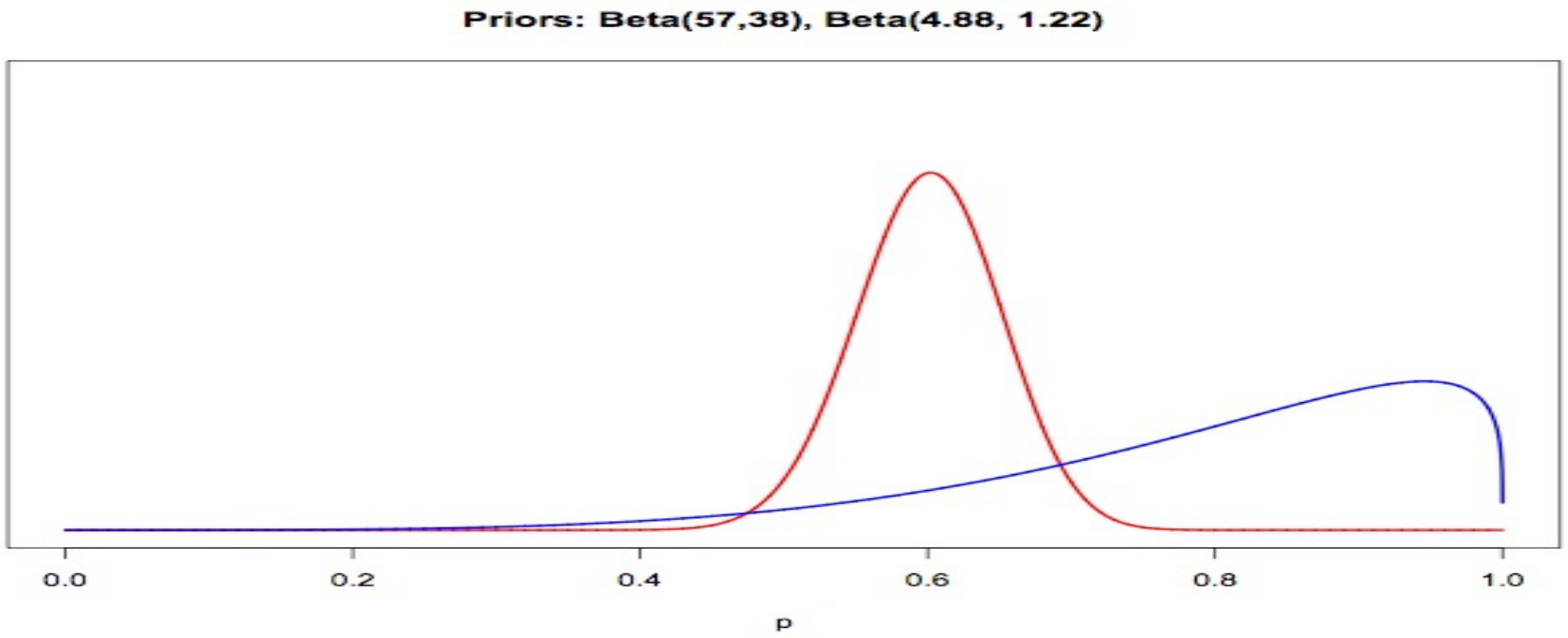


```
alpha.c <- 57; beta.c <- 38; alpha.t <- 4.888888; beta.t <- 1.222222
xc <- 34; nc <- 50; xt <- 41; nt <- 50
pc <- rbeta(100000, alpha.c+xc, beta.c+nc-xc)
pt <- rbeta(100000, alpha.t+xt, beta.t+nt-xt)
xc.total <- xc + rbinom(100000, 50, pc)
xt.total <- xt + rbinom(100000, 50, pt)
p.values <- rep(NA,100000)
for(i in 1:100000){
  p.values[i] <- fisher.test(matrix(c(xc.total[i], 100-xc.total[i],
                                      xt.total[i], 100-xt.total[i]),nrow=2),
                                      alternative="less")$p.value
                    }
> mean(p.values<0.025)
[1] 0.73422
```



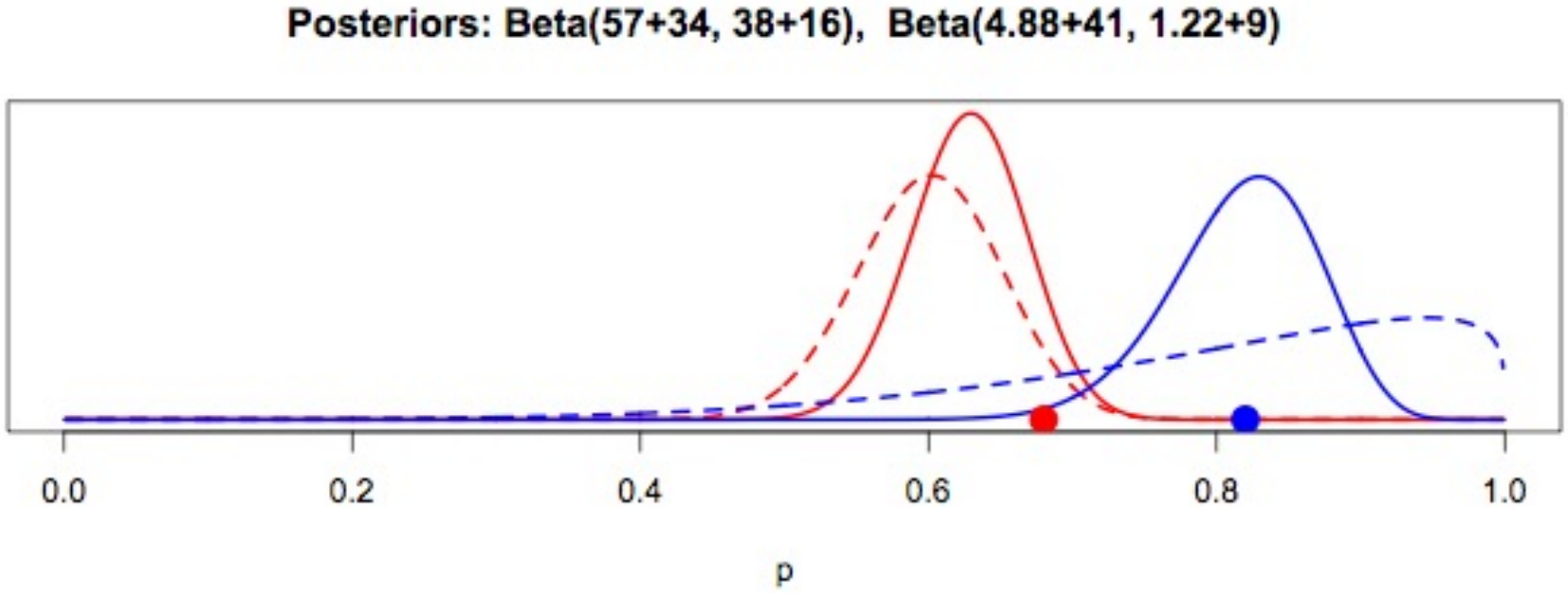
Downweight Historical Information

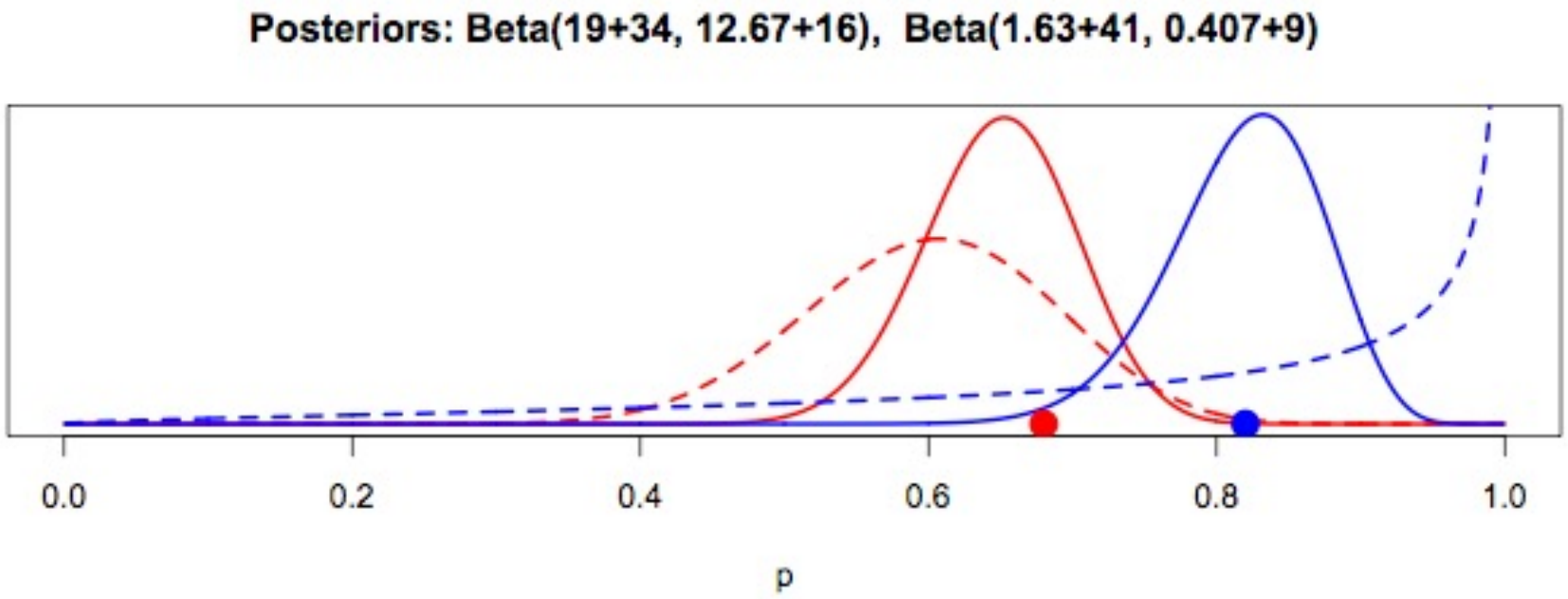
- Well known historical data, $p_c = 60\% \pm 5\%$
  - $\alpha_c = 57$, $\beta_c = 38$, 95 patients' worth of info
- Expected from pilot studies, $p_t = 80\% \pm 15\%$
  - $\alpha_t = 4.8888$, $\beta_t = 1.2222$ 6.1 pts' worth of info



Downweight Historical Information

- Well known historical data, $p_c = 60\% \pm 5\%$
  - $\alpha_c = 57$, $\beta_c = 38$, 95 patients' worth of info
  - New data is 50/(50+95) = 34% of information
- Expected from pilot studies, $p_t = 80\% \pm 15\%$
  - $\alpha_t = 4.8888$, $\beta_t = 1.2222$, 6.1 patients' worth of info
  - New data is 50/(50+6) = 89% of information
- Downweight each prior so it includes 1/3 as much information
  - $\alpha_c = 19$, $\beta_c = 12.6667$, 31.67 patients' worth of info
  - $\alpha_t = 1.63$, $\beta_t = 0.407$, 2 patients' worth of info


Posteriors: Beta(57+34, 38+16), Beta(4.88+41, 1.22+9)
0.0
0.2
0.4
0.6
0.8
1.0
p


Posteriors: Beta(19+34, 12.67+16), Beta(1.63+41, 0.407+9)
0.0
0.2
0.4
0.6
0.8
1.0
p

Phase 3 Cancer Design

- Binary endpoint, complete response observed at 45 days post treatment
  - Consider CR vs. PFS vs. OS?
  - Primary analysis chi-square test
- Expect 20% improvement vs. control
- Use Bayesian prediction to determine sample size necessary for success in frequentist trial
  - Bayesian 'behind the curtain'

Statistical Model

- Final analysis: Chi-square test
- Interim analyses with
  - $N = N_c + N_t$ patients enrolled; $n = n_c + n_t$ complete
  - $x_c \sim \text{Binomial}(n_c, p_c)$; $p_c \sim \text{Beta}(1,1)$
  - $x_t \sim \text{Binomial}(n_t, p_t)$; $p_t \sim \text{Beta}(1,1)$
  - $N = N_c + N_t$ $N_c = n_c + n_c^*$ $N_t = n_t + n_t^*$
  - $x_c^* \sim \text{Beta-binomial}(n_c^*, 1+x_c, 1+n_c-x_c)$
  - $x_t^* \sim \text{Beta-binomial}(n_t^*, 1+x_t, 1+n_t-x_t)$

$$PP_N = \sum_{x_c^*=0}^{n_c^*} \sum_{x_t^*=0}^{n_t^*} pr\left(x_c^*\right) pr\left(x_t^*\right) I\left\{\chi^2_{p-value}\left(x_c + x_c^*, N_c, x_t + x_t^*, N_t\right) < 0.05\right\}$$

Design Questions

- What should sample size range be?
  - Most sponsor can do is 300 patients
    - Step 1, calculate power of fixed 300 patient trial

```
> bpower(n1=150, n2=150, p1=0.6, p2=0.8)
  Power
  0.969
```

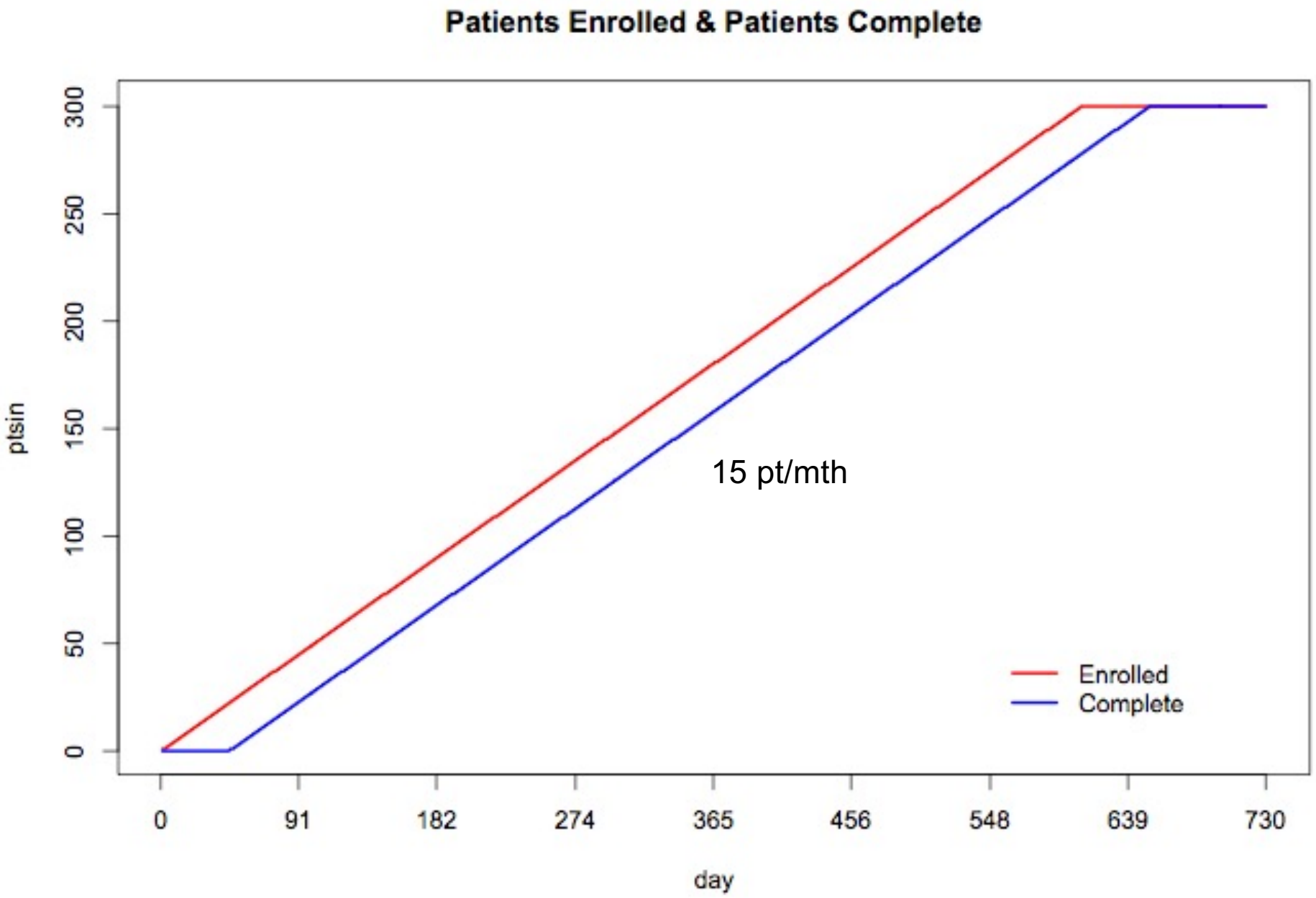
  - Best case want to go to FDA with ≥150 patients
  - We'll see if 300 is enough, if not we'll go back to the company with evidence they need to up the cap

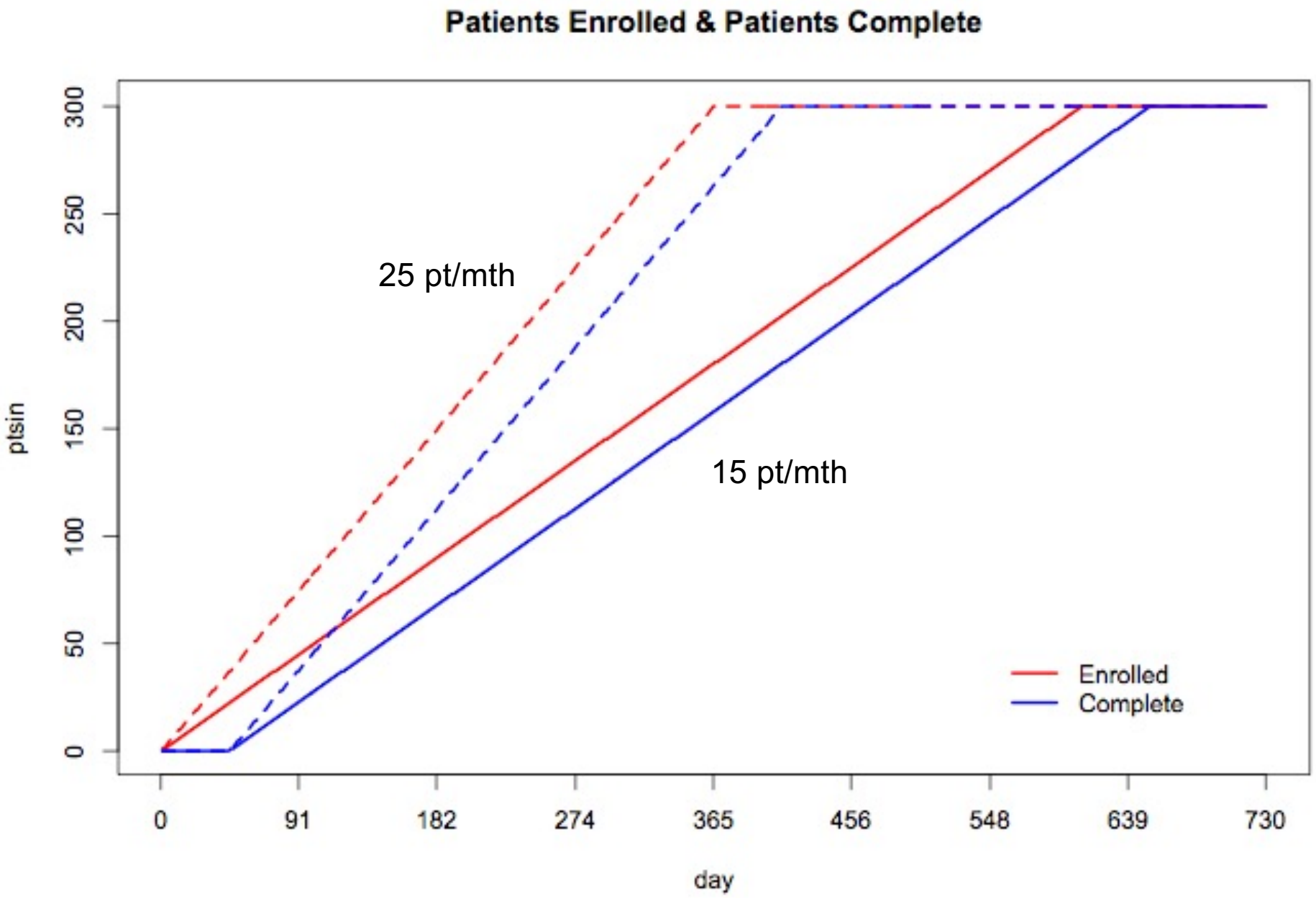
```
> bpower(n1=150, n2=150, p1=0.6, p2=0.75)
  Power
  0.795
```

Smallest win: 60% (80/150) vs. 72% (108/150) → p=0.03

Design Questions

- Can we use an adaptive design?
  - Expect 15-25 patients per month
  - "Fast" outcome at 45 days
  - 22-37 outstanding patients at any analysis
  - If we do first look @ 150 patients enrolled
    - 128 with complete data with 15 pt/month accrual
    - 113 with complete data with 25 pt/month accrual
  - Usually accrual ramps up, assume constant here
  - Don't want to interfere with accrual
    - Don't pause accrual at each interim analysis
    - Decide whether to stop accrual while accruing


Patients Enrolled & Patients Complete
ptsin
0
50
100
150
200
250
300
0
91
182
274
365
456
548
639
730
day
15 pt/mth
Enrolled
Complete


Patients Enrolled & Patients Complete
25 pt/mth
15 pt/mth
Enrolled
Complete
ptsin
0
50
100
150
200
250
300
0
91
182
274
365
456
548
639
730
day

Design Questions

- How often to do interim looks?
  - Every 25 patients is every 1-1⅔ months
  - Manageable, may be CRO fee for every look

Design Questions

- How to decide when to stop accrual for predicted success?

Design Questions

- How to decide when to stop accrual for predicted success?
  - Use predictive probabilities
  - At each interim analysis ask

    "If we stop enrolling & wait for all outstanding patients to reach their 45-day outcomes, what is the probability we 'win'?"
  - If high, stop, wait, & analyze

    How high?

    I never want to stop then lose! (and so far haven't)

Design Questions

- How to decide when to stop accrual for futility (if at all)?

Design Questions

- How to decide when to stop accrual for futility (if at all)?
  - Use predictive probabilities
  - At each analysis ask

    "If we enrolling to the 300-patient maximum then wait for all patients to reach their 45-day outcomes, what is the probability we 'win'?"
  - If low, stop for futility?

    How low?

    More aggressive, more likely to stop a good trial

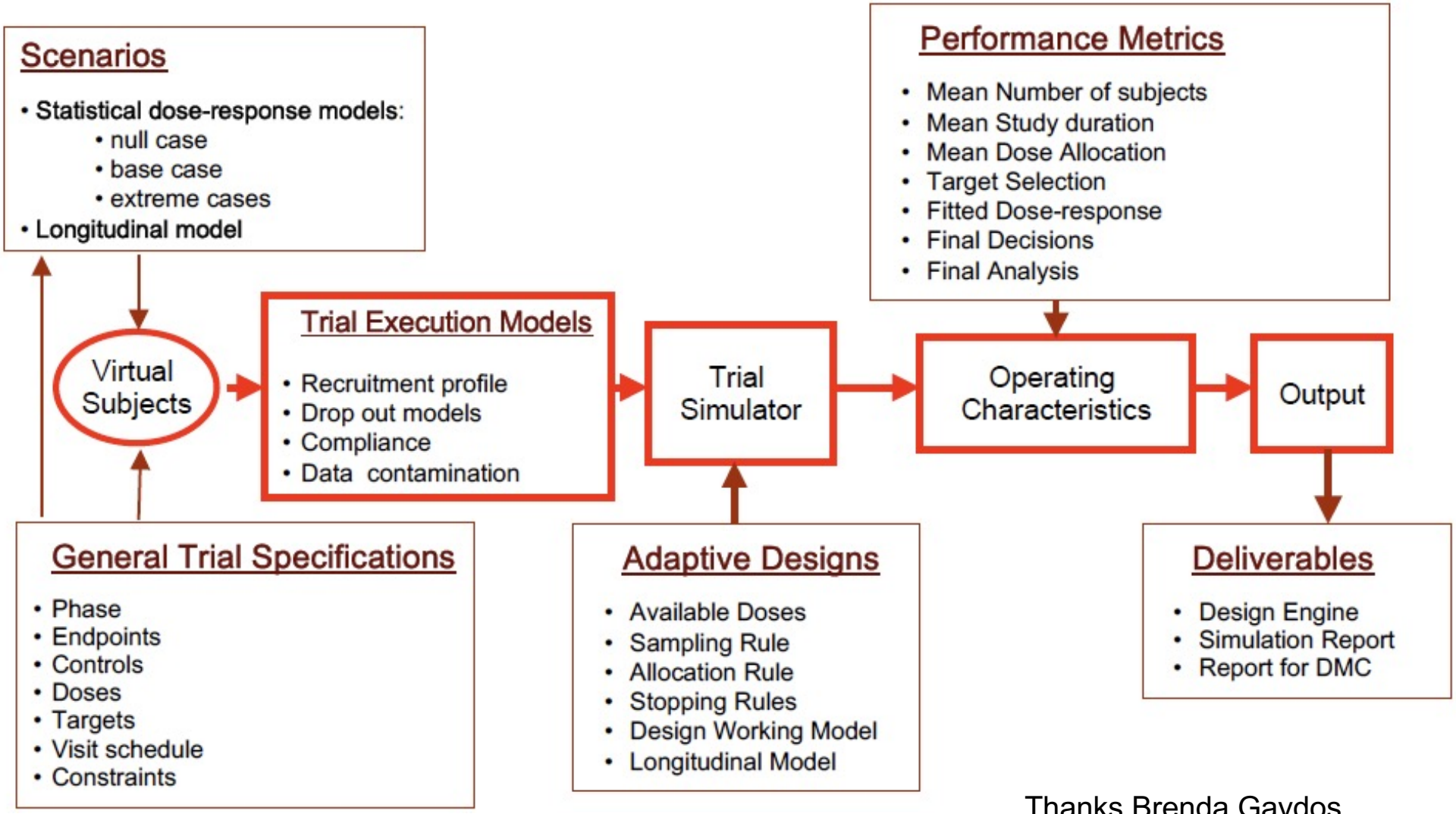
Design Questions

- What priors to use for predictive probabilities Beta dists?
  - Pretty new, let's be conservative with Beta(1,1) for treatment & control
  - Could use historical (or downweighted historical) priors here Incentive to have an 'honest' prior
  - Don't use prior in final analysis, frequentist test
- Stop for predicted success if $PP_N > S_N = 0.90$
- Stop for futility if $PP_{Nmax} < F_N = 0.10$

Sketch of my simulation code

- Define when to analyze, priors, cap, accrual rate, alpha level, efficacy
  - Factors I'll change a lot during discussions with sponsor
- Subroutine for patient accrual & randomization
- Subroutine to generate patient response & dropout
- Subroutine for interim analysis
  - Factors in time of analysis, which patients enrolled, which pts have outcomes
  - Outputs predictive probability of success with current *N* and at maximum *Nmax*
- Subroutine for decision
  - Stop for predicted success, stop for cap, stop for futility, keep going
- Final analysis at *n* where trial stopped
- Track trial size, win or lose, reason for stopping, number of looks, trial duration

Simulation Plan



Thanks Brenda Gaydos

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9000 0.1000

	Mean	SD
Sample Size	179.60	45.10

	Lose	Win
Success	0.008	0.897
Cap	0.012	0.048
Futility	0.035	0.000
Total	0.055	0.945

Look	Lose	Win	Total
150	0.020	0.565	0.585
175	0.005	0.118	0.123
200	0.002	0.091	0.093
225	0.004	0.069	0.073
250	0.006	0.028	0.034
275	0.006	0.026	0.032
300	0.012	0.048	0.060
Tot	0.055	0.945	1.000

```
Control Rate=     0.6000
 Exper Rate =     0.8000

Accrual Rate (pts/month):   15.00
        Number of Sims        1000
    Minimum Sample Size        150
    Maximum Sample Size        300
                     CV     0.0250
           Cuts   0.9000    0.1000

                    Mean        SD
    Sample Size   179.60     45.10

                   Lose       Win
   Success        0.008     0.897
       Cap        0.012     0.048
  Futility        0.035     0.000
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 275     0.006     0.026     0.032
 300     0.012     0.048     0.060
 Tot     0.055     0.945     1.000
```

Fixed trial of 300 provided 96.9% power

This design provides 94.5% power with average sample size just 180 patients

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9000 0.1000

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Tot	0.055	0.945	1.000

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9000 0.0000

	Mean	SD
Sample Size	182.65	49.86

	Lose	Win
Success	0.013	0.894
Cap	0.026	0.067
Futility	0.000	0.000
Total	0.039	0.961

Look	Lose	Win	Total
150	0.011	0.586	0.597
175	0.000	0.097	0.097
200	0.001	0.082	0.083
225	0.000	0.071	0.071
250	0.001	0.022	0.023
275	0.000	0.036	0.036
300	0.026	0.067	0.093
Tot	0.039	0.961	1.000

Stopping Boundaries, S_n, F_n

- Need not be constant
- We stopped for predicted success but lost at the first interim analysis in 1.1% of trials
  - I never want this to happen if I can avoid it!
- Let S_n be the success stopping bound
- Let F_n be the futility stopping bound
- Current $S_n = 0.9$ & $F_n = 0.1$ for all n
- Could choose $S_n = 0.99$ for small n

  & $S_n = 0.9$ for higher n

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9000 0.0000

	Mean	SD
Sample Size	182.65	49.86

	Lose	Win
Success	0.013	0.894
Cap	0.026	0.067
Futility	0.000	0.000
Total	0.039	0.961

Look	Lose	Win	Total
150	0.011	0.586	0.597
175	0.000	0.097	0.097
200	0.001	0.082	0.083
225	0.000	0.071	0.071
250	0.001	0.022	0.023
275	0.000	0.036	0.036
300	0.026	0.067	0.093
Tot	0.039	0.961	1.000

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.0000

	Mean	SD
Sample Size	186.47	53.61

	Lose	Win
Success	0.001	0.905
Cap	0.032	0.062
Futility	0.000	0.000
Total	0.033	0.967

Look	Lose	Win	Total
150	0.000	0.520	0.520
175	0.001	0.135	0.136
200	0.000	0.110	0.110
225	0.000	0.054	0.054
250	0.000	0.053	0.053
275	0.000	0.033	0.033
300	0.032	0.062	0.094
Tot	0.033	0.967	1.000

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.0000

	Mean	SD
Sample Size	186.47	53.61

	Lose	Win
Success	0.001	0.905
Cap	0.032	0.062
Futility	0.000	0.000
Total	0.033	0.967

Look	Lose	Win	Total
150	0.000	0.520	0.520
175	0.001	0.135	0.136
200	0.000	0.110	0.110
225	0.000	0.054	0.054
250	0.000	0.053	0.053
275	0.000	0.033	0.033
300	0.032	0.062	0.094
Tot	0.033	0.967	1.000

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.0500

	Mean	SD
Sample Size	183.82	46.57

	Lose	Win
Success	0.001	0.915
Cap	0.014	0.048
Futility	0.022	0.000
Total	0.037	0.963

Look	Lose	Win	Total
150	0.012	0.513	0.525
175	0.003	0.139	0.142
200	0.004	0.108	0.112
225	0.001	0.061	0.062
250	0.000	0.056	0.056
275	0.003	0.038	0.042
300	0.014	0.048	0.063
Tot	0.037	0.963	1.000

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.0500

	Mean	SD
Sample Size	183.82	46.57

	Lose	Win
Success	0.001	0.915
Cap	0.014	0.048
Futility	0.022	0.000
Total	0.037	0.963

Look	Lose	Win	Total
150	0.012	0.513	0.525
175	0.003	0.139	0.142
200	0.004	0.108	0.112
225	0.001	0.061	0.062
250	0.000	0.056	0.056
275	0.003	0.038	0.042
300	0.014	0.048	0.063
Tot	0.037	0.963	1.000

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.1000

	Mean	SD
Sample Size	183.20	48.53

	Lose	Win
Success	0.001	0.892
Cap	0.015	0.065
Futility	0.027	0.000
Total	0.043	0.957

Look	Lose	Win	Total
150	0.017	0.546	0.564
175	0.006	0.118	0.124
200	0.001	0.093	0.094
225	0.000	0.054	0.054
250	0.002	0.049	0.051
275	0.002	0.032	0.034
300	0.015	0.065	0.080
Tot	0.043	0.957	1.000

Control Rate= 0.6000
Exper Rate = 0.7500

Accrual Rate (pts/month): 15.00
Number of Sims 5000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.0500

	Mean	SD
Sample Size	217.45	59.78

	Lose	Win
Success	0.009	0.639
Cap	0.083	0.152
Futility	0.116	0.000
Total	0.209	0.791

Look	Lose	Win	Total
150	0.044	0.260	0.304
175	0.017	0.100	0.117
200	0.012	0.086	0.098
225	0.016	0.068	0.084
250	0.018	0.067	0.085
275	0.019	0.057	0.076
300	0.083	0.152	0.235
Tot	0.209	0.791	1.000

Control Rate= 0.6000
Exper Rate = 0.7500

Accrual Rate (pts/month): 15.00
Number of Sims 5000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.1000

	Mean	SD
Sample Size	211.28	57.80

	Lose	Win
Success	0.008	0.654
Cap	0.063	0.128
Futility	0.148	0.000
Total	0.219	0.781

Look	Lose	Win	Total
150	0.064	0.263	0.327
175	0.024	0.105	0.129
200	0.020	0.088	0.108
225	0.016	0.072	0.088
250	0.017	0.073	0.090
275	0.015	0.053	0.068
300	0.063	0.128	0.191
Tot	0.219	0.781	1.000

Control Rate= 0.6000
Exper Rate = 0.6000

Accrual Rate (pts/month): 15.00
Number of Sims 5000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.0500

	Mean	SD
Sample Size	187.32	49.97

	Lose	Win
Success	0.002	0.020
Cap	0.066	0.012
Futility	0.900	0.000
Total	0.968	0.032

Look	Lose	Win	Total
150	0.519	0.008	0.527
175	0.117	0.002	0.119
200	0.079	0.002	0.081
225	0.079	0.003	0.082
250	0.062	0.002	0.064
275	0.046	0.002	0.048
300	0.066	0.012	0.078
Tot	0.968	0.032	1.000

Control Rate= 0.6000
Exper Rate = 0.6000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.1000

	Mean	SD
Sample Size	176.31	44.02

	Lose	Win
Success	0.002	0.019
Cap	0.041	0.009
Futility	0.929	0.000
Total	0.972	0.028

Look	Lose	Win	Total
150	0.634	0.006	0.640
175	0.103	0.004	0.107
200	0.073	0.003	0.076
225	0.047	0.003	0.050
250	0.042	0.002	0.044
275	0.033	0.001	0.034
300	0.041	0.009	0.050
Tot	0.972	0.028	1.000

Enough!

- Settle on
  - Success Bound = 0.95
  - Futility Bound = 0.10
- Type I error was 0.028 -- too high
  - Pivotal trial, we need this to be ≤ 0.025
  - Hard to calculate analytically
  - Need to simulate over many scenarios
  - Then convince ourselves & FDA we've explored the whole null space

Intuition Check

- Use critical value = 0.025
- Simulate with 4 accrual rates, 10k sims/scenario
- Will the Type I error rates change with accrual rate? If so how?
- How will sample sizes change?

Accrual (pts/mth)	Mean N	Type I error
5		HIGHER OR LOWER
15*	177	0.030
25		
50		

*Slightly different than previous slide because 10,000 sims each

Intuition Check

- Use critical value = 0.025
- Simulate with 4 accrual rates, 10k sims/scenario
- Will the Type I error rates change with accrual rate? If so how?
- How will sample sizes change?

Accrual (pts/mth)	Mean N	Type I error
5	172	0.039
15	177	0.030
25	182	0.028
50	195	0.027

Find Critical Value for $\alpha = 0.025$

- Assume accrual won't be slower than 15/month
- Explore range of true p_c & p_t
- Find right critical value by trial & error
  - 10,000 sims each using 0.6 vs. 0.6
  - Sqrt(0.025*0.975/10000) = 0.0016

Critv	0.40	0.50	0.60	0.70	0.80
0.025			0.030		

Find Critical Value for $\alpha = 0.025$

- Assume accrual won't be slower than 15/month
- Explore range of true p_c & p_t
- Find right critical value by trial & error
  - 10,000 sims each using 0.4 vs. 0.4 to 0.8 vs. 0.8
  - Sqrt(0.025*0.975/10000) = 0.0016

Critv	0.40	0.50	0.60	0.70	0.80
0.025			0.030		
0.020	0.024	0.026	0.026	0.024	0.025

Find Critical Value for $\alpha = 0.025$

- Assume accrual won't be slower than 15/month
- Explore range of true p_c & p_t
- Find right critical value by trial & error
  - 10,000 sims each using 0.4 vs. 0.4 to 0.8 vs. 0.8
  - Sqrt(0.025*0.975/10000) = 0.0016

Critv	0.40	0.50	0.60	0.70	0.80
0.025			0.030		
0.020	0.024	0.026	0.026	0.024	0.025
0.018	0.024	0.021	0.023	0.023	0.020

Find Critical Value for $\alpha = 0.025$

- Assume accrual won't be slower than 15/month
- Explore range of true p_c & p_t
- Find right critical value by trial & error
  - 10,000 sims each using 0.4 vs. 0.4 to 0.8 vs. 0.8
  - Sqrt(0.025*0.975/10000) = 0.0016

Critv	0.40	0.50	0.60	0.70	0.80
0.025			0.030		
0.020	0.024	0.026	0.026	0.024	0.025
0.018	0.024	0.021	0.024	0.023	0.020
0.019	0.022	0.026	0.024	0.024	0.024

Let's go with 0.018

If a real trial I'd run 100,000 or 1M sims and try to get as much power as possible

Example Trial #1

```
Simulation #  14        Analysis #  150
 Group           N    Obs    Suc
 Control        75     68     35      51%
 Treatment      75     68     49      72%
 P_N    =  0.9360 >  0.950 ? No,    P_Nmax =  0.9180 <  0.100 ? No
 Continue to enroll
```

Example Trial #1

```
Simulation #  14        Analysis #  150
 Group           N    Obs    Suc
 Control        75     68     35     51%
 Treatment      75     68     49     72%
 P_N    =  0.9360 >  0.950 ? No,   P_Nmax =  0.9180 <  0.100 ? No
 Continue to enroll

Simulation #  14        Analysis #  175
 Group           N    Obs    Suc
 Control        88     73     39     53%
 Treatment      87     72     53     74%
 P_N    =  0.9370 >  0.950 ? No,   P_Nmax =  0.9360 <  0.100 ? No
 Continue to enroll
```

Example Trial #1

```
Simulation #  14        Analysis #  150
 Group           N    Obs    Suc
 Control        75     68     35     51%
 Treatment      75     68     49     72%
 P_N    =  0.9360 >  0.950 ? No,   P_Nmax =  0.9180 <  0.100 ? No
 Continue to enroll

Simulation #  14        Analysis #  175
 Group           N    Obs    Suc
 Control        88     73     39     53%
 Treatment      87     72     53     74%
 P_N    =  0.9370 >  0.950 ? No,   P_Nmax =  0.9360 <  0.100 ? No
 Continue to enroll

Simulation #  14        Analysis #  200
 Group           N    Obs    Suc
 Control       100     91     48     53%
 Treatment     100     90     68     76%
 P_N    =  >.9999 >  0.950 ? YES,  P_Nmax =  0.9900 <  0.100 ? No
 Stop for predicted success
```

Example Trial #1

```
Simulation #  14        Analysis #  150
 Group           N    Obs    Suc
 Control        75     68     35     51%
 Treatment      75     68     49     72%
 P_N    =  0.9360 >  0.950 ? No,   P_Nmax =  0.9180 <  0.100 ? No
 Continue to enroll

Simulation #  14        Analysis #  175
 Group           N    Obs    Suc
 Control        88     73     39     53%
 Treatment      87     72     53     74%
 P_N    =  0.9370 >  0.950 ? No,   P_Nmax =  0.9360 <  0.100 ? No
 Continue to enroll

Simulation #  14        Analysis #  200
 Group           N    Obs    Suc
 Control       100     91     48     53%
 Treatment     100     90     68     76%
 P_N    =  >.9999 >  0.950 ? YES,  P_Nmax =  0.9900 <  0.100 ? No
 Stop for predicted success

Simulation #  14    Final Analysis  200
     Group       N    Obs    Suc
 Control       100    100     52     52%
 Treatment     100    100     76     76%
 Successful trial,   p-value = 0.001 < 0.0180
```

Example Trial #2

```
Simulation #  10        Analysis #  150
 Group           N    Obs    Suc
 Control        75     66     40      61%  (need to see +20
 Treatment      75     65     44      68%   successes for win @
   150)
 P_n    =  0.0000 >  0.950 ? No,    P_Nmax =  0.2590 <  0.100 ? No
 Continue to enroll

Simulation #  10        Analysis #  175
 Group           N    Obs    Suc
 Control        88     80     47      59%
 Treatment      87     79     51      65%
 P_n    =  0.0000 >  0.950 ? No,    P_Nmax =  0.1020 <  0.100 ? No
 Continue to enroll

Simulation #  10        Analysis #  200
 Group           N    Obs    Suc
 Control       100     90     55      61%  (need to see +18
 Treatment     100     89     57      64%   successes for win @
   300)
 P_n    =  0.0000 >  0.950 ? No,    P_Nmax =  0.0360 <  0.100 ? YES
 Stop for futility
 Unsuccessful trial
```

Final Operating Characteristics

$$S_n = 0.95, F_n = 0.10$$

p_c	p_t	Mean N	Futility	Max & Win	PredSuc & Win	Power
0.60	0.60	175	0.937	0.046 0.009	0.016 0.015	0.024
0.60	0.65	199	0.775	0.145 0.041	0.081 0.075	0.117
0.60	0.70	220	0.478	0.247 0.114	0.275 0.267	0.381
0.60	0.75	216	0.195	0.216 0.143	0.590 0.580	0.723
0.60	0.80	189	0.039	0.088 0.073	0.873 0.868	0.942

Final Operating Characteristics

$S_n = 0.95, F_n = 0.05$

p_c	p_t	Mean N	Futility	Max & Win	PredSuc & Win	Power
0.60	0.60	185	0.913	0.071 0.009	0.017 0.015	0.025
0.60	0.65	212	0.716	0.200 0.053	0.084 0.079	0.132
0.60	0.70	231	0.407	0.314 0.131	0.280 0.271	0.401
0.60	0.75	221	0.143	0.256 0.155	0.601 0.591	0.746
0.60	0.80	190	0.025	0.095 0.074	0.880 0.876	0.950

Final Operating Characteristics vs. Fixed Frequentist Trials

p_c	p_t	B-A Mean N	B-A Power	F-Power 300	F-Power BA Mean
0.60	0.60	175 185	0.024 0.025	0.025	0.025
0.60	0.65	199 212	0.12 0.13	0.14	0.11
0.60	0.70	220 231	0.38 0.40	0.44	0.34
0.60	0.75	216 221	0.72 0.75	0.79	0.66
0.60	0.80	189 190	0.94 0.95	0.969	0.86

Digression

Imagine

- Imagine investigators do a case-control study
- Identify cases
  - Patients with hypertension
- Identify controls
  - People without hypertension with the same demographics (age, gender, marital status)
- See statistically significant increase in blood pressure between cases & controls
- Would JAMA publish this paper?

- They did: Bassler et al, March 23/31, 2010, V303, No12, 1180-1187.

Stopping Randomized Trials Early for Benefit and Estimation of Treatment Effects

Systematic Review and Meta-regression Analysis

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Victor M. Montori, MD, MSc
Melanie Lane, BA
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and the STOPIT-2 Study Group

Context Theory and simulation suggest that randomized controlled trials (RCTs) stopped early for benefit (truncated RCTs) systematically overestimate treatment effects for the outcome that precipitated early stopping.

Objective To compare the treatment effect from truncated RCTs with that from meta-analyses of RCTs addressing the same question but not stopped early (nontruncated RCTs) and to explore factors associated with overestimates of effect.

Data Sources Search of MEDLINE, EMBASE, Current Contents, and full-text journal content databases to identify truncated RCTs up to January 2007; search of MEDLINE, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects to identify systematic reviews from which individual RCTs were extracted up to January 2008.

Study Selection Selected studies were RCTs reported as having stopped early for benefit and matching nontruncated RCTs from systematic reviews. Independent reviewers with medical content expertise, working blinded to trial results, judged the eligibility of the nontruncated RCTs based on their similarity to the truncated RCTs.

Data Extraction Reviewers with methodological expertise conducted data extraction independently.

Results The analysis included 91 truncated RCTs asking 63 different questions and 424 matching nontruncated RCTs. The pooled ratio of relative risks in truncated RCTs vs matching nontruncated RCTs was 0.71 (95% confidence interval, 0.65-0.77). This difference was independent of the presence of a statistical stopping rule and the methodological quality of the studies as assessed by allocation concealment and blinding. Large differences in treatment effect size between truncated and nontruncated RCTs (ratio of relative risks <0.75) occurred with truncated RCTs having fewer than 500 events. In 39 of the 63 questions (62%), the pooled effects of the nontruncated RCTs failed to demonstrate significant benefit.

Conclusions Truncated RCTs were associated with greater effect sizes than RCTs not stopped early. This difference was independent of the presence of statistical stopping rules and was greatest in smaller studies.

ALTHOUGH RANDOMIZED CONtrolled trials (RCTs) generally provide credible evidence of treatment effects, multiple problems may emerge when investigators terminate a trial earlier than planned,[1] especially when the decision to terminate the trial is based on the finding of an apparently beneficial treatment effect. Bias may arise because large random fluctuations of the estimated treatment effect can occur, particularly early in the progress of a trial.[2] When investigators stop a trial based on an apparently beneficial treatment effect, their

JAMA. 2010;303(12):1180-1187 www.jama.com

From Abstract Study Selection

"Selected studies were RCTs reported as having stopped early for benefit and matching nontruncated RCTs from systematic reviews. Independent reviewers with medical content expertise, working blinded to trial results, judged the eligibility of the nontruncated RCTs based on their similarity to the truncated RCTs."

From Abstract Results

- Large differences in treatment effect size between truncated and nontruncated RCTs occurred ….
- In 39 of the 63 questions (62%), the pooled effects of the nontruncated RCTs failed to demonstrate significant benefit.

```
Control Rate=     0.6000
 Exper Rate =     0.7500

Accrual Rate (pts/month):   15.00
        Number of Sims        5000
    Minimum Sample Size        150
    Maximum Sample Size        300
                    CV     0.0250
          Cuts   0.9500    0.0500

                   Mean        SD
    Sample Size  217.45     59.78

                  Lose       Win
   Success       0.009     0.639
       Cap       0.083     0.152
  Futility       0.116     0.000
     Total       0.209     0.791

Look      Lose       Win     Total
 150     0.044     0.260     0.304
 175     0.017     0.100     0.117
 200     0.012     0.086     0.098
 225     0.016     0.068     0.084
 250     0.018     0.067     0.085
 275     0.019     0.057     0.076
 300     0.083     0.152     0.235
 Tot     0.209     0.791     1.000
```

- Example 1 Revisited
- Truth is 15% benefit
- But 23.5% of time trial goes to maximum … and 8.3% it fails to be stat sig.
- The reason it goes to max is because data is ambiguous
- So of course the ones that go to max have small effects

S. Berry, Carlin, Connor

"To illustrate the issue, consider a clinical trial in which analysis is as follows: participants found to be performing better are retrospectively placed in the experimental group and participants found not to be performing well are retrospectively placed in the control group; a statistically significant difference in outcome is found when the groups are compared. It is clear that post-treatment selection of participants, based on their outcomes, would be responsible for any observed difference."

"This is logically equivalent to the analysis reported by Bassler et al."

Goodman, D. Berry, Wittes

"So comparing the truncated trials to the nontruncated trials is similar to comparing completed trials with large effects with those with lower effects. The difference the authors observed was both predictable and uninformative."

"Bias is a property of study procedures; it is not logically applicable to a subset of results."

Goodman SN. Systematic reviews are not biased by results from trials stopped early for benefit. *J Clin Epidemiol.* 2008;61(1):95-96.

$p_t = 0.8$ vs. $p_c = 0.6$

n=180 → 80% Power

- What is average effect size in the statistically significant trials?

$p_t = 0.8$ vs. $p_c = 0.6$

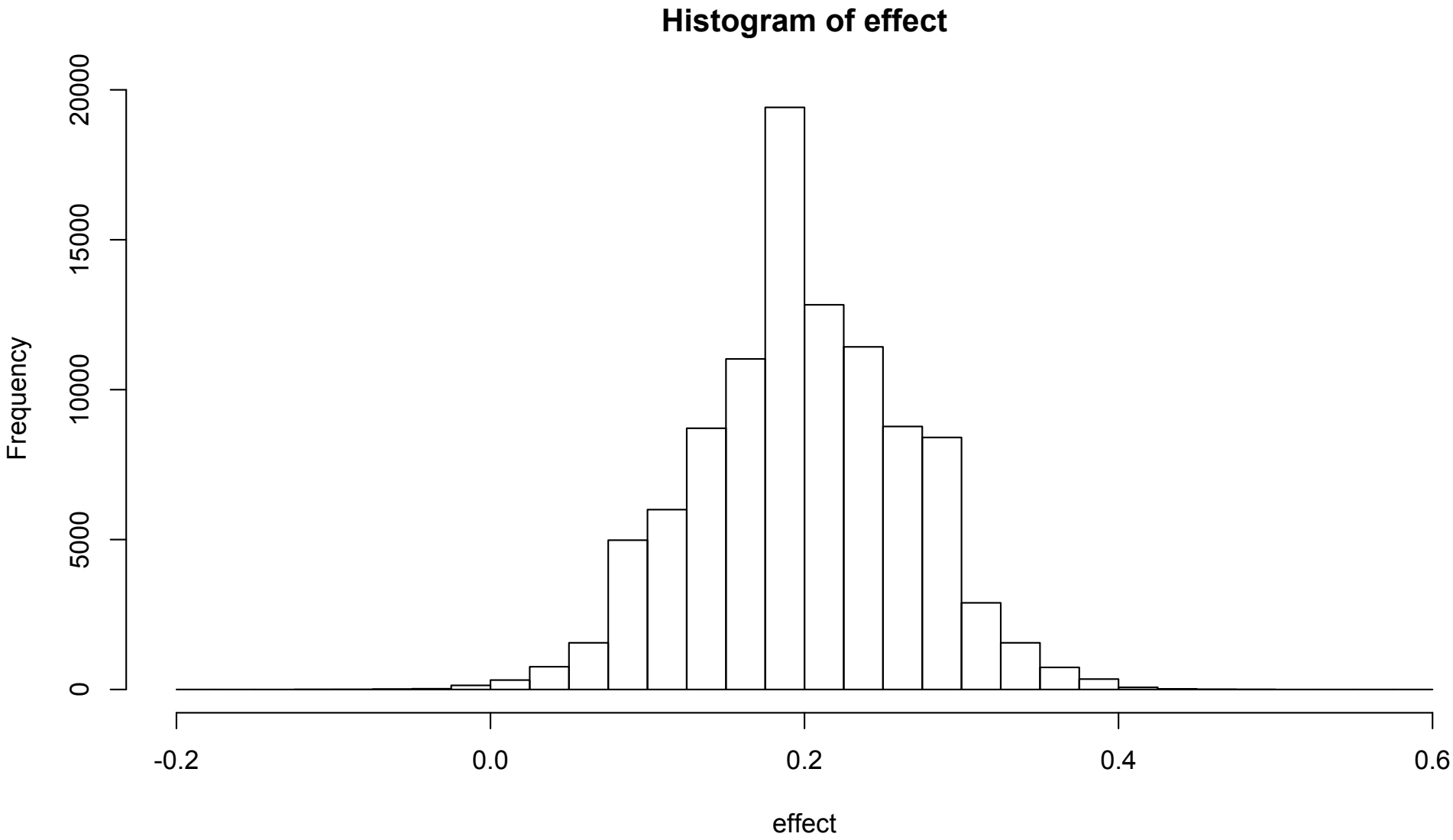
n=180 → 80% Power

- What is average effect size in the statistically significant trials?
- What is the average effect size in 100,000 simulated trials?

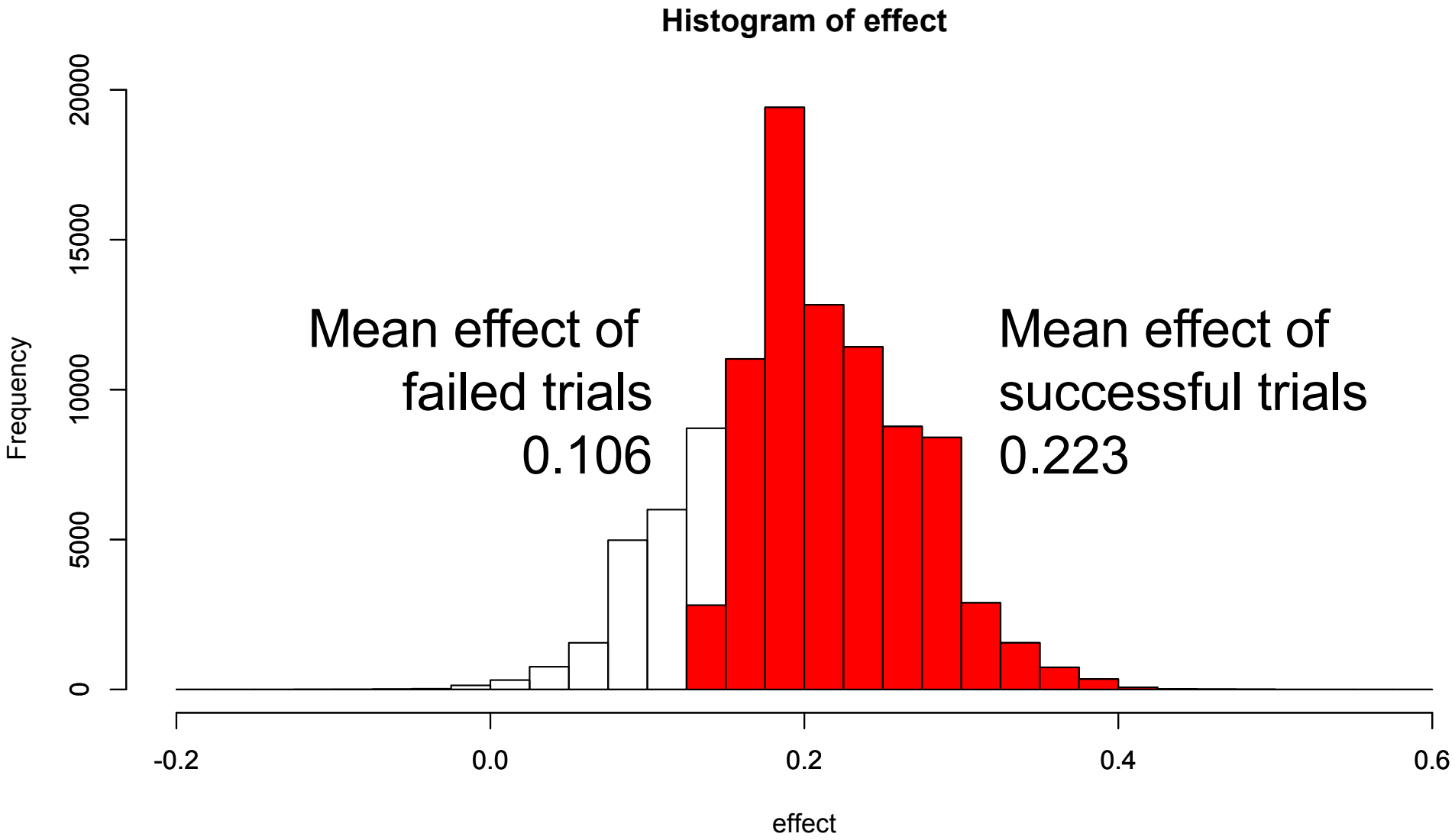
```
pvalue <- NULL; effect <- NULL

for(i in 1:100000){
x.c <- rbinom(1, 90, 0.6)
x.t <- rbinom(1, 90, 0.8)
mat <- rbind(c(x.c, 90-x.c), c(x.t, 90-x.t))
test <- chisq.test(mat)
pvalue[i] <- test$p.value
effect[i] <- x.t/90 - x.c/90
print(i)
}

hist(effect, breaks=seq(-.2, .6, by=0.025))
par(new=T)
hist(effect[pvalue<0.05], breaks=seq(-.2, .6, by=0.025), col=2, main=" ", xlab="
", ylab= " " )

> mean(pvalue < 0.05)     ### CHECK power = 80%
[1] 0.80313
> mean(effect)            ### CHECK mean effect = 0.20
[1] 0.2003593
>
> mean(effect[pvalue < 0.05])
[1] 0.2233924
> mean(effect[pvalue >= 0.05])
[1] 0.1063962
>
> 0.80 * .2233924 + 0.20 * 0.1063962
[1] 0.1999932
```

```
count <- 0
outcome <- matrix(nrow=8281, ncol=5)
for(xc in 0:90){
  for(xt in 0:90){
  count <- count + 1
  prob.of.pair <- dbinom(xc, 90, 0.6) * dbinom(xt, 90, 0.8)

  mat <- rbind(c(xc, 90-xc), c(xt, 90-xt))
  test <- chisq.test(mat)
  effect <- xt/90 - xc/90

  outcome[count, ] <- c(xc, xt, prob.of.pair, test$p.value, effect)
  print(c(xc, xt))
}}

outcome <- data.frame(outcome)
names(outcome) <- c("xc","xt","pr","pvalue","effect")

> sum(outcome$pr[outcome$pvalue < 0.05])
[1] 0.80168

> sum((outcome$effect * outcome$pr) [outcome$pvalue < 0.05]) /
sum(outcome$pr[outcome$pvalue<0.05])
[1] 0.2231661

> sum((outcome$effect * outcome$pr) [outcome$pvalue > 0.05]) /
sum(outcome$pr[outcome$pvalue>0.05])
[1] 0.1063544
```

100k sims 0.8 vs. 0.6, n=180



100k sims 0.8 vs. 0.6, n=180



Revisit Example #1

- Binary outcome
- Adaptive trial from 150 to 300 patients
- Expected difference 60% vs. 80%

Control Rate= 0.6000
Exper Rate = 0.8000

Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.1000

	Mean	SD
Sample Size	183.20	48.53

	Lose	Win
Success	0.001	0.892
Cap	0.015	0.065
Futility	0.027	0.000
Total	0.043	0.957

Look	Lose	Win	Total
150	0.017	0.546	0.564
175	0.006	0.118	0.124
200	0.001	0.093	0.094
225	0.000	0.054	0.054
250	0.002	0.049	0.051
275	0.002	0.032	0.034
300	0.015	0.065	0.080
Tot	0.043	0.957	1.000

Control Rate= 0.6000
Exper Rate = 0.6000

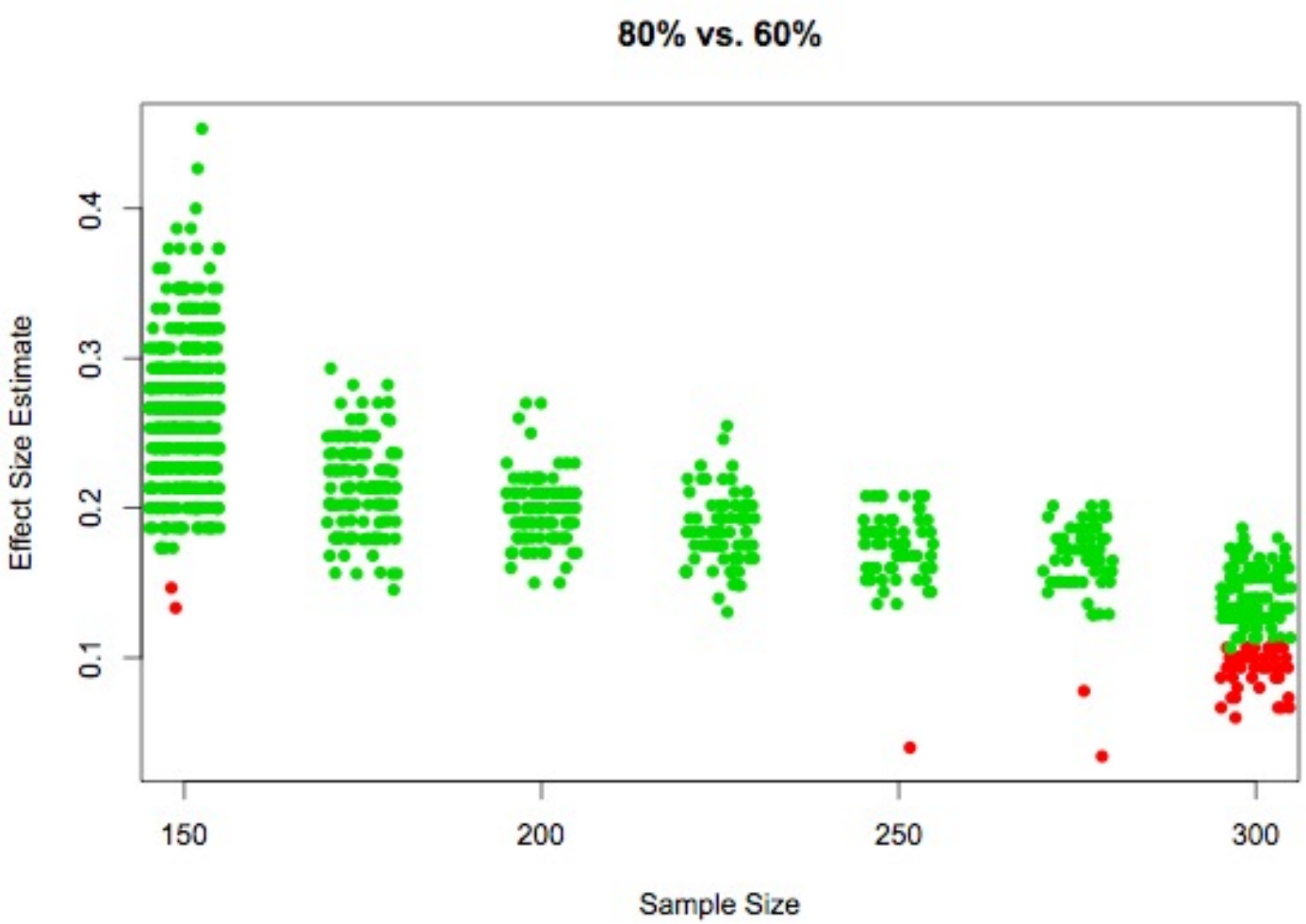
Accrual Rate (pts/month): 15.00
Number of Sims 1000
Minimum Sample Size 150
Maximum Sample Size 300
CV 0.0250
Cuts 0.9500 0.1000

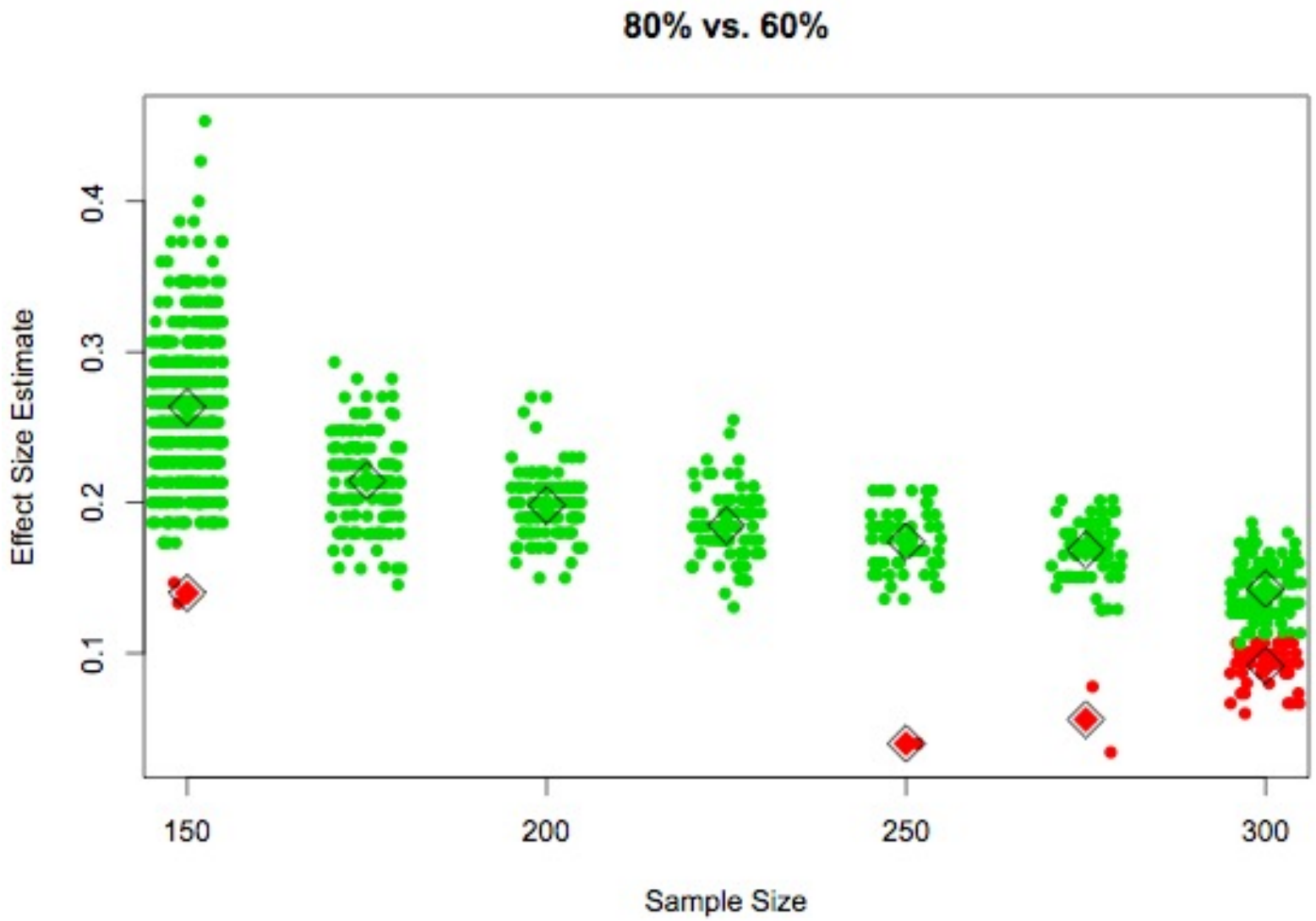
	Mean	SD
Sample Size	176.31	44.02

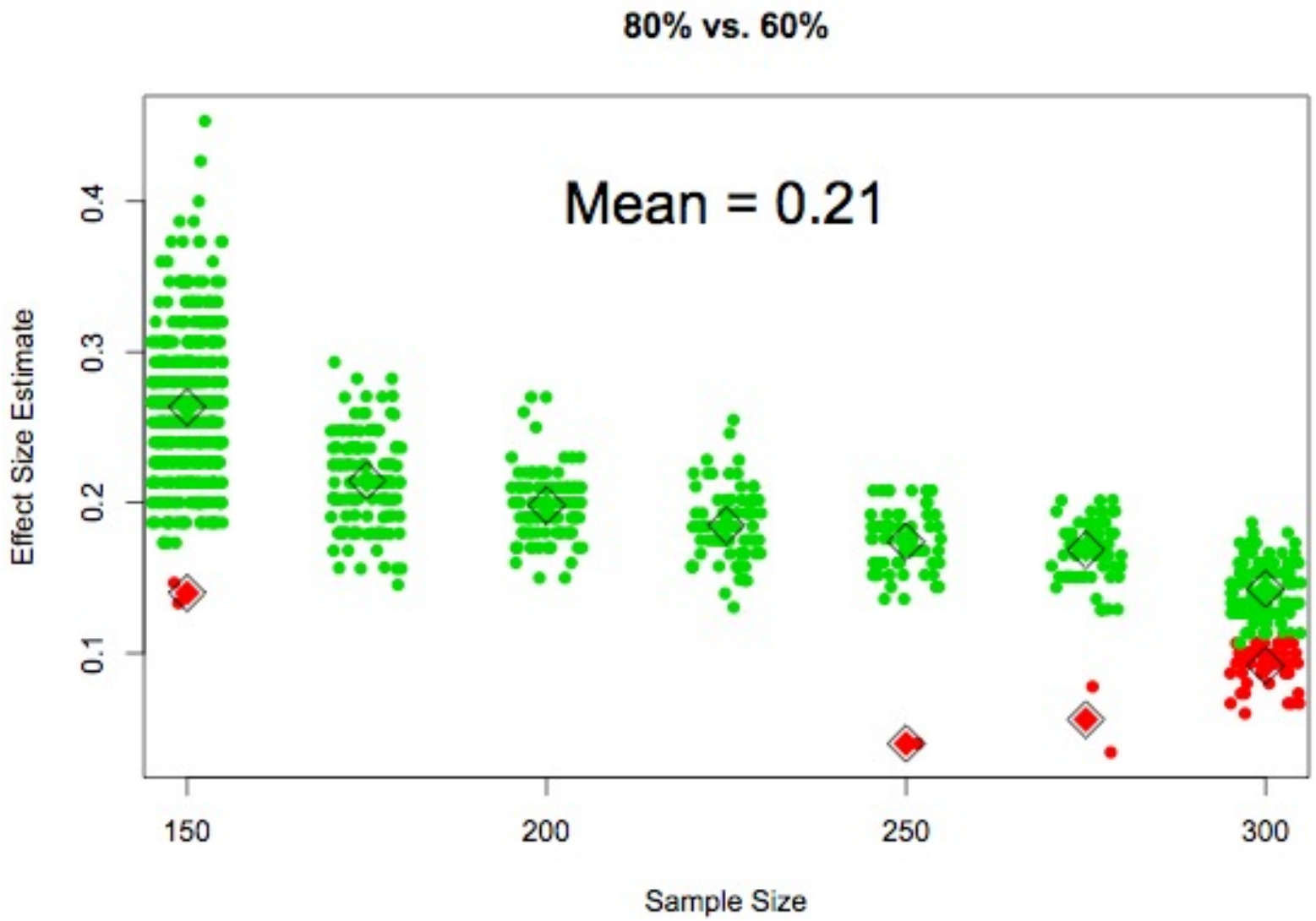
	Lose	Win
Success	0.002	0.019
Cap	0.041	0.009
Futility	0.929	0.000
Total	0.972	0.028

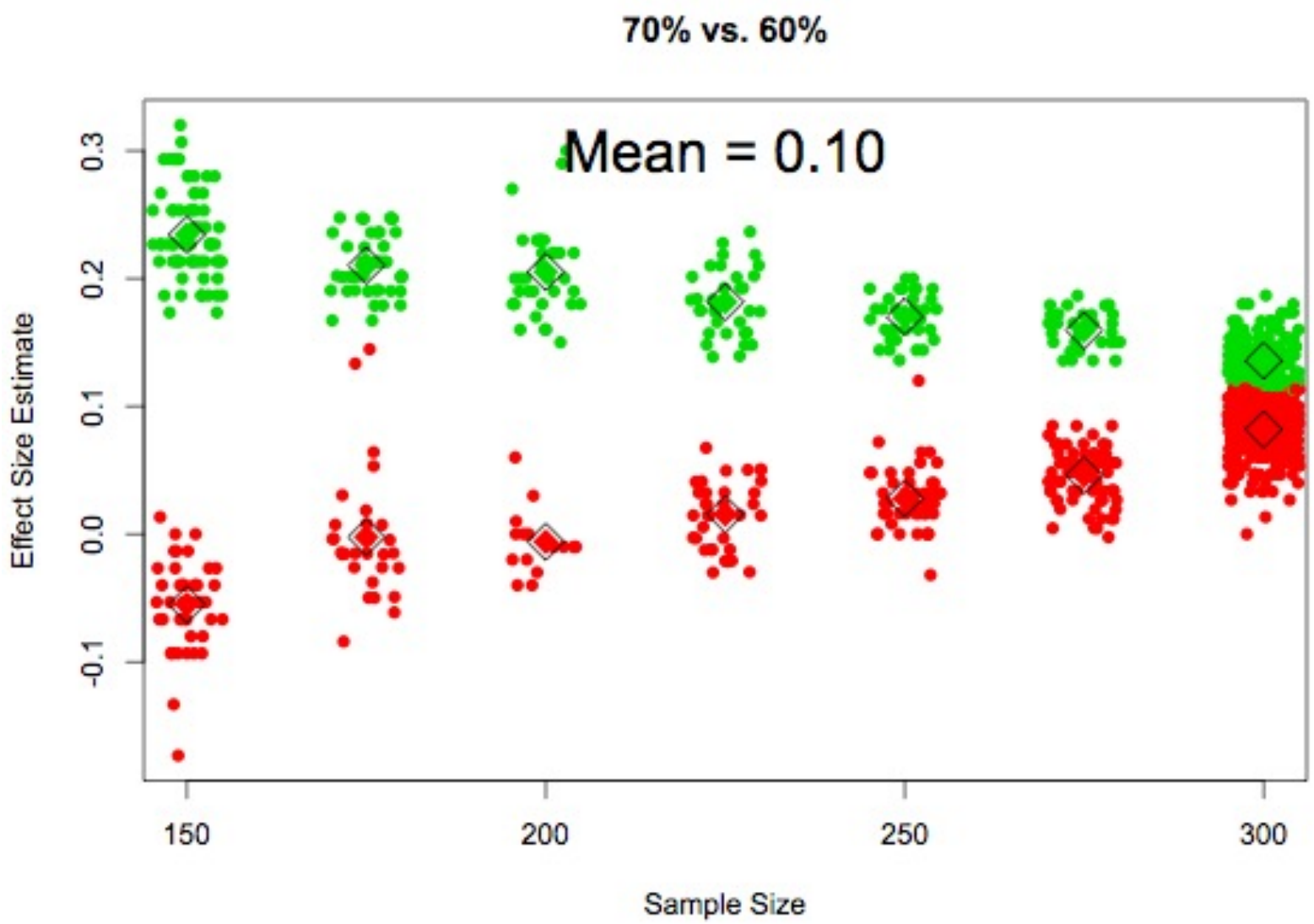
Look	Lose	Win	Total
150	0.634	0.006	0.640
175	0.103	0.004	0.107
200	0.073	0.003	0.076
225	0.047	0.003	0.050
250	0.042	0.002	0.044
275	0.033	0.001	0.034
300	0.041	0.009	0.050
Tot	0.972	0.028	1.000

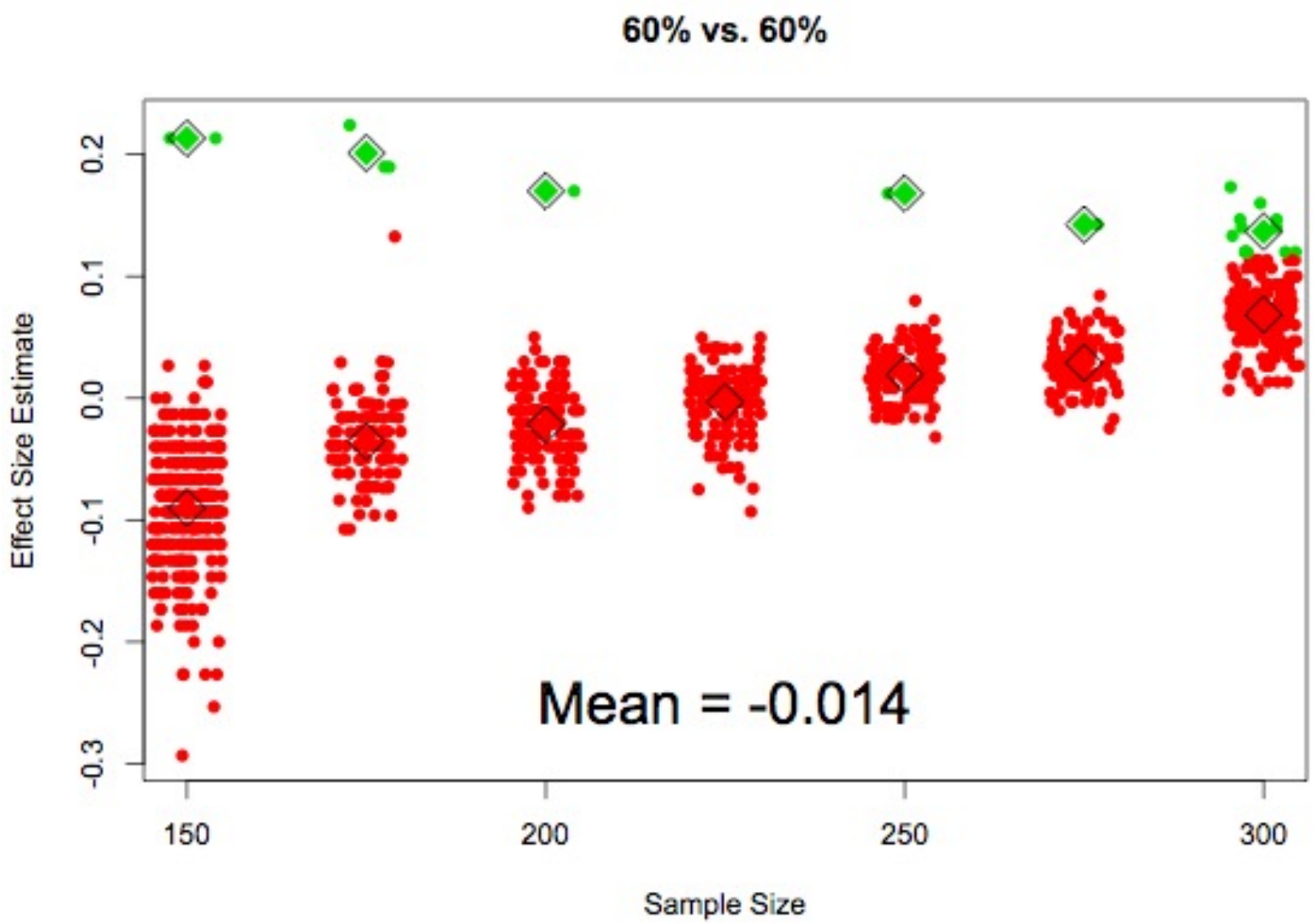
Example 1


80% vs. 60%
Effect Size Estimate
0.1
0.2
0.3
0.4
150
200
250
300
Sample Size


80% vs. 60%
Effect Size Estimate
0.1
0.2
0.3
0.4
150
200
250
300
Sample Size


80% vs. 60%
Mean = 0.21
Effect Size Estimate
0.1
0.2
0.3
0.4
150
200
250
300
Sample Size


70% vs. 60%
Mean = 0.10
Effect Size Estimate
0.3
0.2
0.1
0.0
-0.1
150
200
250
300
Sample Size


60% vs. 60%
Effect Size Estimate
0.2
0.1
0.0
-0.1
-0.2
-0.3
Mean = -0.014
150
200
250
300
Sample Size

Summary

- A process is biased
- Individual trials are not biased
- Individual trials do vary about their true mean
- Larger trials have narrower CIs
- They stopped early because it was a random observation in the right or left tail
- Tradeoff – is it worth deciding earlier and offering benefit to those outside the trial?
- Many adaptive trials are larger so tighter CIs

Example #2: Goldilocks Trial with 2 Endpoints & Informative Prior on Longitudinal Model

Background

- Medical device to treat atrial fibrillation (AF)
- Used during open cardiac surgery
  - Only used when surgery being done for other reason
  - e.g., CABG, Valve replacement
- Label was to 'ablate cardiac tissue' not 'treat AF'
- Trial needed to produce evidence of safety and efficacy for treatment of AF
- Controlled trial not possible due to extensive use

Background

- Early safety study with matched controls failed to enroll
  - Matched control having same cardiac surgery without AF treatment component
  - Stopped @ 32 months when 39 cases & just 5 controls enrolled
- FDA suggested to company to explore Bayesian adaptive trial with safety & efficacy OPCs

Objective Performance Criteria

- Efficacy OPC (6m)
  - AF free & off AF drugs at 6 months
  - Goal: 70%, $\delta_E = 10\%$
  - Based upon published rates of this procedure
    - 10 papers had 60.1% efficacy
- Safety OPC (1m)
  - Free of significant adverse event
  - Goal: 13.95%, $\delta_S = 5\%$
  - Based upon published SAE rates in Cut & Sew MAZE

Statistical Endpoints

- Show Pr($p_E > 0.60$) > 0.975
  - 70% - δ_E = 70% - 10% = 60%
- Show Pr($p_S < 0.1895$) > 0.95
  - 13.95% + δ_S = 13.95% + 5% = 18.95%
- Achievable in 100 patients if
  - observed efficacy ≥ 70%
  - observed safety ≤ 12%
  - basically point estimates have to match or beat OPCs
- p_E, p_S ~ Beta(1,1) priors for both endpoints

Goldilocks Design

- Enroll 50 - 100 patients
  - Must have 20 patients at 6 months or skip analysis
- Interim analyses every 5 patients
- Final sample size based upon predictive probabilities
- Expect to enroll 5 patients per month

  ~30 patients enrolled without complete 6m data

Stopping Decisions

- P_n = Pr(Meet Efficacy & Safety Goals with current sample size n| Current Data)
  - If $P_n \geq S_n$ then stop <u>accrual</u> for predicted success
  - $S_n = 0.90$ for n=50-65
  - $S_n = 0.85$ for n=70-80
  - $S_n = 0.80$ for n=85-95
- P_{max} = Pr(Meet Efficacy @ Safety Goals with 100 patients | Current Data)
  - If $P_n \leq F_n$ then stop <u>trial</u> for futility
  - $F_n = 0.05$ for n=50-70
  - $F_n = 0.10$ for n=75-95

Longitudinal Model

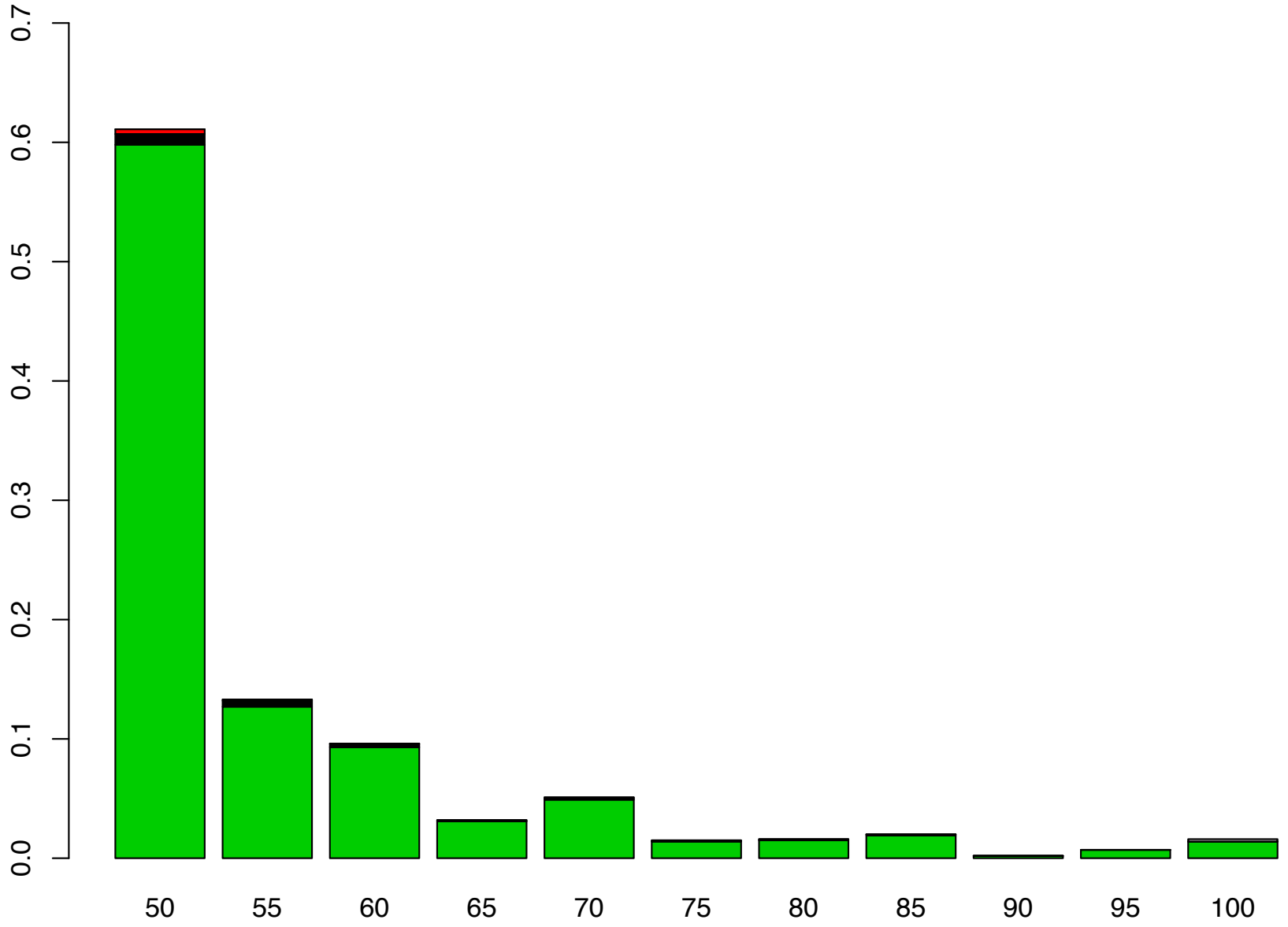
- Efficacy outcome is AF-free and off AADs at 6m
- Interim outcome at 3-months is whether patients are AF-free already
- Predict 6m outcomes using Beta-Binomial

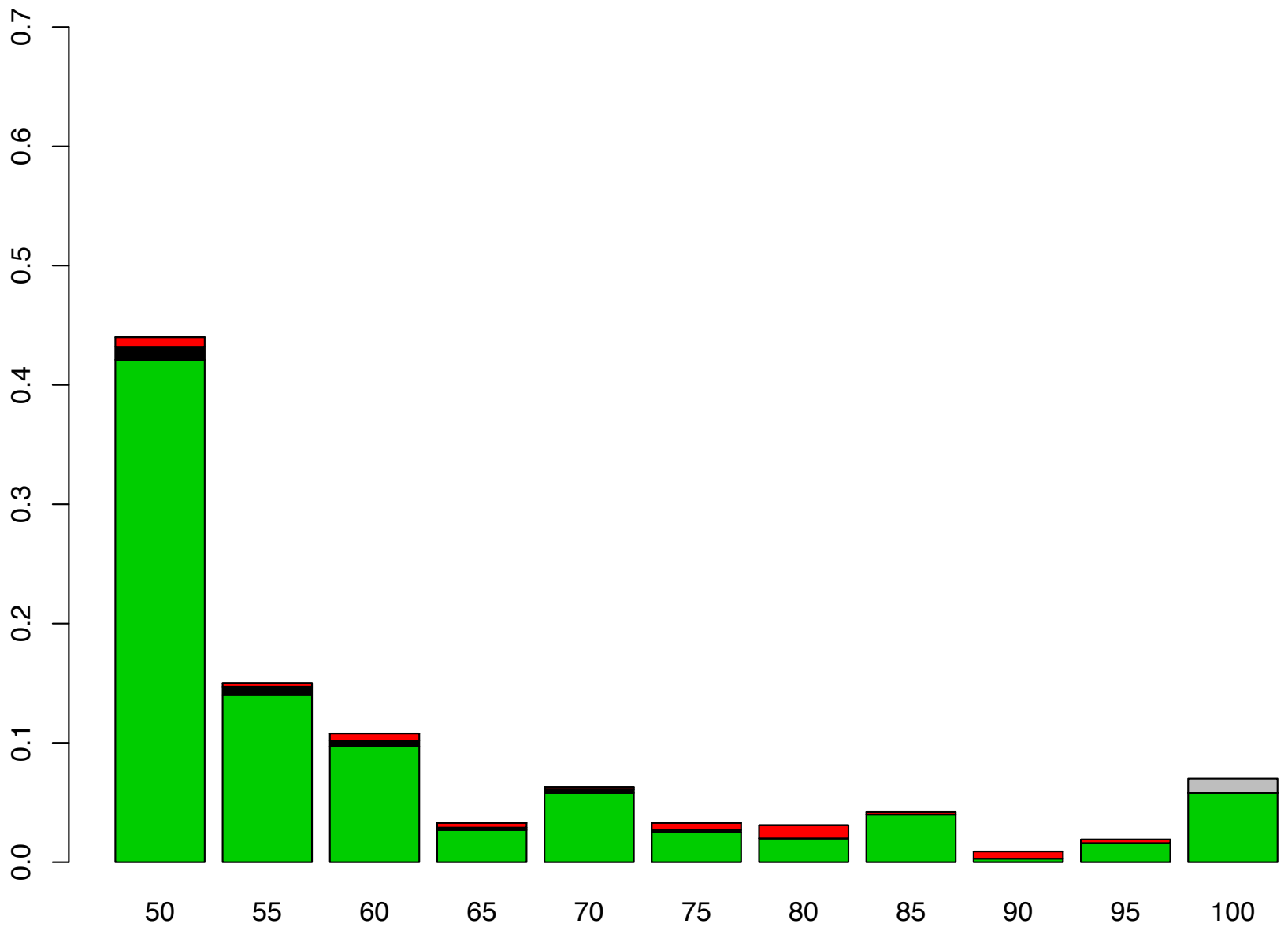
Group	α	β	Prior Mean
No 3m data	5	1	83%
In AF	4.2	1.8	70%
AF-free	5.4	0.6	90%

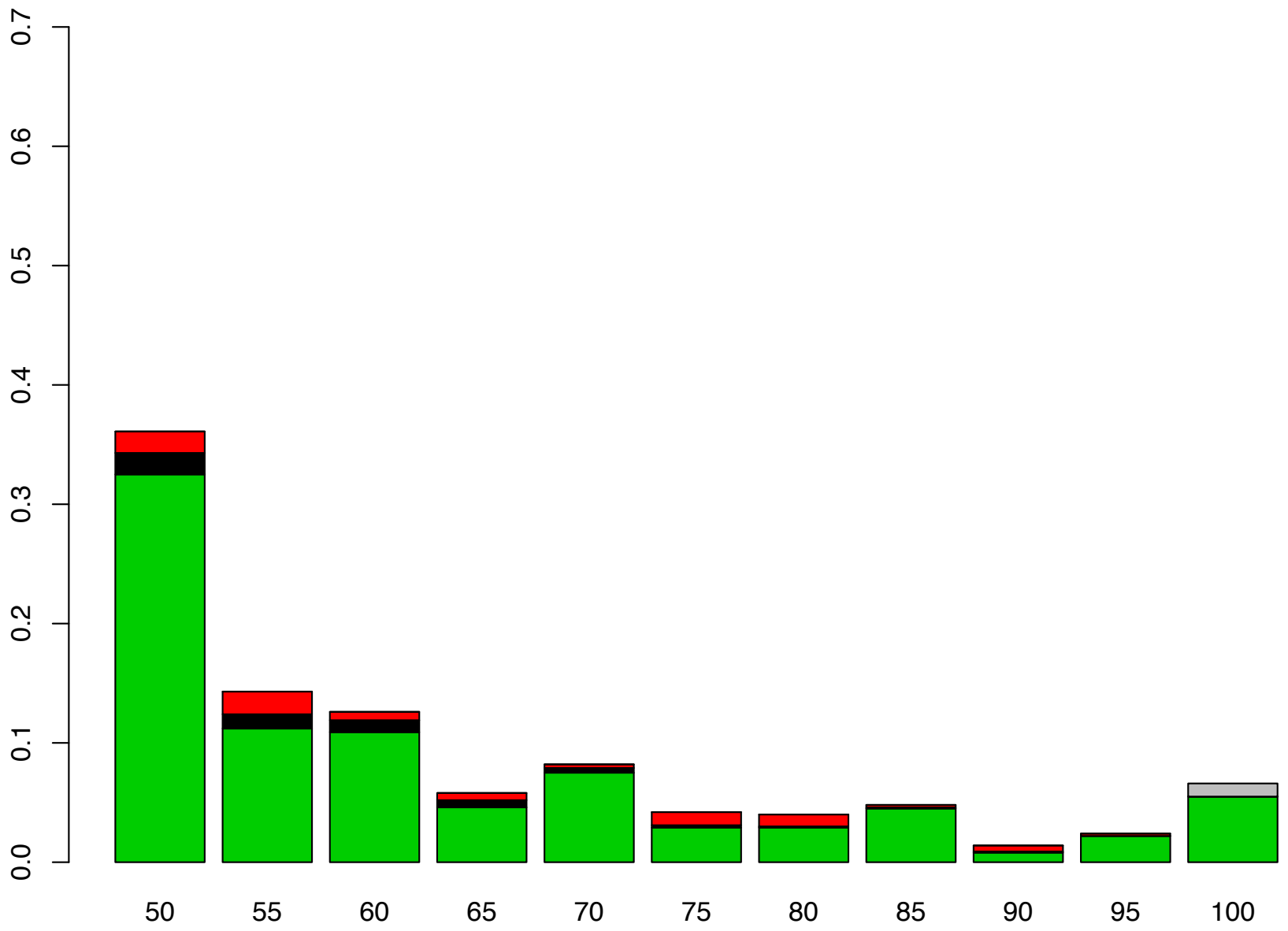
Operating Characteristics for Trial with $p_T = 0.84, p_S = 0.08$

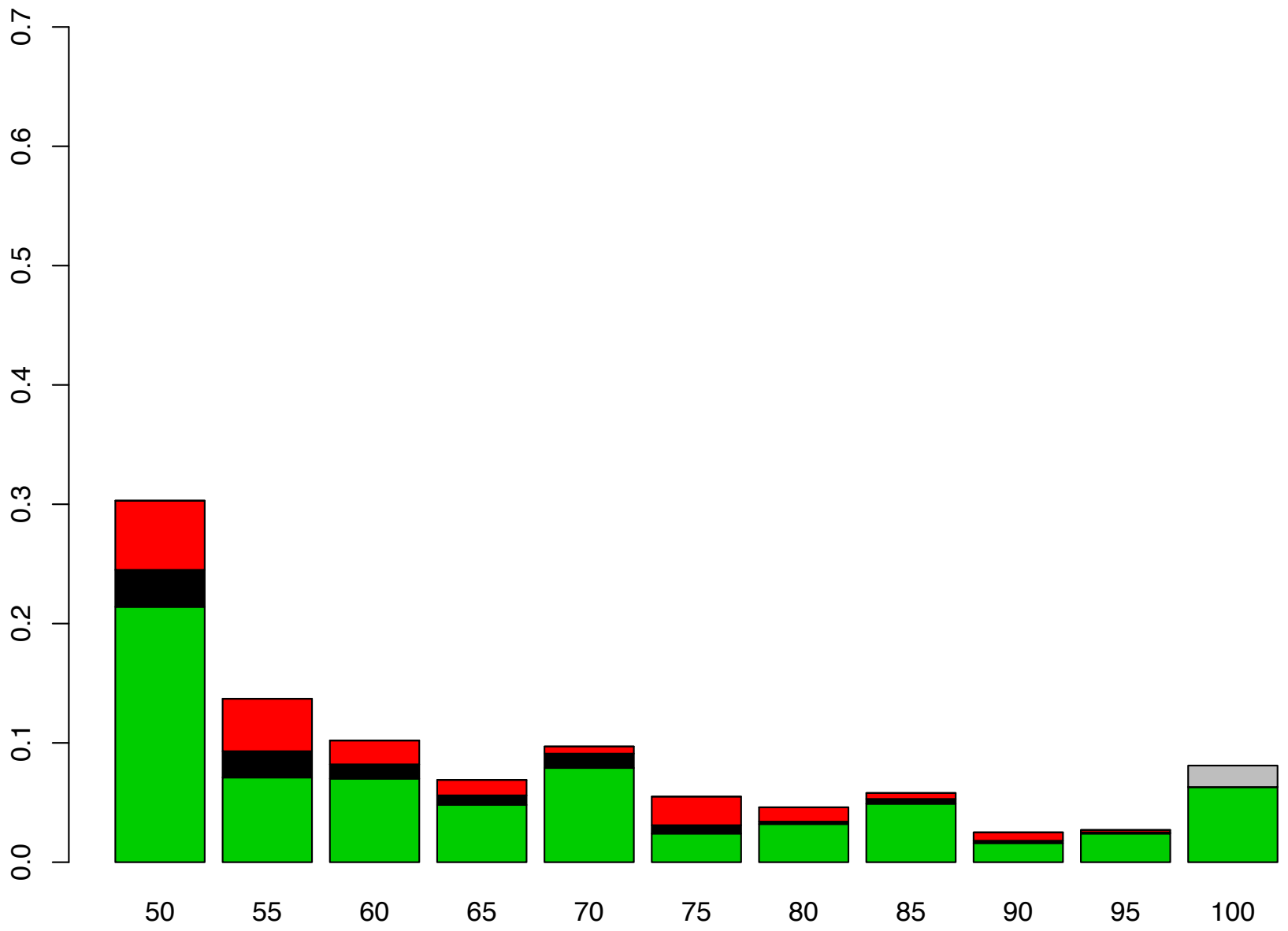
Sample Size	Proportion Of Trials	Stop for Futility	Stop Early For Success	& Lose	& Win
50	0.440	0.008	0.432	0.011	0.421
55	0.150	0.003	0.147	0.007	0.140
60	0.109	0.006	0.102	0.005	0.097
65	0.033	0.004	0.029	0.002	0.027
70	0.063	0.002	0.061	0.002	0.058
75	0.034	0.006	0.027	0.002	0.025
80	0.031	0.011	0.020	0.000	0.020
85	0.042	0.002	0.040	0.000	0.040
90	0.009	0.006	0.003	0.000	0.003
95	0.019	0.003	0.016	0.000	0.016
100	0.070	---	0.070	0.011	0.058
Total	1.000	0.053	0.947	0.042	0.906

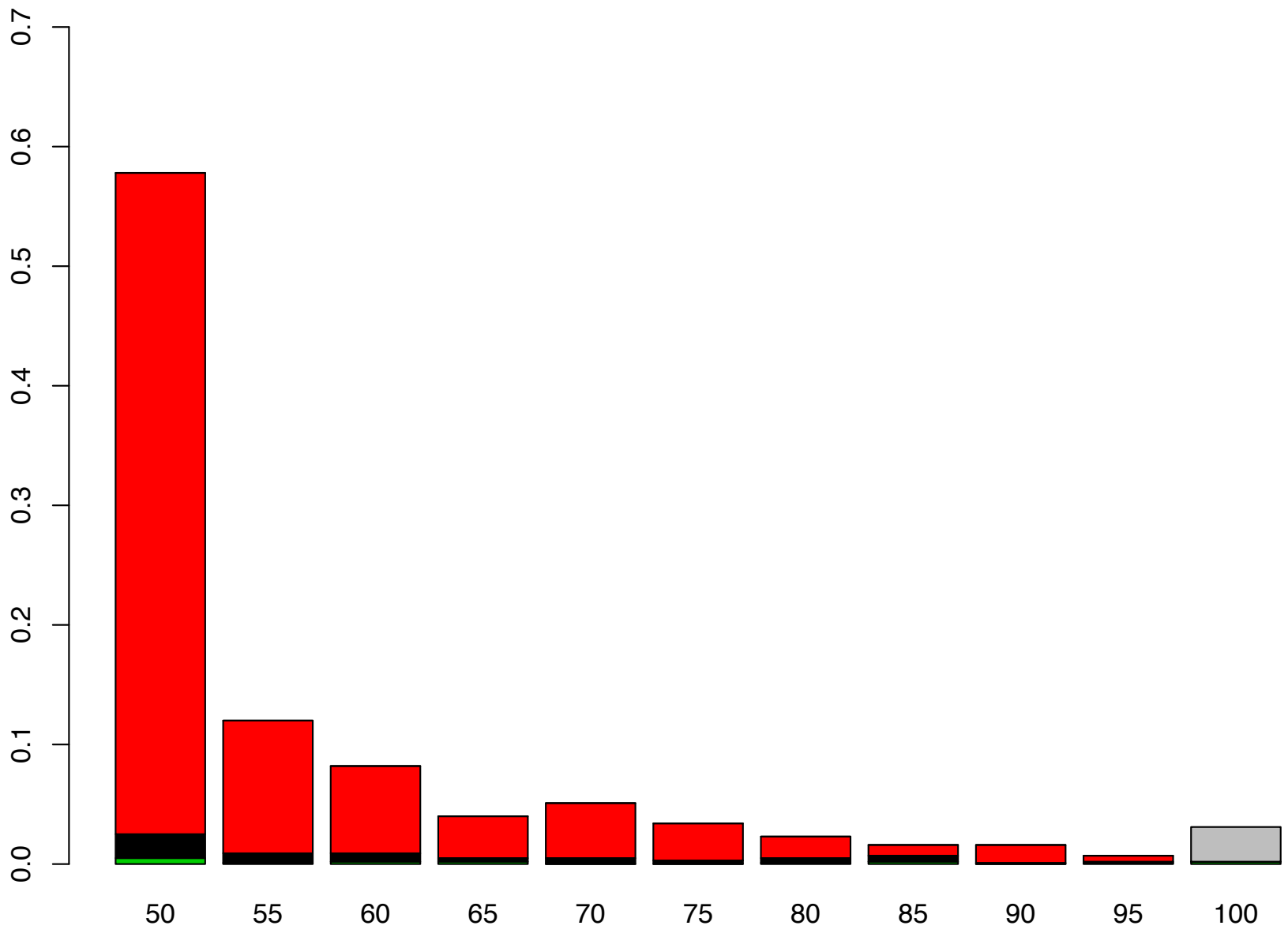
Mean Sample Size = 61.6, SD = 15.6

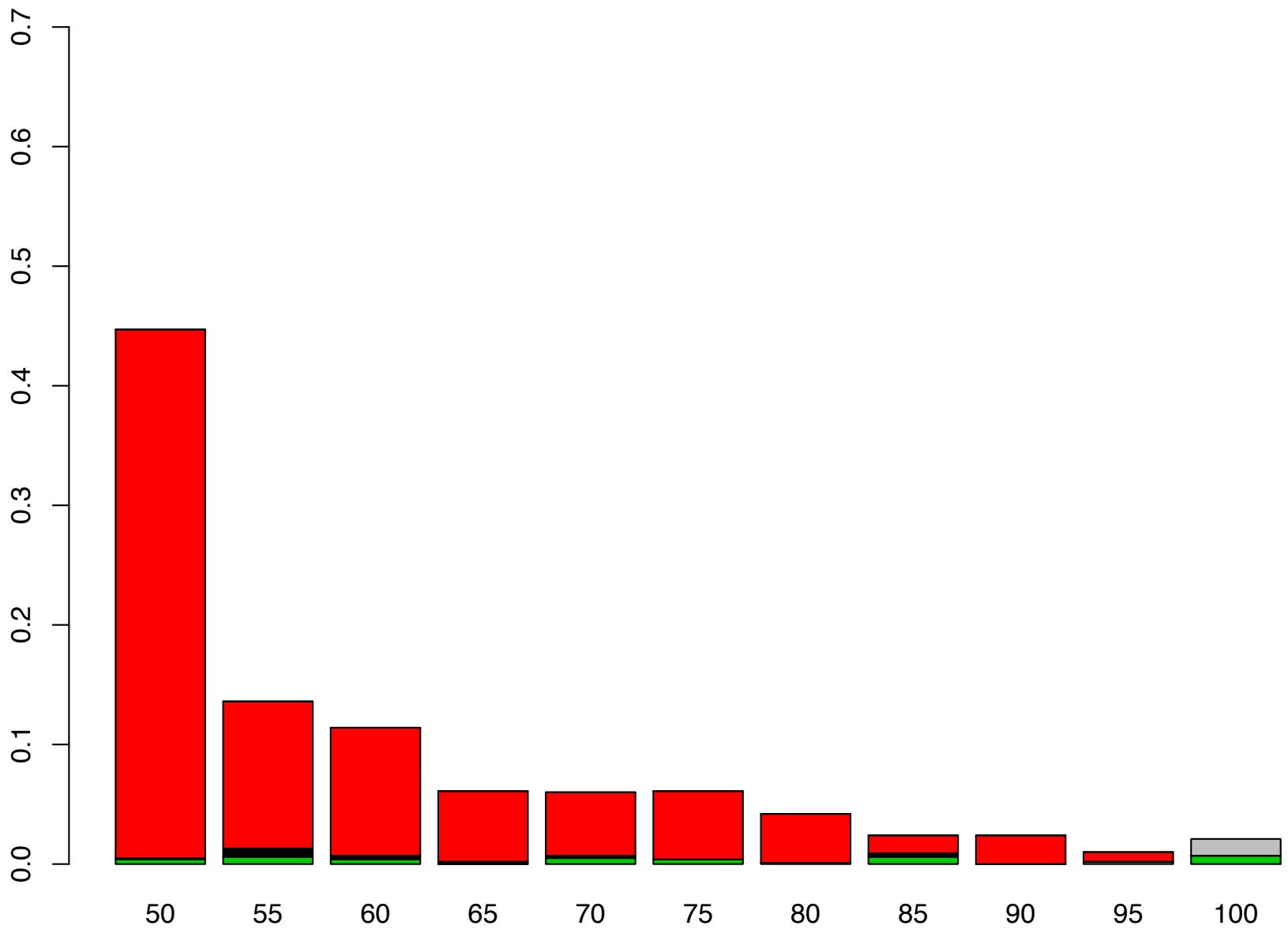

Efficacy = 84% Safety = 6%
Mean N = 55.8 Power = 0.969
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
50
55
60
65
70
75
80
85
90
95
100


Efficacy = 84% Safety = 8%
Mean N = 61.4 Power = 0.905
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
50
55
60
65
70
75
80
85
90
95
100


Efficacy = 79% Safety = 8%
Mean N = 63.6 Power = 0.855
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
50
55
60
65
70
75
80
85
90
95
100


Efficacy = 74% Safety = 8%
Mean N = 65.7 Power = 0.69
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
50
55
60
65
70
75
80
85
90
95
100


Efficacy = 60% Safety = 8%
Mean N = 57.5 Power = 0.016
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
50
55
60
65
70
75
80
85
90
95
100


Efficacy = 79% Safety =19%
Mean N = 60 Power = 0.039
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
50
55
60
65
70
75
80
85
90
95
100

Interim Analysis

- No look at 50 patients
- At 55-patients August 24, 2009
  - All patients through 30-day safety, 5/55 had SAEs
  - 24/29 efficacy successes at 6-months
  - 21 subjects remain under surveillance
  - 37/50 successes would show

    $\Pr(p_t > 0.60 \mid 37 \text{ of } 50) = 0.978 > 0.975$

  - Total number of efficacy successes

    $X = 24 + x_o + x_+ + x_-$

Interim Analysis

- $x_o = 5$ enrolled with < 3mo follow-up
  - $x_o \sim$ Beta-Bin($n_0 = 5$, α=5+24, β=1+5)
- x- = 3 enrolled not AF-free at 3mo
  - $x_- \sim$ Beta-Bin($n_- = 3$, α=4.2+3, β=1.8+1)
- x+ = 13 enrolled AF-free at 3mo
  - x+ ~ Beta-Bin(n+ = 13, □ =5.4+17, □ =0.6+3)
- $\Pr(24+x_o+x_-+x_+ \geq 37) = 0.988$

Interim Analysis

- $x_o = 5$ enrolled with < 3mo follow-up
  - $x_o \sim$ Beta-Bin($n_0 = 5$, α=5+24, β=1+5)
- x- = 3 enrolled not AF-free at 3mo
  - $x_- \sim$ Beta-Bin($n_- = 3$, α=4.2+3, β=1.8+1)
- x+ = 13 enrolled AF-free at 3mo
  - x+ ~ Beta-Bin(n+ = 13, □ =5.4+17, □ =0.6+3)
- $\Pr(24+x_o+x_-+x_+ \geq 37) = 0.988$

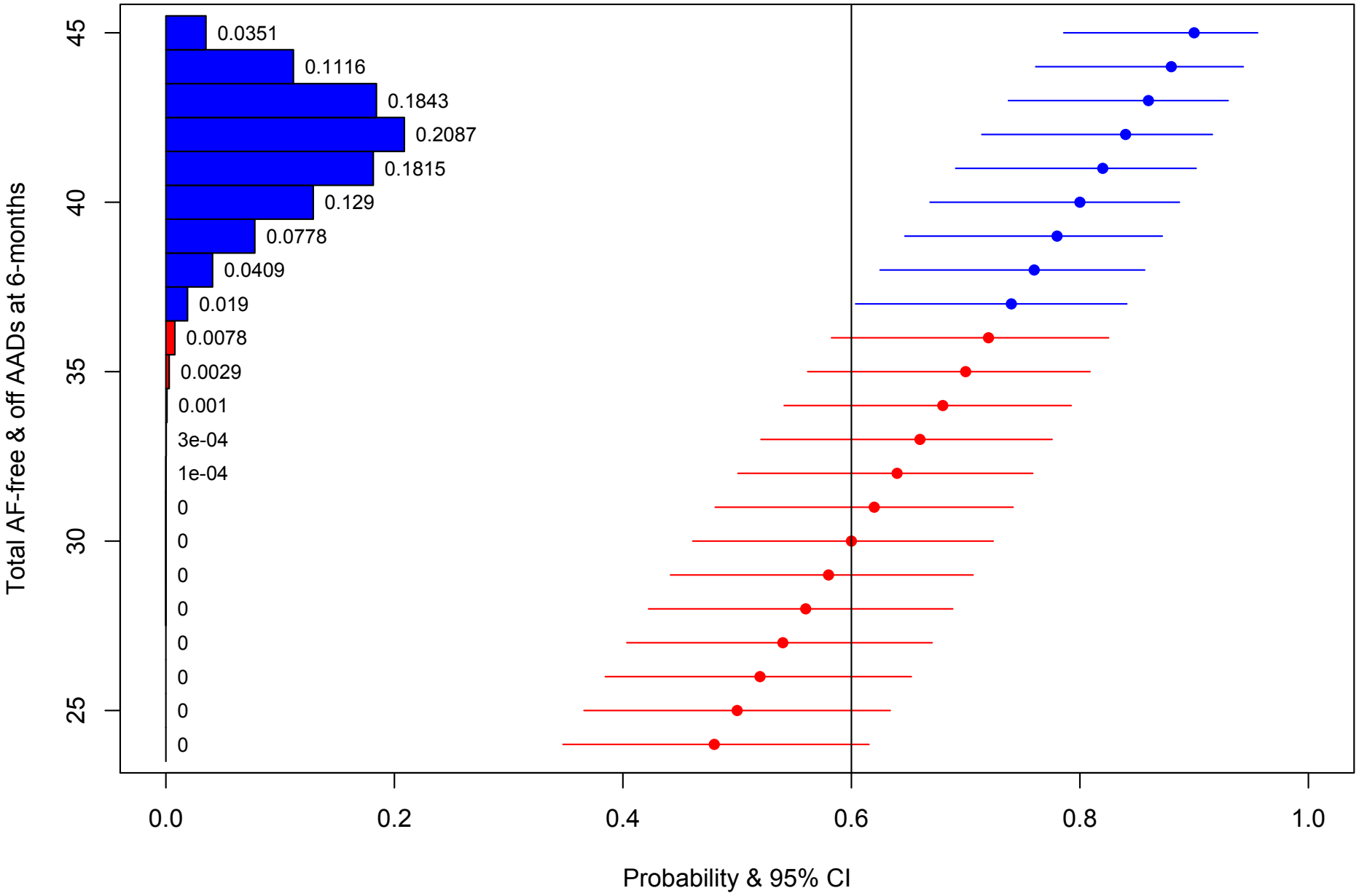
Longitudinal Priors were right on

5/6 = .83
24/29 = .83

4.2/6 = .70
3/4 = .75

5.4/6 = .90
17/20 = .85

Prediction of 21 remaining pts based on 29 observed pts



Sample Size Analysis at 55 pts

```
Current Patients Enrolled: 55
Current patients not contributing to efficacy: 5
Current Safety Events: 5 of 55 patients
Current Efficacy Success: 24 of 29 patients
Current Efficacy Successes: 24 of 29 patients
Current Efficacy Successes: 3 of 4 Efficacy Failures at 3 months
Current Efficacy Successes: 17 of 20 Efficacy Successes at 3 months

0 enrolled patients to predict for 1mo safety outcomes
45 future patients to predict for 1mo safety outcomes
5 enrolled patients with <3mo to predict for efficacy outcomes
3 enrolled patients with AF at 3mo to predict for 6mo efficacy outcomes
13 enrolled patients without AF at 3mo to predict for 6mo efficacy outcomes
45 future patients to predict for 6mo efficacy outcomes

Predicted Safety Events with Current Accrual: 5 ( 5 - 5 ) of 55 patients
       5  or fewer needed for safety success
Predicted Safety Events with Maximum Accrual: 9.7 ( 6 - 16 ) of 100 patients
       12  or fewer needed for safety success
Predicted Efficacy Successes with Current Accrual: 41.5 ( 37 - 45 ) of 50 patients
       37  or more needed for efficacy success
Predicted Efficacy Successes with Maximum Accrual: 78.8 ( 69 - 86 ) of 95 patients
       67  or more needed for efficacy success
```

Decision Rule: Stop Enrolling Due to Predicted Success

	Prob Win Efficacy	Prob Win Safety	Prob Win Both
Now	0.988	1.000	0.988
Max N	0.992	0.846	0.838

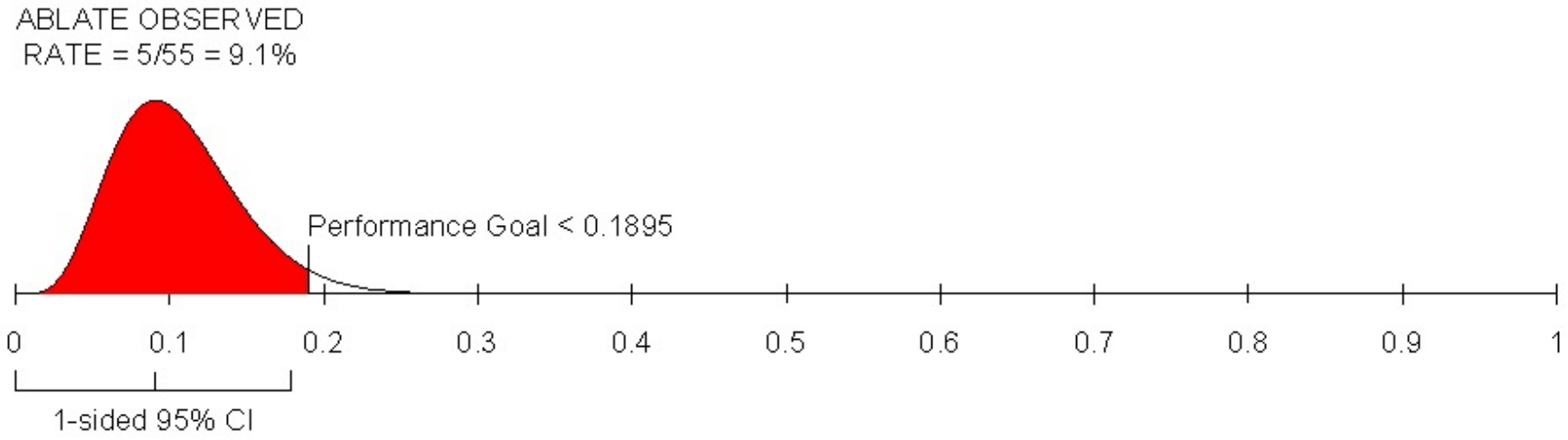
.988 > .90
Stop for
predicted success

Stopped Accrual for Predicted Success

- Accrual stopped with 55 patients in
- Continue to follow 21 enrolled patients
- Perform final analysis on complete data

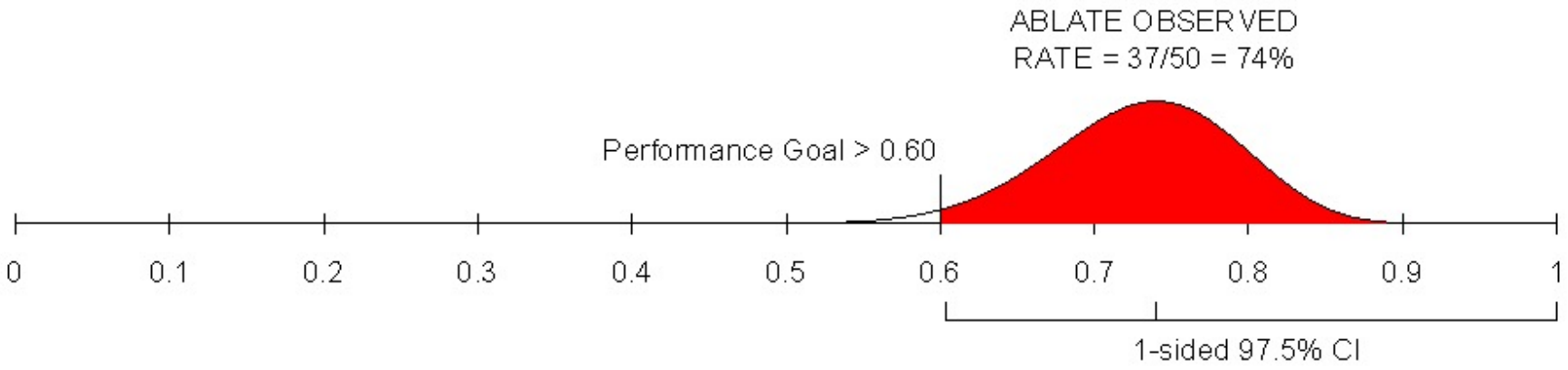
- Final Data
  - 5/55 SAEs
  - 37/50 AF-free and off AADs

Safety



ABLATE STUDY
96.7% Probability Rate < 0.1895

Efficacy

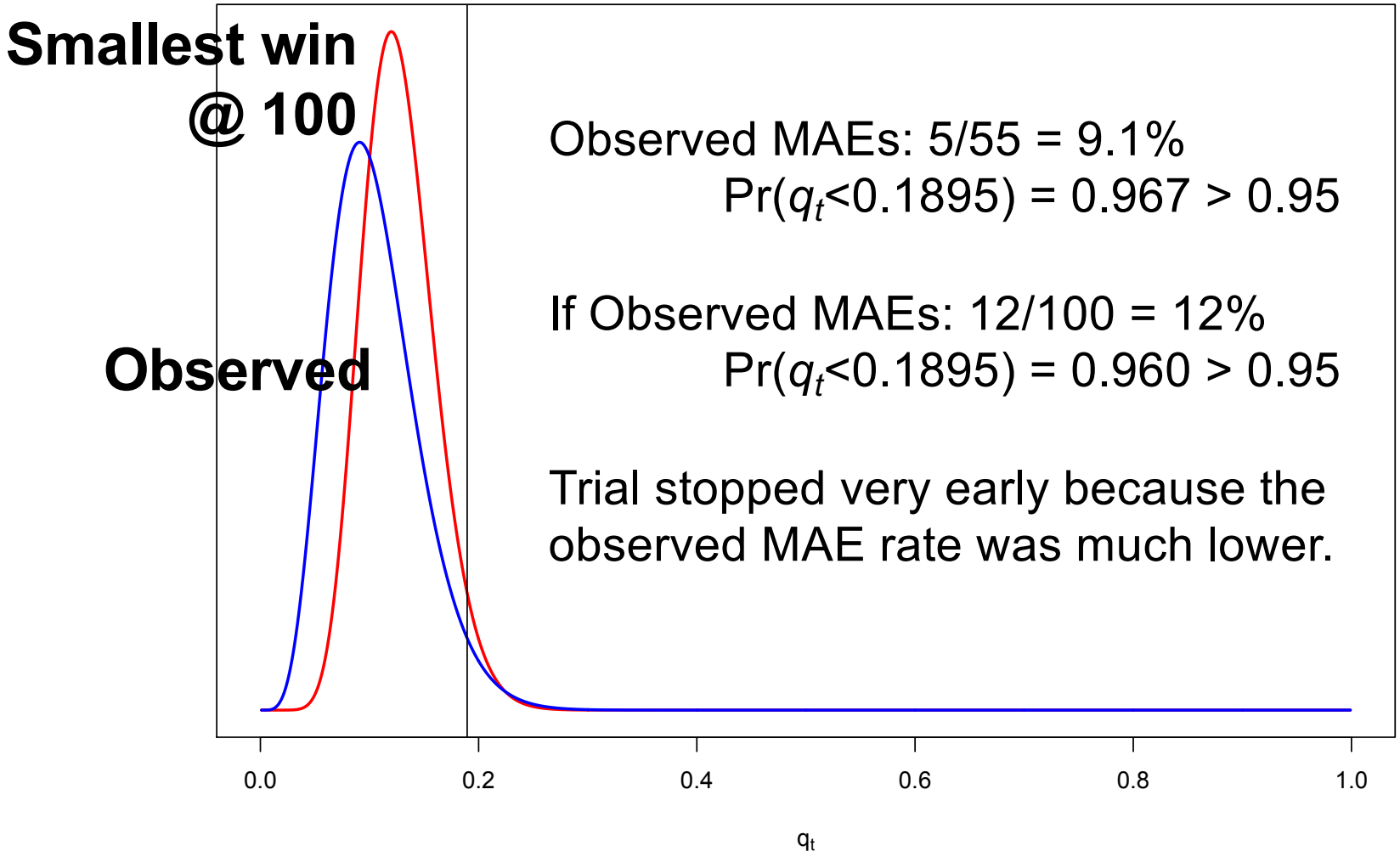


ABLATE STUDY
97.8% Probability Rate > 0.60

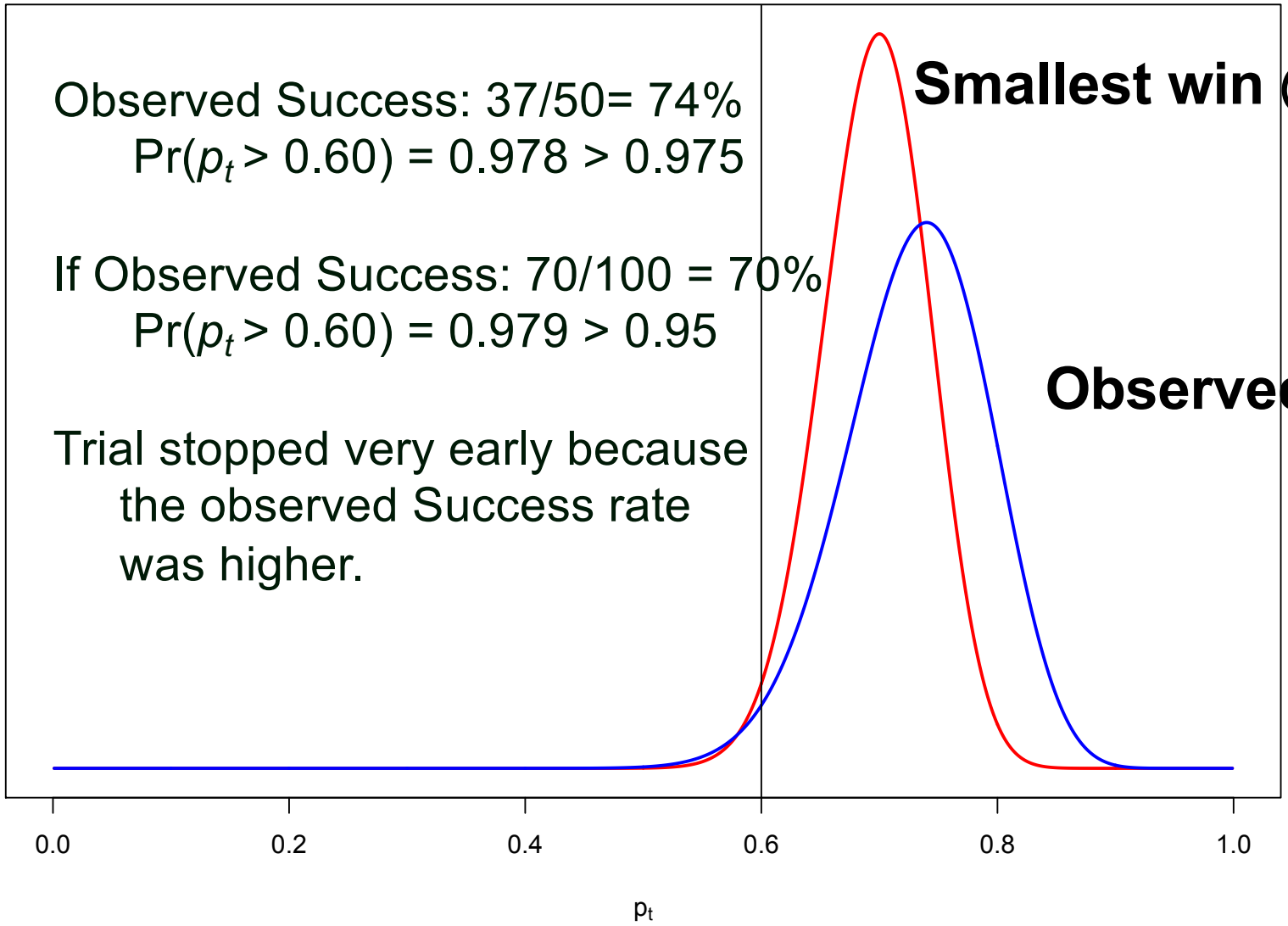
Post Trial Discussion with FDA

- Efficacy barely won
  - One less success would have failed to meet primary endpoint
  - Not a robust win, in part due to post-hoc changes related to inc/excl criteria
- Some concern with n=55
  - But this was possible based upon design
  - Safety OPC = 0.1395, observed 0.091
  - Efficacy OPC = 0.70, observed 0.74

Safety: Compare Stopping at n=55 to Maximum Trial Size n=100



Efficacy: Compare Stopping at n=50 to Maximum Trial Size n=100



FDA Advisory Panel Vote Oct 2011

- Is there reasonable assurance that the AtriCure Synergy Ablation System is effective …?
  - 9 for, 0 against
- Is there reasonable assurance that the AtriCure Synergy Ablation System is safe…?
  - 5 for, 4 against, 1 abstain (chair broke 4-4 tie)
  - Largely due to patients needing pacemakers
- Do the benefits … outweigh the risks …?
  - 5 for, 3 against, 1 abstain

[heartwire]

ARRHYTHMIA/EP

AtriCure AF ablation system gets cautious thumbs-up from FDA advisors

OCTOBER 26, 2011 Michael O'Riordan

Rockville, MD (updated) – The **AtriCure Synergy Ablation System** squeaked by today in a meeting of the **Food and Drug Administration**'s Circulatory System Devices advisory panel when panelists gave a cautious nod of approval for the device.

Five panel members believed the benefits of the ablation system outweighed the risks when used in the treatment of atrial-fibrillation (AF) patients undergoing open concomitant coronary artery bypass graft (CABG) surgery and/or valve replacement or repair. Three panelists expressed doubts about the system and cautioned against device approval, voting that they did not believe the benefits outweighed the risks.

One panelist abstained from voting on the benefit/risk trade-off question.

In a vote on efficacy alone, all panelists believed the ablation system is effective in restoring sinus rhythm, but they were split for the vote on safety. Chair of the advisory panel, **Dr John Hirschfeld** (University of Pennsylvania, Philadelphia), cast the deciding vote on safety, saying he believes there is reasonable assurance the device is safe for use in patients who meet the indication criteria. Overall, the panel voted 9 to 0 on efficacy and 5 to 4 on safety (with one abstention).

Panel member **Dr David Slotwiner** (Long Island Jewish Medical Center, New Hyde Park, NY) voted in favor of the ablation system, saying that he believes the benefits outweigh the risks.

"I think it's effective at creating these ablation lesions, and I think it's effective in many people for maintaining sinus rhythm, although what that means [clinically] for many patients remains unanswered," he said. "But I hope, mostly, that if an approval is granted, it will allow us to get more information and to educate more surgeons so that the procedure becomes more widely available and we understand better who will benefit the most."

FDA Approved Dec 14, 2011

- **Study Design (from device label)**
- ABLATE was a multi-center, prospective, non-randomized study based on a Bayesian adaptive design that provides high probability of demonstrating safety and effectiveness of the AtriCure Synergy Ablation System for the treatment of permanent atrial fibrillation. The safety and effectiveness of the device was compared to performance goals derived from historical information. The Bayesian adaptive clinical design incorporated interim analyses of the data to determine the point of completion of trial enrollment. Enrollment was targeted to be between 50 and 100 subjects at 20 sites. The study was designed to have an initial assessment of results at the point that 50 subjects were enrolled with a minimum of 20 subjects completing their six-month follow-up visit. Nine investigational sites enrolled 55 subjects.

Lessons

- Ensure minimum sample size will suffice
  - Not just statistical, but impactful
  - Company did a continue access protocol to get more patients during review, leading to panel
- Ensure data isn't coded optimistically
- Ensure inclusion / exclusion criteria rigorously followed
- Goldilocks gets the size 'just right' but that means you can be close to 'just wrong' if some data changes post hoc

Example 3: SHINE TRIAL

with Karen Johnston, Valerie Durkalski
Kristine Broglio, & Will Meurer

- Trial for SOC vs. tight glycemic control after stroke
- Designed as Group Sequential
- Run with "Shadow" Bayesian Trial
- Design papers online
  - Compares GSD to Goldilocks Trial

Platform Trials

& Master Protocols

Woodcock & Lavange, NEJM 2017

- High-quality evidence is what we use to guide medical practice. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered.
- A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure. Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions.

Woodcock & Lavange, NEJM 2017

- Master protocols may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions, each targeting a particular biomarker-defined population or disease subtype. Included under this broad definition of a master protocol are three distinct entities: umbrella, basket, and platform trials (Table 1 and Figs. 1 and 2). All constitute a collection of trials or substudies that share key design components and operational aspects to achieve better coordination than can be achieved in single trials designed and conducted independently.

Master Protocols

- May or may not compare treatment across groups
  - One structure, but each TX vs. common control
  - Reported as multiple trials (e.g. 1 per intervention)
  - Sites have one set of rules, execute like 1 trial
- Intensive pretrial discussion among sponsors
  - data use, publication rights, and the timing of regulatory submission
- Matchmaker
  - Therapies to targeted subpopulations

Master Protocols

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

NEJM 377, 1, p63, Table 1

Master Protocols

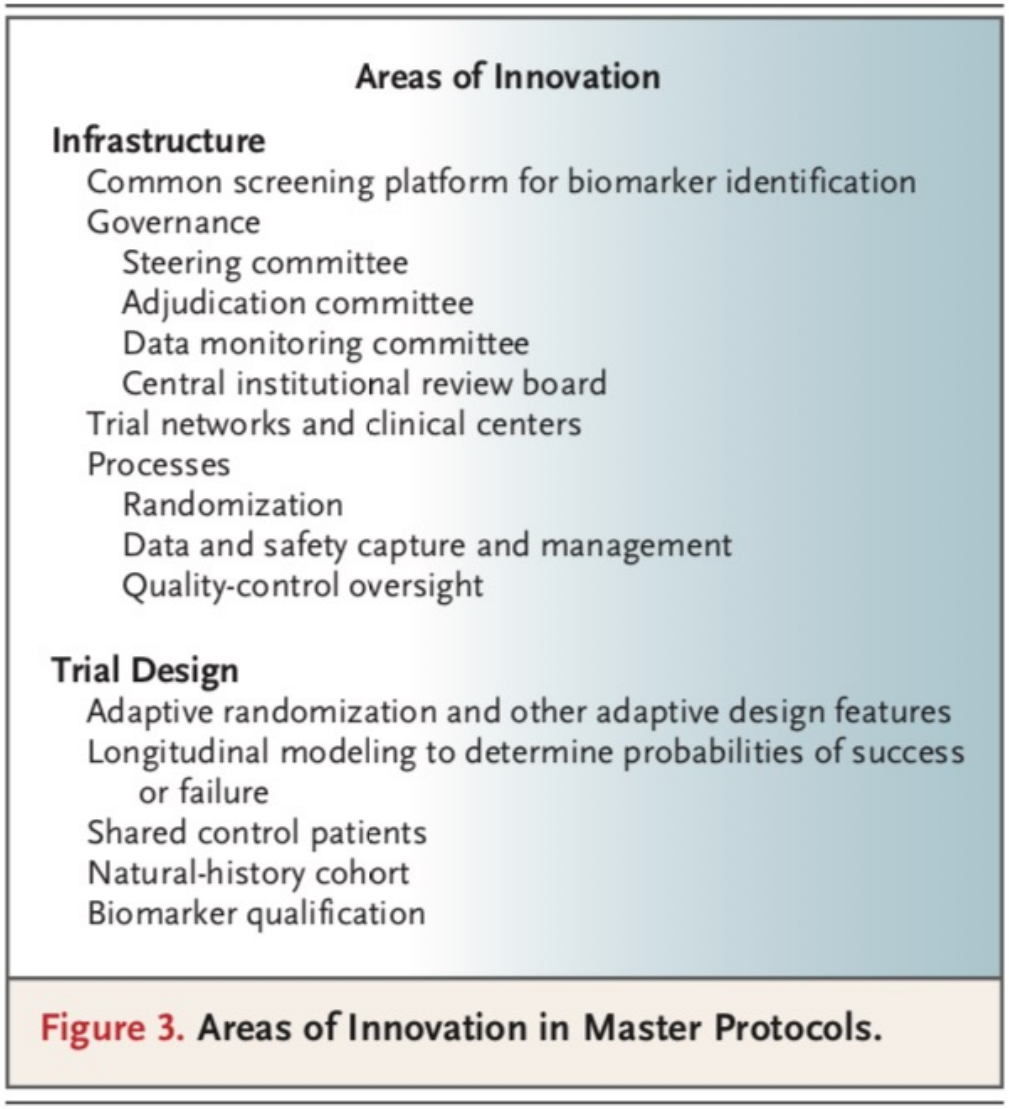


Figure 3. Areas of Innovation in Master Protocols.

NEJM 377, 1, p63, Figure 3

- Master protocols come in different sizes and shapes but share many commonalities.
- Increased planning efforts and coordination to satisfy the objectives of different stakeholders.
- Maximum information is obtained from the research effort
- Infrastructure required for implementation increases data quality and trial efficiencies, as compared with those in stand-alone trials.
- Can last many years, even decades, with innovations from the laboratory translating quickly to clinical evaluation.

Platform Trials

Asking the Right Question

- Current Clinical Trials

  Is this drug effective and safe?

  More precisely

  What is the probability of the observed data assuming the treatment is no good?

Asking the Right Question

- Current Clinical Trials
  - Is this drug effective and safe compared to a placebo?
  - Is this drug effective & safe compared to the SOC
- Correction Question
  - What is the best treatment for this Patient?
  - What is the best treatment for this type of patient?

Traditional Trial Design

- Single treatment vs. Control
- Homogenous patient population
- 1 or 2 questions per 1 trial
- Start with assuming a particular control group effect and a particular (usually optimistic) treatment group effect
- Assume 'average' effect relevant to all patients
- Calculate a sample size as if we know the true effect

Platform Trial

- An experimental infrastructure to evaluate multiple treatments, often for a group of diseases, and intended to function continually and be productive beyond the evaluation of any individual treatment
  - Designed around a group of related diseases rather than a single treatment
  - Disease focused not treatment focused
  - Dynamic list of available treatments, assigned with response-adaptive randomization
  - Preferred treatments may depend on health system, patient, or disease-level characteristics

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

Scott M. Berry, PhD
Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

Jason T. Connor, PhD
Berry Consultants LLC, Austin, Texas; and University of Central Florida College of Medicine, Orlando.

Roger J. Lewis, MD, PhD
Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California; and Berry Consultants LLC, Austin, Texas.

The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population, one drug, one disease" strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants for stroke.[2] Effective treatments for such diseases will likely require combining treatments to affect multiple targets in complex cellular pathways and, perhaps, tailoring treatments to subgroups defined by genetic, proteomic, metabolomic, or other markers.[3]

There has been increasing interest in efficient trial strategies designed to evaluate multiple treatments and combinations of treatments, in heterogeneous patient benefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

What Is a Platform Trial?

A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy. A platform trial is often intended to continue beyond the evaluation of the initial treatments and to investigate treatment combinations, to quantify differences in treatment effects in subgroups, and to treat patients as effectively as possible within the trial. Although some of the statistical tools used in platform trials are frequently used in other settings and some less so, it is the integrated application of multiple tools that allows a platform trial to address its multiple goals. The **Table** summarizes the general differences between a traditional clinical trial and a platform trial

JAMA. Published online March 23, 2015. doi:10.1001/jama.2015.2316

From: **The Platform Trial: An Efficient Strategy for Evaluating Multiple Treatments**

JAMA. Published online March 23, 2015. doi:10.1001/jama.2015.2316

Table. General Characteristics of Traditional and Platform Trials[a]

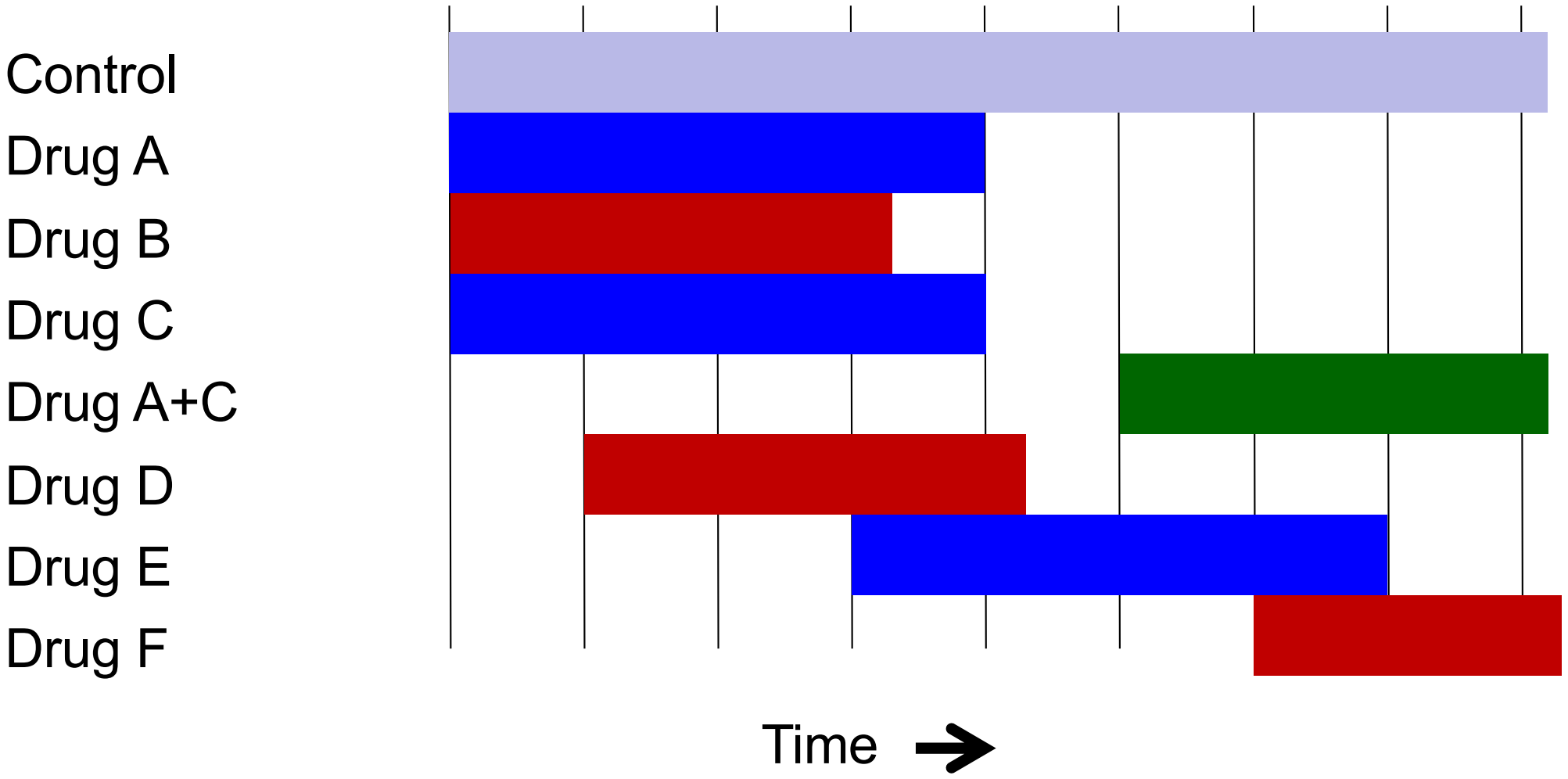
Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

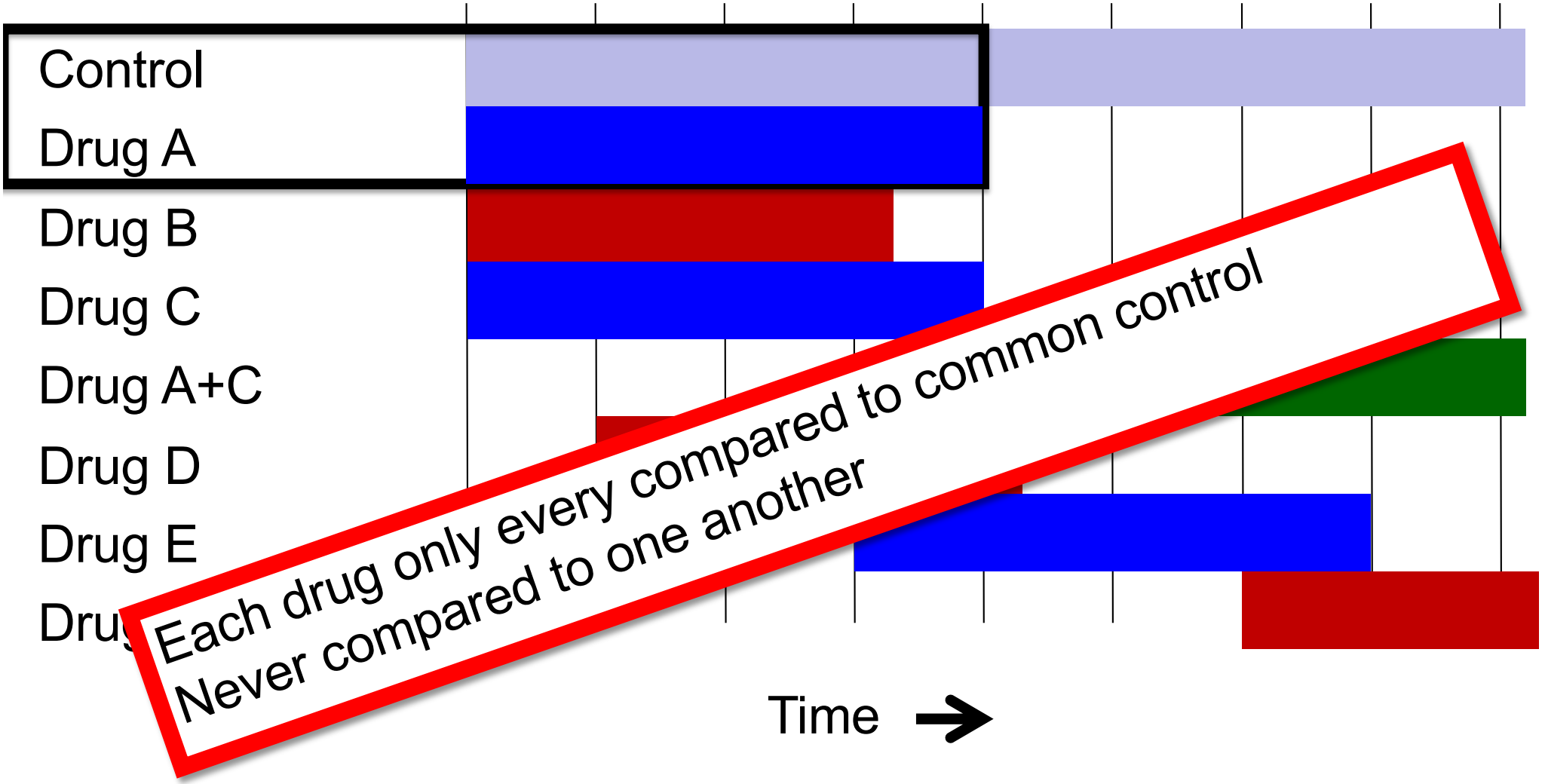
Table Title:

General Characteristics of Traditional and Platform Trials[a]

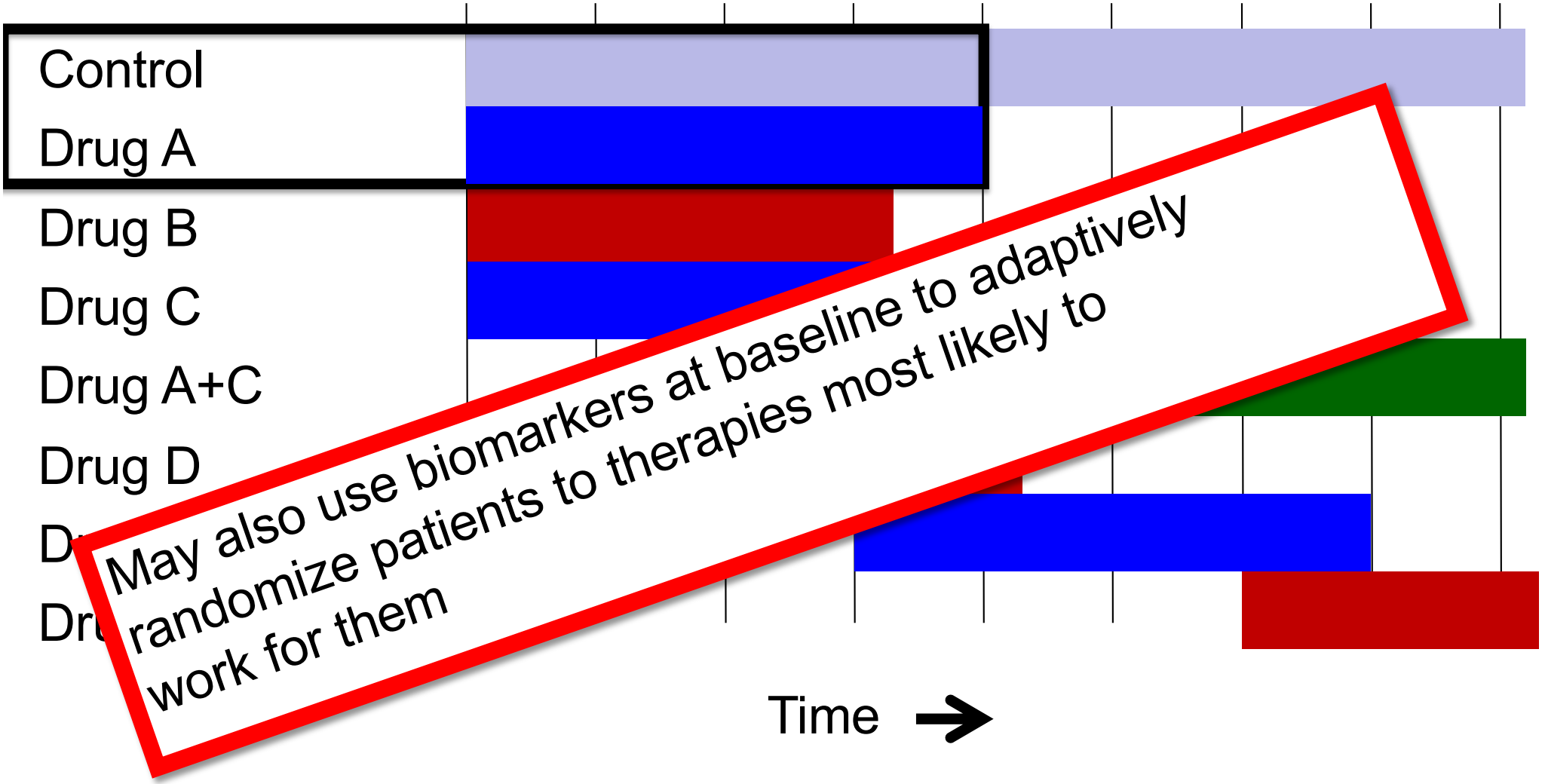
Platform Trial



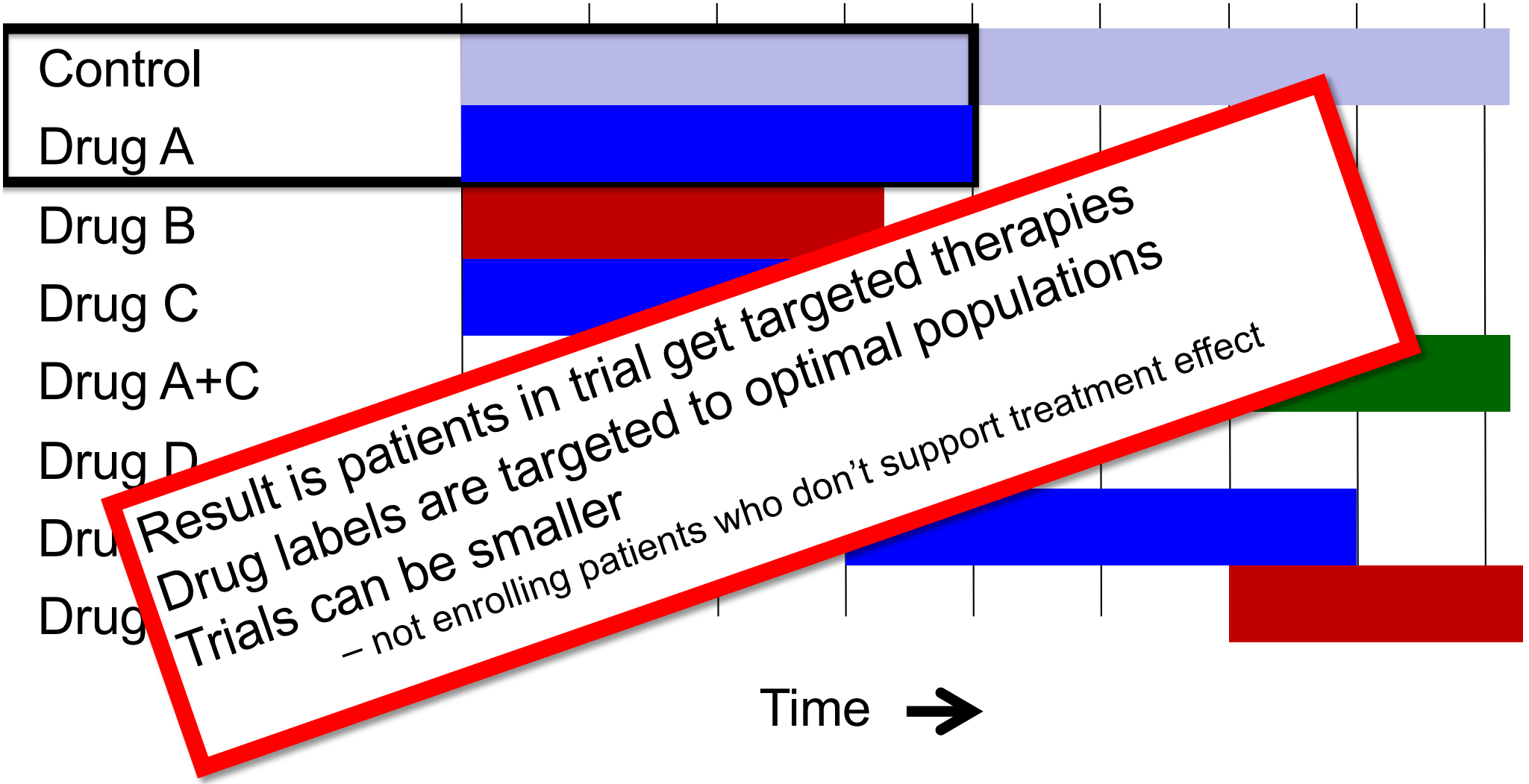
Platform Trial



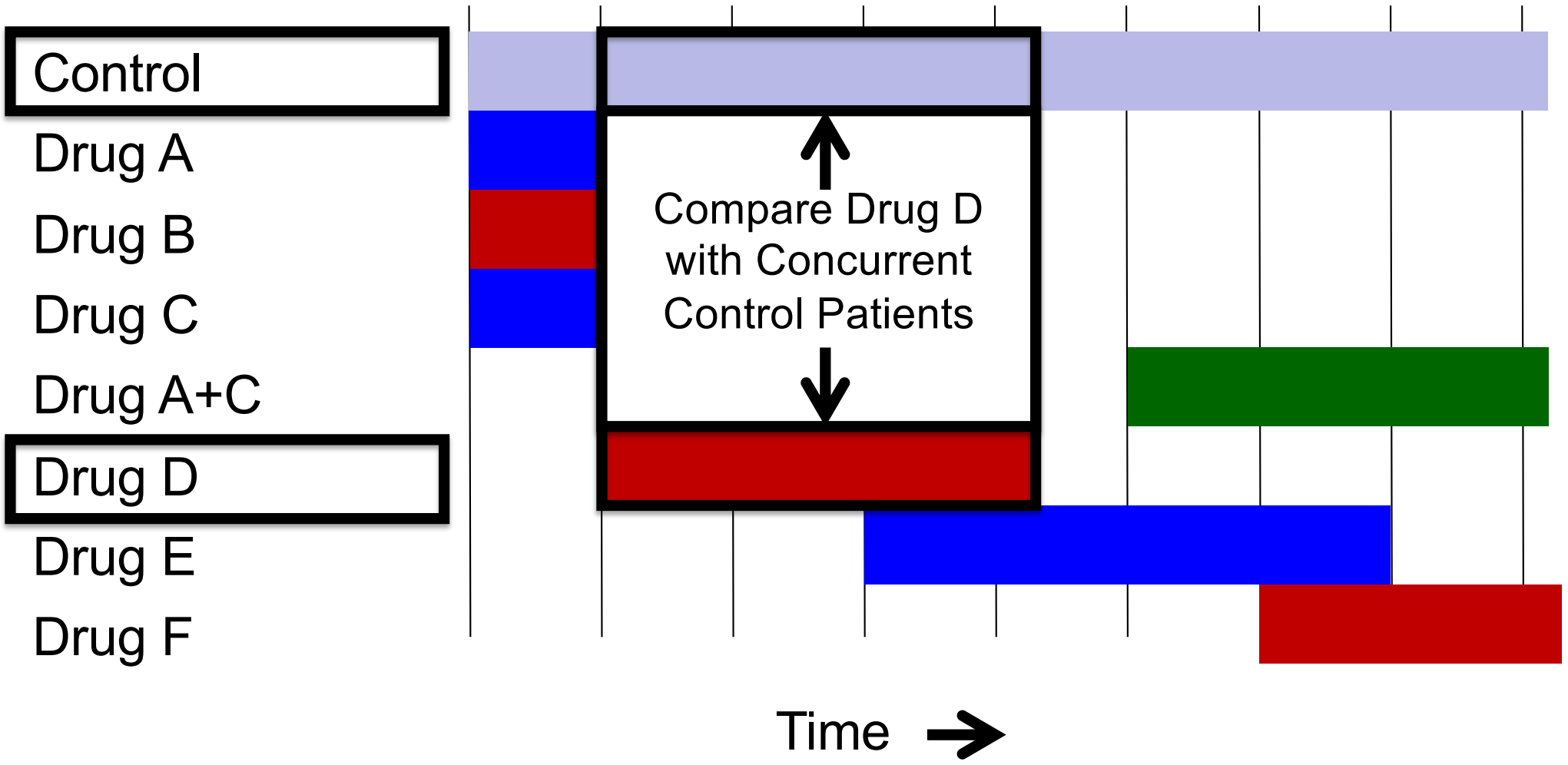
Platform Trial



Platform Trial

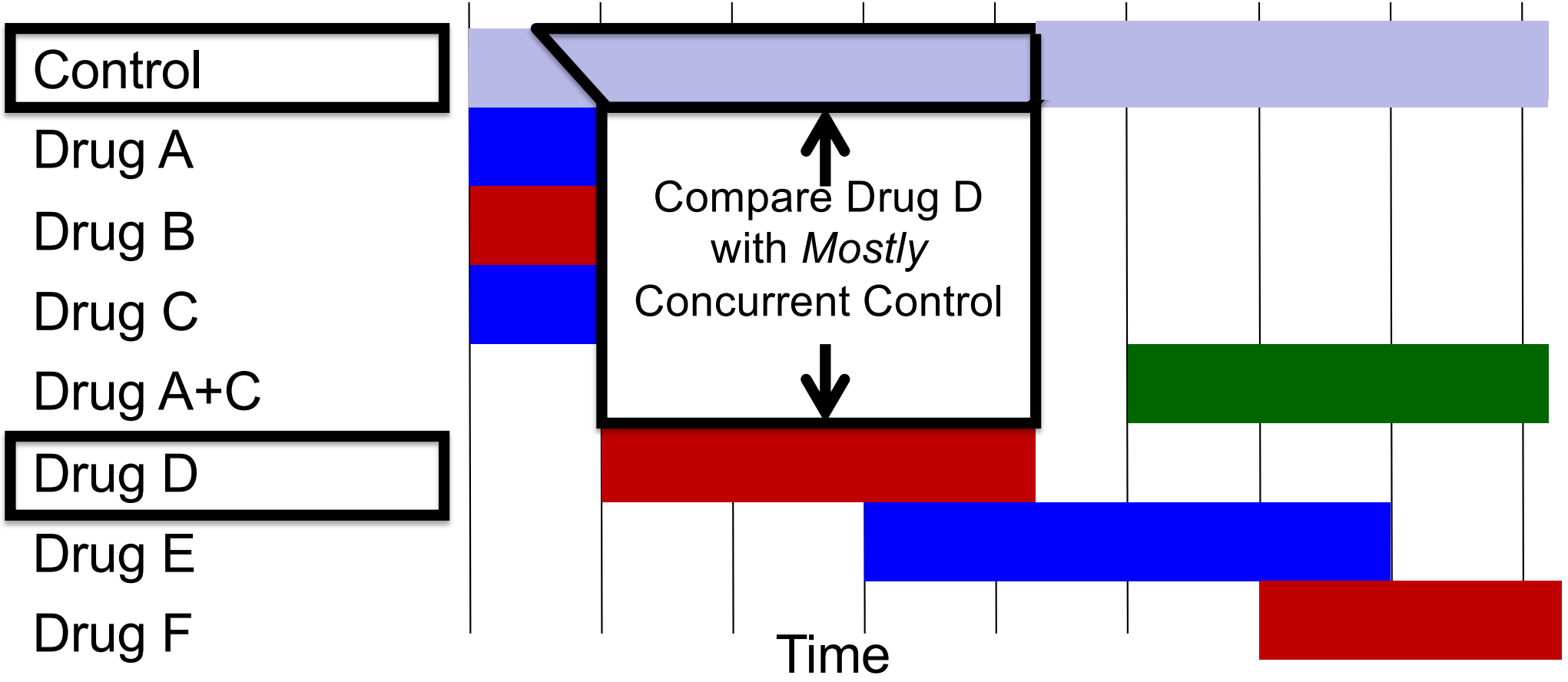


Platform Trial



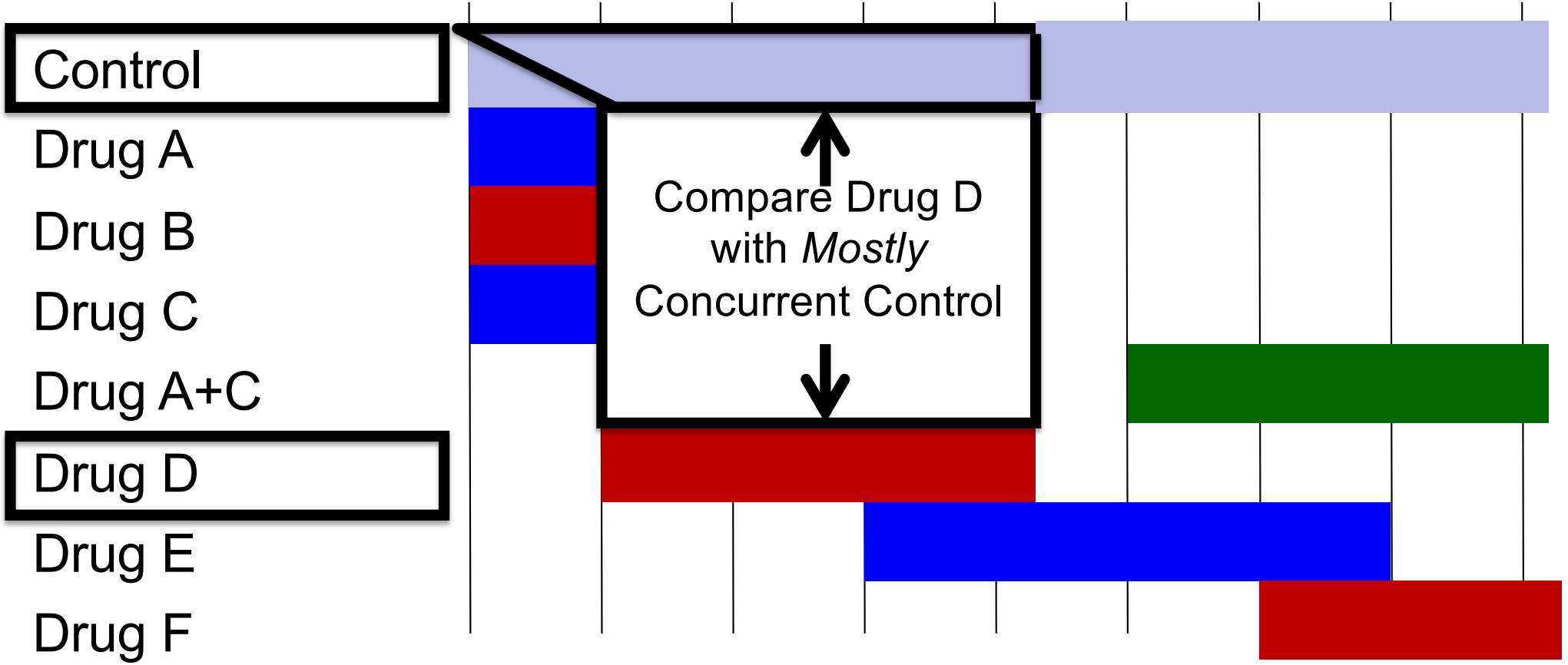
Time Machine

Model how controls change over time, if similar, then use some controls outside concurrent window

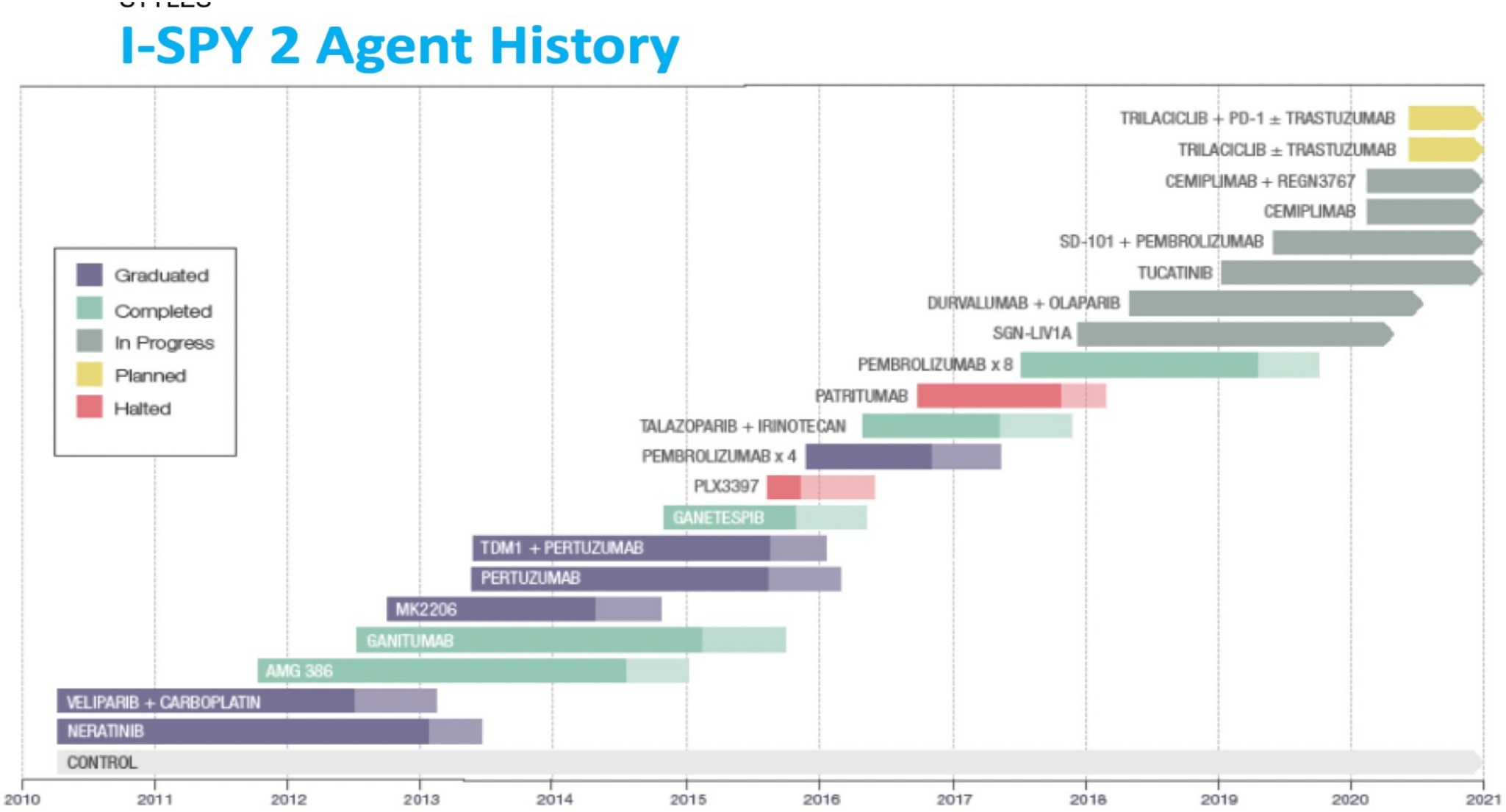


Time Machine

If controls change little over time, then use more weight from non-concurrent controls, increases power & efficiency



I-SPY2



Used with permission from Dr. Laura Esserman, I-SPY2 PI

Platform Trials are Happening

- Cancer
  - I-SPY2 in Breast Cancer
  - GBM AGILE in Glioblastoma multiforme
  - LUNG-MAP in Lung Cancer
  - PANCAN in Pancreatic Cancer
- Alzheimer's
  - EPAD: European Prevention of Alzheimer's Dementia
  - DIAN: Dominantly Inherited Alzheimer's Network
- ALS
  - Healey ALS Platform Trial, Phase 2/3 with 5 drugs

Platform Trials are Happening

- Infection diseases
  - Gates Foundation sponsored Ebola design
  - NIH Ebola design
  - PREPARE: European Consortium for Disease Preparedness
    - Pandemic flu, Butler at al Lancet, Jan 2020
    - REMAP CAP (Community Acquired Pneumonia) ongoing, REMAPCAP.org
- COVID-19
  - RECOVERY
  - ACTT by NIAID -- the Remdesivir trial
  - SOLIDARITY by WHO, 4 arms
  - REMAP-COVID by International consortium critical care trial
  - PRINCIPLE in UK, pre-hospital trial
  - ISPY-COVID: UCSF & WISDOM Network, Phase 2
  - ACTIV by NIH

Characteristics of Modern Platform Trials	Cancer Trials							
	I-SPY 2	MICAT	BATTLE	LUNG-MAP	UK MATRIX	GBM-AGILE	Alzheimer's	Ebola
Screen markers for all pts	✔	✔	✔	✔	✔	✔	—	—
Master protocol	✔	✔	✔	✔	✔	✔	✔	✔
Many regimens	✔	✔	✔	✔	✔	✔	✔	✔
Combination therapies	✔	✔	✔			✔	✔	✔
Sequential therapies		✔				✔		
Assembly line	✔	✔			✔	✔	✔	✔
Learn off-target effects	✔	✔	✔			✔	—	—
Pair regimens/biomarkers	✔	✔	✔			✔	—	—
Common control arm	✔	✔				✔	✔	✔
Adaptive randomization	✔	✔	✔			✔	✔	✔
Adaptive sample size	✔	✔				✔	✔	✔
Early "curable" disease	✔					✔	✔	✔
Registration endpoint	✔					✔	✔	✔
Seamless phases						✔		
Longitudinal modeling	✔	✔				✔	✔	
Bayesian	✔	✔	✔			✔	✔	✔

From Don Berry

Article

CLINICAL TRIALS

Clinical Trials
1–9

DOI: 10.1177/1740774515626362
ctj.sagepub.com
SAGE

Efficiencies of platform clinical trials: A vision of the future

Benjamin R Saville[1,2] and Scott M Berry[1,3]

Abstract

Background: A "platform trial" is a clinical trial with a single master protocol in which multiple treatments are evaluated simultaneously. Adaptive platform designs offer flexible features such as dropping treatments for futility, declaring one or more treatments superior, or adding new treatments to be tested during the course of a trial.

Methods: A simulation study explores the efficiencies of various platform trial designs relative to a traditional two-arm strategy.

Results: Platform trials can find beneficial treatments with fewer patients, fewer patient failures, less time, and with greater probability of success than a traditional two-arm strategy.

Conclusion: In an era of personalized medicine, platform trials provide the innovation needed to efficiently evaluate modern treatments.

Keywords

Platform trial, master protocol, multi-arm, adaptive, Bayesian, clinical trial design

CLINICAL TRIALS

Clinical Trials
1–9

DOI: 10.1177/1740774515621721
ctj.sagepub.com
SAGE

A response adaptive randomization platform trial for efficient evaluation of Ebola virus treatments: A model for pandemic response

Scott M Berry[1,2], Elizabeth A Petzold[3], Peter Dull[4], Nathan M Thielman[5], Coleen K Cunningham[6], G Ralph Corey[5], Micah T McClain[6], David L Hoover[7], James Russell[8], J McLeod Griffiss[7] and Christopher W Woods[3,5,6]

Abstract

The outbreak of Ebola virus disease in West Africa is the largest ever recorded. Numerous treatment alternatives for Ebola have been considered, including widely available repurposed drugs, but initiation of enrollment into clinical trials has been limited. The proposed trial is an adaptive platform design. Multiple agents and combinations will be investigated simultaneously. Additionally, new agents may enter the trial as they become available, and failing agents may be removed. In order to accommodate the many possible agents and combinations, a critical feature of this design is the use of response adaptive randomization to assign treatment regimens. As the trial progresses, the randomization ratio evolves to favor the arms that are performing better, making the design also suitable for all-cause pandemic preparedness planning. The study was approved by US and Sierra Leone ethics committees, and reviewed by the US Food and Drug Administration. Additionally, data management, drug supply lines, and local sites were prepared. However, in response to the declining epidemic seen in February 2015, the trial was not initiated. Sierra Leone remains ready to rapidly activate the protocol as an emergency response trial in the event of a resurgence of Ebola. (ClinicalTrials.gov Identifier: NCT02380625.) In summary, we have designed a single controlled trial capable of efficiently identifying highly effective or failing regimens among a rapidly evolving list of proposed therapeutic alternatives for Ebola virus disease and to treat the patients within the trial effectively based on accruing data. Provision of these regimens, if found safe and effective, would have a major impact on future epidemics by providing effective treatment options.

EBOLA

Thanks to: Scott Berry,

Elizabeth Petzold,

Chris Woods, David Hoover

The Problem: Ebola Treatment Trial

- Acknowledge universe of possible treatments
  - Will evolve over time
  - Recognition that combinations may play an important role
- Uncertainty over role of standard of care
- Our Goal: To determine best treatment for treating ebola
  - Not a trial to determine if a single drug X works

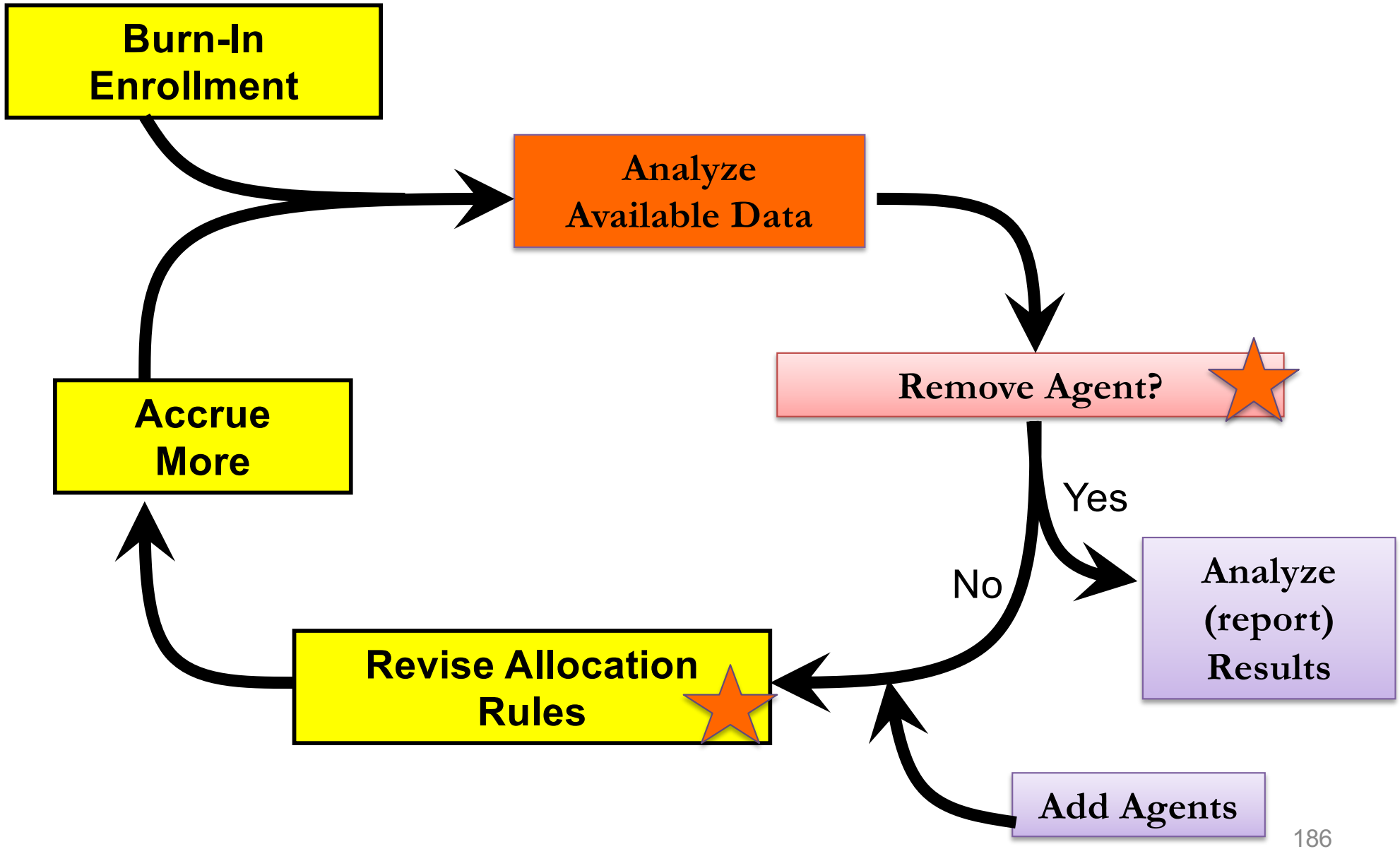
EV-003 Adaptive Platform Design

- Reviewed and approved by:
  - Duke University IRB
  - University of Sierra Leone ethics committee
- *Master Protocol* dictates trial behavior, each treatment included as an appendix
- Multiple Agents
  - Primary & Secondary agents
  - Combination + Single agents
- Response Adaptive Randomization (RAR)
  - Run by a single algorithm
  - Assigns treatment regimens that are performing better using collection of primary endpoint data
- Protocol is built so trial arms evolve (part of the protocol!), trial is **perpetual**
- Endpoint is 14-day mortality

Primary/Secondary Agents

- All arms receive optimized standard of care (SOC)
- Primary and Secondary agents
  - Primary: Expected capability to work as single agent (e.g. anti-viral efficacy)
  - Secondary: Expected to work with other agents (not given alone)

Adaptive Platform Design



Design Details

Burn-In Enrollment

- Endpoint: Death (Dichotomous, events are bad)
- Start with burn-in period to all 10 regimens
  - Equal randomization to 10 arms
  - 30 subjects / 3 per arm
- After burn-in
  - Response adaptive randomization
  - Proportional to probability regimen is optimal
    - Adjusted for information
  - Continue perpetually (committee can change vote)

Decision Criteria (In/Out)

Analyze (report) Results

- If there is a less than 0.01 probability an agent is part of the optimal regimen
  - Candidate for futility
- If the probability an agent is in the optimal regimen is greater than 0.95
  - Report to the steering committee for public dissemination
- If a regimen has at least a 0.95 probability of being superior to SOC Alone then SOC Alone is reported for removal

Allocation Rules

Revise Allocation Rules

- If a SOC it gets minimum of 20%...
- Randomize to regimens with probability proportional to:

$$r_{ij} \sim \frac{\Pr\left(\pi_{ij} = \max\left(\pi\right)\right)}{n_{ij}+1}$$

Statistical Model

Analyze Available Data

$$\log\left(\frac{p}{1-p}\right) = \alpha + \sum_{X=1}^{M}[X] + \sum_{X=1}^{M}\sum_{Y=X+1}^{M}[X,Y] + \lambda_{TIME}$$

- Priors:

$$[X] \sim N(0,1^2) \qquad [X,Y] \sim N(0,0.2^2)$$

Statistical Model

Analyze Available Data

$$\log\left(\frac{p}{1-p}\right) = \alpha + \sum_{X=1}^{M}[X] + \sum_{X=1}^{M}\sum_{Y=X+1}^{M}[X,Y] + \lambda_{TIME}$$

- Priors:

$$[X] \sim N(0,1^2) \qquad [X,Y] \sim N(0,0.2^2)$$

N(0,1) has 95% CI from about 1/7 to 7.

Statistical Model

Analyze Available Data

$$\log\left(\frac{p}{1-p}\right) = \alpha + \sum_{X=1}^{M}[X] + \sum_{X=1}^{M}\sum_{Y=X+1}^{M}[X,Y] + \lambda_{TIME}$$

- Priors:

$$[X] \sim N(0,1^2) \qquad [X,Y] \sim N(0,0.2^2)$$

$N(0,0.2^2)$ has 95% CI from about 2/3 to 3/2.

Statistical Model

Analyze Available Data

$$\log\left(\frac{p}{1-p}\right) = \alpha + \sum_{X=1}^{M}[X] + \sum_{X=1}^{M}\sum_{Y=X+1}^{M}[X,Y] + \lambda_{TIME}$$

- Priors:

$$[X] \sim N(0,1^2) \qquad [X,Y] \sim N(0,0.2^2)$$

- Time:
  - Incorporate time "buckets" to model time trend or 'drift'

$$[\lambda] \sim NDLM(0,\tau^2)$$

Example Trial

Regimens		Agents			
		1	2	3	4
Agents	1				
	2				
	3				
	4				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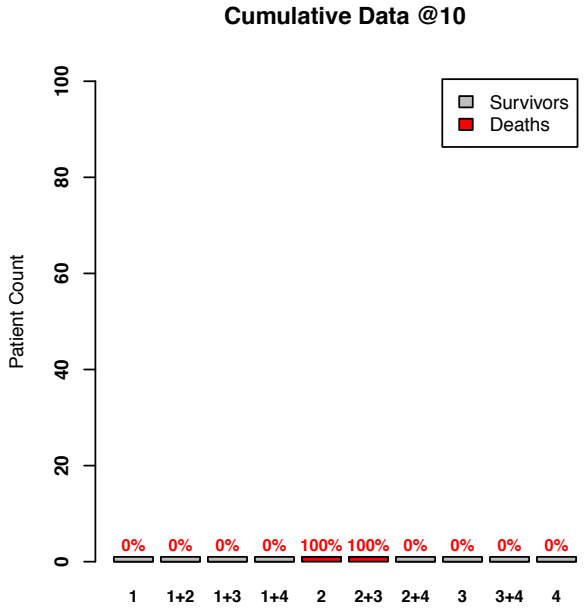
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4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3+4
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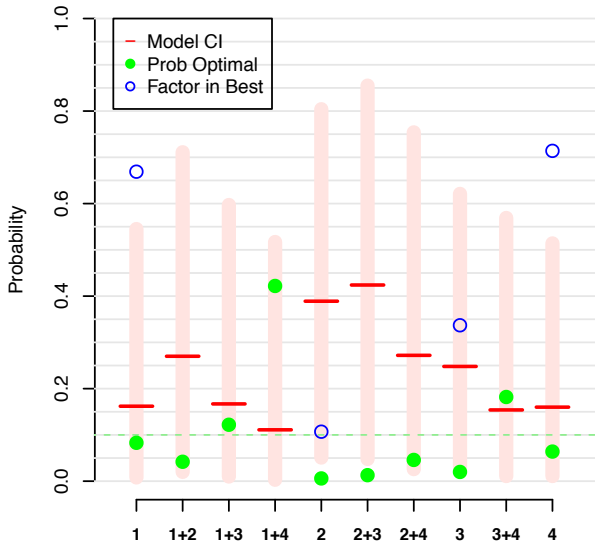
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Factor in Best
Probability
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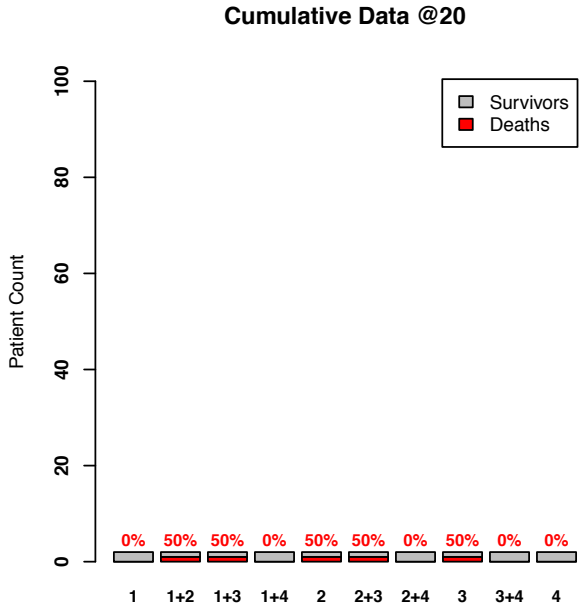
1+3
1+4
2
2+3
2+4
3
3+4
4


New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4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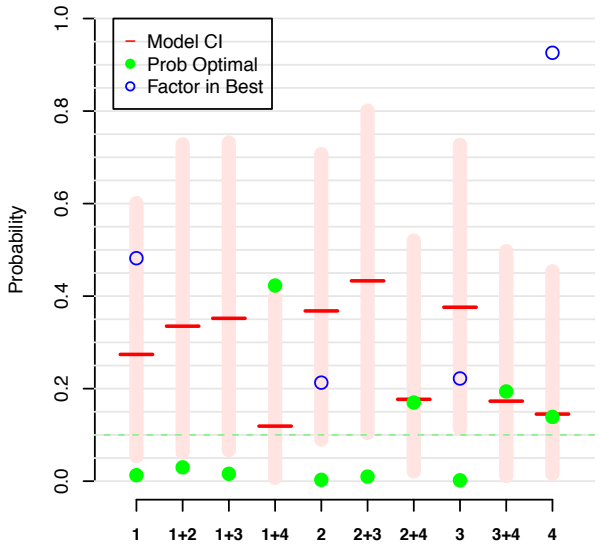
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Factor in Best
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1
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1+3
1+4
2
2+3
2+4
3
3+4
4


New Data
Deaths
Survivors
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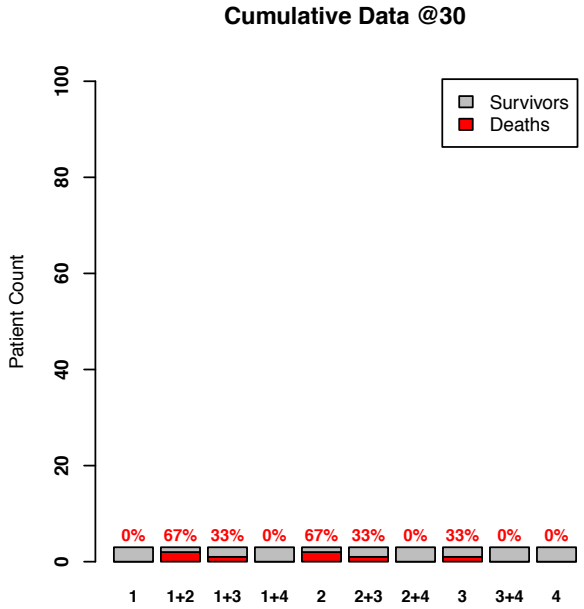
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4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Patient Count
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3
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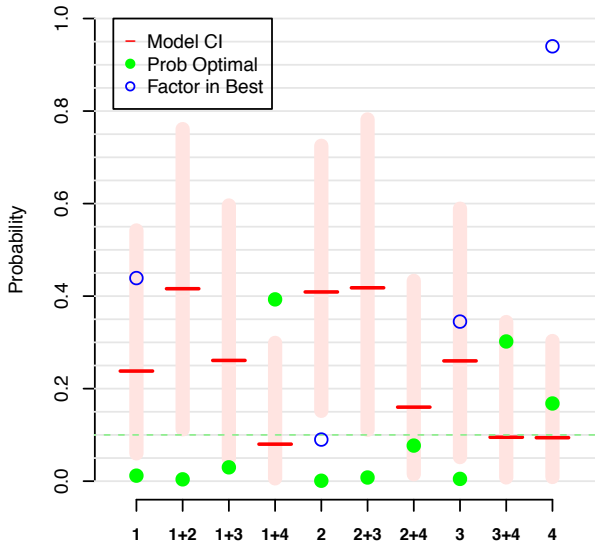
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Model CI
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Factor in Best
Probability
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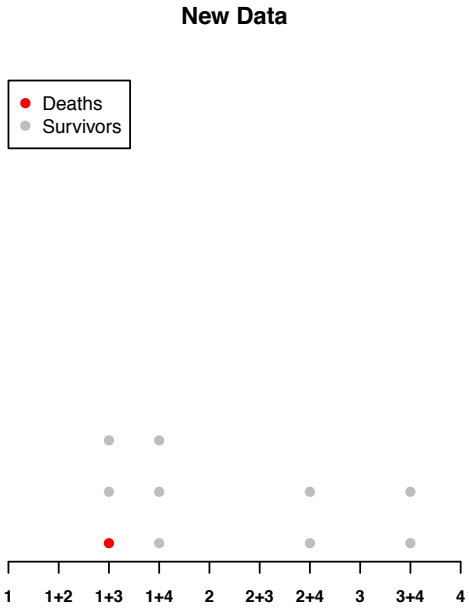
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Survivors
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1+3
1+4
2
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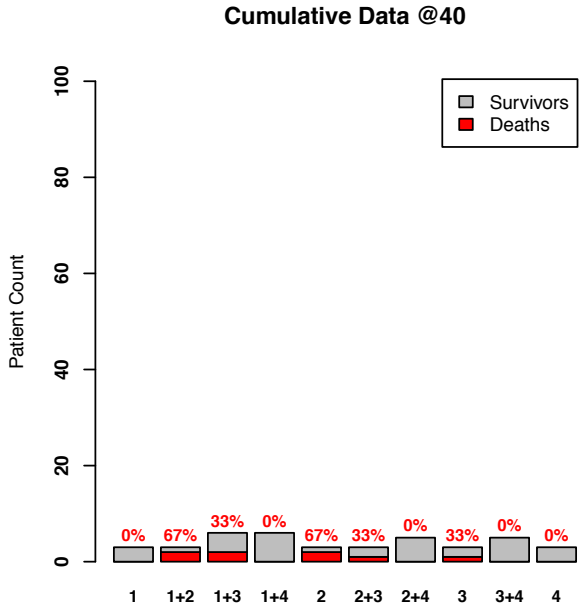
2+4
3
3+4
4


Cumulative Data @40
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Deaths
Patient Count
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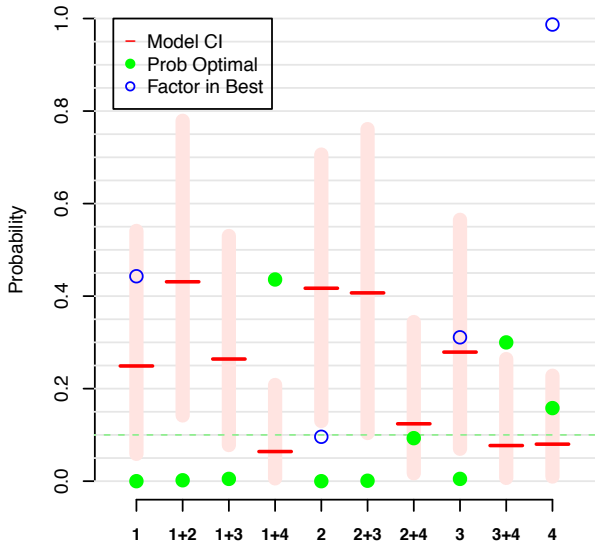
4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Factor in Best
Probability
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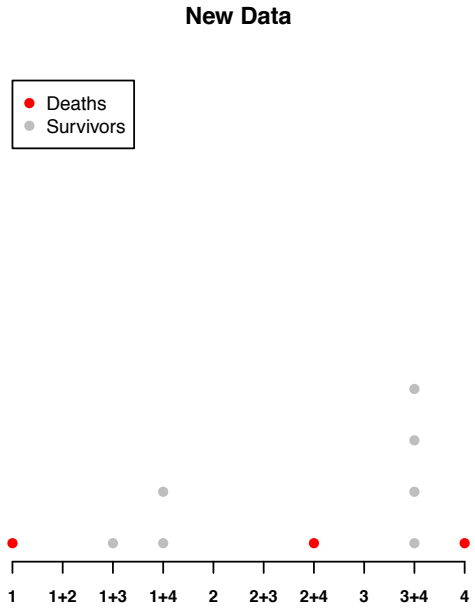
4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Deaths
Survivors
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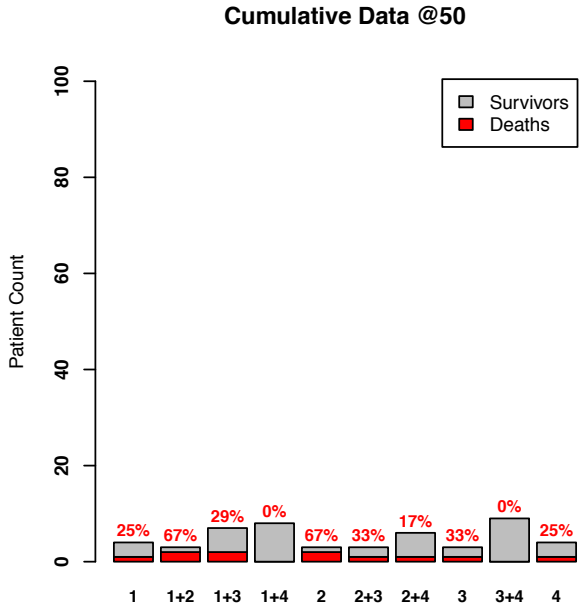
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @50
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Deaths
Patient Count
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40
60
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100
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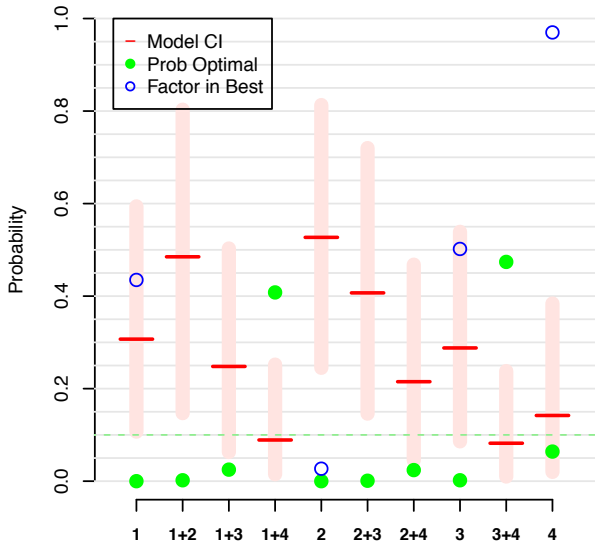
3
3+4
4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Model CI
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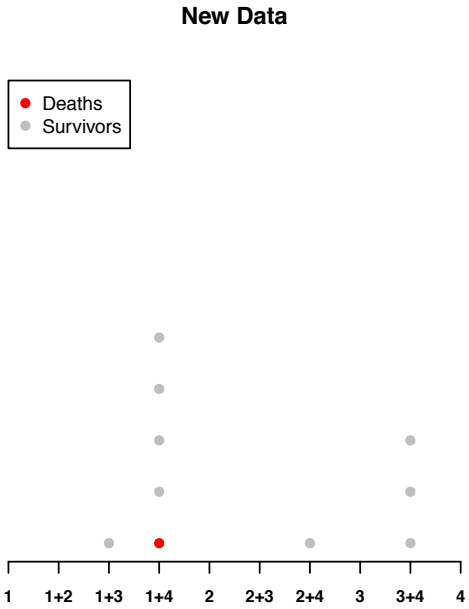
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Deaths
Survivors
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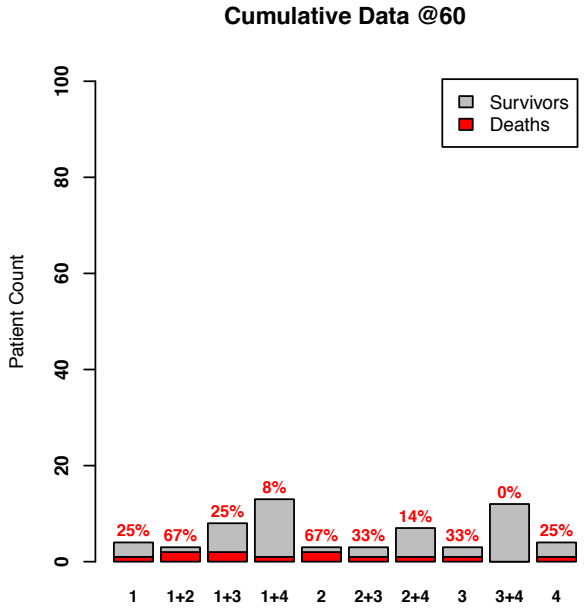
3
3+4
4


Cumulative Data @60
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Deaths
Patient Count
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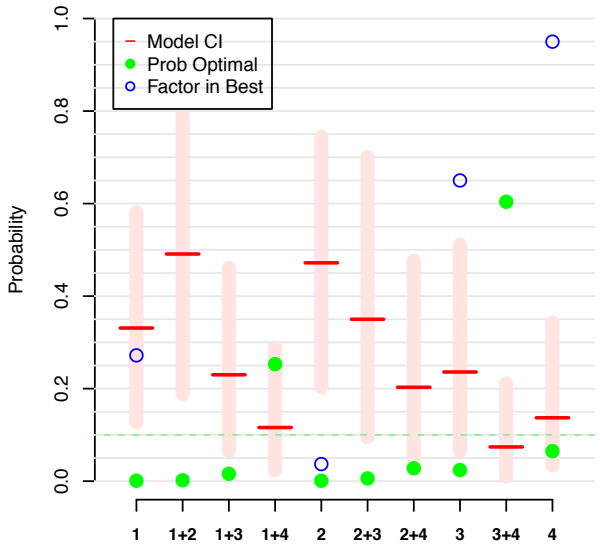
Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
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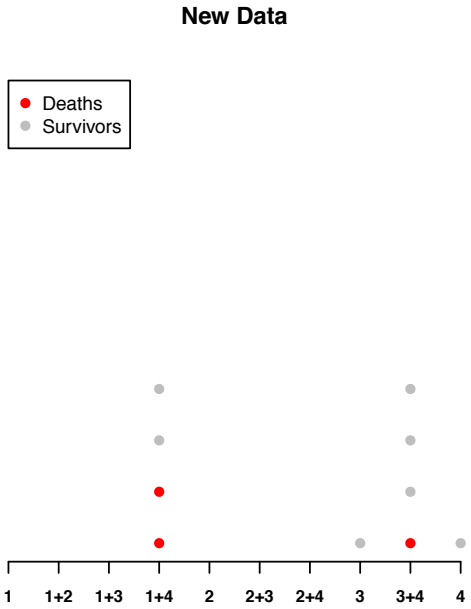
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Deaths
Survivors
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2
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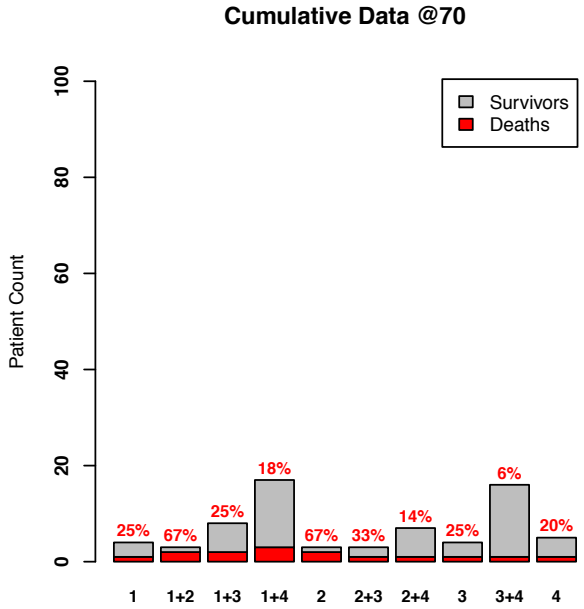
4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Deaths
Patient Count
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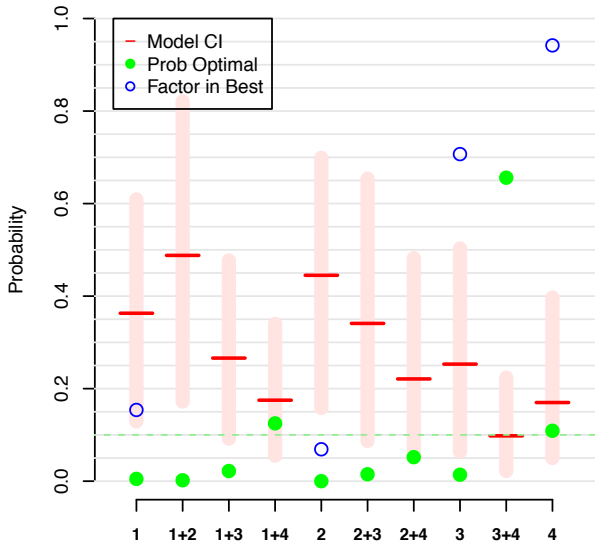
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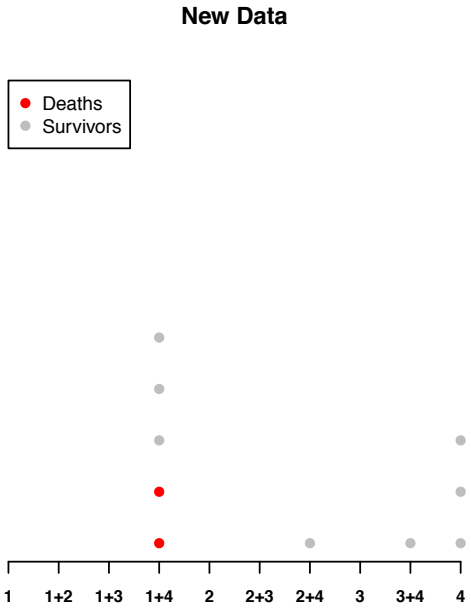
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Survivors
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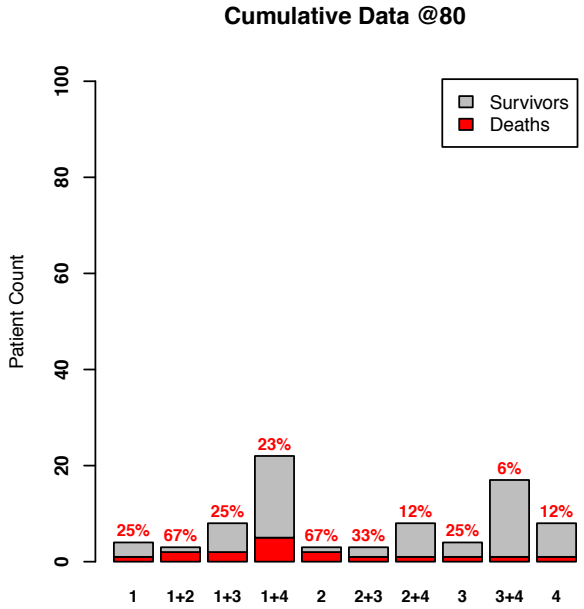
Cumulative Data @80
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Deaths
Patient Count
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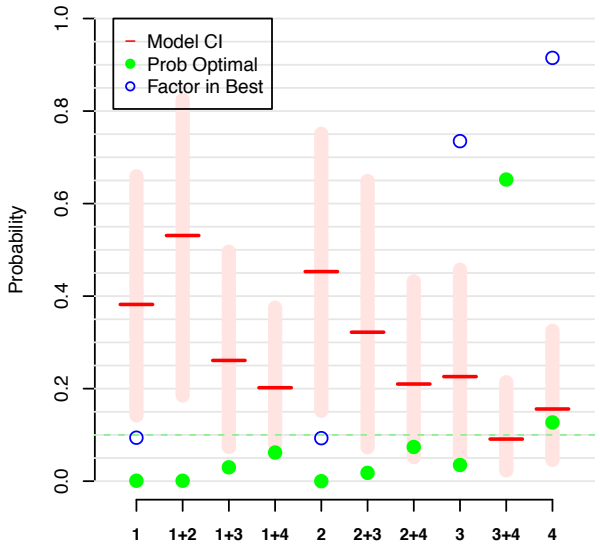
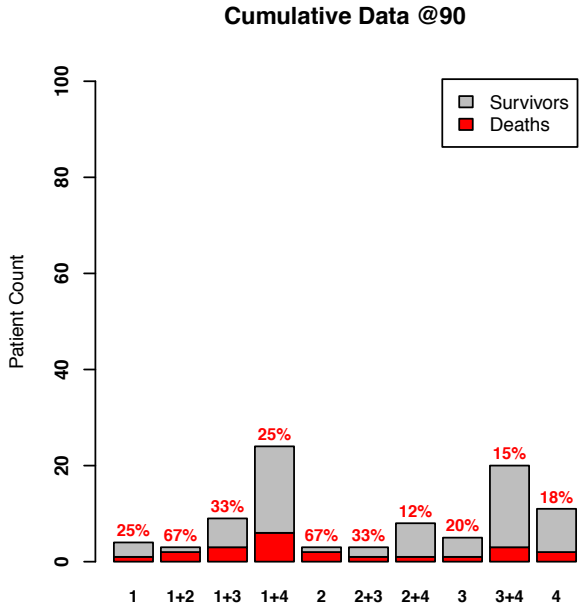
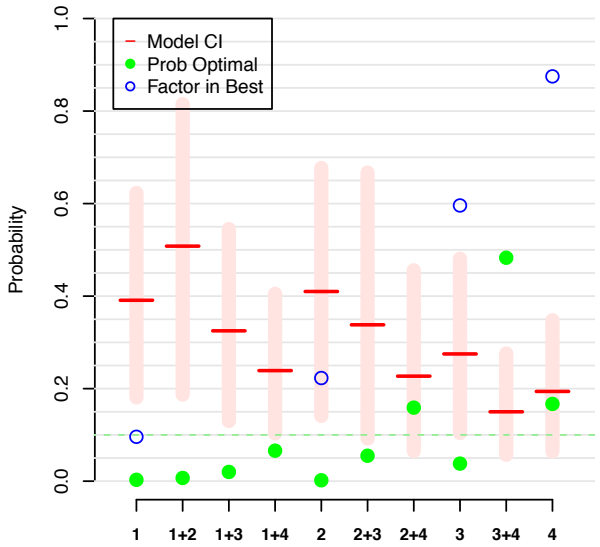
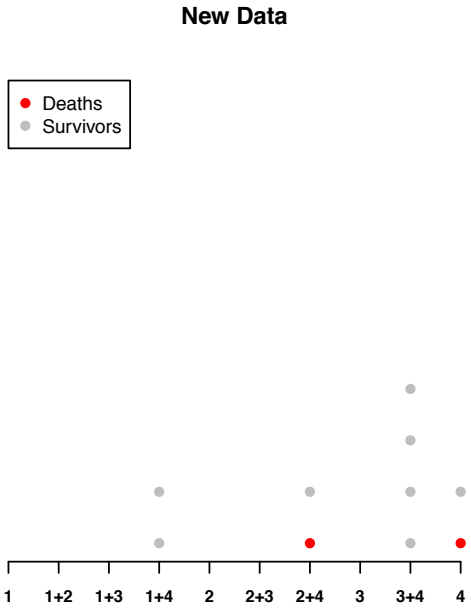
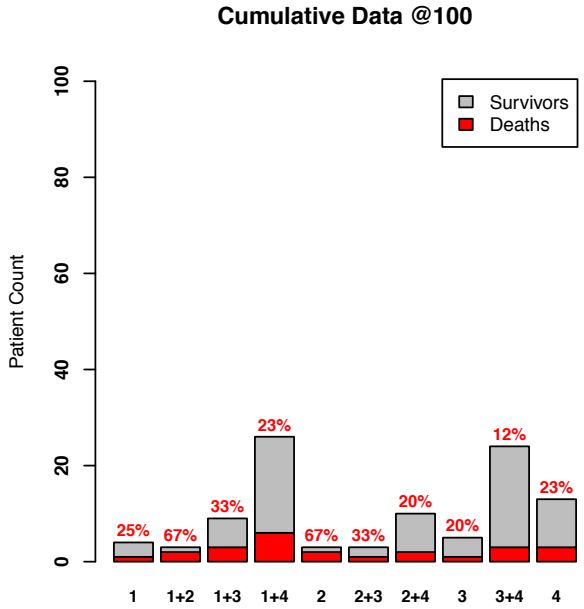

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

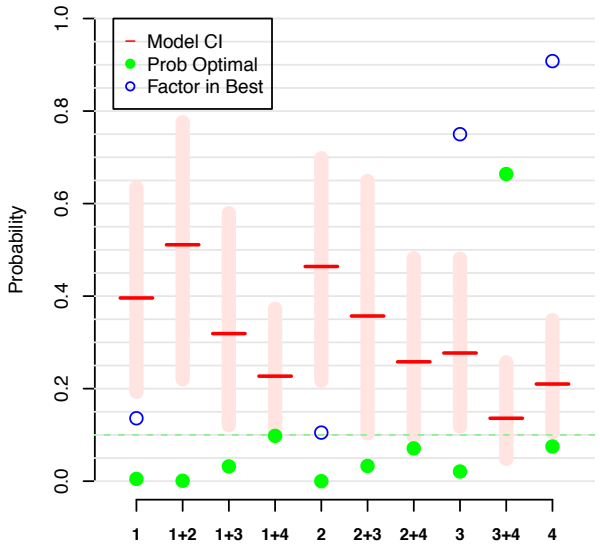

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

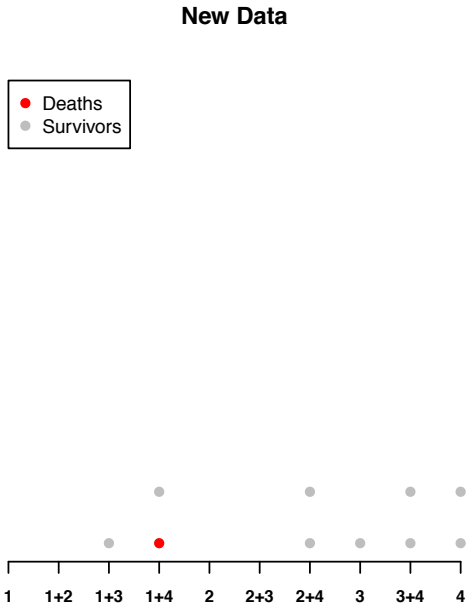

Cumulative Data @90
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
33%
25%
67%
33%
12%
20%
15%
18%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

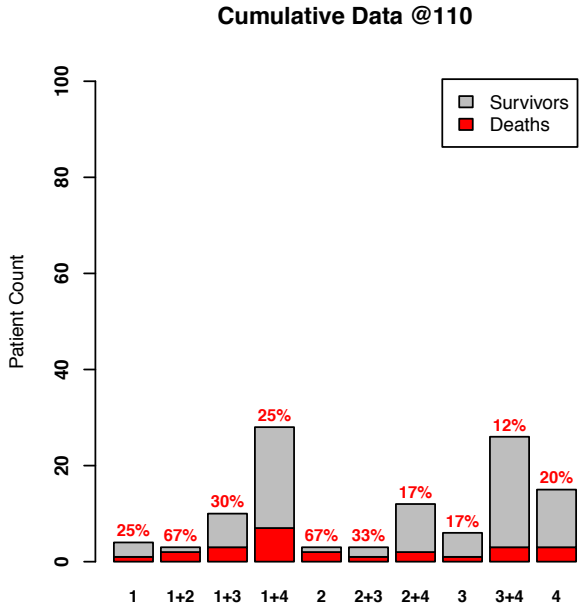

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

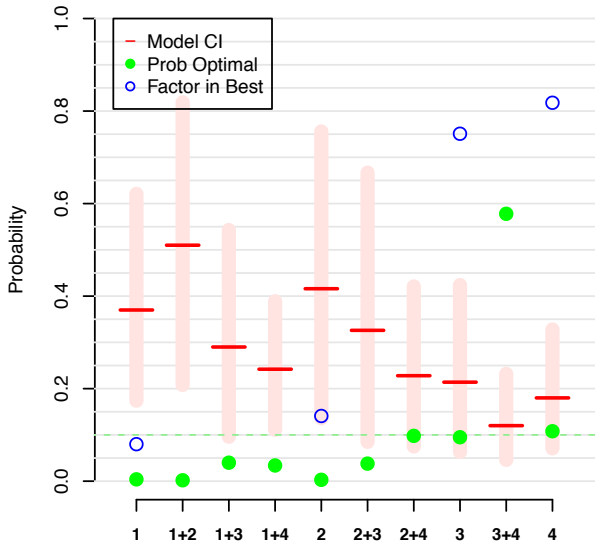

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

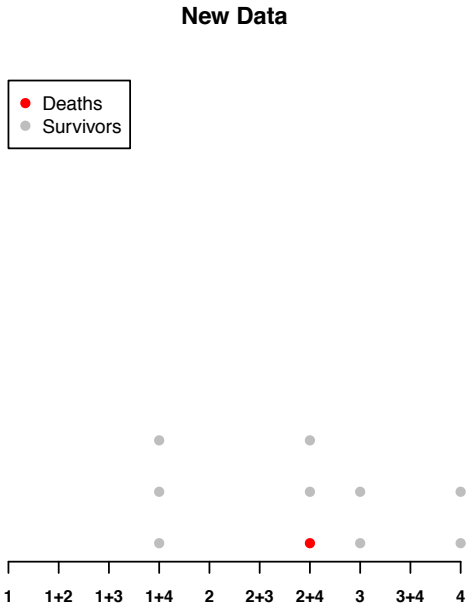

Cumulative Data @100
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
33%
23%
67%
33%
20%
20%
12%
23%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

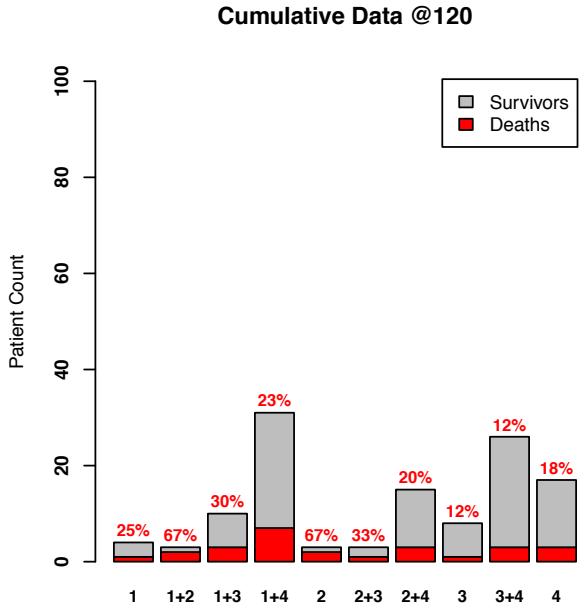

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

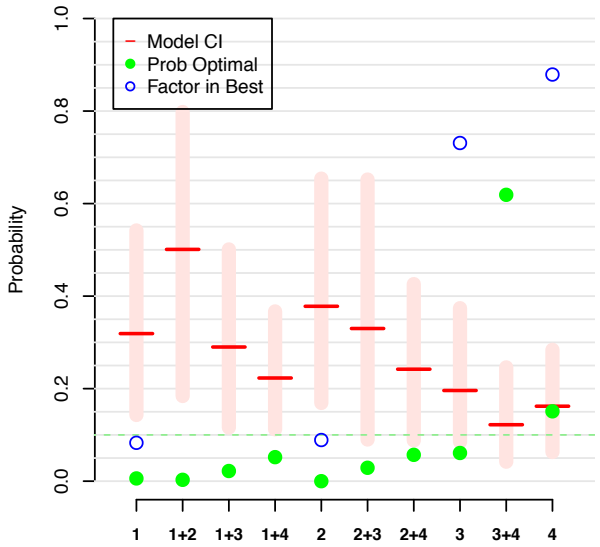

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @110
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
30%
25%
67%
33%
17%
17%
12%
20%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

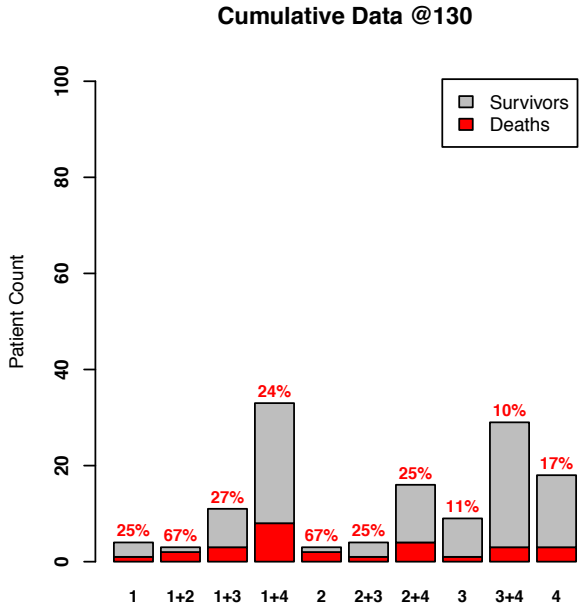

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

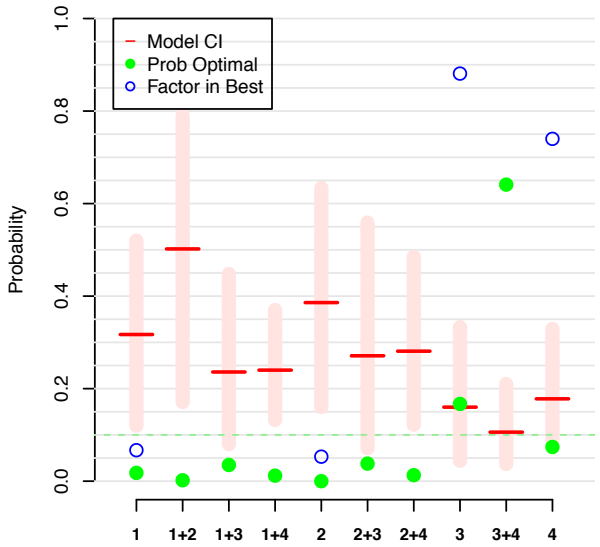

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

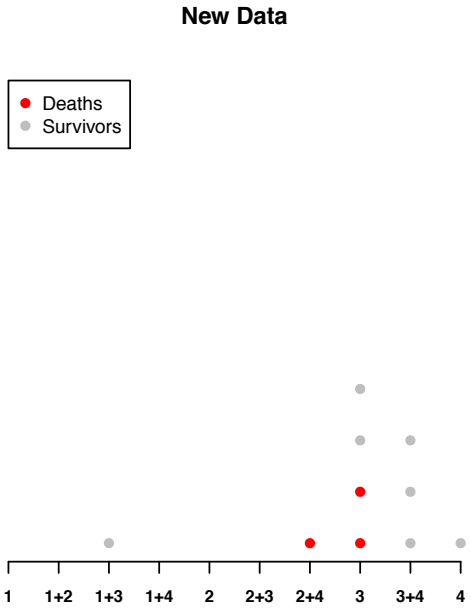

Cumulative Data @120
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
30%
23%
67%
33%
20%
12%
12%
18%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

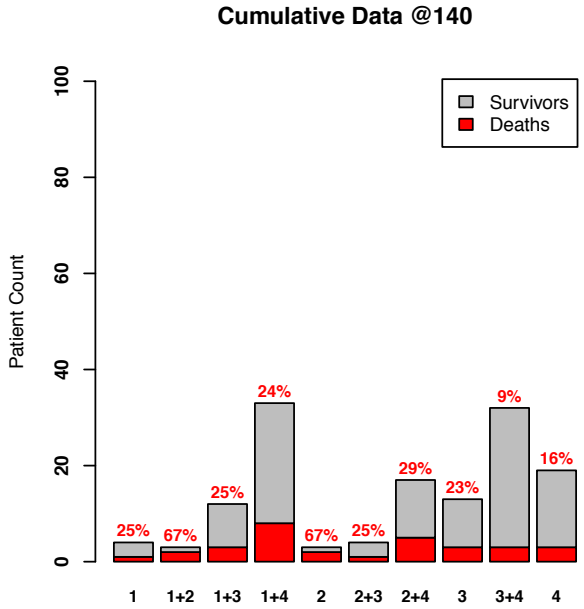

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

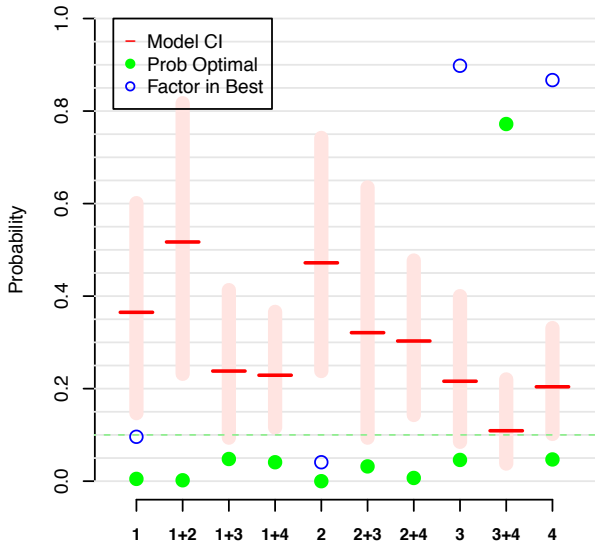

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

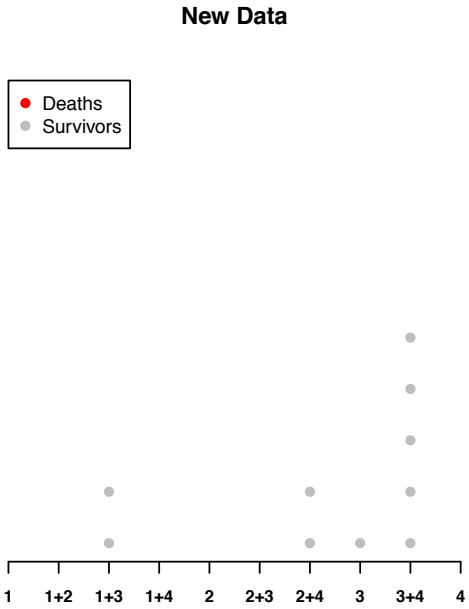

Cumulative Data @130
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
27%
24%
67%
25%
25%
11%
10%
17%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

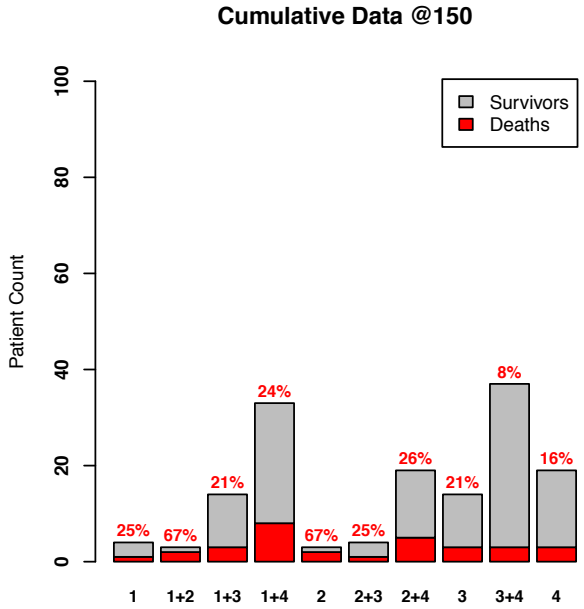

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

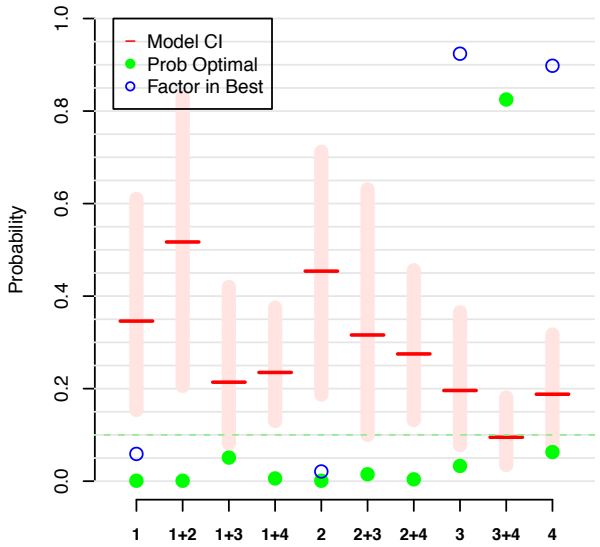

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

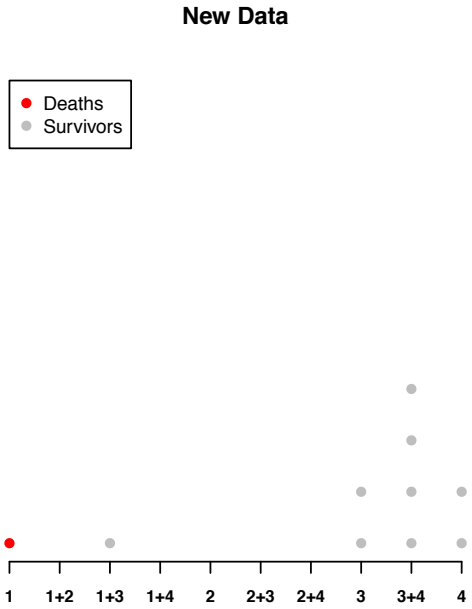

Cumulative Data @140
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
25%
24%
67%
25%
29%
23%
9%
16%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

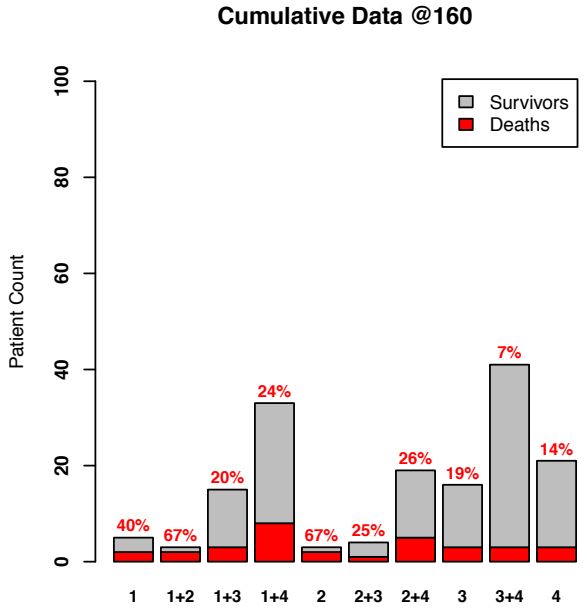

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

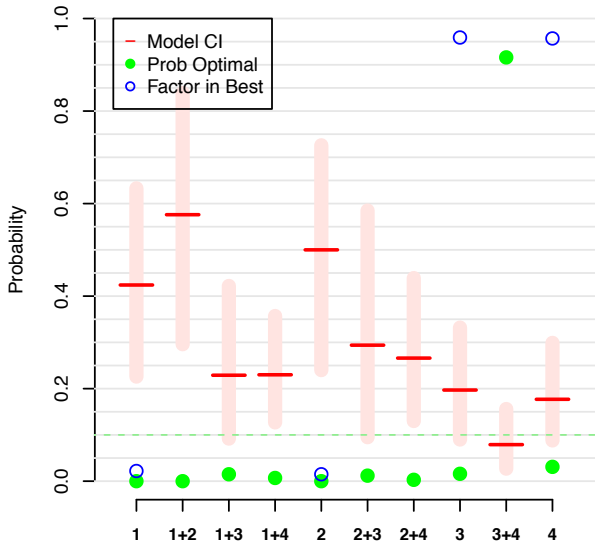

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

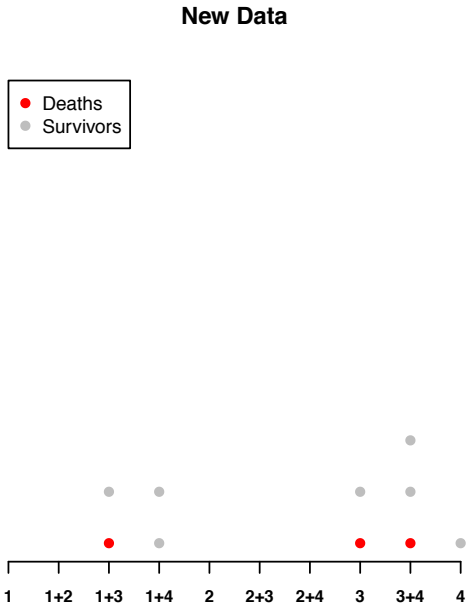

Cumulative Data @150
Survivors
Deaths
Patient Count
0
20
40
60
80
100
25%
67%
21%
24%
67%
25%
26%
21%
8%
16%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

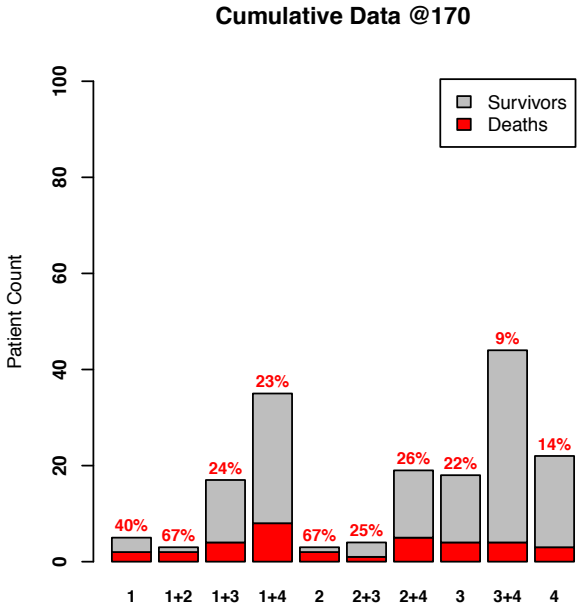

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

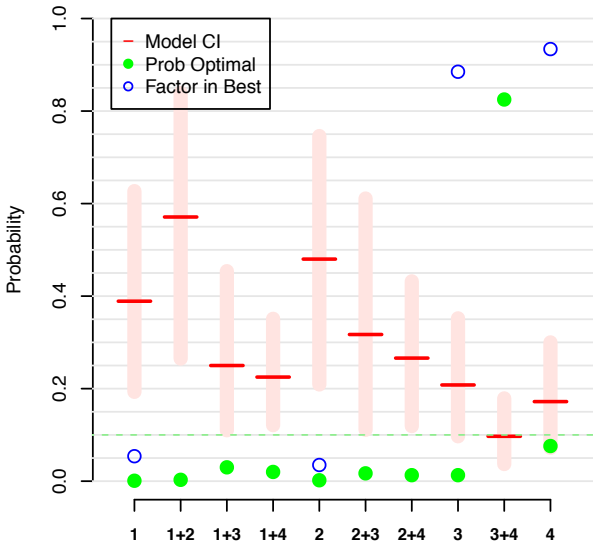

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @160
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
20%
24%
67%
25%
26%
19%
7%
14%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

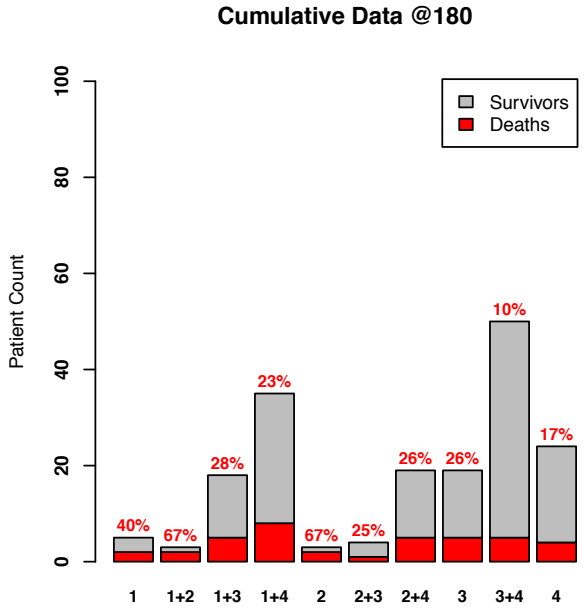

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

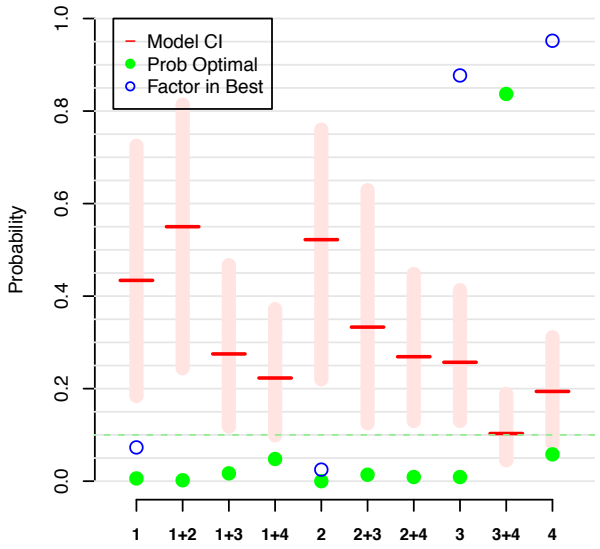

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

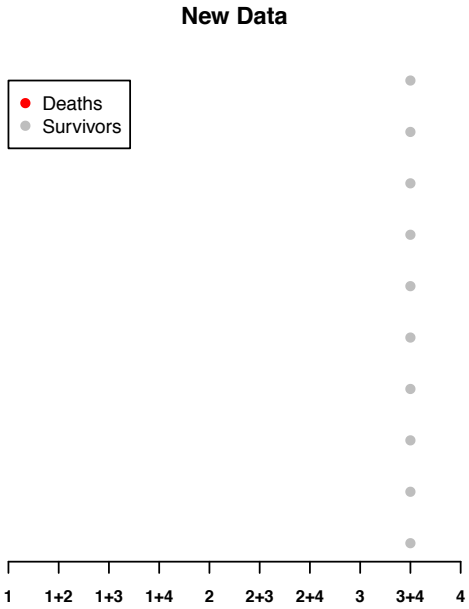

Cumulative Data @170
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
24%
23%
67%
25%
26%
22%
9%
14%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

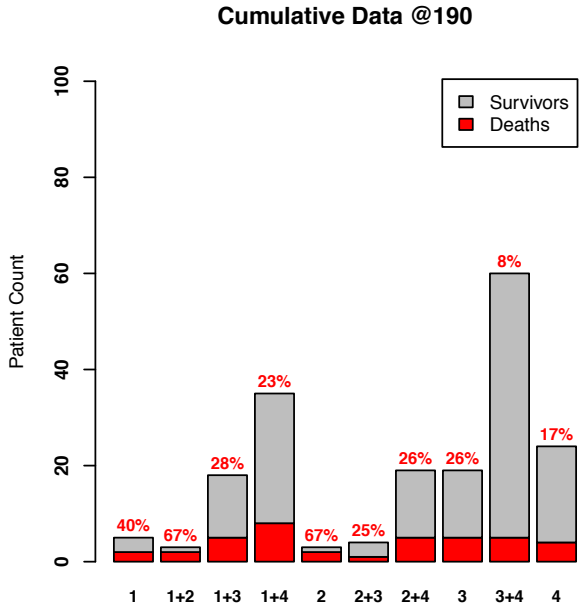

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

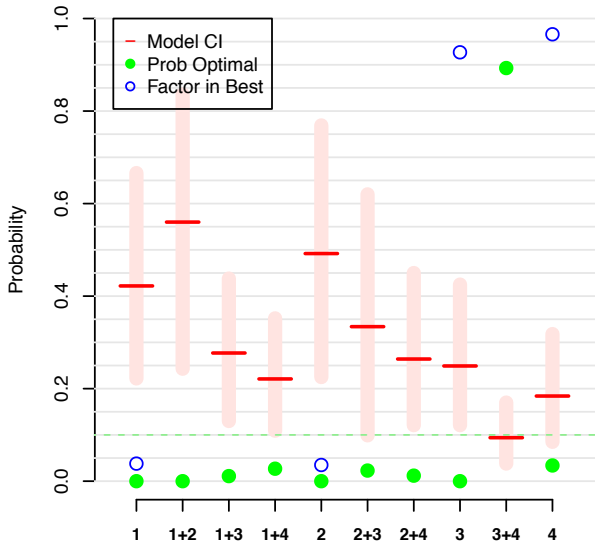

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

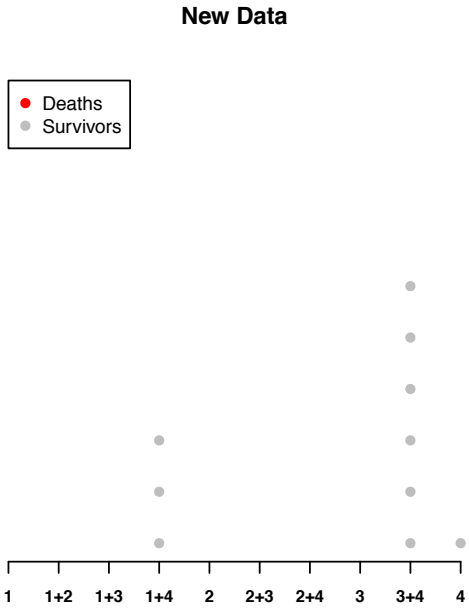

Cumulative Data @180
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
28%
23%
67%
25%
26%
26%
10%
17%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

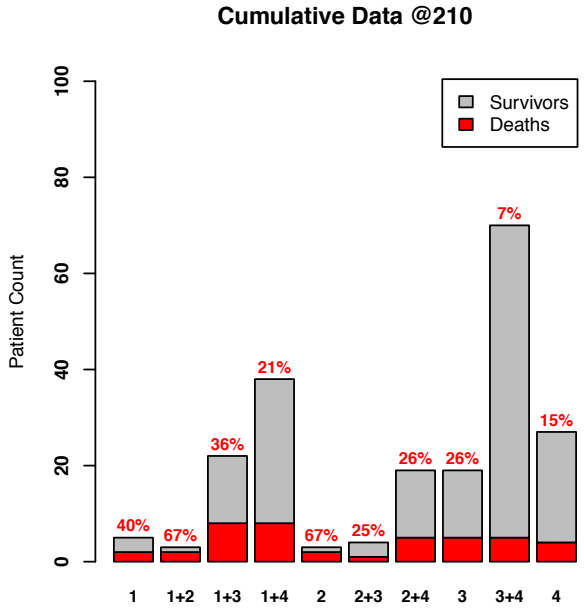

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

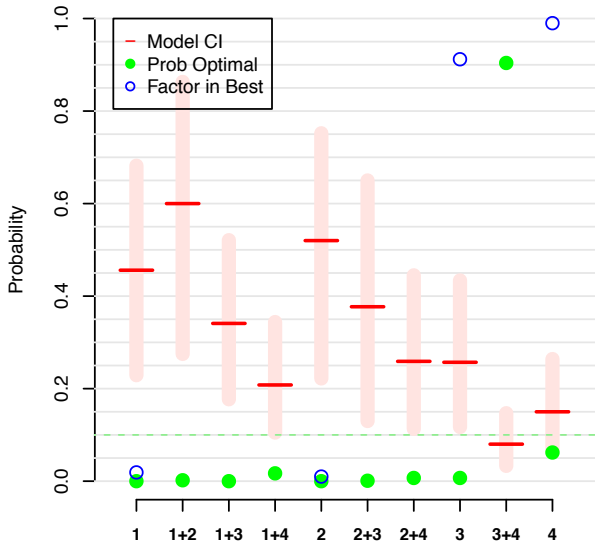

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

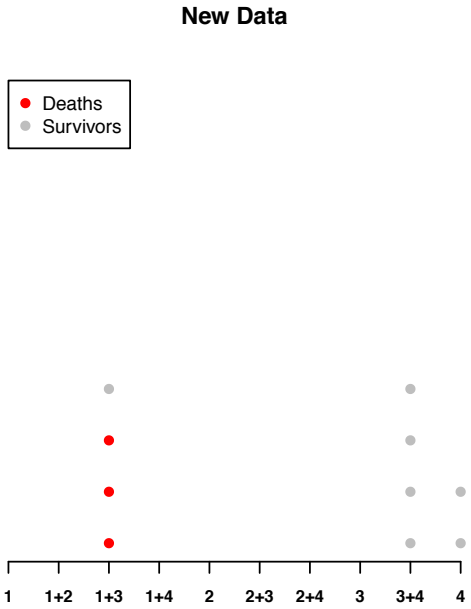

Cumulative Data @190
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
28%
23%
67%
25%
26%
26%
8%
17%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

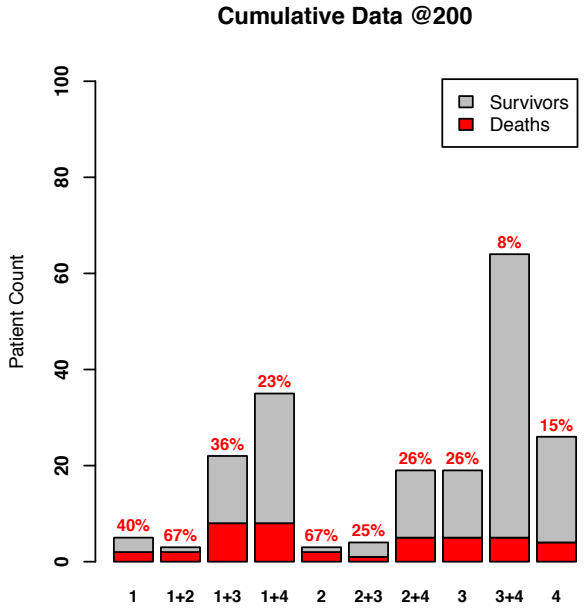

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

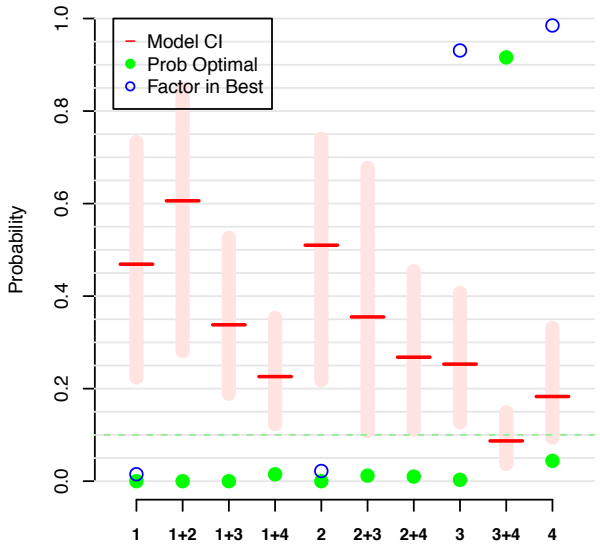

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

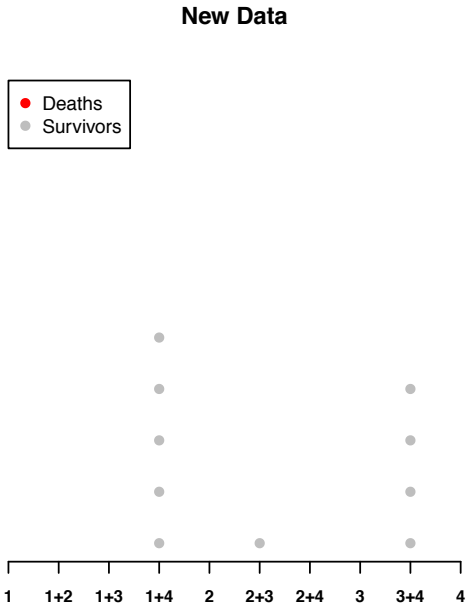

Cumulative Data @210
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
36%
21%
67%
25%
26%
26%
7%
15%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

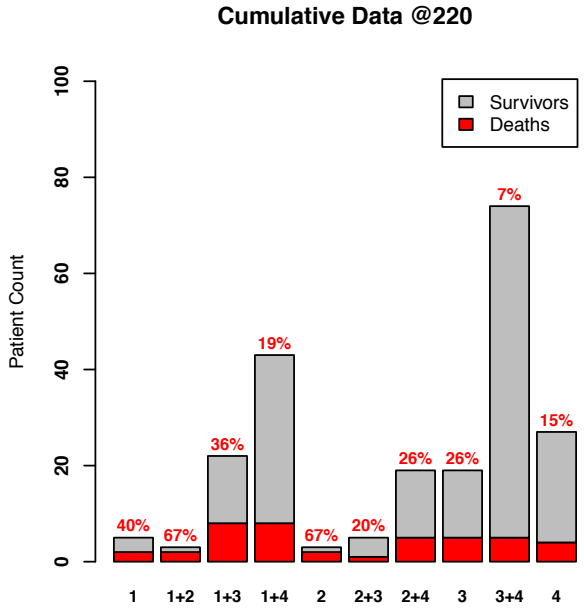

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

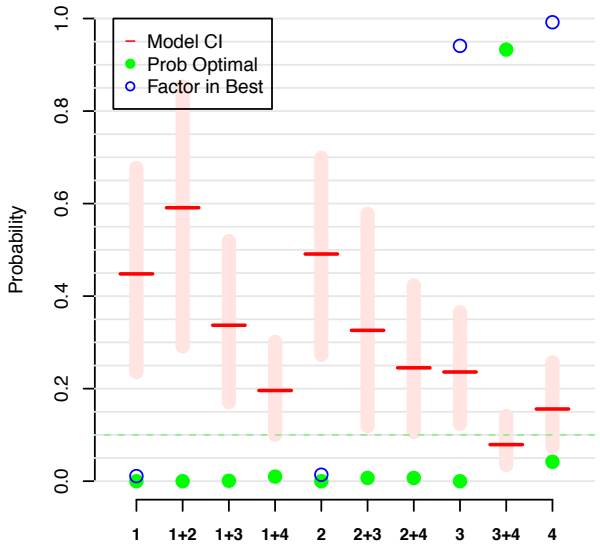

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @200
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
36%
23%
67%
25%
26%
26%
8%
15%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

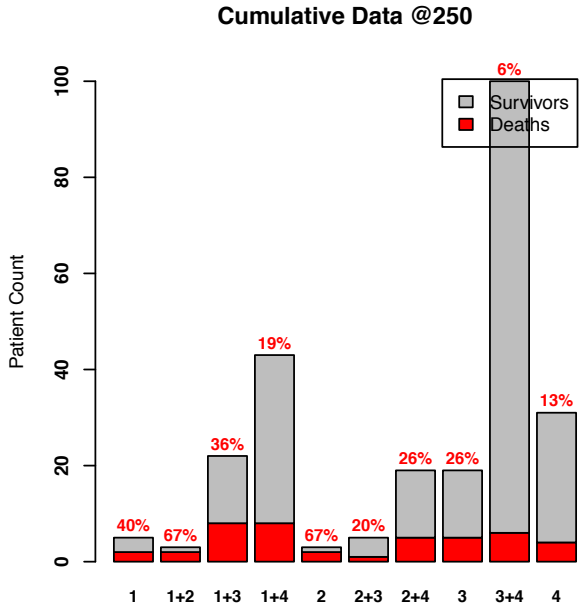

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

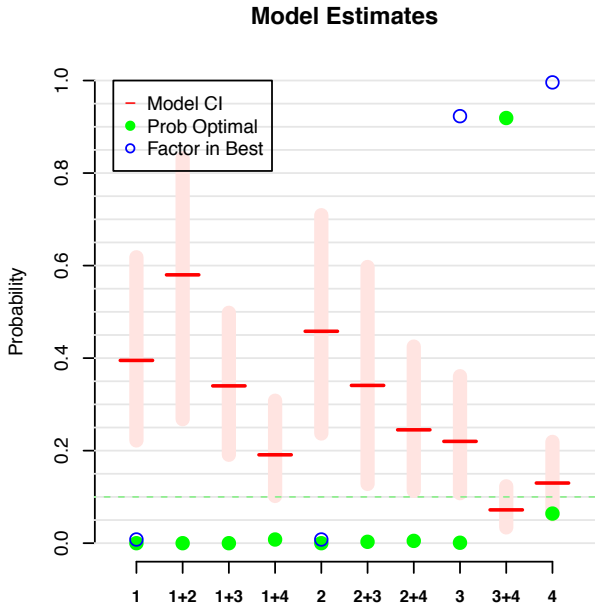

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

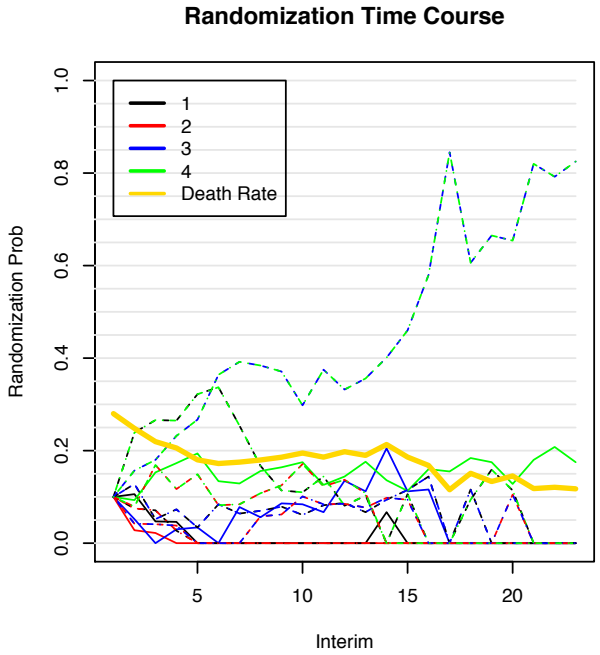

Cumulative Data @220
Survivors
Deaths
Patient Count
0
20
40
60
80
100
40%
67%
36%
19%
67%
20%
26%
26%
7%
15%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

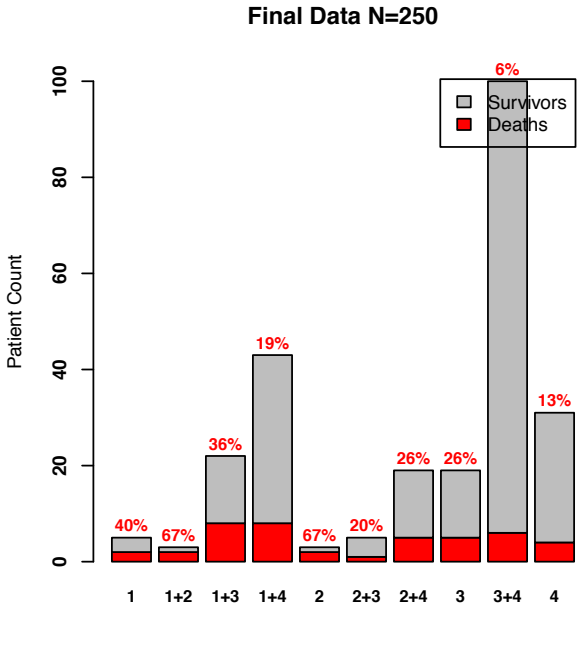

Model Estimates
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

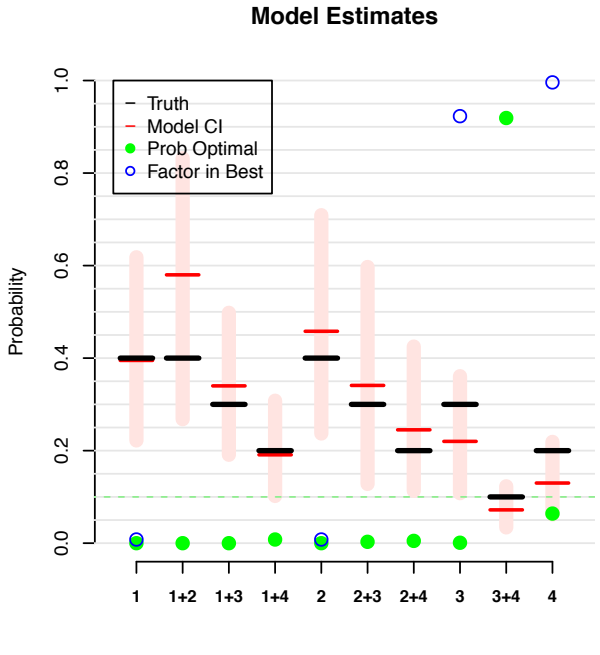

New Data
Deaths
Survivors
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Cumulative Data @250
Patient Count
0
20
40
60
80
100
Survivors
Deaths
40%
67%
36%
19%
67%
20%
26%
26%
6%
13%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Model Estimates
Probability
0.0
0.2
0.4
0.6
0.8
1.0
Model CI
Prob Optimal
Factor in Best
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4


Randomization Time Course
Randomization Prob
Interim
1
2
3
4
Death Rate
0.0
0.2
0.4
0.6
0.8
1.0
5
10
15
20


Final Data N=250
Patient Count
Survivors
Deaths
0
20
40
60
80
100
40%
67%
36%
19%
67%
20%
26%
26%
6%
13%
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

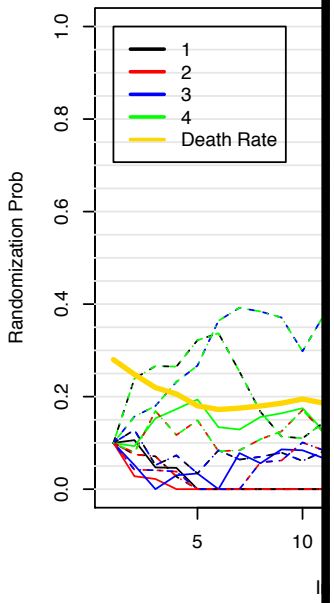

Model Estimates
Probability
Truth
Model CI
Prob Optimal
Factor in Best
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

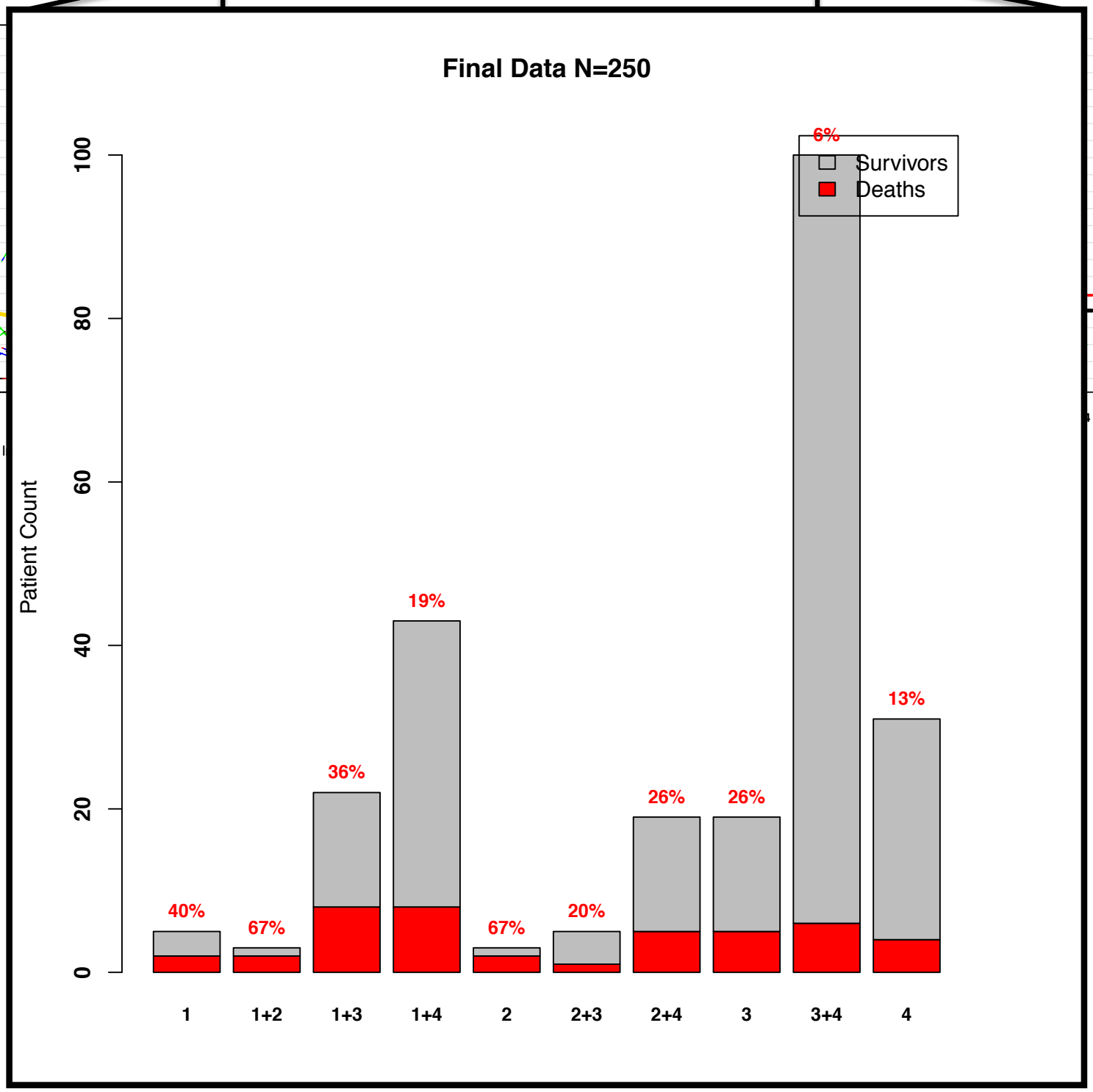

Randomization Time Course
1
2
3
4
Death Rate
Randomization Prob
0.0
0.2
0.4
0.6
0.8
1.0
5
10
15
20
Interim

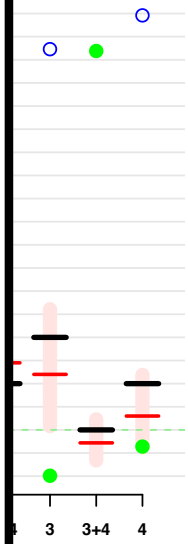
Randomization Time Course

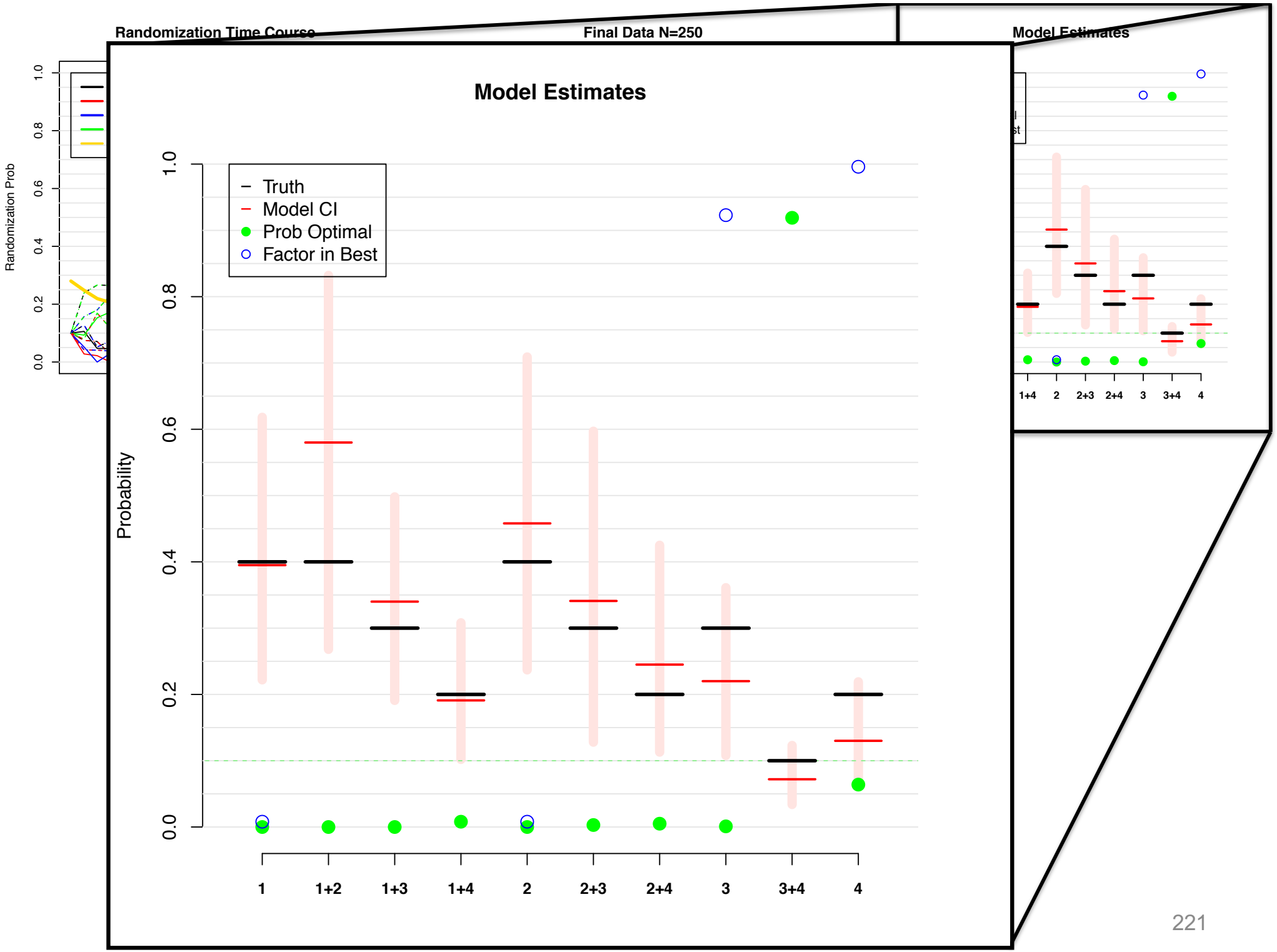
Final Data N=250

Model Estimates

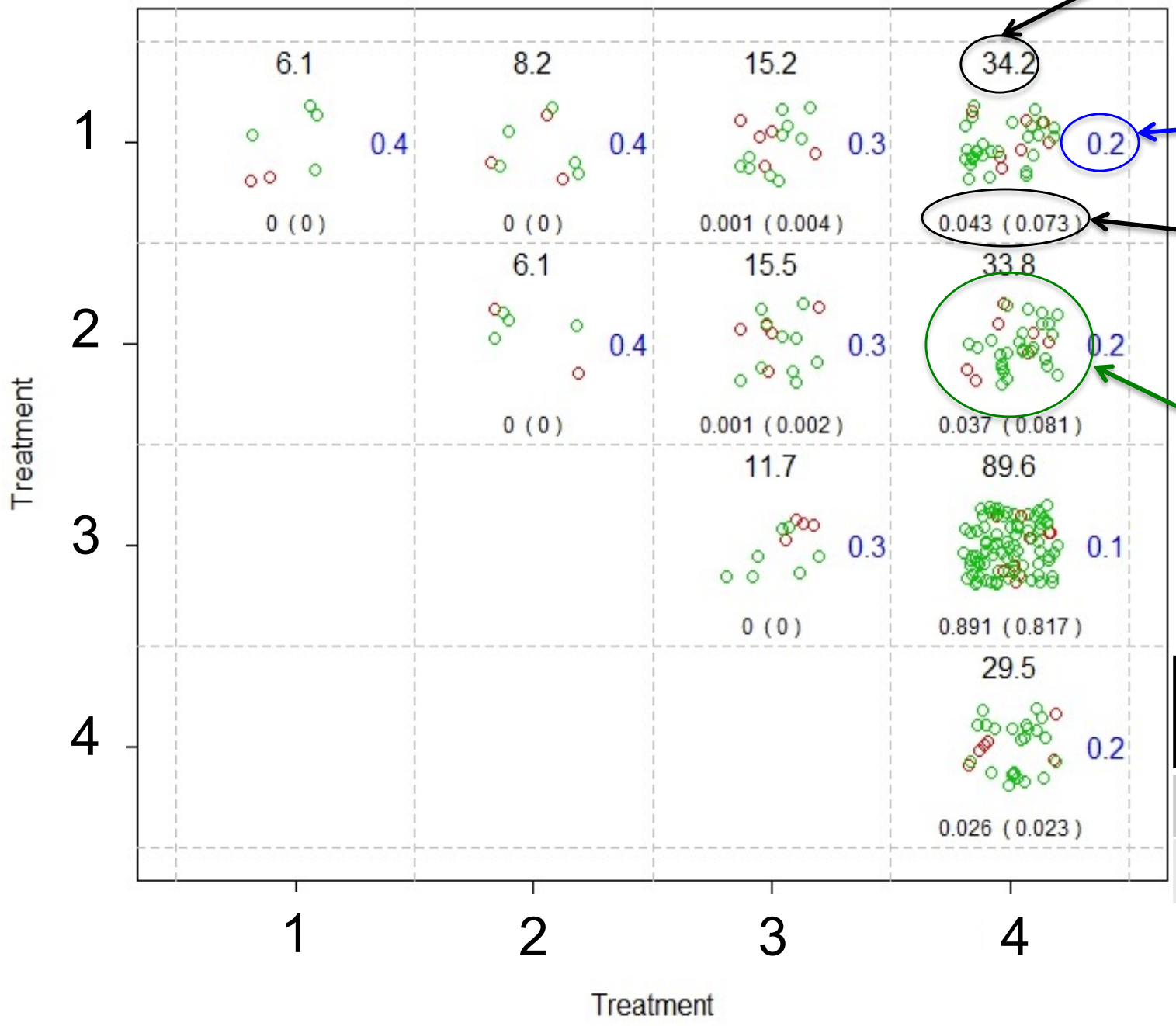




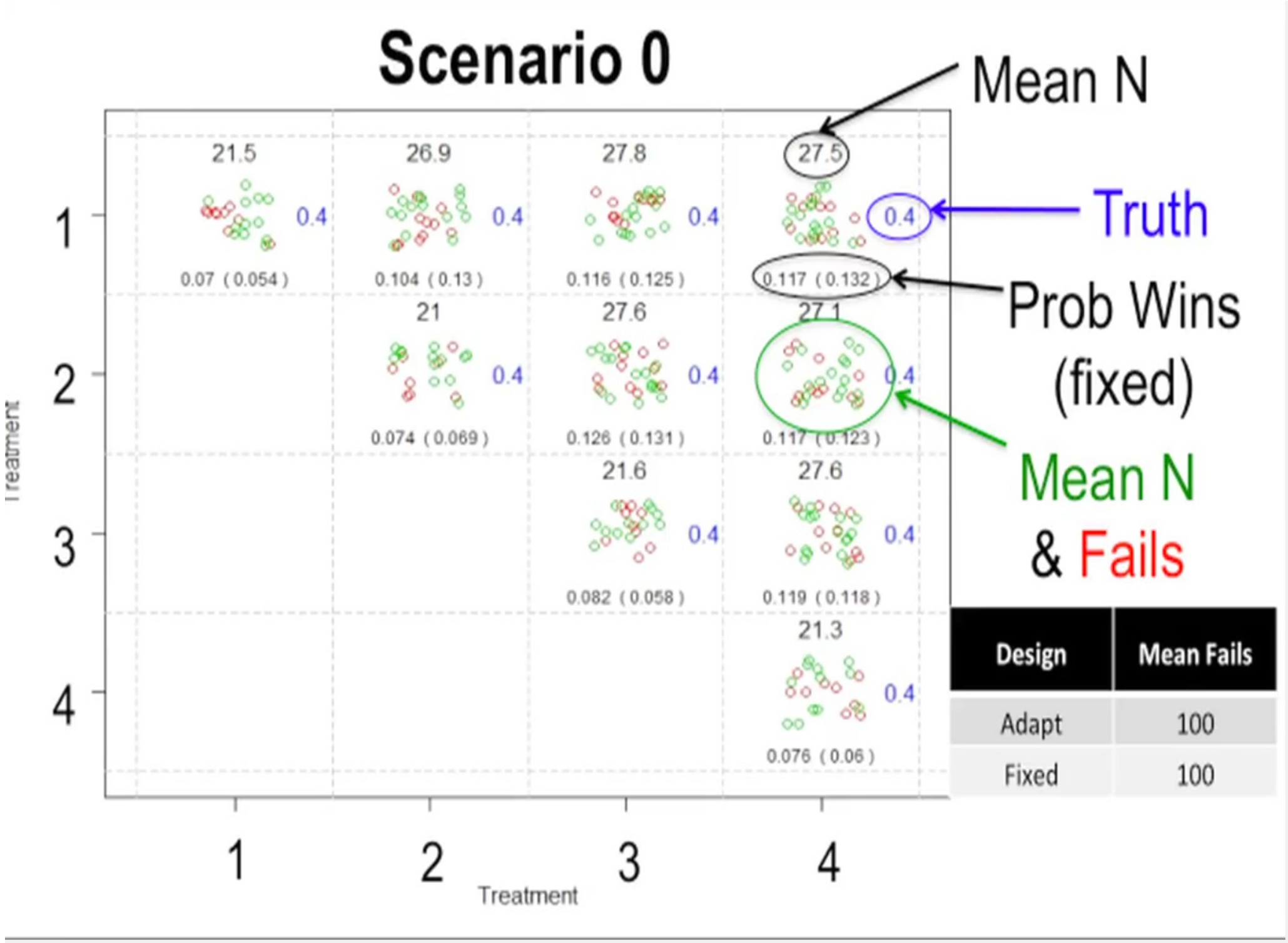



Randomization Time Course
Final Data N=250
Model Estimates
Randomization Prob
0.0
0.2
0.4
0.6
0.8
1.0
Model Estimates
Truth
Model CI
Prob Optimal
Factor in Best
Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
1+2
1+3
1+4
2
2+3
2+4
3
3+4
4

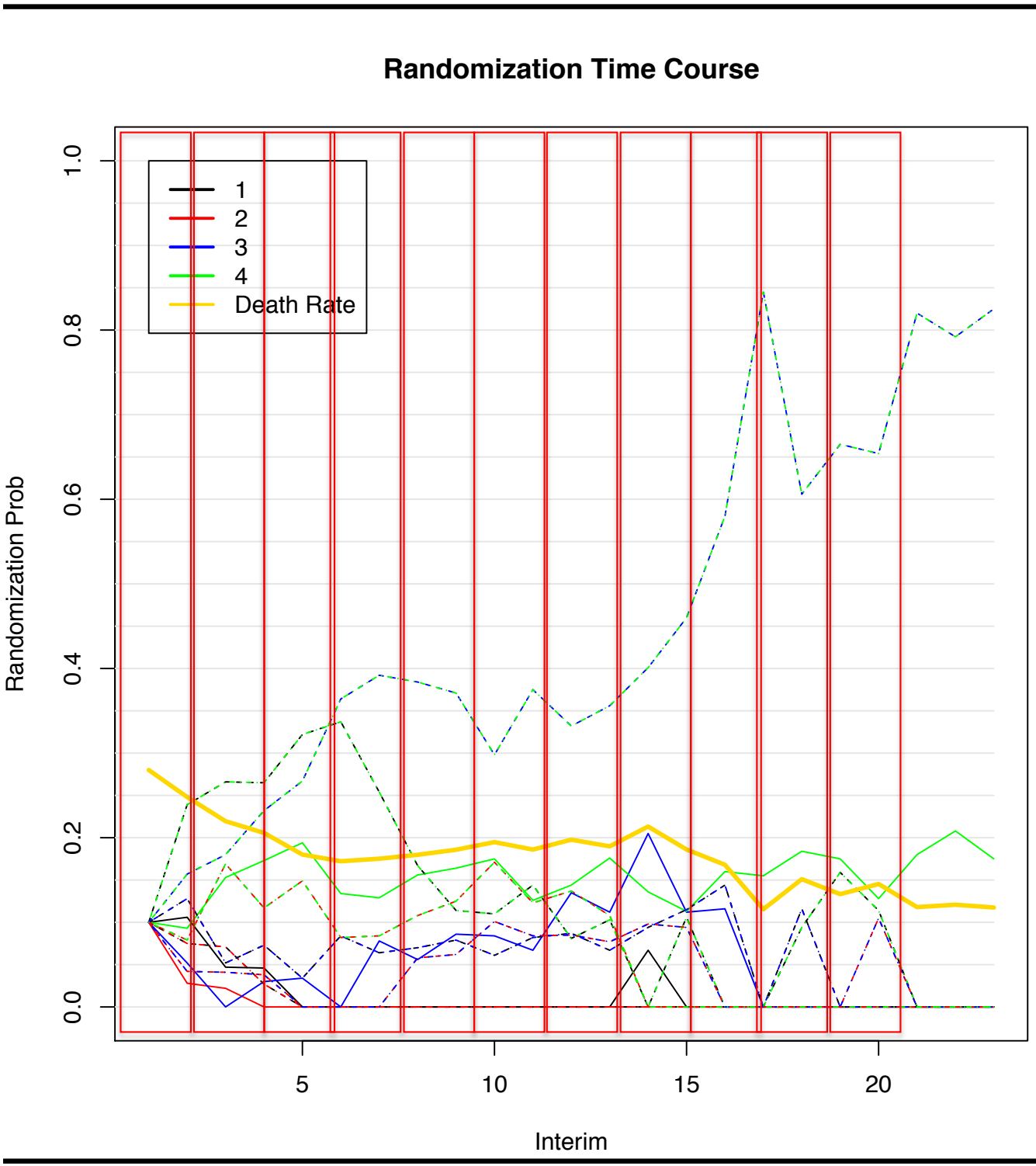
Scenario 3



Design	Mean Deaths
Adapt	49.4
Fixed	69.9



Design	Mean Fails
Adapt	100
Fixed	100



The model adjusts for time trends by modeling the patient drift within "buckets" or months.

Summary

- Incredibly powerful design for finding effective therapies and combinations in the universe of treatments
  - Type III Error (the question never asked!)
- Allows the arms to evolve internally and externally to changing science
- Improved Embedded Care: Efficiently and quickly identifies best agents, *while treating patients more effectively*
- Have design ready—on the shelf for next pandemic
  - A number of parameters can be optimized quickly
  - Protocol ready (add appendices)
  - Models + simulations ready
- Need independent committee to decide which drugs to plug in

Platform Example 2

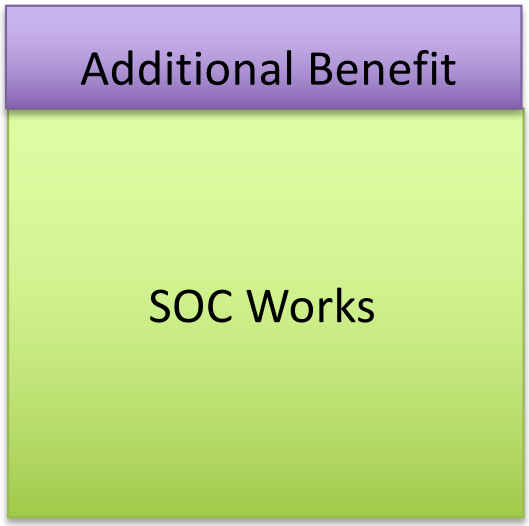
The Role of Biomarkers in Treatments & Trials

Testing a New Treatment

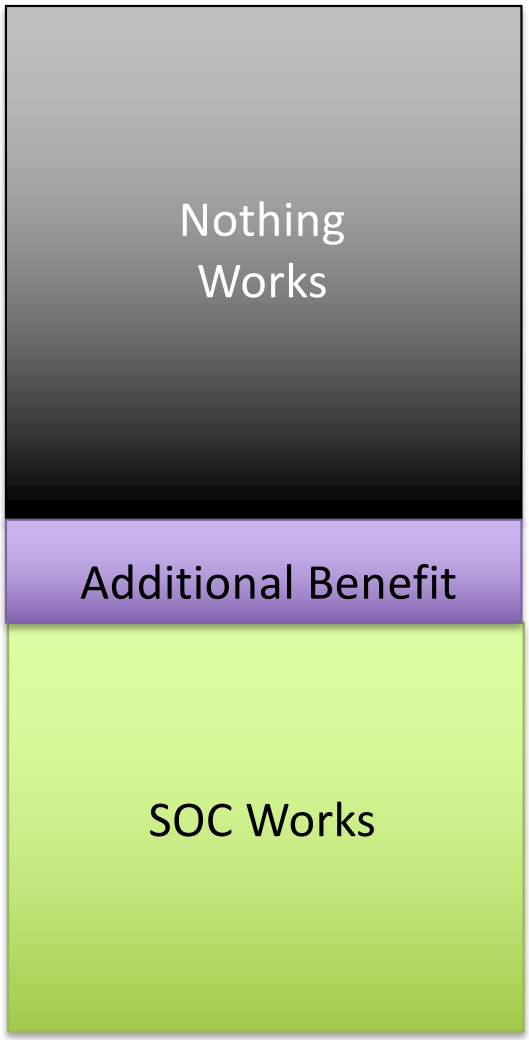
- Standard of Care works in 40%

10% of Patients Benefit

- Standard of Care works in 40%
- New therapy works in 50%

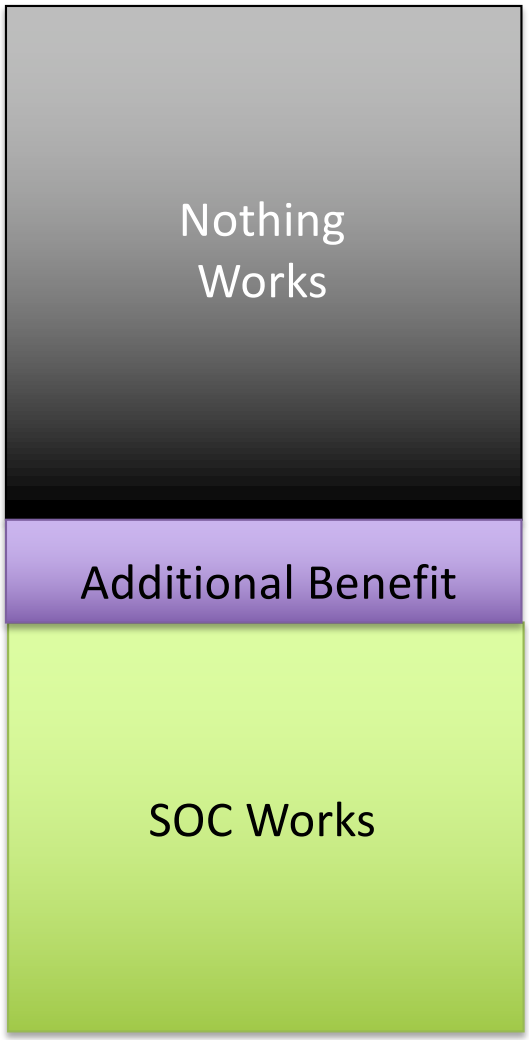


50% still untreatable



- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

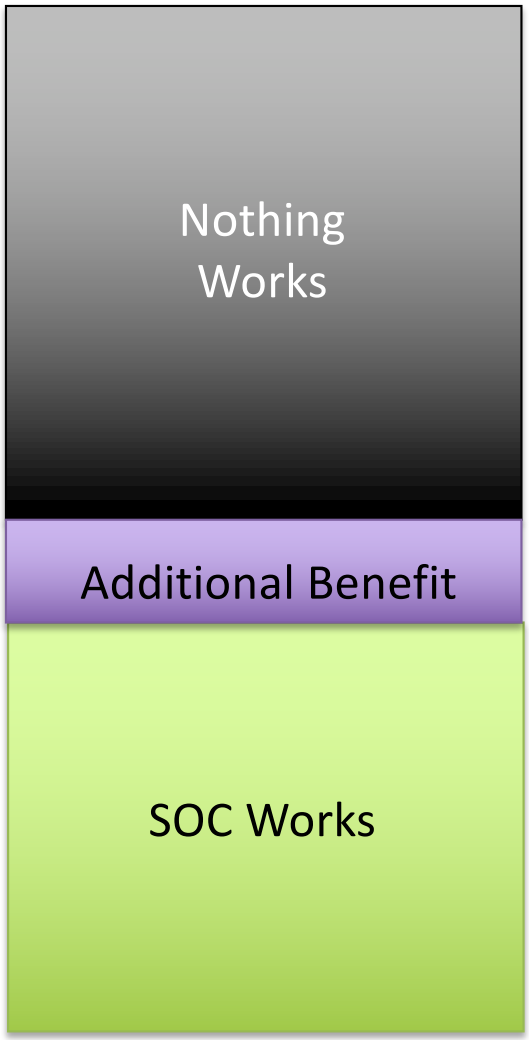
50% still untreatable



- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

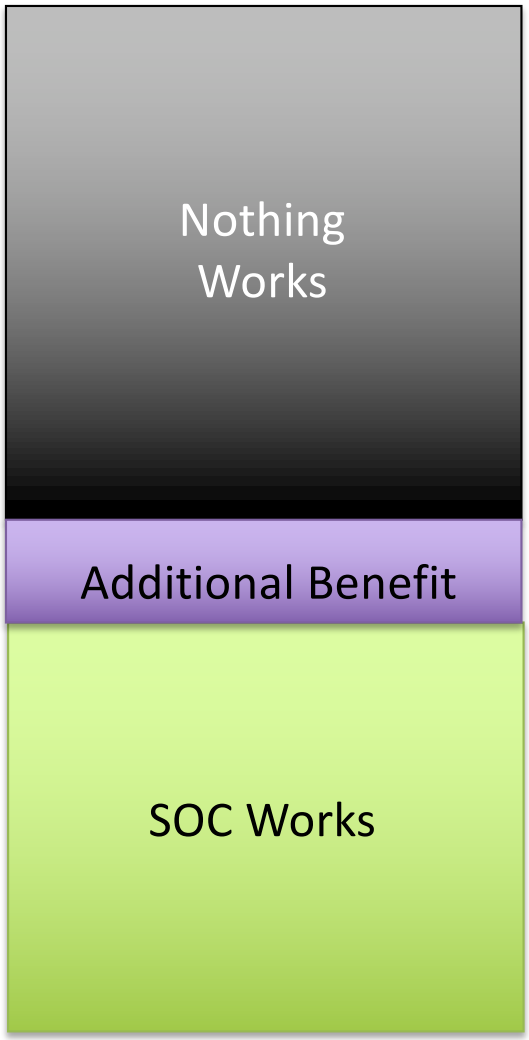
- How many patients do we need to have 90% chance to see a 'statistically significant' difference?

Need 1036 patients for 90% Power



- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

Need 1036 patients for 90% Power



- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

- 90% of patients you enroll tell you nothing

Need 1036 patients for 90% Power

- Standard of Care works in 40%
- New therapy works in 50%
- Nothing works in 50%

- 90% of patients you enroll tell you nothing
- What if you knew which 10% of patients benefited?

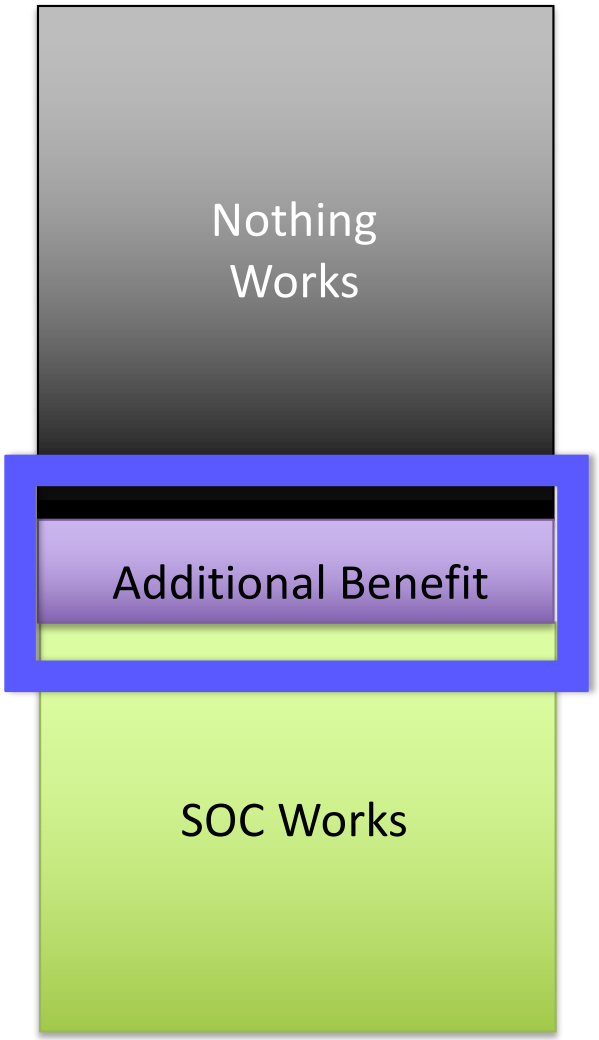
What if you KNEW which 10% Benefit

- If you just enrolled the purple patients how many patients do you need for 90% power?

What if you KNEW which 10% Benefit

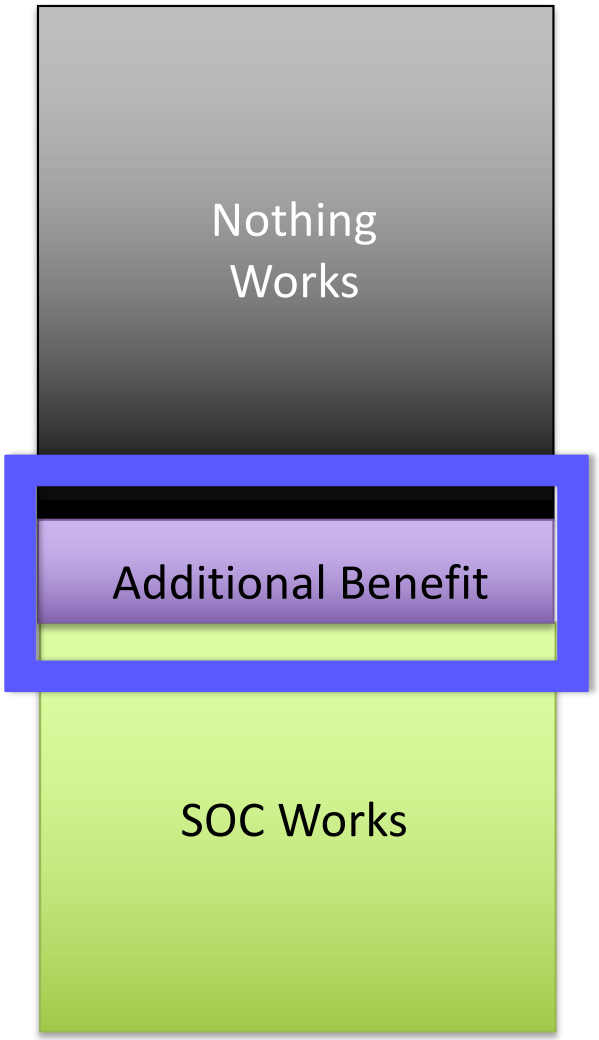
- If you just enrolled the purple patients you need 8 patients for 100% power
- If you could perfectly predict
  - 0/4 on standard of care
  - 4/4 on new treatment
  - Fisher's exact test p-value = 0.029

What if you^KNEW which 10% sorta Benefit



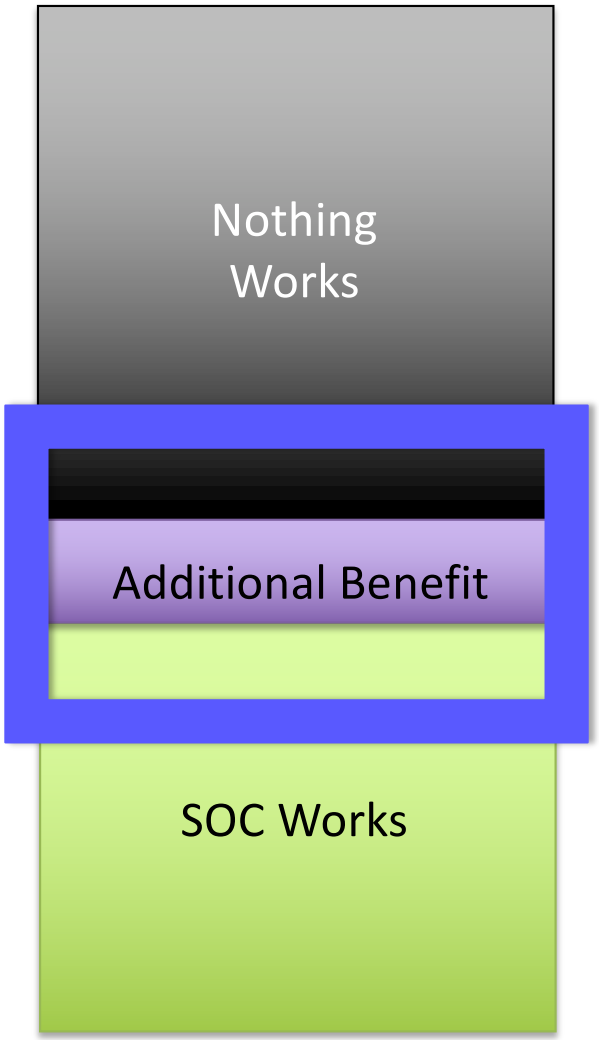
- Enroll 20% to capture the 10%
- 25% cured by SOC
- 25% still not cured
- 50% of enrolled patients benefit

What if you^KNEW which 10% sorta Benefit



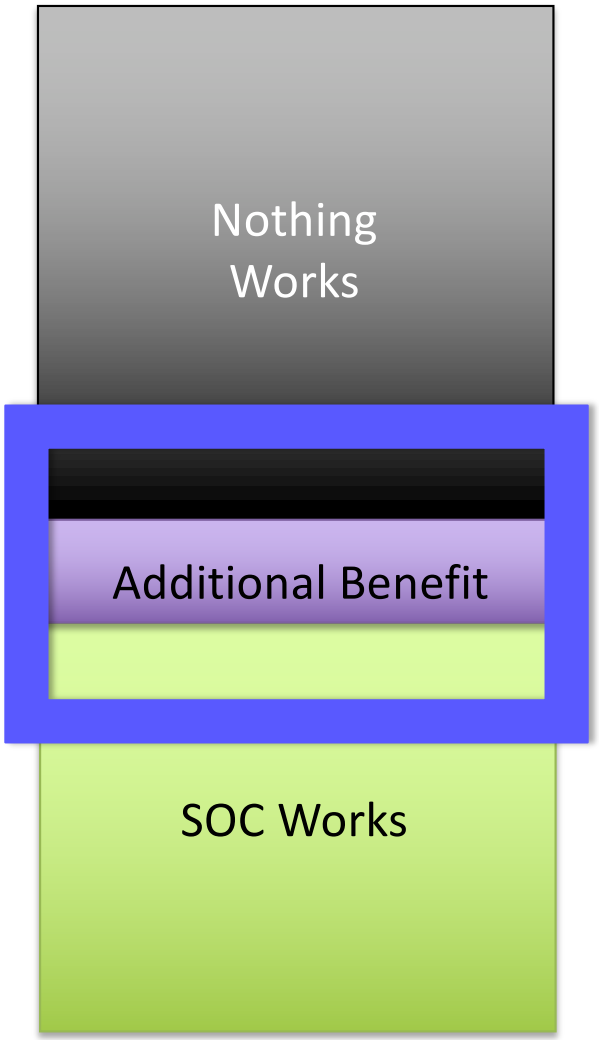
- Enroll 20% to capture the 10%
- 25% cured by SOC
- 25% still not cured
- 50% of enrolled patients benefit
- Need 36 patients for 90% power

What if you KNEW which 10% kinda sorta Benefit



- Enroll 30% to capture the 10%
- 33% cured by SOC
- 33% not cured
- 33% of enrolled patients benefit

What if you KNEW which 10% kinda sorta Benefit



- Enroll 30% to capture the 10%
- 33% cured by SOC
- 33% not cured
- 33% of enrolled patients benefit
- Need 90 patients for 90% power

Platform Example 2

GBM AGILE

Adaptive Global Innovative Learning Environment

Trial Design V1

EXAMPLE TRIAL ONLY
TRIAL HAS CHANGED DRAMATICALLY SINCE THIS

Thanks to Todd Graves & Don Berry

Statistical Model

- Primary outcome: Overall Survival
- Time-to-event model including
  - Age
  - Tumor Size
  - Performance Status
  - Site (to be defined)
  - Drug
  - Drug × Biomarker
  - Drug × Biomarker × Biomarker
- Flexible to add drugs & biomarkers on the fly

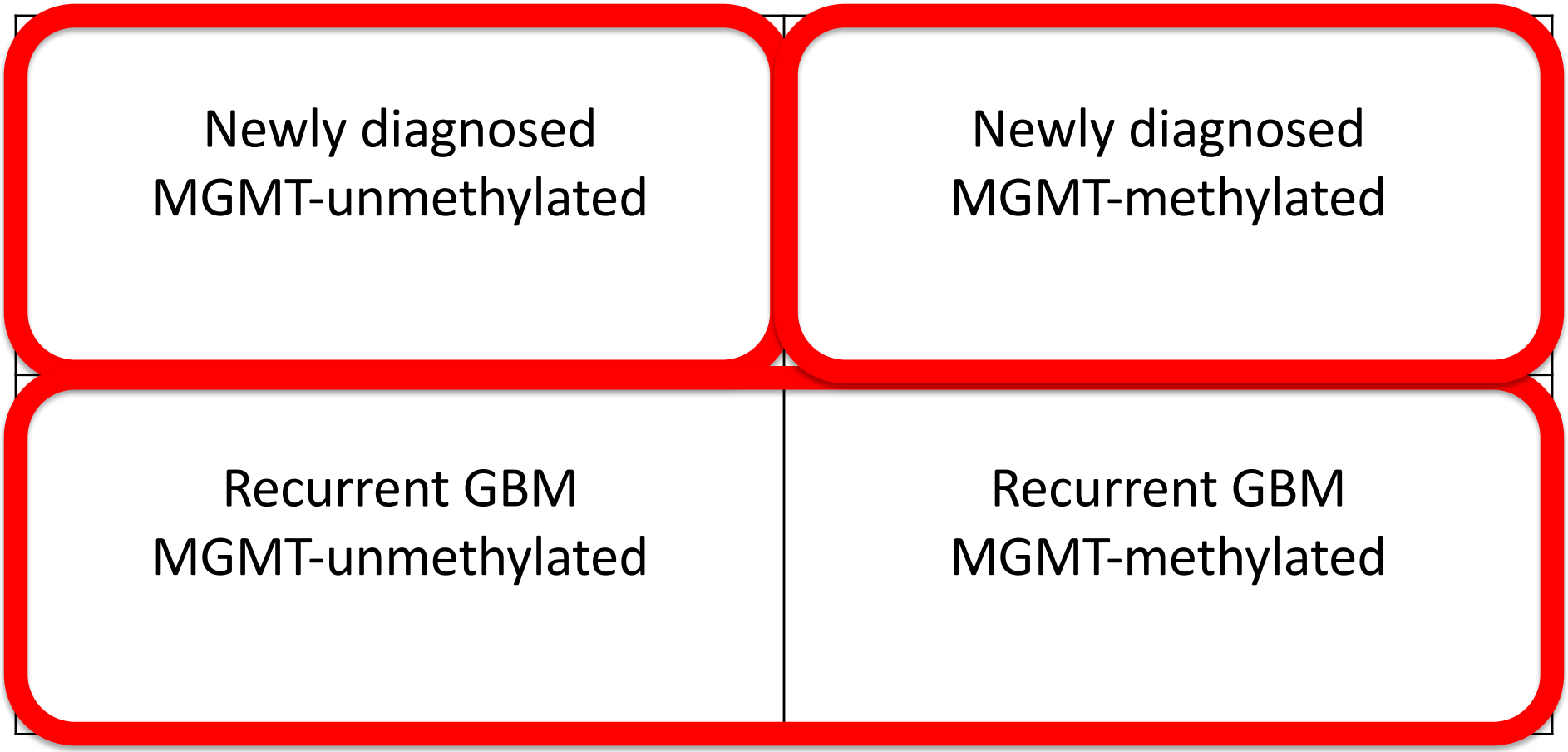
Biomarkers → Signatures

Newly diagnosed MGMT-unmethylated	Newly diagnosed MGMT-methylated
Recurrent GBM MGMT-unmethylated	Recurrent GBM MGMT-methylated

2 × 2 Biomarkers → 4 Signatures

Newly diagnosed MGMT-unmethylated	Newly diagnosed MGMT-methylated
Recurrent GBM MGMT-unmethylated	Recurrent GBM MGMT-methylated

2 × 2 Biomarkers → 3 Signatures



2 × 2 Biomarkers → 1 Signature

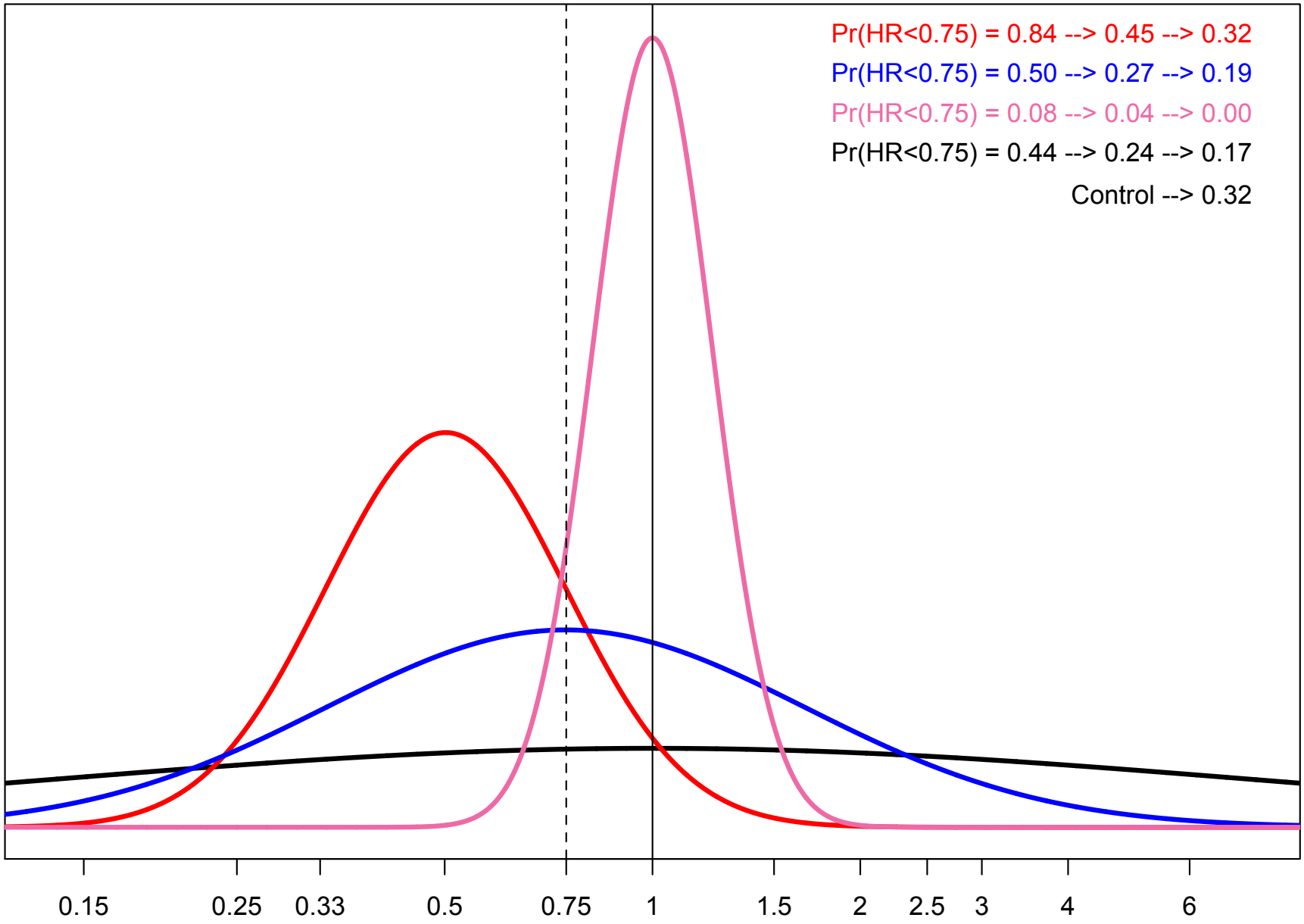
Newly diagnosed MGMT-unmethylated	Newly diagnosed MGMT-methylated
Recurrent GBM MGMT-unmethylated	Recurrent GBM MGMT-methylated

Response-adaptive randomization

- Randomize separately within signature
- Randomization probability proportional to Pr(HR < 0.75)
- If randomization probability < 5%, round to 0
- If N < 50, min rand prob = 1/ # of drugs
- Probability randomize to control =

  Probability randomize to best drug
- Update monthly

Why proportional to Pr(HR<0.75)?



Graduation

A drug graduates if, *within any signature*,

- Pr(HR < 1) > 99%
- Min 75 patients on that drug overall
- Min 300 pt-months exposure on that signature

When a drug graduates

- Drug out of trial
- Data for all subtypes delivered to sponsor

Futility

A drug is removed from the trial for futility if

- Pr(HR < 0.75) < 5% for all signatures
- At least 50 patients

Or

- Been enrolling for 3 years

Stop at Max N=150 over all signatures

Identifying the Right Target Population

	Newly Diagnosed	Recurrent
Methylated	It works here	
Unmethlylated		

Identifying the Right Target Population

	Newly Diagnosed	Recurrent
Methylated	It works here	But not here
Unmethlylated	Or here	Or here

Identify it works in red lasso:
We made the right choice

Identifying the Right Target Population

	Newly Diagnosed	Recurrent
Methylated	It works here	But not here
Unmethlylated	Or here	Or here

Identify it works in red lasso:
Have we made the right choice?
Is this a Type 1 error?
Call this a SUPERSET error

Identifying the Right Target Population

	Newly Diagnosed	Recurrent
Methylated	It works here	And here
Unmethlylated	But not here	Or here

Identify it works in red lasso:
We made the right choice

Identifying the Right Target Population

	Newly Diagnosed	Recurrent
Methylated	It works here	And here
Unmethlylated	But not here	Or here

Identify it works in red lasso:
Did we made the right choice?
We made a “Type 2 error”
Call this a SUBSET error

Identifying the Right Target Population

	Newly Diagnosed	Recurrent
Methylated	It works here	And here
Unmethlylated	But not here	Or here

Identify it works in red lasso:
Did we made the right choice?
We got one right but made a “Type 1 Error” & “Type 2 error”!
Call this a “MIXED TYPE ERROR”

Factors We Can Tune

- Max N per drug
- Signatures (Biomarker-drug interactions)
- Randomization algorithm
- Futility rule
  - Pr(HR<0.75)
  - Min N
  - Max time allowed to accrue
- Graduation rule
  - Pr(HR<1)
  - Min N, Min Exposure

Learn & Confirm Using Biomarkers

- Make confirmatory trials dramatically smaller
  - Or learn & confirm within a trial
- Lead us toward personalized medicine
  - What works best in whom?
- May require larger platforms trials, data sharing & adaptive randomization to efficiently identify
- Different drugs work in different types of patients
  - Not one trial, one patient type
  - Learn, confirm, perpetually

Challenges in Platform Trials

- Complexity in trial implementation and planning
- Collaborations across sponsors - who initiates the planning?
- Timely communication between participating sites and data coordinating units
- Sponsors sacrifice autonomy in running the trial
- Determining shared costs
- Identifying what to report when
  - iSpy2 has rules for 'graduating'
  - When to report subgroup results broadly?

Platform Trial Efficiencies

- Useful for evaluating combinations of treatments and for direct comparisons between competing treatments
  - Decide a prior whether each vs. control or vs. each other
- Do not require a new trial infrastructure for every treatment under investigation
- Easier for regulators given evidence comes in common form
- Always new drugs on horizon
  - Even if lull, get SOC in the process
- Can build in Phase 2/3 design
  - Learn & confirm
- Need to prospectively define control group
  - Concurrent controls
  - 'Time machine'
  - What if control group changes

Conclusions

- Adaptive trial designs can be used to create a seamless process in which new evidence about effectiveness is immediately used to improve patient care
- A platform trial can extend this process beyond a single treatment or few treatments
- Current work is focused on embedding this approach into the health care infrastructure
- Patients will benefit if we merge clinical trials and decision support into a single, continuous process

Thank you!

- Thank you for a great class.

- Please complete evaluations

To access evaluations, log in to https://si.biostat.washington.edu/user/login,

click "My Account" in the upper right,

the evaluations will appear on your dashboard.

After you have completed your evaluations, a link to download the certificate of completion will appear within 24 hours.