The University of Texas at Austin
Dell Medical School

LEVERAGING HISTORICAL CONTROLS USING MULTI-SOURCE ADAPTIVE DESIGN

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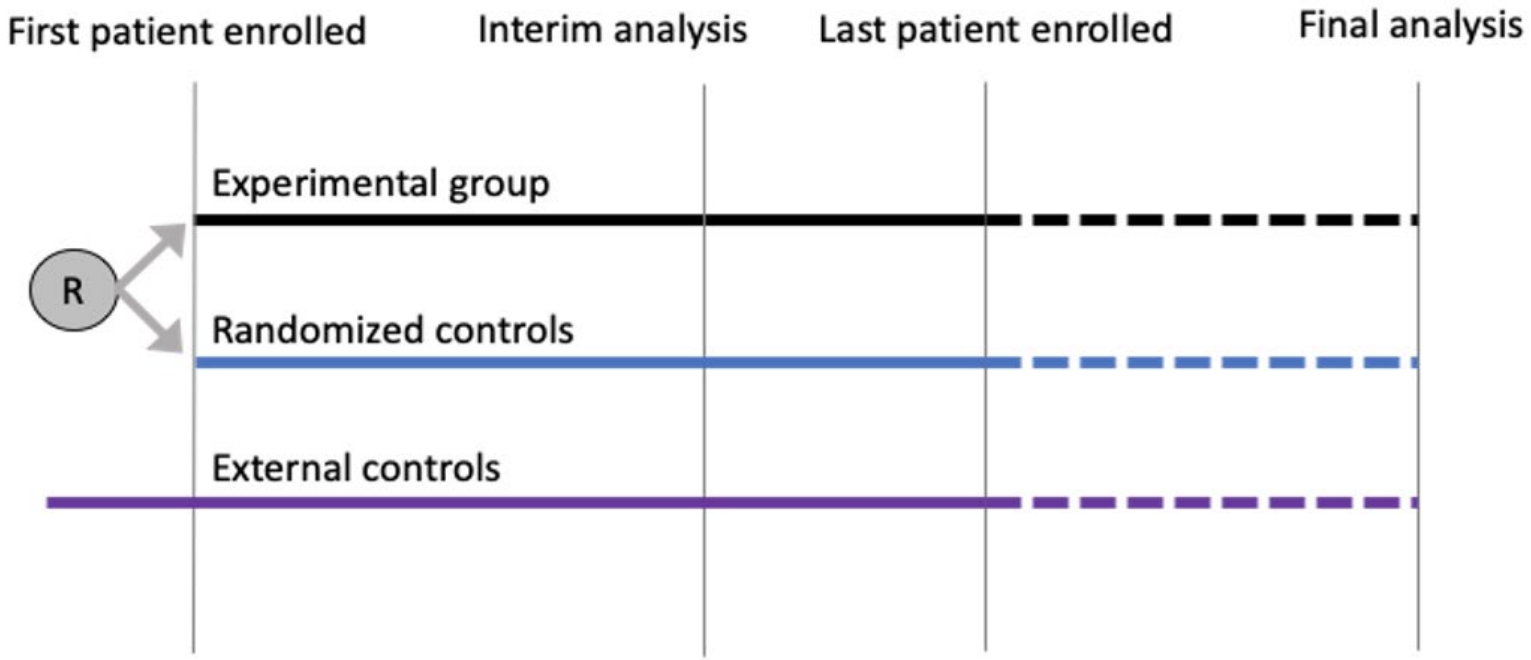
COI Disclosures

- **Scientific Advisory: Amgen**
- **Scientific Advisory: CSL Behring**
- **Scientific Advisory: Bayer HealthCare Pharmaceuticals**
- **Co-Founder, Owner & Scientific Advisory: Telperian**

Expert in External Controls

Hybrid control arm methods and considerations



Apply same I/E criteria to all groups to extent possible, align endpoint definitions

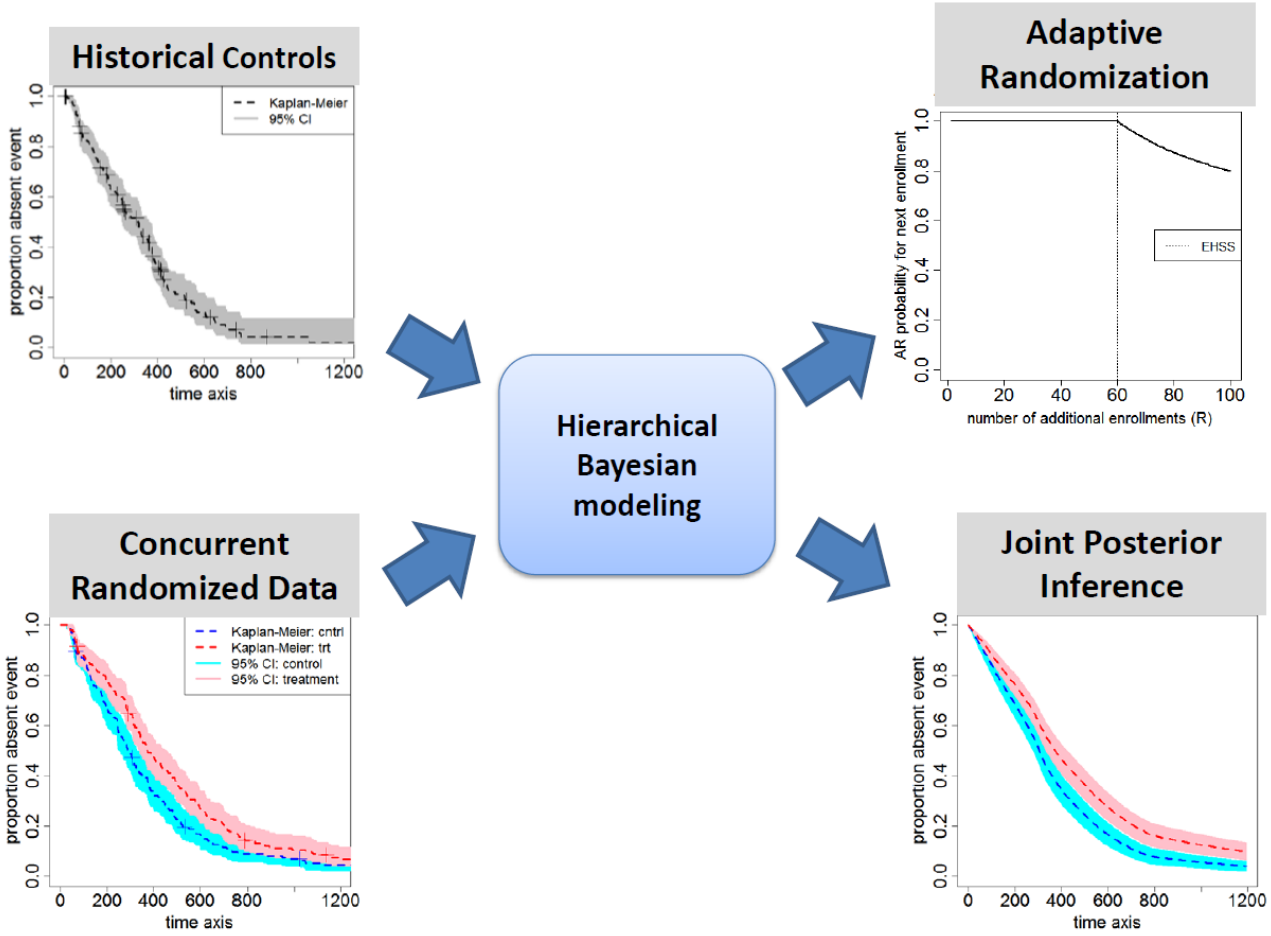
Assess feasibility of borrowing; potential to change randomization ratio

Compare experimental arm against (Randomized + external controls)

R = randomization, I/E = inclusion/exclusion

Expert in External Controls

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



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 Please refer to draft guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019).

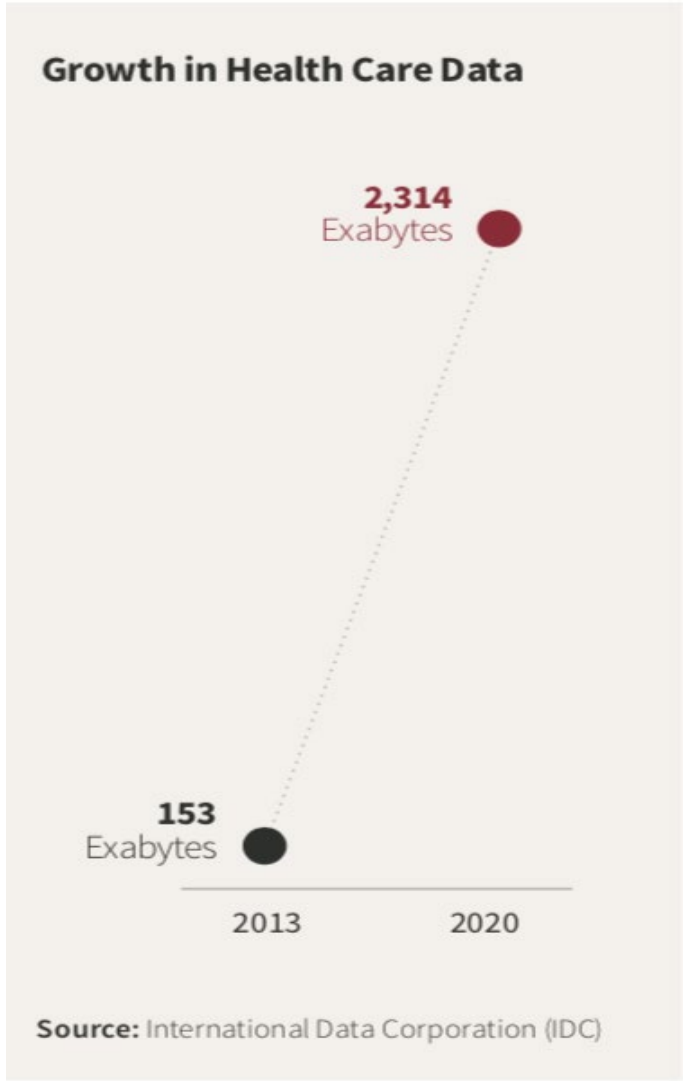
- Master Protocol Case Study
- Lupus Case Study
- DLBCL Case Study

Innovative Characteristics:

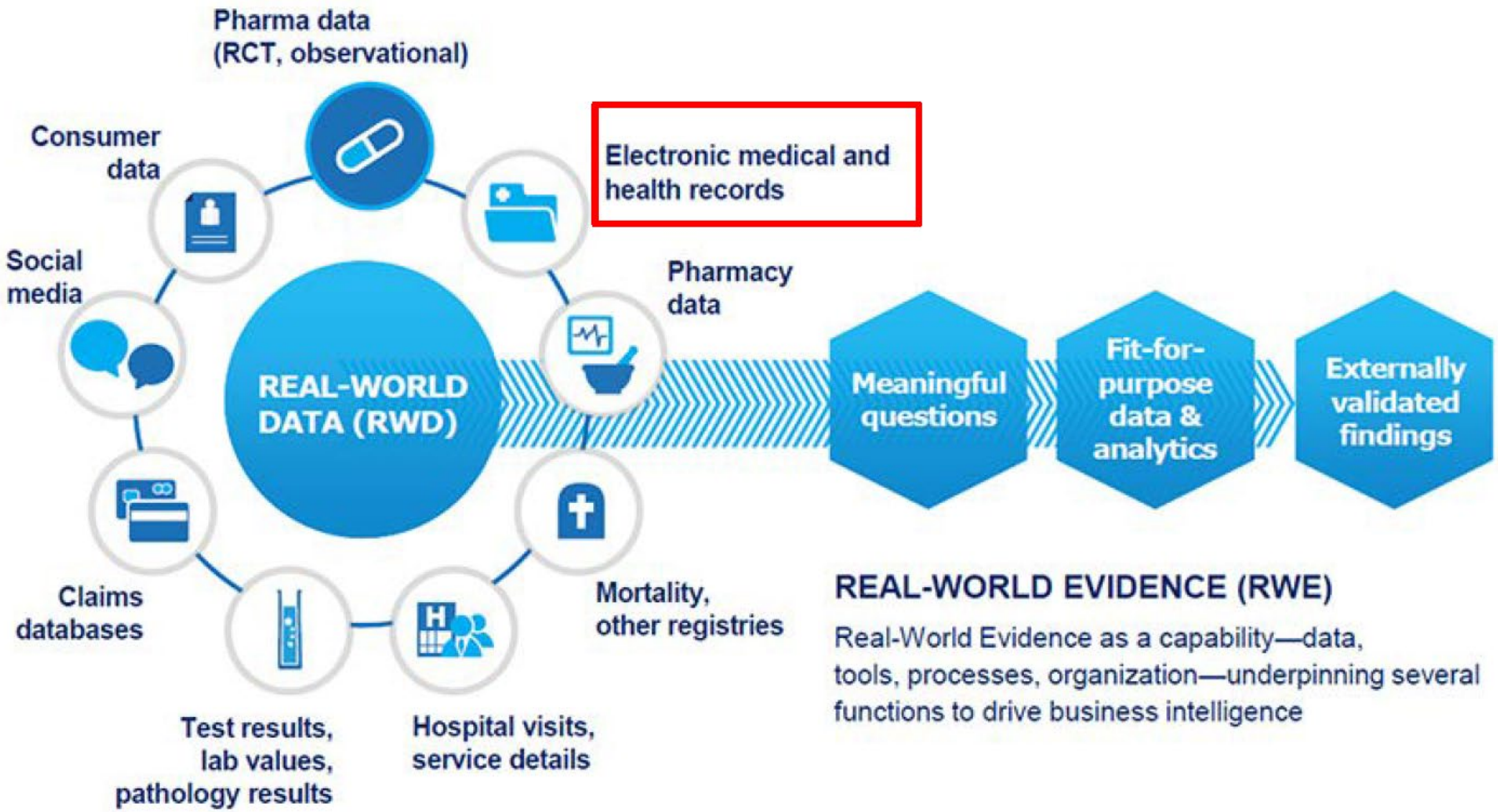
FDA considers the following trial design features to be innovative, making it appropriate to review the design under the Complex Innovative Trial Design (CID) pilot meeting program:

- 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

Emerging RWD Biosphere



What is real-world evidence?



REAL-WORLD EVIDENCE (RWE)

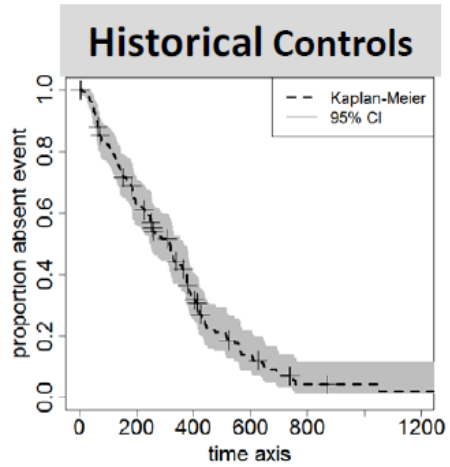
Real-World Evidence as a capability—data, tools, processes, organization—underpinning several functions to drive business intelligence

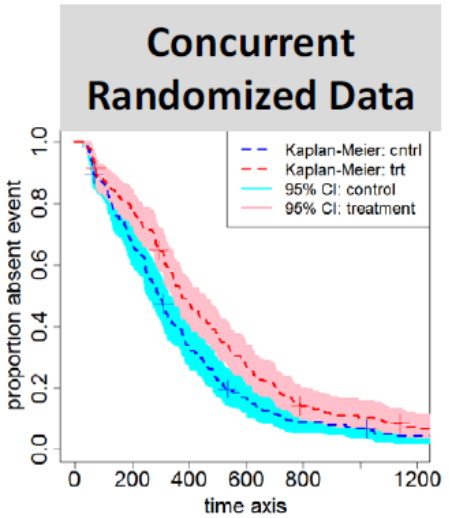
Outline

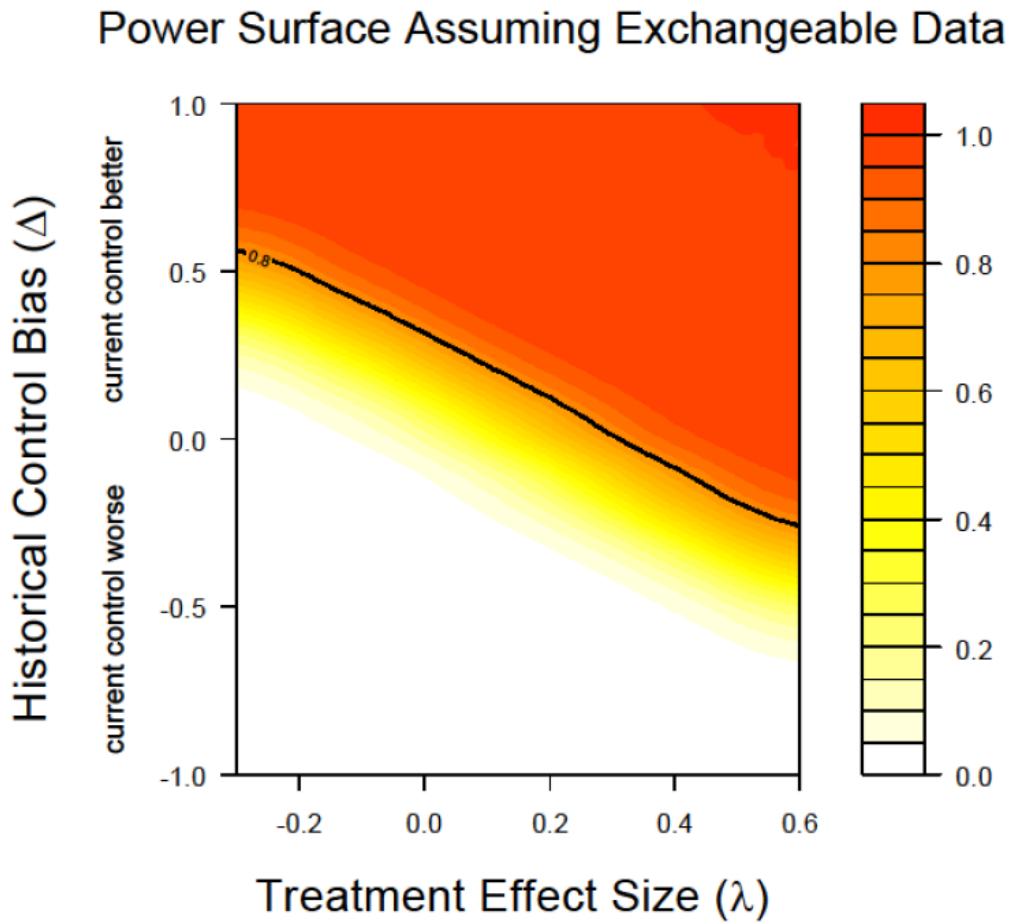
- Methodology Idea of multi-source adaptive design
- Flexible borrowing methods with MEMs
- Context for application (Protocol Violations; Hist Trial Data; RWD; digitized data)


“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

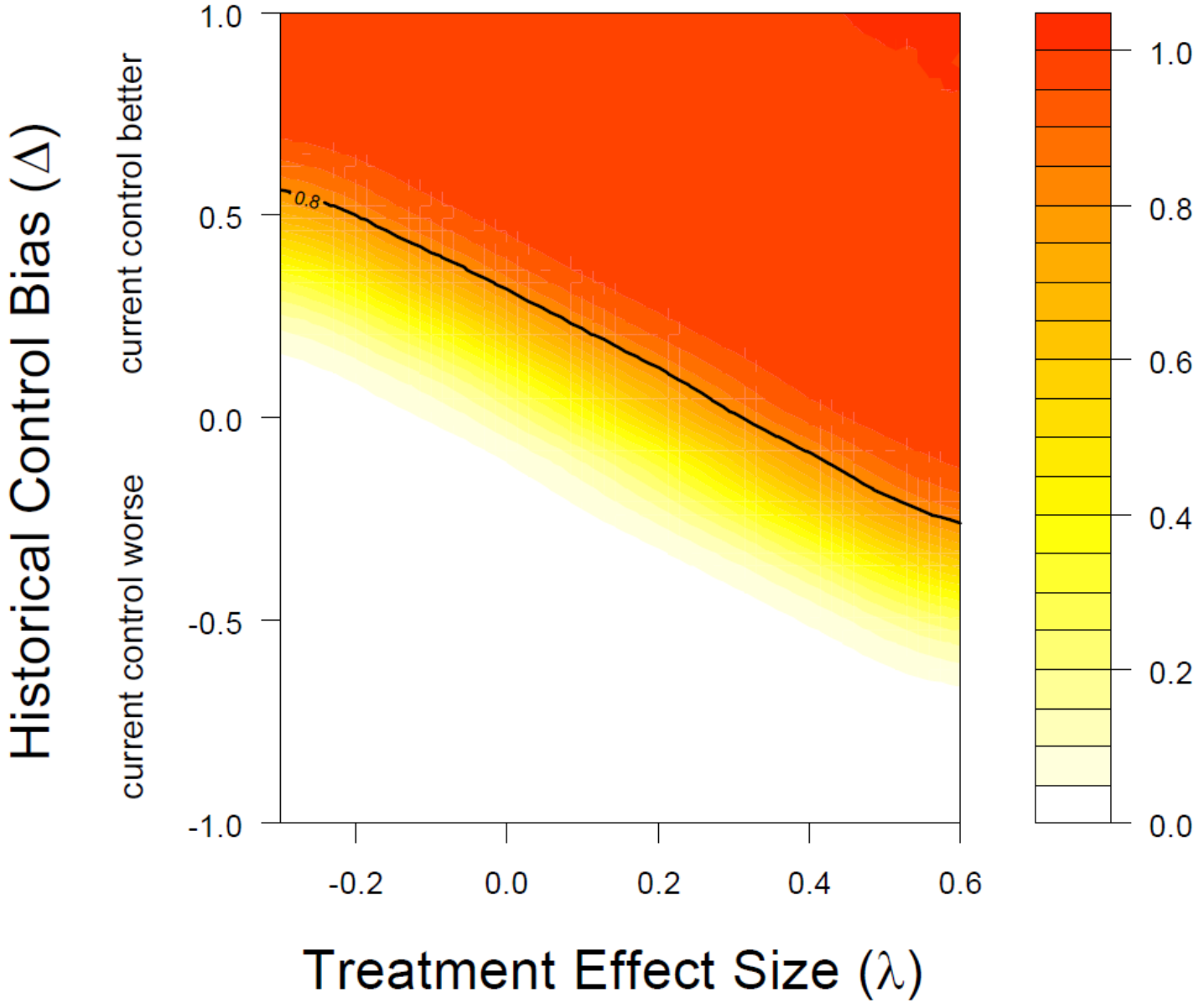
Exchangeability Assumptions Highly Sensitive to Bias



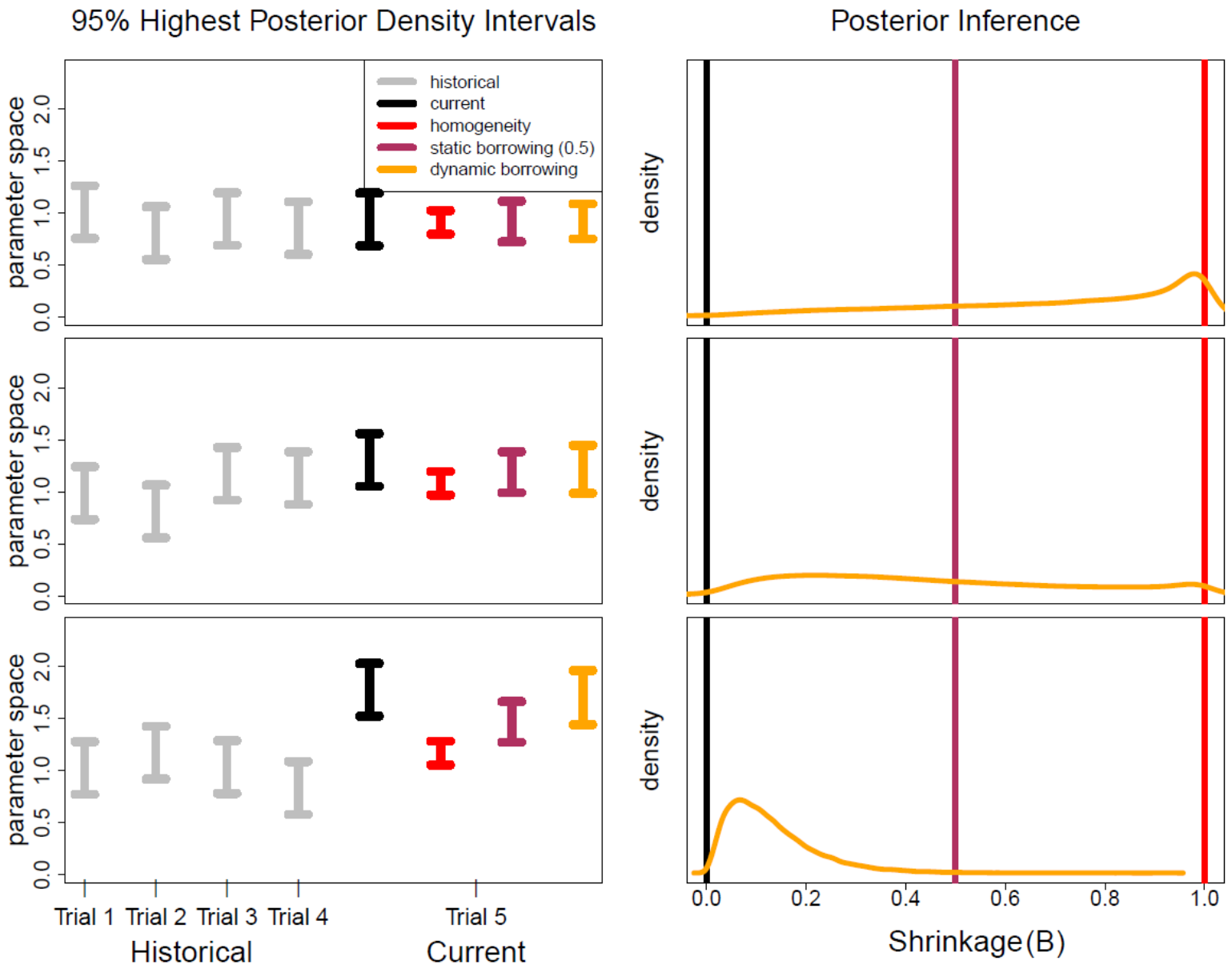




Power Surface Assuming Exchangeable Data



Hierarchical Modeling: Biased historical data



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)

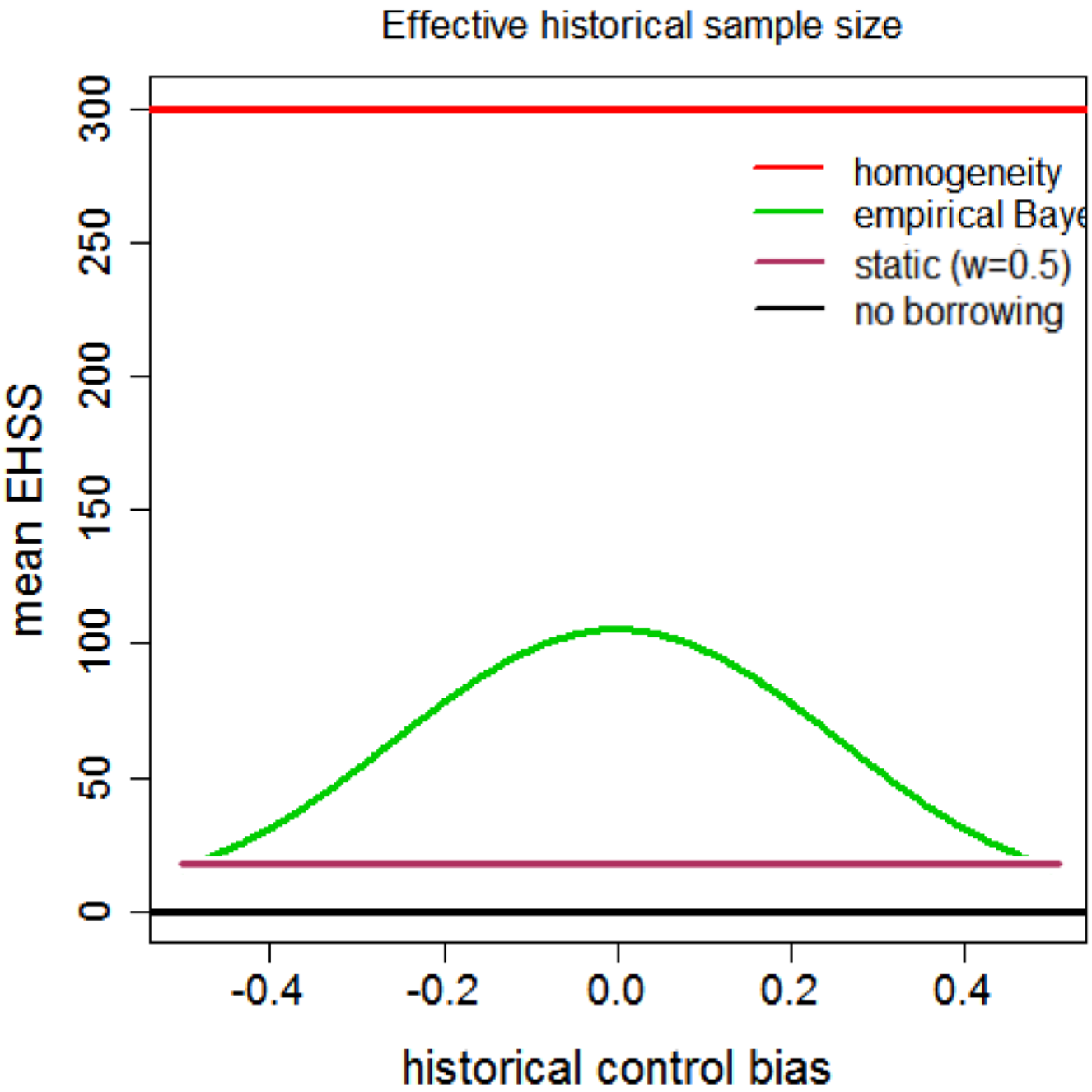
EHSS is a measure of "shrinkage"

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")


Effective historical sample size
mean EHSS
0
50
100
150
200
250
300
-0.4
-0.2
0.0
0.2
0.4
historical control bias
homogeneity
empirical Baye
static (w=0.5)
no borrowing

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

πB 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 $EHSS(t)$:

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

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 DA1, 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.

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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

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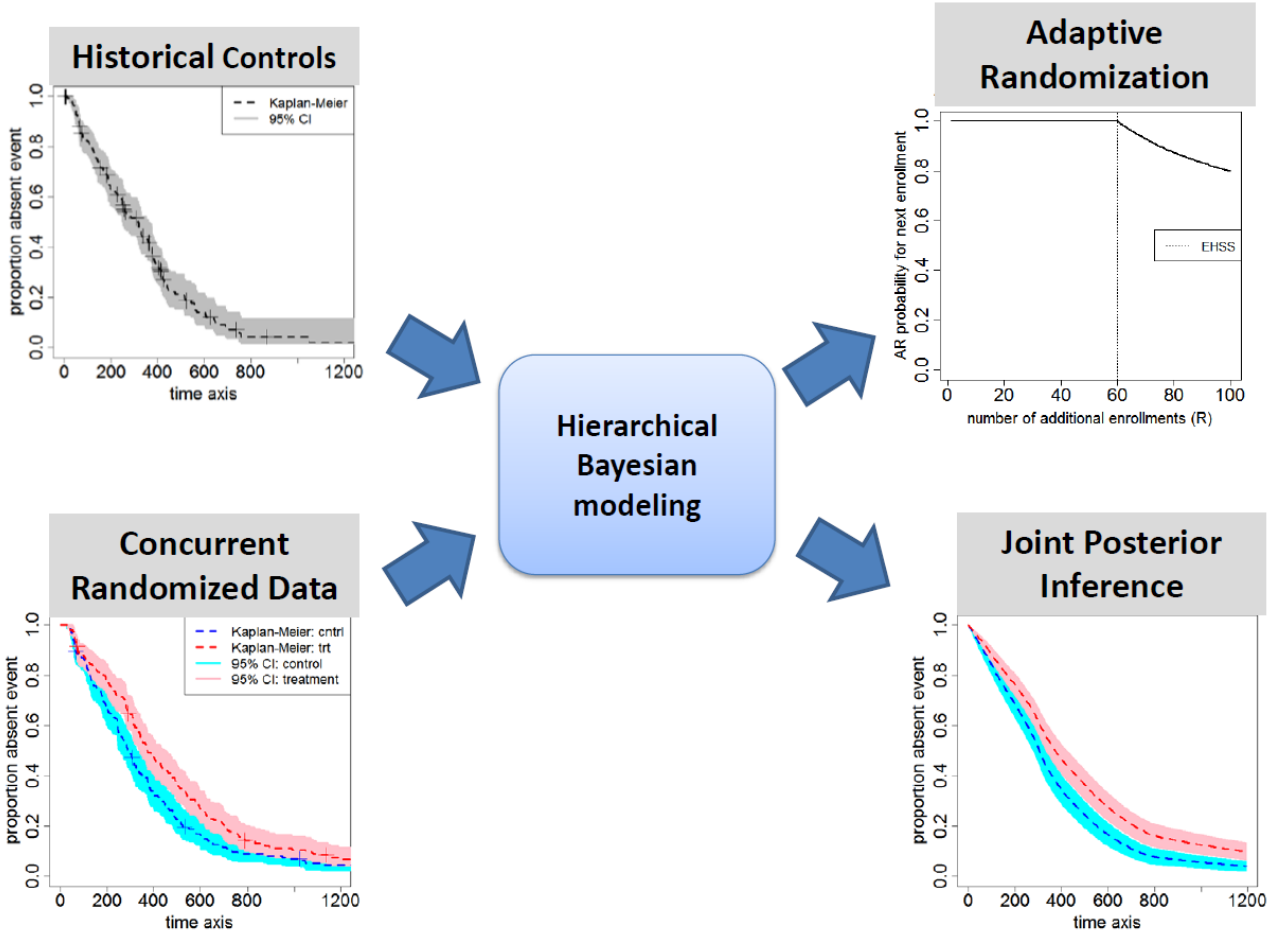
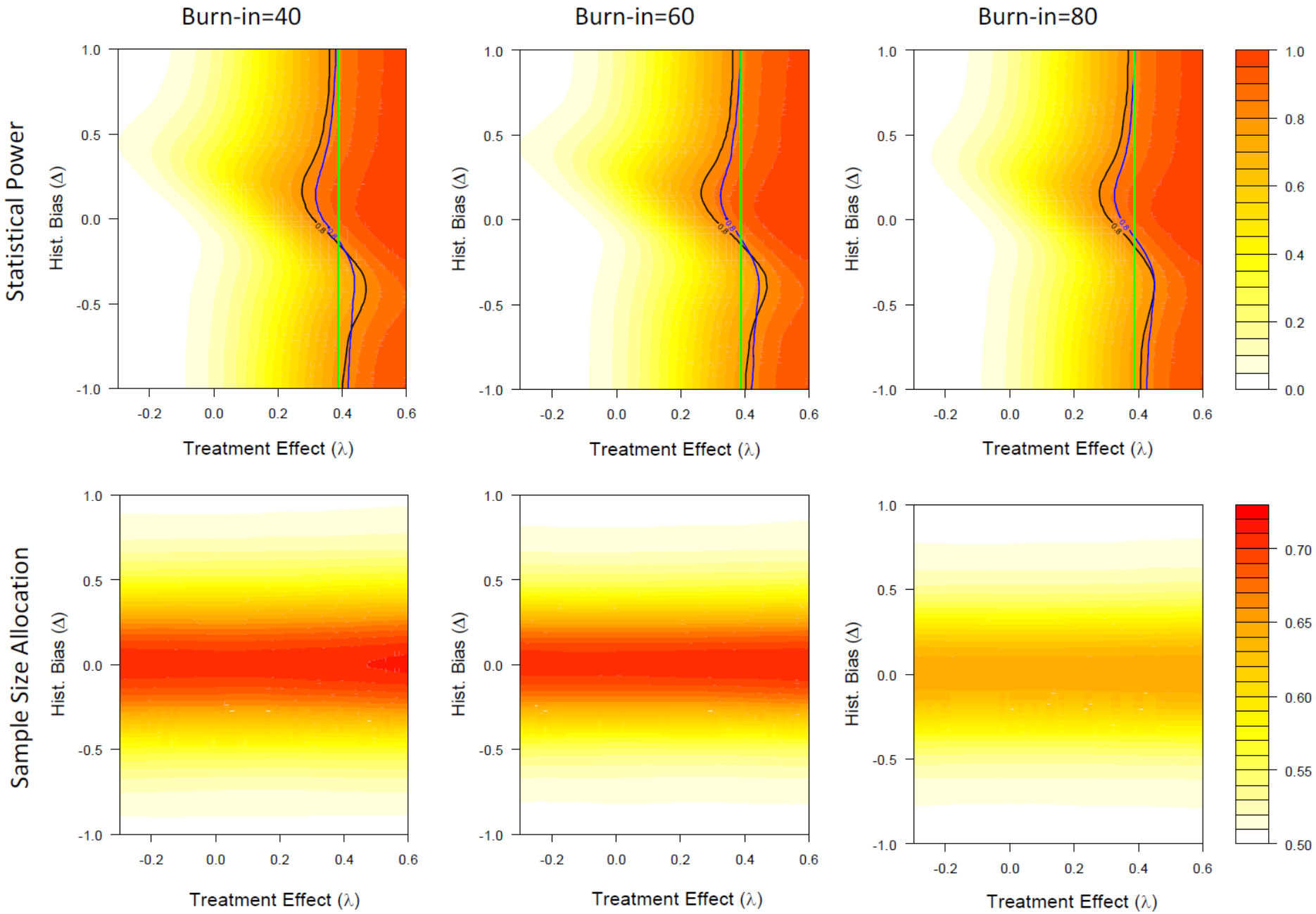
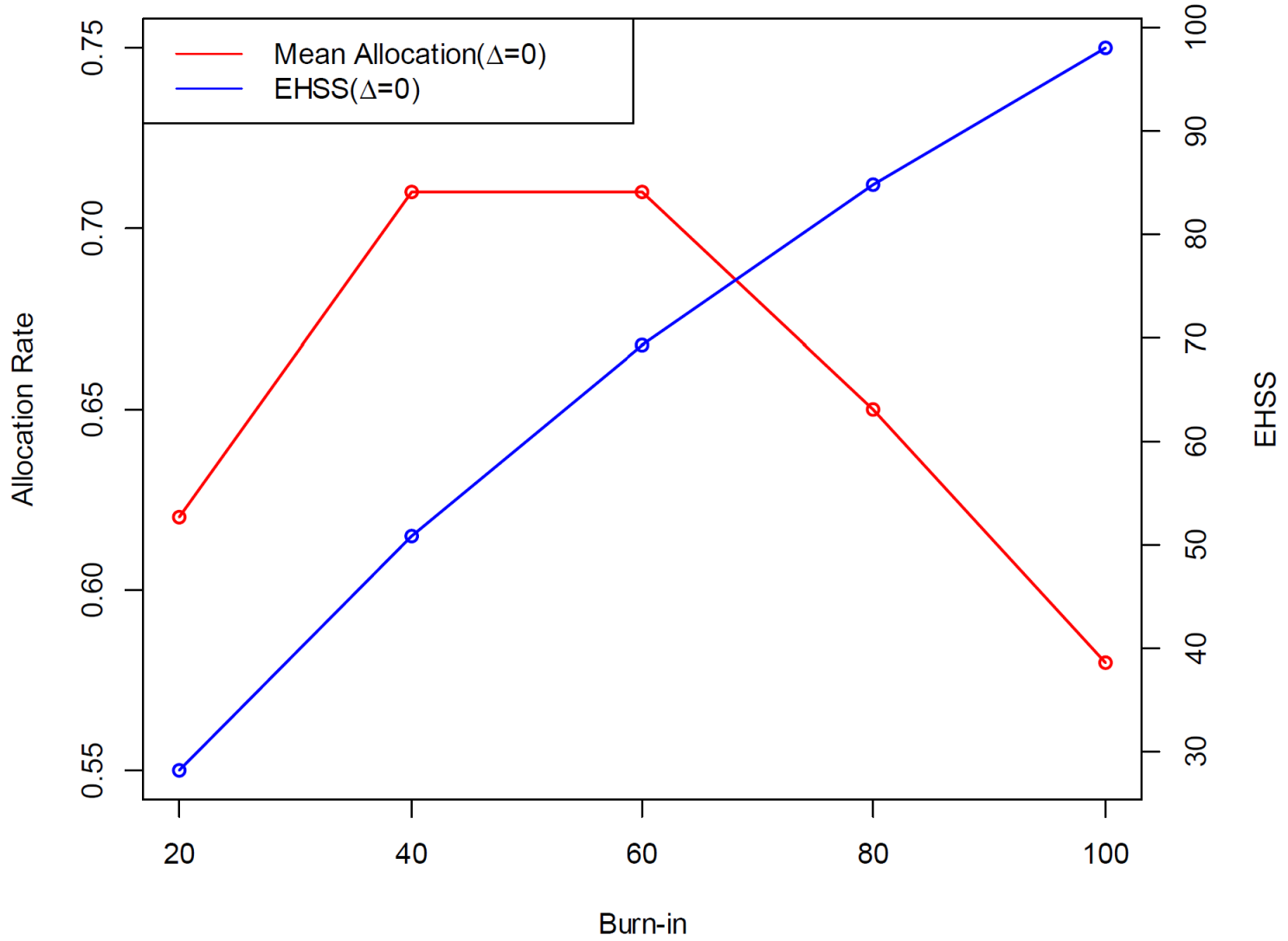
Expert in External Controls

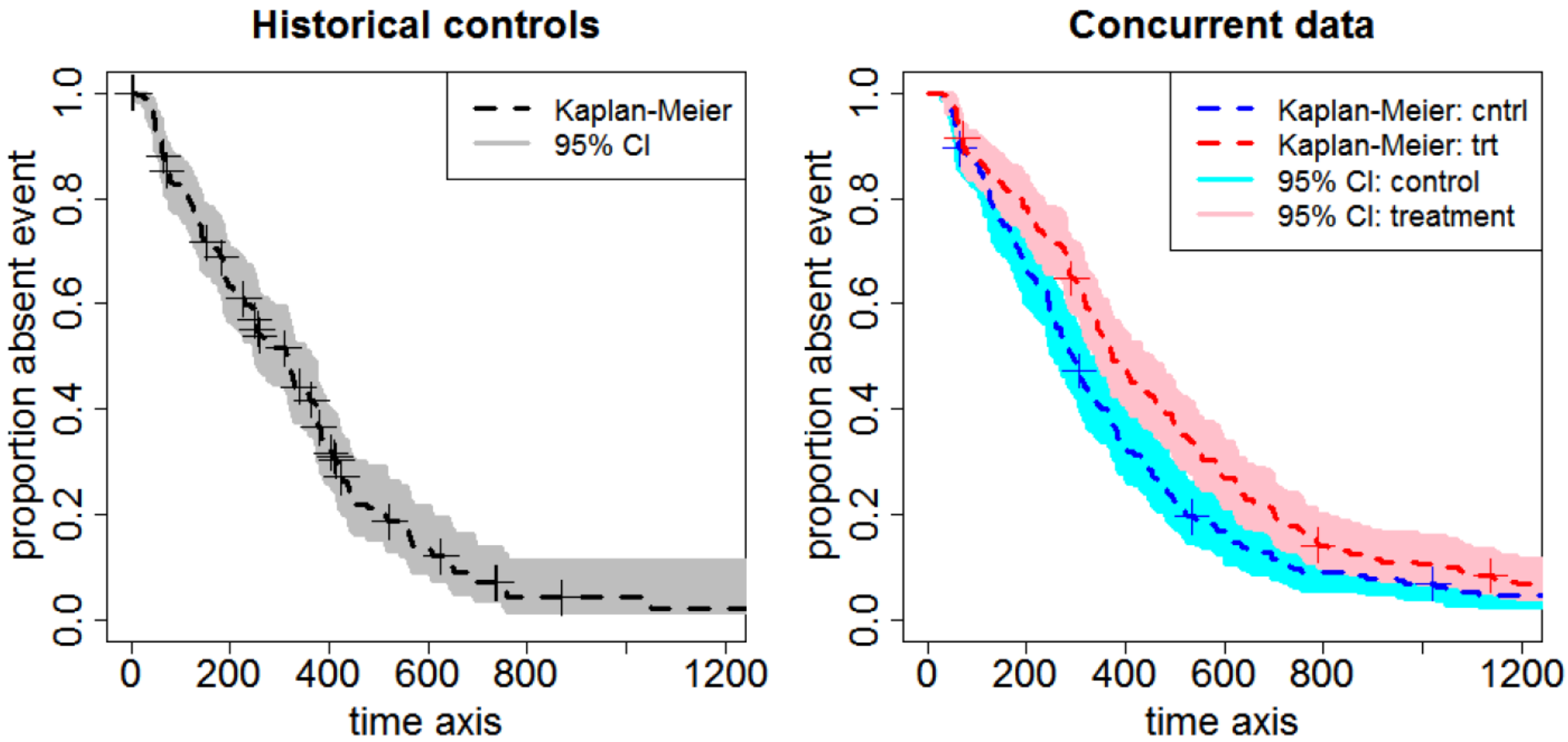
Multi-source Adaptive Randomization (Hobbs et al. 2013)




Burn-in=40
Burn-in=60
Burn-in=80
Statistical Power
Sample Size Allocation
Hist. Bias (Δ)
Treatment Effect (λ)
1.0
0.5
0.0
-0.5
-1.0
-0.2
0.0
0.2
0.4
0.6
0.8
0.70
0.65
0.60
0.55
0.50

Design Calibration for Single Interim Analysis





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 ξ, 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)

Parameter		Mean	SD	Mean HR (95% HPD)	Pr(HR<1 | Data)
ξ		-0.372	0.098	0.72(0.57-0.87)	0.999
		Mean (95% HPD)			
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

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

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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

Review Article | Published: 11 June 2020

Histology-agnostic drug development — considering issues beyond the tissue

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Nature Reviews Clinical Oncology **17**, 555–568(2020)

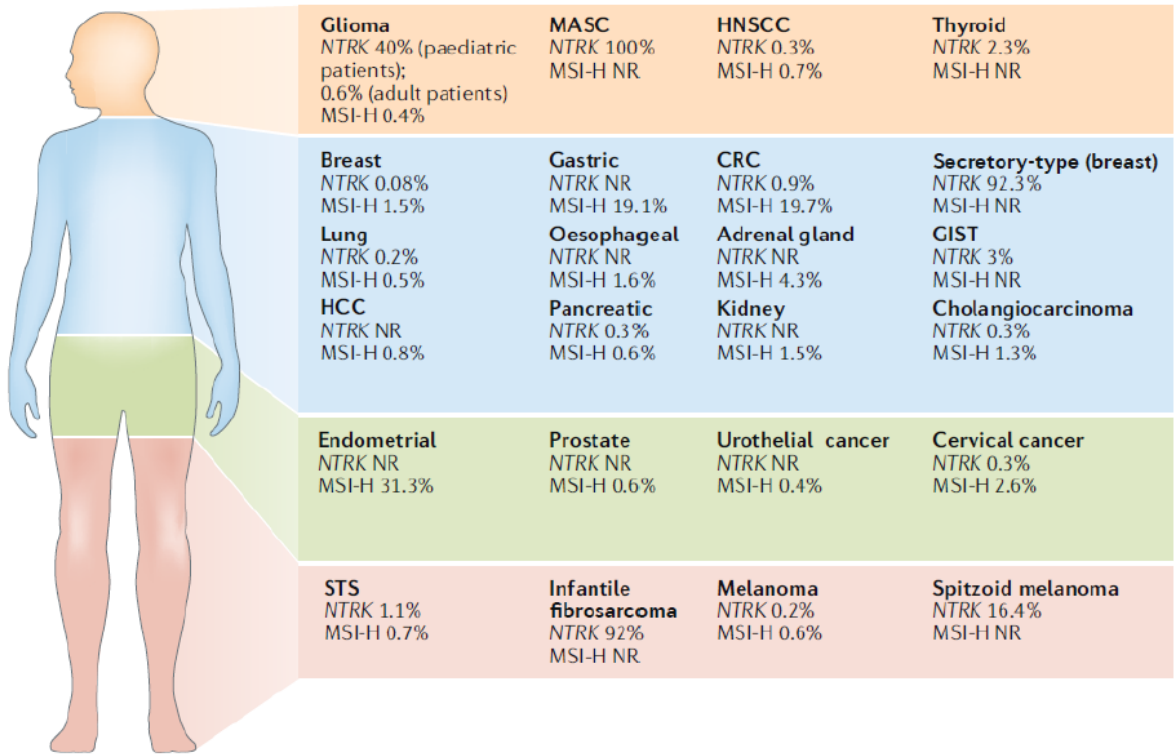

Fig. 2 | **Prevalence of specific alterations for which histology-agnostic drugs are approved across tumour types**[33,57,125,153–156]. *NTRK* gene fusions and microsatellite instability-high (MSI-H) or mismatch-repair deficiency (dMMR) phenotypes are present across multiple tumour types. Knowledge of the prevalence of these features in each tumour

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An American Society of Clinical Oncology Journal

TABLE 1. Summary of Select Oncology Basket Studies

Identifier	Drug	Target	Phase	Sample Size	No. of Histologies	Primary End Point	Statistical Analysis
NCT00154388[21]	Imatinib	KIT; PDGFRA/B	II	168	40	ORR	Pooled
NCT01226316[26]	Capivasertib	AKT1	I/II	58	14	Safety	Basket-independent
NCT01078662[27]	Olaparib	BRCA1/2	II	298	10	ORR	Pooled
NCT01524978[28]	Vemurafenib	BRAFV600	II	122	16	ORR	Basket-independent
NCT02628067[29]	Pembrolizumab	MSI-H/dMMR	II	233	27	ORR	Pooled
NCT02122913[30] NCT02637687[30] NCT02576431	Larotrectinib	NTRK	I/II	159	19	ORR	Pooled
NCT02091141[31]	Pertuzumab plus trastuzumab Erlotinib Vemurafenib Vismodegib	HER2 EGFR BRAF Hedgehog pathway	II	230	35	ORR	Basket-independent
NCT02097810[10] NCT02568267[10] EudraCT, 2012–000148–88[10]	Entrectinib	NTRK	I/II	54	19	ORR	Pooled
NCT02715284 [11]	Dostarlimab	MSI-H/dMMR status	I	106	14	ORR	Pooled
NCT02628067[32]	Pembrolizumab	TMB-H status	II	102	10	ORR	Pooled
NCT02693535[33]	Multiple[a]	Multiple[a]	II	Ongoing	12	ORR	Basket-independent
NCT01631552[34]	Sacituzumab govitecan	Trop-2	I/II	498	17	Safety and ORR	Basket-independent
NCT01953926[35]	Neratinib	HER2; EGFR exon 18	II	141	21	ORR	Basket-independent

Abbreviations: dMMR, XXX; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability high; ORR, overall response rate; TMB-H, high tumor mutational burden.

WHO CAN BE AVERAGED?

PRECISION MEDICINE FROM THE PERSPECTIVE OF DATA = ASCERTAINING STATISTICAL EXCHANGEABILITY

Received: 11 August 2017 | Revised: 17 March 2018 | Accepted: 8 June 2018
DOI: 10.1002/sim.7893

RESEARCH ARTICLE

WILEY Statistics in Medicine

Bayesian basket trial design with exchangeability monitoring

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Email: BPHobbs@gmail.com

Precision medicine endeavors to conform therapeutic interventions to the individuals being treated. Implicit to the concept of precision medicine is heterogeneity of treatment benefit among patients and patient subpopulations. Thus, precision medicine challenges conventional paradigms of clinical translational which have relied on estimates of population-averaged effects to guide clinical practice. Basket trials comprise a class of experimental designs used to study solid malignancies that are devised to evaluate the effectiveness of a therapeutic strategy among patients defined by the presence of a particular drug target (often a genetic mutation) rather than a particular tumor histology. Acknowledging the potential for differential effectiveness on the basis of traditional criteria for cancer subtyping, evaluations of treatment effectiveness are con-

The R Journal

Analyzing Basket Trials under Multisource Exchangeability Assumptions

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Yale University

Nan Chen
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Alexander M. Kaizer
University of Colorado

Xun Jiang
Amgen Inc.

H. Amy Xia
Amgen Inc.

Brian P. Hobbs
Cleveland Clinic

Abstract

Basket designs are prospective clinical trials that are devised with the hypothesis that the presence of selected molecular features determine a patient's subsequent response to a particular "targeted" treatment strategy. Basket trials are designed to enroll multiple clinical subpopulations to which it is assumed that the therapy in question offers beneficial efficacy in the presence of the targeted molecular profile. The treatment, however, may not offer acceptable efficacy to all subpopulations enrolled. Moreover, for rare dis-

The Single-Source Exchangeability Model

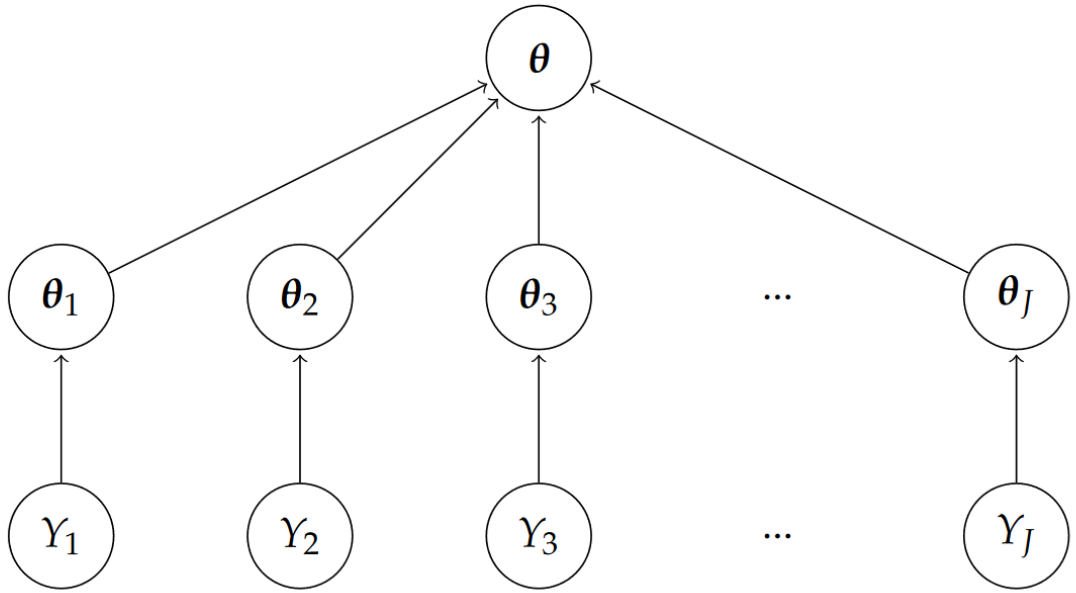
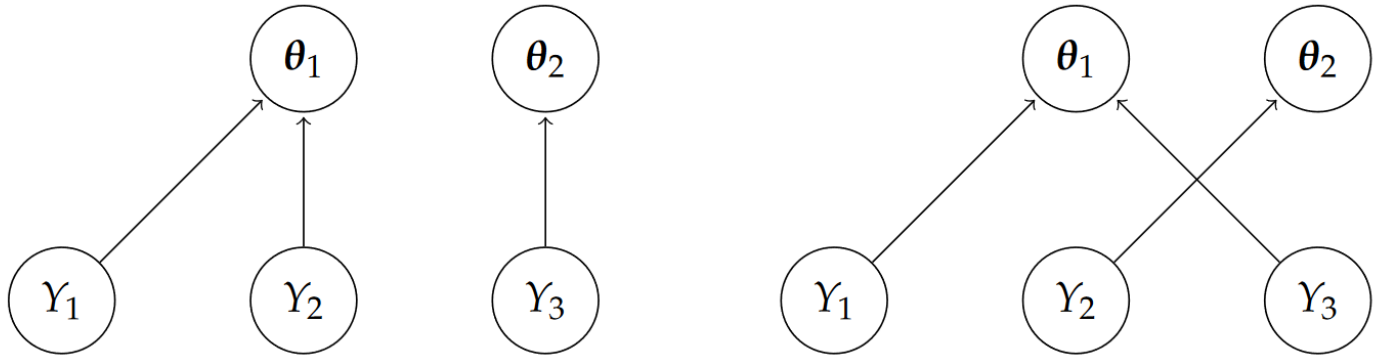


Figure 1: A conventional single-source Bayesian hierarchical model with J subtypes.

The symmetric MEM is the motivation and focus of the **basket** package. While SEMs are parameterized by a single set of parameters $\boldsymbol{\theta}$, the MEM may have up to J (the number of subtypes) sources of exchangeability with each set of data Y_j contributing to only one set of parameters. All possible combinations of exchangeability can be enumerated, denoted as K possible configurations $(\Omega_k, k = 1, ..., K)$.

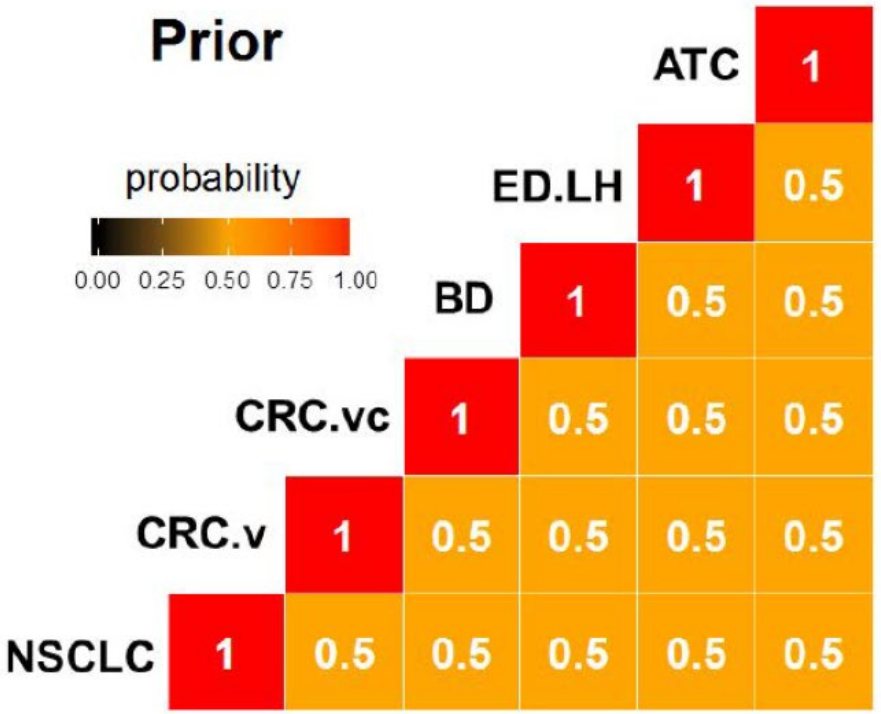


(a) Model where Y_1 and Y_2 are exchangeable. **(b)** Model where Y_1 and Y_3 are exchangeable.

Figure 2: Two example exchangeability configurations of the MEM.

Bayesian Basket Trial Design with Exchangeability Monitoring

Brian P. Hobbs[1] **and Rick Landin**[2]



Case Study Analysis: Vemurafenib non-melanoma basket trial

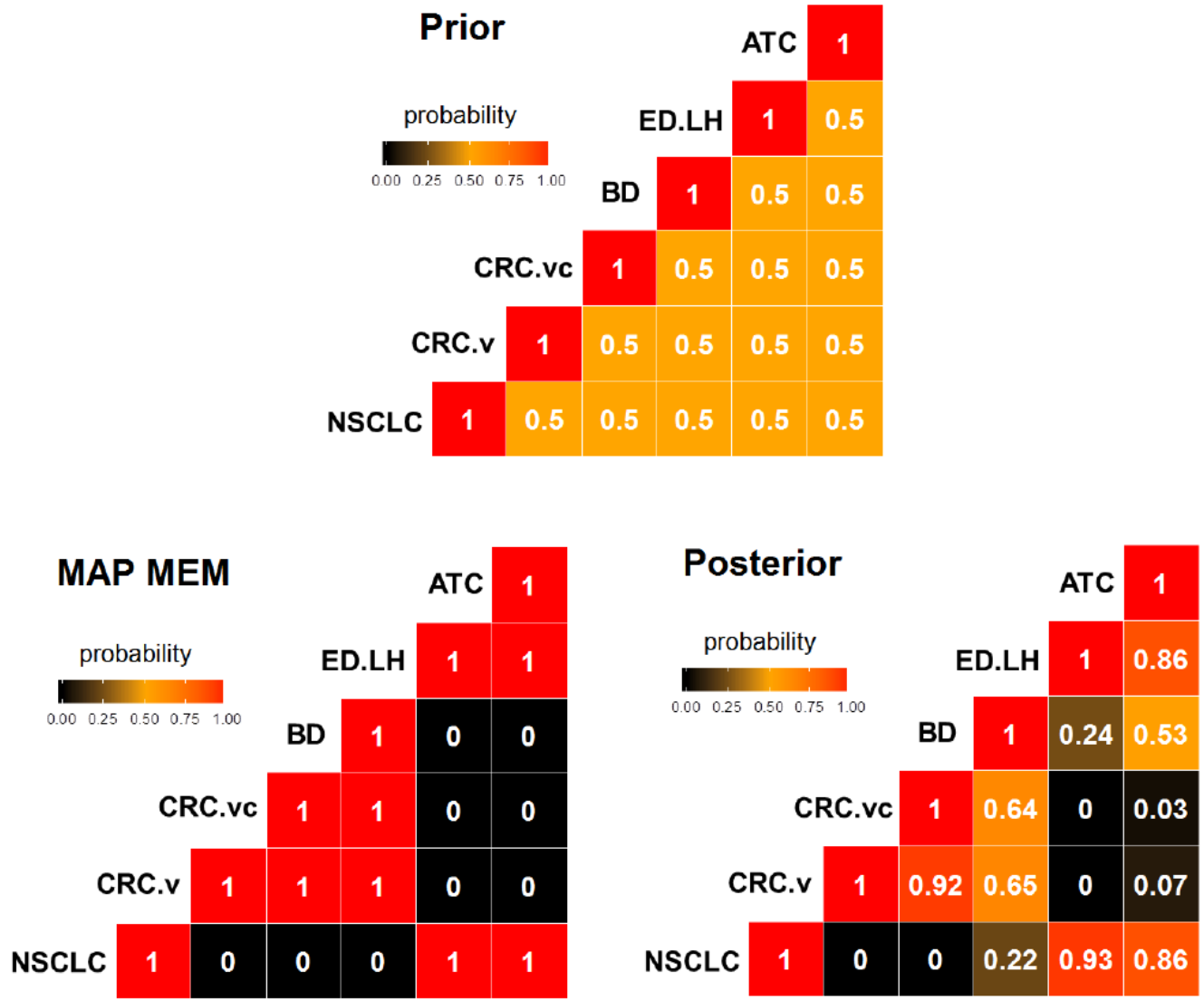


Figure 2. Prior, MAP, and PEP that result from Bayesian inference using the observed vemurafenib basket trial data

Review Article | Published: 11 June 2020

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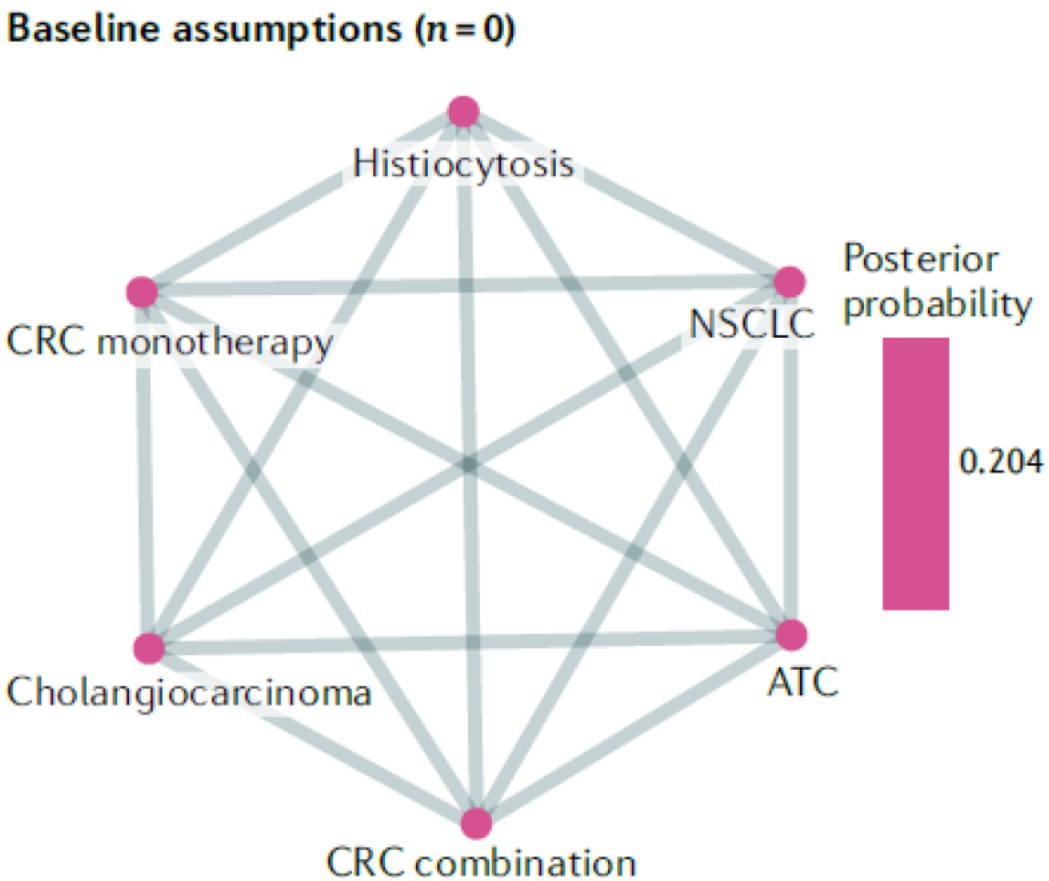

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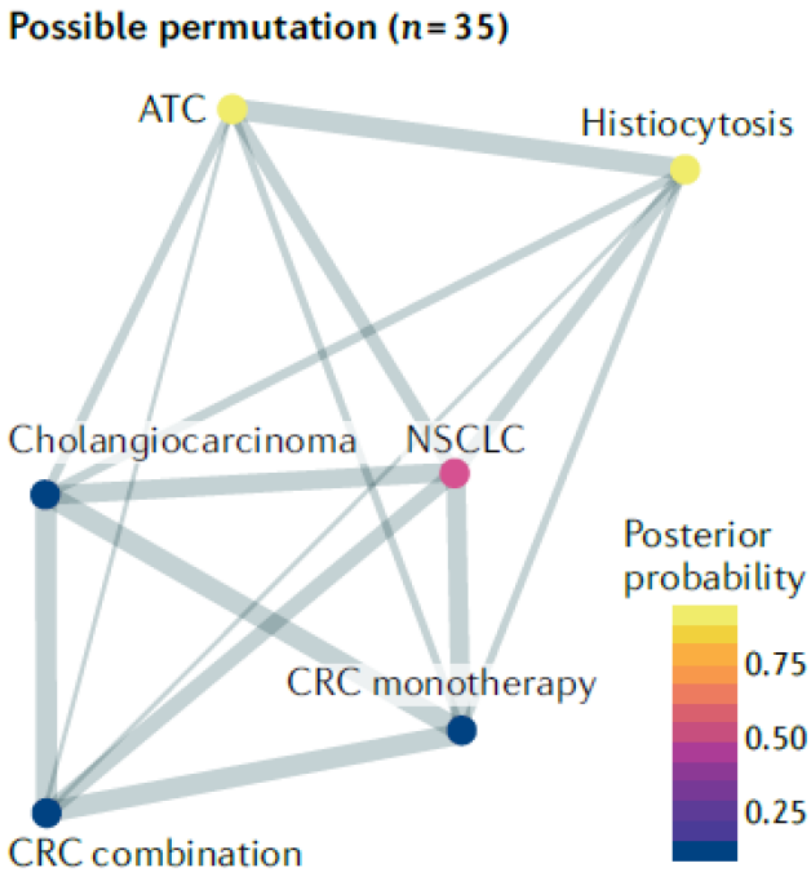

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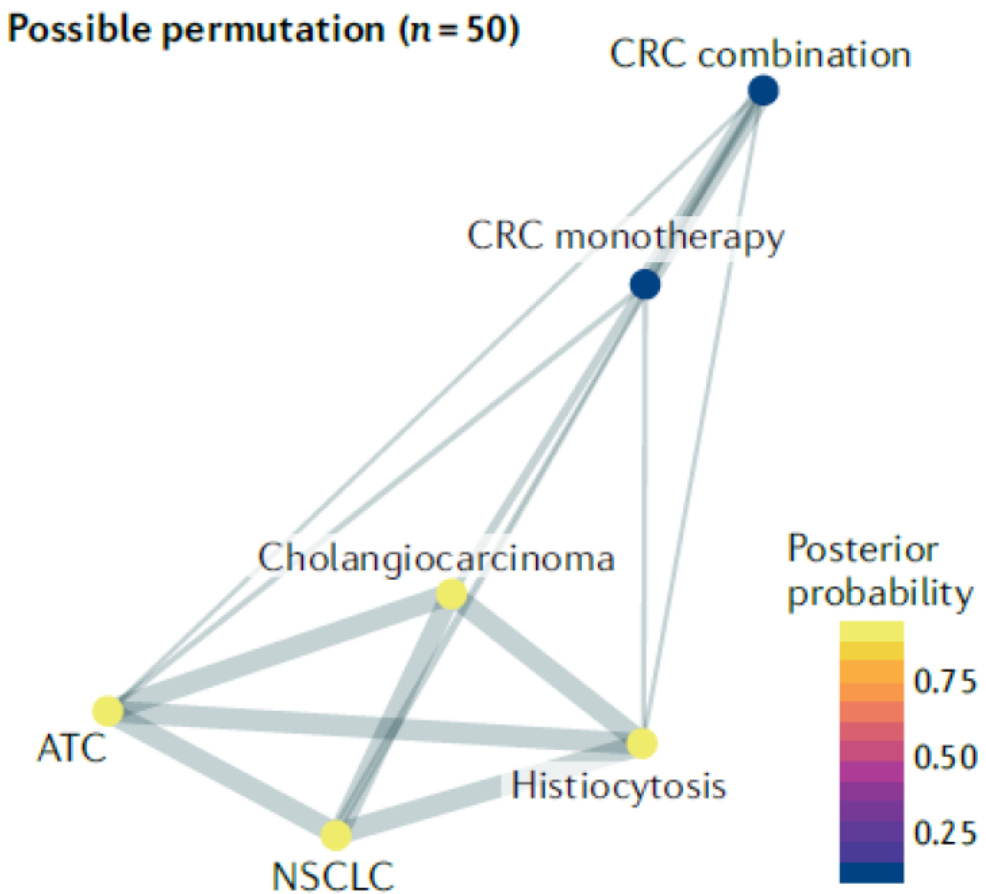

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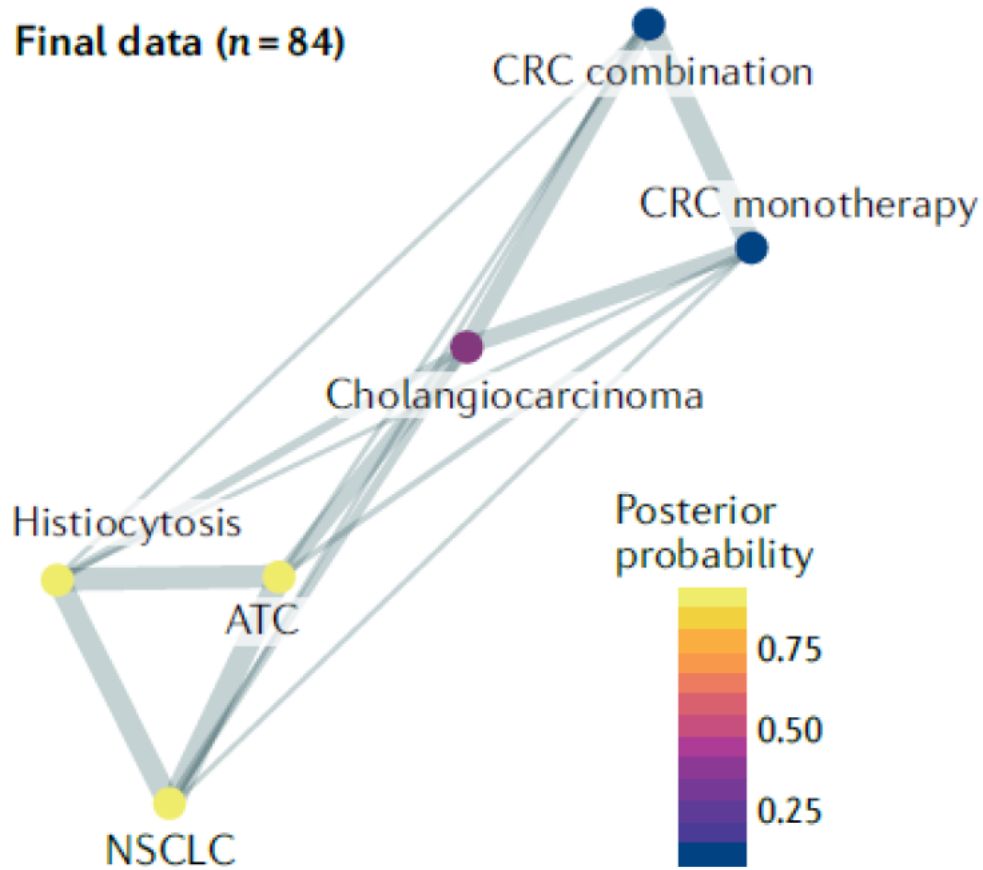

Network graph of SUMMIT results

```
plot_pep_graph(nerat_basket, pep_cutoff = 0.25)
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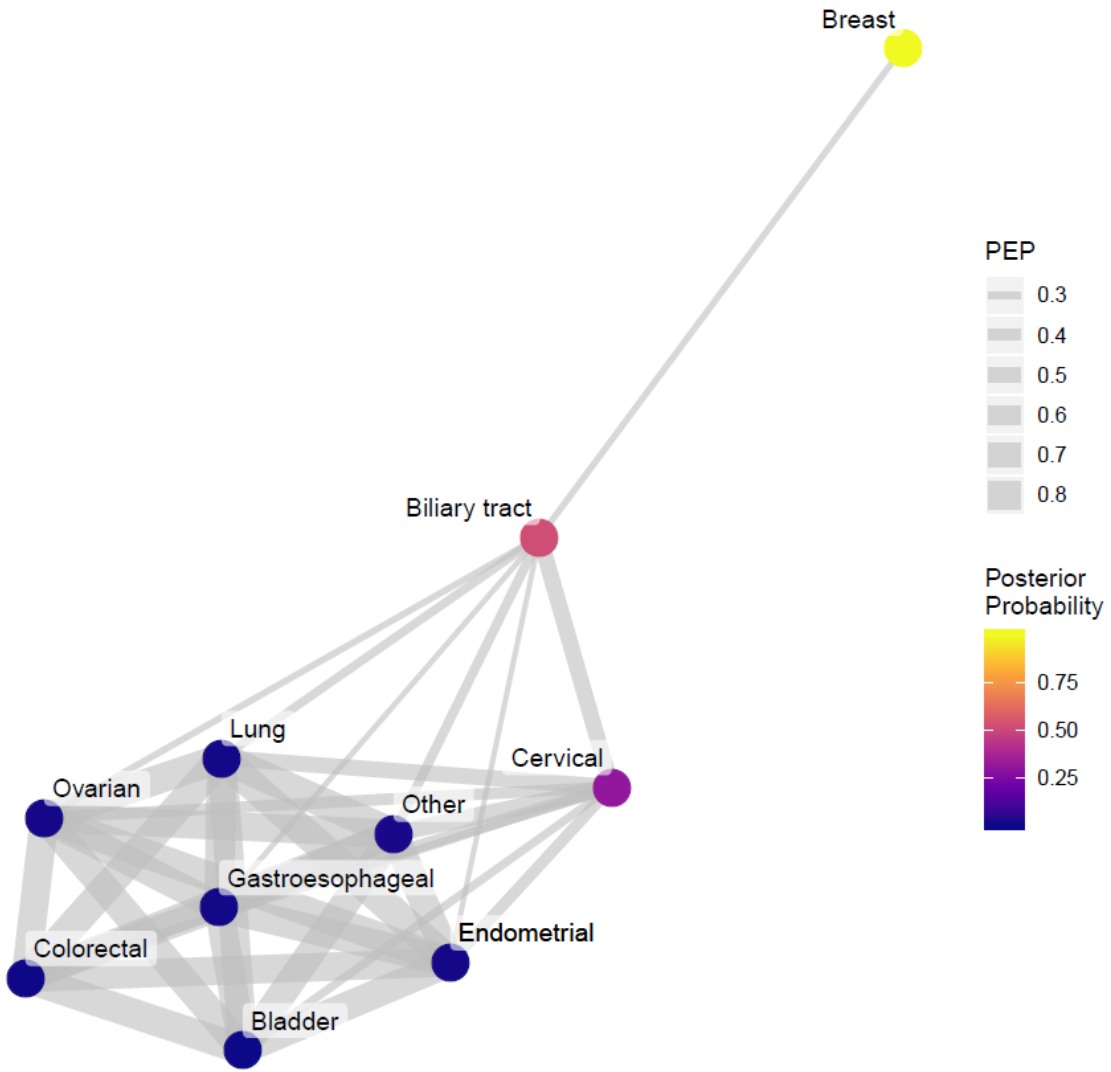

MULTI-SOURCE EXCHANGEABILITY MODELS (MEMS)

Bayesian models that allow for multiple "sources" of exchangeability

- Asymmetric settings (primary & supple cohorts); Kaizer et al. 2017, *Biostatistics*
- Symmetric settings (all cohorts primary) and sequential design; Hobbs and Landin 2018, *Stat in Med*
- Adaptive Platform Design; Kaizer et al. 2018, *Biometrics*
- Frequentist Trial Operating Characteristics; Kaizer et al. 2019, *JCO Precision Oncology*
- Open-source statistical software with the *Basket package;* Kane et al. 2020, *The R Journal*
- Multiple Indication Design Criteria; Kaizer et al. 2021, *SMMR*
- False Discovery Control; Zabor et al. 2022, *Clinical Trials*
- Sequential Master protocol; Kaizer et al. 2022, *PLOS One*

BIOTECH

FDA oncology chief aims to open u accelerated approval for earlier cancer treatment under 'Project FrontRunner'

By **Angus Liu** • Apr 6, 2022 11:15am

U.S. FDA | Richard Pazdur | Oncology drugs | accelerated approval

Cancer And Accelerated Approval: FDA To Crack Down On Single-Arm Trials, Refractory Disease Focus

10 Jun 2022 | **NEWS**

Executive Summary

US FDA cancer chief Rick Pazdur plans to send industry to 'rehab' with Project Frontrunner, which will push for development of cancer drugs in randomized controlled trials in earlier disease. Goal is to reduce time of uncertainty between accelerated approval and confirmatory evidence.

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

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

CLINICAL TRIALS

Clinical Trials
2021, Vol. 18(6) 706–710

DOI: 10.1177/17407745211050580
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SAGE

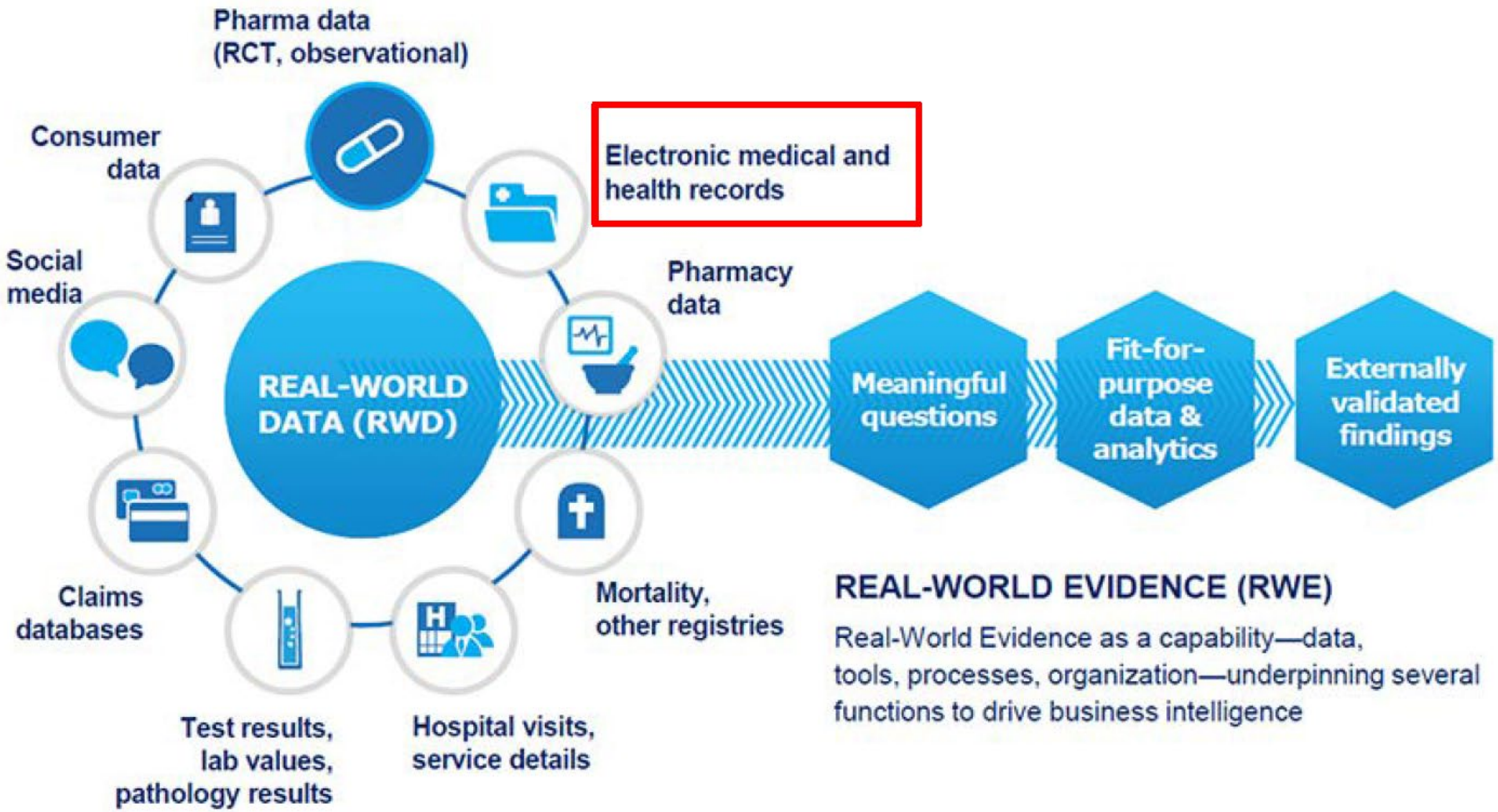
The U.S. Food and Drug Administration's Complex Innovative Trial Design Pilot Meeting Program: Progress to date

Dionne Price and John Scott

Abstract

Background: The Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research of the U.S. Food and Drug Administration have been leaders in advancing science to protect and promote public health by ensuring that safe and effective drugs and biological products are available to those who need them. Recently, new therapeutic discoveries, increased understanding of disease mechanisms, the need for innovation to optimally use resources, and global public health crises have led to an evolving drug development landscape. As a result, the U.S. Food and Drug Administration and medical product developers are faced with unique challenges and opportunities. The U.S. Food and Drug Administration is proactively meeting the challenges of this evolving landscape through various efforts, including the Complex Innovative Trial Design Pilot Meeting Program. Our focus, here, will be on the pilot meeting program.

What is real-world evidence?



REAL-WORLD EVIDENCE (RWE)

Real-World Evidence as a capability—data, tools, processes, organization—underpinning several functions to drive business intelligence

Atul Butte, MD, PhD, explores huge datasets to find life-saving patterns

A digital treasure hunter, Atul Butte spends his days diving into oceans of data in search of new ways to improve health and save lives. Teasing out hidden patterns and correlations, he is on an endless quest for fresh insights.

"Hiding in these seas of data is knowledge that could change a patient's life – or the entire world. There's priceless stuff out there. With a little funding, we can find it."
- Atul Butte, MD, PhD

A tsunami of medical data is crashing all around us. Since the advent of electronic medical records, virtually every patient leaves a detailed data trail. These days, everything gets saved. Prescriptions, test results, imaging studies, DNA sequences, clinical trials data, and more all end up in vast databases, contributing to a flood of information that's growing by a zettabyte (1021 bytes or a billion terabytes) every year.

Making sense of all this data and putting it to work for patients is no small task. That's where a visionary like Atul, supported by Stanford's world-class programs in computer science and quantitative analysis, has an edge. With a multidisciplinary crew of collaborators, Atul searches these seas of information for what he calls "biomedical moments."

These moments are tipping points – crucial times when things can either go well or wrong for patients – and precious insights often hide in the data surrounding them. "We want to know what will keep patients on the right track to a good outcome," Atul says, "and these moments tell us where to look."

Healthcare IT News TOPICS

Analytics

Atul Butte: Precision medicine makes doctors nervous

The noted physician, software engineer and open science champion said that the hardest part of big data is knowing what questions to ask and finding people capable of figuring that out.

By Tom Sullivan | June 14, 2016 | 01:11 PM

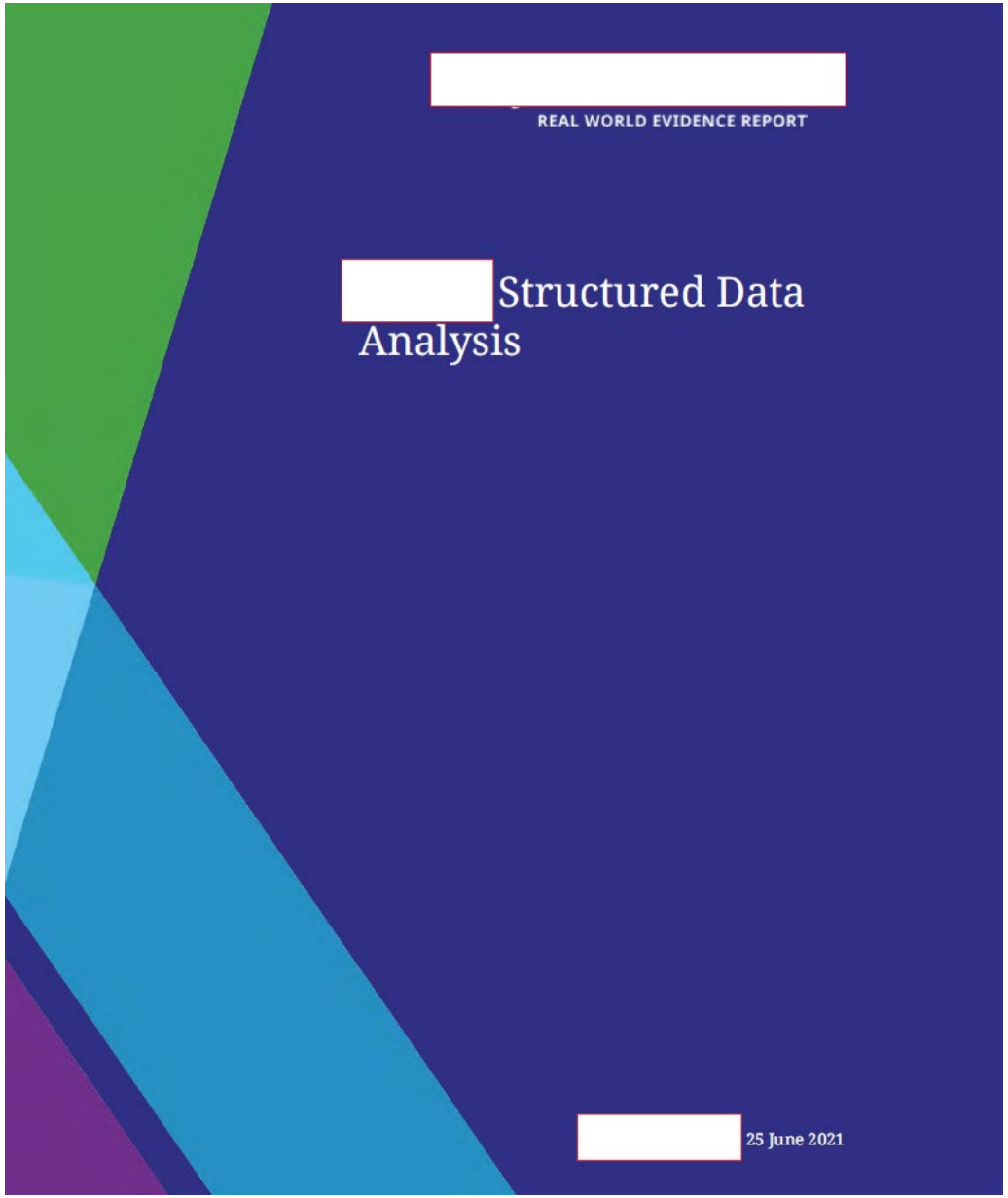
SAN FRANCISCO — The University of California at San Francisco is embarking on an ambitious project to track 15 million patients, map them, predict what will happen in 90 days and what could occur in one year to establish what Atul Butte, MD, described as the new definition of an accountable care organization.

Analytics, big data and ultimately precision medicine will figure prominently into that future state, just not likely overnight.

"Precision medicine makes doctors nervous because if we're moving into an era of precision medicine that means, by nature, what came before was not precise," Butte, who is director of UCSF's Institute for Computational Health Science, said here at the Big Data and Healthcare Analytics Forum.

"When I think of public big data like that, it's retroactive crowdsourcing," Butte said. "If a high school kid can do that, every scientist is going to have to be able to, as well."

Real-world data reports?



RWD and Regulators

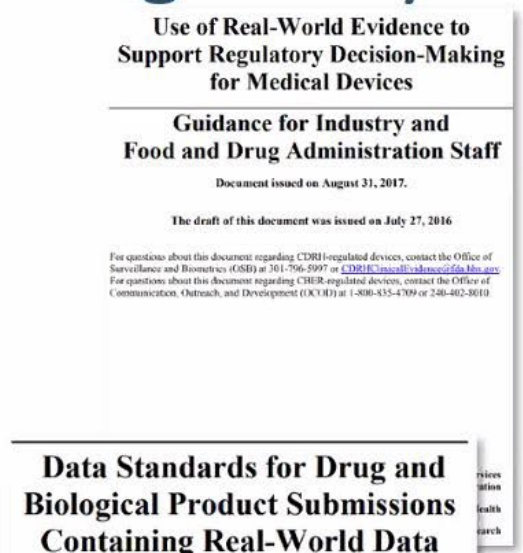
RWD can also be used to improve the efficiency of clinical trials, even if not used to generate RWE regarding product effectiveness. For example, RWD can help with:

- Generating hypotheses for testing in randomized controlled trials
- Identifying drug development tools (including biomarker identification)
- Assessing trial feasibility by examining the impact of planned inclusion/exclusion criteria in the relevant population, both within a geographical area or at a particular trial site
- Informing prior probability distributions in Bayesian statistical models
- Identifying prognostic indicators or patient baseline characteristics for enrichment or stratification
- Assembling geographically distributed research cohorts (e.g., in drug development for rare diseases or targeted therapeutics)

"As the breadth and reliability of RWE increases, so do the opportunities for FDA to make use of this information."

Scott Gottlieb, FDA Commissioner
National Academies of Science, Engineering, and Medicine,
Examining the Impact of RWE on Medical Product Development,
September 19, 2017

Regulatory Environment for using RWD/RWE



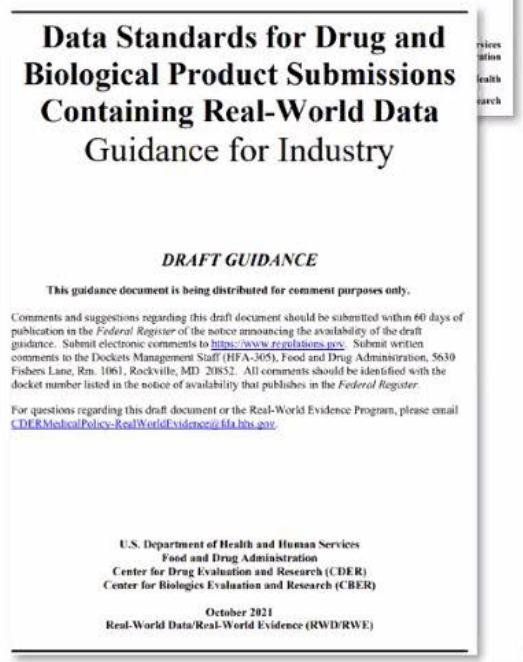
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHCenterEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.



Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Guidance for Industry

DRAFT GUIDANCE

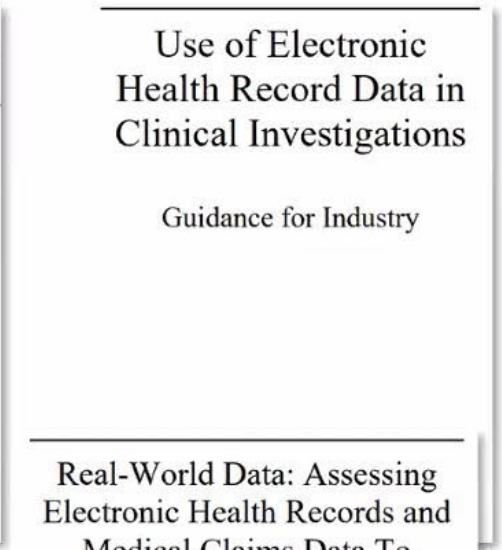
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the Real-World Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov.

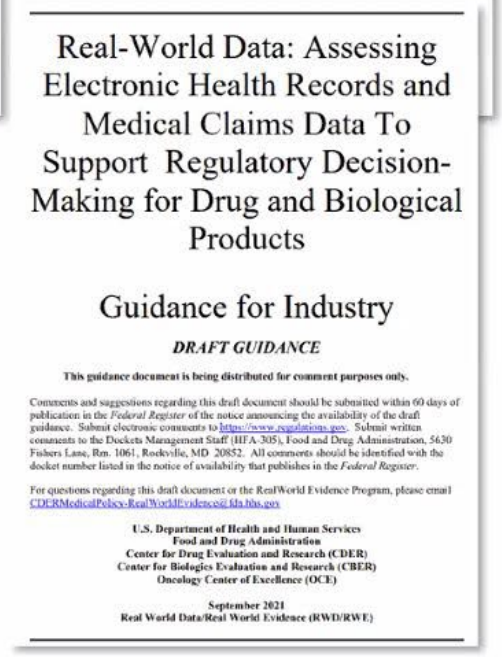
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2021
Real-World Data/Real-World Evidence (RWD/RWE)



Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry



Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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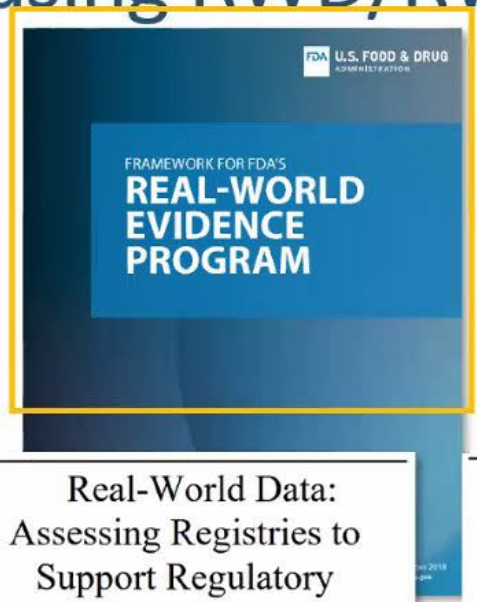
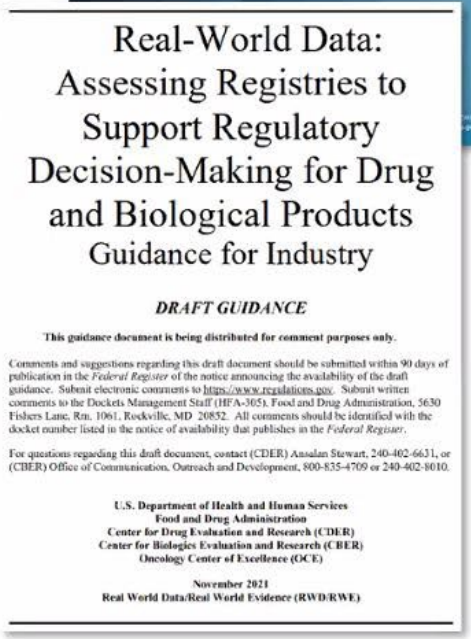
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2021
Real World Data/Real World Evidence (RWD/RWE)





Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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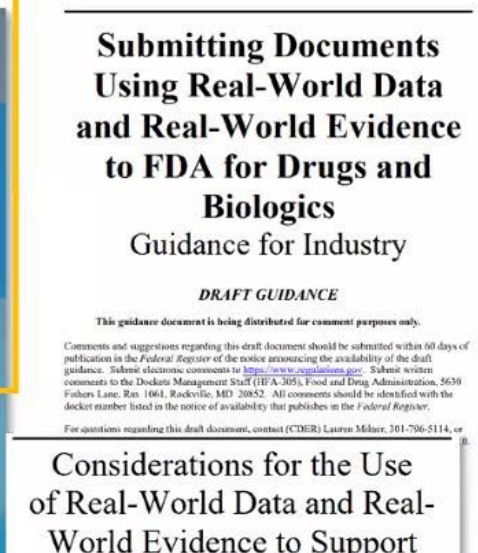
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Anselan Stewart, 240-402-6631, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)
Oncology Center of Excellence (OCE)

November 2021
Real World Data/Real World Evidence (RWD/RWE)



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

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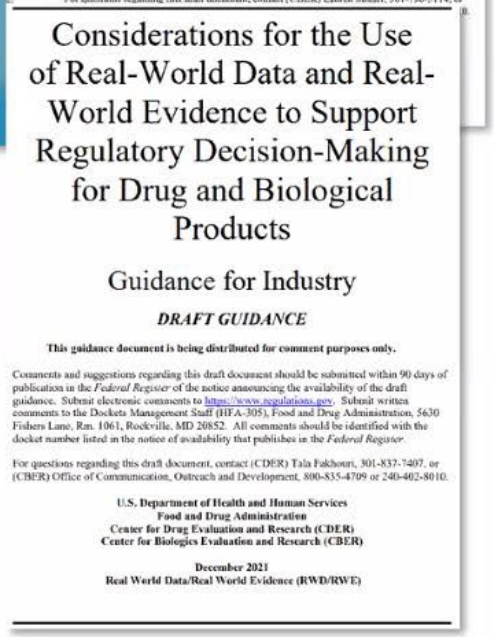
For questions regarding this draft document, contact (CDER) Lauren Meher, 301-796-5114, or



Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

December 2021
Real World Data/Real World Evidence (RWD/RWE)

The standard for drug approval remains the same

- The basis for approval remains the same (Section 314.50, CFR)
  - “substantial evidence that the drugs will have the effect”
  - “adequate and well-controlled clinical investigations”

- Regulatory agencies exercise great flexibility to address practical and unmet medical needs, e.g. considering
  - rarity of the disease
  - lack of a suitable control

- Issues confronting the use of RWD: **Data quality, Bias/Confouding, Heterogeneity**

Challenges with EMR data for Precision Oncology

Data Reliability/Quality

a) Is the EMR data reliable within academic medical centers, what about community?
b) To what extent are basic clinical prognostic attributes captured (T-stage, N-stage, histology, line of therapy, time since last platinum-based chemotherapy)

Patient Identification

a) FDA approved targeted agents: EGFR, ALK, ROS1, BRAF, MET, RET, KRAS G12C, and a tumor agnostic designation for NTRK
b) wide variation between clinical settings in rates & type of testing
c) 59% of academic practices using multigene panels, while only 28% of community practices
d) complete recommendation guided testing was only 18% in 2018

Endpoints

a) Tumor response?
b) Real-world counterparts for OS, PFS, TTP

Real-World Endpoint Recommendations

ARTICLE

The Friends of Cancer Research Real-World Data Collaboration Pilot 2.0: Methodological Recommendations from Oncology Case Studies

Donna R. Rivera[1], Henry J. Henk[2], Elizabeth Garrett-Mayer[3], Jennifer B. Christian[4], Andrew J. Belli[5], Suanna S. Bruinooge[3], Janet L. Espirito[6], Connor Sweetnam[7], Monika A. Izano[7], Yanina Natanzon[8], Nicholas J. Robert[6], Mark S. Walker[8], Aaron B. Cohen[9], Marley Boyd[6], Lindsey Enewold[10], Eric Hansen[5], Rebecca Honnold[11], Lawrence Kushi[12], Pallavi S. Mishra Kalyani[1], Ruth Pe Benito[11], Lori C. Sakoda[12], Elad Sharon[10], Olga Tymejczyk[9], Emily Valice[12], Joseph Wagner[4], Laura Lasiter[13] and Jeff D. Allen[13,*]

The purpose of this study was to evaluate the potential collective opportunities and challenges of transforming real-world data (RWD) to real-world evidence for clinical effectiveness by focusing on aligning analytic definitions of oncology end points. Patients treated with a qualifying therapy for advanced non-small cell lung cancer in the frontline setting meeting broad eligibility criteria were included to reflect the real-world population. Although a trend toward improved outcomes in patients receiving PD-(L)1 therapy over standard chemotherapy was observed in RWD analyses, the magnitude and consistency of treatment effect was more heterogeneous than previously observed in controlled clinical trials. The study design and analysis process highlighted the identification of pertinent methodological issues and potential innovative approaches that could inform the development of high-quality RWD studies.

Table 1 Harmonized definitions employed in the pilot project

Term	Harmonized definition	Decision impact
Population		
Advanced NSCLC	All data sources had the ability to identify patients diagnosed with NSCLC. Evidence of advanced disease was defined as either stage IIIB, IIIC, or IV NSCLC or early-stage (stages I, II, and IIIA) NSCLC with a recurrence or progression at initial diagnosis.	Including patients diagnosed early stage (stages I, II, and IIIA) NSCLC with a recurrence or progression to advanced or metastatic status improved sample size for analysis but created a less homogeneous population of both newly diagnosed and previously treated (vs. patients newly diagnosed lung cancer).
Frontline	Patients were required to have no evidence of treatment in 180 days before the date of diagnosis and evidence of an eligible treatment within 120 days after diagnosis	Patients who have delays to treatment initiation would not be included.
Histologic subtype	Histology was not required for inclusion	Histology was not universally collected, although subanalysis feasible. Results reflected overall aNSCLC trends but were less specific to a histology subtype.
Eligibility criteria	The study population was not limited to those meeting eligibility criteria common for inclusion in a clinical trial (e.g., kidney function, performance status)	Data on organ function and performance status at or prior to treatment initiation was not often available or difficult to ascertain in RWD sources, although subanalysis was feasible. The population may be less like the RCT population(s).
Regimens		
Drugs	The following medications were included representing traditional chemotherapy or IO given after the date of diagnosis: cisplatin/carboplatin, oxaliplatin, or nedaplatin with pemetrexed, paclitaxel, nab-paclitaxel, or gemcitabine; atezolizumab, nivolumab, or pembrolizumab. Oral agents were not included.	Regimens are subject to misclassification, particularly in the doublet chemotherapy cohort. Patients starting on a PD-(L)1 should not be ALK or EFGR positive.
Frontline (first line regimen) assignment	Frontline regimen was defined as all administered agents received within 30 days following the day of first infusion.	Misclassification or omission of patients with delays to full treatment initiation in the first 30 days was possible. This would not impact the PD-(L)1 monotherapy cohort, as additional therapy would not be expected.

Term	Harmonized definition	Decision impact
End points		
rwOS	Length of time from the date of treatment initiation to the date of death or end of follow-up; or end of study	Date of initiation may bias toward slightly shorter event times compared with clinical trials which can use date of randomization or enrollment instead. Missing events, on average, tend to make survival outcomes look better than in trials, especially if missingness is not independent of timing of death events.
rwTTNT	Length of time from the date of treatment initiation to the date of the next systemic treatment. When subsequent treatment is not received (e.g., continuing current treatment or disenrollment not due to confirmed death), patients were censored at their last known activity.	Missingness for subsequent treatment, including receiving treatment outside the system of capture is a limitation. This measure is also affected by the clinical guideline recommendations for administration of treatment cycles which can vary by regimen and has to be evaluated for comparability prior to the study to ensure appropriate interpretation.
rwTTD	Length of time from the date of treatment initiation to the date of patient treatment discontinuation the. The study treatment discontinuation date was defined as the last administration or noncancelled order of a drug contained within the regimen. Discontinuation was defined as having a subsequent systemic therapy after the initial regimen, having a gap of more than 120 days with no systemic therapy following the last administration, or having a date of death while on the initial regimen. Patients without a discontinuation were censored at the end of follow-up.	At the patient level, TTD is associated with PFS across therapeutic classes.[21]
rwTTP	Progression was omitted as claims-based algorithms are inadequate and among the EHRs progression events are not consistently captured in structured data. Unlike in clinical trials, there is not a uniform criterion (e.g., RECIST) in the off-protocol setting for determination of disease progression.	As TTP and PFS are accepted outcomes in clinical trials, comparison of these outcomes to randomized trials of similar regimens were limited by the data available.

Leveraging digitized historical trial data

Sunday, Mar 7, 2021

Genentech Provides Update on Tecentriq U.S. Indication in Prior-Platinum Treated Metastatic Bladder Cancer

South San Francisco, CA -- March 7, 2021 --

Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), today announced that the company is voluntarily withdrawing the U.S. indication for Tecentriq® (atezolizumab) in prior-platinum treated metastatic urothelial carcinoma (mUC, bladder cancer). This decision was made in consultation with the U.S. Food and Drug Administration (FDA) as part of an industry-wide reviev confirmatory trials that have not met their primary endp approvals. Genentech will work with the FDA over the withdrawal process. This decision does not affect other Genentech is notifying healthcare professionals about t treated with Tecentriq for prior-platinum treated mUC healthcare provider.

Durvalumab FDA indication for bladder cancer voluntarily withdrawn

February 22, 2021
Jason M. Broderick

The withdrawal comes after the confirmatory phase 3 DANUBE trial missed its primary end points.

AstraZeneca has voluntarily withdrawn the FDA indication for the PD-L1 inhibitor durvalumab (Imfinzi) for use in previously treated patients with locally advanced or metastatic bladder cancer.[1]

Durvalumab received an accelerated approval from the FDA for this indication in May 2017 based on the single-arm phase 1/2 Study 1108.[2] However, an FDA accelerated approval is contingent upon the results of a confirmatory trial, and in November 2020, AstraZeneca reported that the phase 3 DANUBE trial exploring durvalumab in frontline urothelial cancer missed its primary end points.[3]

"The science of immunotherapy has moved swiftly over the past few years, bringing new options to patients at an unprecedented pace. While the withdrawal in previously treated metastatic bladder cancer is disappointing, we respect the principles FDA set out when the accelerated approval pathway was founded and remain committed to bringing new and innovative options to patients. In the last three years, Imfinzi has become an important standard of care in multiple lung cancer settings, an area of considerable focus for AstraZeneca," Dave Fredrickson, executive vice president, Oncology Business Unit, AstraZeneca, stated in a press release.

Wednesday, May 18, 2016

FDA Grants Genentech's Cancer Immunotherapy TECENTRIQ™ (atezolizumab) Accelerated Approval for People with a Specific Type of Advanced Bladder Cancer

- **First and only anti-PDL1 cancer immunotherapy approved by the FDA**
- **First FDA-approved treatment for people with a specific type of bladder cancer in more than 30 years**

South San Francisco, CA -- May 18, 2016 --

Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), today announced that the U.S. Food and Drug Administration (FDA) granted accelerated approval to TECENTRIQ™ (atezolizumab) for the treatment of people with locally advanced or metastatic urothelial carcinoma (mUC) who have disease progression during or following platinum-based chemotherapy, or whose disease has worsened within 12 months of receiving platinum-based chemotherapy before surgery (neoadjuvant) or after surgery (adjuvant). Urothelial carcinoma accounts for 90 percent of all bladder cancers and can also be found in the renal pelvis, ureter and urethra.

Interpretation Atezolizumab showed durable activity and good tolerability in this patient population. Increased levels of PD-L1 expression on immune cells were associated with increased response. This report is the first to show the association of TCGA subtypes with response to immune checkpoint inhibition and to show the importance of mutation load as a biomarker of response to this class of agents in advanced urothelial carcinoma.

Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial

Thomas Powles, Ignacio Durán, Michiel S van der Heijden, Yohann Loriot, Nicholas J Vogelzang, Ugo De Giorgi, Stéphane Oudard, Margitta M Retz, Daniel Castellano, Aristotelis Bamias, Aude Fléchon, Gwenaëlle Gravis, Syed Hussain, Toshimi Takano, Ning Leng, Edward E Kadel III, Romain Banchereau, Priti S Hegde, Sanjeev Mariathasan, Na Cui, Xiaodong Shen, Christina L Derleth, Marjorie C Green, Alain Ravaud

Lancet 2018; 391: 748–57

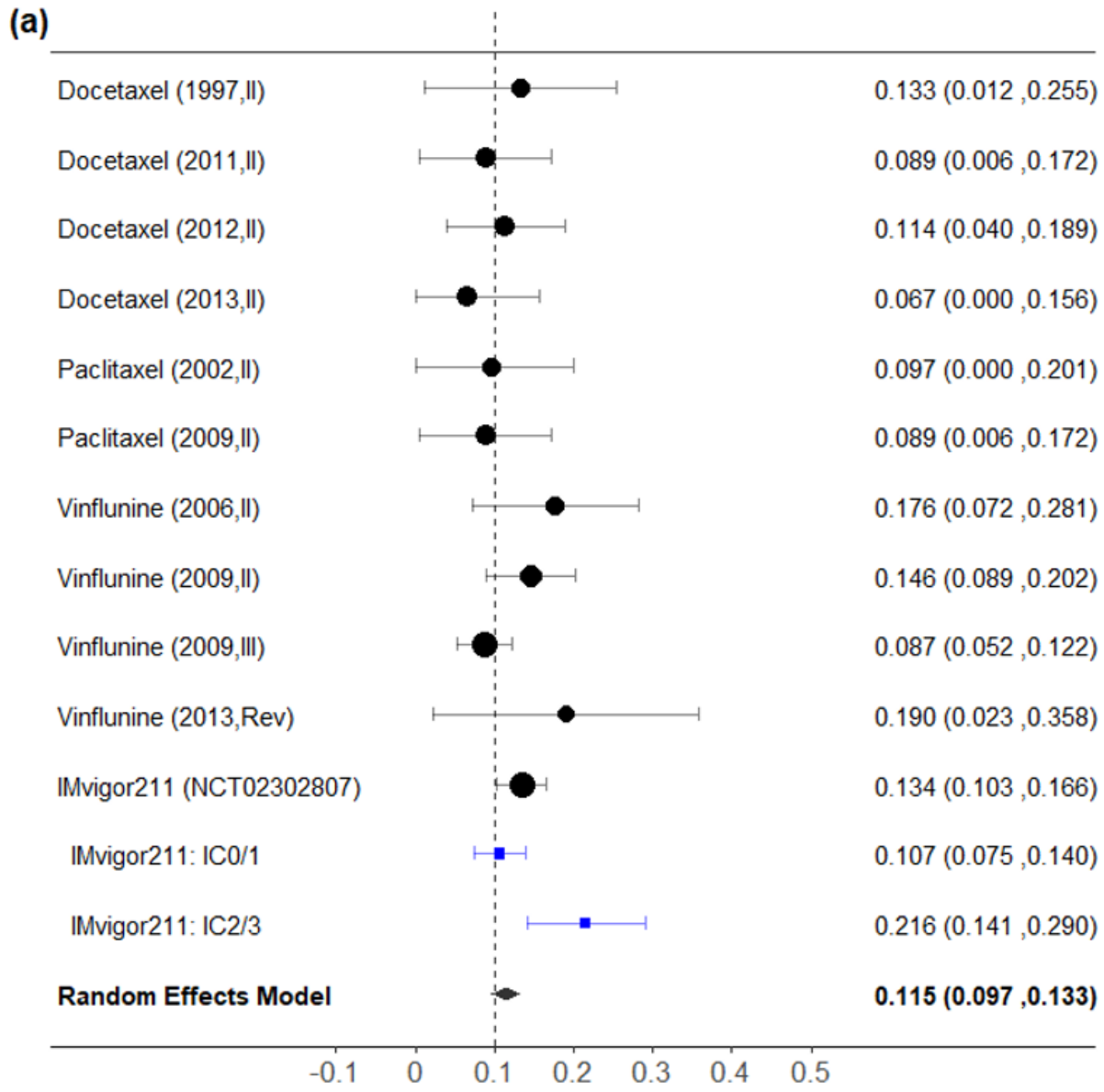
Published Online
December 18, 2017
http://dx.doi.org/10.1016/

Summary

Background Few options exist for patients with locally advanced or metastatic urothelial carcinoma after progression with platinum-based chemotherapy. We aimed to assess the safety and efficacy of atezolizumab (anti-programmed death-ligand 1 [PD-L1]) versus chemotherapy in this patient population.

Findings Between Jan 13, 2015, and Feb 15, 2016, we randomly assigned 931 patients from 198 sites to receive atezolizumab (n=467) or chemotherapy (n=464). In the IC2/3 population (n=234), overall survival did not differ significantly between patients in the atezolizumab group and those in the chemotherapy group (median 11·1 months [95% CI 8·6–15·5; n=116] *vs* 10·6 months [8·4–12·2; n=118]; stratified hazard ratio [HR] 0·87, 95% CI 0·63–1·21; p=0·41), thus precluding further formal statistical analysis. Confirmed objective response rates were similar between treatment groups in the IC2/3 population: 26 (23%) of 113 evaluable patients had an objective response in the atezolizumab group compared with 25 (22%) of 116 patients in the chemotherapy group. Duration of response was

OS for 2nd line chemotherapy (Docetaxel, Paclitaxel & Vinflunine)



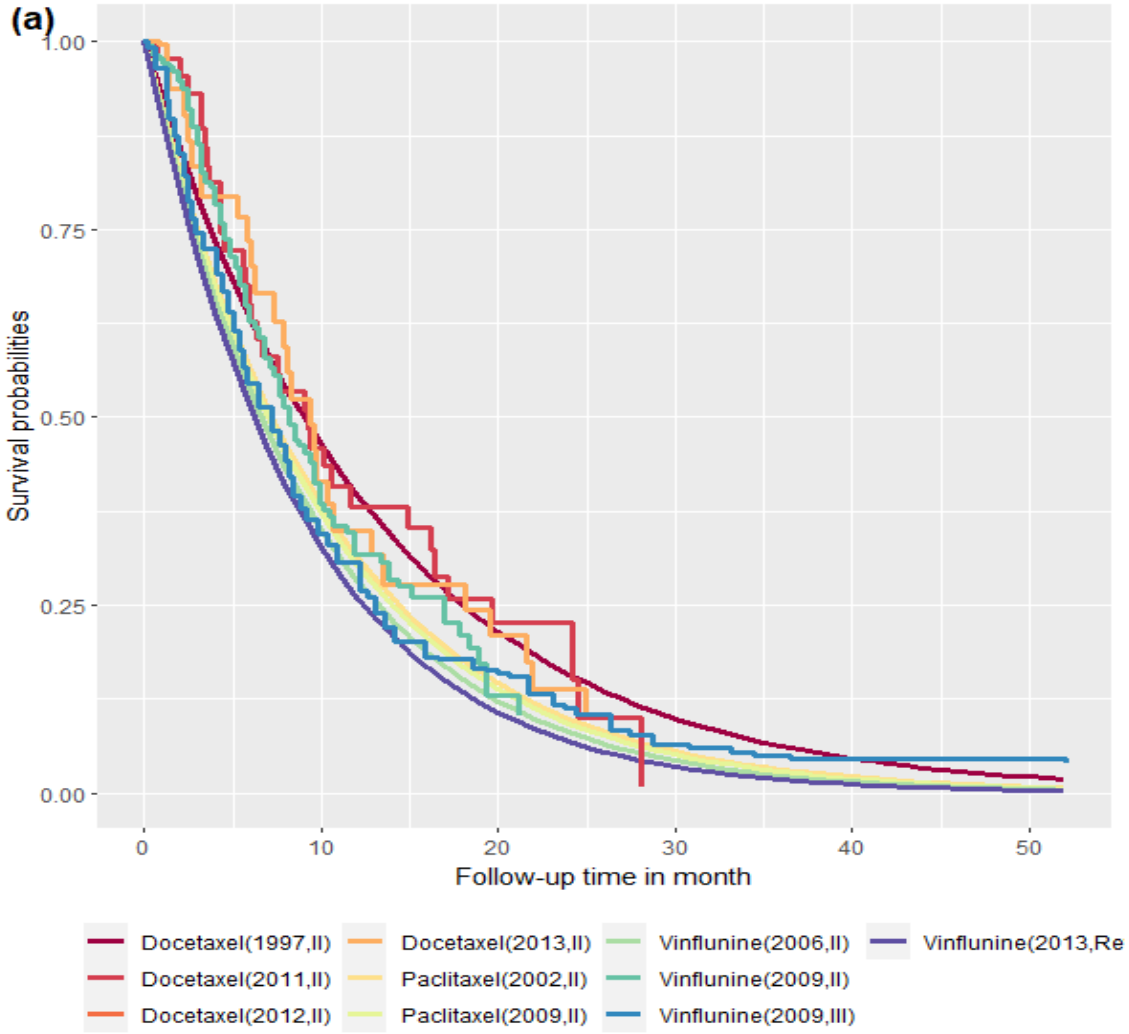
ORR for 2nd line chemotherapy

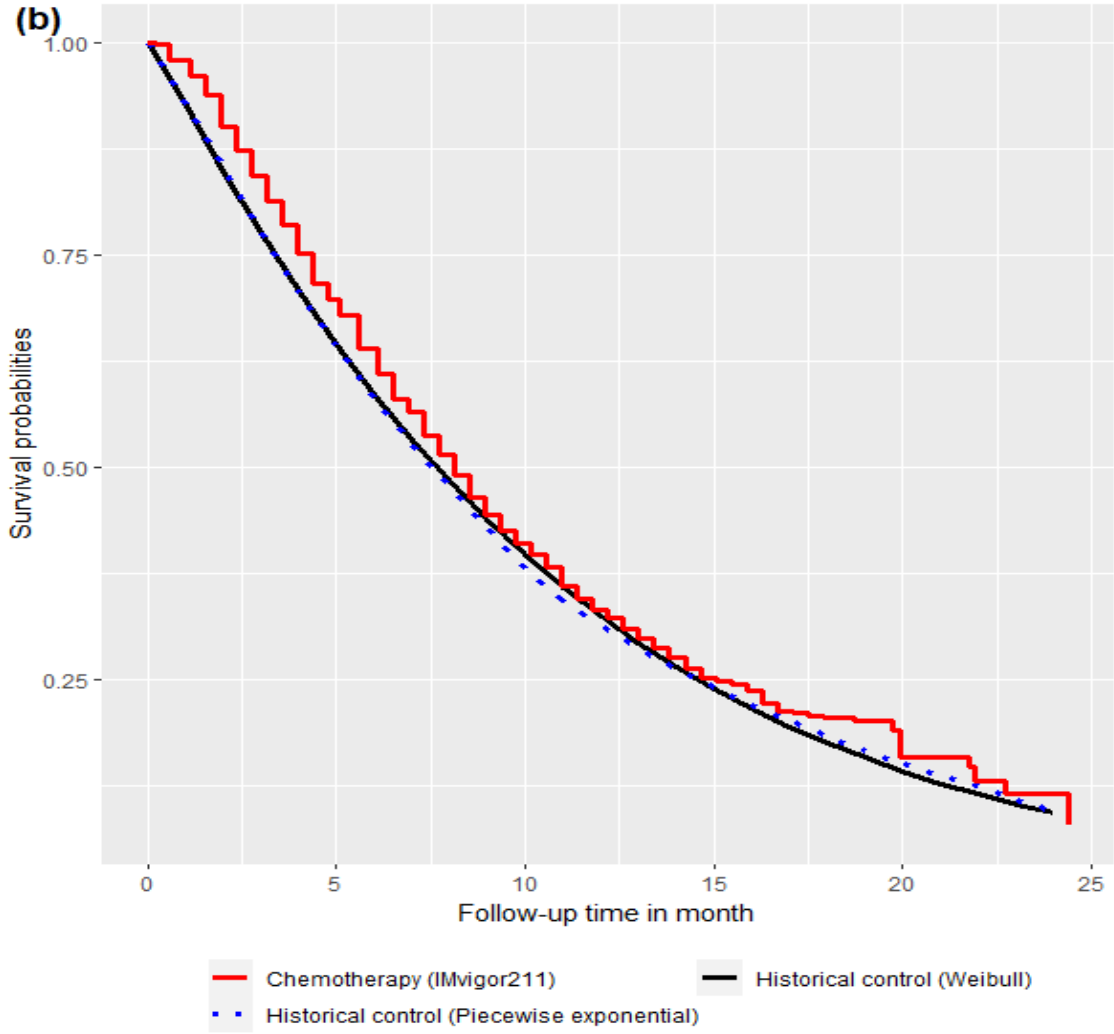
(Docetaxel, Paclitaxel & Vinflunine)

- Historical control data: ranges from 7% to 19%
- Phase III study has ORR 13.4% in ITT population
- Overall estimate of ORR is 11.5% using random effect model
- The ORR in **IC2/3 subpopulation in Phase III study was 21.6%**

OS for 2nd line chemotherapy (Docetaxel, Paclitaxel & Vinflunine)

- (a) Historical control data (chemotherapy)
- (b) Overall distribution compared with Phase III control





OS for 2nd line chemotherapy (Docetaxel, Paclitaxel & Vinflunine)

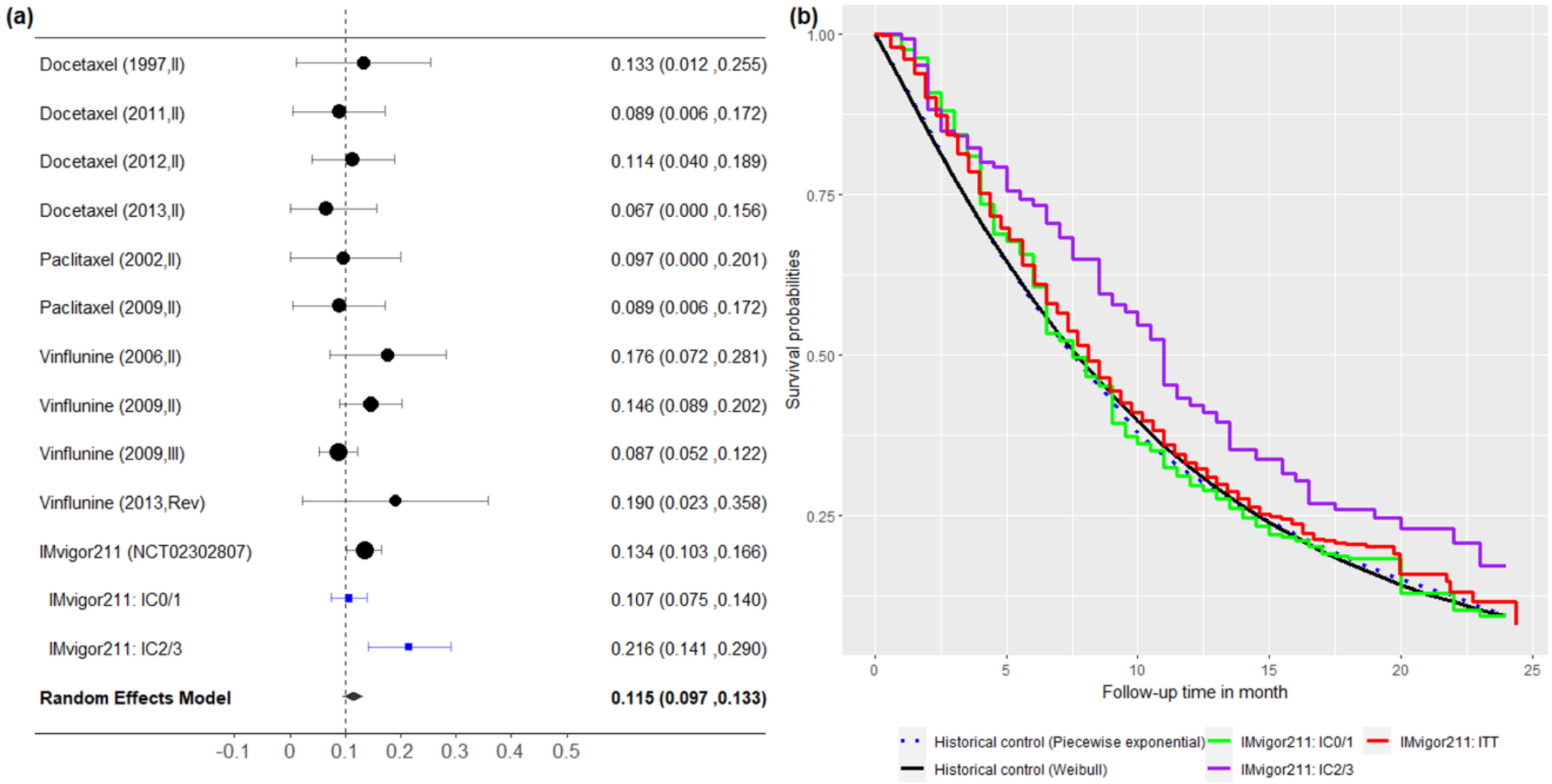


Figure 3. Chemotherapy in second-line treatment of urothelial carcinoma: (a) forest plot of objective response rates under meta-analysis using the random effects model (note the subgroup results for IC0/1 and IC2/3 in study IMvigor211 are added for comparison purpose, not included in the calculation of random effect model) and (b) survival curves comparing IMvigor211 study ITT, PD-L1 (IC2/3) and Non-PD-L1 (IC0/1) populations with combined results from historical control.

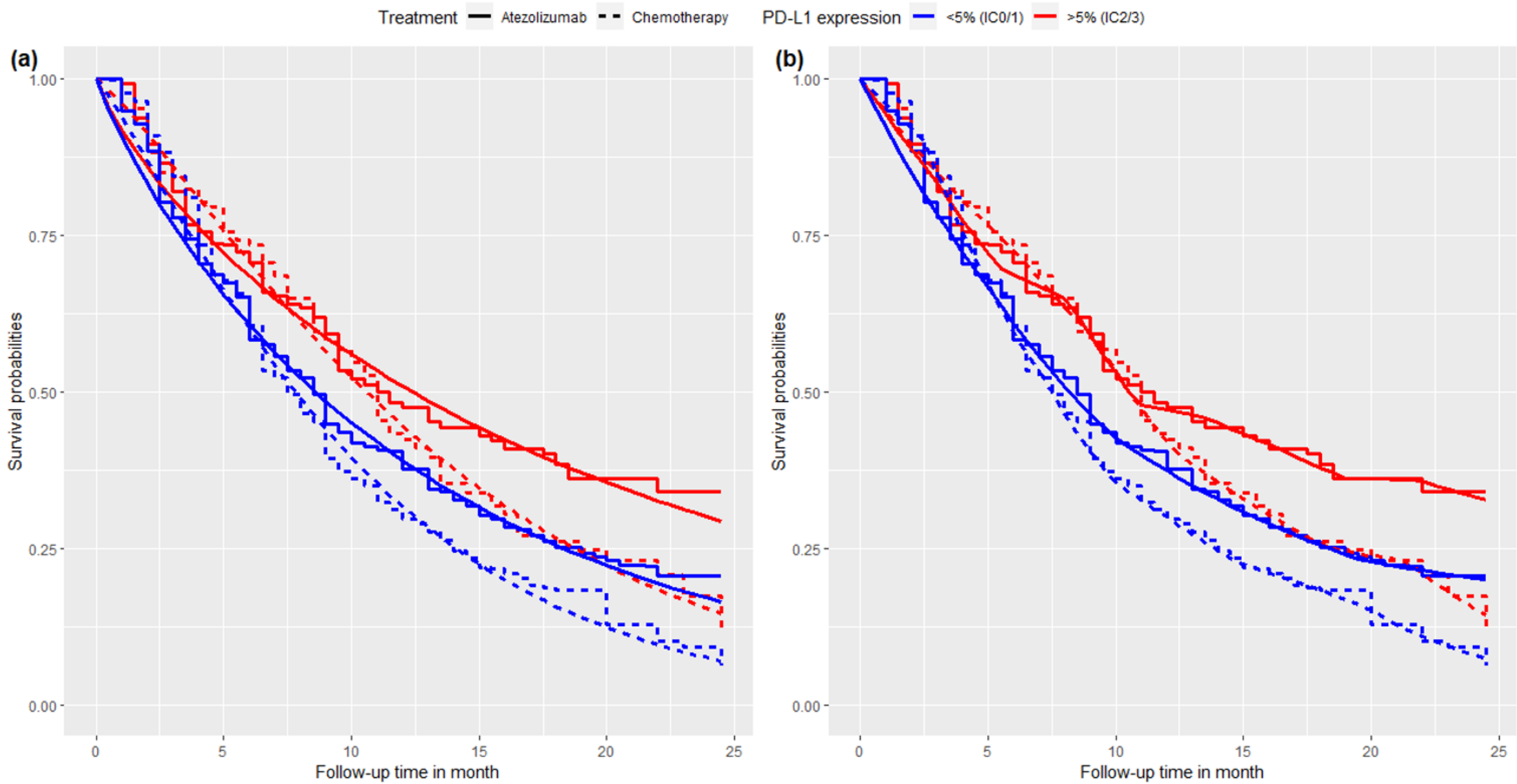
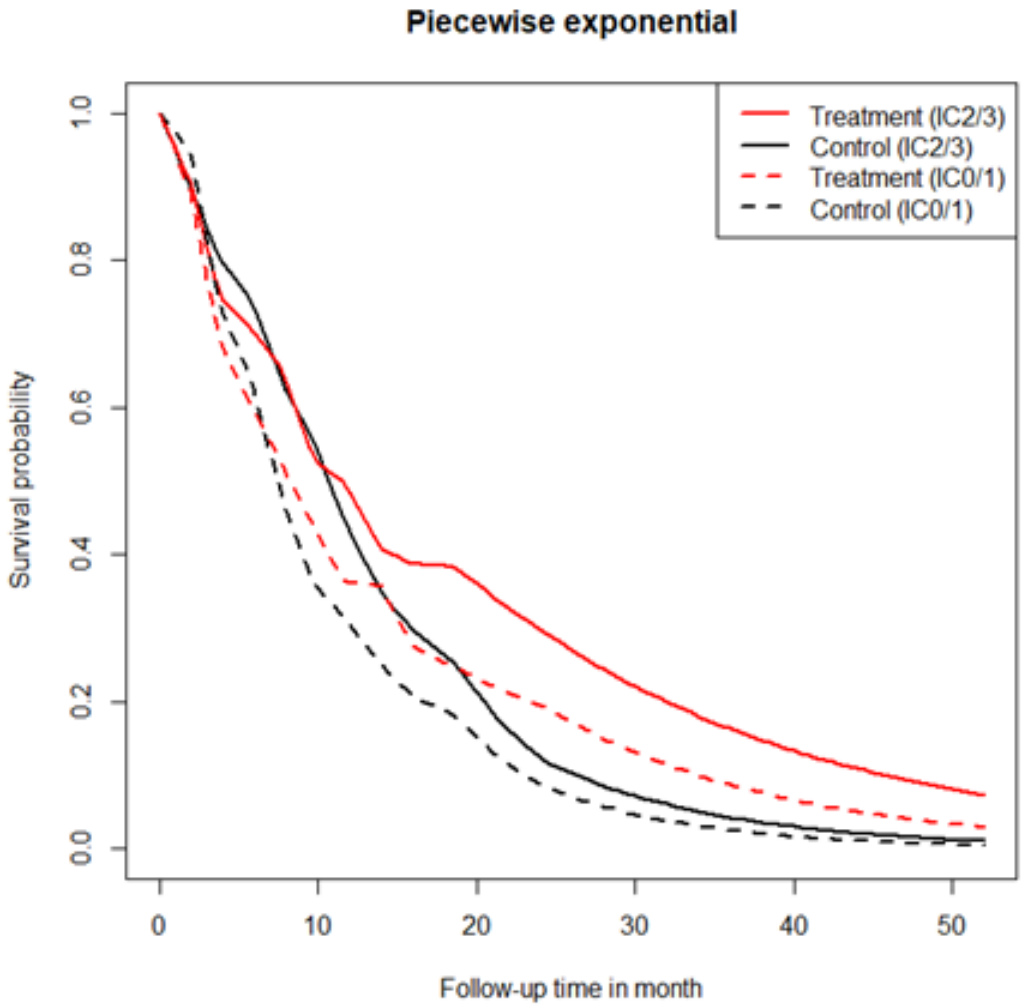


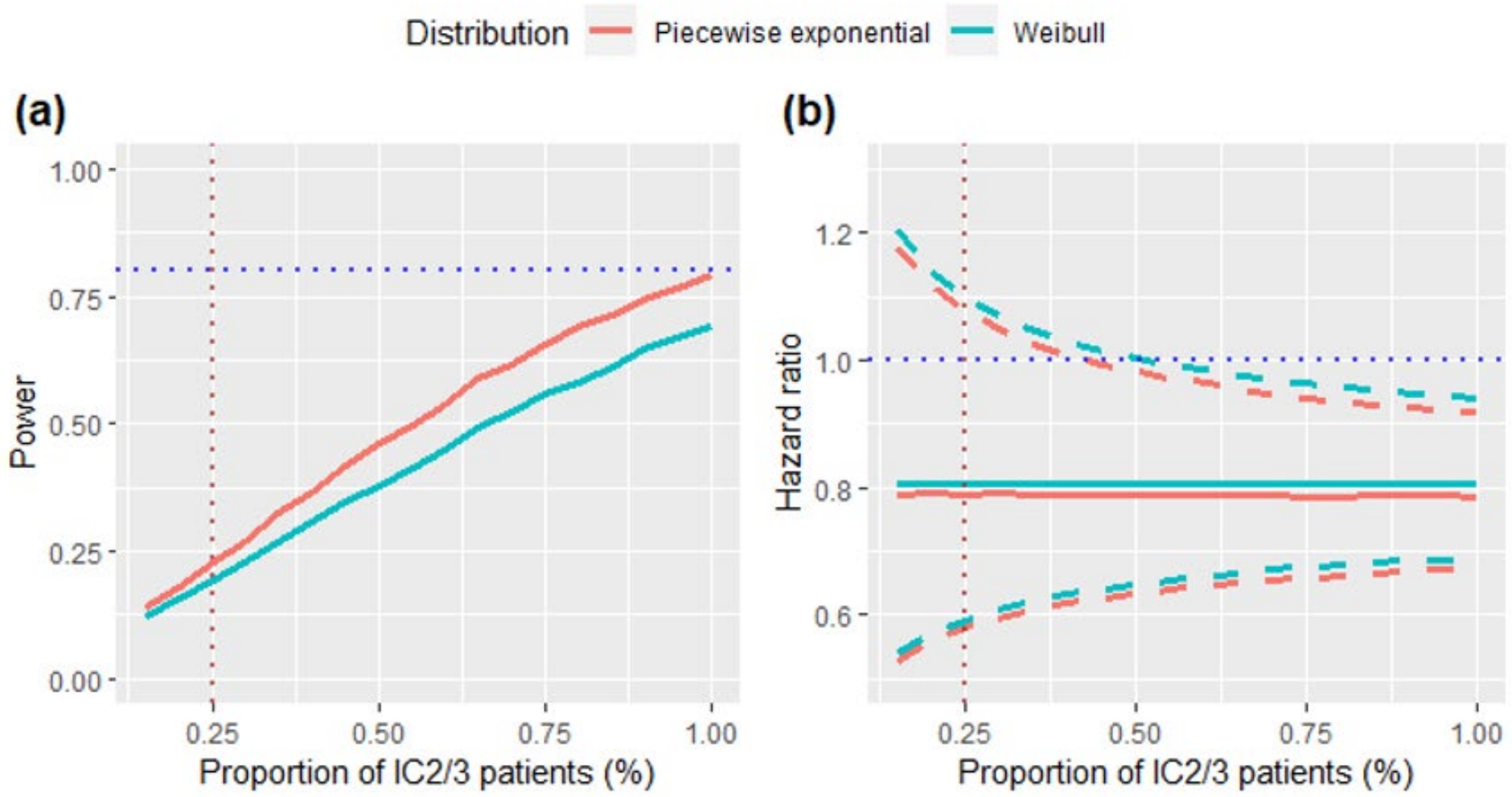
Figure 4. Estimated survival curves based on IMvigor211study for treatment and control groups by subpopulations PD-L1 (IC2/3) and Non-PD-L1 (IC0/1) under (a) Weibull and (b) piecewise exponential distributions

Simulated Success Probability with Current Design



Piecewise exponential	ITT	0.830932	0.716964	0.963016	0.5888
	PD-L1	0.787595	0.578029	1.073139	**0.2368**

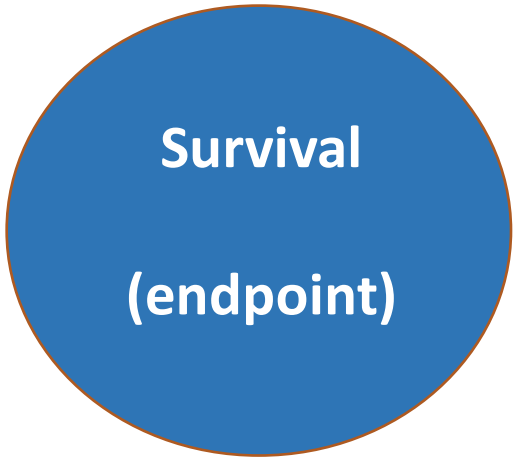
Simulated Success Probability as a function of PD-L1



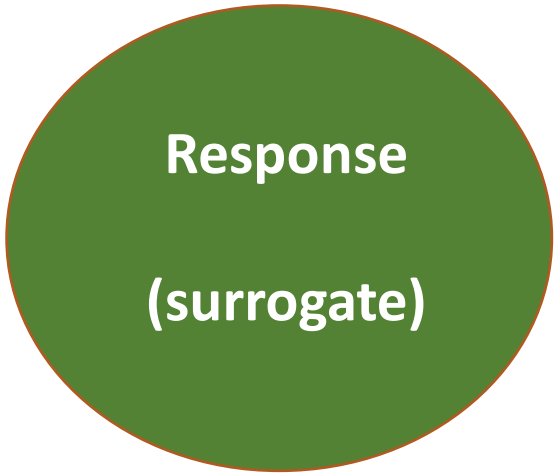
Using historical data to train mediation models

Mediation Models for Drug Development

- Characterize the local mechanism of drug
- Partially observed at the time of an investment decision for novel drug



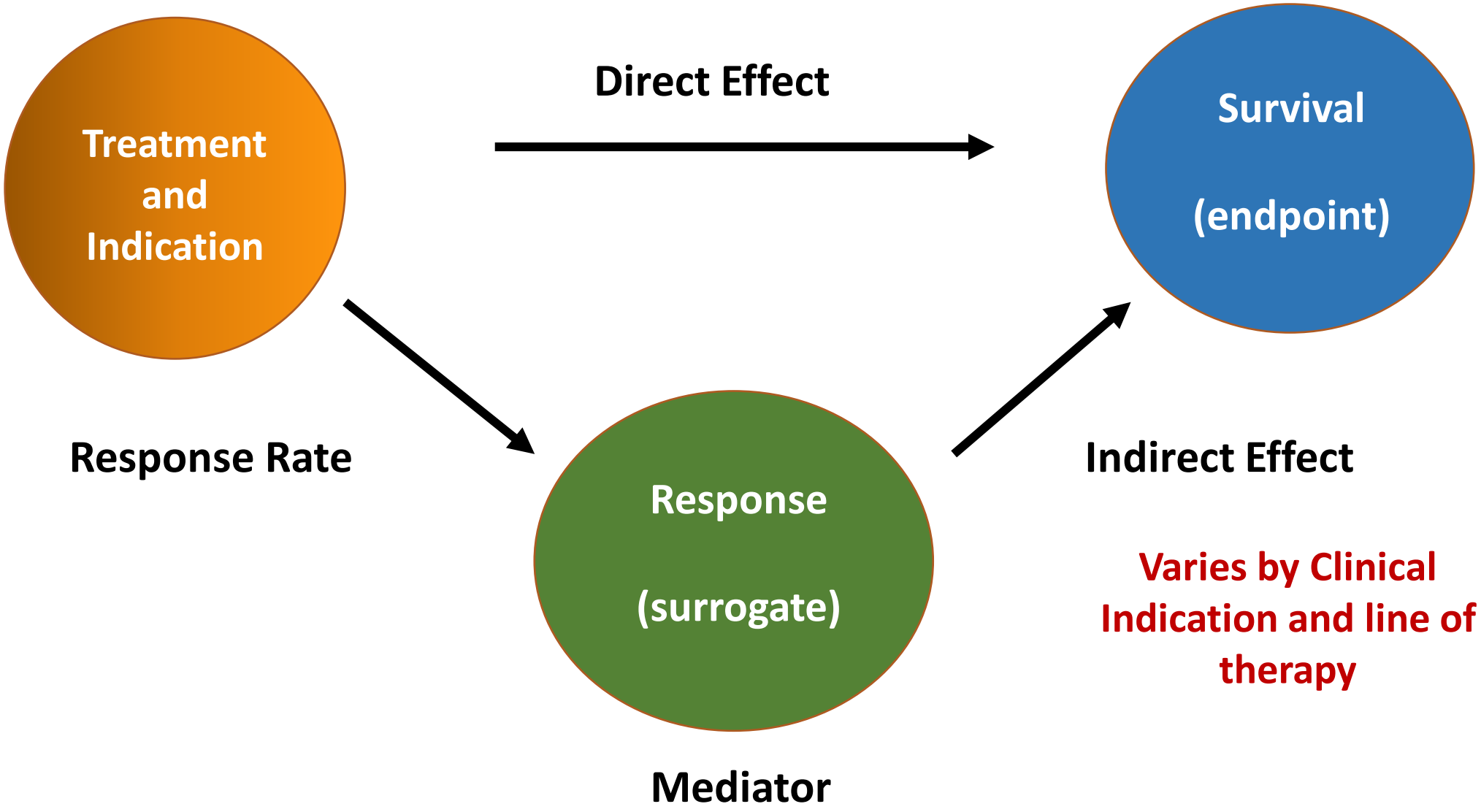
- Intervention and target population
- Controlled by investigators and design



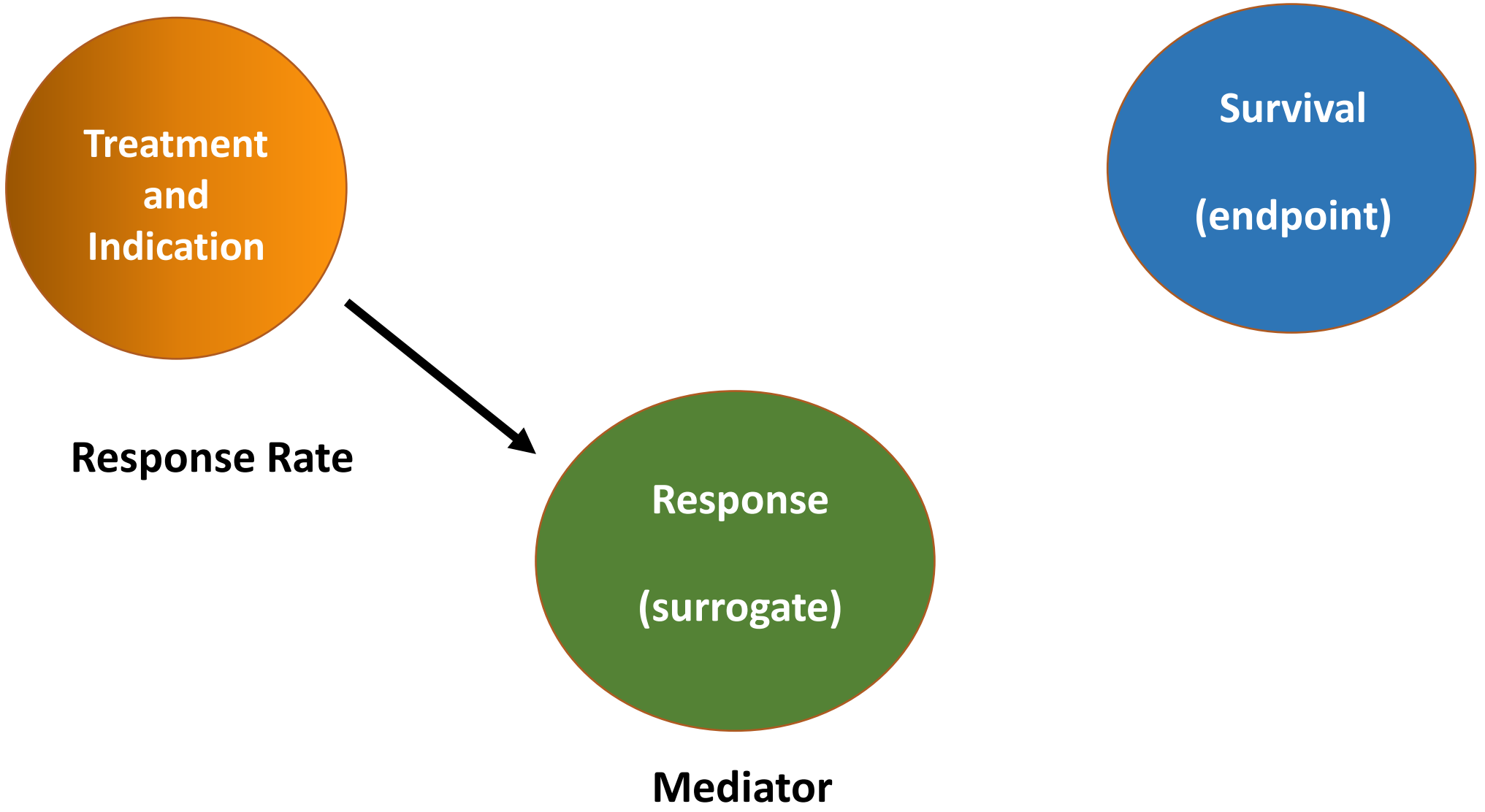
- Downstream clinical efficacy
- Basis for regulatory approval
- Unknown from early phase inquiry

Mediator

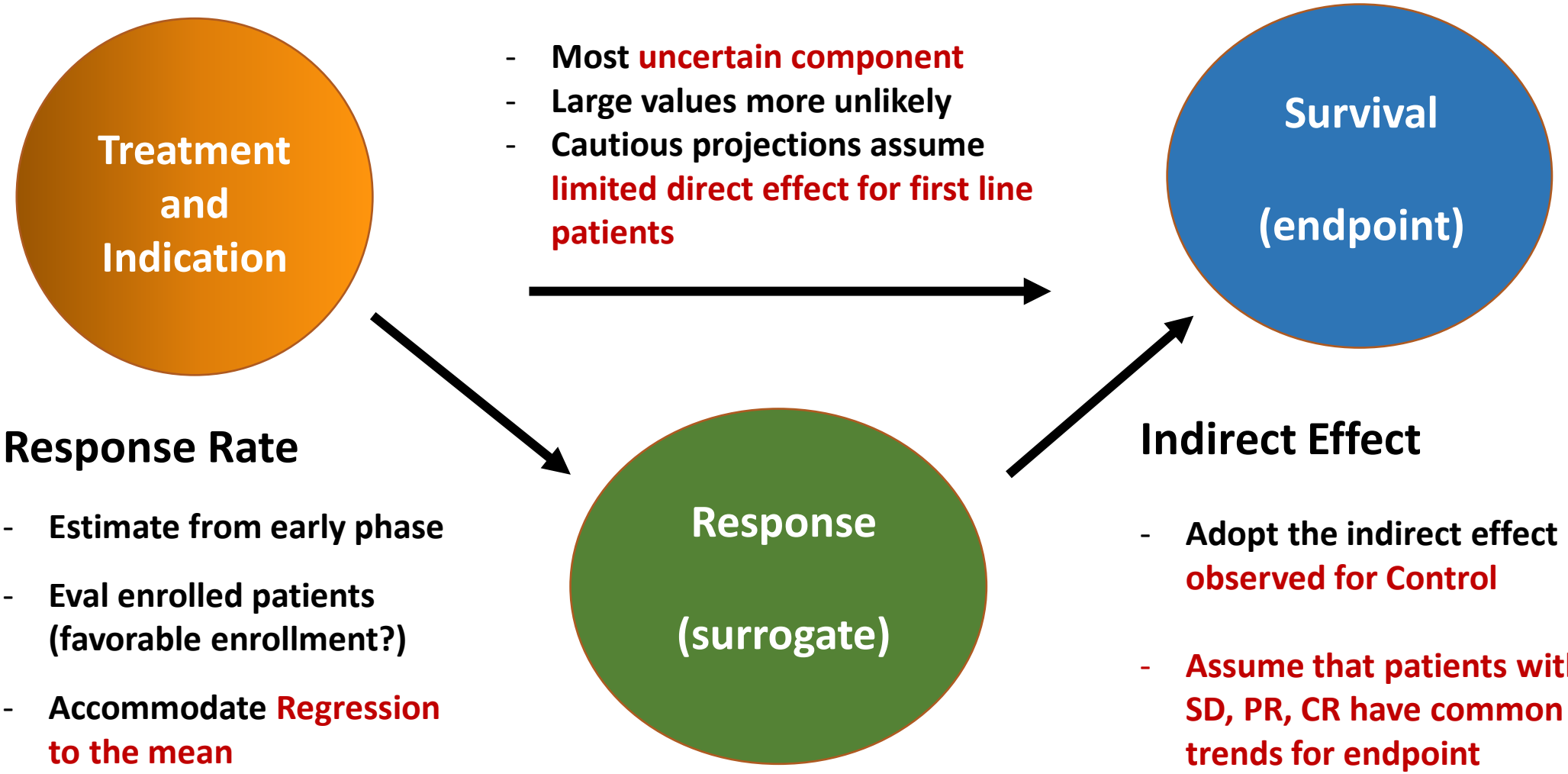
Mediation Models underly Drug Development



Conventional Go / No-Go Decision-making



Mediation Model



Direct Effect

- Most uncertain component
- Large values more unlikely
- Cautious projections assume limited direct effect for first line patients

Response Rate

- Estimate from early phase
- Eval enrolled patients (favorable enrollment?)
- Accommodate Regression to the mean

Indirect Effect

- Adopt the indirect effect observed for Control
- Assume that patients with PD, SD, PR, CR have common trends for endpoint

Mediation Modeling for Trial Simulation

ORIGINAL ARTICLE

Journal Section

Predicting outcomes of phase III oncology trials with Bayesian mediation modeling

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Pivotal cancer trials often fail to yield evidence in support of new therapies thought to offer promising alternatives to standards-of-care. Conducting randomized controlled trials in oncology tends to be considerably more expensive than studies of other diseases with comparable sample size. Moreover, phase III trial design often takes place with

- ✓ **Inputs Existing Databases**
  - Future control arm
  - Patient-level data
  - Historical trial reports
- ✓ **Captures the relationships among**
  - Tumor response (surrogate)
  - Phase III Endpoint (OS or PFS)
  - Patient enrollment
- ✓ **Outputs the Probability of Success (statistically significant p-value at the trials completion) for a given design**

Discussion

- RWD has been socialized throughout biomedical research
- considerable investment has occurred in the last 5 years
- numerous applications for EMR data, but its role in precision oncology remains ill-defined
- sources vary greatly in the reliability and usefulness to registration trials

EMR data

- offers 3 endpoints for oncology: rwOS, rwTTNT, rwTTD
- incomplete w/ unknown reliability across academic & community clinics

Historical Trial data

- concrete criteria for patient eligibility
- reliable outcome ascertainment for registration trial analysis
- but likely lacks specificity to novel biomarker profiles

Discussion

Digitizing Trial Results

- concrete criteria for patient eligibility
- reliable outcome ascertainment for registration trial analysis
- may lack specificity to novel biomarker profiles
- outcome distributions available for all studied arms
- use to set statistical assumption required for design
- set targets for ORR and Duration of Response based on historical successes

- Signal for understanding Go/No-Go or Stop decisions exists from the relationships between ORR, duration of response, predicted survival benefit