FRIENDS OF CANCER RESEARCH

Annual Meeting

Panel 1

Characterizing the Use of External Controls for Augmenting Randomized Control Arms and Confirming Benefit

#FriendsAM19

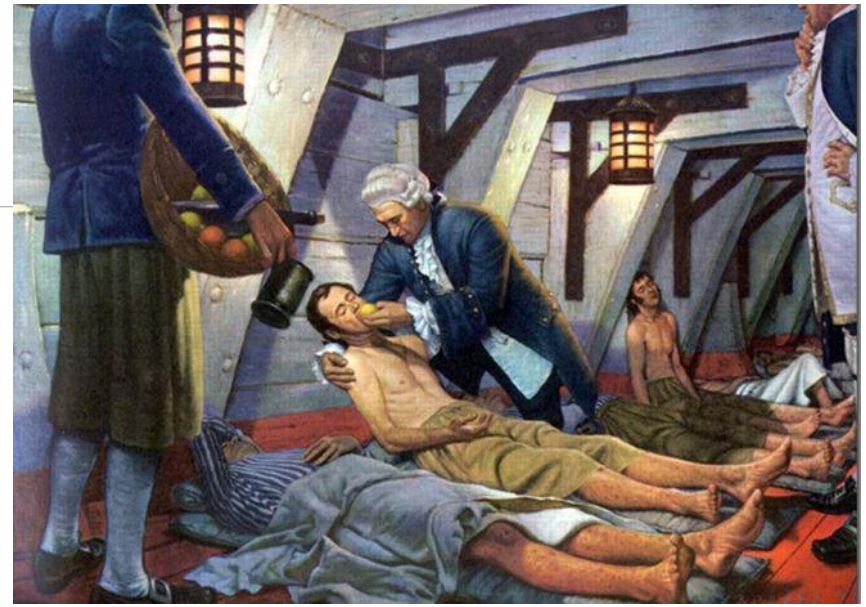
Password: FOCR2019

Panel 1 Participants

Moderator: Gary Rosner, Johns Hopkins University

- Bill Capra, Genentech
- Ruthie Davi, Acorn AI, a Medidata Company
- Bindu Kanapuru, FDA
- Erik Pulkstenis, AbbVie
- Jeremy Rassen, Aetion
- Dirk Reitsma, PPD
- Meghna Samant, Flatiron Health

Randomized Controlled Trials



- History
  - Dr. James Lind clinical trial in 1747
    - 12 sailors w/scurvy: 6 pairs
      - "their cases as similar as I could have them"
      - Multiple trts, including 2 oranges & 1 lemon a day
    - After 1 week, the men on citrus recovered
      - 1 back to active duty; 1 nursed the rest

Regulatory Considerations

- External controls generally allowed only in “special circumstances,” such as “diseases with high and predictable mortality” and when the “effect of the drug is self-evident”
- *RCT not always feasible*
  - Sometimes many patients refuse randomization
  - Rare condition
  - Small numbers of available patients
  - Control patients crossover to new treatment
  - Lack of equipoise

Renewed Interest in External Controls

- Widening availability of electronic health records
- Expanding access to clinical trial data from the pharmaceutical industry
- Availability of statistical methods for achieving balance in baseline characteristics between the clinical trial and external controls

Types of Control Groups (see glossary in white paper)

- Control Arm: Group of participants in a clinical trial not given the experimental intervention under study
  - Establishes expected outcome without the effect of the new experimental therapy
- Randomized Control Arm: Group randomly selected not to receive the experimental intervention
  - Provides high levels of assurance that observed differences between randomized control and experimental intervention attributable to intervention, not imbalances in baseline characteristics or differences in time, place, or circumstances of treatment

Types of Control Groups (cont'd)

- External Control Arm: Any control not a randomized control
- Concurrent Control Arm: Pts from same or similar pop'n as study pop'n & treated over same period
- Historical Control: Non-concurrent comparator group treated in the past for whom data available
- Synthetic Control Arm: Pts external to the study & selected with statistical methods (e.g., propensity scores) to provide confidence that baseline characteristics of study and external pts are balanced and comparable for the two groups

Consider Two Main Study Designs with External Controls

- Single-arm study with external control
  - Control group for study completely external to study
- Hybrid design:
  - Supplement or augment the control group in the RCT with data from an external population sample
    - Included (if comparable) with randomized control arm

Biases to Consider (see Table 1)

Bias	Explanation	Bias Reduction
Confounding Bias	Patient characteristics systematically different across treatment groups	Randomization
Selection Bias	Patients do not represent broader population	Broaden eligibility criteria
Performance Bias	Different follow-up by trt; Systematic diff in care or exposure to other factors	Standardization of trt, follow-up, etc.
Assessment Bias	Systematic differences in outcome determination	Masking
Attrition Bias	Systematic diff between groups in withdrawals	Intention to treat
Time-trend Bias	Prognostic characteristics change over time	Maintain randomization

Some Scenarios That Might Benefit from External Controls (Table 3)

- Uncontrolled (e.g., single-arm trial, expanded access)
  - Difficult to interpret outcomes w/o knowing what to expect
- Studies of orphan diseases, rare diseases, rare biomarker-defined cohorts
  - Accrual of patients challenging
- Post-marketing confirmatory study following accelerated approval
  - Recruitment challenging if available outside of study
- Presence of high rate of treatment cross over
  - RCT's controls use same or similar drug if available

Our Question:

- While not meeting same gold standard as RCT, can a well-designed study with an external control still provide adequate evidence of treatment effectiveness?

medidata

Exploration of whether a Synthetic Control Arm derived from Historical Clinical Trials can Replicate the Overall Survival of a Randomized Control Arm, including Assessment of Unobserved Confounders

Case Study in Multiple Myeloma

Case Study Motivation

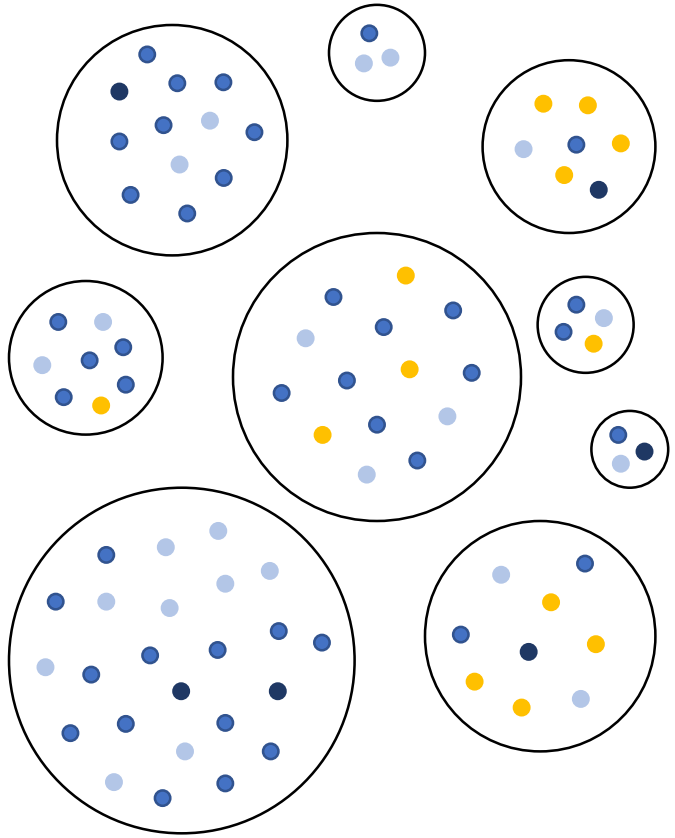
Synthetic Control Arm Exploration

The Challenge: Recruitment, Retention, and Compliance in Randomized Control

- Maintaining a concurrent control arm can be difficult due to rarity of the disease or availability of the investigational agent outside the study
- BRAVO study in BRCA+ breast cancer[1]
  - Unusually high rate of censoring in the control arm likely associated with increased availability of PARP inhibitors
  - Unlikely to produce data that is interpretable
- Sunitinib Malate in gastrointestinal stromal tumor[2]
  - Large effect on progression free survival (HR 0.33, 95% CI (0.24, 0.47))
  - After 84% of placebo patients elected to receive sunitinib malate, effect on overall survival was not observed (HR 0.88, 95% CI (0.68, 1.1))

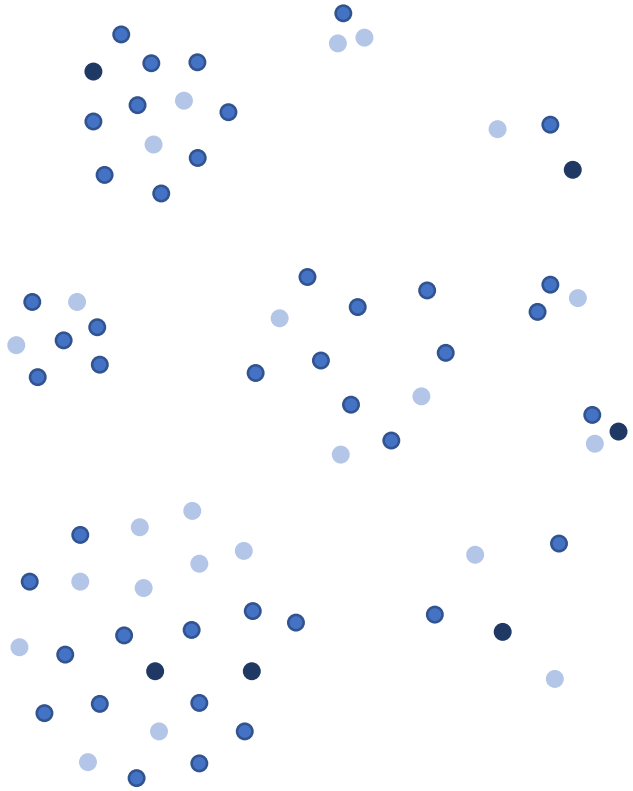
1. Tesaro press release (2017)
2. Sunitinib malate capsule prescribing information (2006)

Historical Clinical Trials Data

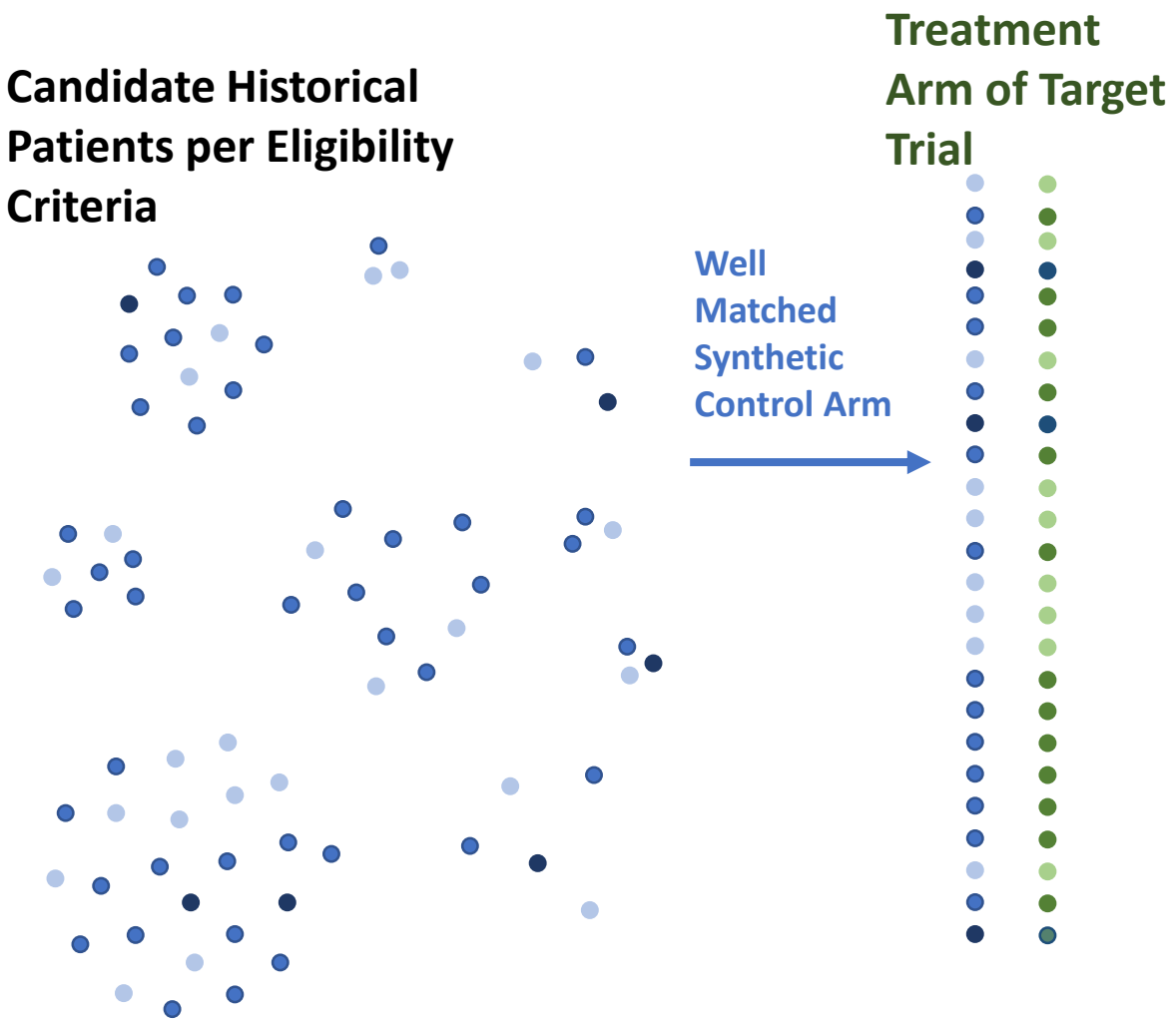


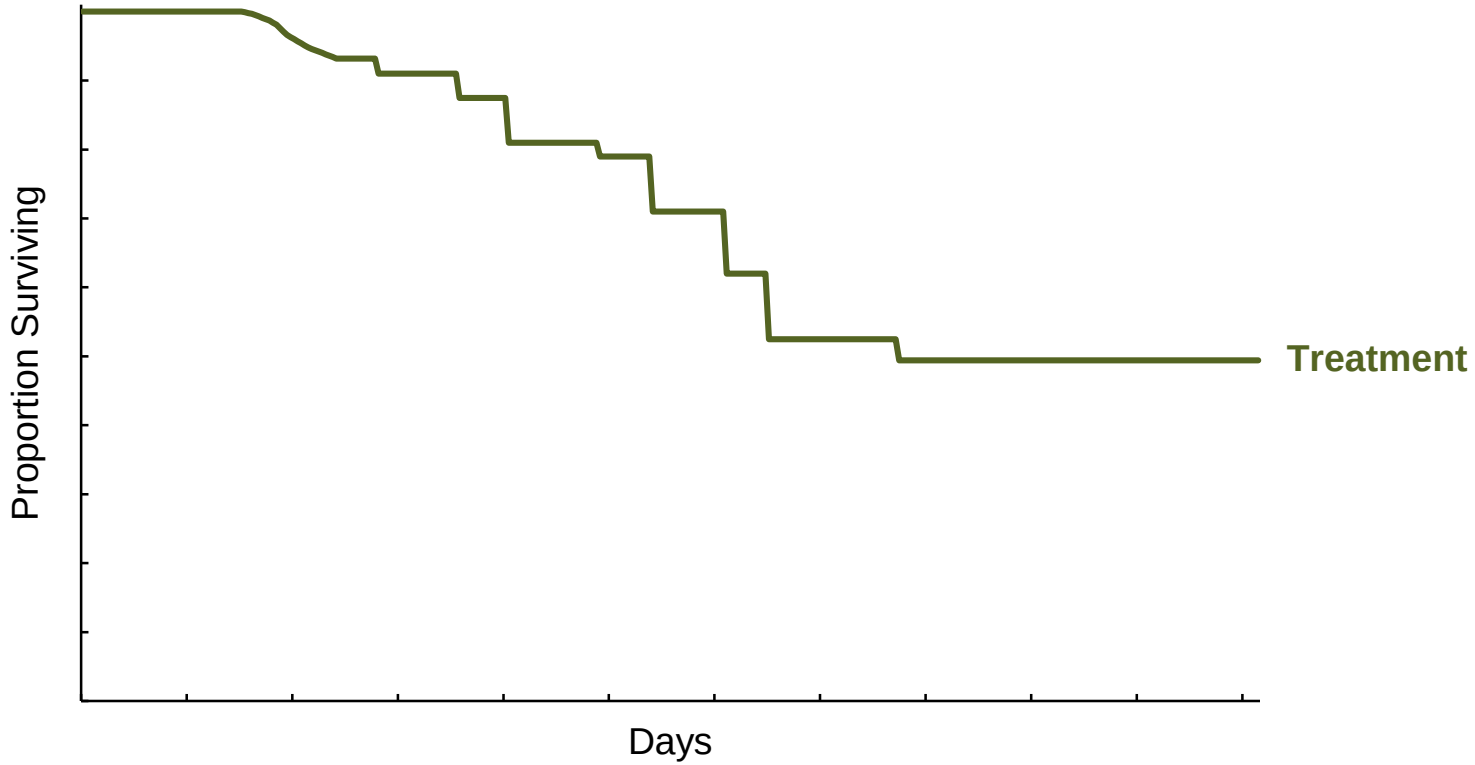
Treatment Arm of Target Trial

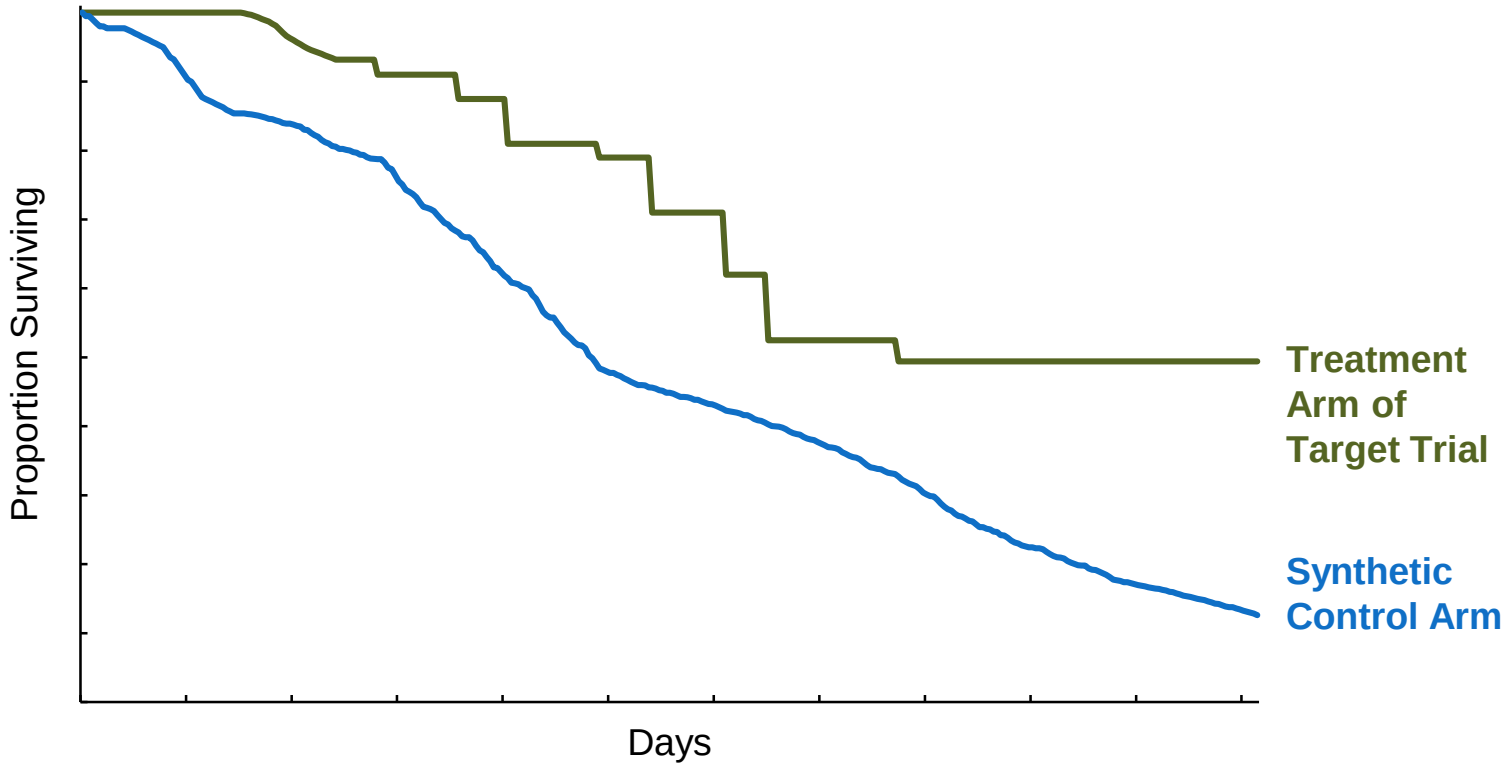
Candidate Historical Patients per Eligibility Criteria

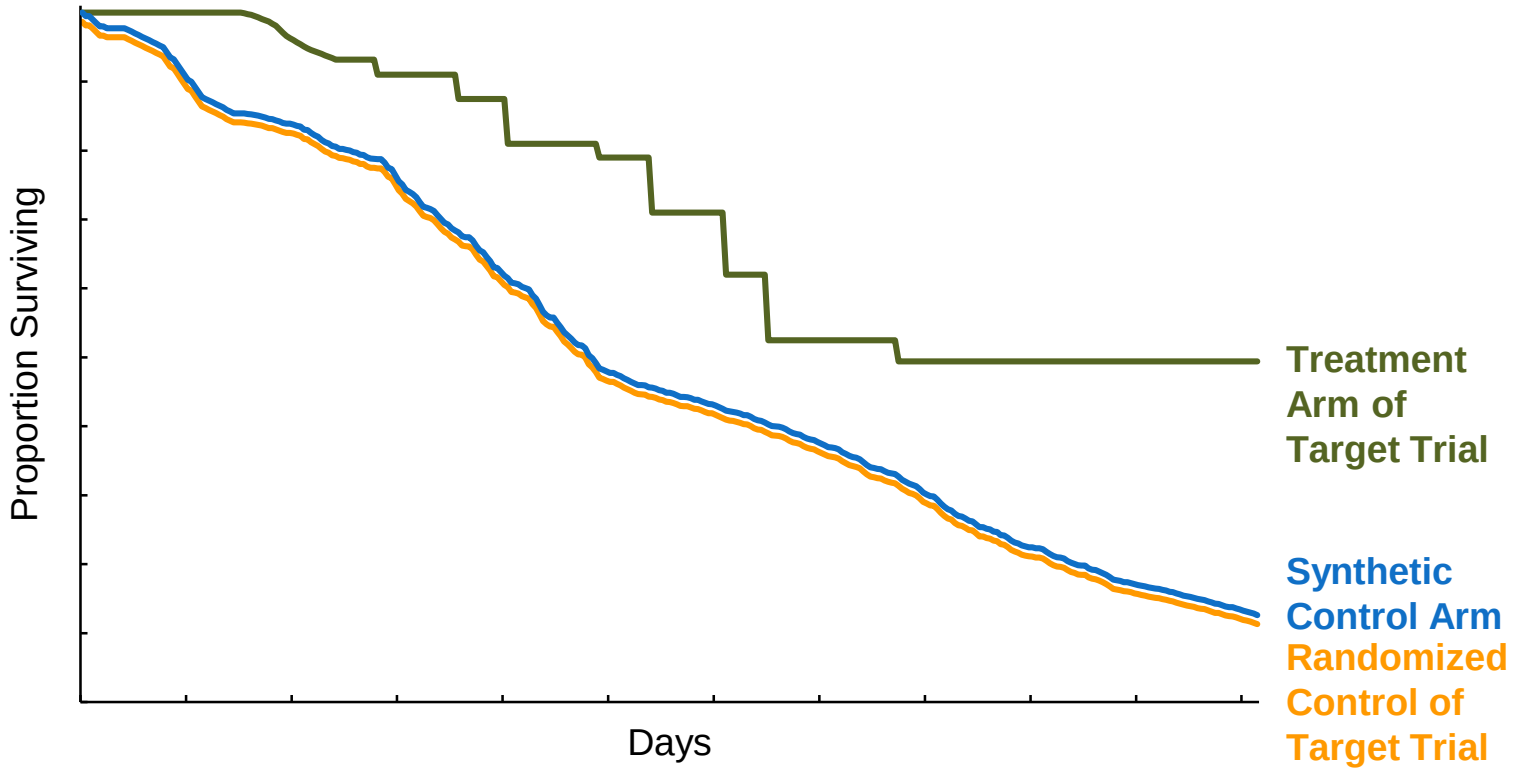


Treatment Arm of Target Trial

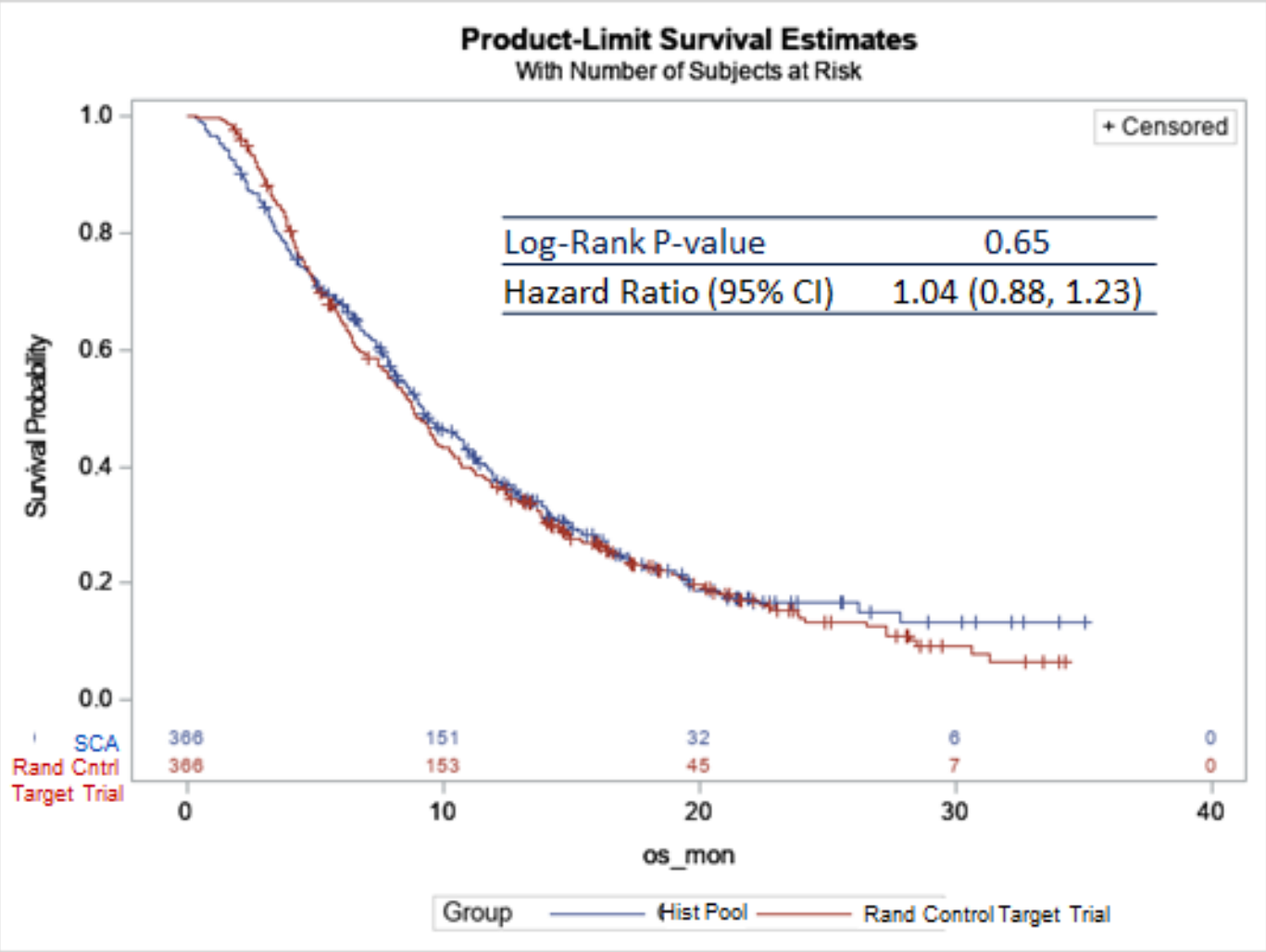


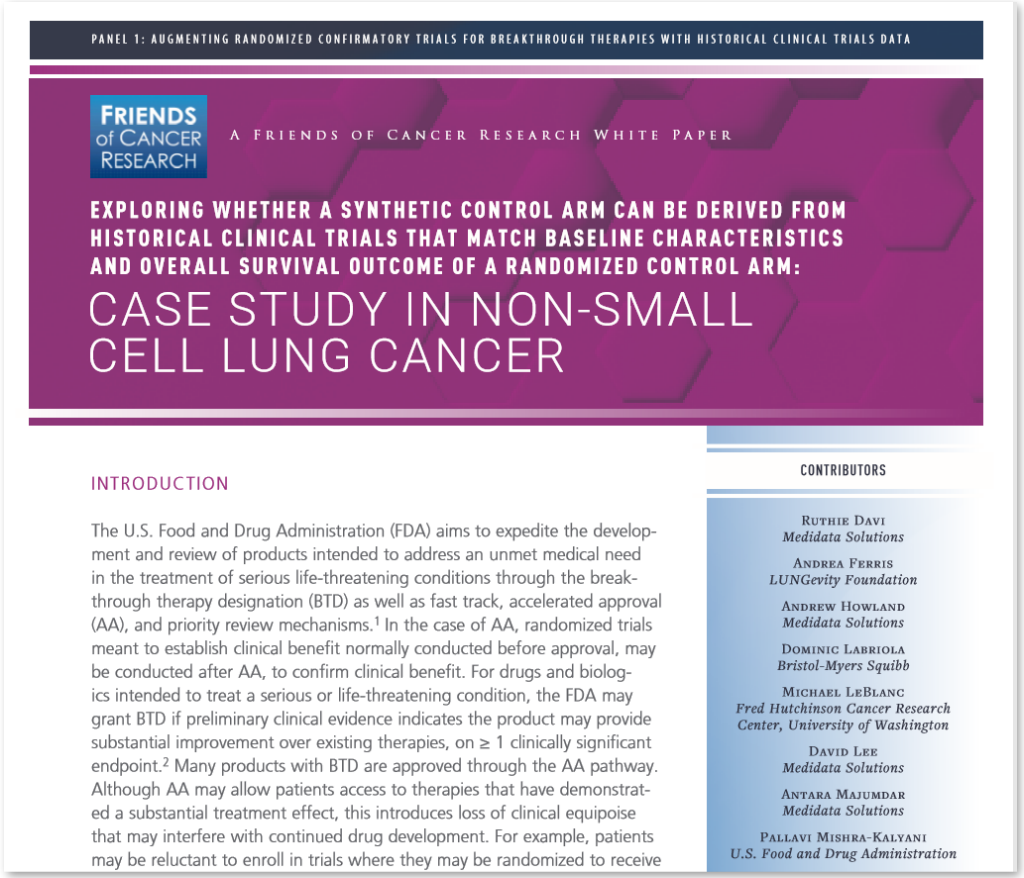






Exploring the Validity of Synthetic Control Arms (SCA) with Friends of Cancer Research 2018





PANEL 1: AUGMENTING RANDOMIZED CONFIRMATORY TRIALS FOR BREAKTHROUGH THERAPIES WITH HISTORICAL CLINICAL TRIALS DATA

FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

EXPLORING WHETHER A SYNTHETIC CONTROL ARM CAN BE DERIVED FROM HISTORICAL CLINICAL TRIALS THAT MATCH BASELINE CHARACTERISTICS AND OVERALL SURVIVAL OUTCOME OF A RANDOMIZED CONTROL ARM:

CASE STUDY IN NON-SMALL CELL LUNG CANCER

CONTRIBUTORS

RUTHIE DAVI
Medidata Solutions

ANDREA FERRIS
LUNGevity Foundation

ANDREW HOWLAND
Medidata Solutions

DOMINIC LABRIOLA
Bristol-Myers Squibb

MICHAEL LEBLANC
Fred Hutchinson Cancer Research Center, University of Washington

DAVID LEE
Medidata Solutions

ANTARA MAJUMDAR
Medidata Solutions

PALLAVI MISHRA-KALYANI
U.S. Food and Drug Administration

INTRODUCTION

The U.S. Food and Drug Administration (FDA) aims to expedite the development and review of products intended to address an unmet medical need in the treatment of serious life-threatening conditions through the breakthrough therapy designation (BTD) as well as fast track, accelerated approval (AA), and priority review mechanisms.[1] In the case of AA, randomized trials meant to establish clinical benefit normally conducted before approval, may be conducted after AA, to confirm clinical benefit. For drugs and biologics intended to treat a serious or life-threatening condition, the FDA may grant BTD if preliminary clinical evidence indicates the product may provide substantial improvement over existing therapies, on ≥ 1 clinically significant endpoint.[2] Many products with BTD are approved through the AA pathway. Although AA may allow patients access to therapies that have demonstrated a substantial treatment effect, this introduces loss of clinical equipoise that may interfere with continued drug development. For example, patients may be reluctant to enroll in trials where they may be randomized to receive

Objectives of Case Study in Multiple Myeloma

- Objective 1: Explore whether the treatment effect relative to a SCA mimics that of a Randomized Control in Multiple Myeloma

- Objective 2: Demonstrate statistical methods, tipping point analyses, for understanding the treatment effect impact of unknown patient characteristic(s) in the SCA

Building the SCA

Propensity Score Matching

Patient level data from multiple previous relapse refractory multiple myeloma trials

Data Source

- Medidata Enterprise Data Store (MEDS)[1]

Trial Characteristics

- Open label phase 3 trials
- Multinational
- Timespan of trial conduct (2010 to 2017)
- Overall survival measured

SCA Patient Eligibility Criteria

- Inclusion in a historical clinical trial accessible within this project
- Relapse or refractory multiple myeloma
- Received at least 2 prior lines of treatment
- Received prior treatment with lenalidomide and bortezomib
- Men and women ≥ 18 years of age
- Assigned to treatment with dexamethasone

1. Includes thousands of previous clinical trials conducted by the pharmaceutical industry for drug or medical product development with patient level data recorded through the Medidata electronic data capture system. Legal agreements permit use in deidentified (i.e., patients and original sponsor of the trial cannot be identified) and aggregated (i.e., every analysis must include data from two or more sponsors) form.

Choice of Propensity Score Methods

Target Randomized Trial

- Randomization was 2:1
- 294 experimental vs. 149 control patients

All Other Available Historical Clinical Trials

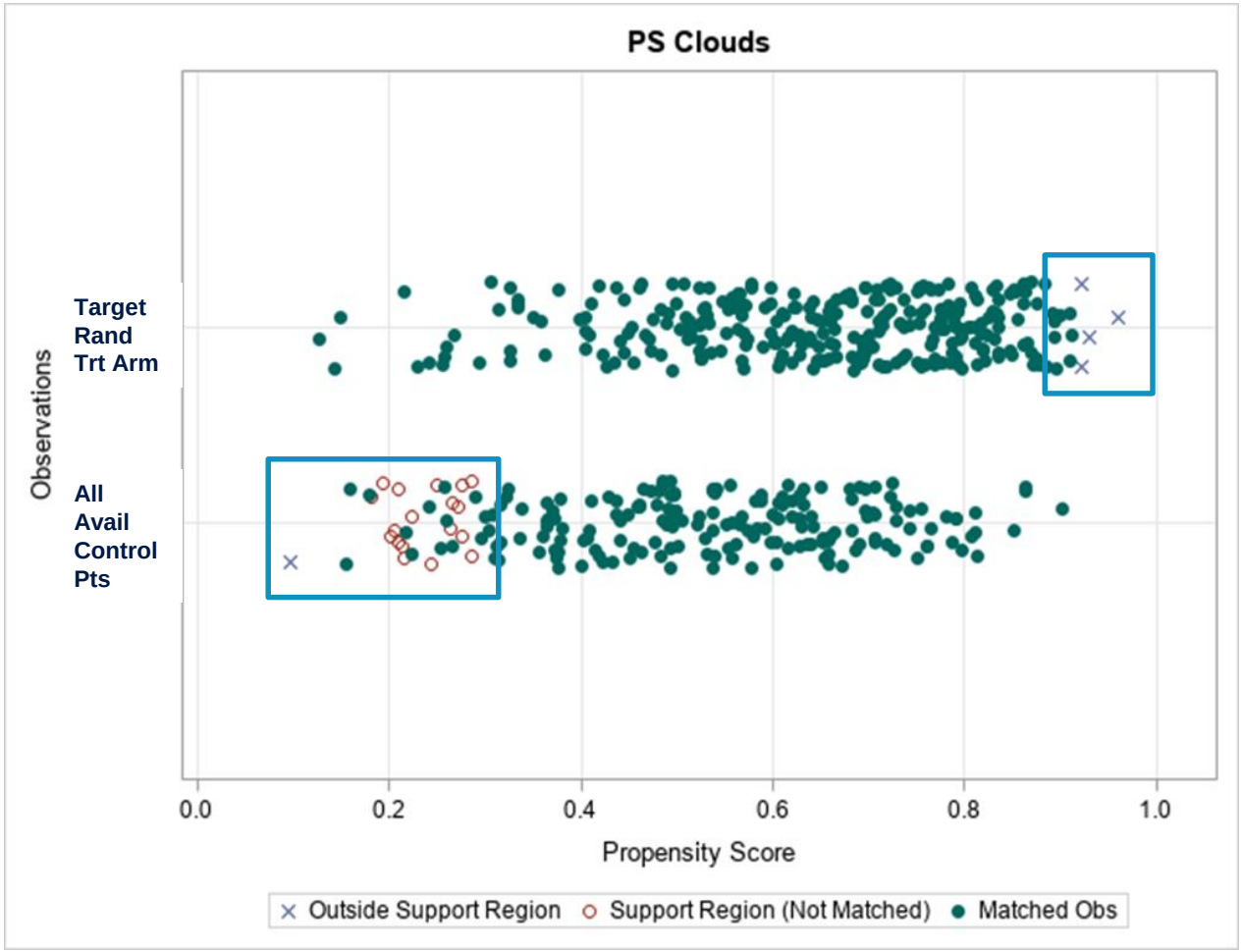
- 201 control patients

- *Greedy 1-1 Matching*
  - Commonly used, Appealing in simplicity and similarity to a randomized design
  - Not possible with limited number of historical control patients
- *Full Matching*
  - Appealing since still matching
  - Possible with limited number of historical control patients
  - Allows reuse of control patient (max of 4 times)
  - Necessary exclusion of target experimental patients very low

Prospectively Chosen Propensity Score Matching

Baseline Characteristics for Matching

- Race (White vs. Others/unknown)
- Region (Europe vs. Others/unknown)
- ECOG=0 (Yes vs. No)
- ECOG=1 (Yes vs. No)
- ECOG=2 or 3 (Yes vs. No)
- Number Drug Classes Refractory (≥4 vs. <4)
- Cytogenetic Risk (high vs. standard/unknown)
- Prior Stem Cell Transplant (Yes vs. No/unknown)
- Age (continuous)
- Days since last PD / relapse to first study dose (continuous)
- Sex (F vs. M)
- Bone lesion (Yes vs. No/unknown)
- Best response to last therapy (≥PR vs. <PR/unknown)
- Number of prior lines of therapy (continuous)
- Years since diagnosis (continuous)
- Weight (continuous)

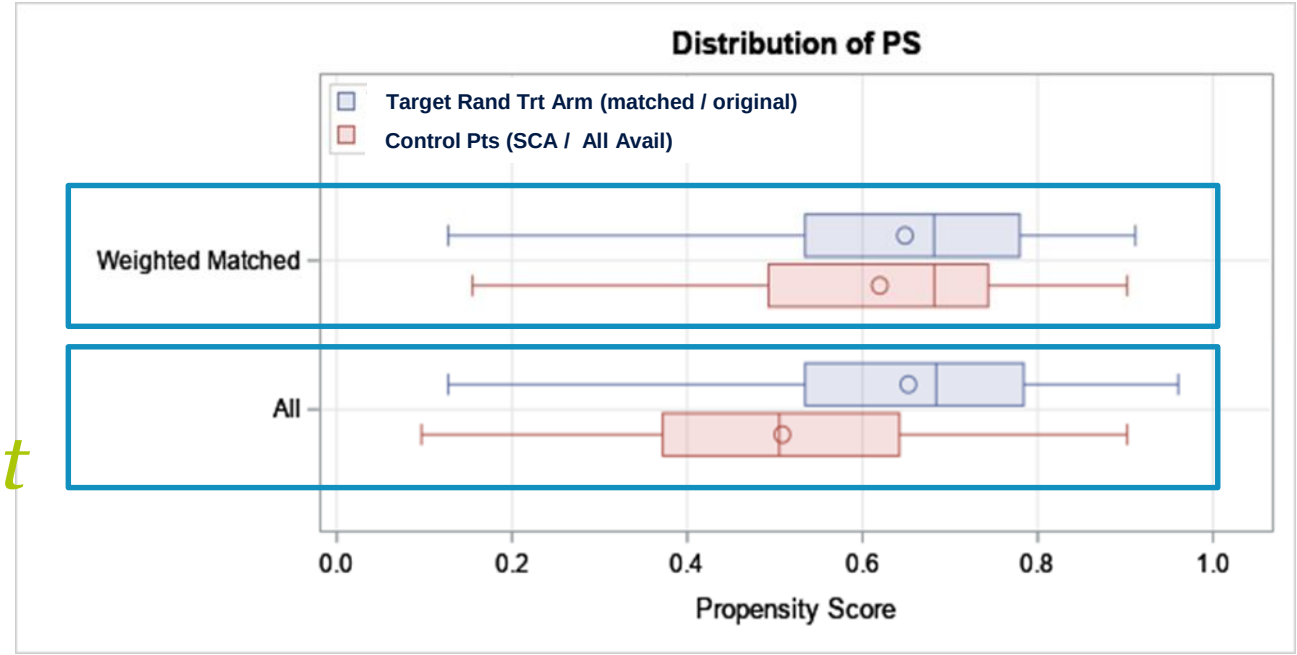


Matching Performance

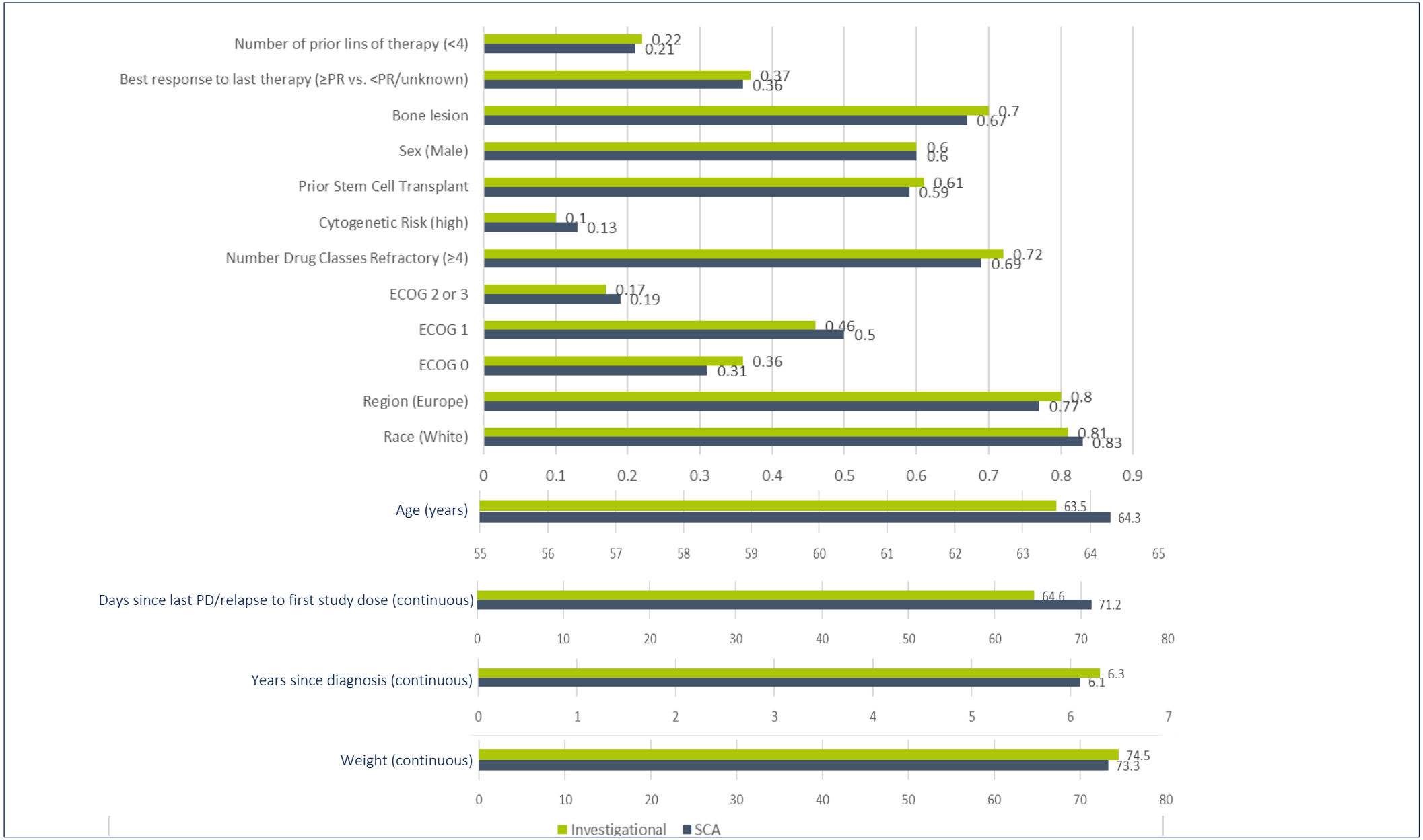
Baseline Comparability

Comparability of SCA & Target Experimental Arm

- *Considerable mismatch of propensity scores before matching*
- *After matching and weighting, SCA and Target Rand Trt Arm (matched) have similar propensity score distributions*



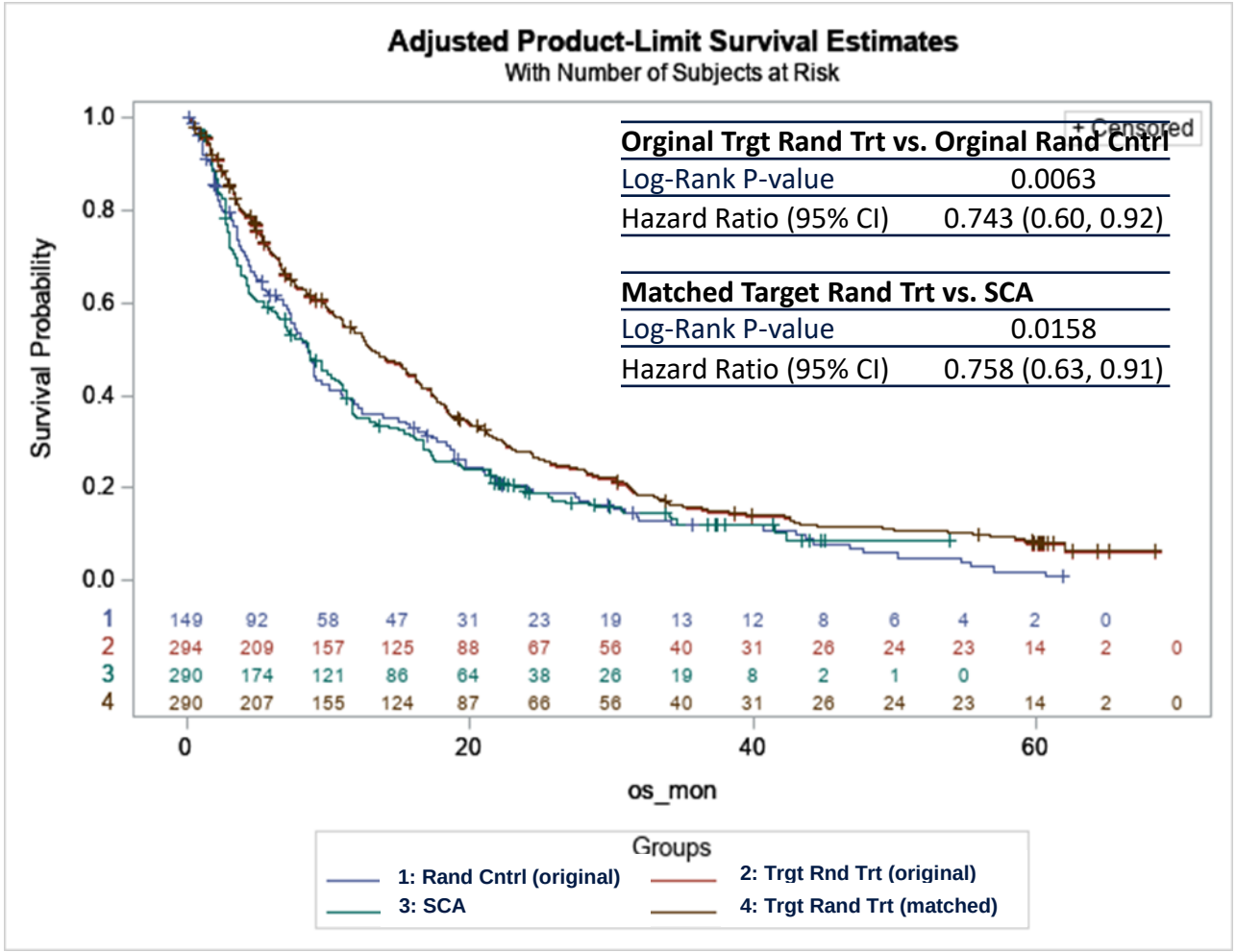
SCA and Investigational Arm Well Balanced After Matching



Objective 1: SCA Validation

Overall Survival

Objective 1: Treatment Effect relative to SCA Mimics that of Randomized Control in Terms of Overall Survival



Objective 2: Unobserved Confounders

Tipping Point Analyses

Unobserved Covariates, Potential Confounders

- *The possible problem: unobserved or unknown covariate*

  e.g., Biomarker not measured in historical trials but recently found to be prognostic

- *The treatment effect may be biased if the unobserved covariate is*
  - *related to outcome and*
  - *imbalanced between the experimentally treated patients and SCA*
- *We want to test the robustness of the treatment effect to an unobserved or unknown covariate*

Adjustment for Unobserved Covariate

Using the methods of Lin, 1998

- *'Full' model (all covariates known)*
  - estimate β, the parameter associated with the treatment effect **with adjustment for covariates**
- *'Reduced' model (when there is unobserved covariate)*
  - estimate β*, the parameter associate with the treatment effect **without adjustment for the covariate**

$$\beta \approx \beta^* - log\frac{e^{\gamma_1}P_1 + (1 - P_1)}{e^{\gamma_0}P_0 + (1 - P_0)}$$

  - P_0 and P_1 are the assumed prevalence of the unmeasured confounder among the investigational group and SCA respectively
  - Relationship between covariate and outcome expressed as assumed hazard ratio of the unmeasured confounder on the event of interest among the investigational group and SCA is $\Gamma_0 = e^{\gamma_0}$ and $\Gamma_1 = e^{\gamma_1}$, respectively. Without loss of generalizability, we can assume $\Gamma = e^{\gamma_0} = e^{\gamma_1}$

Lin D, Psaty B, Kronmal R. 1998. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics. 54:948–963.

Tipping Point Analyses

	Assumed prevalence of unobserved confounder in SCA																
	0.0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8

Tipping Point Analyses

		Assumed prevalence of unobserved confounder in SCA																
		0.0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8
Assumed prevalence of unobserved confounder in investigational arm	0.0																	
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Tipping Point Analyses

Table 4: Statistical and Clinical Tipping Points for Overall Survival Analysis (when HR for overall survival of those with and without confounder set to 1.5)																		
		Assumed prevalence of unobserved confounder in SCA																
		0.0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8
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	0.7																	
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Tipping Point Analyses

Table 4: Statistical and Clinical Tipping Points for Overall Survival Analysis (when HR for overall survival of those with and without confounder set to 1.5)

Adjusted Trt Effect HR (95% CI)		Assumed prevalence of unobserved confounder in SCA																
		0.0	**0.05**	**0.1**	**0.15**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**	**0.45**	**0.5**	**0.55**	**0.6**	**0.65**	**0.7**	**0.75**	**0.8**
Assumed prevalence of unobserved confounder in investigational arm	**0.0**	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.80 (0.66,0.95)	0.81 (0.68,0.98)	0.83 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.73,1.04)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.93 (0.77,1.11)	0.95 (0.79,1.14)	0.97 (0.81,1.16)	0.99 (0.82,1.18)	1.00 (0.84,1.20)	1.02 (0.85,1.23)	1.04 (0.87,1.25)	1.06 (0.88,1.27)
	0.05	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.89 (0.74,1.06)	0.91 (0.76,1.09)	0.92 (0.77,1.11)	0.94 (0.79,1.13)	0.96 (0.80,1.15)	0.98 (0.82,1.17)	1.00 (0.83,1.20)	1.02 (0.85,1.22)	1.04 (0.86,1.24)
	0.1	0.72 (0.60,0.86)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.88 (0.74,1.06)	0.90 (0.75,1.08)	0.92 (0.77,1.10)	0.94 (0.78,1.12)	0.96 (0.80,1.15)	0.97 (0.81,1.17)	0.99 (0.83,1.19)	1.01 (0.84,1.21)
	0.15	0.71 (0.59,0.84)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.85 (0.71,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.06)	0.90 (0.75,1.08)	0.92 (0.76,1.10)	0.93 (0.78,1.12)	0.95 (0.79,1.14)	0.97 (0.81,1.16)	0.99 (0.82,1.18)
	0.2	0.69 (0.57,0.83)	0.71 (0.59,0.85)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.84 (0.70,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.05)	0.90 (0.75,1.07)	0.91 (0.76,1.09)	0.93 (0.78,1.11)	0.95 (0.79,1.14)	0.96 (0.80,1.16)
	0.25	0.67 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.97)	0.83 (0.69,0.99)	0.84 (0.70,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.05)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.93 (0.77,1.11)	0.94 (0.79,1.13)
	0.3	0.66 (0.55,0.79)	0.68 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.97)	0.82 (0.69,0.99)	0.84 (0.70,1.01)	0.86 (0.71,1.03)	0.87 (0.73,1.05)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.92 (0.77,1.11)
	0.35	0.65 (0.54,0.77)	0.66 (0.55,0.79)	0.68 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.97)	0.82 (0.69,0.99)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.73,1.04)	0.89 (0.74,1.06)	0.90 (0.75,1.08)
	0.4	0.63 (0.53,0.76)	0.65 (0.54,0.78)	0.66 (0.55,0.79)	0.68 (0.57,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.96)	0.82 (0.68,0.98)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.88 (0.74,1.06)
	0.45	0.62 (0.52,0.74)	0.63 (0.53,0.76)	0.65 (0.54,0.78)	0.67 (0.55,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.95)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)
	0.5	0.61 (0.51,0.73)	0.62 (0.52,0.74)	0.64 (0.53,0.76)	0.65 (0.54,0.78)	0.67 (0.56,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.83 (0.70,1.00)	0.85 (0.71,1.02)
	0.55	0.59 (0.50,0.71)	0.61 (0.51,0.73)	0.62 (0.52,0.75)	0.64 (0.53,0.77)	0.65 (0.55,0.78)	0.67 (0.56,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.83 (0.69,1.00)
	0.6	0.58 (0.49,0.70)	0.60 (0.50,0.72)	0.61 (0.51,0.73)	0.63 (0.52,0.75)	0.64 (0.53,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.80)	0.69 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)
	0.65	0.57 (0.48,0.69)	0.59 (0.49,0.70)	0.60 (0.50,0.72)	0.61 (0.51,0.74)	0.63 (0.52,0.75)	0.64 (0.54,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.81)	0.69 (0.57,0.82)	0.70 (0.58,0.84)	0.72 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)
	0.7	0.56 (0.47,0.67)	0.58 (0.48,0.69)	0.59 (0.49,0.71)	0.60 (0.50,0.72)	0.62 (0.51,0.74)	0.63 (0.53,0.76)	0.65 (0.54,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.81)	0.69 (0.57,0.82)	0.70 (0.59,0.84)	0.72 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.92)	0.79 (0.66,0.94)

Tipping Point Analyses

Table 4: Statistical and Clinical Tipping Points for Overall Survival Analysis (when HR for overall survival of those with and without confounder set to 1.5)

Trt Effect HR (95% CI)		Assumed prevalence of unobserved confounder in SCA																
		0.0	**0.05**	**0.1**	**0.15**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**	**0.45**	**0.5**	**0.55**	**0.6**	**0.65**	**0.7**	**0.75**	**0.8**
Assumed prevalence of unobserved confounder in investigational arm	**0.0**	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.80 (0.66,0.95)	0.81 (0.68,0.98)	0.83 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.73,1.04)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.93 (0.77,1.11)	0.95 (0.79,1.14)	0.97 (0.81,1.16)	0.99 (0.82,1.18)	1.00 (0.84,1.20)	1.02 (0.85,1.23)	1.04 (0.87,1.25)	1.06 (0.88,1.27)
	0.05	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.89 (0.74,1.06)	0.91 (0.76,1.09)	0.92 (0.77,1.11)	0.94 (0.79,1.13)	0.96 (0.80,1.15)	0.98 (0.82,1.17)	1.00 (0.83,1.20)	1.02 (0.85,1.22)	1.04 (0.86,1.24)
	0.1	0.72 (0.60,0.86)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.88 (0.74,1.06)	0.90 (0.75,1.08)	0.92 (0.77,1.10)	0.94 (0.78,1.12)	0.96 (0.80,1.15)	0.97 (0.81,1.17)	0.99 (0.83,1.19)	1.01 (0.84,1.21)
	0.15	0.71 (0.59,0.84)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.85 (0.71,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.06)	0.90 (0.75,1.08)	0.92 (0.76,1.10)	0.93 (0.78,1.12)	0.95 (0.79,1.14)	0.97 (0.81,1.16)	0.99 (0.82,1.18)
	0.2	0.69 (0.57,0.83)	0.71 (0.59,0.85)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.84 (0.70,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.05)	0.90 (0.75,1.07)	0.91 (0.76,1.09)	0.93 (0.78,1.11)	0.95 (0.79,1.14)	0.96 (0.80,1.16)
	0.25	0.67 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.97)	0.83 (0.69,0.99)	0.84 (0.70,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.05)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.93 (0.77,1.11)	0.94 (0.79,1.13)
	0.3	0.66 (0.55,0.79)	0.68 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.97)	0.82 (0.69,0.99)	0.84 (0.70,1.01)	0.86 (0.71,1.03)	0.87 (0.73,1.05)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.92 (0.77,1.11)
	0.35	0.65 (0.54,0.77)	0.66 (0.55,0.79)	0.68 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.97)	0.82 (0.69,0.99)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.73,1.04)	0.89 (0.74,1.06)	0.90 (0.75,1.08)
	0.4	0.63 (0.53,0.76)	0.65 (0.54,0.78)	0.66 (0.55,0.79)	0.68 (0.57,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.96)	0.82 (0.68,0.98)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.88 (0.74,1.06)
	0.45	0.62 (0.52,0.74)	0.63 (0.53,0.76)	0.65 (0.54,0.78)	0.67 (0.55,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.95)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)
	0.5	0.61 (0.51,0.73)	0.62 (0.52,0.74)	0.64 (0.53,0.76)	0.65 (0.54,0.78)	0.67 (0.56,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.83 (0.70,1.00)	0.85 (0.71,1.02)
	0.55	0.59 (0.50,0.71)	0.61 (0.51,0.73)	0.62 (0.52,0.75)	0.64 (0.53,0.77)	0.65 (0.55,0.78)	0.67 (0.56,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.83 (0.69,1.00)
	0.6	0.58 (0.49,0.70)	0.60 (0.50,0.72)	0.61 (0.51,0.73)	0.63 (0.52,0.75)	0.64 (0.53,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.80)	0.69 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)
	0.65	0.57 (0.48,0.69)	0.59 (0.49,0.70)	0.60 (0.50,0.72)	0.61 (0.51,0.74)	0.63 (0.52,0.75)	0.64 (0.54,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.81)	0.69 (0.57,0.82)	0.70 (0.58,0.84)	0.72 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)
	0.7	0.56 (0.47,0.67)	0.58 (0.48,0.69)	0.59 (0.49,0.71)	0.60 (0.50,0.72)	0.62 (0.51,0.74)	0.63 (0.53,0.76)	0.65 (0.54,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.81)	0.69 (0.57,0.82)	0.70 (0.59,0.84)	0.72 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.92)	0.79 (0.66,0.94)

Tipping Point Analyses

Table 4: Statistical and Clinical Tipping Points for Overall Survival Analysis (when HR for overall survival of those with and without confounder set to 1.5)

Trt Effect HR (95% CI)		Assumed prevalence of unobserved confounder in SCA																
		0.0	**0.05**	**0.1**	**0.15**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**	**0.45**	**0.5**	**0.55**	**0.6**	**0.65**	**0.7**	**0.75**	**0.8**
Assumed prevalence of unobserved confounder in investigational arm	**0.0**	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.80 (0.66,0.95)	0.81 (0.68,0.98)	0.83 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.73,1.04)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.93 (0.77,1.11)	0.95 (0.79,1.14)	0.97 (0.81,1.16)	0.99 (0.82,1.18)	1.00 (0.84,1.20)	1.02 (0.85,1.23)	1.04 (0.87,1.25)	1.06 (0.88,1.27)
	0.05	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.89 (0.74,1.06)	0.91 (0.76,1.09)	0.92 (0.77,1.11)	0.94 (0.79,1.13)	0.96 (0.80,1.15)	0.98 (0.82,1.17)	1.00 (0.83,1.20)	1.02 (0.85,1.22)	1.04 (0.86,1.24)
	0.1	0.72 (0.60,0.86)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	CI overlaps 1		92 7,1.10)	0.94 (0.78,1.12)	0.96 (0.80,1.15)	0.97 (0.81,1.17)	0.99 (0.83,1.19)	1.01 (0.84,1.21)
	0.15	0.71 (0.59,0.84)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.85 (0.71,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.06)	0.90 (0.75,1.08)	0.92 (0.76,1.10)	0.93 (0.78,1.12)	0.95 (0.79,1.14)	0.97 (0.81,1.16)	0.99 (0.82,1.18)
	0.2	0.69 (0.57,0.83)	0.71 (0.59,0.85)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.84 (0.70,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.05)	0.90 (0.75,1.07)	0.91 (0.76,1.09)	0.93 (0.78,1.11)	0.95 (0.79,1.14)	0.96 (0.80,1.16)
	0.25	0.67 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.97)	0.83 (0.69,0.99)	0.84 (0.70,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.05)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.93 (0.77,1.11)	0.94 (0.79,1.13)
	0.3	0.66 (0.55,0.79)	0.68 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.97)	0.82 (0.69,0.99)	0.84 (0.70,1.01)	0.86 (0.71,1.03)	0.87 (0.73,1.05)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.92 (0.77,1.11)
	0.35	0.65 (0.54,0.77)	0.66 (0.55,0.79)	0.68 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.97)	0.82 (0.69,0.99)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.73,1.04)	0.89 (0.74,1.06)	0.90 (0.75,1.08)
	0.4	0.63 (0.53,0.76)	0.65 (0.54,0.78)	0.66 (0.55,0.79)	0.68 (0.57,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.96)	0.82 (0.68,0.98)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.88 (0.74,1.06)
	0.45	0.62 (0.52,0.74)	0.63 (0.53,0.76)	0.65 (0.54,0.78)	0.67 (0.55,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.95)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)
	0.5	0.61 (0.51,0.73)	0.62 (0.52,0.74)	0.64 (0.53,0.76)	0.65 (0.54,0.78)	0.67 (0.56,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.83 (0.70,1.00)	0.85 (0.71,1.02)
	0.55	0.59 (0.50,0.71)	0.61 (0.51,0.73)	0.62 (0.52,0.75)	0.64 (0.53,0.77)	0.65 (0.55,0.78)	0.67 (0.56,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.83 (0.69,1.00)
	0.6	0.58 (0.49,0.70)	0.60 (0.50,0.72)	0.61 (0.51,0.73)	0.63 (0.52,0.75)	0.64 (0.53,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.80)	0.69 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)
	0.65	0.57 (0.48,0.69)	0.59 (0.49,0.70)	0.60 (0.50,0.72)	0.61 (0.51,0.74)	0.63 (0.52,0.75)	0.64 (0.54,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.81)	0.69 (0.57,0.82)	0.70 (0.58,0.84)	0.72 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)
	0.7	0.56 (0.47,0.67)	0.58 (0.48,0.69)	0.59 (0.49,0.71)	0.60 (0.50,0.72)	0.62 (0.51,0.74)	0.63 (0.53,0.76)	0.65 (0.54,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.81)	0.69 (0.57,0.82)	0.70 (0.59,0.84)	0.72 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.92)	0.79 (0.66,0.94)

Tipping Point Analyses

Table 4: Statistical and Clinical Tipping Points for Overall Survival Analysis (when HR for overall survival of those with and without confounder set to 1.5)

Trt Effect HR (95% CI)		Assumed prevalence of unobserved confounder in SCA																
		0.0	**0.05**	**0.1**	**0.15**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**	**0.45**	**0.5**	**0.55**	**0.6**	**0.65**	**0.7**	**0.75**	**0.8**
Assumed prevalence of unobserved confounder in investigational arm	**0.0**	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.80 (0.66,0.95)	0.81 (0.68,0.98)	0.83 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.73,1.04)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.93 (0.77,1.11)	0.95 (0.79,1.14)	0.97 (0.81,1.16)	0.99 (0.82,1.18)	1.00 (0.84,1.20)	1.02 (0.85,1.23)	1.04 (0.87,1.25)	1.06 (0.88,1.27)
	0.05	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.89 (0.74,1.06)	0.91 (0.76,1.09)	0.92 (0.77,1.11)	0.94 (0.79,1.13)	0.96 (0.80,1.15)	0.98 (0.82,1.17)	1.00 (0.83,1.20)	1.02 (0.85,1.22)	1.04 (0.86,1.24)
	0.1	0.72 (0.60,0.86)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69,0.99)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	CI overlaps 1	92 7,1.10)	0.94 (0.78,1.12)	0.96 (0.80,1.15)	0.97 (0.81,1.17)	0.99 (0.83,1.19)	1.01 (0.84,1.21)	
	0.15	0.71 (0.59,0.84)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.68,0.97)	0.83 (0.69 99)	0.85 (0.71,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.06)	0.90 (0.75,1.08)	0.92 (0.76,1.10)	0.93 (0.78,1.12)	0.95 (0.79,1.14)	0.97 (0.81,1.16)	0.99 (0.82,1.18)
	0.2	0.69 (0.57,0.83)	0.71 (0.59,0.85)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.78 (0.65,0.93)	0.79 (0.66,0.95)	0.83 (0.68, 99)	0.84 (0.70,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.05)	0.90 (0.75,1.07)	0.91 (0.76,1.09)	0.93 (0.78,1.11)	0.95 (0.79,1.14)	0.96 (0.80,1.16)	
	0.25	0.67 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.72 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.83 (0.67, 99)	0.84 (0.70,1.01)	0.86 (0.72,1.03)	0.88 (0.73,1.05)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.93 (0.77,1.11)	0.94 (0.79,1.13)	
	0.3	0.66 (0.55,0.79)	0.68 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.60,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.82 (0.67, 99)	0.84 (0.70,1.01)	0.86 (0.71,1.03)	0.87 (0.73,1.05)	0.89 (0.74,1.07)	0.91 (0.76,1.09)	0.92 (0.77,1.11)	
	0.35	0.65 (0.54,0.77)	0.66 (0.55,0.79)	0.68 (0.56,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.82 (0.67, 99)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.73,1.04)	0.89 (0.74,1.06)	0.90 (0.75,1.08)	
	0.4	0.63 (0.53,0.76)	0.65 (0.54,0.78)	0.66 (0.55,0.79)	0.68 (0.57,0.81)	0.69 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.65,0.93)	0.79 (0.66,0.95)	0.81 (0.67,0.96)	0.82 (0.68,0.98)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)	0.88 (0.74,1.06)
	0.45	0.62 (0.52,0.74)	0.63 (0.53,0.76)	0.65 (0.54,0.78)	0.67 (0.55,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.83)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.95)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.84 (0.70,1.00)	0.85 (0.71,1.02)	0.87 (0.72,1.04)
	0.5	0.61 (0.51,0.73)	0.62 (0.52,0.74)	0.64 (0.53,0.76)	0.65 (0.54,0.78)	0.67 (0.56,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.83 (0.70,1.00)	0.85 (0.71,1.02)
	0.55	0.59 (0.50,0.71)	0.61 (0.51,0.73)	0.62 (0.52,0.75)	0.64 (0.53,0.77)	0.65 (0.55,0.78)	0.67 (0.56,0.80)	0.68 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.59,0.85)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)	0.83 (0.69,1.00)
	0.6	0.58 (0.49,0.70)	0.60 (0.50,0.72)	0.61 (0.51,0.73)	0.63 (0.52,0.75)	0.64 (0.53,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.80)	0.69 (0.57,0.82)	0.70 (0.58,0.84)	0.71 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)	0.82 (0.68,0.98)
	0.65	0.57 (0.48,0.69)	0.59 (0.49,0.70)	0.60 (0.50,0.72)	0.61 (0.51,0.74)	0.63 (0.52,0.75)	0.64 (0.54,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.81)	0.69 (0.57,0.82)	0.70 (0.58,0.84)	0.72 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.93)	0.79 (0.66,0.94)	0.80 (0.67,0.96)
	0.7	0.56 (0.47,0.67)	0.58 (0.48,0.69)	0.59 (0.49,0.71)	0.60 (0.50,0.72)	0.62 (0.51,0.74)	0.63 (0.53,0.76)	0.65 (0.54,0.77)	0.66 (0.55,0.79)	0.67 (0.56,0.81)	0.69 (0.57,0.82)	0.70 (0.59,0.84)	0.72 (0.60,0.86)	0.73 (0.61,0.87)	0.74 (0.62,0.89)	0.76 (0.63,0.91)	0.77 (0.64,0.92)	0.79 (0.66,0.94)

Statistical Tipping Point

Objective 2: Tipping Point Analysis Conclusion

Removal of the statistical significance of the treatment effect would require a confounder that has

- *This degree of imbalance between arms (prevalences assumed)*
- *This degree of association with outcome (Hazard ratio assumed)*

Reader then answers whether such a covariate is likely in this clinical setting.

Summary

- *In last year's NSCLC case study,* ***SCA successfully replicated the control arm of the target trial***
- *In this MM case study, the treatment effect relative to* ***SCA successfully replicated the original randomized comparison*** *of the target trial*
  - Even when amount of historical data is limited
  - Without exclusion of large amount of treated arm
- ***Tipping point analyses illustrated*** *in this case study*
  - Help determine whether the observed treatment effect is robust to the impact of possible unobserved covariates
- *Body of evidence is building demonstrating* ***how SCA may mitigate challenges faced with a concurrent control arm in difficult-to-study indications***

Thank you.

Panel 1 Participants

Moderator: Gary Rosner, Johns Hopkins University

- Bill Capra, Genentech
- Ruthie Davi, Acorn AI, a Medidata Company
- Bindu Kanapuru, FDA
- Erik Pulkstenis, AbbVie
- Jeremy Rassen, Aetion
- Dirk Reitsma, PPD
- Meghna Samant, Flatiron Health