SWITCH Trial

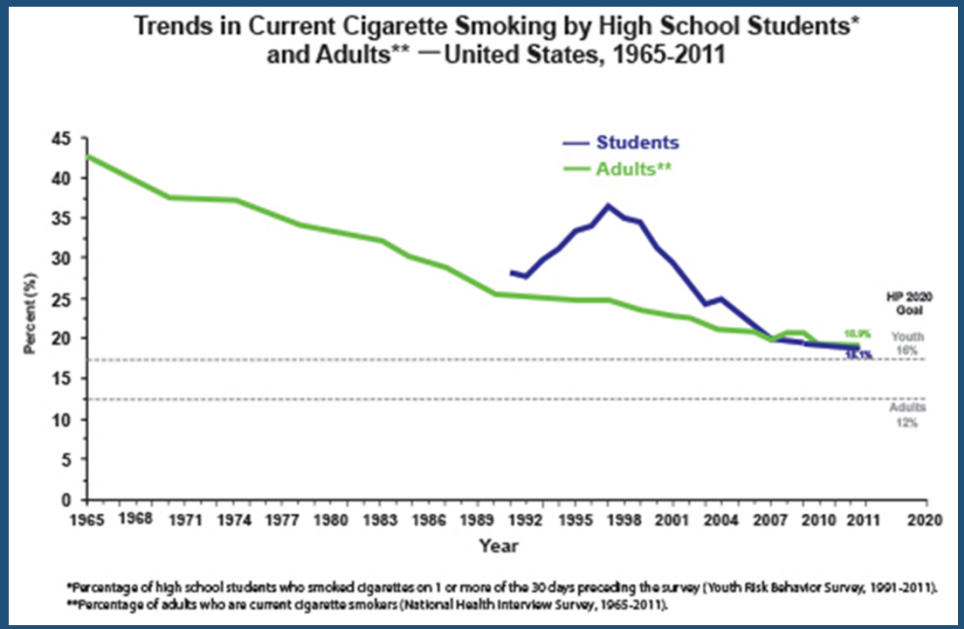
A Sequential Multiple Adaptive Randomization Trial

Background

- Cigarette Smoking (CDC Estimates)
- Morbidity
  - Smoking-caused diseases ≥16 million Americans (1 in 30)
- Mortality
  - 480,000 deaths per year attributable to smoking in U.S. (5,000,000 globally)
  - 1 in 5 deaths annually or 1,300 deaths per day.
  - 41,000 deaths per year attributable to second-hand smoking
- Cost
  - $289 billion/year
  - $133 billion direct medical costs + $156 billion in lost productivity
  - $5.6 billion/year attributable to second-hand smoke (2006 data)

Background (CDC Estimates)

- U.S.
  - 18.1 % of U.S. adults
  - 42.1 million
- Texas
  - 19.2% of adults
  - 17.4% of children in grades 9-12
  - 50% of adults in Texas report second-hand smoke exposure within the preceding seven days.



http://www.cdc.gov/tobacco/data_statistics/tables/trends/cig_smoking/

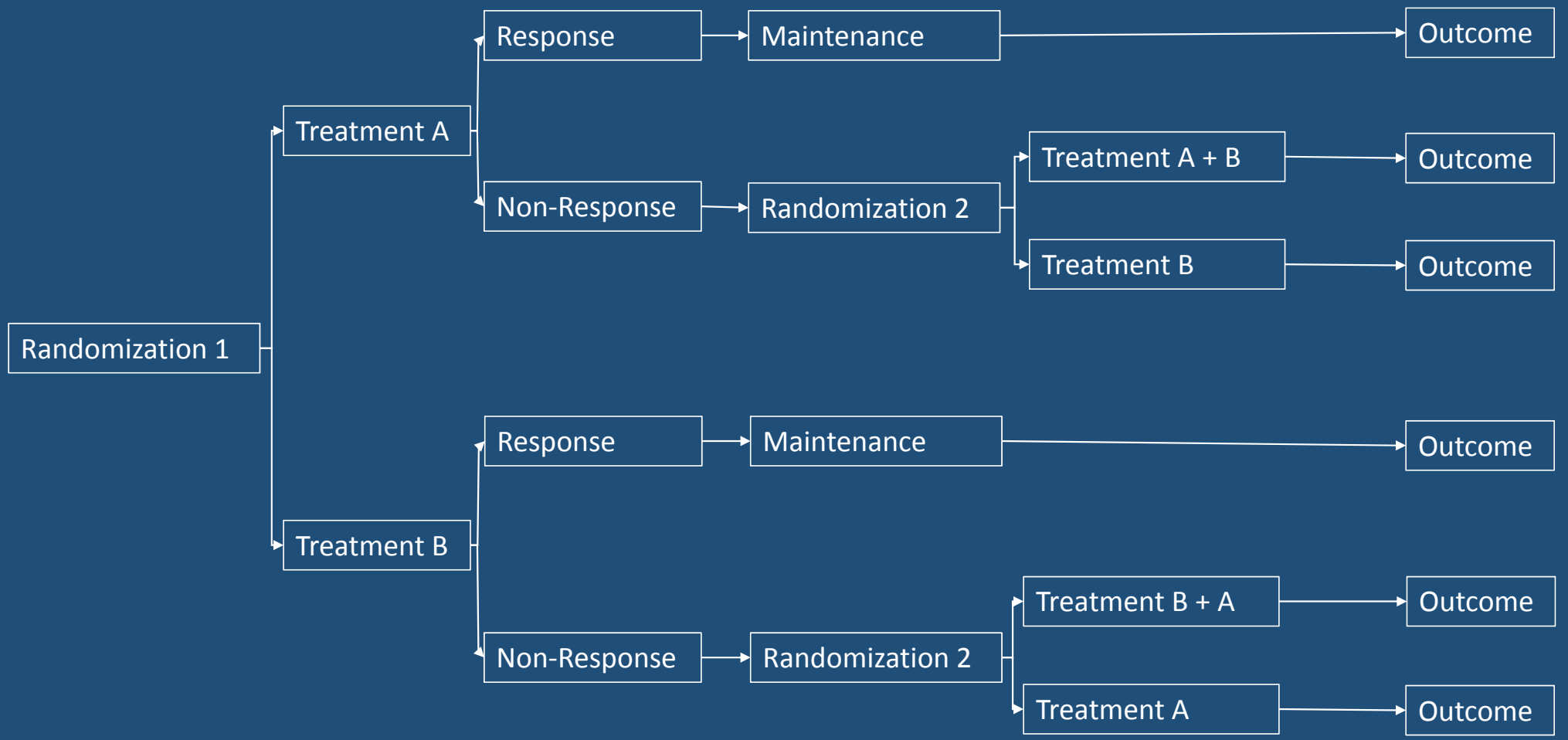
Background

- ~70% of smokers want to quit
- 42.1% of U.S. Adult Smokers report quitting for $\geq$ 24 hrs as part of a cessation attempt (2010)
- < 5% are abstinent 1 year after a quit attempt
- Multiple quit attempts often required to achieve abstinence.
- Chronic, frequently relapsing course of tobacco dependence.
- Very few clinical trials (~3) evaluate how to proceed with individuals following a failure to quit.
- Addressing chronic, relapsing character of tobacco dependence is *sine non qua* of effective treatment.
- Sequential decision-making should maximize the probability of subsequent treatment success:
  - Choice of treatment initiation
  - Choice of subsequent treatments if initial attempts at cessation do not succeed.
- Given the chronic, relapsing nature of cigarette smoking how can we design a trial that informs sequential treatment decisions?

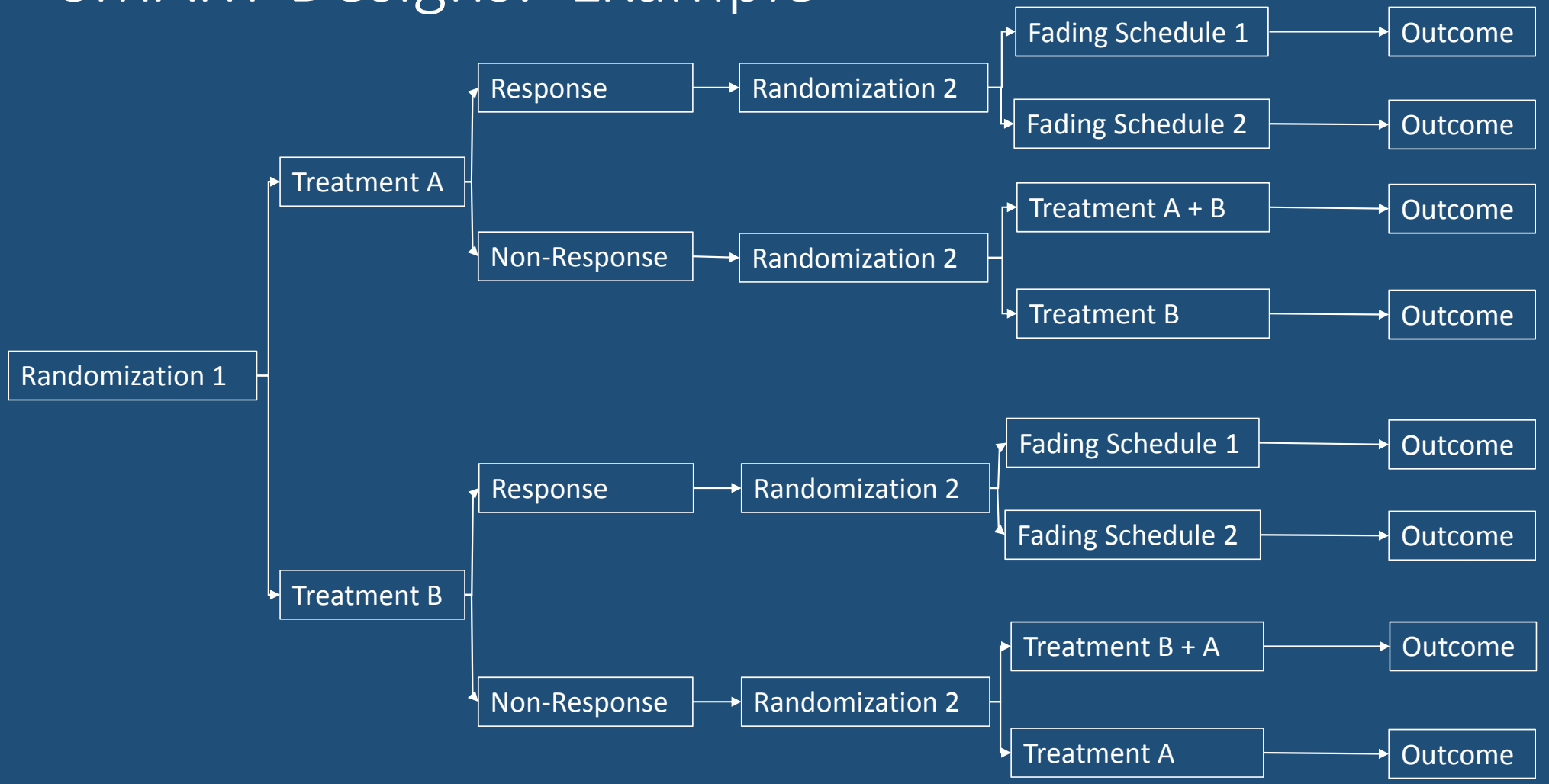
SMART: Sequential Multiple Adaptive Randomization Trials

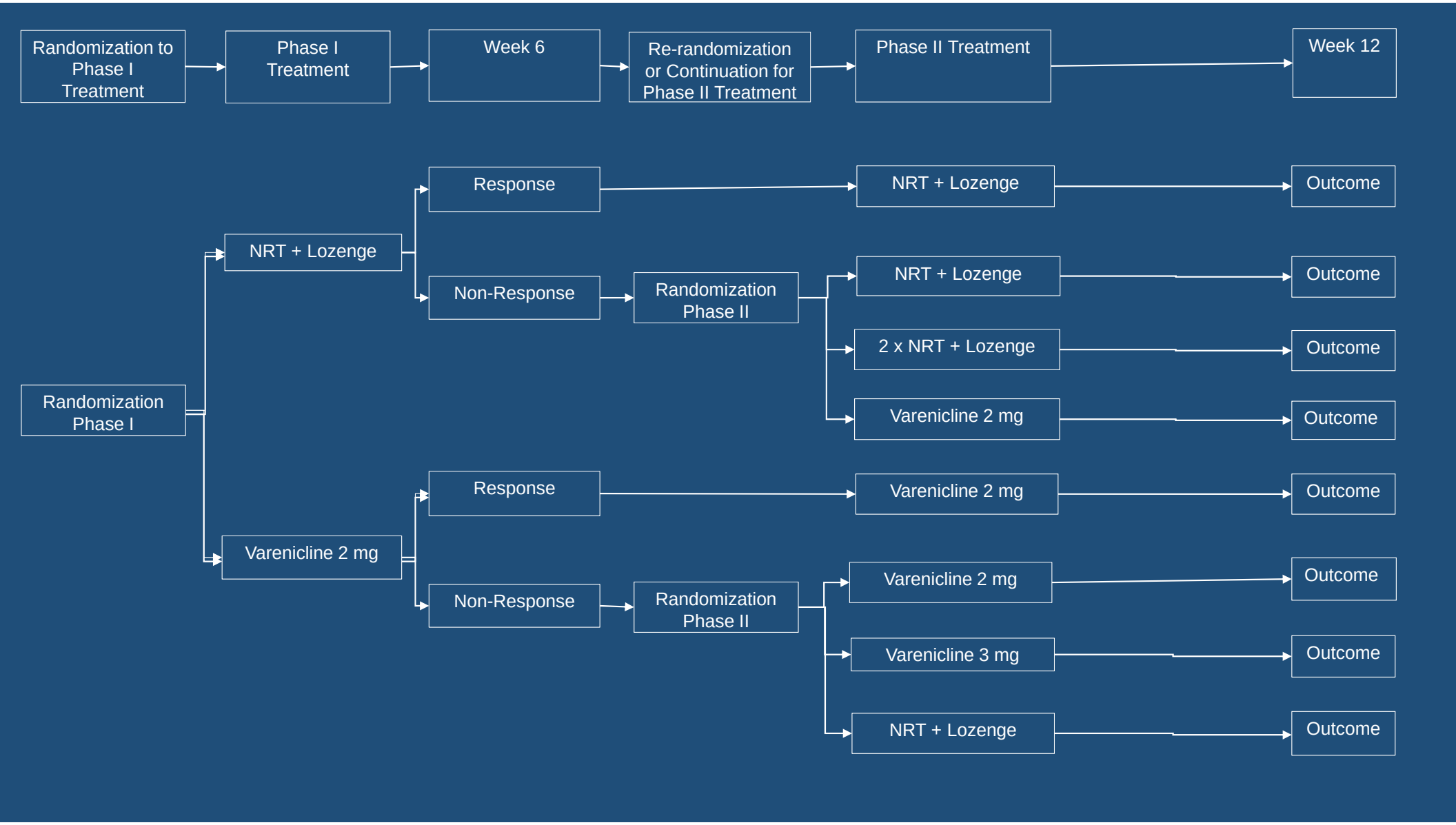
- Evaluate clinical decision-making options.
- Re-randomization at a decision-making point:
- Completed or Ongoing Trials:
    - Cocaine Dependence
    - Relapse Prevention Among Pregnant Drug Abusers
    - Alcohol Abuse
    - Adolescent Substance Abuse
    - ADHD
    - Bipolar Disorder
    - Autism
    - Weight-Loss
    - Obsessive Compulsive Disorder
    - Child and Adolescent Depression

SMART Designs: Example



SMART Designs: Example




Randomization to Phase I Treatment
Phase I Treatment
Week 6
Re-randomization or Continuation for Phase II Treatment
Phase II Treatment
Week 12
Randomization Phase I
NRT + Lozenge
Response
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Outcome
Non-Response
Randomization Phase II
NRT + Lozenge
Outcome
2 x NRT + Lozenge
Outcome
Varenicline 2 mg
Outcome
Varenicline 2 mg
Response
Varenicline 2 mg
Outcome
Non-Response
Randomization Phase II
Varenicline 2 mg
Outcome
Varenicline 3 mg
Outcome
NRT + Lozenge
Outcome

Hypotheses

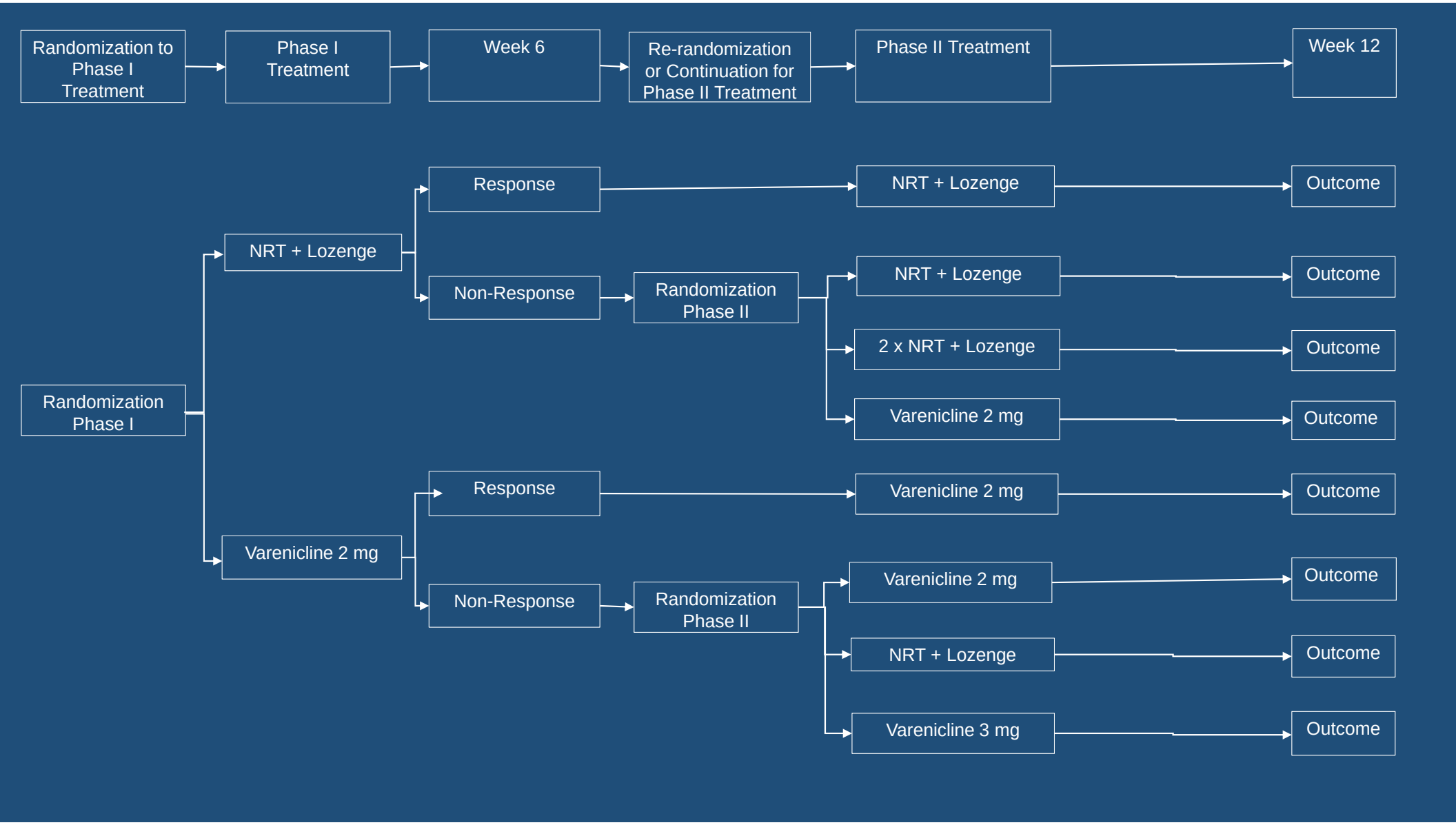
- **Aim 1:** To estimate the main effects of VAR 2 mg and nicotine NPL on smokers initially assigned to those treatments in Phase 1 and remaining on these medications through Phase 2.
  - We hypothesize t*he probability of abstinence at week 12 will demonstrate superiority of VAR to NPL.*

- **Aim 2:** To estimate the probability that abstinence at the week 12 for those re-randomized to augmentation at week 6 is moderated by their initial treatment assignment.
  - *We hypothesize that the probability of abstinence at the end of treatment will demonstrate superiority for augmented participants originally receiving VAR compared to those who received NPL.*

- **Aim 3:** To estimate the probability that abstinence at the end of treatment for those re-randomized to switch treatments is moderated by initial treatment assignment.
  - *We hypothesize the probability of abstinence at week 12 will demonstrate superiority for switched participants originally receiving NPL compared to those receiving VAR.*

- **Aim 4:** To estimate the probability that abstinence at the end of treatment for those re-randomized to continue, switch or augment treatment in phase 2, confers differential benefit for those initially assigned to NPL.
  - *We hypothesize that the probability of abstinence at the end of treatment will demonstrate superiority for those switched to 2 mg VAR vs. either augmentation, or continuation of their original treatment, and that augmentation (NPL+) will be superior to continuation (NPL).*

- **Aim 5:** To estimate the probability that abstinence at the end of treatment for those re-randomized to continue, switch or augment treatment in phase 2, confers differential benefit for those initially assigned to VAR.
  - *We hypothesize the probability of abstinence at the end of treatment will demonstrate superiority for those* receiving *augmentation (VAR+) vs. switching to NPL or remaining on VAR.*


Randomization to Phase I Treatment
Phase I Treatment
Week 6
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NRT + Lozenge
Response
NRT + Lozenge
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2 x NRT + Lozenge
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Varenicline 2 mg
Outcome
Varenicline 2 mg
Response
Varenicline 2 mg
Outcome
Non-Response
Randomization Phase II
Varenicline 2 mg
Outcome
NRT + Lozenge
Outcome
Varenicline 3 mg
Outcome

Problems

- Contrast coding exists only for the case of randomization to two groups, followed by rerandomization to two groups.
  - Development (Sanjay Schete) of a new coding scheme.
- Sample sizes can rapidly diminish across re-randomizations.
  - Adopting a Bayesian statistical perspective.
- How to judge the operating characteristics of the design?
  - Simulation.
- Given the design complexity how can we develop as robust a trial plan as possible?
  - Take uncertainty into account using predictive priors.

Coding Solution

$$logit(y) = \beta_0 + \beta_1 * a_1 + \beta_2 * anr_{21} + \beta_3 * anr_{22} + \beta_4 * anr_{23} + \beta_5 * a_1 * anr_{21} + \beta_6 * a_1 * anr_{22} + \beta_7 * a_1 * anr_{23}$$

Coding

Treatment I $\begin{cases} a = 1: \ Var\ 2mg \\ a = -1: \ NRT + Loz \end{cases}$

Continuation $\begin{cases} anr_{21} = 1: \ Continue \\ anr_{21} = 0: \ Otherwise \end{cases}$

Augmentation $\begin{cases} anr_{22} = 1: \ Augment \\ anr_{22} = 0: \ Otherwise \end{cases}$

Switch $\begin{cases} anr_{21} = -1: \ Augment \\ anr_{21} = 0: \ Otherwise \end{cases}$

Effects

$$NRT + Loz_{responders} = \beta_0 - \beta_1$$
$$Var\ 2mg\ _{responders} = \beta_0 + \beta_1$$

$$NRT + Loz_{nonresponders} \rightarrow NRT + Loz = \beta_0 - \beta_1 + \beta_2 - \beta_5$$

$$NRT + Loz_{nonresponders} \rightarrow 2 * NRT + Loz = \beta_0 - \beta_1 + \beta_3 - \beta_6$$

$$NRT + Loz_{nonresponders} \rightarrow Var\ 2mg = \beta_0 - \beta_1 - \beta_4 + \beta_7$$

$$Var\ 2mg\ _{nonresponders} \rightarrow Var\ 2mg = \beta_0 + \beta_1 + \beta_2 + \beta_5$$

$$Var\ 2mg\ _{nonresponders} \rightarrow Var\ 3mg = \beta_0 + \beta_1 + \beta_3 + \beta_6$$

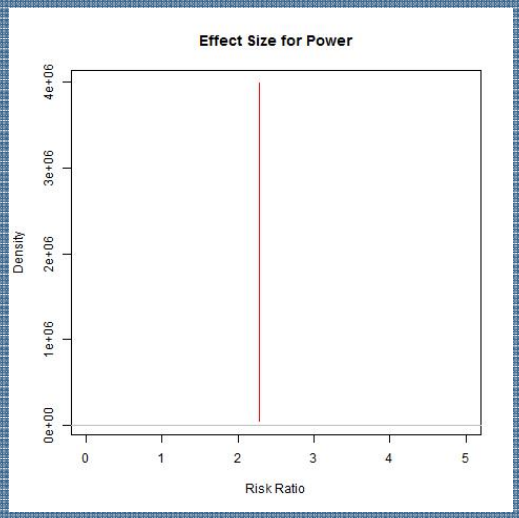
$$Var\ 2mg\ _{nonresponders} \rightarrow NRT + Loz = \beta_0 + \beta_1 - \beta_3 + \beta_7$$

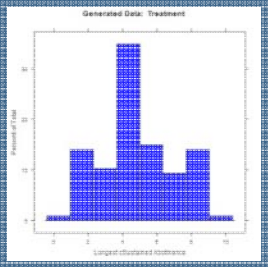
Bayesian Inference

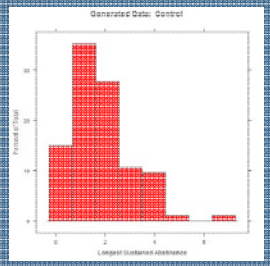
- Logistic Regression
  - Vague, neutral prior distributions for coefficients in the log-odds ~Normal(Mean = 0, Variance = 1×10^6)
- Analyses would yield:
  - Estimate of the posterior probability of benefit of participants responding to Phase I treatment.
  - Estimate the posterior probability of benefit conferred by specific sequential treatment strategies among initial non-responders.
  - Estimate of the posterior probability of benefit of continuation/augmentation/switching following Phase I failure.
- Stipulate that 90% chance (posterior probability) of benefit warrants further investigation of the treatment or treatment sequence.
    - $p(O.R.>1 \mid Data) \geq 0.90$

Conventional Design Simulation: Power

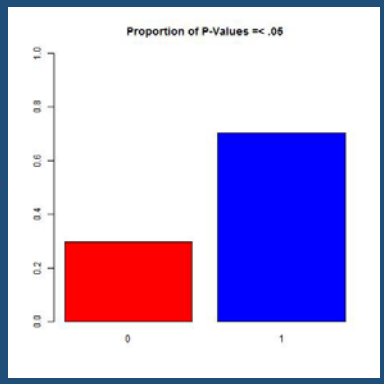
Repeat ≈ 10,000 Times







p-values



Specify a Distribution of Plausible Parameters

Randomly Draw Set of Parameters

Generate a Sample of Data

Analyze the Generated Sample

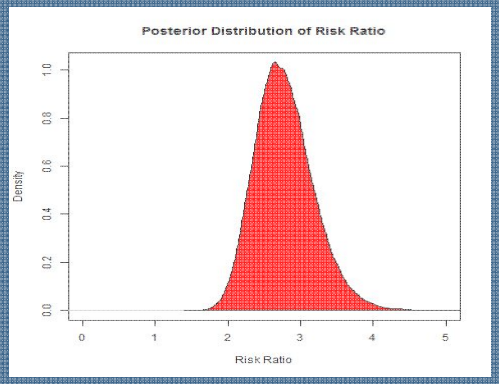
Capture Estimates

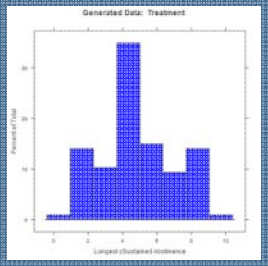
Record Whether Estimates Meet Threshold

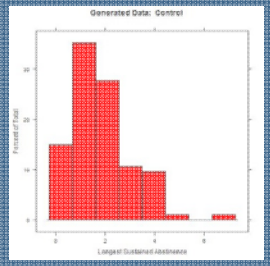
Proportion meeting Threshold is Power

Robust Design: Predictive Power

Repeat ≈ 10,000 Times







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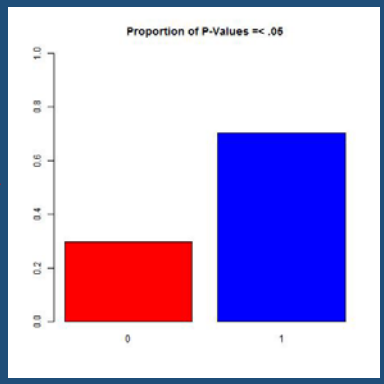

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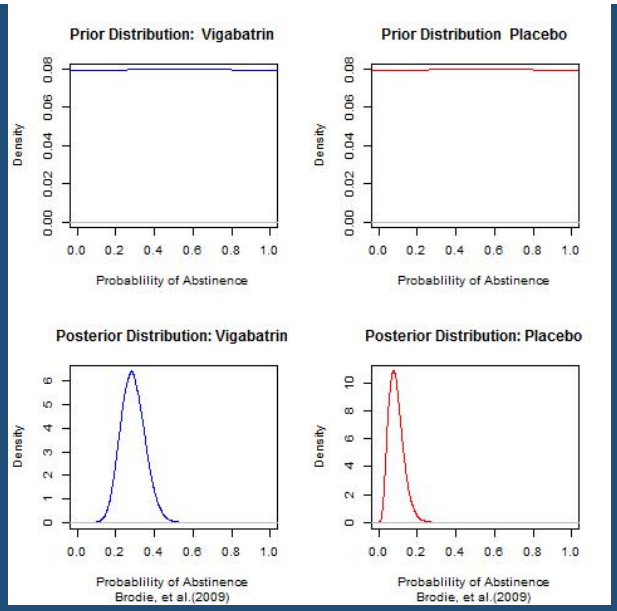
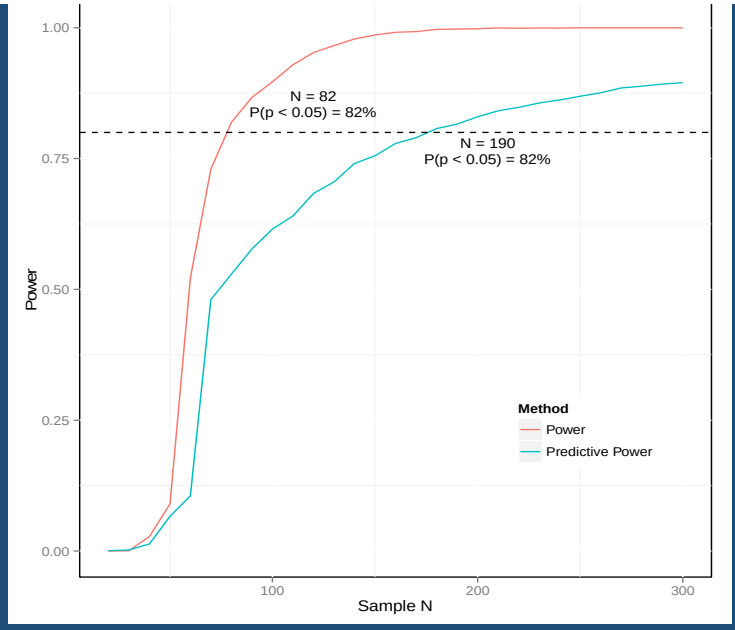
ORIGINAL ARTICLE

A Multisite, Double-blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Vigabatrin for Treating Cocaine Dependence

Eugene C. Somoza, MD, PhD; Douglas Winship, BS; Charles W. Gorodetzky, MD, PhD; Daniel Lewis, BS; Domenic A. Ciraulo, MD; Gantt P. Galloway, PharmD; Scott D. Segal, MD; Michael Sheehan, MD; John D. Roache, PhD; Warren K. Bickel, PhD; Donald Jasinski, MD; Donnie W. Watson, PhD; Steven R. Miller, PhD; Peggy Somoza, MS; Theresa Winhusen, PhD

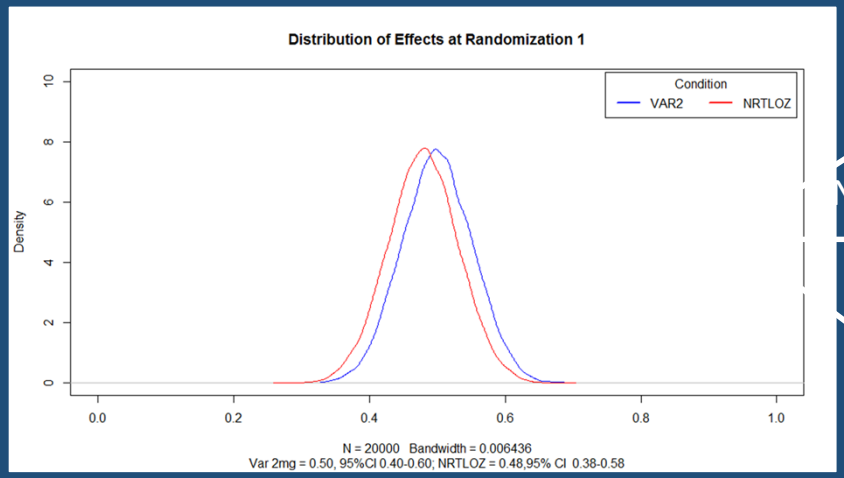




Specify Prior Distributions for Predictive Simulation

- Dichotomous Outcome
  - Beta-Binomial Model
    - $\pi \sim$ Beta(a,b)
      - a = previously observed successes
      - b = previously observed failures
    - Abstinence ~ Binomial (π)
- Specify Priors Based on Meta-Analytic Reviews
- Consult with a clinical panel to adjust priors derived from the literature.
  - Best estimate regarding probability of abstinence? 50^{th} percentile.
  - Lowest potential estimate for probability of abstinence? 2.5^{th} percentile.
  - Highest potential estimate for probability of abstinence? 97.5^{th} percentile.
  - Back calculate the corresponding Beta density based on two quantiles.
- Do so for outcomes in each cell at six and twelve weeks.

Probability of Success at Six Weeks

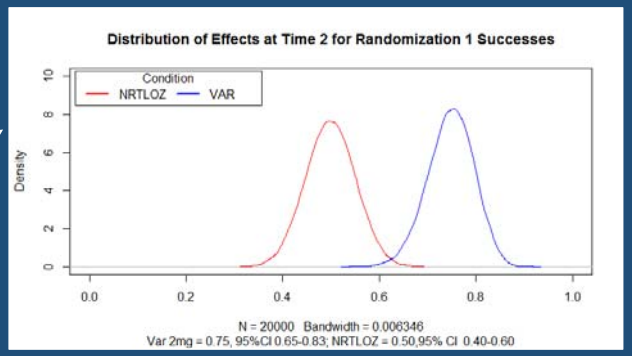


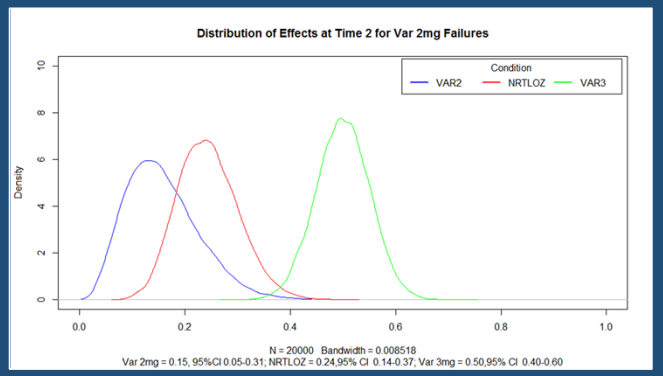
Response

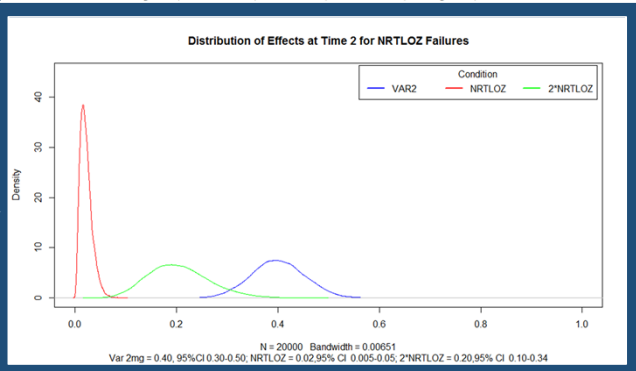
Non-Response to Var 2mg

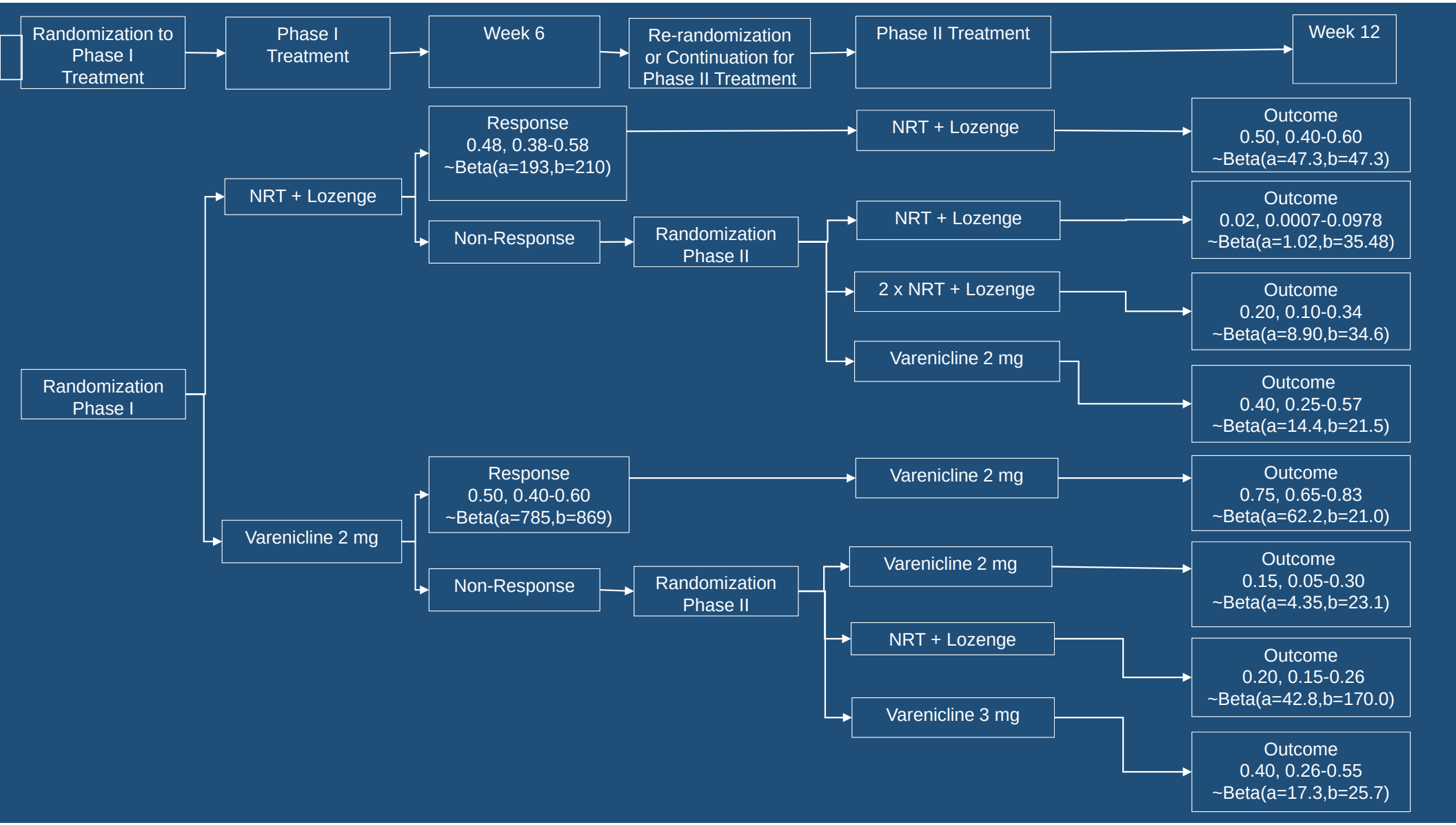
Non-Response to NRT + Loz. 2mg

Probability of Success at Twelve Weeks



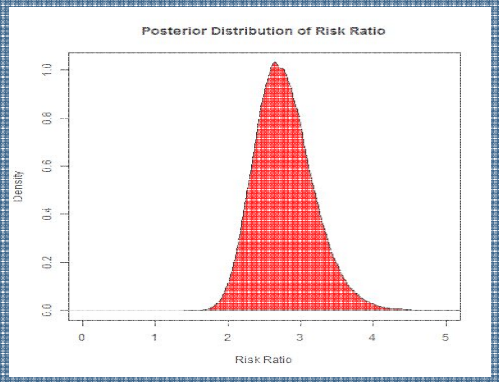


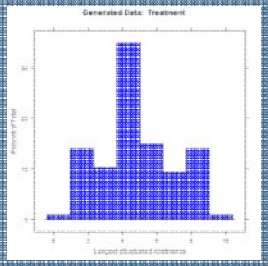


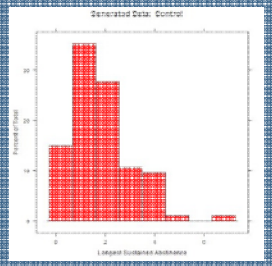

Randomization to Phase I Treatment
Phase I Treatment
Week 6
Re-randomization or Continuation for Phase II Treatment
Phase II Treatment
Week 12
Randomization Phase I
NRT + Lozenge
Response 0.48, 0.38-0.58 ~Beta(a=193,b=210)
Non-Response
Randomization Phase II
NRT + Lozenge
Outcome 0.50, 0.40-0.60 ~Beta(a=47.3,b=47.3)
NRT + Lozenge
Outcome 0.02, 0.0007-0.0978 ~Beta(a=1.02,b=35.48)
2 x NRT + Lozenge
Outcome 0.20, 0.10-0.34 ~Beta(a=8.90,b=34.6)
Varenicline 2 mg
Outcome 0.40, 0.25-0.57 ~Beta(a=14.4,b=21.5)
Varenicline 2 mg
Response 0.50, 0.40-0.60 ~Beta(a=785,b=869)
Non-Response
Randomization Phase II
Varenicline 2 mg
Outcome 0.75, 0.65-0.83 ~Beta(a=62.2,b=21.0)
Varenicline 2 mg
Outcome 0.15, 0.05-0.30 ~Beta(a=4.35,b=23.1)
NRT + Lozenge
Outcome 0.20, 0.15-0.26 ~Beta(a=42.8,b=170.0)
Varenicline 3 mg
Outcome 0.40, 0.26-0.55 ~Beta(a=17.3,b=25.7)

Robust Bayesian Design

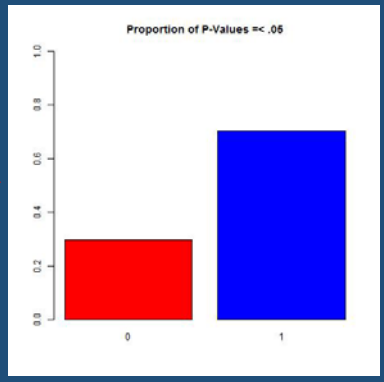
Repeat ≈ 500 Times







Posterior Distributions



Specify a Distribution of Plausible Parameters

Randomly Draw Set of Parameters

Generate a Sample of Data

Analyze the Generated Sample

Capture Posterior Distributions

Record Whether Estimate Meets Threshold

Proportion meeting threshold is PPP

Simulation

- K = 500 clinical trials simulations
- Evaluate sample sizes ranging from 200 to 400.
- Examine various decision-rules p(O.R. > 1|data) = 0.80, 0.85…0.95
- Calculate the proportion of trials that detect a given probability of benefit at each sample size.
- Repeat the preceding for each contrast implied by Hypotheses 1 -5.

Estimates Recovered from Simulations

Effect	Average Point Estimate	Average Interval (95% C.I.) Estimate
Responders		
NRT+Loz	0.507	0.427-0.587
Var 2mg	0.748	0.673-0.814
Non-Responders		
NRT+Loz→NRT+Loz	0.029	0.015-0.049
NRT+Loz→2*NRT+Loz	0.198	0.143-0.262
NRT+Loz→Var 2mg	0.406	0.333-0.481
Var 2mg→Var 2mg	0.153	0.107-0.210
Var 2mg → Var 3mg	0.395	0.322-0.471
Var 2mg → NRT+Loz	0.202	0.147-0.266

Predictive Probabilities and Effects from Simulations

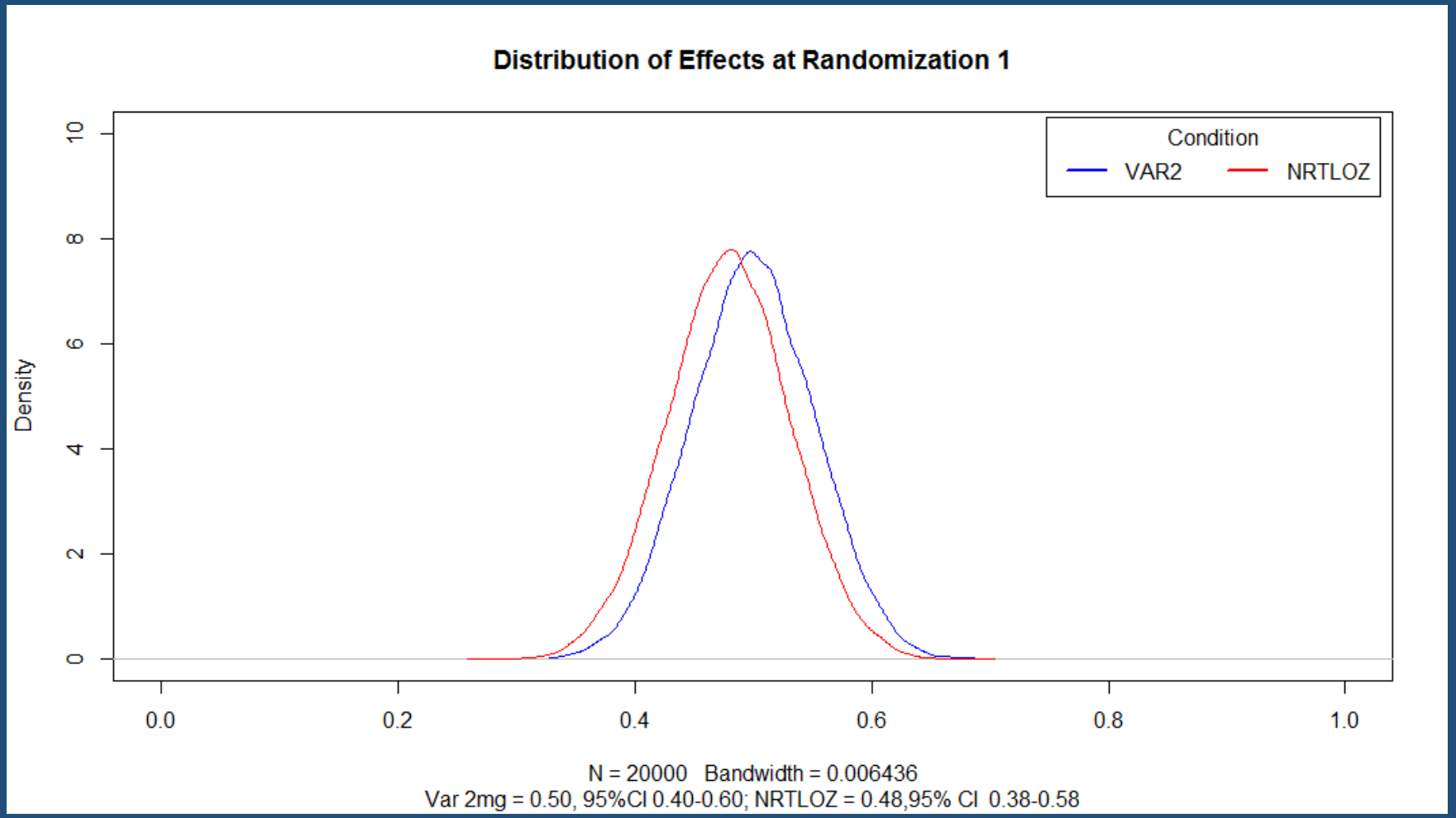
Effect	Probability of Benefit	Power to Detect Probability of Benefit	Average Point Estimate	Average Interval (95% C.I.) Estimate
Effect of Treatment Phase I Responders	0.80	0.948	0.240	0.132-0.346
	0.85	0.934		
	0.90	0.924		
	0.95	0.902		
Treatment Phase I * Augmention	0.80	0.828	0.197	0.099-0.293
	0.85	0.818		
	0.90	0.804		
	0.95	0.766		
Treatment I * Switching	0.80	0.874	0.203	0.106-0.298
	0.85	0.858		
	0.90	0.838		
	0.95	0.798		

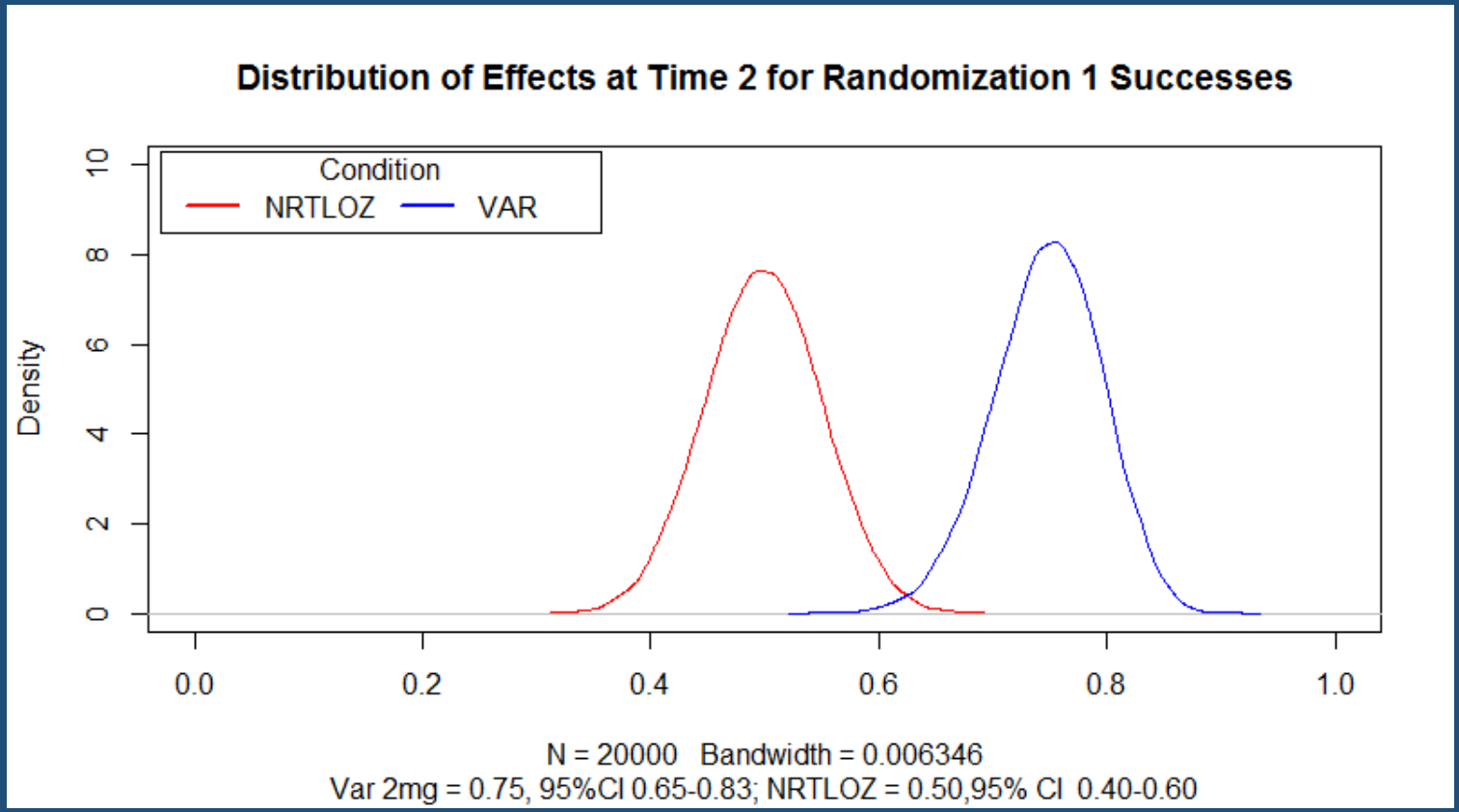
Predictive Probabilities and Effects from Simulations

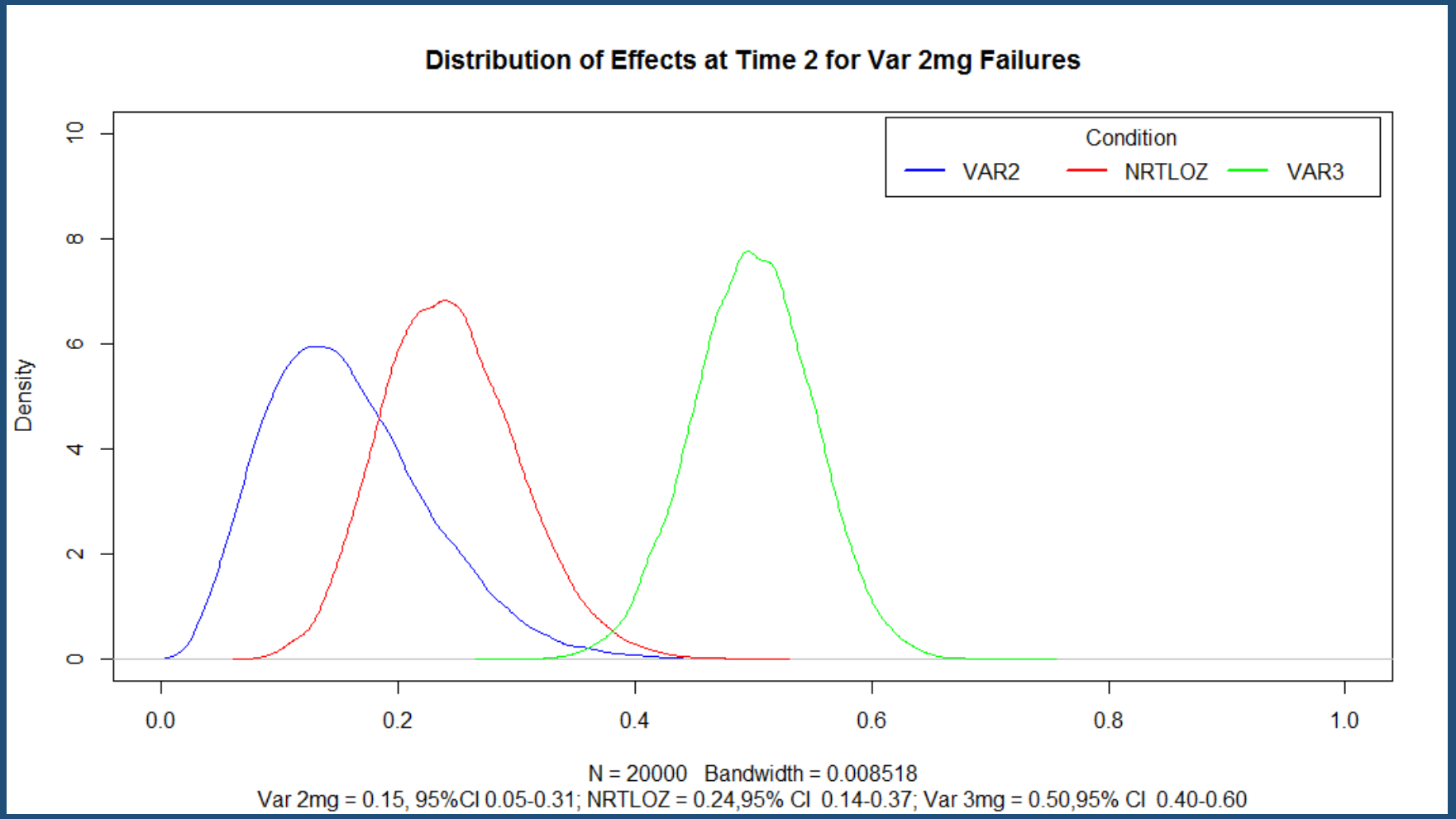
Effect	Probability of Benefit	Power to Detect Probability of Benefit	Average Point Estimate	Average Interval (95% C.I.) Estimate
Treatment Phase II Following Non-Response to NRT + Lozenge				
Varenicline 2mg vs. NRT + Lozenge	0.80	0.998	0.376	0.298-0.455
	0.85	0.998		
	0.90	0.996		
	0.95	0.996		
2 x NRT + Lozenge vs. NRT + Lozenge	0.80	0.922	0.168	0.106-0.237
	0.85	0.914		
	0.90	0.906		
	0.95	0.894		
Varenicline 2mg vs. 2 x NRT + Lozenge	0.80	0.848	0.207	0.110-0.302
	0.85	0.834		
	0.90	0.822		
	0.95	0.802		
Treatment Phase II Following Non-Response to Varenicline 2 mg				
Varenicline 3mg vs. Varenicline 2mg	0.80	0.898	0.241	0.148-0.333
	0.85	0.886		
	0.90	0.874		
	0.95	0.852		
Varenicline 3mg vs. NRT + Lozenge	0.80	0.858	0.193	0.096-0.288
	0.85	0.844		
	0.90	0.818		
	0.95	0.788		

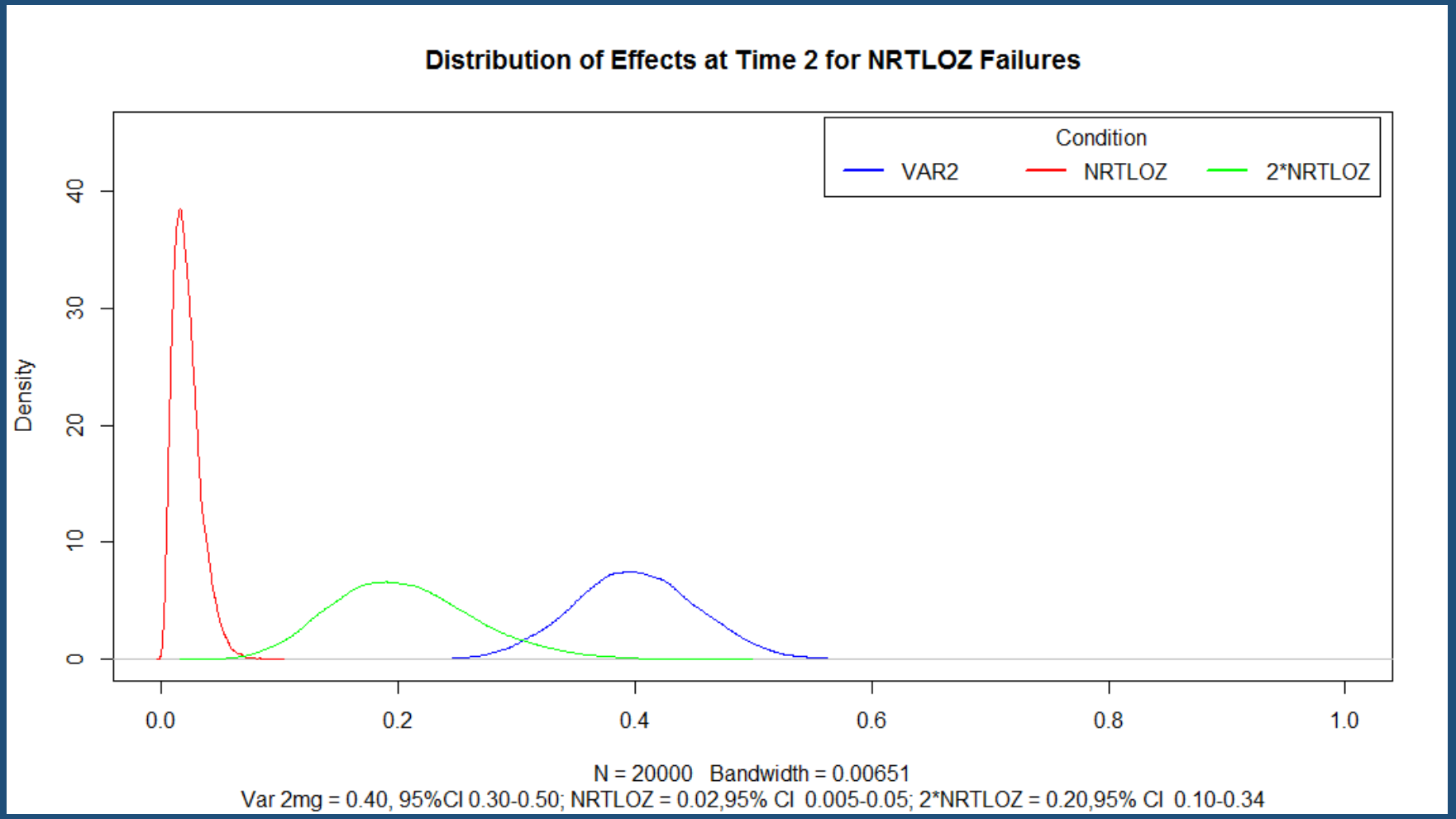
Summary

- Chronic, frequently relapsing disorders may require specialized designs.
- Simulation provides the only readily available means of evaluating the operating characteristics of such designs.
- Bayesian inference
  - Appealing for the decisions required at the conclusion of any pilot/early phase trial.
    - Probability model is more applicable than a Frequentist model
    - Optimizes the available evidence conditional upon the observed data.
- Robust planning should account for uncertainty surrounding investigator expectations.


Distribution of Effects at Randomization 1
Condition
VAR2
NRTLOZ
Density
0
2
4
6
8
10
0.0
0.2
0.4
0.6
0.8
1.0
N = 20000 Bandwidth = 0.006436
Var 2mg = 0.50, 95%CI 0.40-0.60; NRTLOZ = 0.48,95% CI 0.38-0.58


Distribution of Effects at Time 2 for Randomization 1 Successes
Condition
NRTLOZ
VAR
Density
0
2
4
6
8
10
0.0
0.2
0.4
0.6
0.8
1.0
N = 20000 Bandwidth = 0.006346
Var 2mg = 0.75, 95%CI 0.65-0.83; NRTLOZ = 0.50,95% CI 0.40-0.60


Distribution of Effects at Time 2 for Var 2mg Failures
Condition
VAR2
NRTLOZ
VAR3
Density
0
2
4
6
8
10
0.0
0.2
0.4
0.6
0.8
1.0
N = 20000 Bandwidth = 0.008518
Var 2mg = 0.15, 95%CI 0.05-0.31; NRTLOZ = 0.24,95% CI 0.14-0.37; Var 3mg = 0.50,95% CI 0.40-0.60


Distribution of Effects at Time 2 for NRTLOZ Failures
Condition
VAR2
NRTLOZ
2*NRTLOZ
Density
0
10
20
30
40
0.0
0.2
0.4
0.6
0.8
1.0
N = 20000 Bandwidth = 0.00651
Var 2mg = 0.40, 95%CI 0.30-0.50; NRTLOZ = 0.02,95% CI 0.005-0.05; 2*NRTLOZ = 0.20,95% CI 0.10-0.34