Society for Clinical Trials 32nd Annual Meeting

Workshop P8
Adaptive Clinical Trials

Sunday, May 15, 2011
1:00 PM - 5:00 PM
Plaza C

Bayesian Adaptive Designs for Clinical Trials

Jason Connor
Presented at
Adaptive Clinical
Trials Workshop
May 15, 2011

FDA Critical Path Initiative

From FDA website:

> Many of the tools used today to predict and evaluate product safety and efficacy are badly outdated from a scientific perspective. We have not made a concerted effort to apply new scientific knowledge -- in areas such as gene expression, analytic methods, and bioinformatics -- to medical product development. There exists tremendous opportunities to create more effective tests and tools, if we focus on the hard work necessary to turn these innovations into reliable applied sciences.

http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/ucm077015.htm

What are Adaptive Trials?

Trials that change based on <u>prospective</u> rules & the accruing information

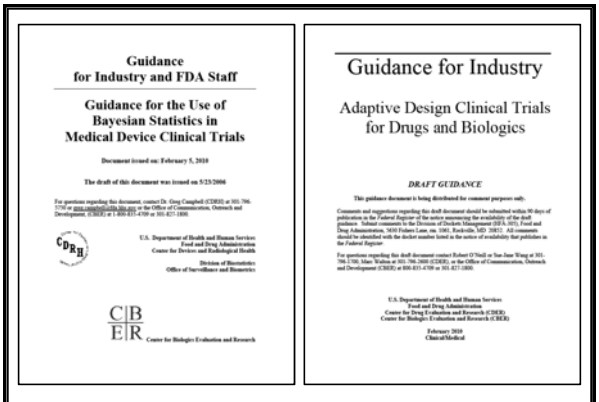
- Adaptive sample sizes based on predictive probabilities
  - Stop early for success
  - Terminate early for futility
- Adaptive randomization
  - For statistical efficiency
  - For improved patient treatment
  - Drop/Re-enter arms or dose groups
- Adaptive accrual rate
- Combination therapies
- Adapt to responding sub-populations
- Adaptive borrowing of information
- Seamlessly combine phases of development

Answering the Right Question

- What will we know & when will we know it?
  - Consider accrual rate & timing of endpoints
  - Consider what adaptations we may want to make
  - Often can use historical/subjective priors in longitudinal model
    …but not final analysis
- What do we want to know?
  - Not p-value with current data
  - Probability of trial success if we stop enrolling now
  - Probability of trial success if we enroll to maximum
  - Probability of trial success if we drop a subgroup
- What will we want to know when this trial is over?
  - Pr(Efficacious), Pr(Safe)
  - In Phase 2 the probability we win a Phase III trial
  - Which dose is best (safest & most efficacious)
  - Which dose is most profitable

Time is Right for Adaptive Designs

- Janet Woodcock, FDA's CDER Director, 2006
  - Improved utilization of adaptive and Bayesian methods **could help resolve low success rate of and expense of phase 3 clinical trials**
- Margaret Hamburg, FDA Commissioner 2010
  - "The final guidance on the use of Bayesian statistics is **consistent with the FDA's commitment to streamline clinical trials**, when possible, in order to get safe and effective products to market faster."
- CDRH produced guidelines for Bayesian statistics Feb 5, 2010
  - "Agency says Bayesian statistical methods could trim costs, boost efficiency" from press release
  - "**They beauty is** you do not end up doing a trial that is too big or too small; **you end up doing a trial that is just right**." Greg Campbell
- CDER/CBER produced draft guidance for adaptive designs Feb 2010



Guidance
for Industry and FDA Staff

Guidance for the Use of
Bayesian Statistics in
Medical Device Clinical Trials

Document issued on: February 5, 2010

The draft of this document was issued on 5/23/2006

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Biostatistics
Office of Surveillance and Biometrics

C|B
E|R
Center for Biologics Evaluation and Research

Guidance for Industry

Adaptive Design Clinical Trials
for Drugs and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2010
Clinical/Medical

Some Current Areas of Application

- Alzheimer's Disease
- Aneurysm
- Asthma
- Atrial Fibrillation
- Cancer Diagnostics
- Crohn's Disease
- Diabetes
- DVT
- Emphysema
- GI Motility
- Heart Valves
- HIV
- Libido
- Lymphoma
- Lung Cancer
- Lupus
- Migraines
- Multiple Sclerosis
- Obesity
- Pain
- Pre-term labor
- Parkinsons
- Rheumatoid Arthritis
- Sepsis
- Smoking Cessation
- Spinal Cord Injury
- Spinal Implants
- Statins
- Stroke
- Tinnitus
- Uterine Cancer
- Vaccines

Adaptive Designs & Collaborators

- Requires buy-in and educating IRB, DSMB, decision-makers, study teams, investigators, and subjects
- Requires more time, resources, and upfront planning, especially at the protocol-design stage
- Show sponsor many many example trials
  - Also great for debugging
- Complex study designs typically require more statistical assumptions, rigorous calculations, and extensive simulations (operating characteristics)
- But also more robust to deviations from our assumptions
- Operationally challenging
  - Work with CROs as early as possible, fit statistical parts within infrastructure
- Make sure sponsors understands what adaptive designs are not

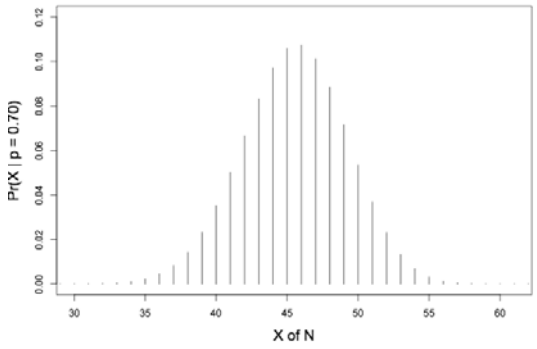
Simulation

- Show a bunch of example trials
  - Don't want surprises during the trial!
- Operating characteristics for a range of scenarios
  - Different efficacy profiles
  - Different accrual rates
  - Different decision rules
- Usually have to control Type I error rate by trial & error
  - Set critical value, run 10,000 sims, check Type I error
  - Adjust to get Type I error in worst case scenario at 2.5% or 5%

Why be adaptive?

- Doctor comes to you.
- Historical success rate = 50%
- Claims his therapy has 70% success
- "How many patients do I need to be statistically significant?"

N = 65 gives 90% power to reject Ho: p = 0.50 when p = 0.7



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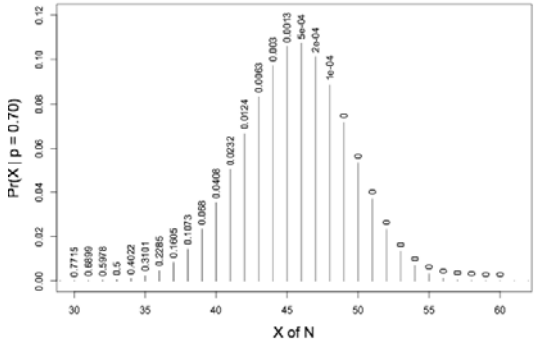
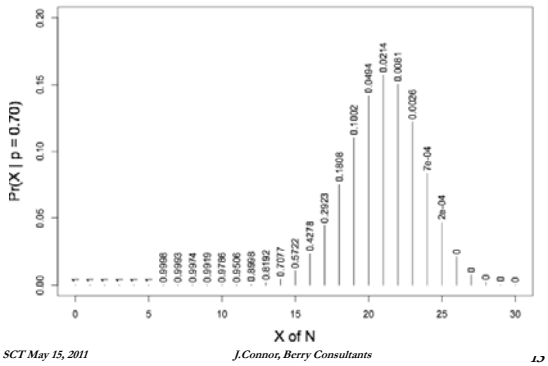
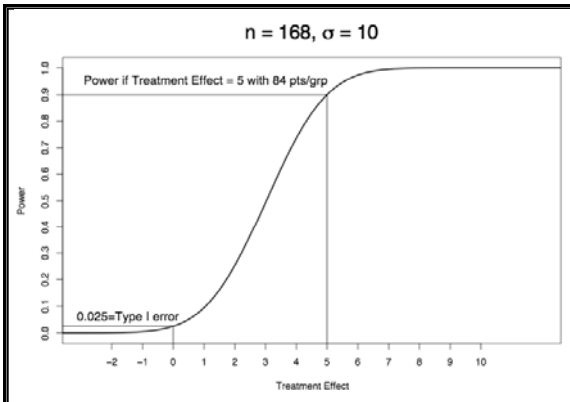


If observed = 70% only need N = 30 not N=65!

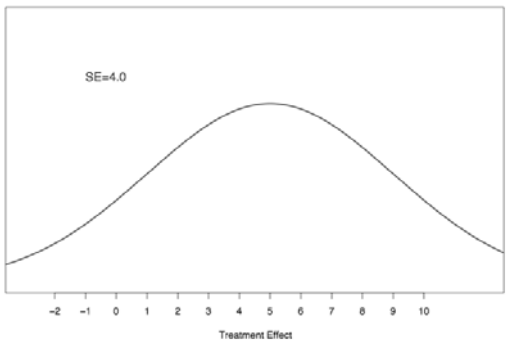


Why be adaptive?

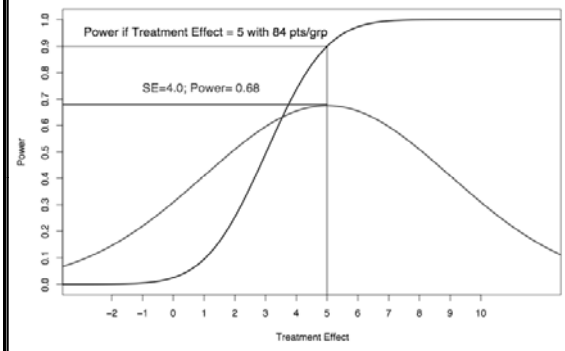
- Doctor comes to you.
- Claims his treatment increases IQ by 5 points
- SD = 10
- "How many patients do I need to have 90% power to demonstrate superiority?"



We've ignored the error in the pilot data



n = 168, σ = 10



Example in Neurology

- Implantable device for previously untreatable aneurysms
- Goal:
  - Demonstrate efficacy & safety of pipeline stent
- Pivotal device trial for FDA CDRH
- 1-armed trial vs. objective performance criteria
- Sample size is 50 to 100 patients
- First analysis with 50 patients
- Interim analyses every 1 month

Trial Setup

- Primary Efficacy Outcome
  - 6-month success, p = success rate
- Primary Safety Outcome
  - No neurological safety event within 30-days of procedure, q = AE rate
- Compare to Objective Performance Criteria
  - Show $p > 0.50$ to demonstrate efficacy
  - Show $q < 0.20$ to demonstrate safety

Summary of Trial

- Efficacy
  - Observe x successes in n patients
  - Show $\Pr(p > 0.50 \mid n, x) > 0.975$
- Safety
  - Observe y adverse events in n patients
  - Show $\Pr(q < 0.20 \mid n, y) > 0.95$
- Priors: Likelihoods Posteriors:

$p \sim \text{Beta}(1,1)$	$x \sim \text{Bin}(n, p)$	$p \mid n, x \sim \text{Beta}(1+x, 1+n-x)$
$q \sim \text{Beta}(1,1)$	$y \sim \text{Bin}(n, q)$	$q \mid n, y \sim \text{Beta}(1+y, 1+n-y)$

Adaptive Sample Size

- Interim looks after 50 patients enrolled and 20 patients with 6-month outcomes
- Then re-analyze every month
- Calculate

  $P_{n,n}$ = predictive probability of trial success with current sample size

  - If $P_{n,n}$ high then Stop for Probable Success

  $P_{n,100}$ = predictive probability of trial success if we enroll to maximum sample size

  - If $P_{n,100}$ low then Stop for Futility

Adaptive Stopping Rules

- Stop enrolling for predicted success if
  - $P_{n,n} > S_n$
  - Wait 6-months for complete data do 1 final analysis
- Stop for futility if
  - $P_{n,100} < F_n$

Sample Size	S_n	F_n
$n < 60$	0.99	0.05
$60 \le n < 75$	0.95	0.05
$75 \le n < 100$	0.90	0.05

Adaptive Stopping Rules

- Stop enrolling for predicted success if
  - $P_{n,n} > S_n$
  - Wait 6-months for complete data **do 1 final analysis**
- Stop for futility if
  - $P_{n,100} < F_n$

Sample Size	S_n	F_n
$n < 60$	0.99	0.05
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$75 \le n < 100$	0.90	0.05

Predictive Probs using Partial Data

- At any interim analysis observe patients with Full data, Partial data, & No data
- First interim analysis with 50 patients
  - Accrued 5 patients per month

Patients Enrolled	50
30-day follow-up	45
90-day follow-up	35
180-day follow-up	20

Predictive Probs using Partial Data

- At any interim analysis observe patients with Full data, Partial data, & No data
- First interim analysis with 50 patients
  - Accrued 5 patients per month

Patients Enrolled	50	
30-day follow-up	45	Predict Safety for 5
90-day follow-up	35	
180-day follow-up	20	Predict Efficacy for 30

Interim Analysis: Safety

- n_S = 45 subjects provide full data for safety
- Observe y adverse events
- Calculate predictive prob. show safety with current n
- $q \mid n_S, y \sim \text{Beta}(1+y, 1+n_S-y)$
- $y^* \sim \text{Bin}(5, q) \sim \text{Beta-Binomial}(5, 1+y, 1+n_S-y \mid n_S)$
- $y_T = y + y^*$ represents "complete" safety events
- Probability distribution for complete data set
- Calculate $\Pr(q < 0.20 \mid 50, y_T)$ for $y_T \in \{y,\ldots, y+5\}$
- Pred probability of demonstrating safety with n patients =

$$= \sum_{k=y}^{y+5} \left[\Pr(y_T = k) \times 1(\Pr(q < 0.20 \mid n = 50, y_T = k) > 0.95) \right]$$

Interim Analysis: Efficacy

- At 50 patient analysis
  - 20 patients with 6-month data (complete), x successes
  - 15 patients with 3-month data
    - May be Success or Not at 3-month visit
  - 15 patients with < 3-month data
- Calculate probability distribution for complete data
  - $x_T = x + x_o^* + x_S^* + x_F^*$
  - x observed successes out of n
  - x_o^* predicted successes in patients with no follow-up
  - x_S^* predicted successes in patients who are successes at 3-mths
  - x_F^* predicted successes in patients who are failures at 3-months

Use Historical Data to form Priors

- Want to predict 6-month success for
  - Patients without 3-month follow-up: 83%
  - Patients successes at 3-months: 90%
  - Patients failures at 3-months: 50%
- Use priors each equal to 6-patients worth of info
- Priors only used to determine sample size
  - Not used in final analysis so okay to be informative
  - Incentive to be 'honest' otherwise could stop too early

Group	Prior	Prior Mean
No 3-month follow-up	$p_o \sim$ Beta(5.0, 1.0)	0.83
Success at 3-month follow-up	$p_F \sim$ Beta(5.4, 0.6)	0.90
Failure at 3-month follow-up	$p_S \sim$ Beta(3.0, 3.0)	0.50

Predict Efficacy Data

- At 50 patient analysis, $c_{++} = 20$ completers

	6mo Success	6mo Failure	Total
3mo Success	c_{SS}	c_{SF}	c_{S+}
3mo Failure	c_{FS}	c_{FF}	c_{F+}
Total	c_{+S}	c_{+F}	$c_{++} = 20$

Group	Posterior
No 3-month follow-up	x_o^* | Interim Data ~ Beta-Bin($5.0+c_{+S}$, $1.0+c_{+F}$)
Success at 3-month follow-up	x_S^* | Interim Data ~ Beta-Bin($5.4+c_{SS}$, $0.6+c_{SF}$)
Failure at 3-month follow-up	x_F^* | Interim Data ~ Beta-Bin($3.0+c_{FS}$, $3.0+c_{FF}$)

Predict Efficacy Data

- Calculate $\Pr(p > 0.50 \mid 50, x_T)$ for $x_T \in \{20,\ldots,50\}$
- Pred probability of demonstrating efficacy with n patients

$$P_{n,n}^{E} = \sum_{j=0}^{30} \left[\Pr(x_T = x + j) \times 1(\Pr(p > 0.50 \mid 50, x_T = x + j) > 0.975) \right]$$

- Repeat predicting with 100 patient data set, $P_{n,100}$

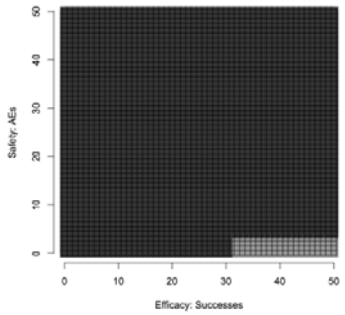
$$P_{n,100}^{E} = \sum_{j=0}^{80} \left[\Pr(x_T = x + j) \times 1(\Pr(p > 0.50 \mid 100, x_T = x + j) > 0.975) \right]$$

Calculating $P_{n,n}$

To win @ 50pts:
Efficacy ≥ 32
Safety ≤ 3

Observe :
Efficacy
x = 18 of 20
30 to be predicted

Safety
y = 2 of 45
5 to be predicted



Calculating $P_{n,n}$

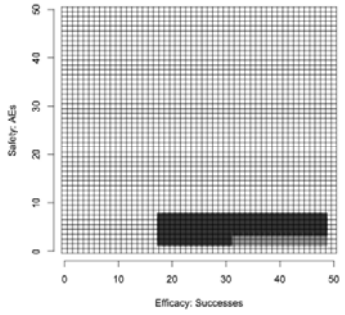
Observe :

x = 18 of 20
30 to be predicted

$x^T \in \{18,\ldots,48\}$

y = 2 of 45
5 to be predicted

$y^T \in \{2,\ldots,7\}$



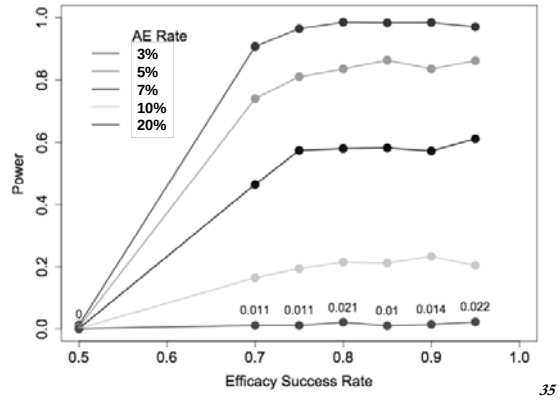
Operating Characteristics

True Eff	True Safe	Power = Prob We Show			Stopping Decision			Sample Size	
p	*q*	E&S	Eff	Safe	Pred Succ	Max N	Futil-ity	Mean	SD
0.85	0.05	0.86	0.99	0.86	0.86	0.05	0.09	67	14
0.75	0.05	0.81	0.96	0.82	0.72	0.13	0.15	74	16
0.50	0.05	0.005	0.005	0.70	0.003	0.06	0.94	60	16
0.85	0.20	0.01	0.94	0.01	0.03	0.004	0.97	56	11

Scenario Breakdown
Efficacy, $p = 0.75$, Safety, $q = 0.05$

Sample Size	Futility	Early	Max	& Win Both	Pr(Win | Go)
50	0.02	0.05		0.047	0.94
55	0.03	0.06		0.058	0.97
60	0.02	0.08		0.078	0.98
65	0.02	0.08		0.077	0.96
70	0.00	0.09		0.088	0.98
75	0.01	0.11		0.109	0.99
80	0.01	0.09		0.086	0.96
85	0.02	0.08		0.076	0.95
90	0.01	0.05		0.048	0.96
95	0.01	0.03		0.029	0.97
100			0.13	0.114	0.88
Total	0.15	0.72	0.13	0.81	

SCT May 15, 2011 *J.Connor, Berry Consultants* *34*



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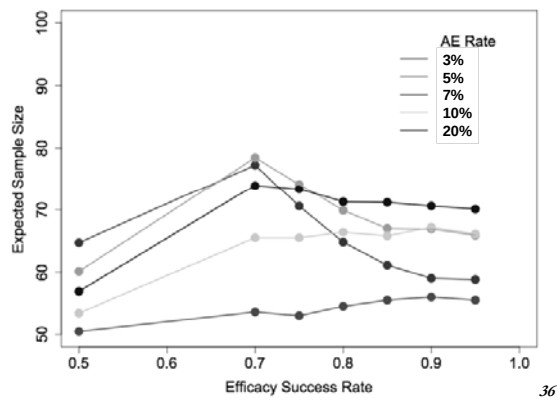

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Trial Results

- Enrolled SUPER fast
  - Many doctors had a queue of these patients since there was previously no treatment
- Didn't adapt, stopped at 106 patients
- 78/106 efficacy successes, $Pr(p>0.5) > 0.9999$
  - 95% CI: 64.4 – 81.0%
- 6/107 safety events, $Pr(q<0.2) > 0.9999$
  - 95% CI: 2.6 – 11.7%
- FDA approved device April 2011

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FDA Okays Aneurysm Device

By Cole Petrochko, Staff Writer, MedPage Today
Reviewed by
April 10, 2011

Review

Washington -- The FDA has approved a flexible mesh tube, Pipeline Embolization Device, to treat brain aneurysms without open surgery.

The device reduces risk of aneurysm rupture by blocking off large, giant, or wide-neck aneurysms in the internal carotid artery, an FDA statement said.

Implantation of the device reduces the likelihood of aneurysm growth and rupture, and may help shrink it over time, the agency statement said.

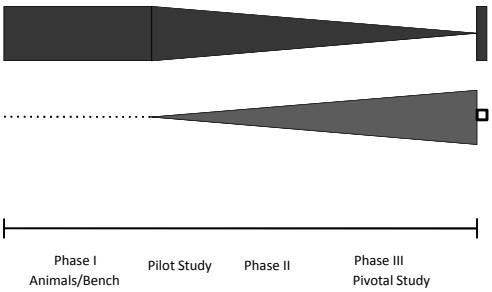
The Pipeline device is made of a platinum and nickel-cobalt chromium alloy.

Approval was based on the results of a study conducted among 108 patients, ages 21 to 75, with a large or giant aneurysm without an apparent neck in internal parts of the carotid artery.

What is Different About Confirmatory Trials

- Type I error is a dominant factor
- Even as Bayesian, we have to live in a Frequentist world
- Must adjusting the design in order to accommodate adaptive aspects
  - control type I error
- Predictive probabilities much more relevant than posterior probabilities!

Posterior/Predictive



Predictive Probabilities

- 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

Predictive Probabilities

- 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
- Observe data half way through
  - See 28/50 successes
  - What is predictive probability of trial success?

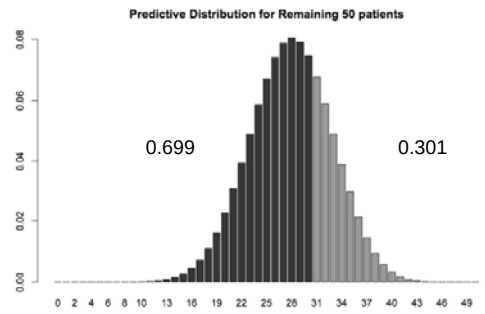
Predictive Probabilities

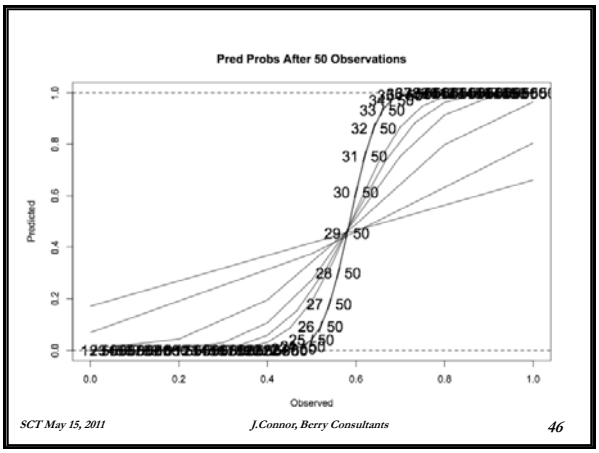
- Know we need $x \geq 59$ at trial's end
- Have $x_1 = 28$
- Need $x_2 \geq 31$
- $p \mid x_1, n_1 \sim$ Beta(1+28, 1+22)
- $x_2 \mid p \sim$ Binomial(50, p)
- $x_2 \mid x_1, n_1, n_2 \sim$ Beta-bin(50, α=1+x_1, β=1+n_1-x_1)

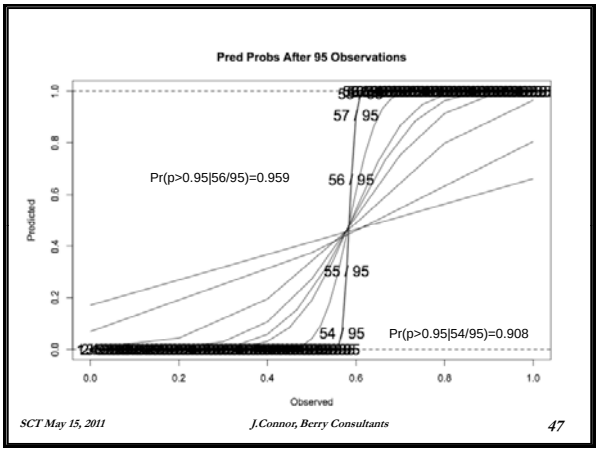
$$\Pr(\text{Win Trial}) = \sum_{x_2=31}^{50} \left\{ \binom{50}{x_2} \frac{B(x_2 + 29, 50 - x_2 + 23)}{B(29,22)} \right\} = 0.301$$

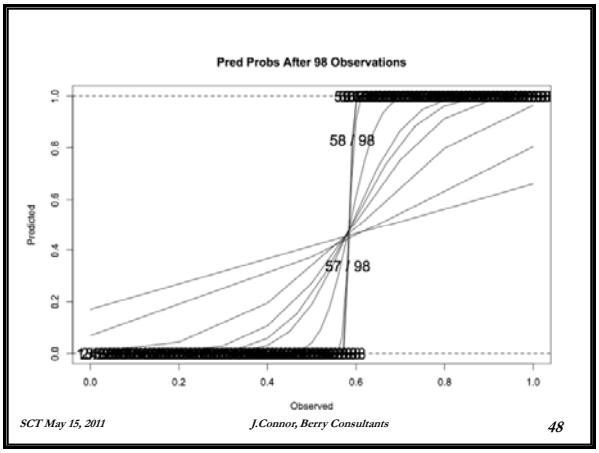
R code for predictive probability

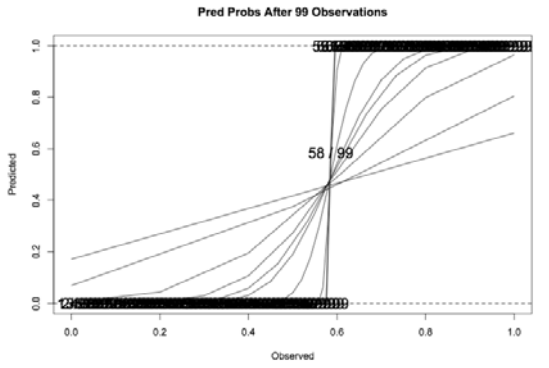
```
> ### VIA SIMULATION
> alpha <- 1; beta <- 1
> x <- 28; N <- 50
>
> p <- rbeta(1000000, alpha+x, beta+N-x)
> x.new <- rbinom(1000000, 50, p)
>
> mean(x.new >= 31)
[1] 0.301132
>
>
>
> ### VIA DIRECT CALCULATION
> N.new <- 50
> x.new <- 0:50
> prob <- choose(N.new,x.new) *
+       beta(alpha+x+x.new,(beta+N-x)+(N.new-x.new)) /
+          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 50 Observations
Predicted
Observed
33 / 50
32 / 50
31 / 50
30 / 50
29 / 50
28 / 50
27 / 50
26 / 50
25 / 50


Pred Probs After 95 Observations
Predicted
Observed
57 / 95
Pr(p>0.95|56/95)=0.959
56 / 95
55 / 95
54 / 95
Pr(p>0.95|54/95)=0.908


Pred Probs After 98 Observations
Predicted
Observed
58 / 98
57 / 98



Phase 3 Cancer Design

- Binary endpoint, complete response observed at 45 days post treatment
  - Consider CR vs. PFS vs. OS?
  - Do simple chi-square test at end
  - Being frequentist but Bayesian 'behind the curtain'
- Expect 20% improvement vs. control
- What to ask, how to start?

Design Questions

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

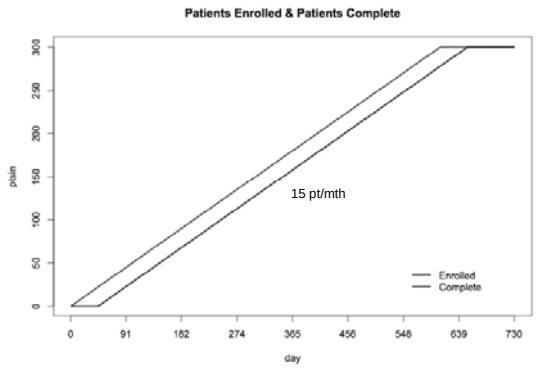
```
> bpower(n1=150, n2=150, p1=0.5, p2=0.7)
Power
0.9462418
```

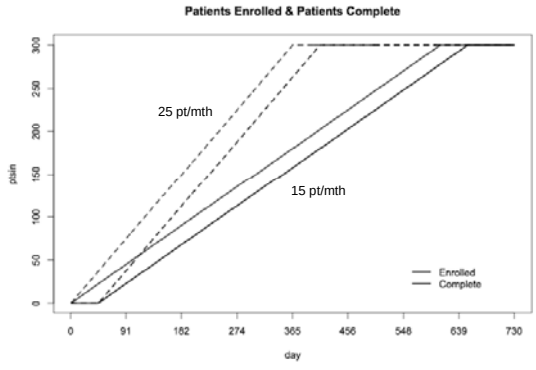
  - Best case want to go to FDA with ≥150 patients
  - We'll see if 300 is enough, if not we'll go back to the company with evidence they need to up the cap

```
> bpower(n1=150, n2=150, p1=0.5, p2=0.65)
Power
 0.750375
```

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
    - 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





Design Questions

- How often to do interim looks?
  - Every 25 patients is every 1-1.5 months
  - Manageable, may be CRO fee for every look

Design Questions

- How to decide when to stop accrual for success?

Design Questions

- How to decide when to stop accrual?
  - Use predictive probabilities
  - At each 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
  - Don't use prior in final analysis

    Incentive to have an 'honest' prior

Sketch of my simulation code

- Define when to analyze, priors, cap, accrual rate, alpha level
- Subroutine for patient accrual & randomization
- Subroutine to generate patient response & dropout
- Subroutine for interim analysis
  - Factors in time of analysis, which patients have data, patient outcomes
  - Outputs predictive probability of success with current n and at maximum N
- Subroutine for decision
  - Stop for predicted success, stop for cap, stop for futility, keep going
- Final analysis
- Track trial size, track win or lose, track reason for stopping

SCT May 15, 2011 *J.Connor, Berry Consultants* *61*

```
 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
```

62 *62*

```
 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   0.0000

                    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
```

63 *63*

Stopping Boundary

- Need not be constant
- See 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 1.0000 0.0000

	Mean	SD
Sample Size	300.00	0.00

	Lose	Win
Success	0.000	0.000
Cap	0.026	0.974
Futility	0.000	0.000
Total	0.026	0.974

Look	Lose	Win	Total
150	0.000	0.000	0.000
175	0.000	0.000	0.000
200	0.000	0.000	0.000
225	0.000	0.000	0.000
250	0.000	0.000	0.000
275	0.000	0.000	0.000
300	0.026	0.974	1.000
Tot	0.026	0.974	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

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              Control Rate=    0.6000
 Exper Rate =    0.8000               Exper Rate =    0.8000

Accrual Rate (pts/month):  15.00     Accrual Rate (pts/month):  15.00
        Number of Sims      1000             Number of Sims      1000
    Minimum Sample Size      150         Minimum Sample Size      150
    Maximum Sample Size      300         Maximum Sample Size      300
                     CV   0.0250                          CV   0.0250
          Cuts   1.0000   0.0000               Cuts   0.9500   0.0000

                   Mean      SD                         Mean      SD
    Sample Size  300.00    0.00          Sample Size  186.47   53.61

               Lose      Win                        Lose      Win
   Success    0.000    0.000            Success    0.001    0.905
       Cap    0.026    0.974                Cap    0.032    0.062
  Futility    0.000    0.000           Futility    0.000    0.000
     Total    0.026    0.974              Total    0.033    0.967

Look     Lose       Win    Total     Look     Lose       Win    Total
 150    0.000     0.000    0.000      150    0.000     0.520    0.520
 175    0.000     0.000    0.000      175    0.001     0.135    0.136
 200    0.000     0.000    0.000      200    0.000     0.110    0.110
 225    0.000     0.000    0.000      225    0.000     0.054    0.054
 250    0.000     0.000    0.000      250    0.000     0.053    0.053
 275    0.000     0.000    0.000      275    0.000     0.033    0.033
 300    0.026     0.974    1.000      300    0.032     0.062    0.094
 Tot    0.026     0.974    1.000      Tot    0.033     0.967    1.000
```

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```
Control Rate=    0.6000              Control Rate=    0.6000
 Exper Rate =    0.8000               Exper Rate =    0.8000

Accrual Rate (pts/month):  15.00     Accrual Rate (pts/month):  15.00
        Number of Sims      1000             Number of Sims      1000
    Minimum Sample Size      150         Minimum Sample Size      150
    Maximum Sample Size      300         Maximum Sample Size      300
                     CV   0.0250                          CV   0.0250
          Cuts   0.9500   0.0000               Cuts   0.9500   0.0500

                   Mean      SD                         Mean      SD
    Sample Size  186.47   53.61          Sample Size  183.82   46.57

               Lose      Win                        Lose      Win
   Success    0.001    0.905            Success    0.001    0.915
       Cap    0.032    0.062                Cap    0.014    0.048
  Futility    0.000    0.000           Futility    0.022    0.000
     Total    0.033    0.967              Total    0.037    0.963

Look     Lose       Win    Total     Look     Lose       Win    Total
 150    0.000     0.520    0.520      150    0.012     0.513    0.525
 175    0.001     0.135    0.136      175    0.003     0.139    0.142
 200    0.000     0.110    0.110      200    0.004     0.108    0.112
 225    0.000     0.054    0.054      225    0.001     0.061    0.062
 250    0.000     0.053    0.053      250    0.000     0.056    0.056
 275    0.000     0.033    0.033      275    0.003     0.038    0.042
 300    0.032     0.062    0.094      300    0.014     0.048    0.063
 Tot    0.033     0.967    1.000      Tot    0.037     0.963    1.000
```

68 *68*

```
Control Rate=    0.6000              Control Rate=    0.6000
 Exper Rate =    0.8000               Exper Rate =    0.8000

Accrual Rate (pts/month):  15.00     Accrual Rate (pts/month):  15.00
        Number of Sims      1000             Number of Sims      1000
    Minimum Sample Size      150         Minimum Sample Size      150
    Maximum Sample Size      300         Maximum Sample Size      300
                     CV   0.0250                          CV   0.0250
          Cuts   0.9500   0.0500               Cuts   0.9500   0.1000

                   Mean      SD                         Mean      SD
    Sample Size  183.82   46.57          Sample Size  183.20   48.53

               Lose      Win                        Lose      Win
   Success    0.001    0.915            Success    0.001    0.892
       Cap    0.014    0.048                Cap    0.015    0.065
  Futility    0.022    0.000           Futility    0.027    0.000
     Total    0.037    0.963              Total    0.043    0.957

Look     Lose       Win    Total     Look     Lose       Win    Total
 150    0.012     0.513    0.525      150    0.017     0.546    0.564
 175    0.003     0.139    0.142      175    0.006     0.118    0.124
 200    0.004     0.108    0.112      200    0.001     0.093    0.094
 225    0.001     0.061    0.062      225    0.000     0.054    0.054
 250    0.000     0.056    0.056      250    0.002     0.049    0.051
 275    0.003     0.038    0.042      275    0.002     0.032    0.034
 300    0.014     0.048    0.063      300    0.015     0.065    0.080
 Tot    0.037     0.963    1.000      Tot    0.043     0.957    1.000
```

69 *69*

Control Rate= 0.6000	Control Rate= 0.6000
Exper Rate = 0.7500	Exper Rate = 0.7500
Accrual Rate (pts/month): 15.00	Accrual Rate (pts/month): 15.00
Number of Sims 5000	Number of Sims 5000
Minimum Sample Size 150	Minimum Sample Size 150
Maximum Sample Size 300	Maximum Sample Size 300
CV 0.0250	CV 0.0250
Cuts 0.9500 0.0500	Cuts 0.9500 0.1000

	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

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	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

70

Control Rate= 0.6000	Control Rate= 0.6000
Exper Rate = 0.6000	Exper Rate = 0.6000
Accrual Rate (pts/month): 15.00	Accrual Rate (pts/month): 15.00
Number of Sims 5000	Number of Sims 1000
Minimum Sample Size 150	Minimum Sample Size 150
Maximum Sample Size 300	Maximum Sample Size 300
CV 0.0250	CV 0.0250
Cuts 0.9500 0.0500	Cuts 0.9500 0.1000

	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

71

	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

71

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
  - Can't calculate analytically
  - Need to simulate over many scenarios
  - Then convince ourselves & FDA weve explored the whole null space

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Intuition Check

- Use critical value = 0.025
- Simulate with 4 accrual rates
- 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		
15*	177	0.030
25		
50		

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

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Intuition Check

- Use critical value = 0.025
- Simulate with 4 accrual rates
- 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

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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		

75

75

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

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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

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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

78 If a real trial I'd run 100,000 or 1M sims and try to get as much power as possible 78

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

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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

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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	0.967	0.87

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Example Trial #1

```
Simulation #  14       Analysis #  150
 Group          N    Obs    Suc
 Control       75     68     35
 Treatment     75     68     49
 Pn,n   =  0.9360 >  0.950 ?,   Pn,Max =  0.9180 <  0.100 ?
 Continue to enroll

Simulation #  14       Analysis #  175
 Group          N    Obs    Suc
 Control       88     73     39
 Treatment     87     72     53
 Pn,n   =  0.9370 >  0.950 ?,   Pn,Max =  0.9360 <  0.100 ?
 Continue to enroll

Simulation #  14       Analysis #  200
 Group          N    Obs    Suc
 Control      100     91     48
 Treatment    100     90     68
 Pn,n   =  >.9999 >  0.950 ?,   Pn,Max =  0.9900 <  0.100 ?
 Stop for predicted success

Simulation #  14   Final Analysis  200
     Group      N    Obs    Suc
 Control      100    100     52
 Treatment    100    100     76
 Successful trial,   p-value = 0.0001 < 0.0180
```


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Example Trial #2

```
Simulation #  10       Analysis #  150
 Group          N    Obs    Suc
 Control       75     66     40
 Treatment     75     65     44
 Pn,n   =  0.0000 >  0.950 ?,   Pn,Max =  0.2590 <  0.100 ?
 Continue to enroll

Simulation #  10       Analysis #  175
 Group          N    Obs    Suc
 Control       88     80     47
 Treatment     87     79     51
 Pn,n   =  0.0000 >  0.950 ?,   Pn,Max =  0.1020 <  0.100 ?
 Continue to enroll

Simulation #  10       Analysis #  200
 Group          N    Obs    Suc
 Control      100     90     55
 Treatment    100     89     57
 Pn,n   =  0.0000 >  0.950 ?,   Pn,Max =  0.0360 <  0.100 ?
 Stop for futility
 Unsuccessful trial
```


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Trial Underway

Bayesian Adaptive Designs

- Fundamental change in the way we conduct medical research
  - Look at the data early & often
  - Make prospectively defined adaptations & decisions
  - Base decisions on predictive probabilities
- Better treatment of patients in & out of trials
- More rapid progress
- Lower development costs
- Accepted by regulators
- More fun for statisticians

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Short Course: Adaptive Clinical Trials

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- AspenBio Pharma
- Cell>Point, LLC
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- Octapharma AG

Outline

- The “philosophy” of adaptive clinical trials
  - Planned change is good!
- Categories of adaptive trial designs
- Specific adaptive strategies
- Implementation/Logistics
- Data and Safety Monitoring Boards
- Acceptability to key stakeholders

“Philosophy” of Adaptive Trials

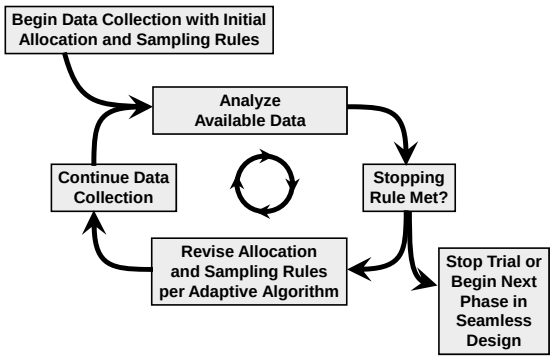
- Clarity of goals
  - E.g., Proof of concept vs identification of dose to carry forward vs confirmation of benefit
- Frequent “looks” at the data and data-driven modification of the trial
- Adaptive “by design”
- Extensive use of simulation to “fine tune” key trial characteristics

JAMA 2006;296:1955-1957.

Adaptation: Definition

- Making planned, well-defined changes in key clinical trial design parameters, during trial execution based on data from that trial, to achieve goals of validity, scientific efficiency, and safety
  - Planned: Possible adaptations defined *a priori*
  - Well-defined: Criteria for adapting defined
  - Key parameters: *Not* minor inclusion or exclusion criteria, routine amendments, etc.
  - Validity: Reliable statistical inference

The Adaptive Process



Historical Context

- Historically, obtaining results that were "reliable and valid" required fixed study designs
- Allowed the determination of theoretical error rates
- Fundamental characteristic of the "culture" of biostatistics and clinical trial methodology

Why are Study Designs Fixed?

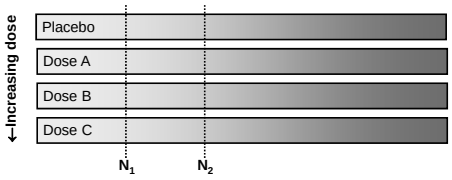
- It's easiest to calculate type I error rates if the design parameters of the trial are all constant
- There are some other reasons:
  - Results obtained using "Standard approaches" are generally considered valid
  - Logistically simpler to execute
  - Fixed designs are less sensitive to "drift" in the characteristics of subjects over time

Type of Adaptive Rules

- **Allocation Rule**: how subjects will be allocated to available arms
- **Sampling Rule**: how many subjects will be sampled at next stage
- **Stopping Rule**: when to stop the trial (for efficacy, harm, futility)
- **Decision Rule**: decision and interim decisions pertaining to design change not covered by the previous three rules

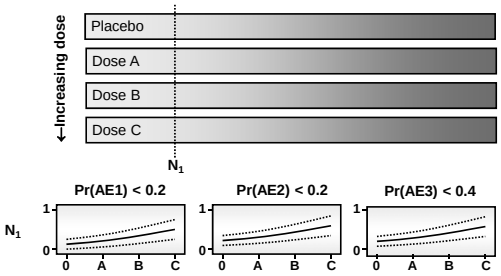
Adapted from Vlad Dragalin

Example



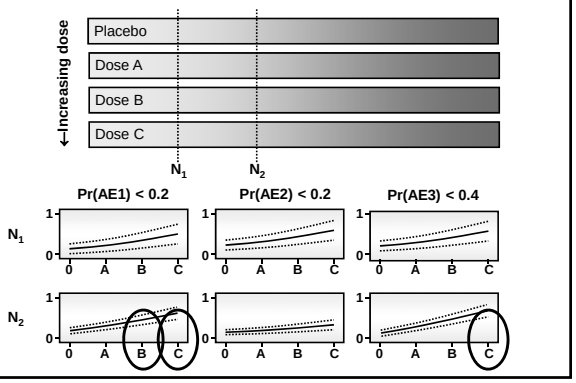
- **Rule:**
  Drop a dose if rate of AE1, AE2, or AE3 appears to be above the tolerable limit at either N_1 or N_2 based on lower limit of model-based 80% CI:
- **Limits:**
  Pr(AE1) < 0.2
  Pr(AE2) < 0.2
  Pr(AE3) < 0.4

Example

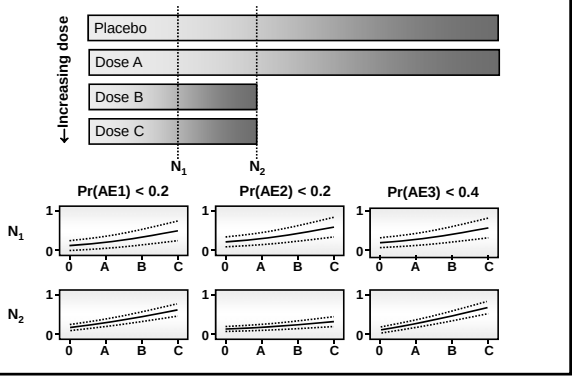


No dose meets criteria for early termination so all will be continued until N_2.

Example

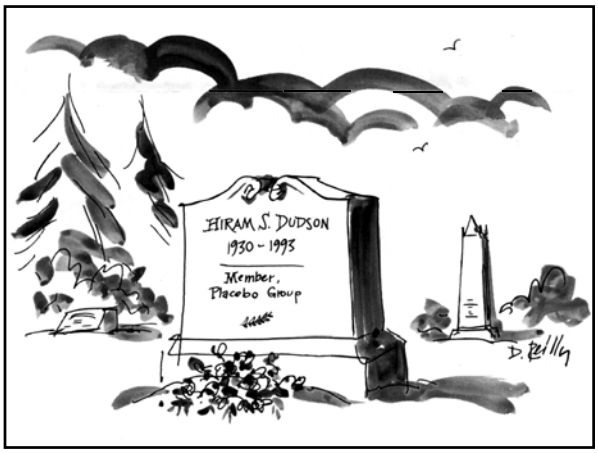


Example



Example

- Simulations, conducted under a wide range of assumptions regarding the rates of AE1, AE2, and AE3, used to verify:
  - Ability of design to reliably terminate poorly tolerated arms
  - Ability of design to reliably retain well-tolerated arms
- Learn phase (phase II dose finding) study
  - Control of type I error rate for efficacy based on taking ≤ 2 active arms forward



When is Adaptation Most Valuable?

- Outcomes or biomarkers available rapidly relative to time required for entire trial
- Substantial morbidity, risks, costs
- Large uncertainty regarding relative efficacy, adverse event rates, etc.
- Logistically practical
- Able to secure buy-in of stakeholders

Why Not Adapt?

- Determining traditional type I and type II error rates is more difficult
  - Usually need to use simulation
- Statistical training issues
  - Most statisticians have never designed or analyzed an adaptive trial
- Logistical Issues
  - Data availability
  - Centralized randomization
  - Drug supply

Categories of Adaptive Trials

- Can be classified based on adaptive component(s)
  - Allocation rule **Response-adaptive dose finding**
  - Sampling rule **Sample size re-estimation**
  - Stopping rule **Group sequential trial**
  - Decision rule **Seamless phase II/III**
- Goal and place in drug development
  - Learn versus confirm
  - Proof of concept, dose finding, seamless phase II/III

Categories of Adaptive Trials

- Information driving adaptation
  - Adaptive
    - Covariates
    - Variance **Sample size re-estimation**
  - Response adaptive
    - Primary endpoint
    - Biomarker **Response-adaptive dose finding**
    - Safety outcomes

Some (Bayesian) Adaptive Strategies

- Frequent interim analyses
- Explicit longitudinal modeling of the relationship between proximate endpoints and the primary endpoint of the trial
- Response-adaptive randomization to efficiently address one or more trial goals
- Explicit decision rules based on predictive probabilities at each interim analysis
- Dose-response modeling
- Extensive simulations of trial performance

Frequent Interim Analyses

- **Frequent interim analyses** based on Markov-chain Monte Carlo (MCMC) estimates of Bayesian posterior probability distributions, with multiple imputation and estimation of unknown trial parameters and patient outcomes.
- Typically quantify
  - Evidence of treatment efficacy
  - Trial futility/predictive probability of success
  - Safety and rates of adverse events

Longitudinal Modeling

- Explicit **longitudinal modeling** of the relationship between proximate endpoints and the primary (generally longer term) endpoint of the trial to better inform interim decision making, based on the data accumulating within the trial and without assuming any particular relationship at the beginning of the trial.
- Used to learn about, and utilize, the relationship between proximate and final endpoints
- Frequently misunderstood as “making assumptions” or using “biomarkers”

Response-adaptive Randomization

- **Response-adaptive randomization** to improve important trial characteristics
- May be used to address one or more of:
  - To improve subject outcomes by preferentially randomizing patients to the better performing arm
  - To improve the efficiency of estimation by preferentially assigning patients to doses in a manner that increases statistical efficiency
  - To improve the efficiency in addressing multiple hypotheses by randomizing patients in a way that emphasizes sequential goals
  - Includes arm dropping

Decision Rules/Predictive Probabilities

- Explicit **decision rules based on predictive probabilities** at each interim analysis to define when to stop for futility, early success, etc.
- Examples
  - May define success or futility based on the predictive probability of success if trial is stopped and all patients followed to completion
  - May define success or futility based on the predictive probability of success of a **subsequent** phase III trial
  - May combine probabilities logically: probability that the active agent is **both** superior to a control arm and non-inferior to an active comparator
  - Design "transitions": e.g., phase II to phase III

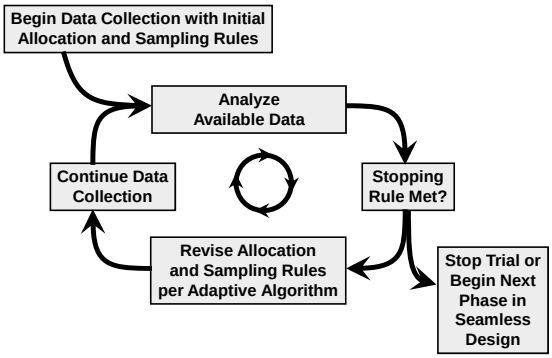
Dose-response Modeling

- **Dose-response modeling**, when applicable, so that information from all patients informs the estimate of the treatment effect at all doses—this improves the reliability of interim decision making and improves accuracy in the updating of interim randomization proportions.
- Examples
  - Logistic dose-response model: assumes monotonicity
  - Normal dynamic linear model (NDLM): borrows information from adjacent doses but doesn't assume a particular shape of the relationship

Extensive Simulations

- **Extensive simulations of trial performance** to ensure that the type I error rate, power and accuracy in estimation of treatment effect(s), the rates of adverse events, or dose finding are well defined and acceptable, across a very wide range of possible true treatment effect sizes, dose-response relationships, and population characteristics.
- Often end up exploring and understanding the performance characteristics across a range of null hypotheses much broader than with traditional approaches

The Adaptive Process



Components of an Adaptive Trial

Management

Adaptive Machinery

Logistics

Drug Supply | Randomization System | CRO/Data Management

Clinical

Site 1 | Site 2 | • • • | Site n

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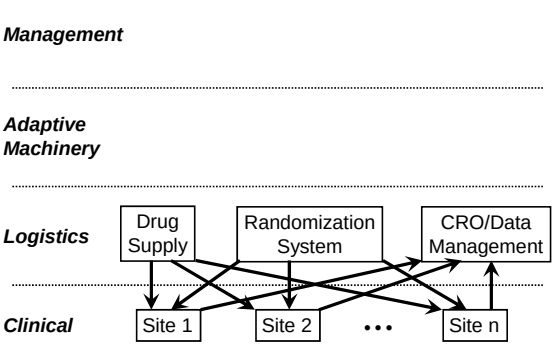

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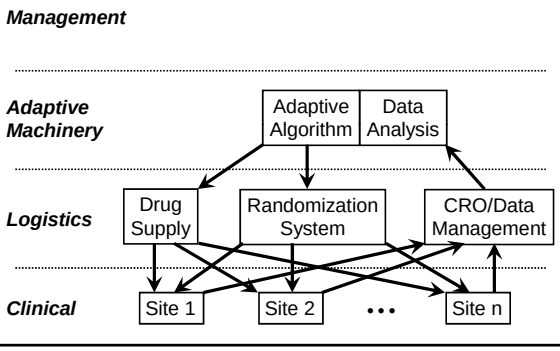

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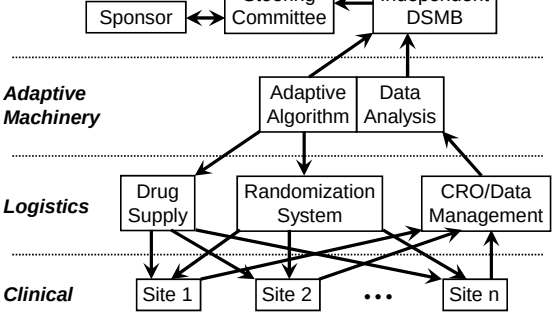

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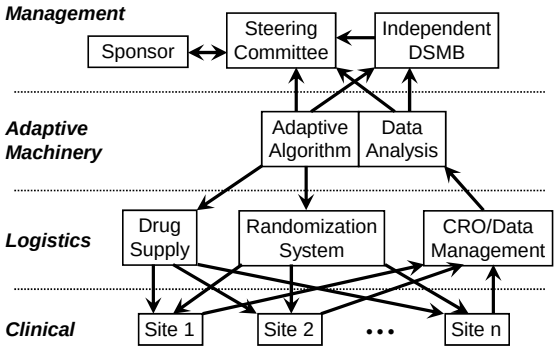

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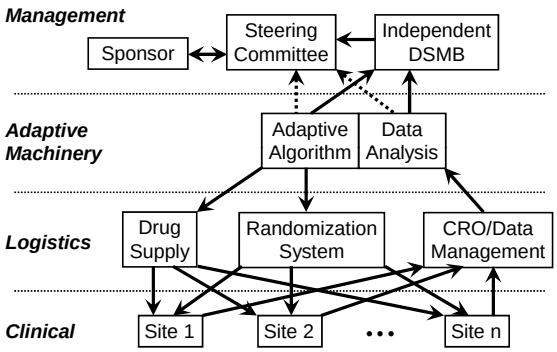


Data and Safety Monitoring Boards

- Purpose
  - To ensure continued safety, validity, feasibility, and integrity of the clinical trial
  - To ensure the trial is conducted according to *a priori* plan, including adaptation
- Structure
  - Learn phase: usually includes internal personnel
  - Confirm phase: generally includes only independent, external members

Data and Safety Monitoring Boards

- What's different in an adaptive trial?
  - Requires expertise to assess whether the planned adaptations continue to be safe and appropriate
  - May increase need to include sponsor personnel
- What's unchanged in an adaptive trial?
  - The DSMB ensures completion of the trial *as planned, including the adaptation*
  - It is the trial that's adaptive, not the DSMB

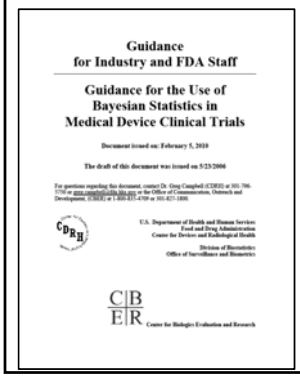
IRB Review

- IRBs review/approve the full protocol, including the planned adaptations
- No new review when adaptations made
  - IRBs may request to be informed (e.g., new sample size, dropping of a surgical arm)
- Amendments are different
  - Not preplanned
- Irony
  - Little changes (e.g., amendments) may require IRB review
  - Big changes (adaptations) are defined by design and only reviewed/approved once

Acceptability to Key Stakeholders

- FDA
  - FDA Critical Path Initiative
  - 2010 Guidance for the Use of Bayesian Statistics in Medical Device Trials
  - 2010 Draft Guidance for Adaptive Design Clinical Trials for Drugs and Biologics
  - Joint Regulatory Science initiative with NIH
  - Multiple adaptive trials accepted in development plans
- PhRMA
  - Highly active "working group" on adaptive trials → DIA
  - 2006 PhRMA/FDA Conference on Adaptive trials
  - Many adaptive trials designed or initiated in industry
- Peer reviewers may be unfamiliar with adaptive design principles

FDA Guidance Documents



Guidance
for Industry and FDA Staff

Guidance for the Use of
Bayesian Statistics in
Medical Device Clinical Trials

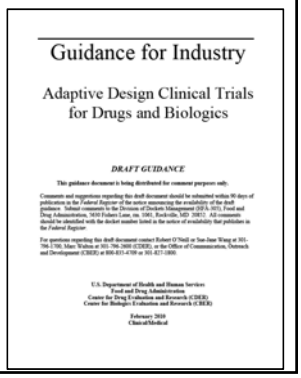
Document issued on: February 5, 2010

The draft of this document was issued on 5/23/2006

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Biostatistics
Office of Surveillance and Biometrics

C|B
E|R
Center for Biologics Evaluation and Research



Guidance for Industry

Adaptive Design Clinical Trials
for Drugs and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2010
Clinical/Medical

The ADAPT-IT Project

- Supported by an NIH U01 grant with funds from both NIH and FDA
- Redesigning four clinical trials for treatments of neurological emergencies
  - control of blood sugar in stroke
  - hypothermia for spinal cord injury with paralysis
  - treatment of prolonged seizures
  - hypothermia after cardiac arrest
- Work closely with project teams and statisticians to create more efficient, ethical version of proposed trials

Online Tools and Resources

- MD Anderson
  - http://biostatistics.mdanderson.org/SoftwareDownload/
  - Lots of good utilities, including “Adaptive Randomization” to help with response adaptive trials
  - Allows 10 arms; minimum number of patients before adapting randomization scheme; maximum number of patients or length of trial
  - Free
- Commercial resources

Conclusions

- Not all trials need (or should have) adaptive designs
- When used appropriately, adaptive designs may:
  - Improve efficiency and reduce cost
  - Maximize the information obtained
  - Minimize risk to subjects and sponsor
- An adaptive design will not save a poorly planned trial or make a treatment effective