

# **Bayesian Modeling in Oncology Trials**

*Part 4: Bayesian models for hybrid randomized controlled trials*

Stat4Onc Short Course

May 10, 2023

# Center for Innovative Design & Analysis

colorado school of public health

---

## Instructors



### **Dr. Brian Hobbs**

Associate Professor of Biostatistics, The University of Texas Dell Medical School

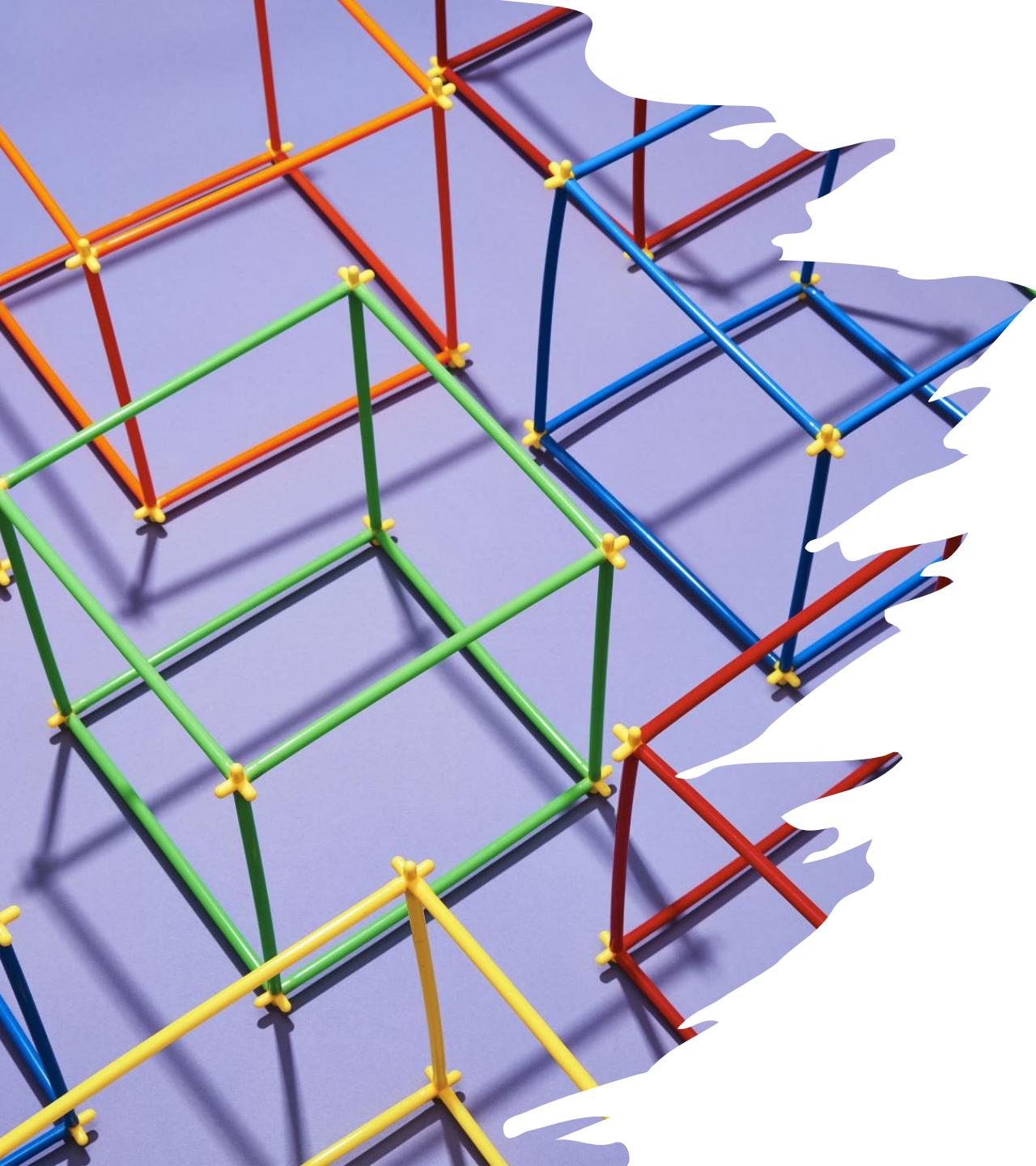
Email: [brian.hobbs@austin.utexas.edu](mailto:brian.hobbs@austin.utexas.edu)



### **Dr. Alex Kaiser**

Assistant Professor of Biostatistics and Informatics, University of Colorado Anschutz Medical Campus

Email: [alex.kaizer@cuanschutz.edu](mailto:alex.kaizer@cuanschutz.edu)



# Short Course Outline

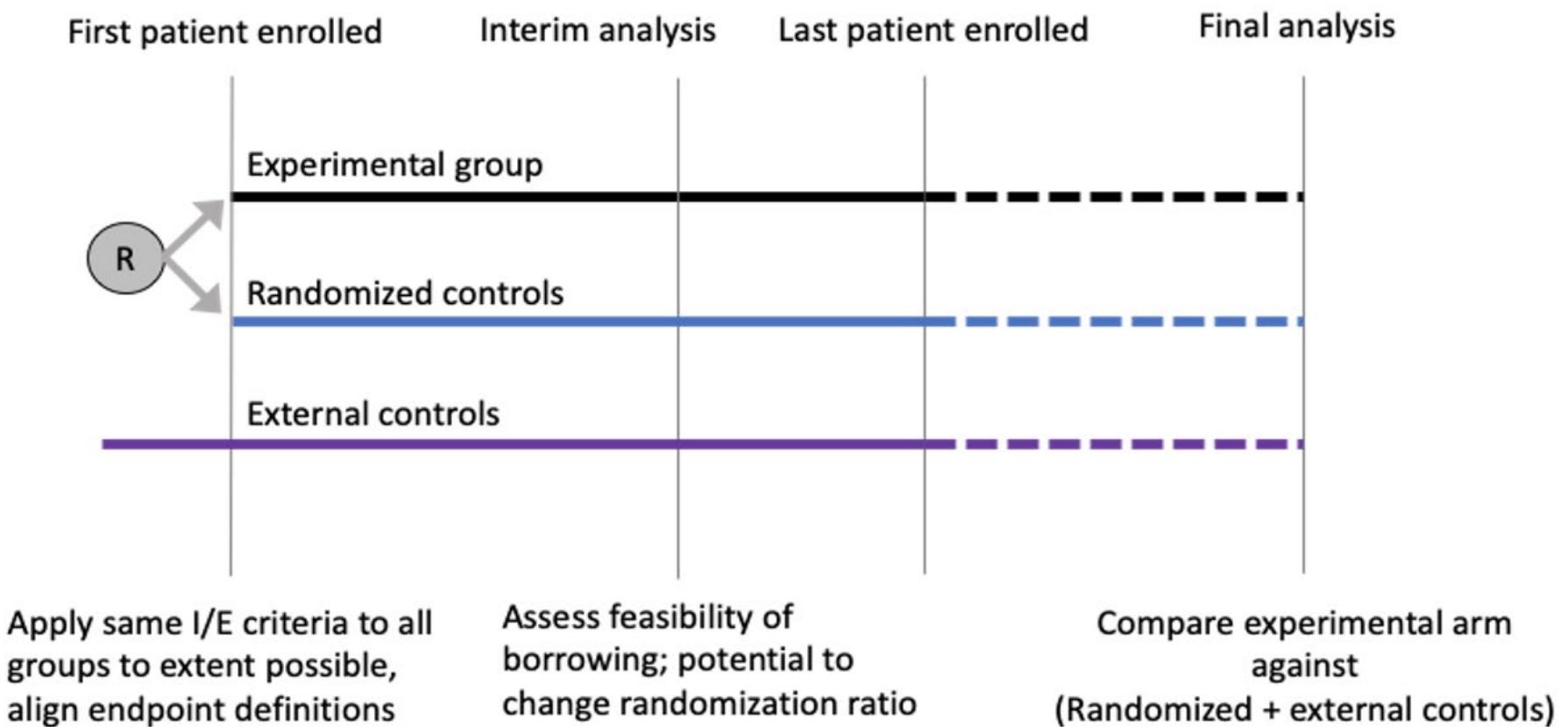
1. Introduction to Bayesian Modeling in Oncology Trials
2. Information Sharing in Clinical Trials
3. Statistical Considerations for Master Protocols
4. Basket Trial Software and Examples

## Overall Learning Objectives

1. Exposure to the basics of Bayesian methods in oncology trials
2. Introduction of methods for sharing information across data sources
3. Understand use of master protocol studies (e.g., platform and basket trials)
4. Bayesian models for hybrid randomized controlled trials

# Augmenting control arms with Real-World Data for cancer trials: Hybrid control arm methods and considerations

Tan, Segal et al. *Contemporary Clinical Trials Communications*, 2022



R = randomization, I/E = inclusion/exclusion

# FDA-Supported RWE Research Projects – Examples

FDA



- ‘OneSource’ project to improve quality of EHR data
- [other projects on data quality, relevancy, linkage]



- Statistical approach for RCT designs w/ “hybrid” control arms
- [other projects on clinical study design]



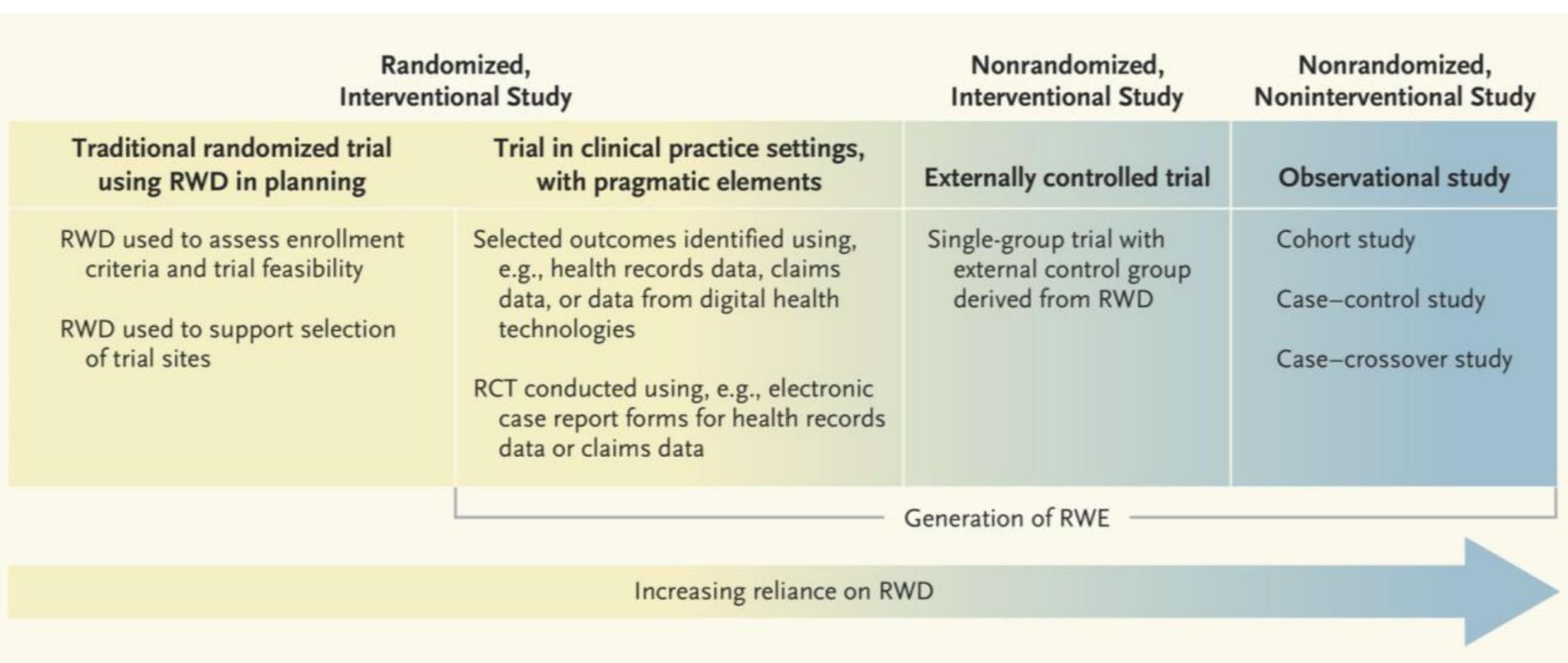
- Evaluate confounded treatment effects
- [other projects using specific approaches]



# Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

FDA



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

# Complex Innovative Trial Designs

Center for Biologics Evaluation & Research  
Center for Drug Evaluation & Research

## Innovative Characteristics:

FDA considers the following trial design features to be innovative, making it appropriate to review the design under the Complex Innovative Trial Design (CID) pilot meeting program:

- Use of external control data
- Use of a commensurate prior for borrowing data
- Use of a Bayesian parametric model as the primary analysis of a secondary endpoint

## New! CID Pilot Program Trial Design Case Studies

The description of each CID Pilot Meeting Program case study focuses on the single clinical trial design that was the focus of the Pilot Program submission. The description does not discuss other potentially important aspects of the development program for the respective drug or biologic, such as any plans to conduct additional adequate and well-controlled trial(s) and/or to obtain confirmatory evidence to help establish substantial evidence of effectiveness. Please refer to draft guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019).

- [Master Protocol Case Study](#)
- [Lupus Case Study](#)
- [DLBCL Case Study](#)

# Background – FDA ‘U01’ Awards for RWD/RWE

## Funding Opportunity Title

Exploring the use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making (U01) Clinical Trials Optional RFA-FD-20-030

**N=31 applications received; n=4 applications funded**

Number	Applicant	Project Title
1 U01FD007213-01	Brigham and Women's Hospital	Enhancing evidence generation by linking RCTs to RWD
1 U01FD007220-01	Critical Path Institute	Advancing standards and methodologies to generate RWE from RWD through a neonatal pilot project
1 U01FD007206-01	Genentech-UNC	Applying novel statistical approaches to develop a decision framework for hybrid RCT designs, combining internal control arms with data from RWD sources
1 U01FD007172-01	Verantos, Inc.	Transforming RWE with Unstructured and Structured data to advance Tailored therapy (TRUST)

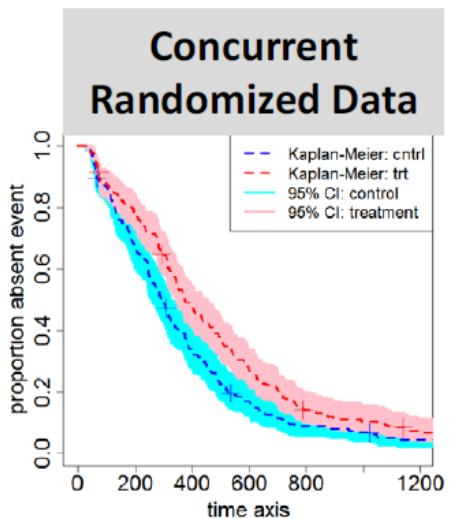
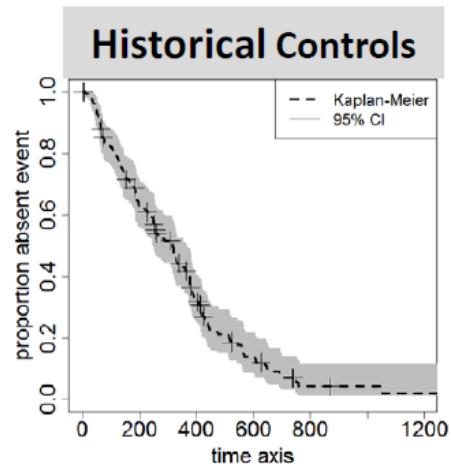


**“One of the most promising ways to make drug development more efficient—while enabling providers and patients to get better information about how a new medicine works—is by developing the science around innovative approaches to the design of clinical trials.”**

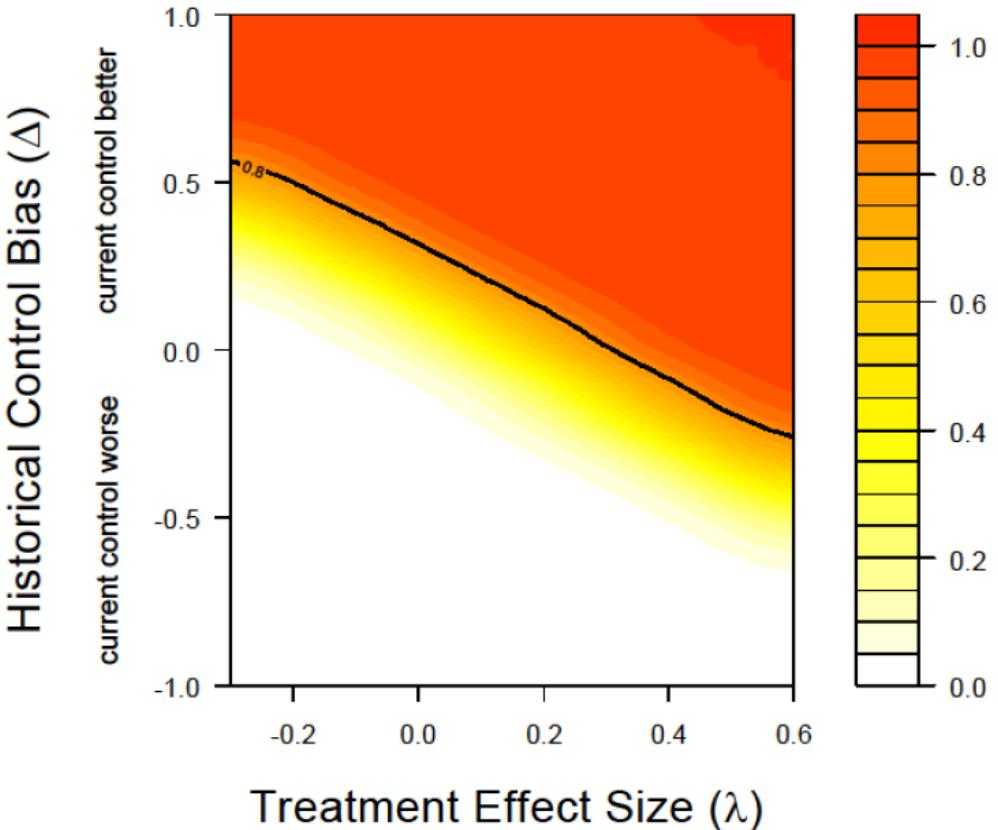
---

**Scott Gottlieb, M.D.**  
Former FDA Commissioner

# Exchangeability Assumptions Highly Sensitive to Bias

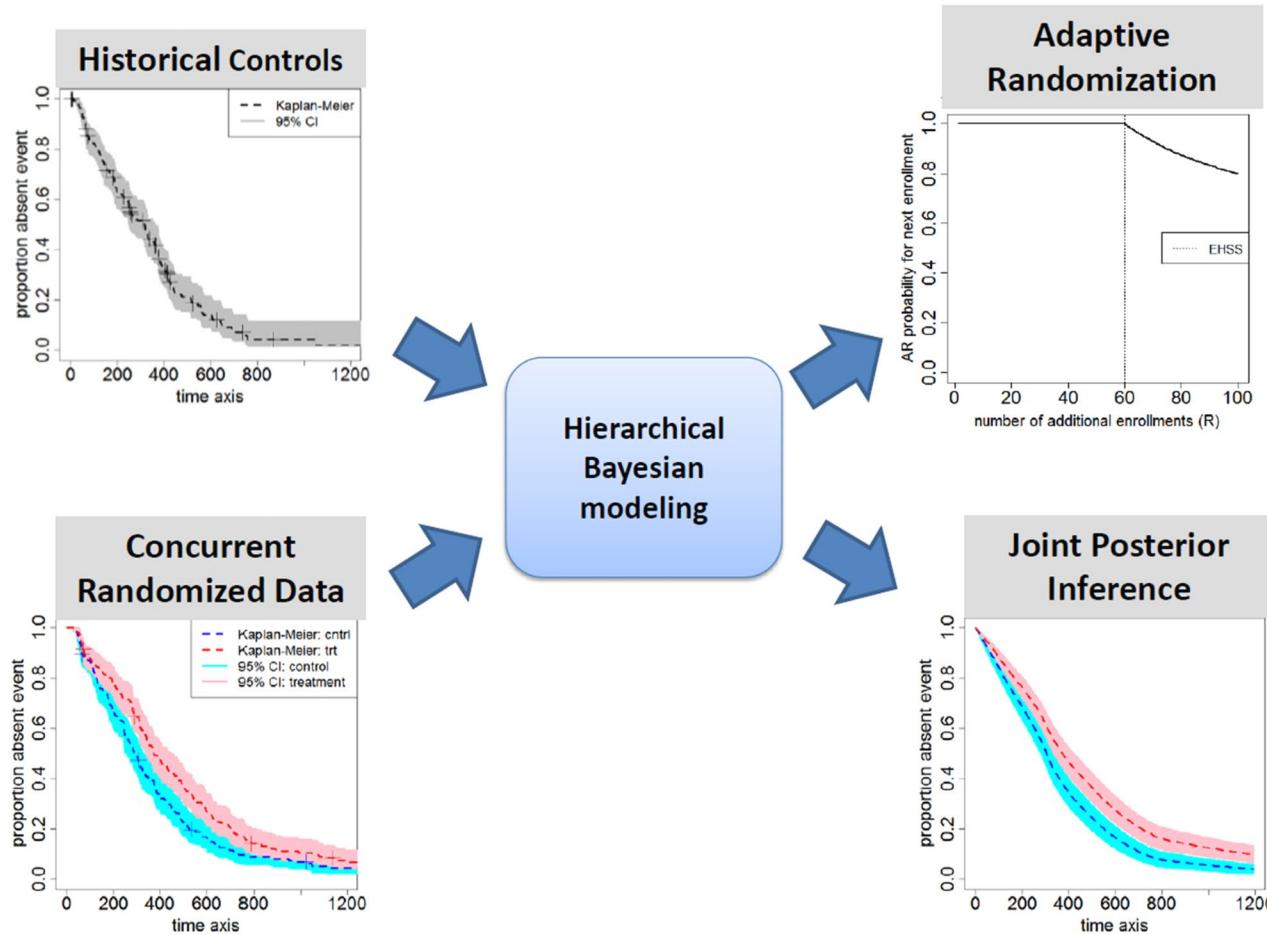


Power Surface Assuming Exchangeable Data



# Hybrid Control Design

## Multi-source Adaptive Randomization (Hobbs et al. 2013)



# Multi-source Adaptive design

## Hobbs, Carlin, and Sargent (2013) Clinical Trials

- ▶ objective attain *balance* relative to extent of dynamic borrowing
- ▶ AR procedure that adapts as a function of EHSS, computed at interim analyses
- ▶ we can map relative gains in posterior precision into a number, the *effective historical sample size* (EHSS), quantifying the *additional effective* number of controls for the inference
- ▶ propose adaptive design based upon an AR procedure that adapts as a function of EHSS, computed at interim analyses
- ▶ do *not* use interim analysis of efficacy *imbalance* treatment allocation (“response-adaptive”)

# Effective Historical Sample Size (EHSS) (cont'd)

## Approximate historical effective sample size

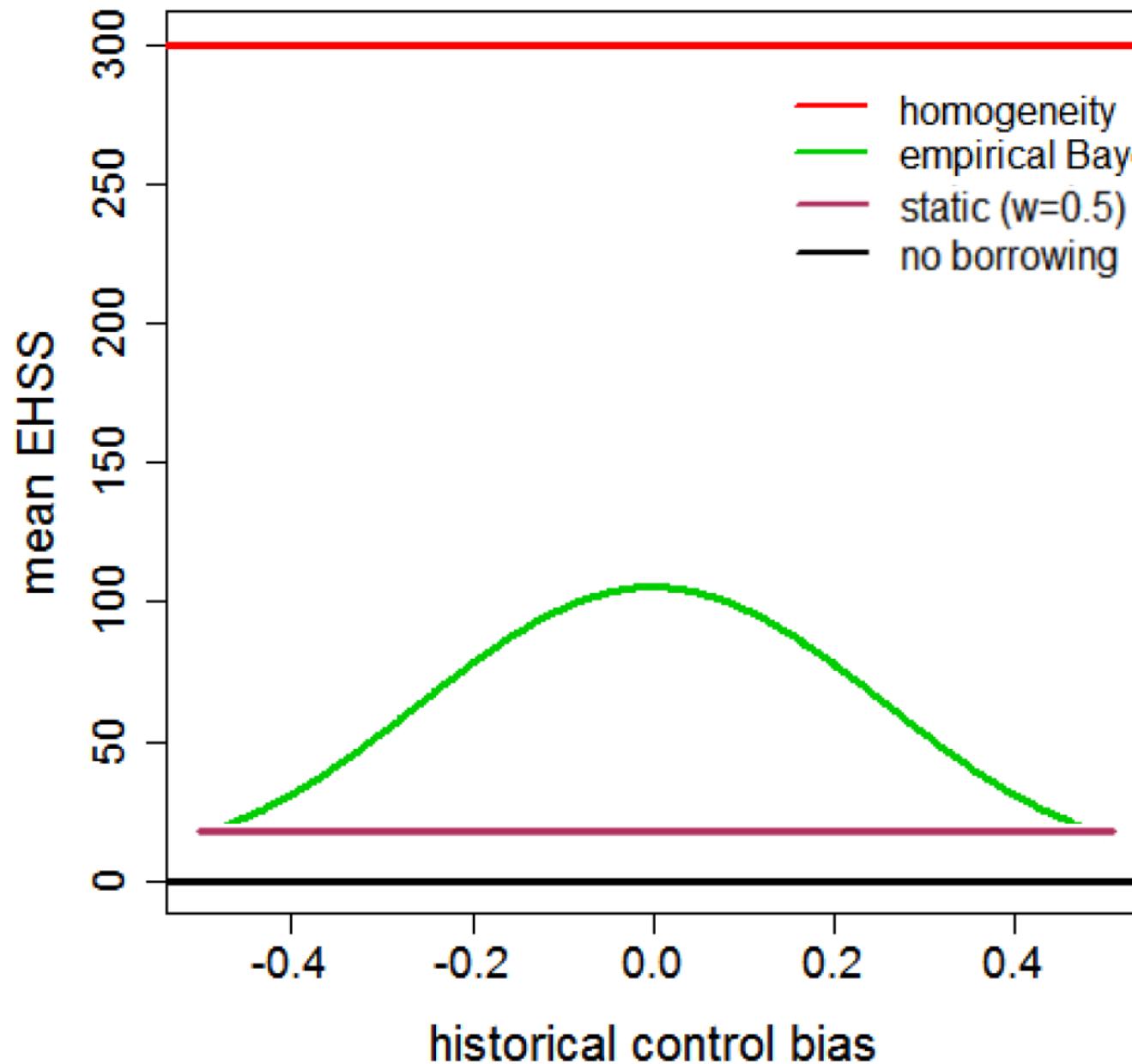
- ▶  $\mathcal{P}^*(y)$  = precision of  $\theta|y$  under the reference model
- ▶  $\mathcal{P}(y_0, y)$  = precision of  $\theta|y_0, y$  under the joint model
- ▶ given *linear* relationship bw sample size and precision *under the reference*
- ▶ *effective sample size* of the *joint* inference is approx.  $n \frac{\mathcal{P}(y_0, y)}{\mathcal{P}^*(y)}$

## Effective historical sample size

$$EHSS \approx n \left\{ \frac{\mathcal{P}(y_0, y)}{\mathcal{P}^*(y)} - 1 \right\}$$

- ▶ maps relative gains in posterior precision into a number quantifying the *additional effective* number of controls for the inference

### Effective historical sample size



# Dynamic Adaptive Randomization Design

Permuted-block randomization procedure with blocks of size  $B$

- ▶  $n^{trt}(t)$  number assigned novel therapy
- ▶  $n^{cnt}(t)$  number assigned to control
- ▶  $R(t)$  denote the number of remaining patients at trial time  $t$
- ▶  $\pi B$  of the next  $B$  will be randomly assigned to novel therapy, where

$$\pi = \frac{1}{2} \left\{ \frac{EHSS(t) + n^{cnt}(t) - n^{trt}(t)}{R(t)} + 1 \right\}$$

- ▶ attempts balance at the *end* of the trial relative to  $EHSS(t)$ :

$$n^{trt}(t) + \pi R(t) = EHSS(t) + n^{cnt}(t) + (1 - \pi)R(t)$$

## Hobbs, Carlin, and Sargent (2013) Clinical Trials

**maximize power** on the basis of interim posterior estimates of bias

### 1. Effective Historical Sample Size

mapping relative gains in posterior precision on to the sample size domain as an *Effective historical sample size* (EHSS)

EHSS is a measure of “shrinkage”

EHSS = the effective number of additional primary/current samples that would be required to achieve the obtained posterior precision

### 2. Balanced Allocation

Adaptive randomization procedure that adapts as a function of EHSS, computed at interim analyses

**Do not use interim analysis of efficacy** which endeavor to *imbalance* treatment allocation (“response-adaptive”)

# Randomization Methods

## 1. Fixed Allocation

- a. Simple randomization
- b. Permuted block (restricted)

## 2. Adaptive Allocation Methods

Treatments are assigned with probabilities which change during the course of the trial

- a. Baseline adaptive randomization (Minimization)
- b. Outcome (or Response) adaptive randomization**
- c. Multi-source adaptive randomization (Hobbs, et al. 2013)

# Outcome-adaptive randomization

Berry DA<sup>1</sup>, Eick SG. Adaptive assignment versus balanced randomization in clinical trials: a decision analysis. *Statistics in Medicine*. 1995

Y. K. Cheung, L. Y. T. Inoue, J. K. Wathen, and P. F. Thall, Continuous Bayesian adaptive randomization based on event times with covariates, *Statistics in Medicine*, 25: 5570, 2006.

Hu, F. and Rosenberger, W.F. (2006) The theory of response-adaptive randomization in clinical trials. John Wiley and Sons. Wiley Series in Probability and Statistics.

P. F. Thall and J. K. Wathen, Practical Bayesian adaptive randomization in clinical trials, *European Journal of Cancer*, 43: 859866, 2007.

O. Sverdlov, Y. Tymofyeyevb, and W. K. Wong: Optimal response-adaptive randomized designs for multi-armed survival trials, *Statistics in Medicine*, 30: 2890-2910, 2011.

Yin G, Chen N and Lee JJ. Phase II trial design with Bayesian adaptive randomization and predictive probability. *Journal of the Royal Statistical Society, Series C* 2012; 61: 219235.

D.A. Berry: Bayesian statistics and the efficiency and ethics of clinical trials, *Statistical Science*, 19: 175-187, 2004.

E. L. Korn and B. Freidlin: Outcome-Adaptive Randomization: Is it Useful?  
Journal of Clinical Oncology, 29: 771-776, 2011.

Y. Yuan and G. Yin: On the usefulness of outcome-adaptive randomization,  
Journal of Clinical Oncology, 29: 390-392, 2011.

B. Freidlin and E. L. Korn: Reply to Y. Yuan et al, Journal of Clinical Oncology,  
29: e393, 2011.

D. A. Berry: Adaptive clinical trials: the promise and the caution, Journal of  
Clinical Oncology, 606-609, 2011.

B. Freidlin and E. L. Korn: Adaptive randomization versus interim monitoring,  
Journal of Clinical Oncology, 29: 969-978, 2013.

P. Thall, P. Fox, J. Wathen (2015) Statistical controversies in clinical research:  
scientific and ethical problems with adaptive randomization in comparative clinical  
trials, Annals of Oncology, 26: 1621–1628.

S.P. Hey and J. Kimmelman. (2015) Are outcome-adaptive allocation trials  
ethical? Clinical Trials, 12(2): 102-106.

Perspective Section of April 2015; 12(2) issue of Clinical Trials

# Randomization Methods

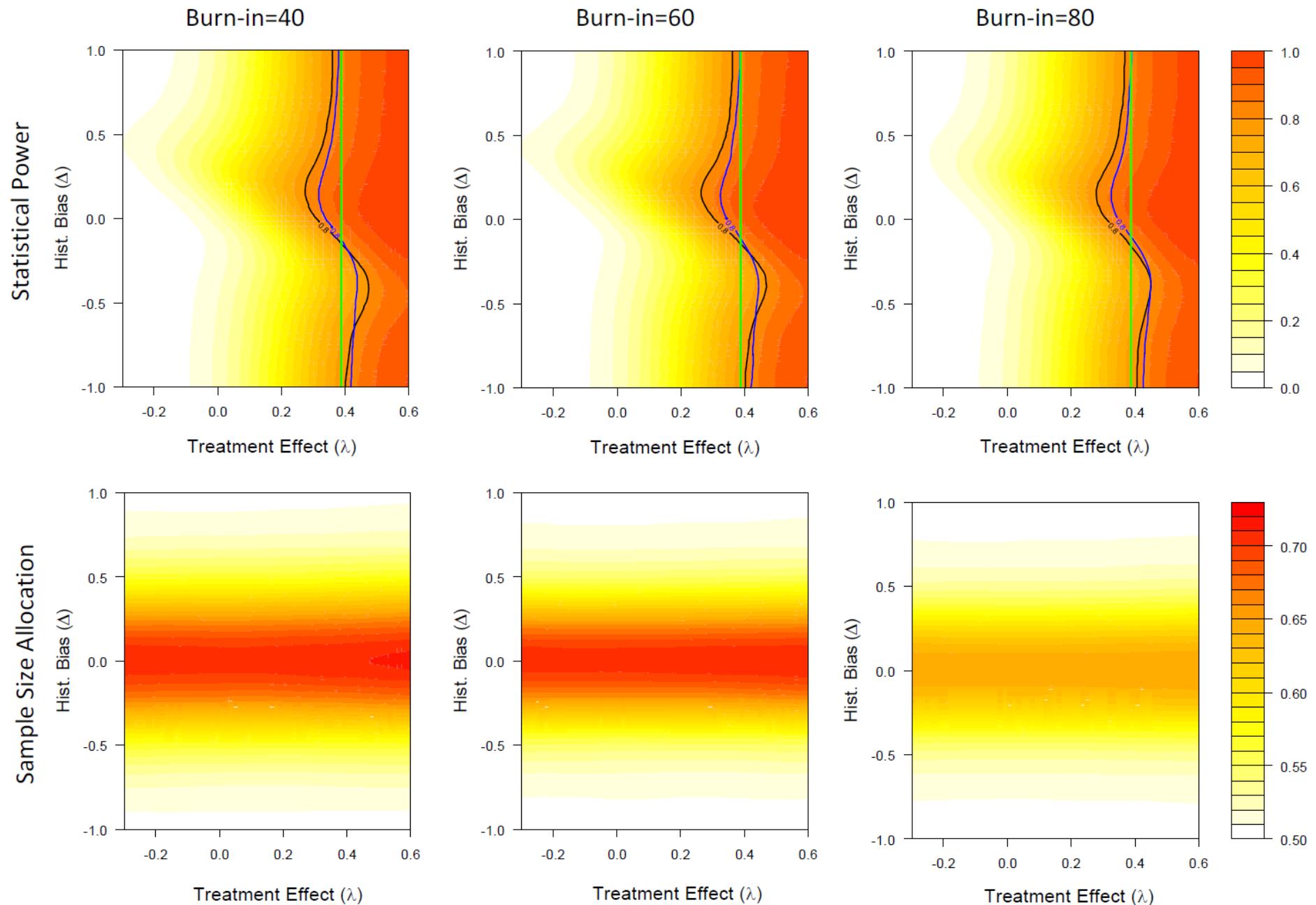
## 1. Fixed Allocation

- a. Simple randomization
- b. Permuted block (restricted)

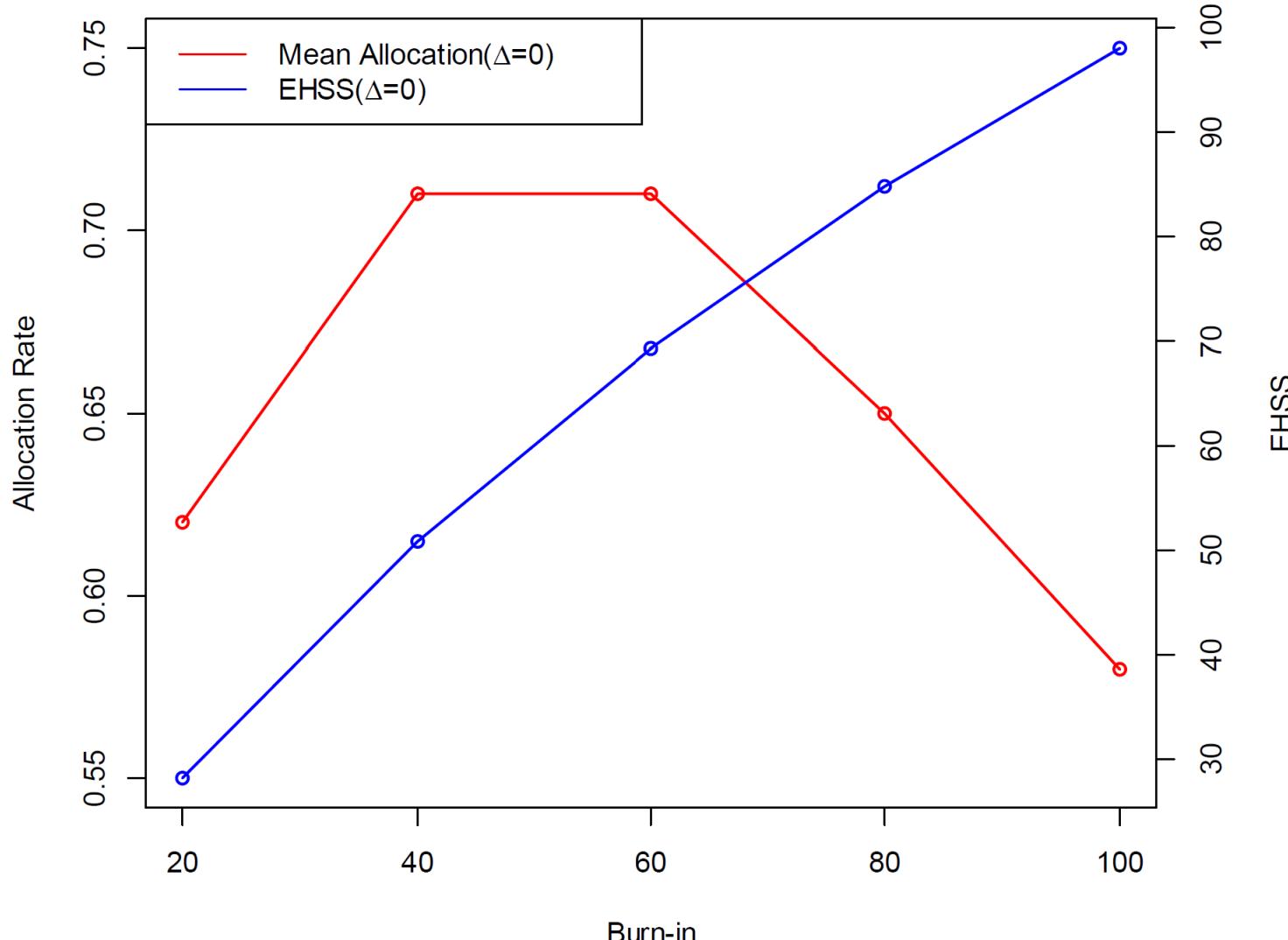
## 2. Adaptive Allocation Methods

Treatments are assigned with probabilities which change during the course of the trial

- a. Baseline adaptive randomization (Minimization)
- b. Outcome (or Response) adaptive randomization
- c. **Multi-source adaptive randomization (Hobbs, et al. 2013)**

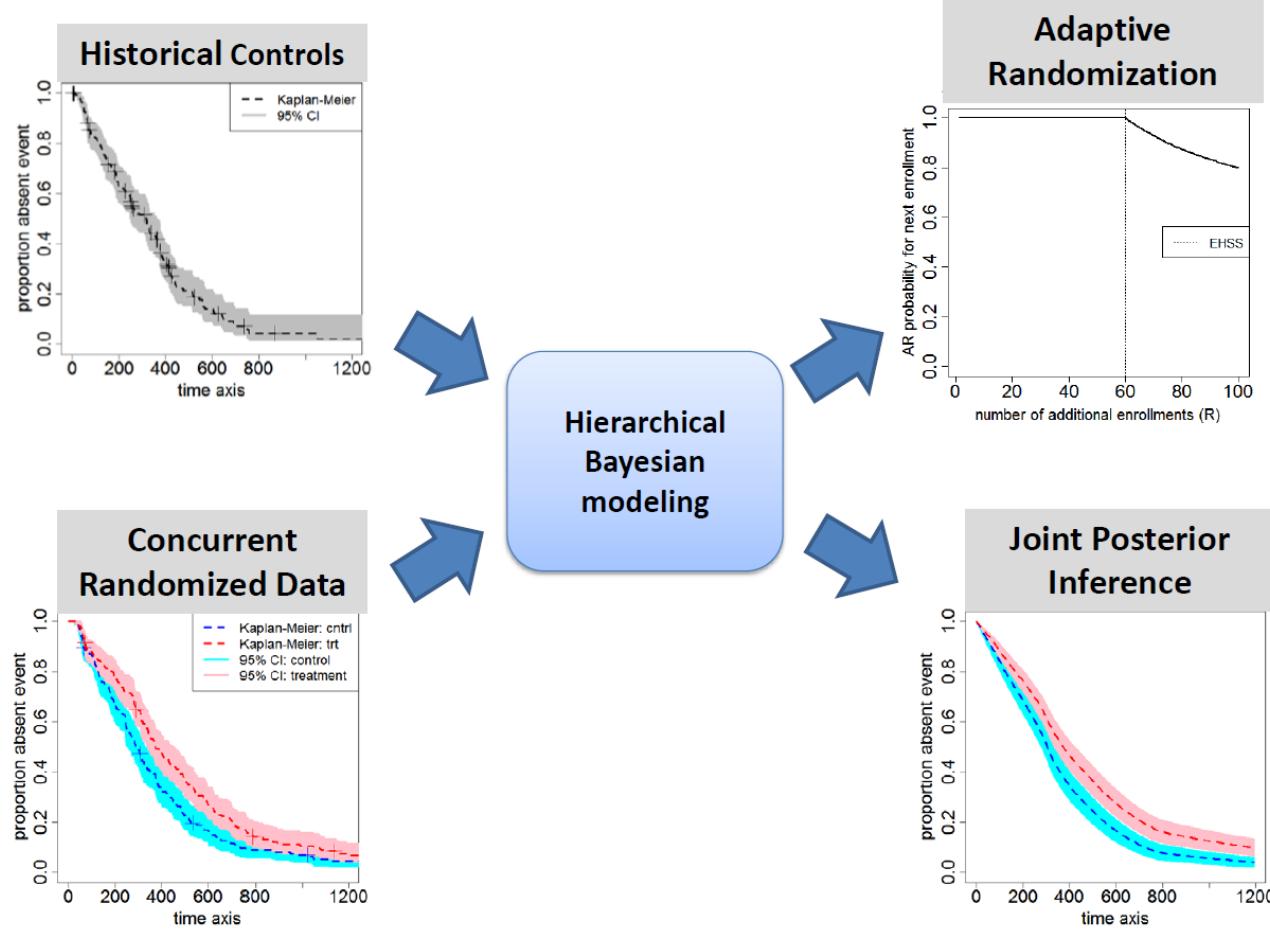


# Design Calibration for Single Interim Analysis



# Expert in External Controls

## Multi-source Adaptive Randomization (Hobbs et al. 2013)



# Example: Randomized Controlled Colorectal Cancer Trials

- ▶ Two successive randomized controlled colorectal cancer trials coord. by NCCTG

Saltz et al. (2000)

1. Irinotecan alone
2. **Irinotecan and bolus Fluorouracil + Leucovorin (IFL) ( $N = 224$ )**
  - ▶ *significantly longer time to disease progression*
  - ▶ *regulatory standard in March 2000*
3. Fluorouracil and Leucovorin (5FU/LV) *standard therapy*

Goldberg et al. (2004)

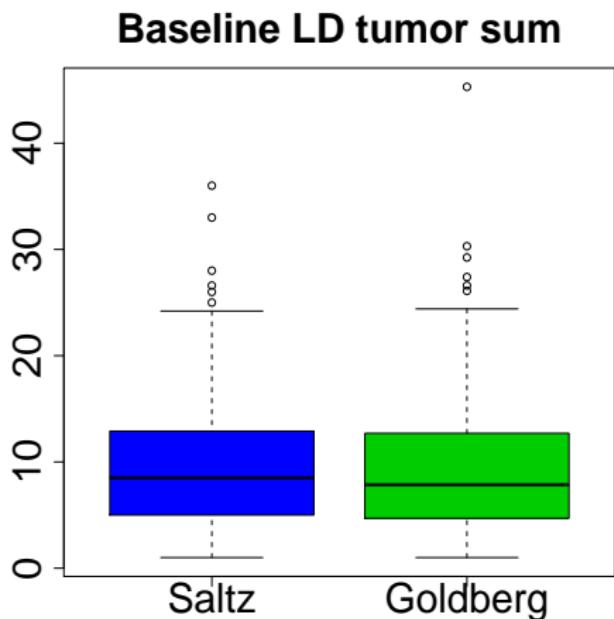
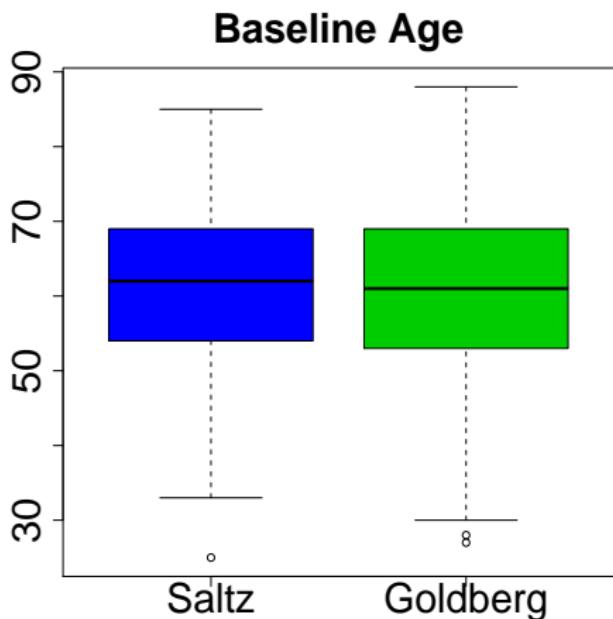
1. **Irinotecan and bolus Fluorouracil + Leucovorin (IFL)**
2. Oxaliplatin and infused Fluorouracil + Leucovorin (FOLFOX) *new regimen*
3. Irinotecan and Oxaliplatin (IROX) *new regimen*

# Randomized Controlled Colorectal Cancer Trials (cont'd)

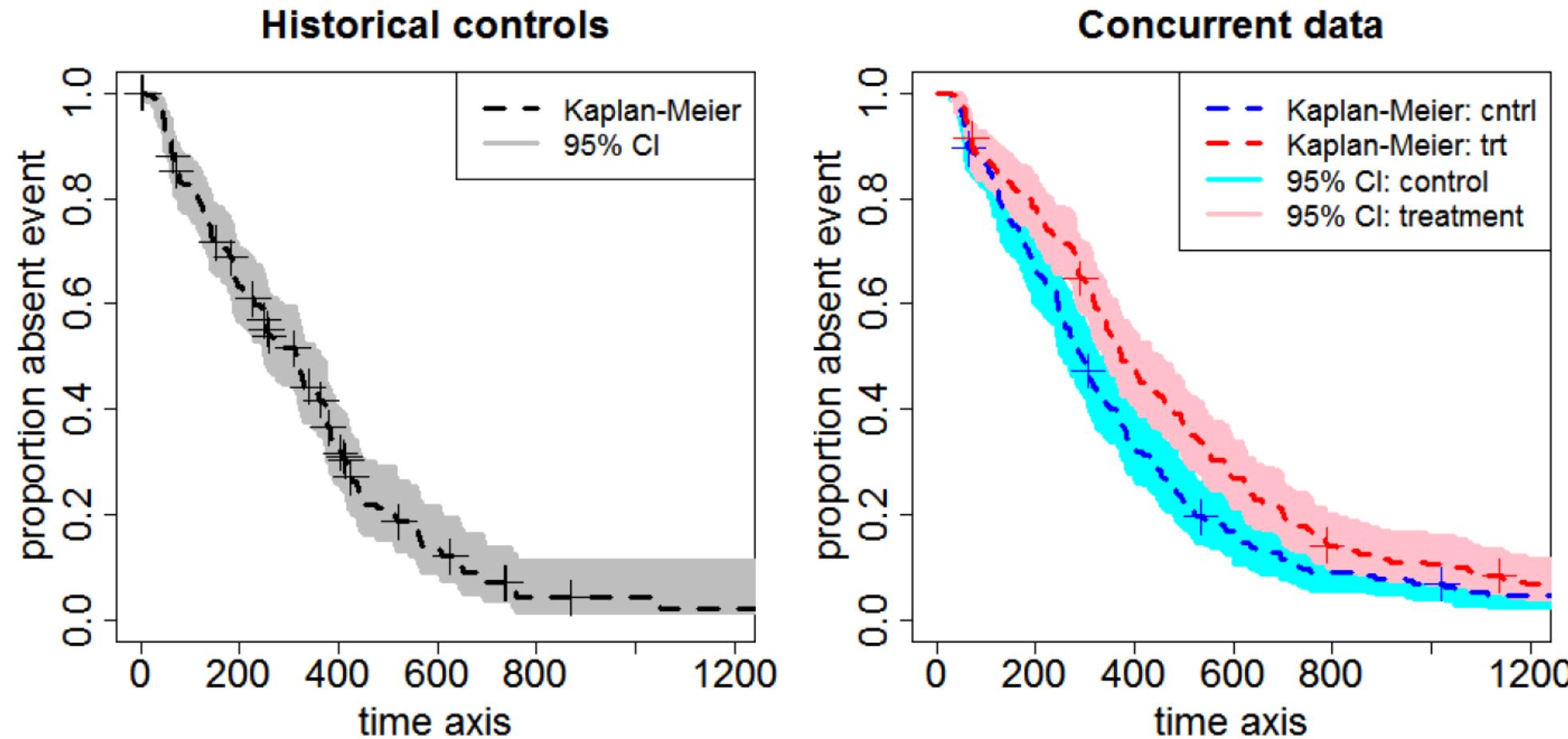
Consider Pocock's acceptability criteria:

- ▶ Identical therapies: (doses in mg/m<sup>2</sup>) IFL was irinotecan 125 and bolus FU 500 plus LV 20 weekly for 4 weeks every 6 weeks
- ▶ Inclusion Criteria:
  - ▶ histologically proven unresectable colorectal adenocarcinoma
  - ▶ Eastern Cooperative Oncology Group performance status  $\leq 2$
  - ▶ adequate organ function
- ▶ Exclusion Criteria:
  - ▶ Prior therapy for metastatic disease
  - ▶ Adjuvant fluorouracil in previous 12 months
- ▶ Tumor measurements at regular 6-week cycles
- ▶ Uniformly defined response (disease progression)
  - ▶ 25% or greater increase in measurable tumor or the appearance of new lesions
- ▶ 1 year from end of Saltz to start of Goldberg
- ▶ 5 years between initiation of Saltz to completion of Goldberg

# Randomized Controlled Colorectal Cancer Trials (cont'd)



Boxplots of age (left) and ld tumor sum (right) at baseline for the Saltz et al. and Goldberg et al. trials.



Kaplan-Meier curves derived from the historical control data (left) and current data (right), with 95% log-transformed pointwise confidence intervals. Right-censored observations are marked by +.

**Table 1: Posterior summary for novel treatment effect  $\xi$ , median survival for control and treatment; effective historical sample size (EHSS), and the probability used to randomized to treatment the next patient to enroll (AR probability)**

<u>Parameter</u>	<u>Mean</u>	<u>SD</u>	<u>Mean HR (95% HPD)</u>	<u>Pr( HR&lt;1   Data )</u>
$\xi$	-0.372	0.098	0.72(0.57-0.87)	0.999
	<u>Mean (95% HPD)</u>			
Median	control	305(279-333)		
	treatment	373(330-420)		
# Current treated	200			
# Current controls	200			
# Historical controls	200			
EHSS	60			
AR probability	0.798			
Calculation Time (sec.)	5			

Note. SD = posterior standard deviation; HR = hazard ratio; HPD = highest posterior density interval; Pr( HR<1 | Data ) = posterior tail probability < 1 for the hazard rate ratio indicating strength of evidence for an improvement associated with treatment arm

# Open Source Software

Web interface

<http://research.mdacc.tmc.edu/SmeeactWeb>



Contents lists available at [ScienceDirect](#)

Computational Statistics and Data Analysis

journal homepage: [www.elsevier.com/locate/csda](http://www.elsevier.com/locate/csda)



Web-based statistical tools for the analysis and design of clinical trials that incorporate historical controls



Nan Chen <sup>a</sup>, Bradley P. Carlin <sup>b</sup>, Brian P. Hobbs <sup>c,\*</sup>

<sup>a</sup> Department of Biostatistics, University of Texas M.D. Anderson Cancer Center, Houston, TX, United States

<sup>b</sup> Division of Biostatistics, University of Minnesota, Minneapolis, MN, United States

<sup>c</sup> Quantitative Health Sciences and The Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, United States

---

## ARTICLE INFO

*Article history:*

Received 12 July 2017

Received in revised form 3 May 2018

Accepted 4 May 2018

Available online 15 May 2018

---

## ABSTRACT

A collection of web-based statistical tools (<http://research.mdacc.tmc.edu/SmeeactWeb/>) are described that enable investigators to incorporate historical control data into analysis of randomized clinical trials using Bayesian hierarchical modeling as well as implement adaptive designs that balance posterior effective sample sizes among the study arms and thus maximize power. With balanced allocation guided by "dynamic" Bayesian hierarchical

# AR Design of Goldberg colon cancer trial

Adaptive design of the Goldberg trial following the Saltz trial:

- ▶ compare FOLFOX (novel) to IFL (control) for time to prog. (TTP)
- ▶ model for TTP with flexible piecewise exponential distribution
- ▶ simulate properties of the design using
  - ▶ *actual* historical data from Saltz study
  - ▶ *actual* enrollment dates from Goldberg study

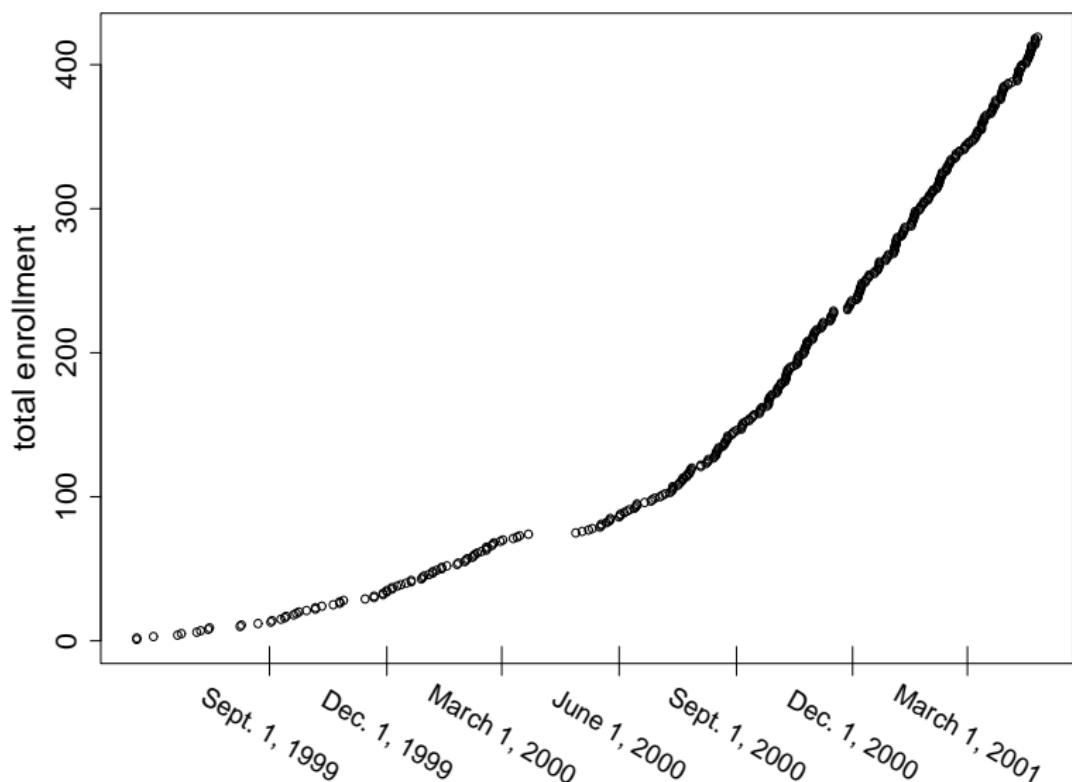
## I. Historical Data

- ▶ patients randomized to IFL in the Saltz study ( $n_0 = 224$ )

## II. Current Data

- ▶  $n = 419$  simulated patients randomized to IFL or FOLFOX in our proposed adaptive version of the Goldberg trial

# Actual Enrollment to Goldberg



# AR Design of Goldberg colon cancer trial (cont'd)

Piecewise exponential joint model:

- ▶ approximates underlying hazard function with a step function
- ▶ *constant baseline hazards within finite partitions* of the time axis (Ibrahim et al., 2001)
- ▶ *ratio of hazards for two individuals is constant over time*

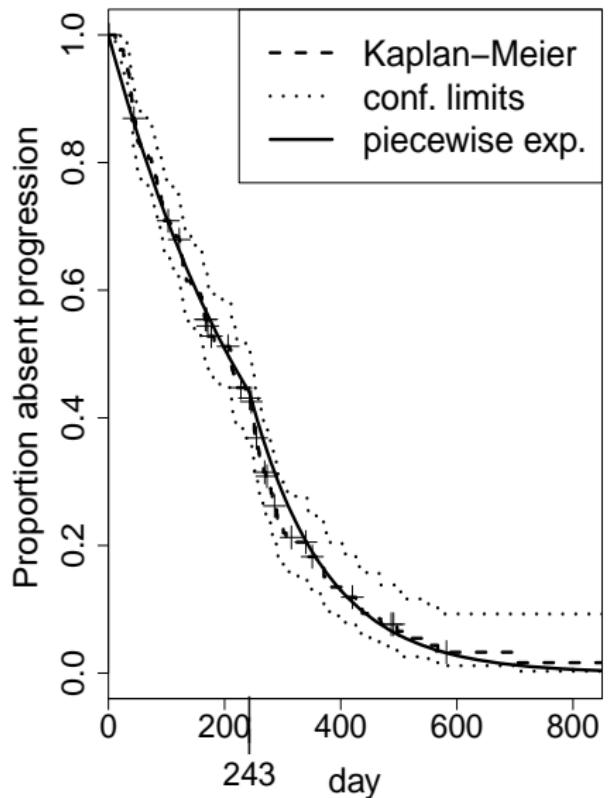
I. Inference on the historical data:

- ▶ Akaike information criterion (AIC) used to select time axis partition
- ▶ contains two intervals with boundary point at 243 days
- ▶ basis for simulation of current controls at the design stage

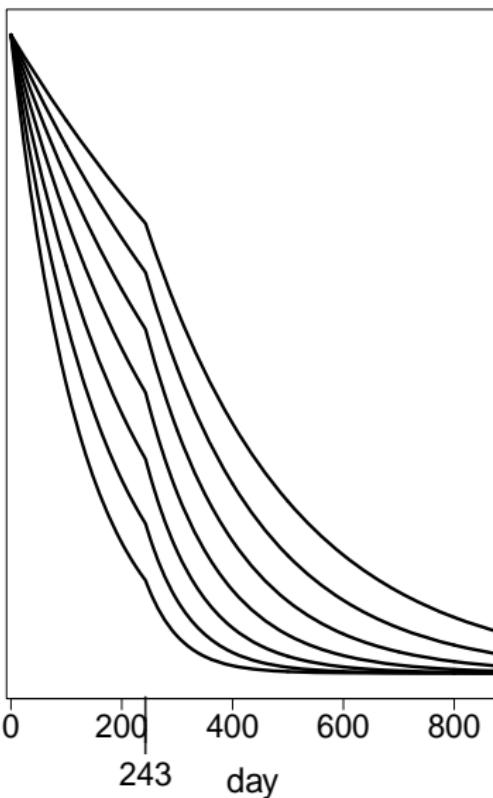
Posterior means and sd from analysis of TTP for historical controls,  $n_0 = 224$ .

	mean	sd
log baseline hazard 1	-5.689	0.094
log baseline hazard 2	-4.858	0.133

actual historical data



current simulation scenarios



# AR Design of Goldberg colon cancer trial (cont'd)

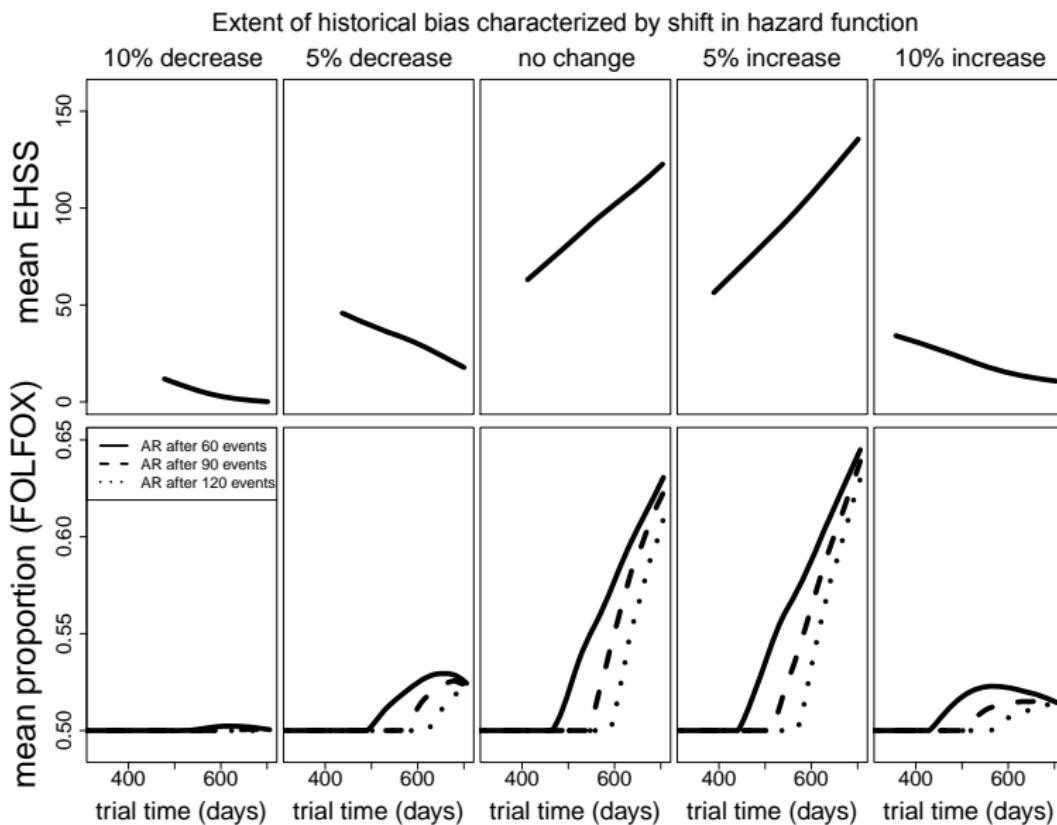
## II. Analysis:

- ▶ time axis partition contains two intervals
- ▶ incorporates an acceleration factor that provides uniform adjustment of the baseline hazards to accommodate the effect of treatment

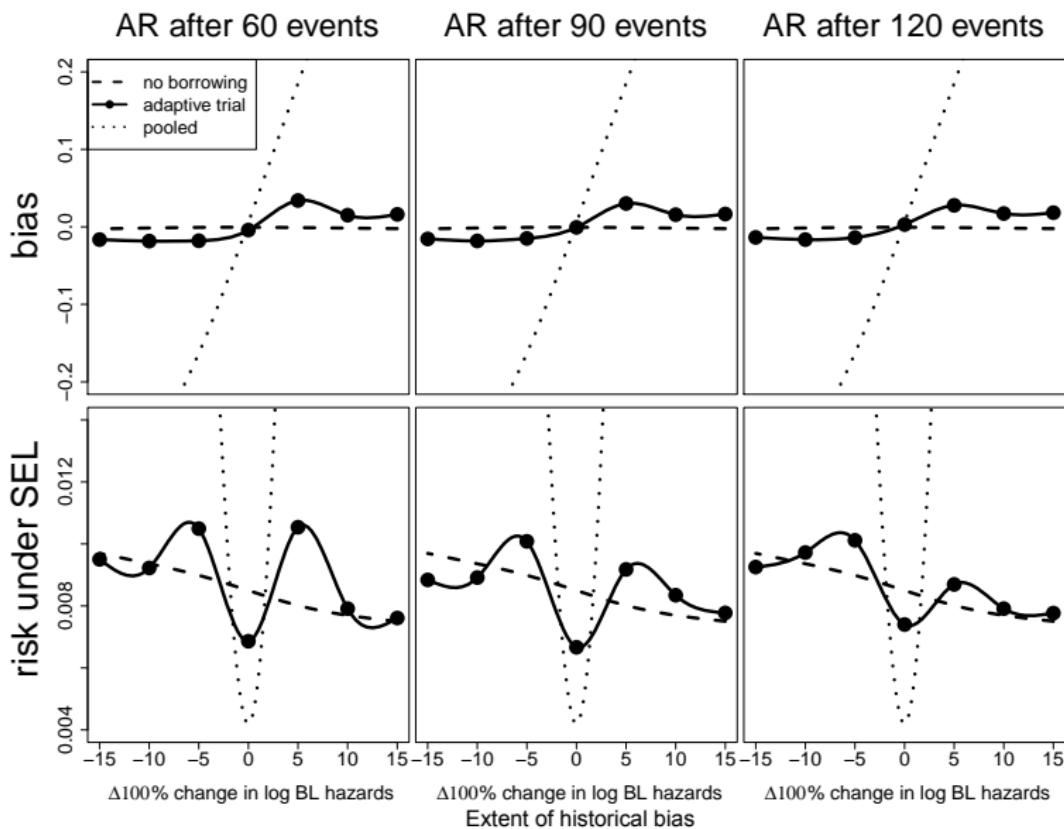
## III. Hierarchical model with spike and slab hyperprior:

- ▶ formulated using spike-and-slab hyperpriors to borrow strength from the historical controls
- ▶ EHSS characterizes the relative gain in precision for estimating the *current* baseline hazards as a number of *additional events* observed for control
- ▶ periodic interim analyses that facilitate adjustment of the randomization ratio

# EHSS and proportion randomized to novel therapy



# Point estimation of effect of novel therapy



## Propensity-score-based meta-analytic predictive prior for incorporating real-world and historical data

Meizi Liu<sup>1</sup> | Veronica Bunn<sup>2</sup>  | Bradley Hupf<sup>2</sup> | Junjing Lin<sup>2</sup> | Jianchang Lin<sup>2</sup> 

<sup>1</sup>Department of Public Health Sciences, University of Chicago, Chicago, Illinois, USA

<sup>2</sup>Statistical and Quantitative Sciences, Takeda Pharmaceuticals, Cambridge, Massachusetts, USA

**Correspondence**  
Veronica Bunn and Jianchang Lin,  
Statistical and Quantitative Sciences,  
Takeda Pharmaceuticals, Cambridge, MA  
02139, USA.  
Email: veronica.bunn@takeda.com and  
jianchang.lin@takeda.com

As the availability of real-world data sources (eg, EHRs, claims data, registries) and historical data has rapidly surged in recent years, there is an increasing interest and need from investigators and health authorities to leverage all available information to reduce patient burden and accelerate both drug development and regulatory decision making. Bayesian meta-analytic approaches are a popular historical borrowing method that has been developed to leverage such data using robust hierarchical models. The model structure accounts for various degrees of between-trial heterogeneity, resulting in adaptively discounting the external information in the case of data conflict. In this article, we propose to integrate the propensity score method and Bayesian meta-analytic-predictive (MAP) prior to leverage external real-world and historical data. The propensity score methodology is applied to select a subset of patients from external data that are similar to those in the current study with regards to key base-

Received: 23 February 2022 | Revised: 19 December 2022 | Accepted: 17 February 2023

DOI: 10.1002/pst.2297

### MAIN PAPER

## Covariate handling approaches in combination with dynamic borrowing for hybrid control studies

Chenqi Fu<sup>1,2</sup>  | Herbert Pang<sup>2,3</sup>  | Shouhao Zhou<sup>1</sup> | Jiawen Zhu<sup>2</sup> 

<sup>1</sup>Department of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania, USA

<sup>2</sup>PD Data Sciences, Genentech, South San Francisco, California, USA

<sup>3</sup>Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina, USA

**Correspondence**  
Herbert Pang, PD Data Sciences,  
Genentech, South San Francisco, CA,  
USA.  
   

### Abstract

Borrowing data from external control has been an appealing strategy when conducting randomized controlled trials (RCTs). In hybrid control trials, they leverage existing control data from potentially real-world data (RWD), enable trial designs to allocate to the novel intervention arm, and improve the efficiency or lower primary RCT. Several methods have been established and developed to handle external control data, among which the propensity score method and dynamic borrowing framework play essential roles. Noticing the unique features of propensity score methods and Bayesian hierarchical models, we propose two covariate handling approaches in combination with dynamic borrowing for hybrid control studies.



## A structured framework for adaptively incorporating external evidence in sequentially monitored clinical trials

Evan Kwiatkowski <sup>a</sup>, Eugenio Andraca-Carrera<sup>b</sup>, Mat Soukup<sup>b</sup>, and Matthew A. Psioda<sup>a</sup>

<sup>a</sup>Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, USA; <sup>b</sup>Division of Biometrics VII, Office of Biostatistics, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA

### ABSTRACT

We present a Bayesian framework for sequential monitoring that allows for use of external data, and that can be applied in a wide range of clinical trial applications. The basis for this framework is the idea that, in many cases, specification of priors used for sequential monitoring and the stopping criteria can be semi-algorithmic byproducts of the trial hypotheses and relevant external data, simplifying the process of prior elicitation. Monitoring priors are defined using the family of generalized normal distributions, which comprise a flexible class of priors, naturally allowing one to construct a prior that is peaked or flat about the parameter values thought to be most likely. External data are incorporated into the monitoring process through mixing an a priori skeptical prior with an enthusiastic prior using a weight that can be fixed or adaptively estimated. In particular, we introduce an adaptive monitoring prior for efficacy evaluation that dynamically weighs skeptical and enthusiastic prior components based on the degree to which observed data are consistent with an enthusiastic perspective. The proposed approach allows for prospective and pre-specified use of external data in the monitoring procedure. We illustrate the method for both single-arm and two-arm randomized controlled trials. For the latter case, we also include a retrospective analysis of actual trial data using the proposed adaptive sequential monitoring procedure. Both examples are motivated by completed pediatric trials, and the designs incorporate information from adult trials to varying degrees. Preposterior analysis and frequentist operating characteristics of each trial design are discussed.

### ARTICLE HISTORY

Received 28 July 2021  
Accepted 22 February 2022

### KEYWORDS

Adaptive trial design;  
bayesian sequential  
monitoring; information  
borrowing; pediatric trials;  
skeptical prior



## Power priors with entropy balancing weights in data augmentation of partially controlled randomized trials

Guanglei Yu <sup>a</sup>, Yuanyuan Bian <sup>a</sup>, and Margaret Gamalo <sup>b</sup>

<sup>a</sup>Eli Lilly & Co, Indianapolis, Indiana, USA; <sup>b</sup>Pfizer, Collegeville, Pennsylvania, USA

### ABSTRACT

In pediatric or orphan diseases, there are many instances where it is unfeasible to conduct randomized and controlled clinical trials. This is due in part to the difficulty of enrolling a sufficient number of patients over a reasonable time period to meet adequate statistical power to demonstrate the treatment efficacy. One solution to reduce the sample size or expedite the trial timeline is to complement the current trial with real-world data. To this end, several propensity score-based methods have been developed to create defined groups of patients that are controlled for confounding based on a set of measured covariates at baseline. However, balance checking on the measured covariates and tweaks to the propensity score models is usually inevitable to achieve the joint balance across all covariates. To mitigate this iterative procedure, we utilize the entropy balancing weighting technique which focuses on balancing the covariates of subjects between the experimental and control groups directly and augments the current trial with the external control data via a power prior. The finite-sample properties of the proposed method are assessed via simulations in the context of asymmetrically randomized controlled trials where only a small portion of patients are randomized to the control group. Other methods such as covariate-balancing propensity score (CBPS) and propensity score matching (PSM) and weighting (PSW) are also compared to provide context on the operating characteristics of the proposed method.

### ARTICLE HISTORY

Received 5 August 2021  
Accepted 24 November 2021

### KEYWORDS

Bayesian-augmented  
control; asymmetrical  
randomization; entropy  
balancing; power prior



## Statistical methods of indirect comparison with real-world data for survival endpoint under non-proportional hazards

Zihan Lin<sup>a</sup>, Dan Zhao , Junjing Lin , Ai Ni<sup>a</sup>, and Jianchang Lin 

<sup>a</sup>Division of Biostatistics, College of Public Health, the Ohio State University, Columbus, Ohio, USA; <sup>b</sup>Biometrics Department, Servier Pharmaceuticals, Boston, Massachusetts, USA; <sup>c</sup>Statistical and Quantitative Sciences, Takeda Pharmaceuticals, Cambridge, Massachusetts, USA

### ABSTRACT

In clinical studies that utilize real-world data, time-to-event outcomes are often germane to scientific questions of interest. Two main obstacles are the presence of non-proportional hazards and confounding bias. Existing methods that could adjust for NPH or confounding bias, but no previous work delineated the complexity of simultaneous adjustments for both. In this paper, a propensity score stratified MaxCombo and weighted Cox model is proposed. This model can adjust for confounding bias and NPH and can be pre-specified when NPH pattern is unknown in advance. The method has robust performance as demonstrated in simulation studies and in a case study.

### ARTICLE HISTORY

Received 31 December 2021  
Accepted 18 April 2022

### KEYWORDS

causal inference; non-proportional hazards; real-world data; survival analysis; propensity score

# psborrow2



## Overview

`psborrow2` is an R package that for conducting Bayesian Dynamic Borrowing (BDB) analyses and simulation studies.<sup>1 2</sup> `psborrow2` has two main objectives:

1. **Facilitate BDB analyses.** `psborrow2` has a user-friendly interface for conducting BDB analyses that handles the computationally-difficult MCMC sampling on behalf of the user.
2. **Facilitate simulation studies of BDB.** `psborrow2` includes a framework to compare different trial and BDB characteristics in a unified way in simulation studies to inform trial design.

## Background

`psborrow2` is the successor to `psborrow`. `psborrow` is still freely available on [CRAN](#) with the same validated functionality; however, the package is not actively developed. Major updates in `psborrow2` include:

- New, more flexible user interface
- New MCMC software (STAN)
- Expanded functionality

The name `psborrow` combines propensity scoring (`ps`) and Bayesian dynamic `borrowing`. As the name implies, this package can be used to combine dynamic borrowing and propensity-score adjustment/weighting methods.

## License

[Full license](#)

Apache License (>= 2)

## Community

[Contributing guide](#)

[Code of conduct](#)

## Citation

[Citing psborrow2](#)

## Developers

Matt Secrest

Maintainer

Isaac Gravestock

Author

[More about authors...](#)

## Dev status

github.com/genentech v.0.0.2.0

lifecycle experimental



**TORONTO**  
Ontario, Canada • August 5–10  
**JSM2023**

**One Community:**  
Informing Decisions and  
Driving Discovery

## Advancements in Adaptive Borrowing from External Real-World Controls in Clinical Trials

**Tongrong Wang** Chair  
Eli Lilly and Company

**Brian Hobbs** Discussant  
University of Texas

**Mingyang Shan** Organizer  
Eli Lilly and Company

Monday, Aug 7: 2:00 PM - 3:50 PM  
1687  
Topic-Contributed Paper Session

Applied

Yes

Main Sponsor

Biopharmaceutical Section