A Case Study of a Hybrid Control Design in Diffuse B-Cell Lymphoma

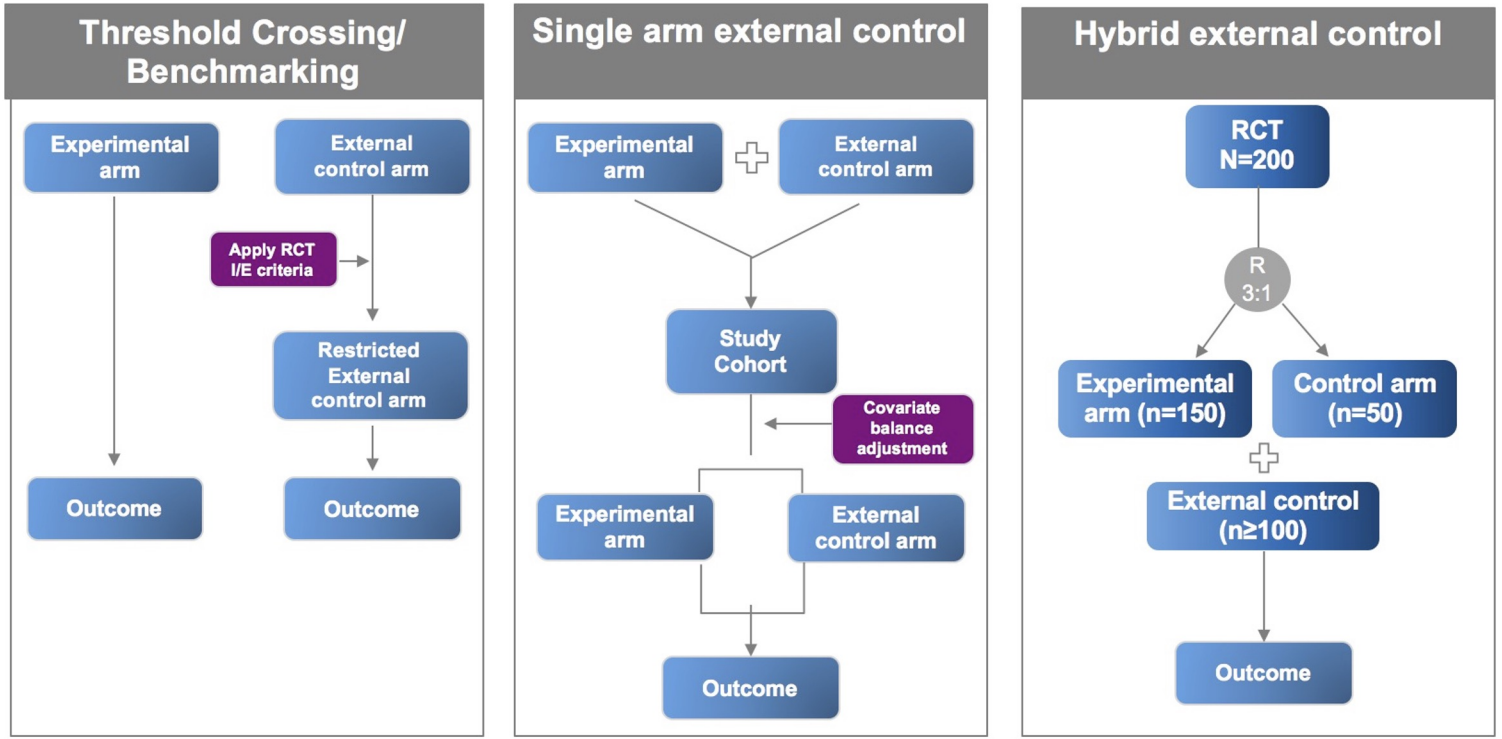
Herbert (Herb) Pang & Jiawen Zhu

March 5 2024 - FDA Public CID Workshop

Outline

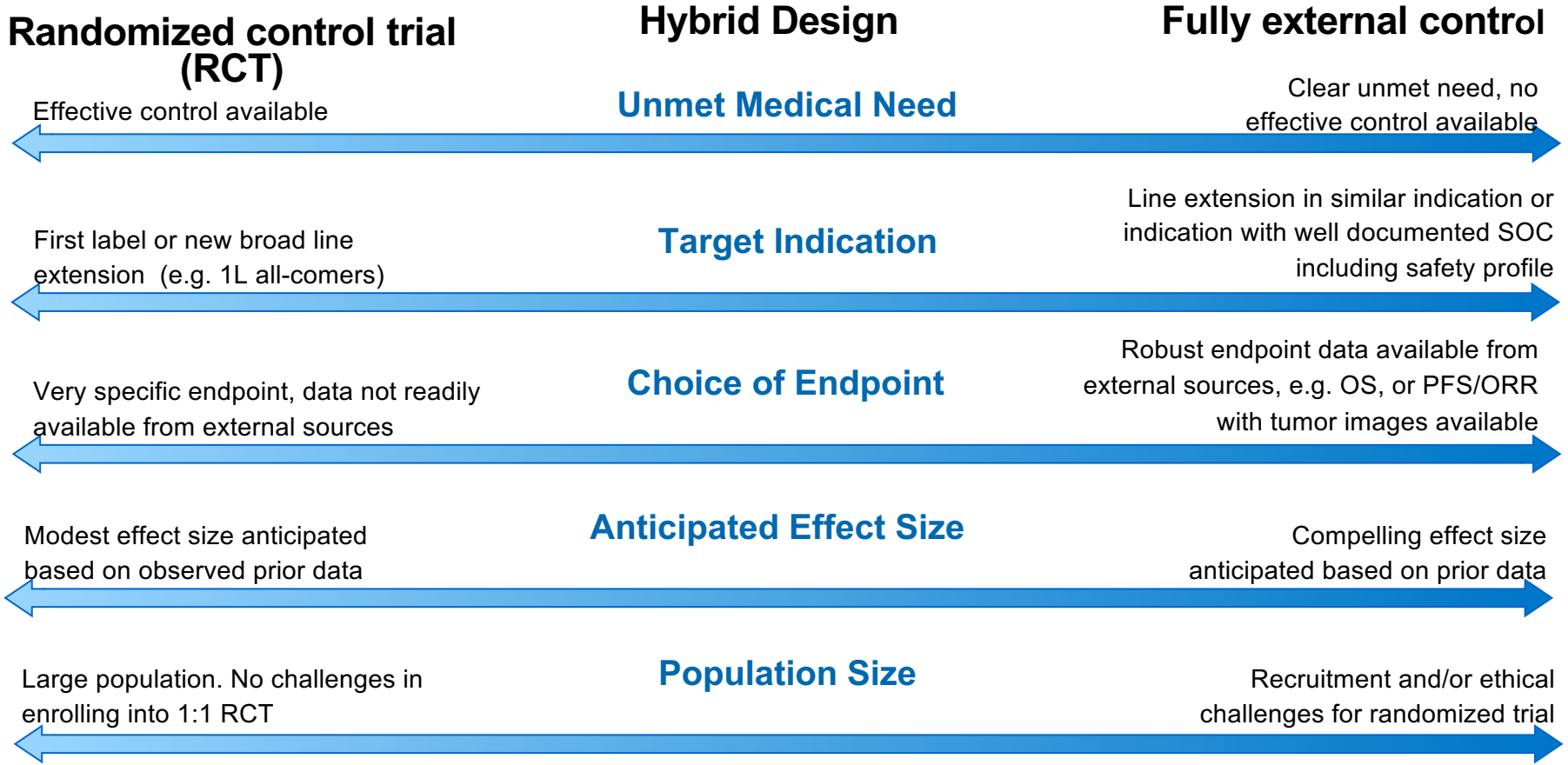
-Introduction: study designs using external controls
-FDA CID pilot program and CID process & timeline
-Genentech/Roche CID pilot in 1L DLBCL
-Hybrid control ongoing research
-Summary

Study designs using external controls



all numbers are just for illustration purposes

Considerations for choosing level of randomization



Potential biases 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)

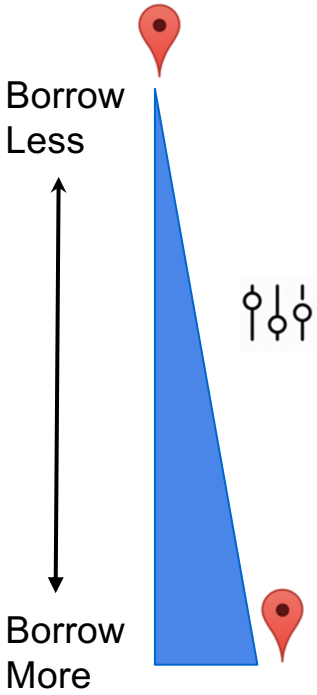
...

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

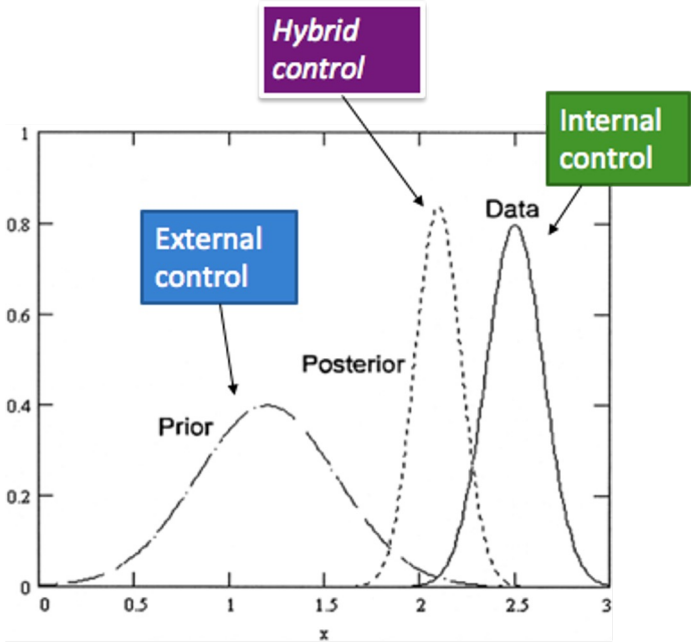


- **No borrowing**
  only RCT data is used to estimate treatment effect
- **Dynamic borrowing: Conservative prior**
  Skeptical on external control
- **Dynamic borrowing: Aggressive prior**
  Optimistic on external control
- **Full borrowing**
  Two controls are pooled together when estimating treatment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

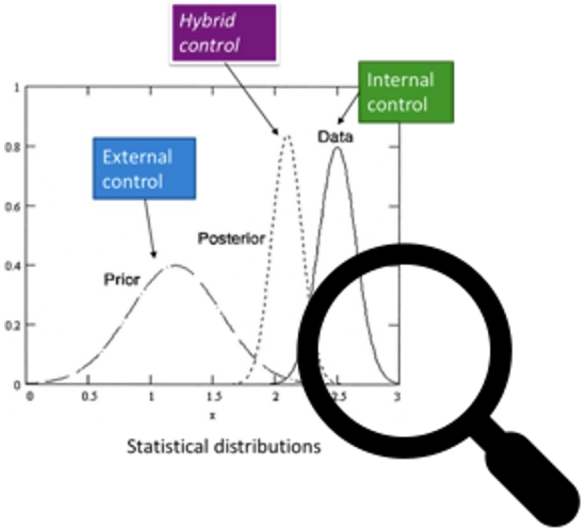


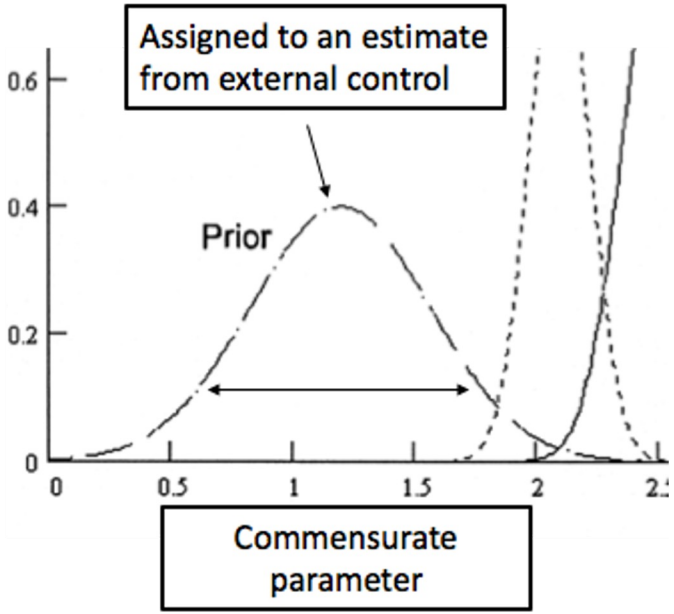
Statistical distributions

- 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

Figure adapted from "Methods for Assessing the Credibility of Clinical Trial Outcomes –Drug information journal; Robert A. Matthews (2001)"

Bayesian methods can adjust the amount of borrowing





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

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

K. Viele et al 2013

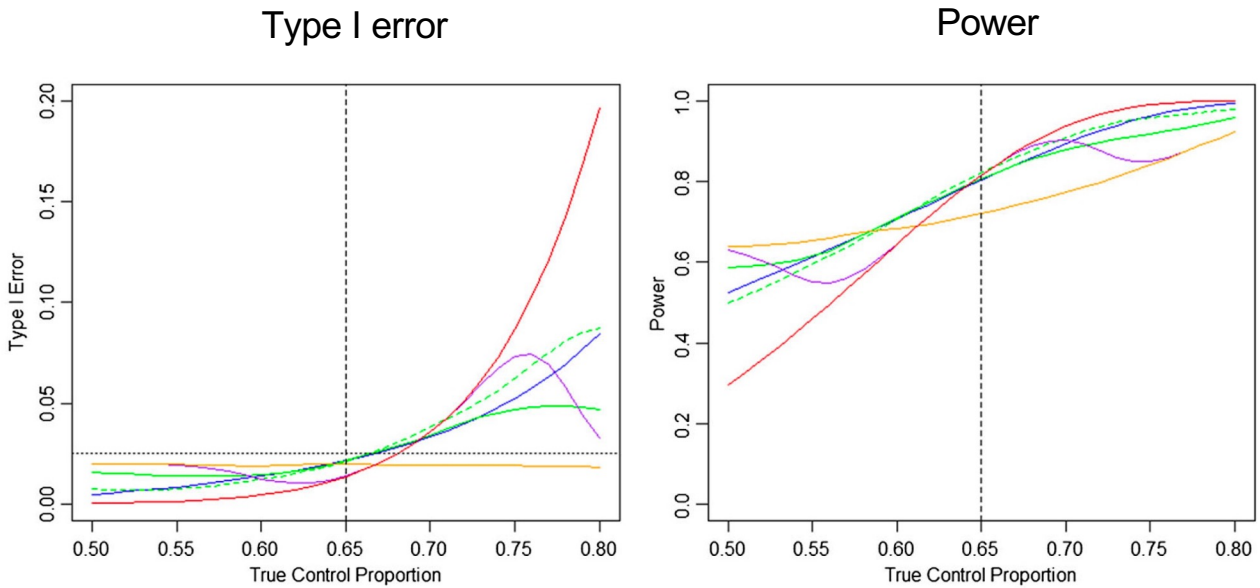


Figure 9. Type I error and power comparison for separate (orange), pooling (red), selected test-then-pool (size 0.10, purple), downweighted power prior (40% weight, blue), and hierarchical model (IGamma(1, 0.01) in dashed green, and IGamma(0.001, 0.001) in solid green). Generally, the test-then-pool 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.

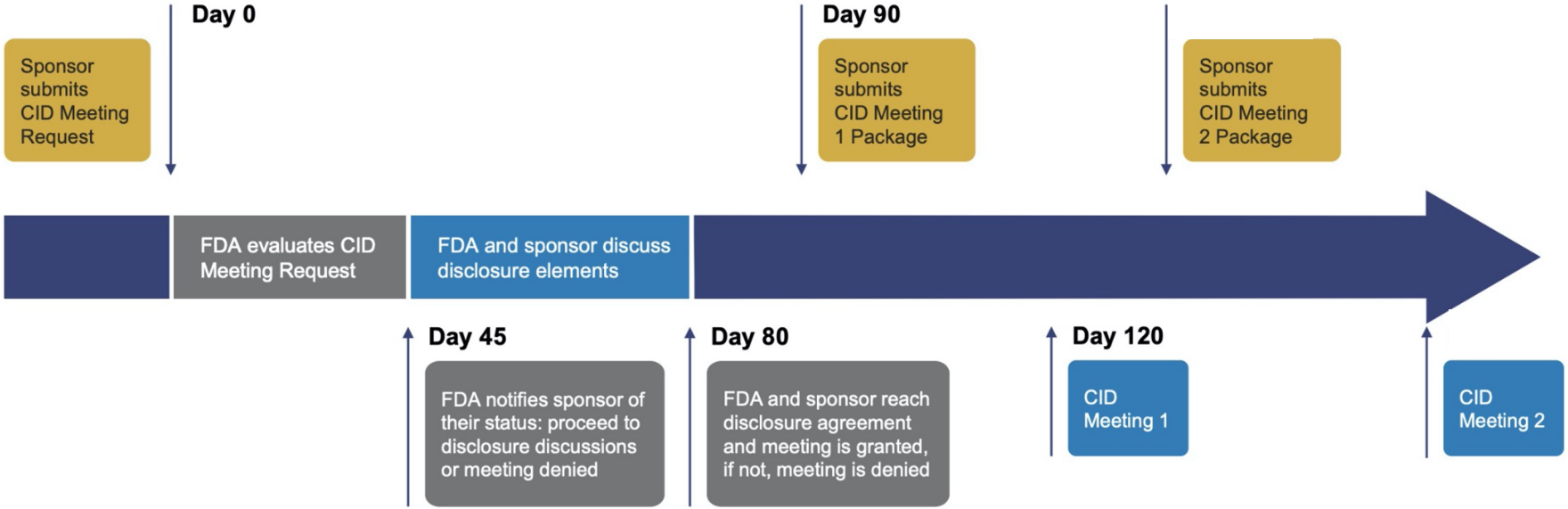
PDUFA VI Provisions: Complex Innovative Trial Designs (CID)

- 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

Link to FDA CID Website -

CID Process & Timelines



Why innovative design was needed for our case

Unmet medical need (earlier slide) 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

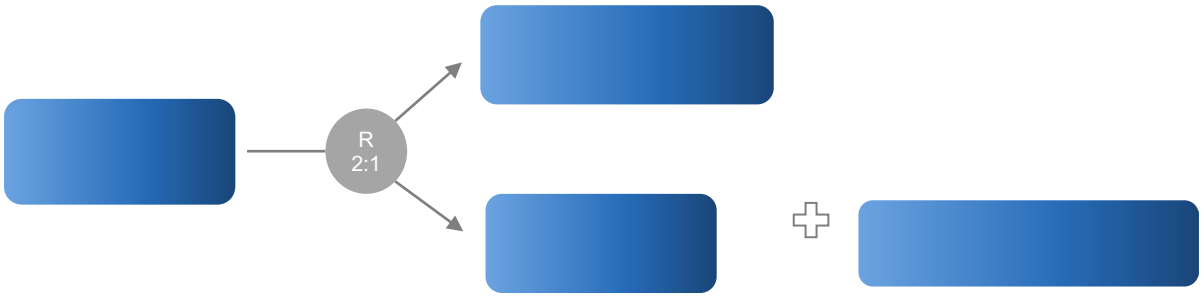
"Borrowing" patients from the control arm of another study helps us

- 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

Proposed Phase 3 Study Design in 1L DLBCL



Primary Endpoint:
- **PFS Investigator Assessed**

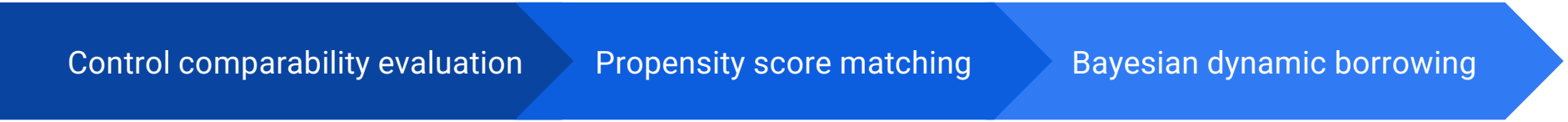
Key Secondary Endpoints
- **OS**, based on randomized patients & matched external control

- 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
- 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 (earlier slide)

Final Analysis Flow Diagram

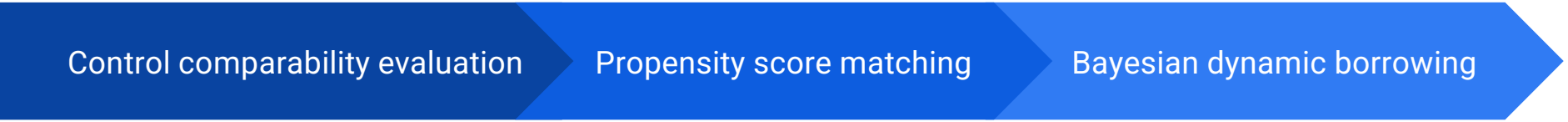


Final Analysis Flow Diagram

Control comparability evaluation → Propensity score matching → Bayesian dynamic borrowing

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

Final Analysis Flow Diagram



- 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

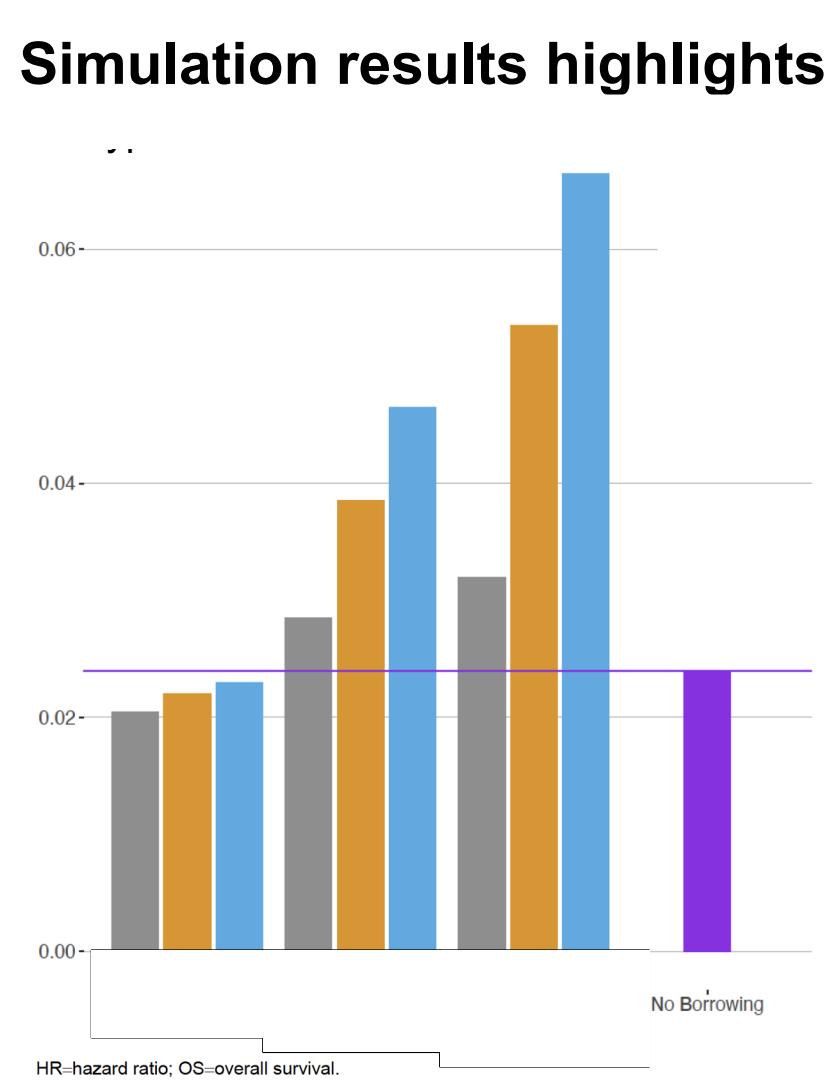
- Focused on the evaluation of the proposed statistical method (PS matching and the Bayesian commensurate prior approach)

- 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***

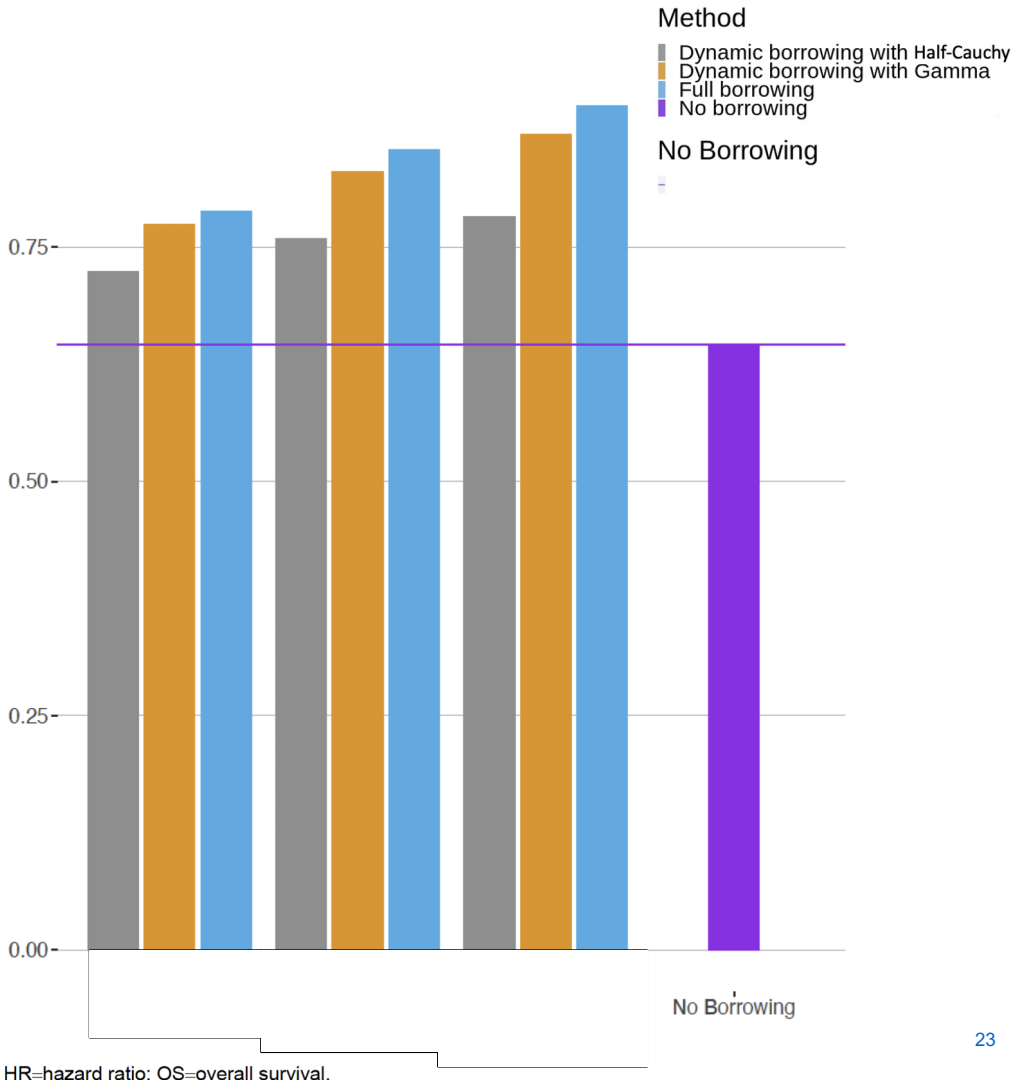
Simulation scope and objective

- 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

Simulation results highlights



HR=hazard ratio; OS=overall survival.



HR=hazard ratio; OS=overall survival.

Simulation scope and objective

- Examined the trial operating characteristics (OC) under:
  - **Violation** of various **assumptions**
    - Unmeasured confounding
    - Survival curve distribution
    - Non-linear/non-additive model

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%.

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?

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	- R Software available: ***psborrow2*** - Roche statistical software and methods experts - Learnings from CID program
	Methods R&D	- FDA HHSU01 grant (ongoing work)

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

Related effort: Methodological research

FDA U.S. FOOD & DRUG ADMINISTRATION

Search Menu

Home / Drugs / Science and Research | Drugs / FDA Announces 4 Grant Awards for Projects Exploring the Use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making

FDA Announces 4 Grant Awards for Projects Exploring the Use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making

Share Tweet Linkedin Email Print

Science and Research | Drugs

Regulatory Science at CDER

Research Tools and Resources

Work With Us

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)

Downweighting external controls

- **Case weighted adaptive power priors** (Kwiatkowski et al. accepted at Biometrics)
  - Bayesian
  - Allow case specific downweighting for incomparable subgroups in the external control

EVALUATING THE IMPACT OF DIFFERENT RANDOMIZATION RATIOS IN DESIGNING HYBRID CONTROL TRIALS

Chenqi Fu (Penn State), Herbert Pang (Genentech), Jiawen Zhu (Genentech)

BIOPHARMACEUTICAL REPORT SUMMER 2022

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

Covariate adjustments & Dynamic Borrowing

MAIN PAPER | Open Access

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

Chenqi Fu, Herbert Pang, Shouhao Zhou, Jiawen Zhu

First published: 07 March 2023 | https://doi.org/10.1002/pst.2297

RocheLink

Funding information: U.S. Food and Drug Administration, Grant/Award Number: 5U01FD007206

SECTIONS PDF TOOLS SHARE

On-going research

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

Summary

- ➢ CID pilot program facilitated a collaborative scientific discussion with the FDA
  - Alignment on critical conceptual design proposals to boost confidence in the future design and outcomes of the study
- ➢ The Agency demonstrated openness to the proposed design with external controls while providing key feedback
- ➢ Early sponsor and health authority engagement is paramount when considering novel trial designs, such as a borrowing approach
- ➢ Successful adoption of novel innovative designs requires a collaborative effort between HA, academia, and industry
  - Highlight an example of such an endeavor to fill methodological research gap

Acknowledgements

- Laura Wong
- Sofia Khan
- Zac Taylor
- Emma Clark
- Hannah Douthwaite-Billing
- Sarah Kirk
- Michelle Boyer
- Alex Bazeos
- Kaspar Rufibach
- Victor Huang
- Aijing Lin
- Samantha Roberts
- YJ Choi
- Yichen Lu (intern)
- Jiaheng Qiu
- Mark Yan
- Yanwen Jiang
- Imola Fodor
- Jane Fridlyand
- Ray Lin
- Uli Burger
- Marcel Wolbers
- FDA colleagues
- Grant #: HHS U01 FD007206
- Genentech & UNC grant team
- UNC students
- Stats Engineering colleagues
- Gracie Lieberman
- Lisa LaVange
- Chenqi Fu
- Gracy Crane
- Evan Kwiatkowski
- Rasika Kalamegham

Doing now what patients need next