



The Clinical Data
Science Conference

APAC 2026

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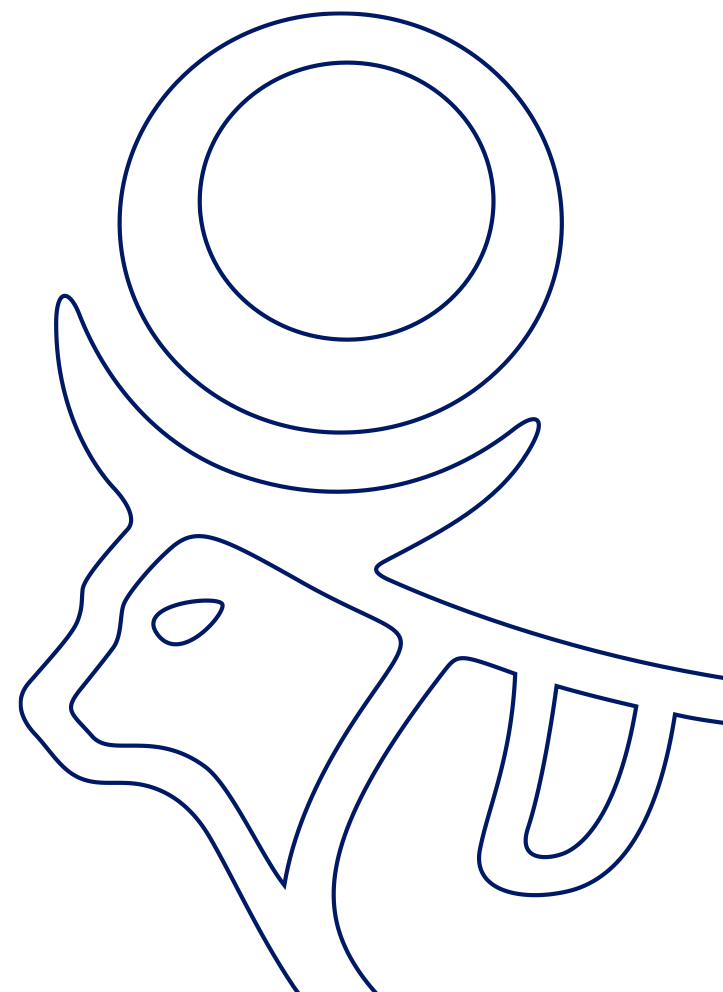
Novotel Hyderabad International Convention Centre



Paper ET06 : Leveraging Historical Control Data Through Adaptive Bayesian Hierarchical Models

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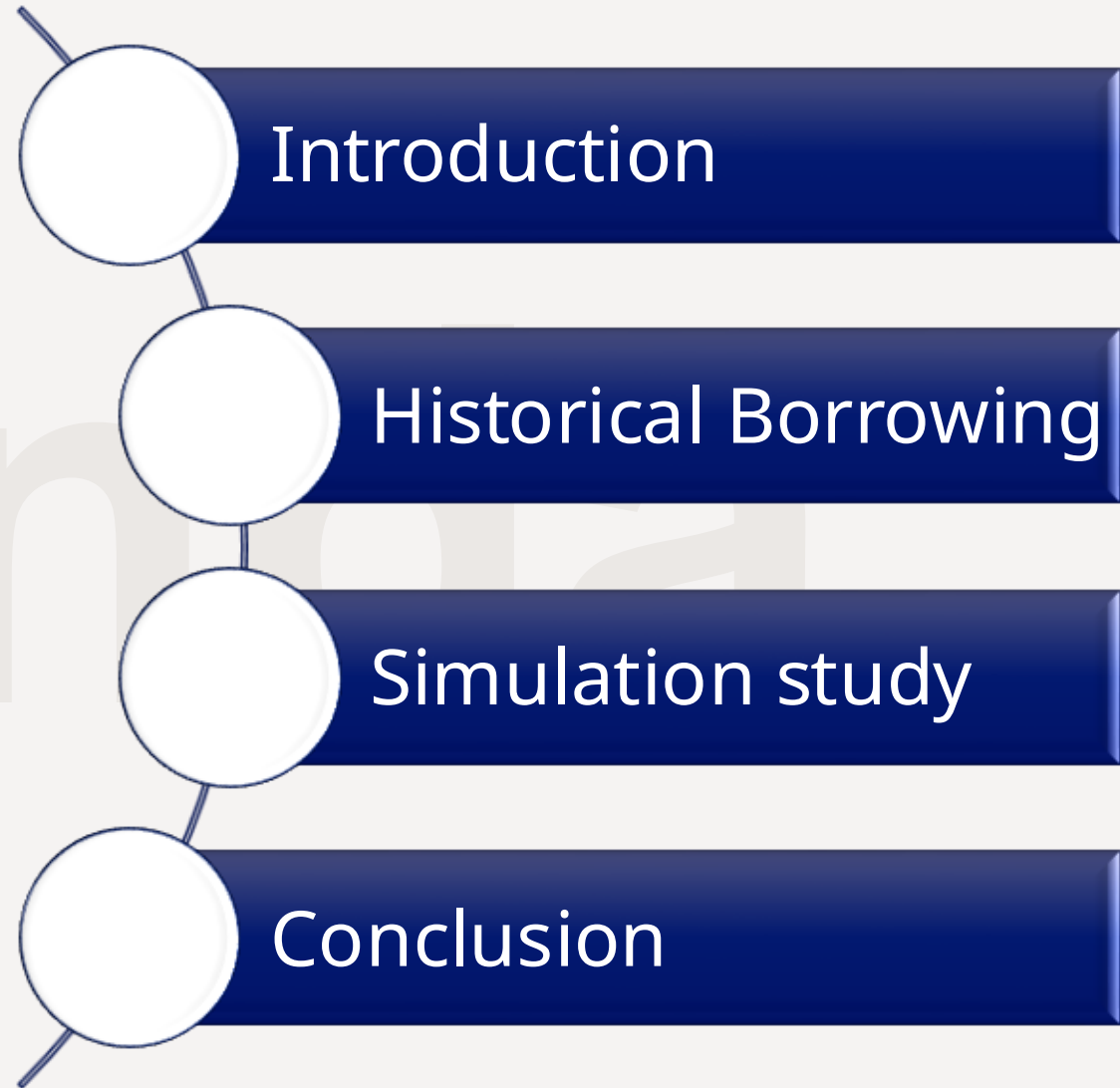


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Agenda



Introduction

Bayesian adaptive clinical trial methodology has evolved dramatically over the last few decades

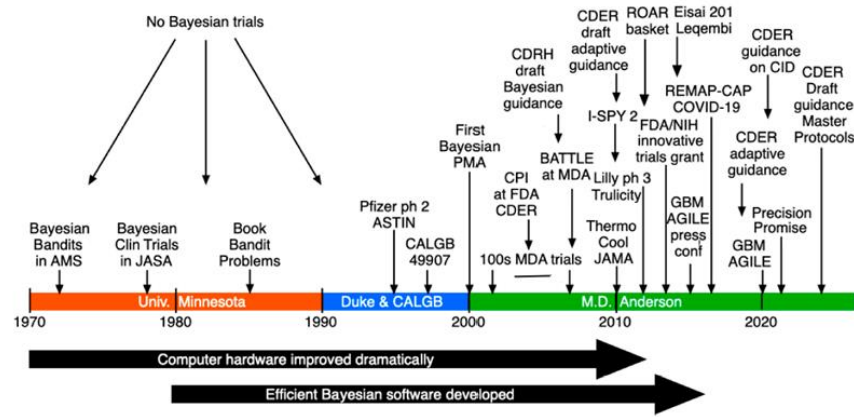


Figure : Timeline of Bayesian adaptive clinical trials. Donald Berry at the University of Minnesota, then Duke University, plus the Cancer & Leukemia Group B (CALGB), and then the University of Texas M.D. Anderson Cancer Center (MDACC) plus Berry Consultants. Arrows on clinical trials indicate time of the initial design. Numbers on the arrows indicate the relevant references.

Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products Guidance for Industry

Additional copies are available from:

Division of Drug Information
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U.S. Department of Health and Human Services
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January 2026
Biostatistics

Historical Borrowing

When should we consider borrowing?

755 therefore it is not recommended for this purpose. First, by borrowing information, one is
 756 assuming that the borrowed information is relevant. Evaluating the degree of borrowing based on
 757 the expected outcome when there is no effect is philosophically inconsistent given a prior which
 758 assumes a non-zero effect. Second, dynamic methods lessen the impact of borrowing when
 759 effects that are smaller and close to the null value are observed. Consequently, borrowing will be
 760 low when the observed data are incompatible with the prior, mitigating any potential increase in
 761 Type I error rate. Hence, the Type I error rate alone will not provide a complete assessment of
 762 the influence of the prior.
 763

Contains Nonbinding Recommendations

Draft — Not for Implementation

A. Borrowing from Previous Clinical Trials

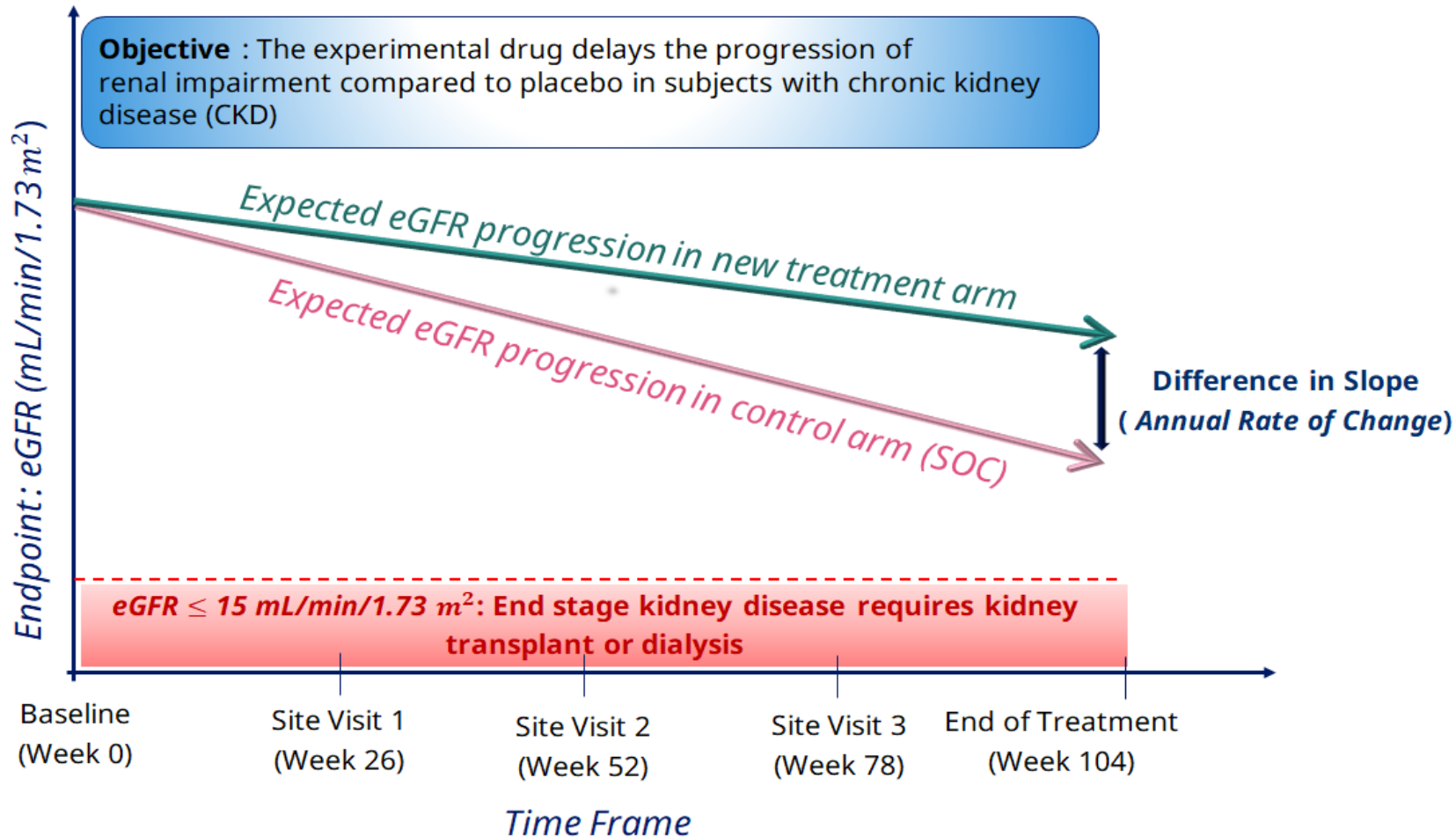
Under certain circumstances, an informative prior for a clinical trial analysis can be formed based on results from previous clinical trial(s) of the same drug. For example, borrowing from a previous trial was used in a phase 3 study to evaluate REBYOTA, a fecal microbiota transplant product, for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals with recurrent CDI. *C. difficile* is a common cause of antibiotic-associated diarrhea and colitis and is a major public health burden. The primary analysis of the randomized, double-blind, placebo-controlled phase 3 study to evaluate the effectiveness of REBYOTA used a Bayesian model to formally incorporate data from a previous phase 2 placebo-controlled study of REBYOTA. This analysis supported the effectiveness of REBYOTA, which was approved in 2022.⁴

B. Augmenting a Randomized Concurrent Control Using an External Control or Nonconcurrent Control Data

In some cases, it can be challenging to conduct an adequately powered randomized trial due to limited population and/or ethical considerations. Borrowing data from an external or nonconcurrent control to augment the randomized concurrent control may be appealing in these situations, and Bayesian methods have been proposed to implement such approaches. For example, Bayesian methods have been proposed to augment the randomized concurrent control and leverage nonconcurrent control data in the oncology platform trials GBM AGILE⁵ and Precision Promise,⁶ which evaluate marker-targeted treatments for patients with glioblastoma and pancreatic cancer, respectively. The analyses use a Bayesian model to try to account for temporal shifts in efficacy outcomes such as tumor response (Saville et al. 2022).⁷ As another example, a non-inferiority study of pediatric patients with multiple sclerosis⁸ was proposed through the Complex Innovative Trial Design (CID) program⁹ with a prespecified Bayesian analysis to leverage information from historical studies of the active comparator.

Simulation study

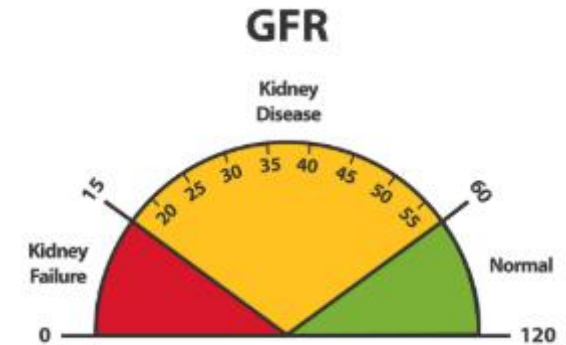
A Phase 2 trial for patients with chronic kidney disease (CKD)



eGFR
Estimated
Glomerular
Filtration Rate



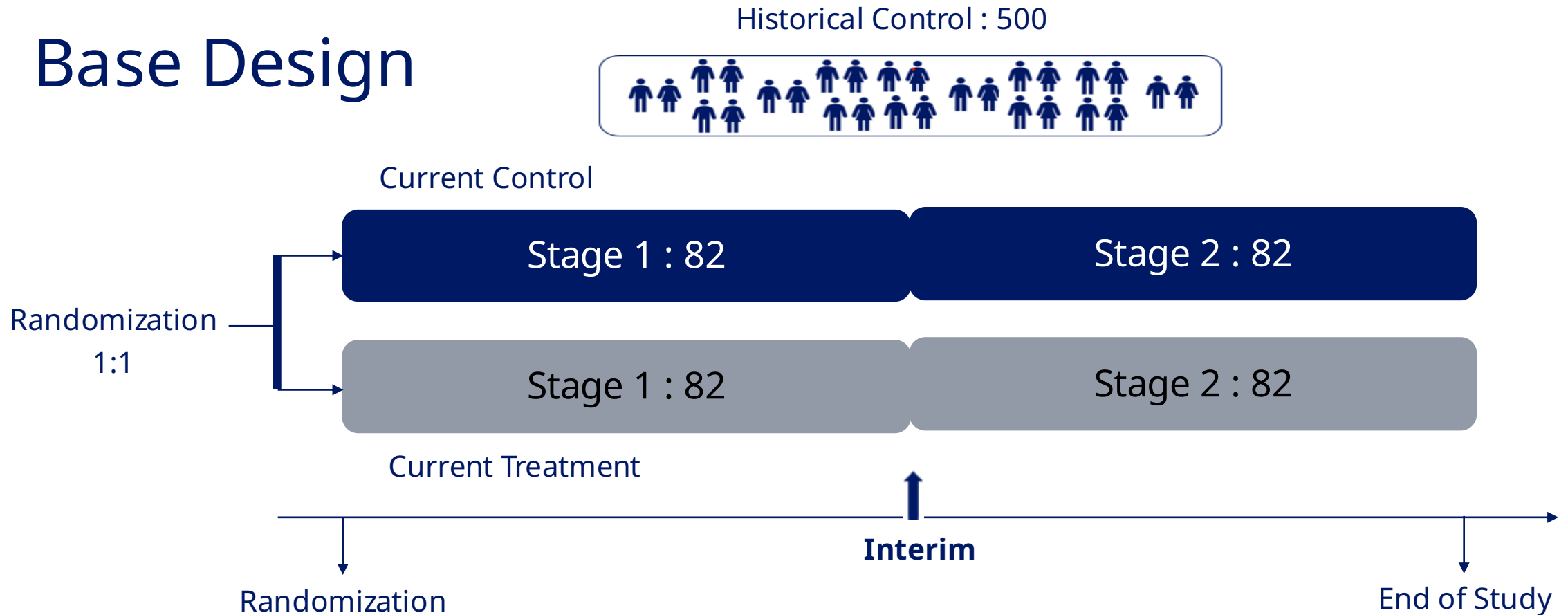
Blood test
Shows how well
your kidneys filter
(clean) your blood



NATIONAL KIDNEY
FOUNDATION.

<https://www.kidney.org/>

Base Design



Q : How did you decide the stage 1 & stage 2 sample sizes ?

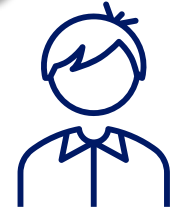
- Group sequential design with planned interim at **50%**
- α : **2.5%**
- Power : **90%**
- Expected treatment effect (Slope difference) : **2 mL/min/m²** per year

Commensurate Prior



.....Well traditionally, we could use it to get realistic assumption on treatment effect

How could we utilize the historical study?

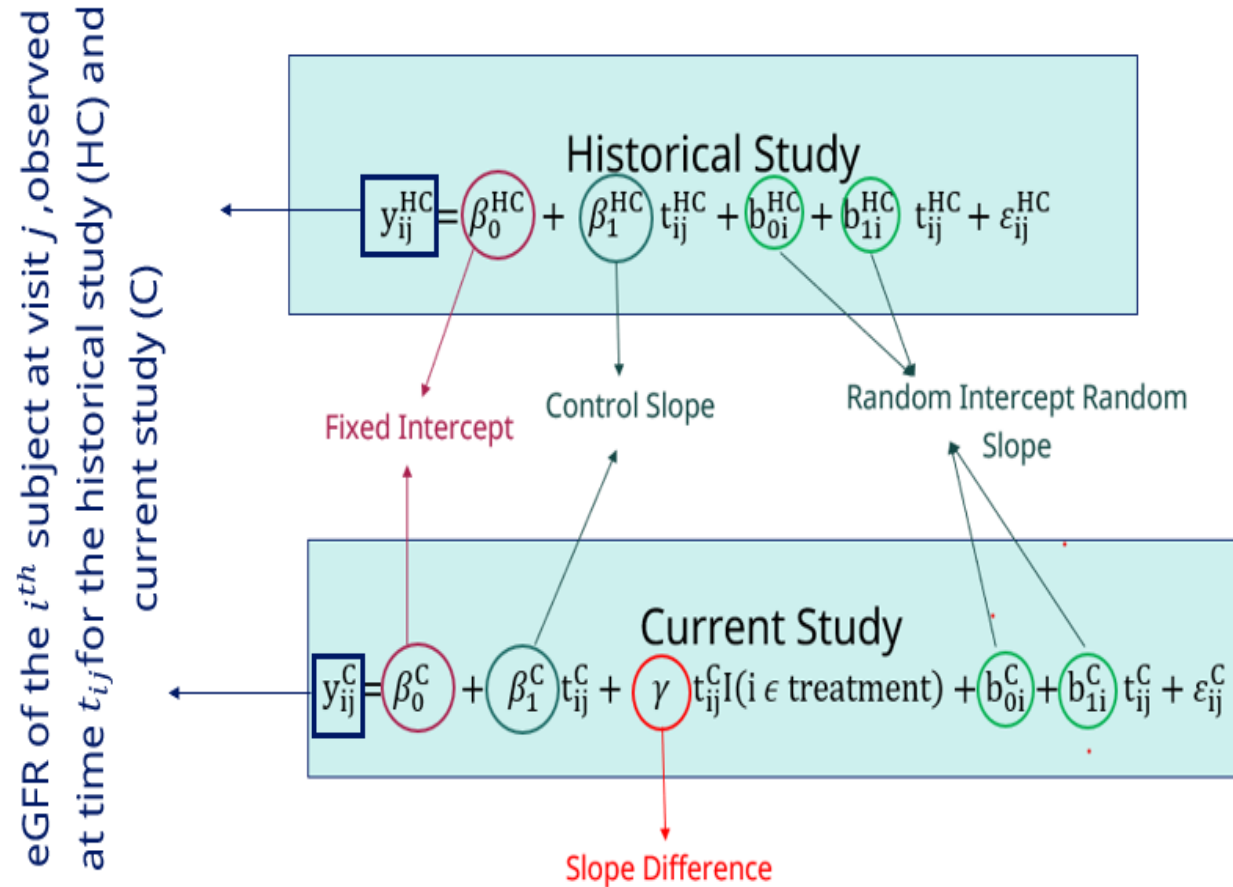


Let's try commensurate prior, it can

1. Bridge the historical control and current control
2. Allows dynamic borrowing

Longitudinal Model for eGFR Slope

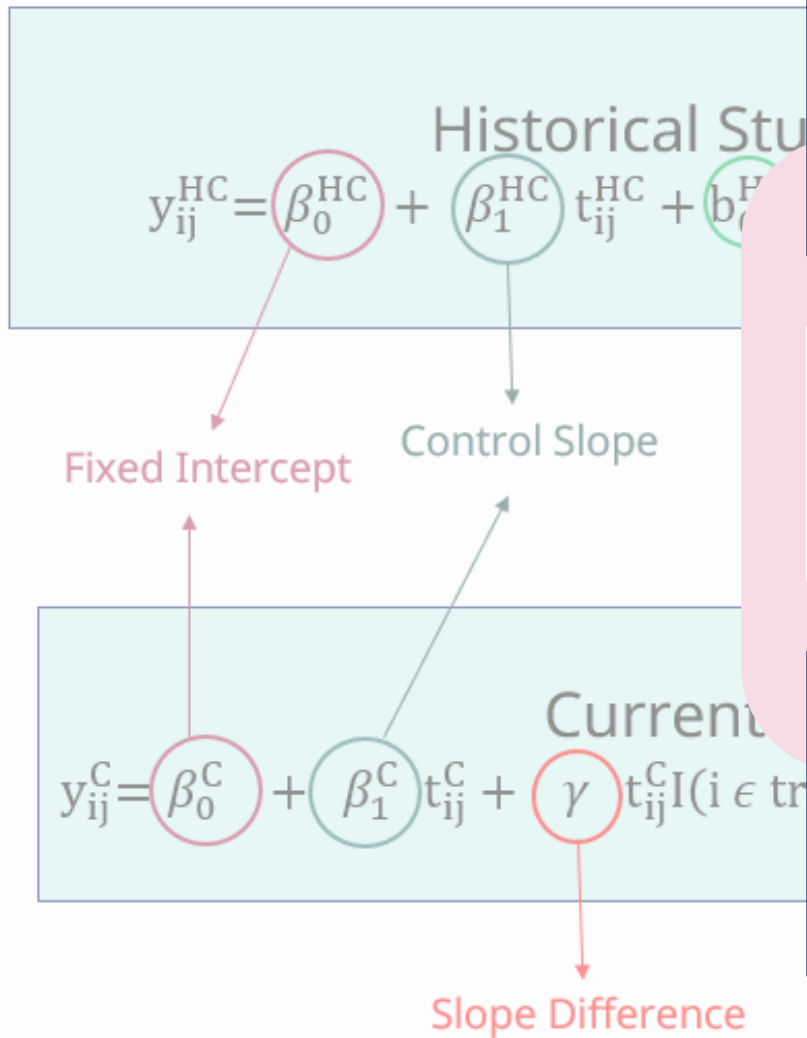
Random Intercept & Random Slope Model



A linear mixed-effects model with subject specific random intercept and random slope is considered for modelling eGFR for the historical control and current study.

- β_0^C, β_0^{HC} : fixed intercept
- β_1^C, β_1^{HC} : control slope
- γ : treatment difference in annual rate of change in eGFR (primary endpoint)
- b_{0i}^C, b_{0i}^{HC} : random intercept for the subject i
- b_{1i}^C, b_{1i}^{HC} : random slope for the subject i
- $(b_{0i}^C, b_{1i}^C)' \sim BVN(\tilde{0}, \Sigma_b^C), (b_{0i}^{HC}, b_{1i}^{HC})' \sim BVN(\tilde{0}, \Sigma_b^{HC})$
- $\varepsilon_{ij}^C, \varepsilon_{ij}^{HC}$: independent residuals with variance σ_C^2 and σ_{HC}^2 respectively

Commensurate Prior on Control Slope



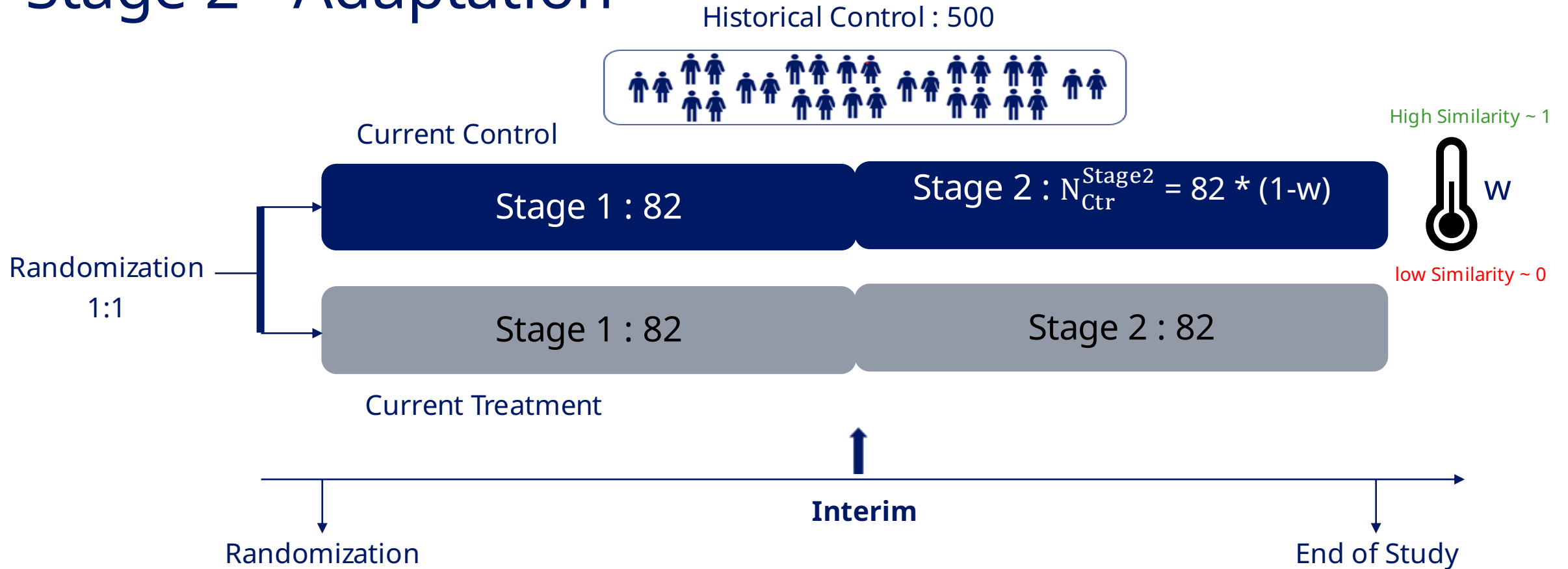
We extend the Hobbs commensurate prior by introducing a mixture of commensurability itself we allow the data to select between two commensurate regimes corresponding to strong and weak borrowing between historical control slope and current control slope.

$$\beta_1^C | \beta_1^{HC}, z \sim \begin{cases} N(\beta_1^{HC}, \tau_{match}^{-1}); & z = 1 \\ N(\beta_1^{HC}, \tau_{no-match}^{-1}); & z = 0 \end{cases}$$

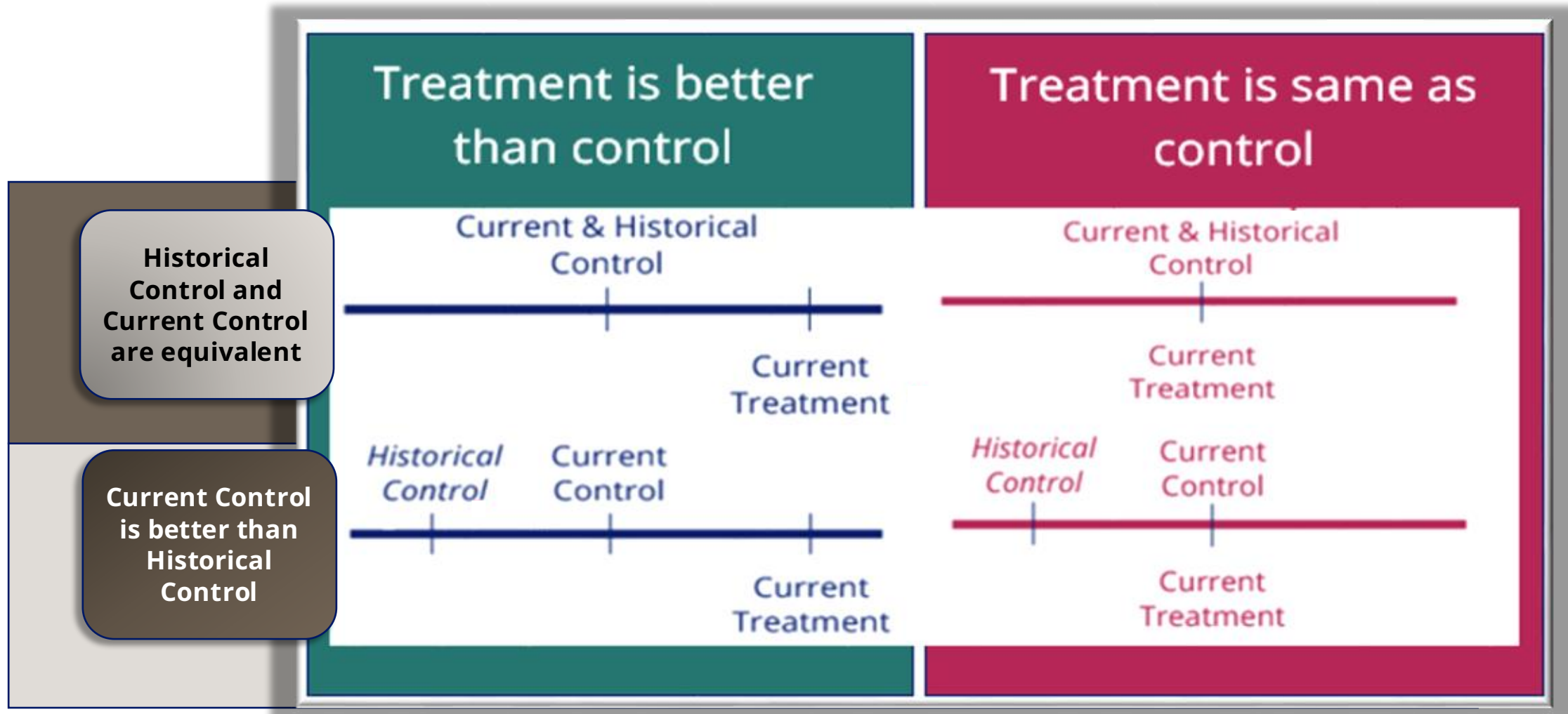
$Z = 1$ corresponds to the standard Hobbs commensurate prior with precision τ_{match} , representing strong commensurability.

$Z = 0$ represents a weakly commensurate prior with fixed low precision $\tau_{no-match}$, reflecting minimal borrowing.

Stage 2 - Adaptation



Sensitivity Analysis



Simulation Results

Historical Control
and Current
Control are
equivalent

Bayesian posterior estimates				
Treatment is better than control – Current & Historical control are equivalent				
Coefficient	Estimate (Median)	LL (2.5%)	UL (97.5%)	N (%)
Stage-1				
Intercept	52.63	50	55.53	
Control Slope	-2.34	-2.55	-2.1	
Borrowing strength (W)	0.87	0.01	1	
SD (Random Intercept)	17.01			
SD (Random Slope)	0.95			
SD (Residual)	1			
Stage-2 control sample size (% reduced from base)				11 (86.59%)
Stage-2				
Intercept	51.48	49.28	53.57	
Control Slope	-2.3	-2.49	-2.11	
SD (Random Intercept)	17.95			
SD (Random Slope)	1.01			
SD (Residual)	0.99			

Bayesian posterior estimates				
Treatment is same as control – Current & Historical control are equivalent				
Coefficient	Estimate (Median)	LL (2.5%)	UL (97.5%)	N (%)
Stage-1				
Intercept	51.3	48.63	54.08	
Control Slope	-2.35	-2.58	-2.09	
Borrowing strength (W)	0.89	0.01	1	
SD (Random Intercept)	17.64			
SD (Random Slope)	1.14			
SD (Residual)	1			
Stage-2 control sample size (% reduced from base)				9 (89.02%)
Stage-2				
Intercept	51.71	49.66	53.67	
Control Slope	-2.31	-2.51	-2.11	
SD (Random Intercept)	16.98			
SD (Random Slope)	1.09			
SD (Residual)	0.98			

1. Results based on R simulated data.

2. **Simulation Inputs** :- Fixed Intercept : 47.5 ; Control Slope (Historical) : -2.5 ; Control Slope (Current) : -2.5 ; Random Intercept Standard Deviation (SD) : 17.5 ; Random Slope Standard Deviation (SD) : 1 ; Residual Standard Deviation (SD) : 1

Simulation Results

Current Control is better than Historical Control

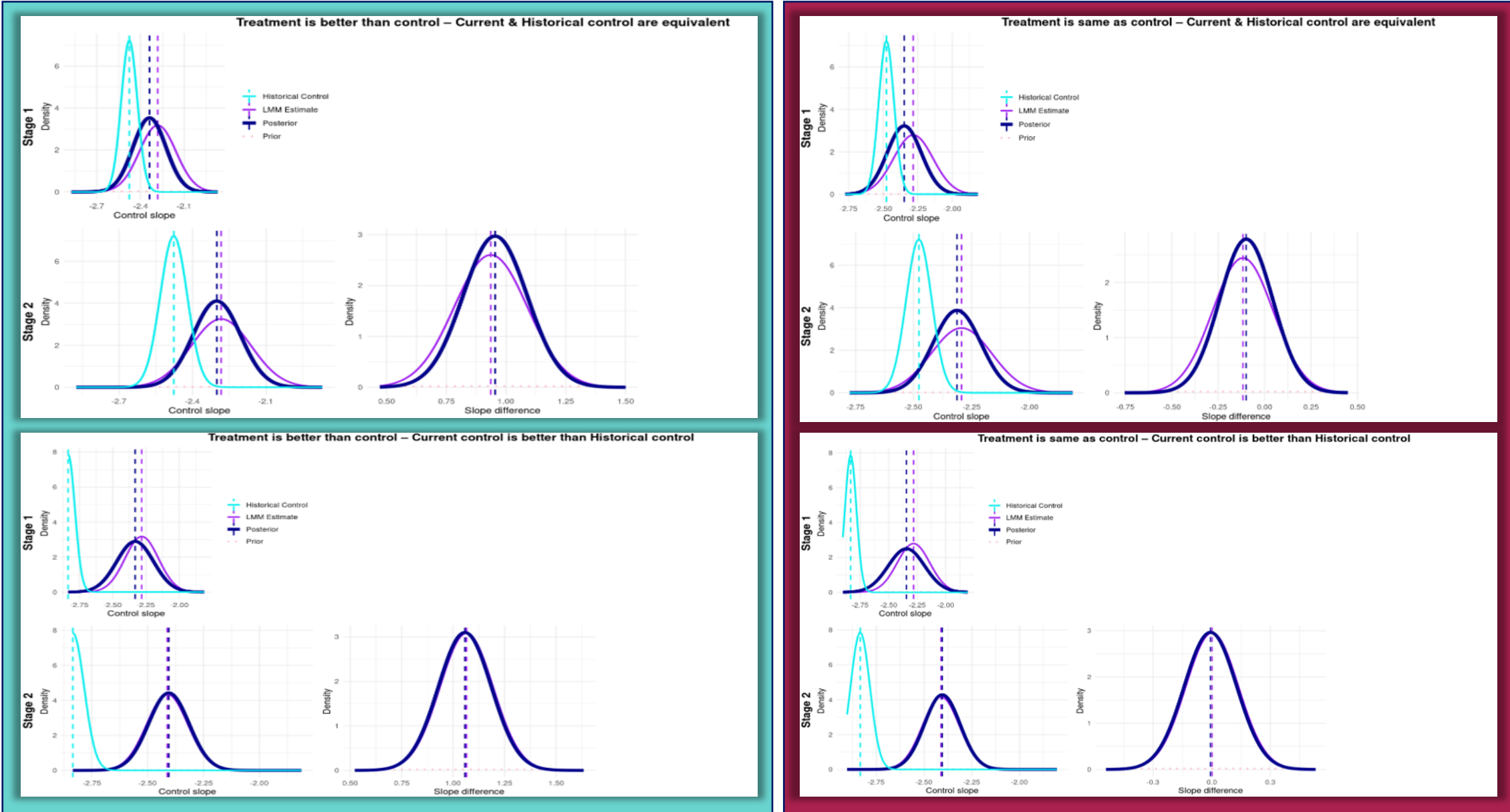
Bayesian posterior estimates				
Treatment is better than control – Current control is better than Historical control				
Coefficient	Estimate (Median)	LL (2.5%)	UL (97.5%)	N (%)
Stage-1				
Intercept	52.96	50.26	55.38	
Control Slope	-2.33	-2.6	-2.06	
Borrowing strength (W)	0.01	0	1	
SD (Random Intercept)	17.03			
SD (Random Slope)	0.95			
SD (Residual)	1			
Stage-2 control sample size (% reduced from base)				81 (1.22%)
Stage-2				
Intercept	51.9	50.09	53.68	
Control Slope	-2.4	-2.58	-2.23	
SD (Random Intercept)	17.87			
SD (Random Slope)	1			
SD (Residual)	0.97			

Bayesian posterior estimates				
Treatment is same as control – Current control is better than Historical control				
Coefficient	Estimate (Median)	LL (2.5%)	UL (97.5%)	N (%)
Stage-1				
Intercept	51.38	48.87	54.07	
Control Slope	-2.34	-2.66	-2.04	
Borrowing strength (W)	0.01	0	1	
SD (Random Intercept)	17.62			
SD (Random Slope)	1.14			
SD (Residual)	1			
Stage-2 control sample size (% reduced from base)				81 (1.22%)
Stage-2				
Intercept	51.72	49.68	53.56	
Control Slope	-2.41	-2.59	-2.22	
SD (Random Intercept)	17.09			
SD (Random Slope)	1.07			
SD (Residual)	0.97			

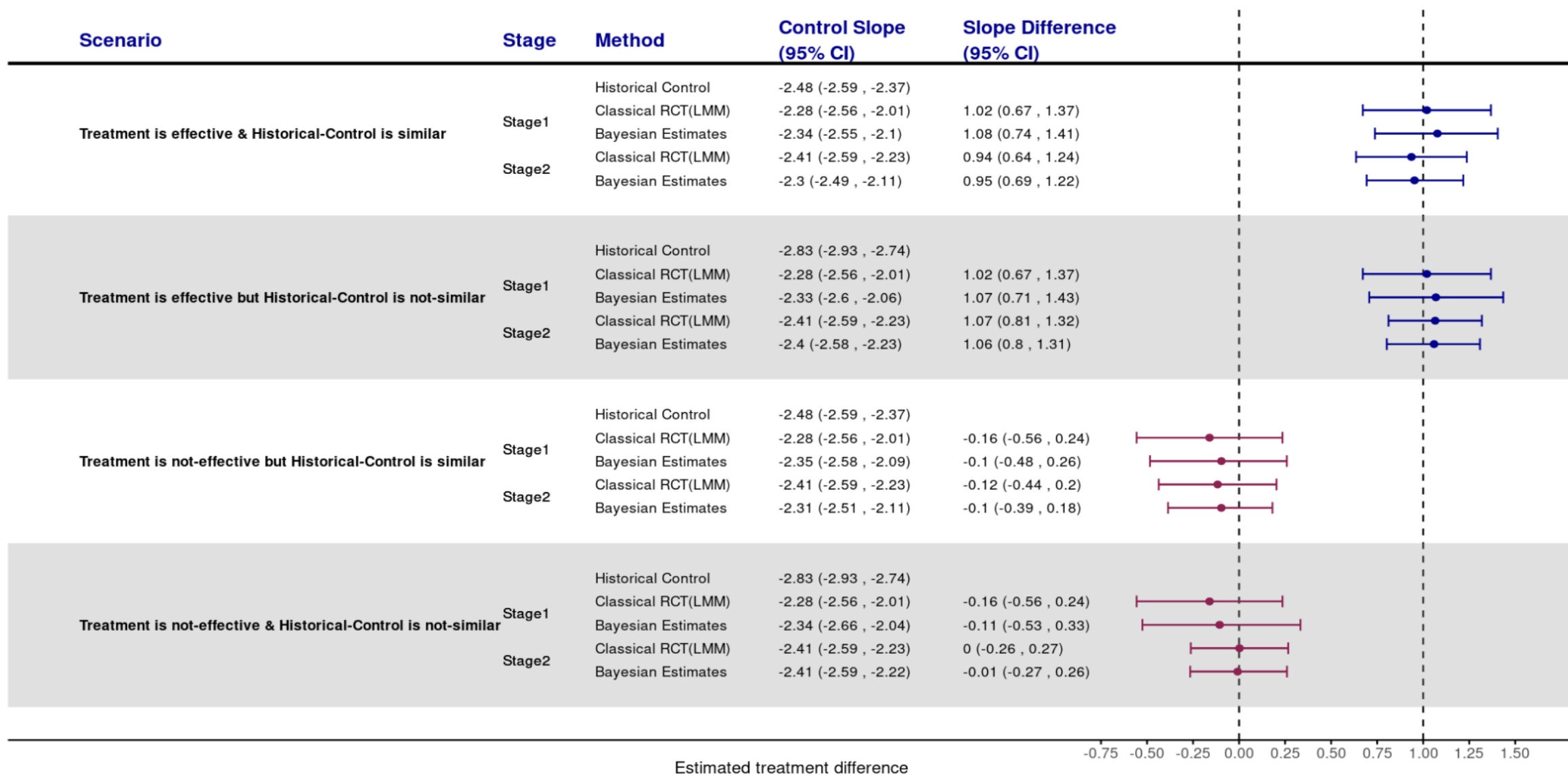
1. Results based on R simulated data.

2. **Simulation Inputs** :- Fixed Intercept : 47.5 ; Control Slope (Historical) : -2.85 ; Control Slope (Current) : -2.5 ; Random Intercept Standard Deviation (SD) : 17.5 ; Random Slope Standard Deviation (SD) : 1 ; Residual Standard Deviation (SD) : 1

Simulation Results



Simulation Results



Results based on R simulated data

Conclusion

A. Further Possibilities

- The current work demonstrates borrowing from one historical study, but the approach can be generalized to **multiple historical studies**. Additional refinement is possible by applying **propensity score matching** to create a more comparable subset, similar to Jiang et al.
- At the planning stage, trial design can be improved by using a **meta-analytic prior** and **effective sample size**–based calculations, instead of relying only on group-sequential sample-size methods (Schmidli et al.).
- When historical and current control groups are well aligned, the posterior treatment-effect estimate obtained at Stage 1 can be more precise, helping to accelerate subsequent phases of drug development.

B. Limitations

- Careful consideration is needed when selecting historical data or specifying priors because inappropriate choices can adversely influence trial results.
- This work focuses on illustrating borrowing methodology alongside a classical RCT and does not define success criteria for efficacy. To establish appropriate efficacy thresholds and ensure type-I error control, rigorous simulation studies are necessary, following the **FDA's 2026 Bayesian methodology guidelines**.

Thank You

Q&A