Case Study of a Phase 3 Study Design with Hybrid Control in 1L DLBCL - FDA Complex Innovative Designs Pilot Program

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Jiawen Zhu & Herb Pang
Senior Principal & Expert Statistical Scientists, Genentech/Roche
zhu.jiawen@gene.com & pang.herbert@gene.com

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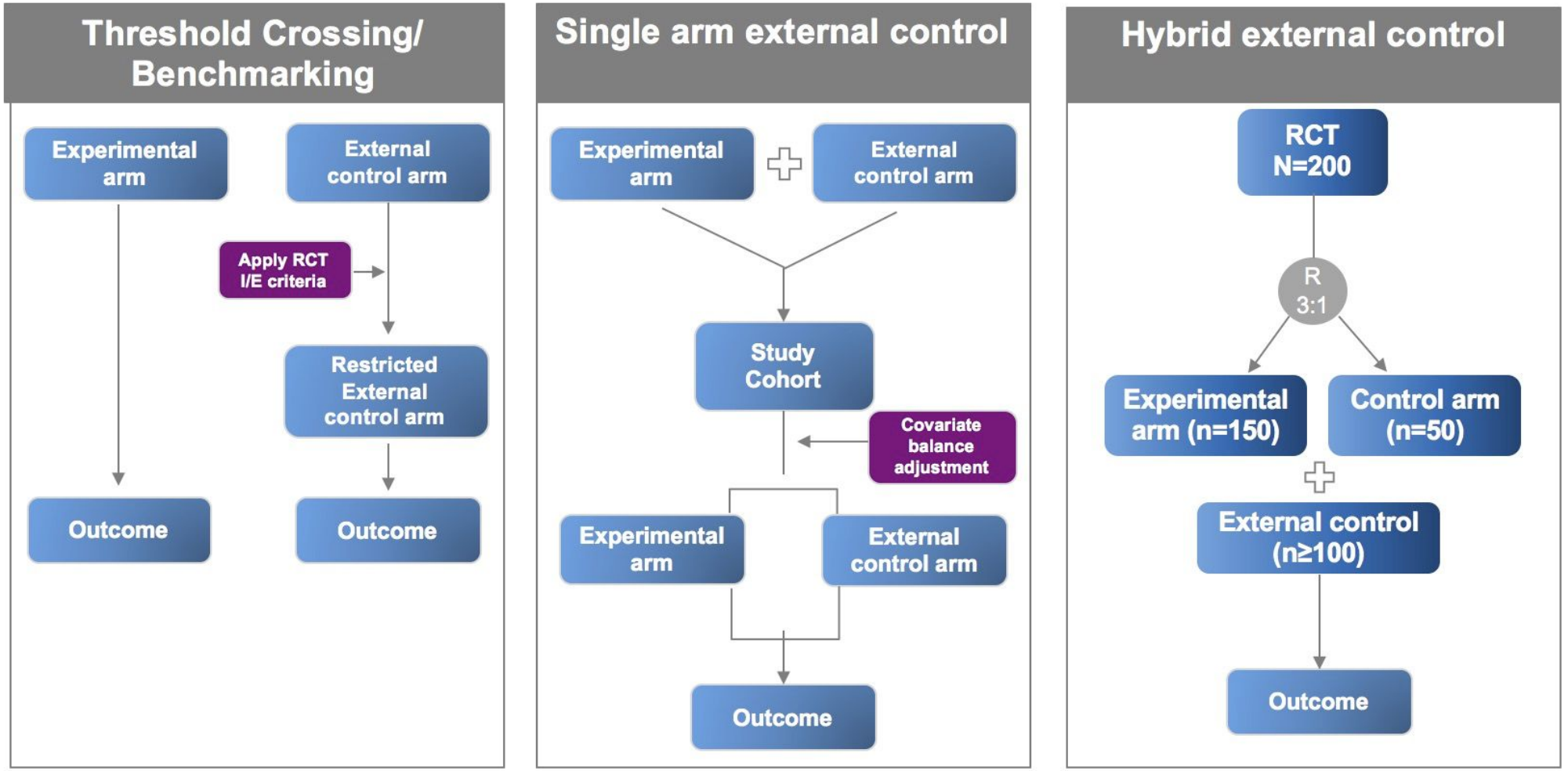
Outline

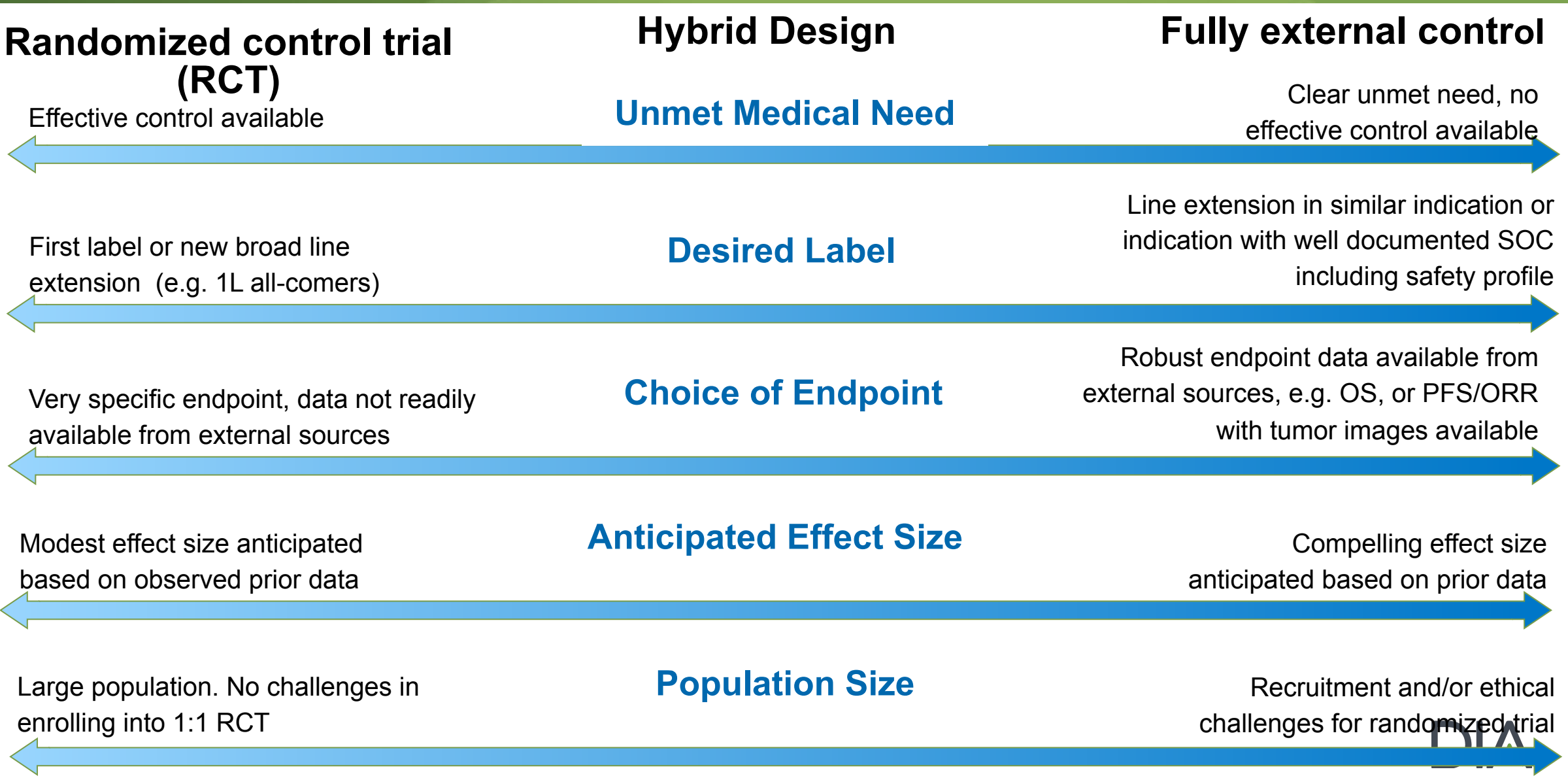
-Introduction: study designs using external controls
-FDA complex innovative trial design program
-Genentech CID pilot in 1L DLBCL
-Hybrid control ongoing research
-Summary

Study designs using external controls

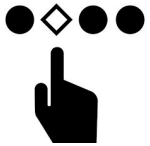


all numbers are just for illustration purposes

Considerations for choosing level of randomization



Potential bias from the external control source



- **Selection bias**
  Patients enrolled in clinical trials are different in some ways compared to patients treated in clinical practice.

- **Calendar time bias**
  Patients treated in the past do differently than those treated today.

- **Regional bias**
  Patient outcome may vary between regions.

- **Assessment bias**
  Knowledge of therapy can influence the outcome assessment.

- **Study bias**
  Patients in clinical trials have different outcomes than in clinical practice. (e.g. due to placebo effect, different care)

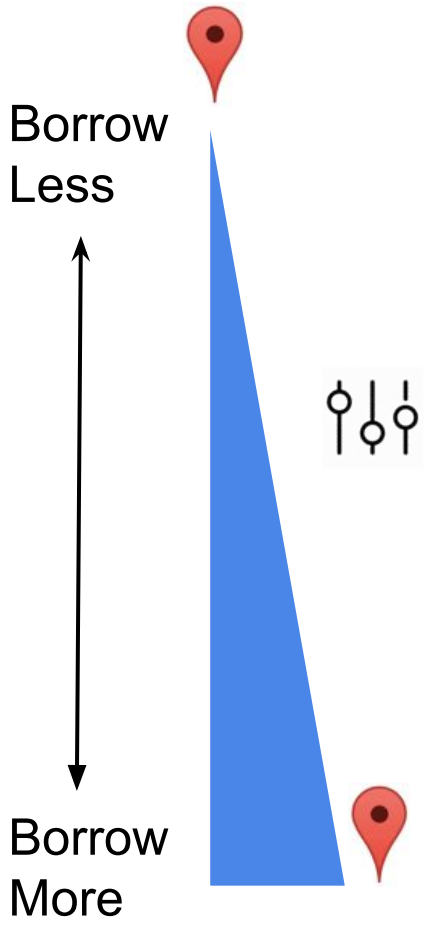
...

Burger, Hans Ulrich, et al. "The use of external controls: To what extent can it currently be recommended?." *Pharmaceutical Statistics* 20.6 (2021): 1002-1016.

How to Mitigate Potential Biases: Pocock (1975) criteria

- Receiving a precisely defined standard treatment, the same as for randomized controls
- Part of a recent clinical study which contained the same requirements for patient eligibility
- Methods of treatment evaluation must be the same
- Previous study must have been performed in the same organization with largely the same Investigators
- There must be no other indications leading one to expect differing results between the randomized and historical controls
- Distributions of important patient characteristics should be comparable to those in the new study

How to Mitigate Potential Biases: Borrowing approaches

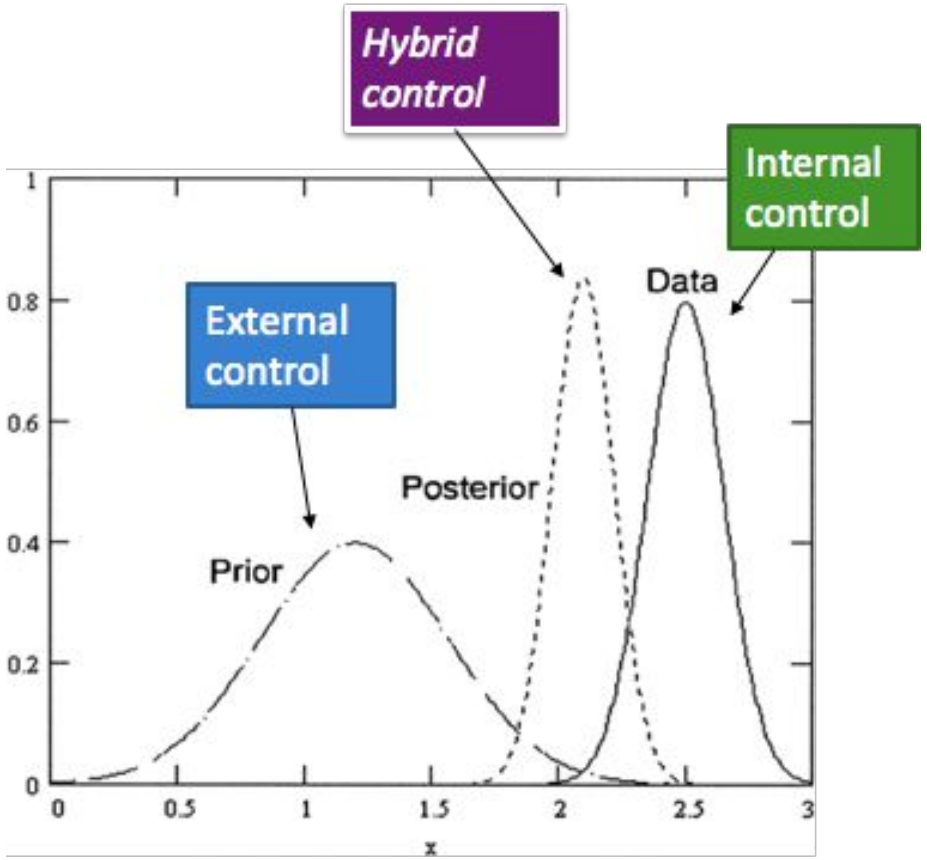


- **No borrowing**
  only RCT data is used to estimate treatment effect
- **Dynamic borrowing: Conservative prior**
  Skeptical on external control
- **Dynamic borrowing: Aggressive prior**
  Optimistic on external control
- **Full borrowing**
  Two controls are pooled together when estimating treatment effect

Dynamic borrowing mitigates risks of borrowing inconsistent external control if there are things that "we don't know we don't know"

Method reference: Lewis, CJ, Sarkar, S, Zhu, J, Carlin, BP et al. Borrowing from historical control data in cancer drug development:A cautionary tale and practical guidelines.Statistics in Biopharmaceutical Research, 11(1):67–78, 2019

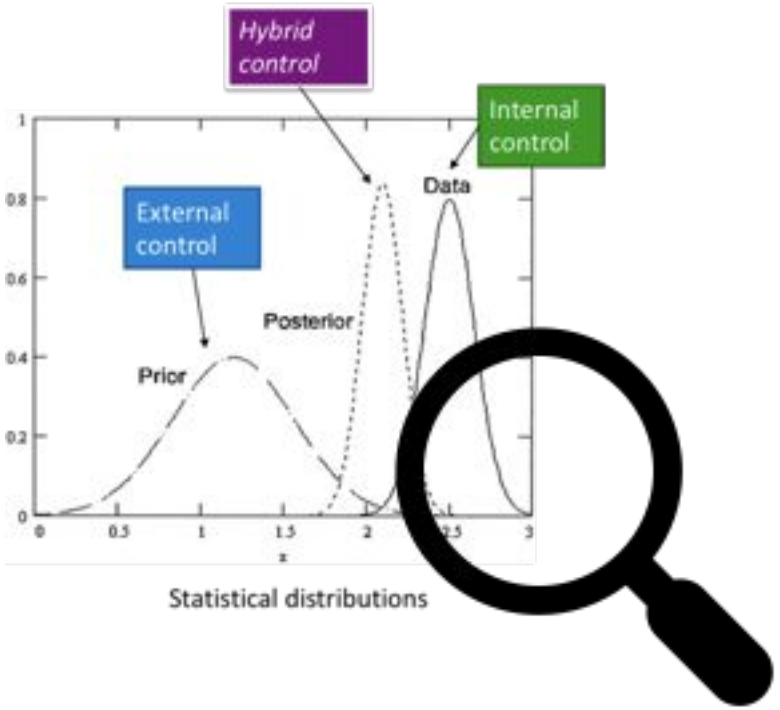
How to Mitigate Potential Biases: Bayesian methods can be used to bring in external controls

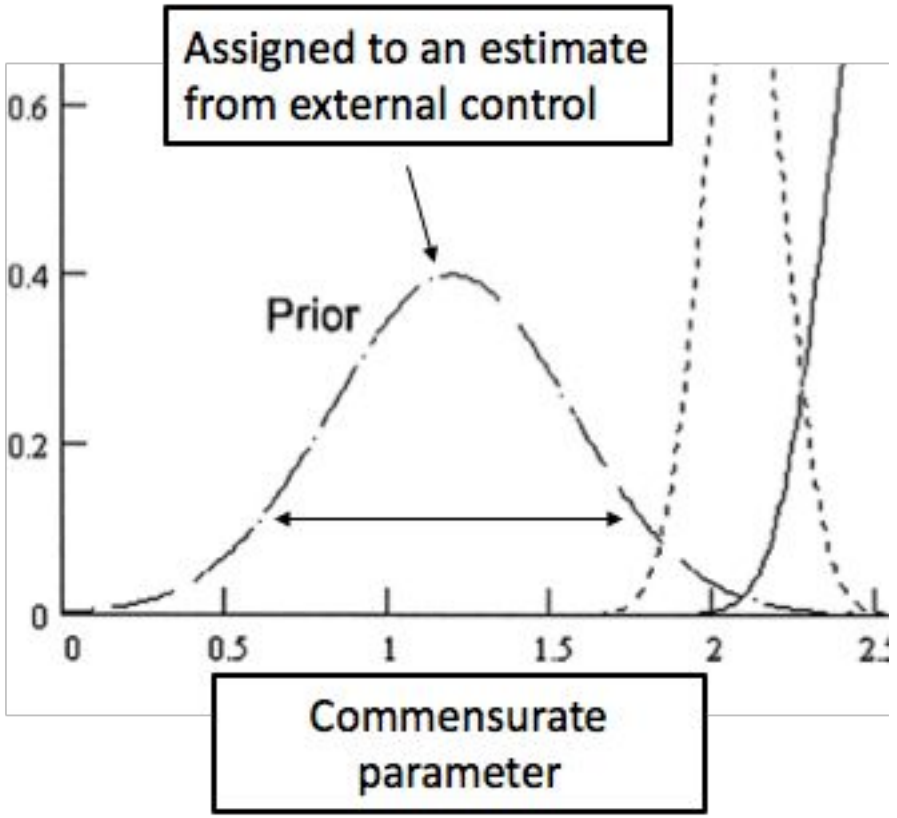


Statistical distributions

- A natural way to borrow information from external or historical controls
  - External trial data can be used in setting up the study prior
- Impacts of informative prior
  - Potential for increased influence of the datasets with bias
- It is important to take into account the difference between internal/external control data
  - A **dynamic borrowing** framework

Bayesian methods can adjust the amount of borrowing





Hierarchical Commensurate Prior (HCP) – Hobbs, Carlin, Sargent (2011)

Dynamic borrowing methods (purple, green, blue) achieve similar power gains as full borrowing (red) with much less type I error inflation

K. Viele et al 2013

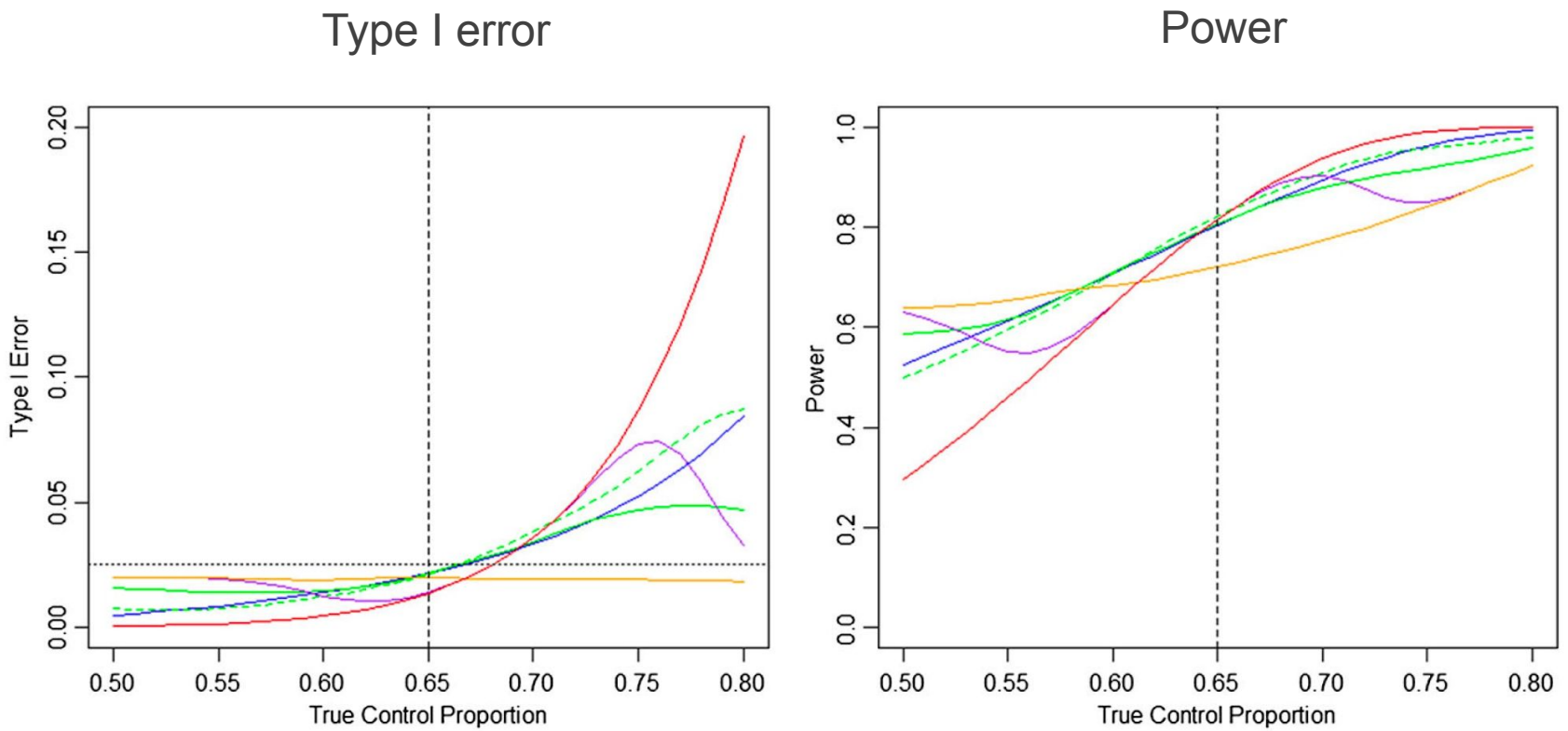


Figure 9. Type I error and power comparison for separate (orange), pooling (red), selected test-then-pool (size 0.10, purple), downweighted power prior (40% weight, blue), and hierarchical model (IGamma(1, 0.01) in dashed green, and IGamma(0.001, 0.001) in solid green). Generally, the test-then-pool approach has lower type I error and also lower power near a control rate of 0.65, but has reduced power compared to power priors and hierarchical models outside that range. For control rates near 0.65, all methods achieve similar power gains as pooling (red) with much less type I error inflation.

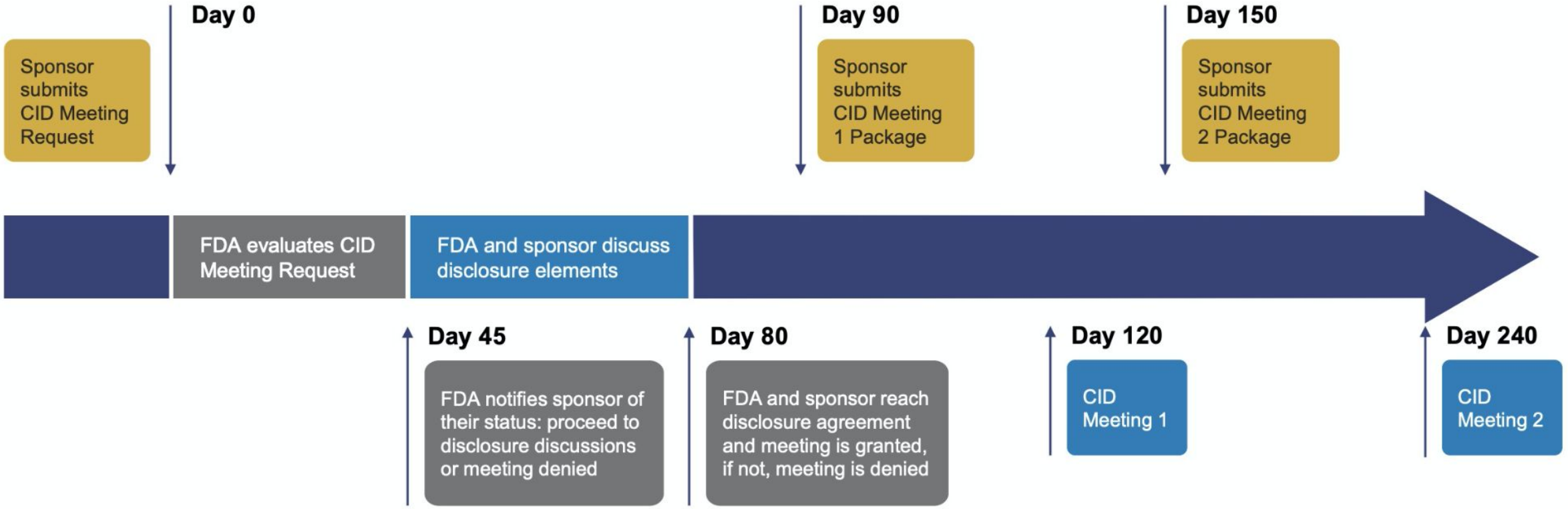
PDUFA VI Provisions: Complex Innovative Trial Designs (CID)

- Objective: To facilitate the advancement and use of CIDs
  - Develop staff capacity
  - Conduct a pilot meeting program
  - Develop or revise relevant Manuals of Policies and Procedures (MAPPs), Standard Operating Policy and Procedures (SOPPs), and/or review templates
  - Publish draft guidance
  - Convene a public workshop

Complex Innovative Trial Designs Introduction

Ref: FDA CID website:
https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

CID Timelines



Why innovative design was needed for our case

Unmet medical need in certain subgroup of DLBCL patients

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL) worldwide, with 25,000 newly diagnosed patients in the United States (US) annually

Standard of care for 1L DLBCL patients established over 20 years ago: it is well characterized and well understood

Patients in certain subgroup of DLBCL have a poorer prognosis and consequently a high unmet medical need

"Borrowing" patients from the control arm of another study helps us

Having fewer 'new' patients treated with a control regimen that is well established and that we know well

Shorten our study

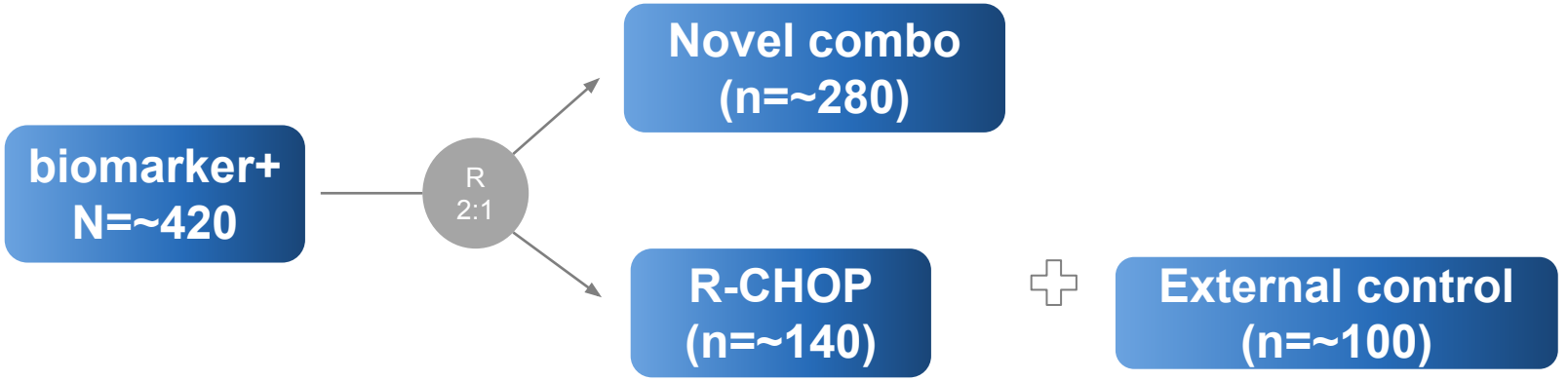
Conducting more efficient trials by sharing control data between trials

Phase 3 Development in 1L DLBCL & Pathway to CID Pilot

- Encouraging data from Ph2 study (Experimental + R-CHOP) compared to historical R-CHOP control, especially in Biomarker-positive patients
- Hybrid control can potentially limit the number of ‘new’ patients exposed to the well established SOC, and reduce study timelines
- FDA Type C meeting on proposed Ph3 study in Biomarker+ 1L DLBCL of Experimental + R-CHOP vs R-CHOP (3:1 randomization) plus external borrowed control, selected from contemporary internal study
- Agency recommended 1° analysis population and analysis plan be based on the randomized trial without an external control: other analysis populations can be used for supportive analyses
- Focus of updated design on external control arm for secondary endpoint OS, a clinically meaningful endpoint with minimal ambiguity in it’s assessment
- FDA’s CID Pilot Meeting Program provided an opportunity to build on the initial external control discussions within a collaborative framework

15

Proposed Phase 3 Study Design in 1L DLBCL



Primary Endpoint:

- **PFS Investigator Assessed**

Key Secondary Endpoints

- **OS**, based on randomized patients & matched external control

- Analysis of primary endpoint (PFS) based on the randomized patients, designed to provide 80% power at the 5% significance level to detect a target HR of 0.6, one IA at 80% of events
- External control patients to be selected from a contemporary, ongoing internal clinical trial
- External control arm intended to support early OS analysis at the time of the primary PFS analysis
- Randomized study with external control arm using matched external controls through Bayesian dynamic borrowing

Rationale for Source of External Control Arm

- Prospective plan to select external controls from an ongoing, contemporary, internal randomized controlled clinical trial
- Consistent eligibility criteria planned
- Aim to target similar Sites and Investigators to aid similarity
- OS is a clear and clinically meaningful endpoint with minimal ambiguity in event determination
- 5 of the 6 proposed criteria outlined by Pocock (1975) for selecting an external control source currently met

Feedback on Labelling Potential of OS with External Controls

- **Model-assumptions assessment**
  - Standard analysis typically requires few assumptions
  - Borrowing: more assumptions and less standard; FDA provided valuable input on where and how to make assessments
- **Pre-specification**
- **What could hamper inclusion of OS in label (similar to traditional designs)?**
  - Examples:
    - Whether the model assumptions appear to be met
    - Any outlying subgroup effects
    - The endpoint was credibly captured or not
    - Overall conduct of the study
    - Missing data
    - Baseline characteristics are the same
- **Non-statistical considerations:**
  - Is the summary of analysis clear?
  - Interpretable by clinicians?
  - Provides valuable information?

Along with these considerations, ultimately, the FDA requires the final data from such a novel design to gain confidence in the ability to utilize external controls more readily

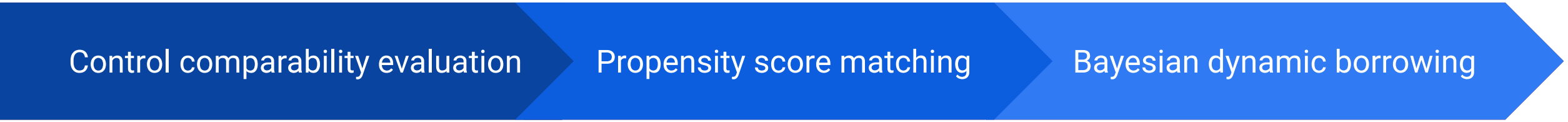
Novel designs – Making it happen

Typical design	vs.	Hybrid Bayesian dynamic borrowing
- Decide on parameters - Fixed scenario	**<Front-loading>**	- Extensive simulations - Many scenarios (~20+ for each FDA meeting)
	Implications	- Plan early - Allocate time/resources
	Solutions	- CRAN R Software available: ***psborrow**** - Roche statistics method group and method experts - Learnings from CID program
	Methods R&D	- FDA NIHU01 grant (ongoing work)

*psborrow: Bayesian Dynamic Borrowing with Propensity Score https://cran.r-project.org/web/packages/psborrow/index.html

Lu, Y., Lin, A., Pang, H., & Zhu, J. (2021). Bayesian Dynamic Borrowing Tool for Complex Innovative Trial Designs. ASA Biopharmaceutical Report, Summer 2021, Volume 28, Issue 3, 11-19

Final Analysis Flow Diagram



Final Analysis Flow Diagram

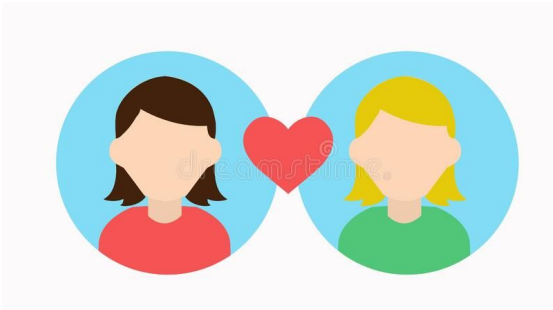
Control comparability evaluation | Propensity score matching | Bayesian dynamic borrowing

- Apply inclusion/exclusion criteria
- Flag baseline factors with significant difference between internal and external trials

Final Analysis Flow Diagram

Control comparability evaluation | Propensity score matching | Bayesian dynamic borrowing

- Match patient population between internal and external trials using propensity score matching (PSM)
- Enhance covariates balance by filtering out unmatched patients



Final Analysis Flow Diagram

Control comparability evaluation → Propensity score matching → Bayesian dynamic borrowing

A method to:

- Automatically downweight external control data based on internal/external control agreement
- Provide inference of treatment effect with hybrid control (i.e. OS analysis)

Sensitivity analysis follows main analysis

Simulation scope and objective

- Focused on the evaluation of the proposed statistical method (PS matching and the Bayesian commensurate prior approach)

- Examined the trial operating characteristics (OC) under:
  - Varying magnitude of ***differences in baseline characteristics***
  - Different ***choices of the commensurate prior*** which influences the degree of borrowing
  - ***Violation*** of various ***assumptions***

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- Examined the trial operating characteristics (OC) under:
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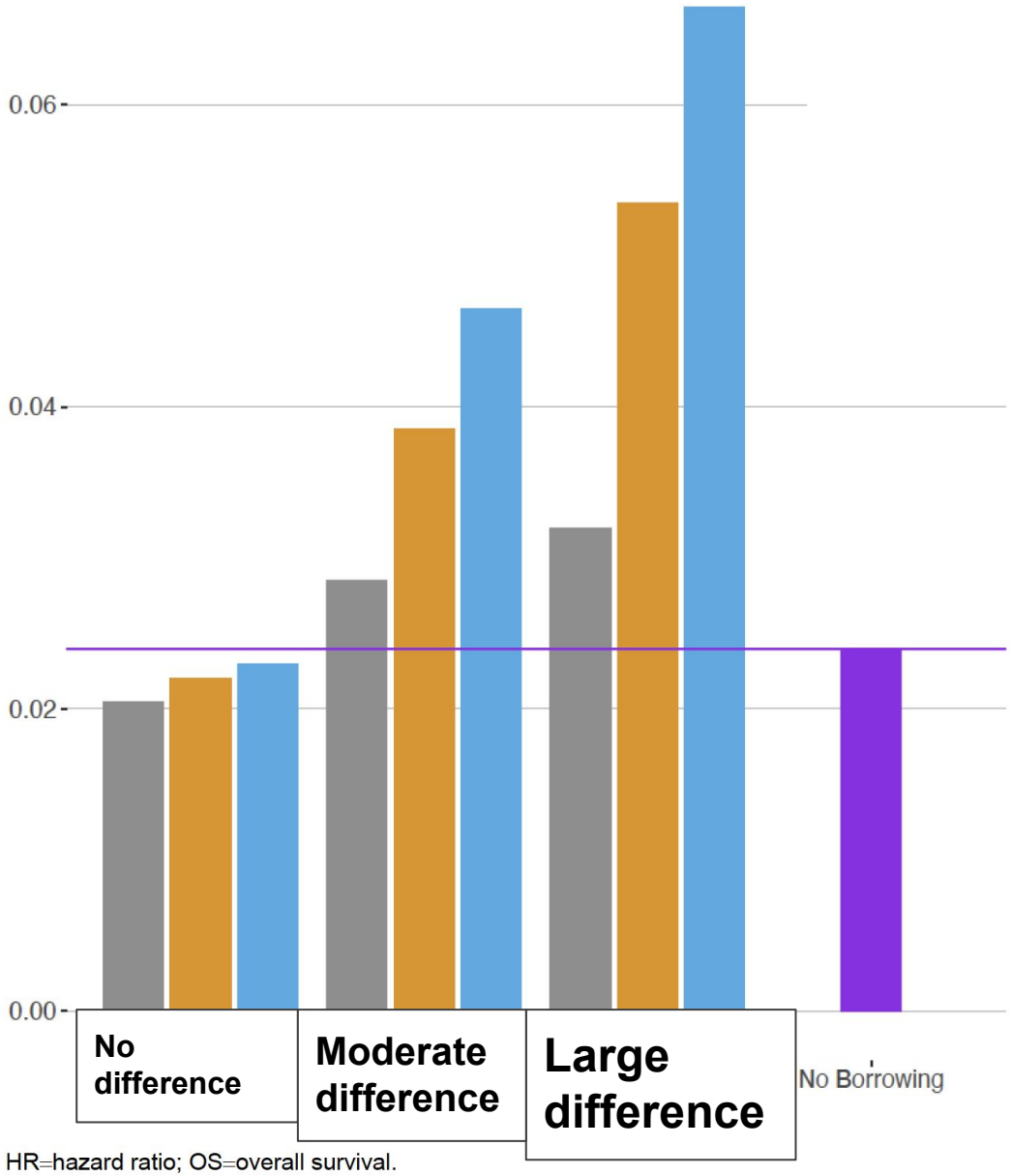
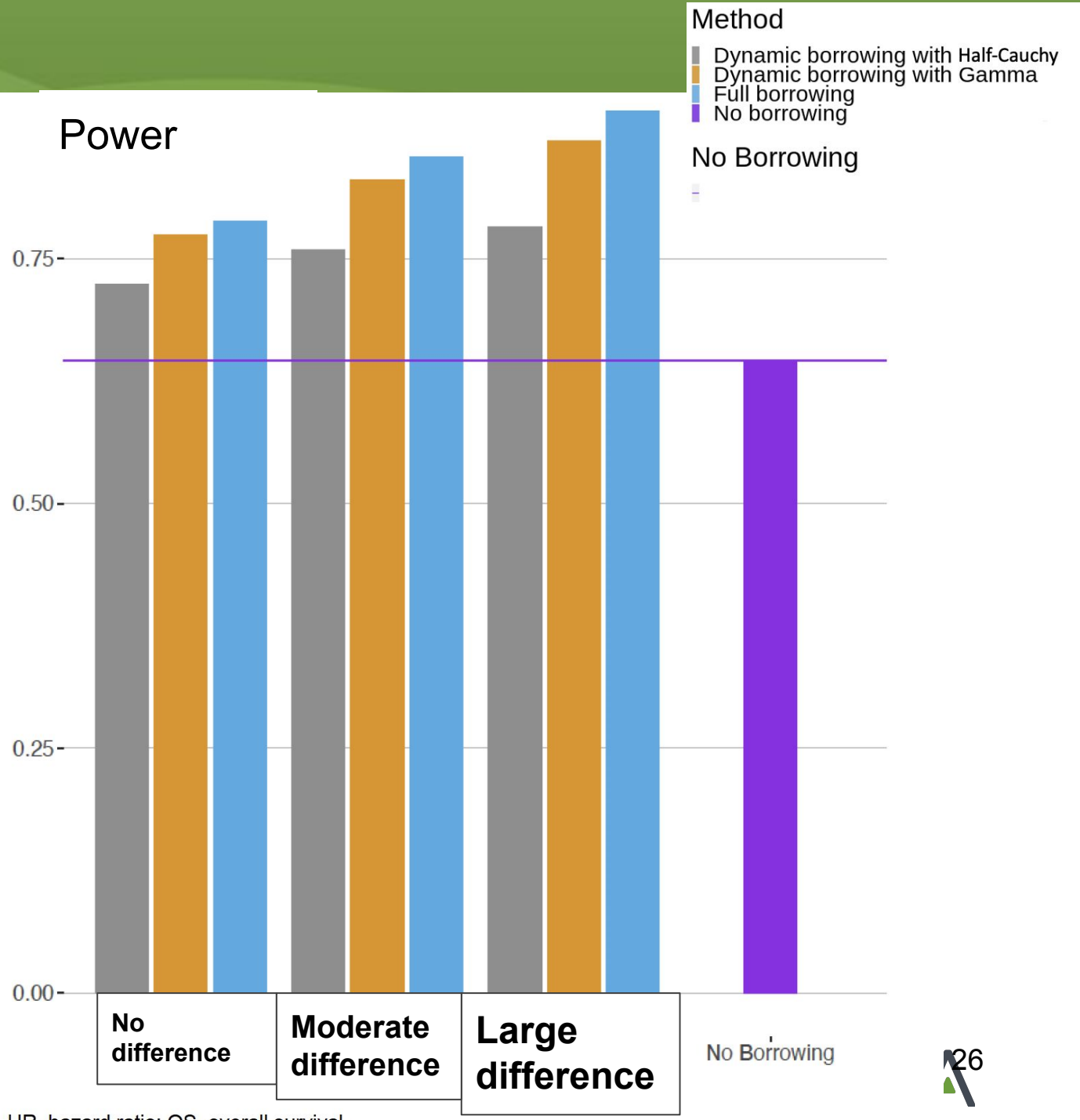
Simulation results highlights

Type I error



HR=hazard ratio; OS=overall survival.

Power



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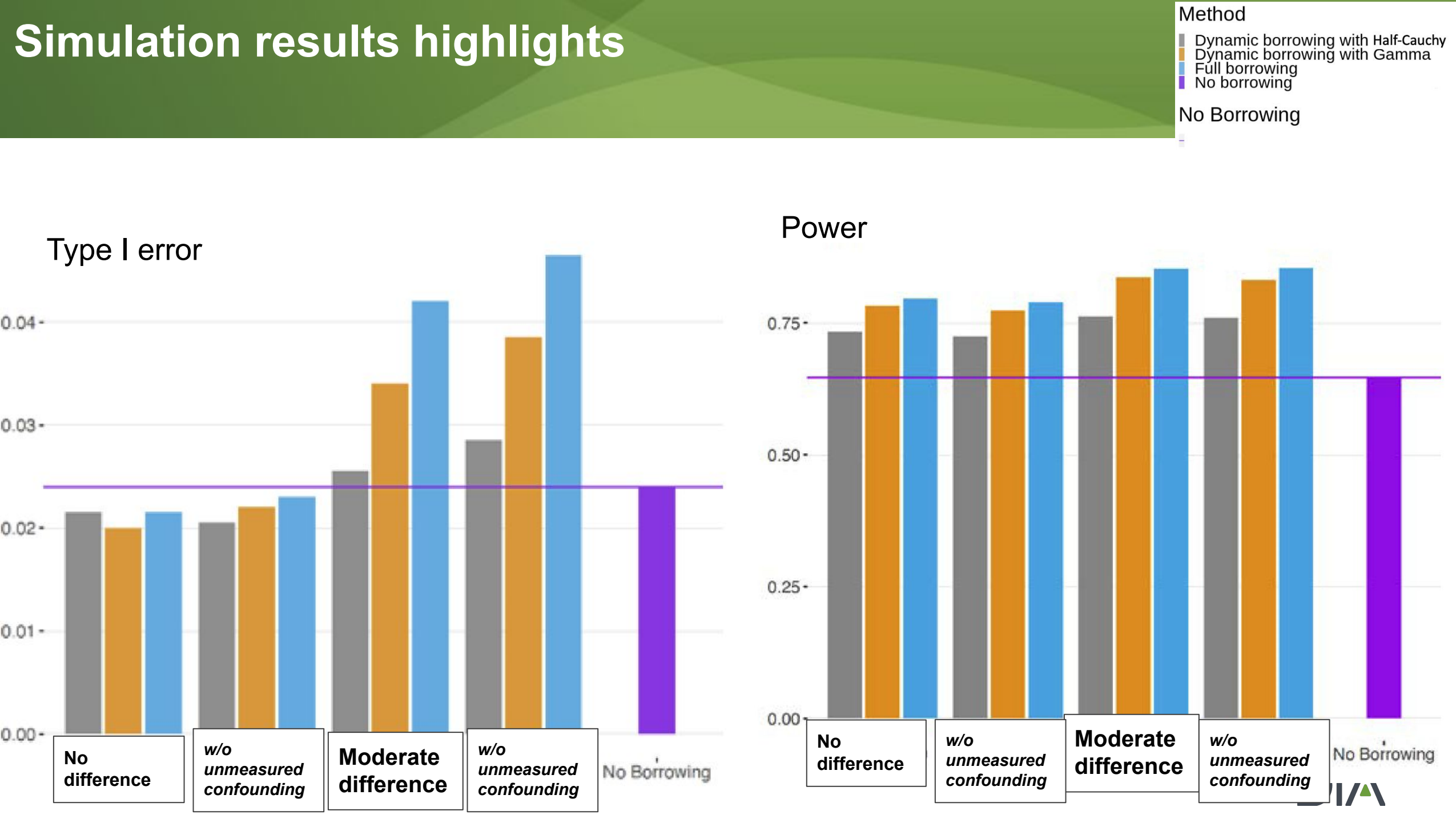
  - **Violation** of various **assumptions**

Violation of assumptions

Typical design	vs.	Hybrid Bayesian dynamic borrowing
- Decide on parameters - Fixed scenario		- Extensive simulations - Complex design
	Implications	- Violation of assumptions
	Scenarios	- ***Unmeasured confounding*** - ***Survival curve distribution*** - ***Non-linear/non-additive model***

Simulation results highlights



Simulation results discussion

Summary Table to Compare Method Performance for Differences in Baseline Characteristics Investigations

Approaches		Average Error Rate	Weighted Type I Error Rate*	Max Type I Error Rate
No borrowing (only RCT data)		0.024	0.024	0.024
Dynamic borrowing (with external control)	Conservative prior	0.023	0.023	0.032
	Aggressive prior	0.028	0.026	0.054
Full borrowing (pooling two control arms)		0.033	0.029	0.067

RCT= randomized controlled trial

* Weighted Type I Error Rate is calculated based on the assumed probability on the various scenarios: The probability for "The same" is assumed to be 62.5%, "moderate", 20%, "large" 5%, "moderate reverse" 10%, and "large reverse" 2.5%.

On-going research

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Regulatory Science in Action

As part of the agency's real-world evidence (RWE) efforts, the U.S. Food and Drug Administration is announcing four grant awards (RFA-FD-20-020) to examine the use of real-world data (RWD) to generate RWE in regulatory decision-making. Through this awards program, the agency seeks to encourage innovative approaches to further explore the use of RWD while ensuring that scientific evidence supporting marketing approvals meet FDA's high evidentiary standards.

As directed by the 21st Century Cures Act, FDA is exploring the potential use of RWD and RWE to support the approval of new drug indications or post-approval study requirements for approved drugs. In December 2018, FDA published a strategic RWE Framework in support of this goal.

Content current as of:
11/30/2020

Regulated Product(s)
Drugs

On-going research

- Applying novel statistical approaches to develop a decision framework for hybrid randomized controlled trial designs which combine internal control arms with patients' data from real-world data source

- This project, led by Herbert Pang, PhD, Jiawen Zhu, PhD, at Genentech and Michael Kosorok, PhD, at the University of North Carolina (UNC)

- Time-to-event (TTE) outcome and beyond
- Oncology and rare disease settings

Subsequent research

- Evaluate the impact of randomization ratios in designing hybrid control trials

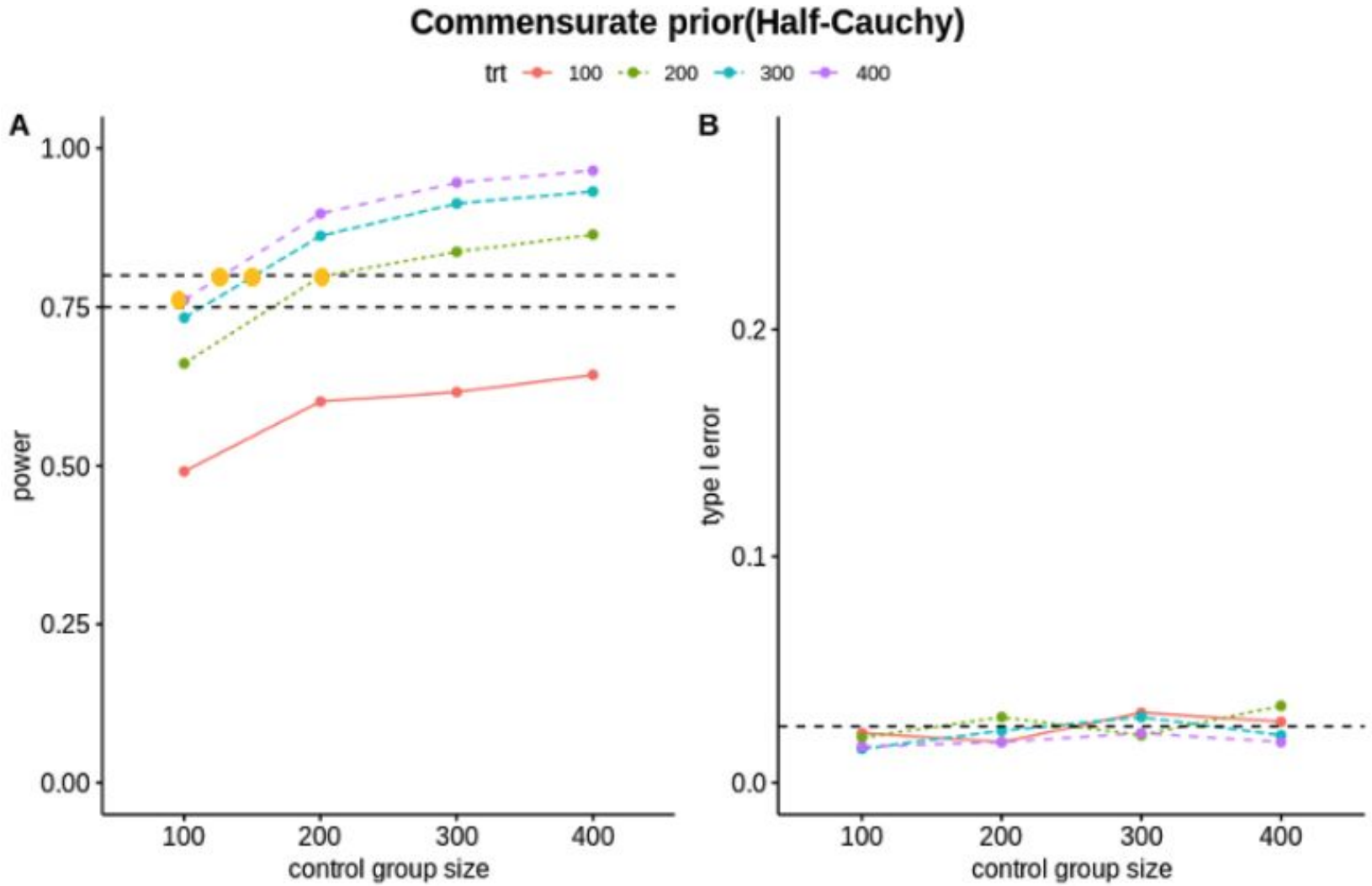
Subsequent research - Simulation

- Investigate the sensitivity of the proposed method for borrowing external controls with respect to different randomization ratios given a fixed number of external control subjects

RCT treatment	RCT control	RCT sample size	Ratio	Power
200	200	400	1:1	0.773
300	150	450	2:1	0.811
400	130	530	3:1	0.833
400	100	500	4:1	0.766

Fu, C., Pang, H., & Zhu, J. (2022). Evaluating the impact of different randomization ratios in designing hybrid control trials. ASA Biopharmaceutical Report, Summer 2022, Volume 29, Issue 2, 22-32

Subsequent research - Simulation



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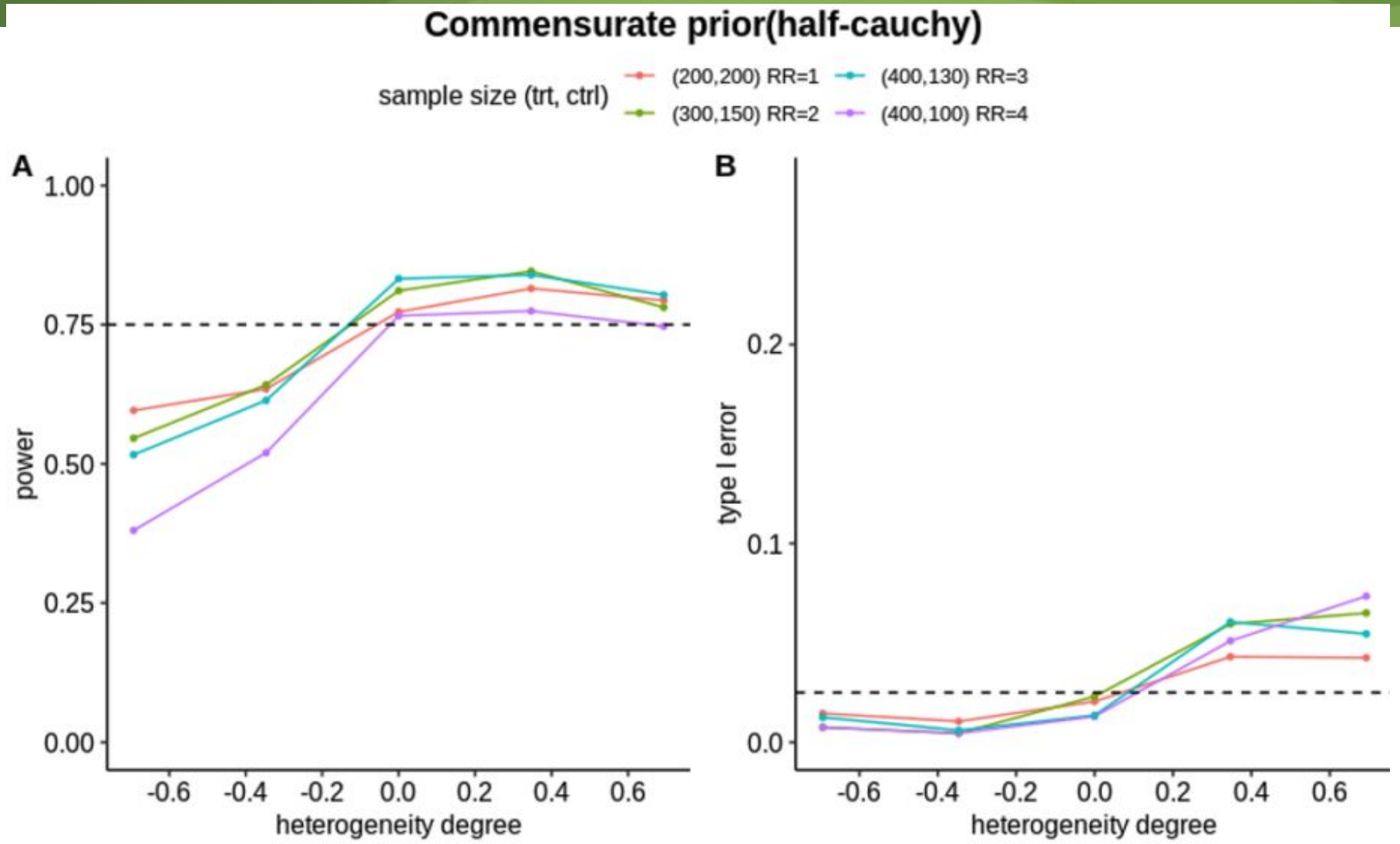
Subsequent research - Results



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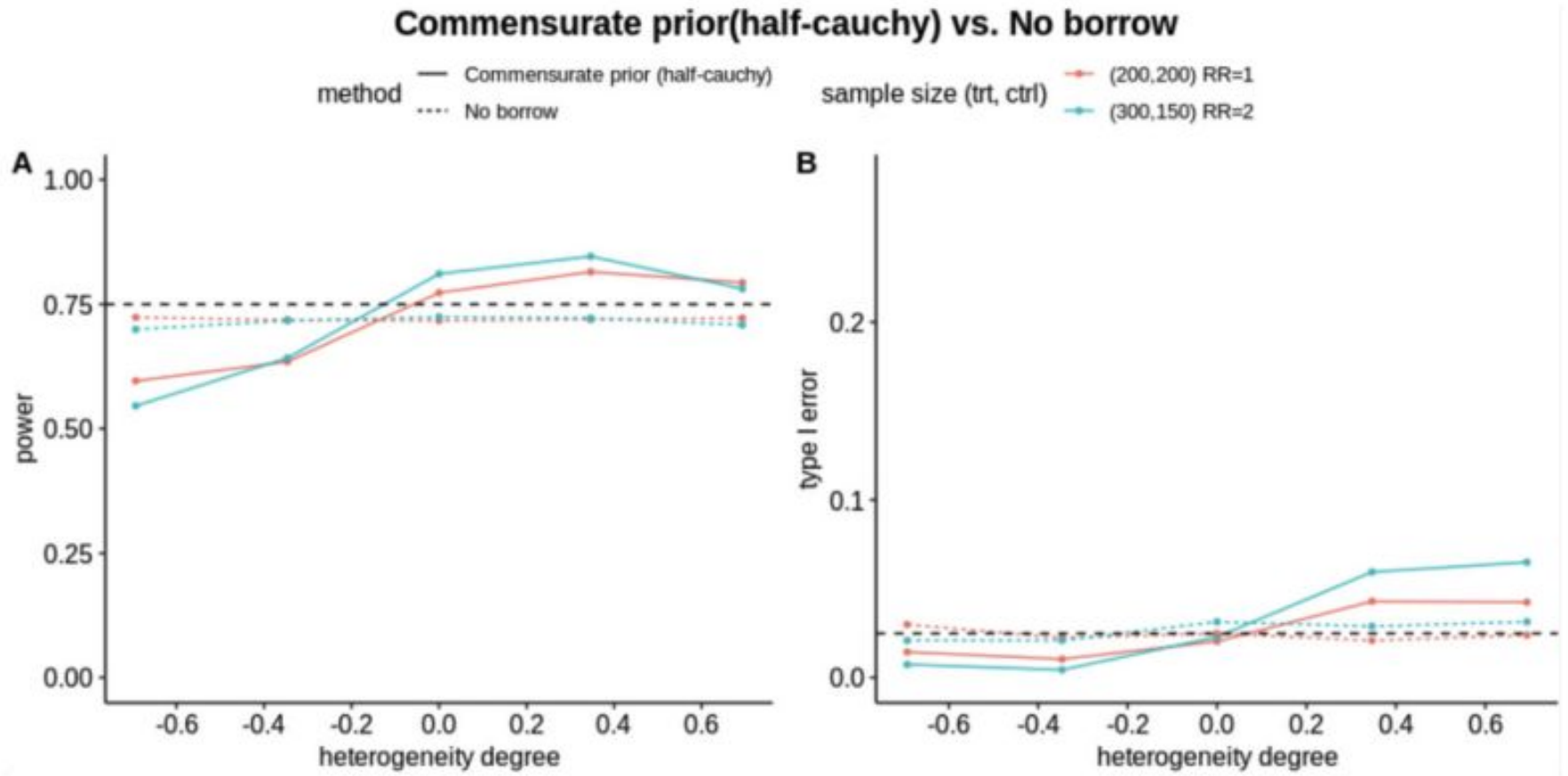

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Subsequent research - Discussion

- when the randomization ratio is 1:1, the commensurate prior method has a good overall performance at various heterogeneity levels
- different randomization ratios demonstrate degree of sensitivity to varied between-trial heterogeneity
- (trt = 300, ctrl = 150) and (trt = 400, ctrl = 130) have similar performance
- ratio of the sample size of RCT internal control to external control

Complex Innovative Designs: remaining challenges and opportunities

- Study design assessment is less standard given the nature of CID
  - Type I error control consideration for regulatory decision making
  - Evaluate CID by working together
  - Sponsors should engage and discuss with HA as early as possible when considering an external borrowing design
- To graduate from a pilot and become normal practice
  - Collaborative effort between HA, academia, and industry

Considerations for Future Studies with External Controls

- Disease setting is an important consideration in determining the suitability of a study design for external borrowing
  - All studies evaluated on a case-by-case basis
  - Studies in which we historically treat patients in the same way (e.g. DLBCL) potentially strong candidates for innovative borrowing approaches
- External control arm source a key aspect
  - Our proposal met 5/6 Pocock criteria – other RWD sources will likely fulfil less
  - Aligning between trials on control treatments, endpoint definitions and other operational aspects will improve the quality of available control data for borrowing
- FDA has shown an openness to our design with external controls for the secondary OS endpoint, although approvability remains a review issue
  - An important step towards the future and an ideal state of borrowing for a primary endpoint

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