The Bayesian Time Machine: Accounting for temporal drift in multi-arm platform trials

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Outline

1. Introduction to Platform Trials
2. Temporal Drift
   - Motivating example
   - Methods
   - Simulations
3. PRINCIPLE trial
   - Temporal adjustment in COVID

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

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N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

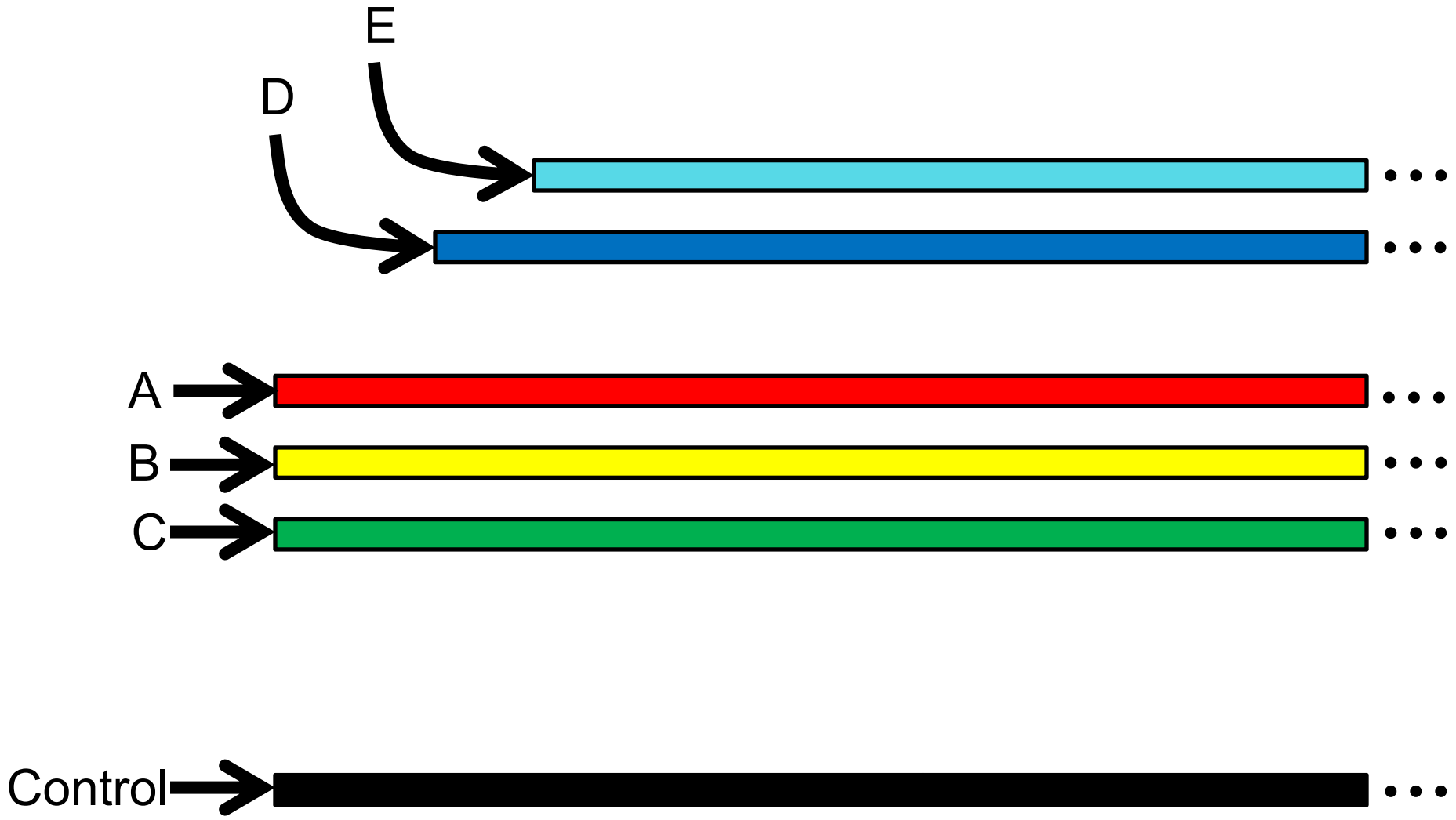
A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure.[1-4] Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions. Master protocols may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions, each targeting a particular biomarker-defined population or disease subtype. Included under this broad definition of a master protocol are three distinct entities: umbrella, basket, and platform trials (Table 1 and Figs. 1 and 2). All constitute a

Adaptive Platform Trials

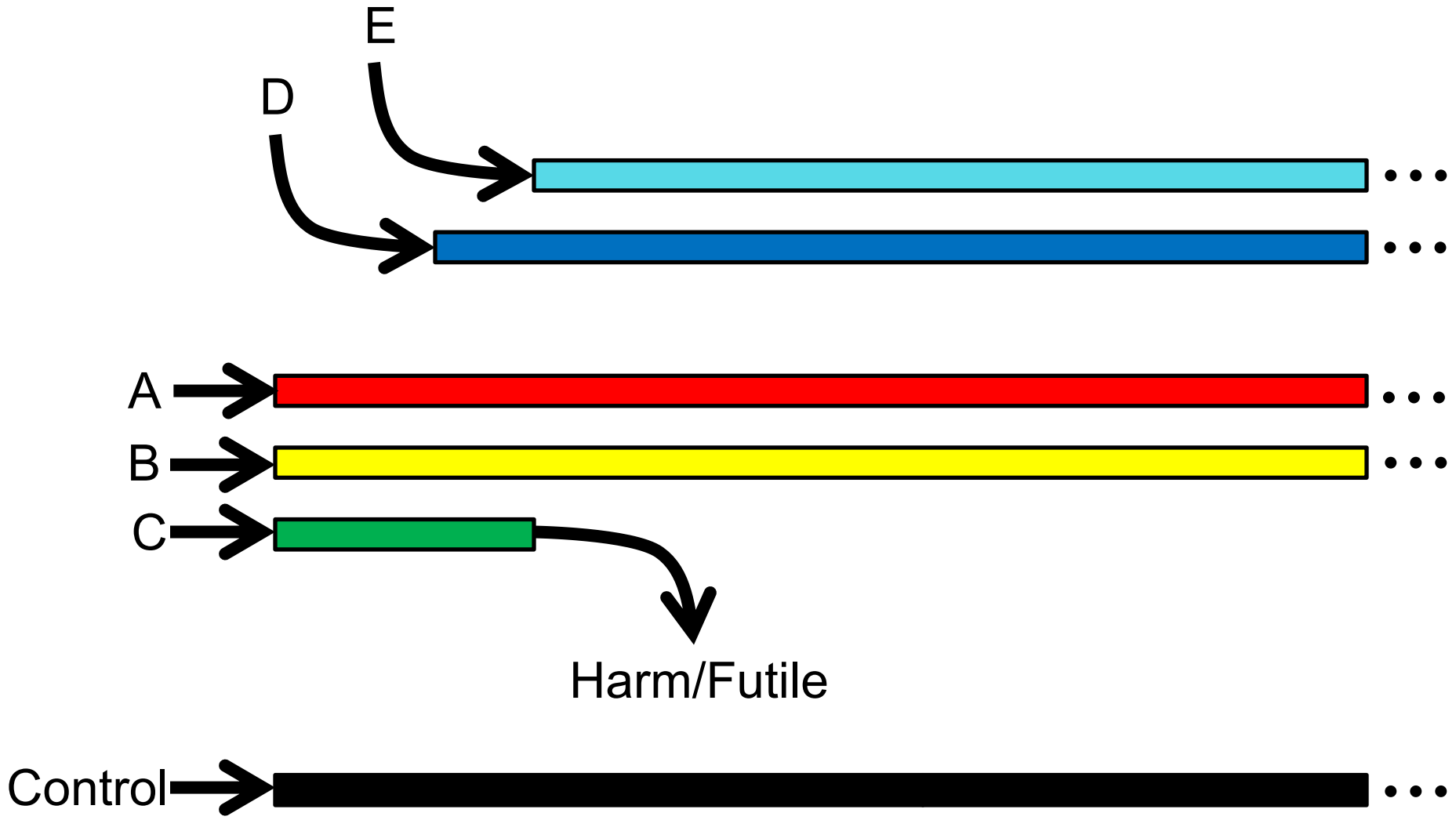
- Master Protocol
- Focus is on the Disease
  - “What is the best treatment for a unique patient with this disease?
- Typical Innovations
  - Staggered entry of interventions
  - Graduation/Removal, “Perpetual” trials
  - Response Adaptive Randomization (RAR)
  - Patient heterogeneity (hierarchical modeling)
  - Combination treatments
  - Statistical Modeling

Potential Features of a Platform Trial

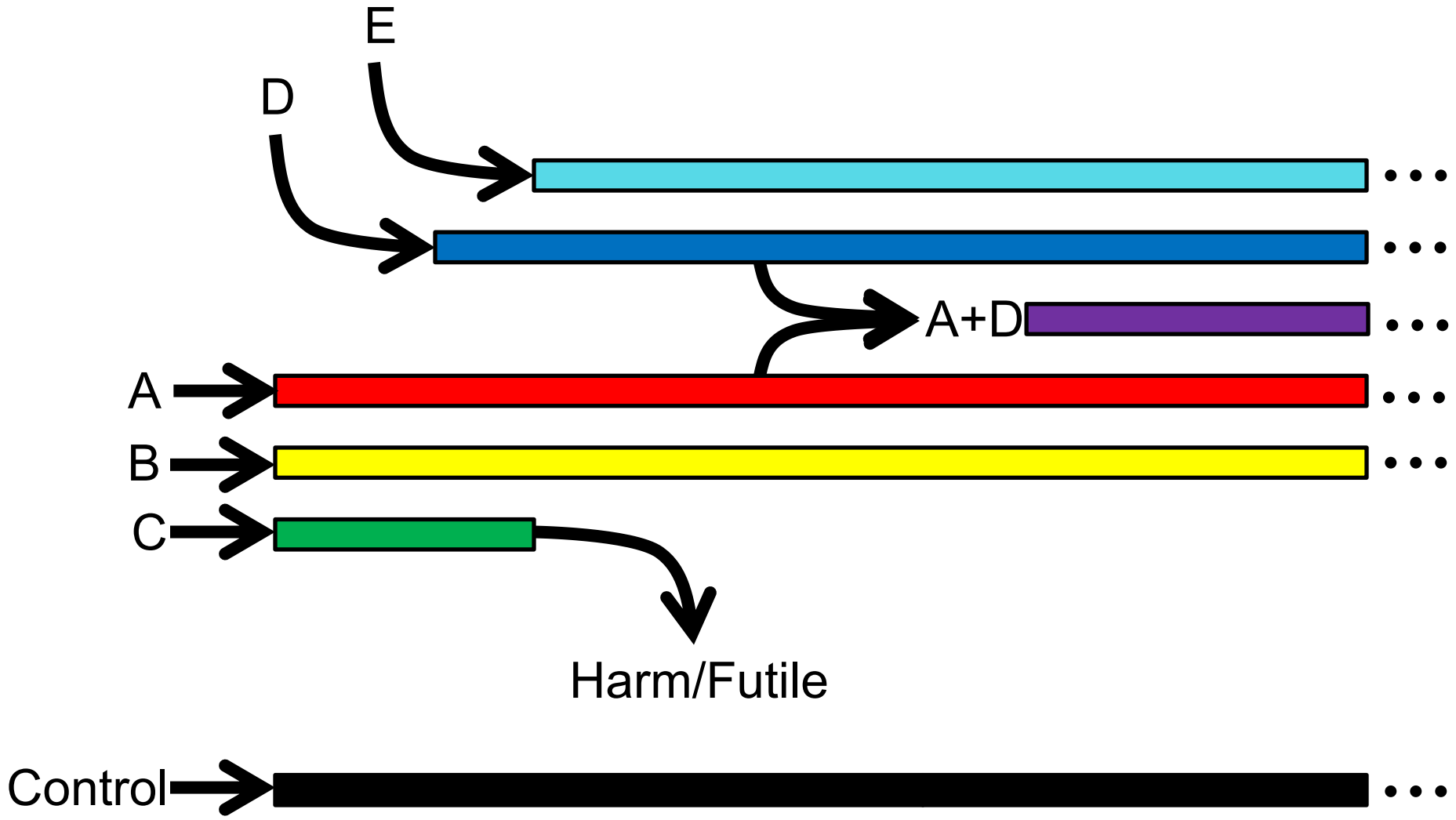
Potential Features of a Platform Trial



Potential Features of a Platform Trial



Potential Features of a Platform Trial



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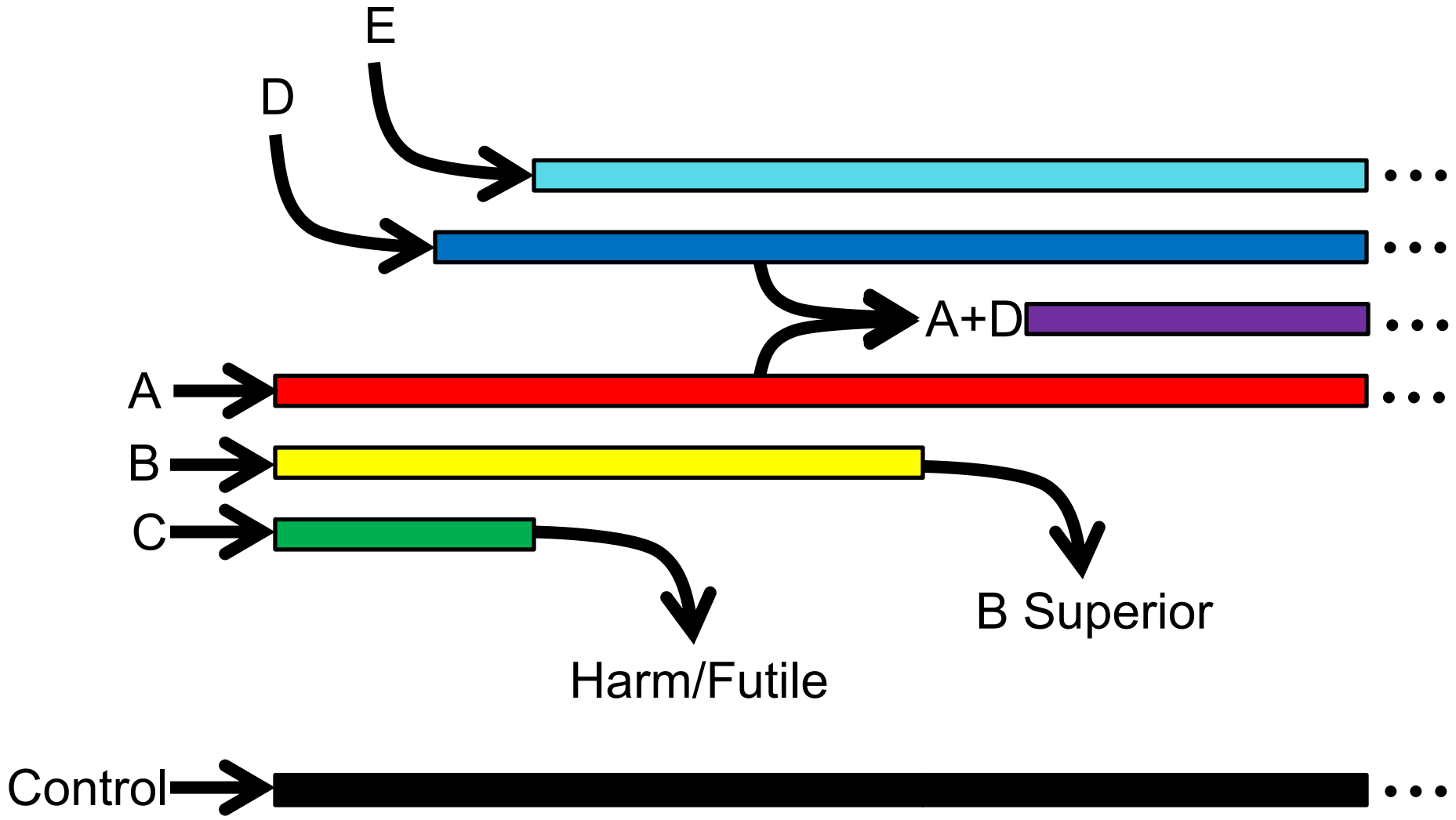

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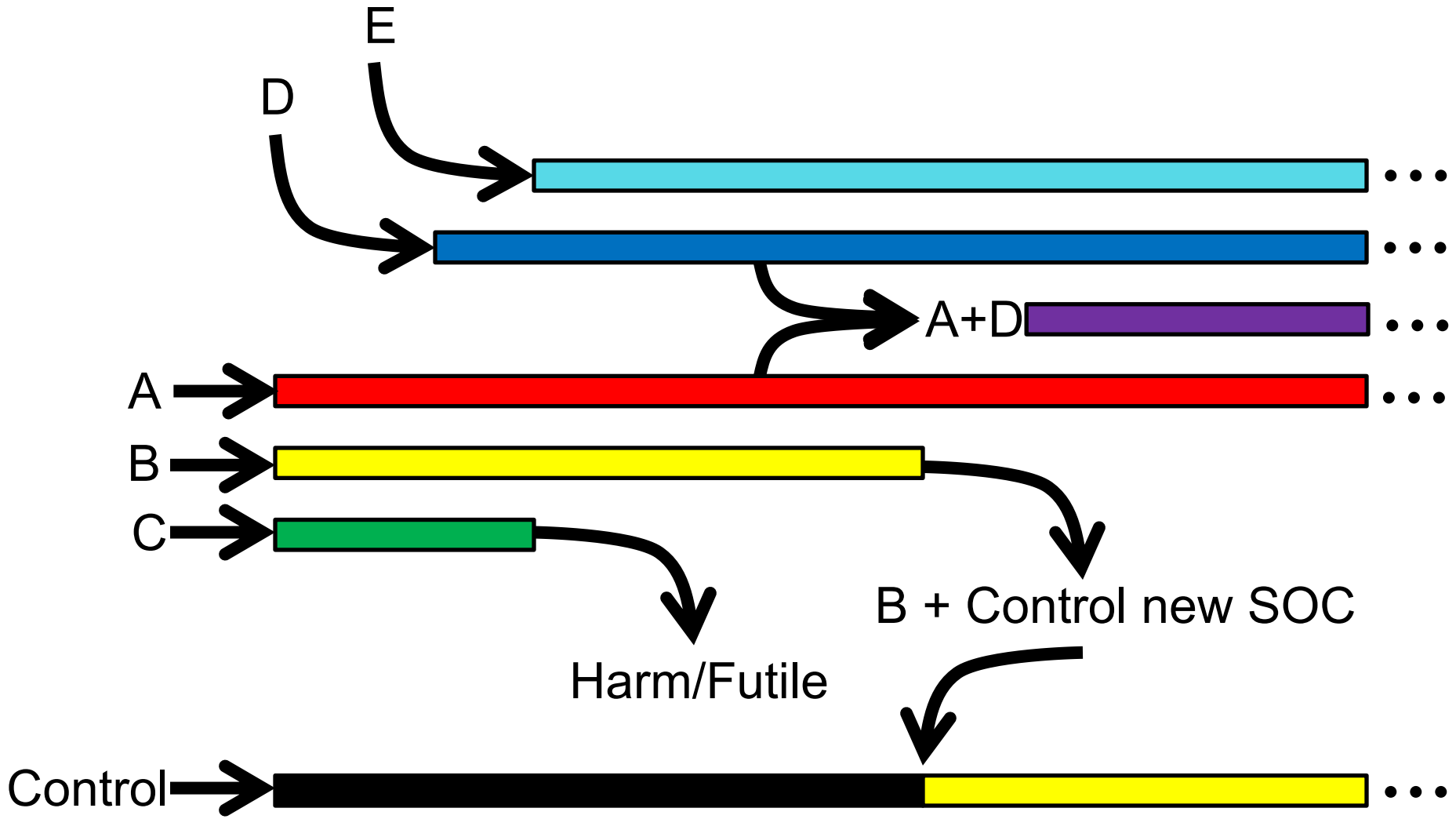

Platform Trials and Temporal Drift

- Platform trials typically span a longer time period than traditional clinical trials
- Typically have staggered entry of interventions
  - Randomization ratios may be changing (RAR)
- Regulators and community have expressed concern over impact of “temporal drift” on platform trials
  - Changes in population, SOC, disease (COVID strain), etc.
- How does one leverage all data on control arms from earlier in trial?

Article

CLINICAL TRIALS

Clinical Trials
1–12

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SAGE

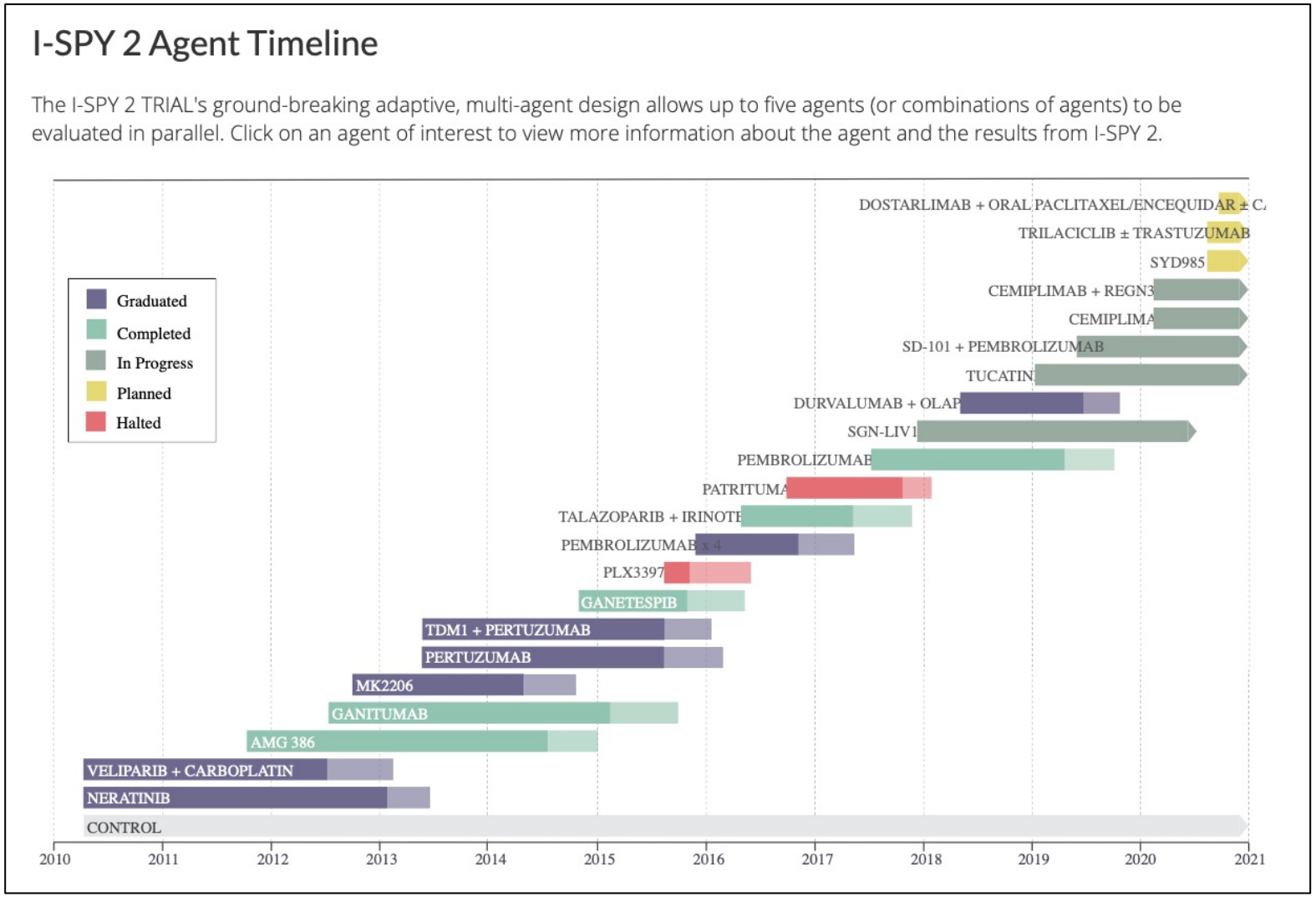
The Bayesian Time Machine: Accounting for temporal drift in multi-arm platform trials

Benjamin R Saville[1,2], Donald A Berry[1,3], Nicholas S Berry[1], Kert Viele[1,4] and Scott M Berry[1,5]

Abstract

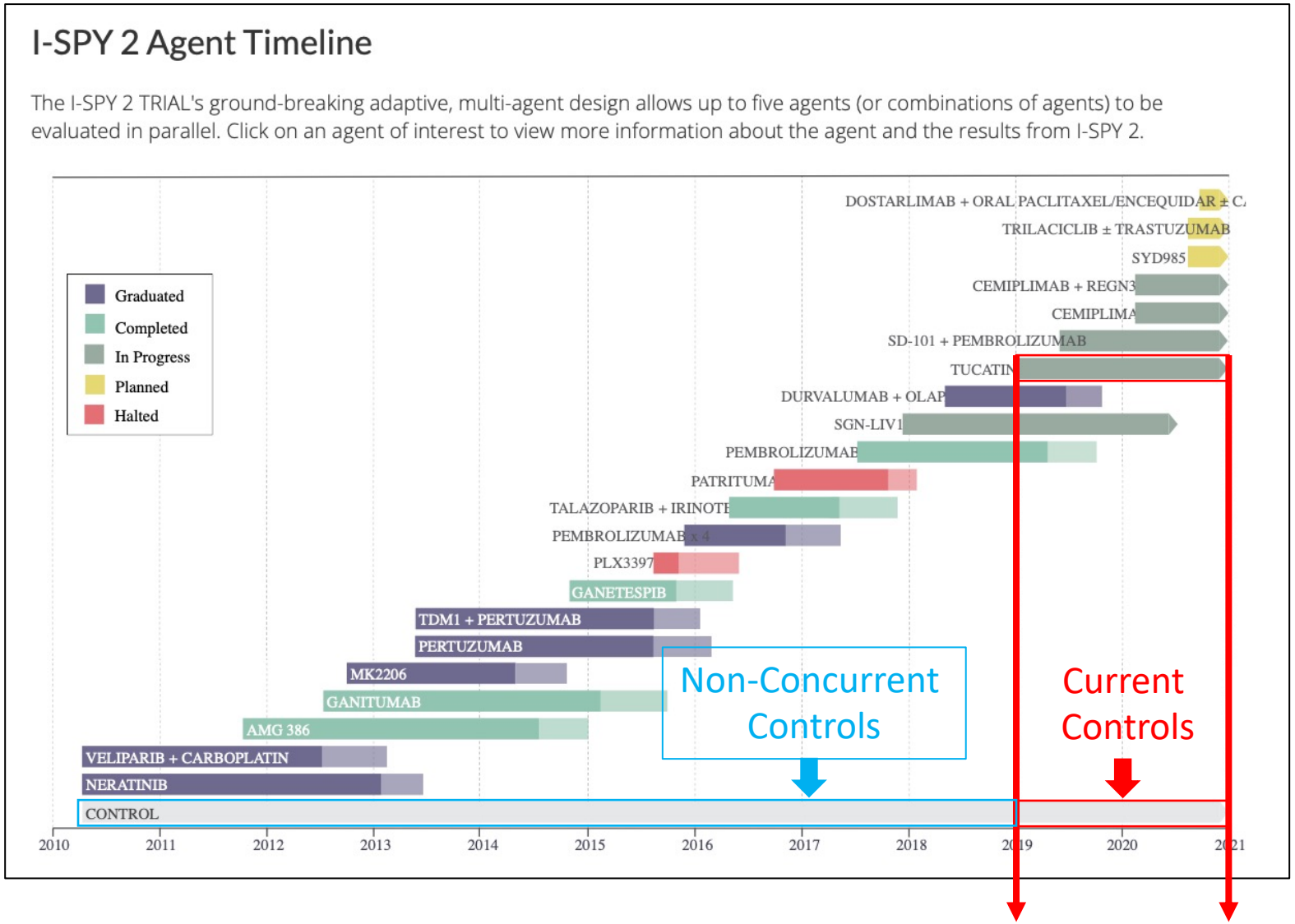
Background: Multi-arm platform trials investigate multiple agents simultaneously, typically with staggered entry and exit of experimental treatment arms versus a shared control arm. In such settings, there is considerable debate whether to limit analyses for a treatment arm to concurrent randomized control subjects or to allow comparisons to both concurrent and non-concurrent (pooled) control subjects. The potential bias from temporal drift over time is at the core of this debate.

Platform Trial & Non-Concurrent Controls



https://www.ispytrials.org/i-spy-platform/i-spy2

Platform Trial & Non-Concurrent Controls



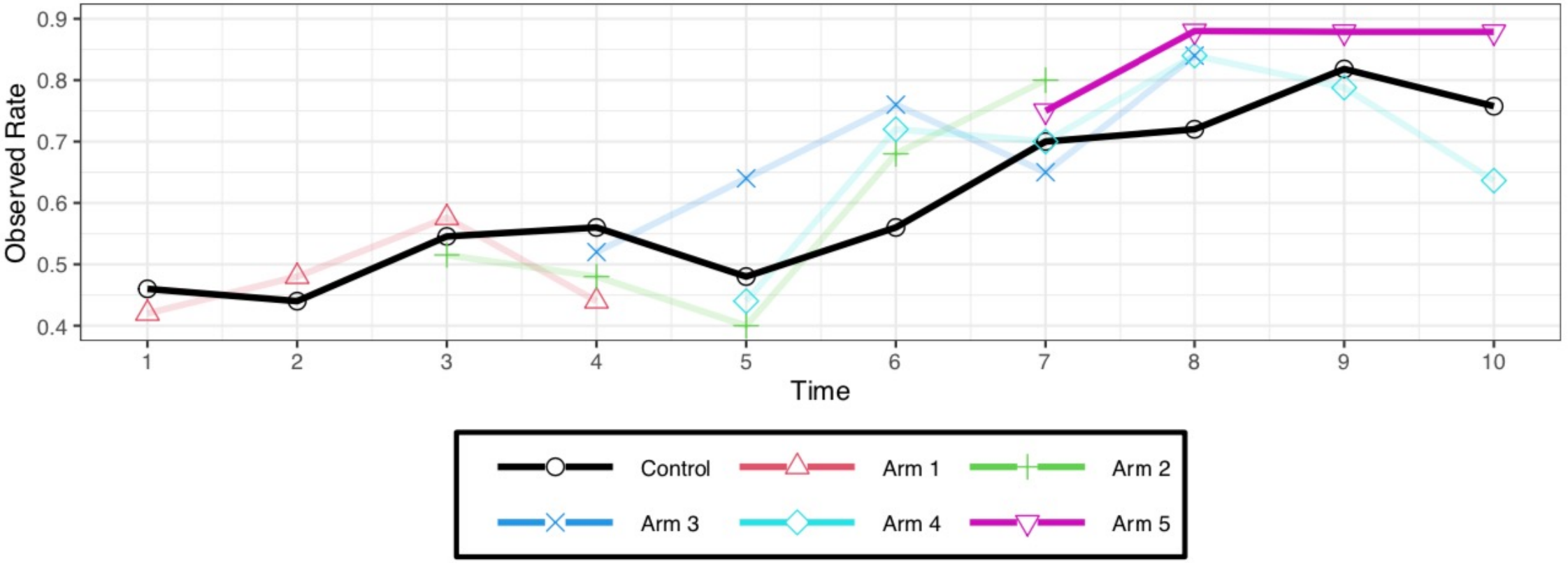
https://www.ispytrials.org/i-spy-platform/i-spy2

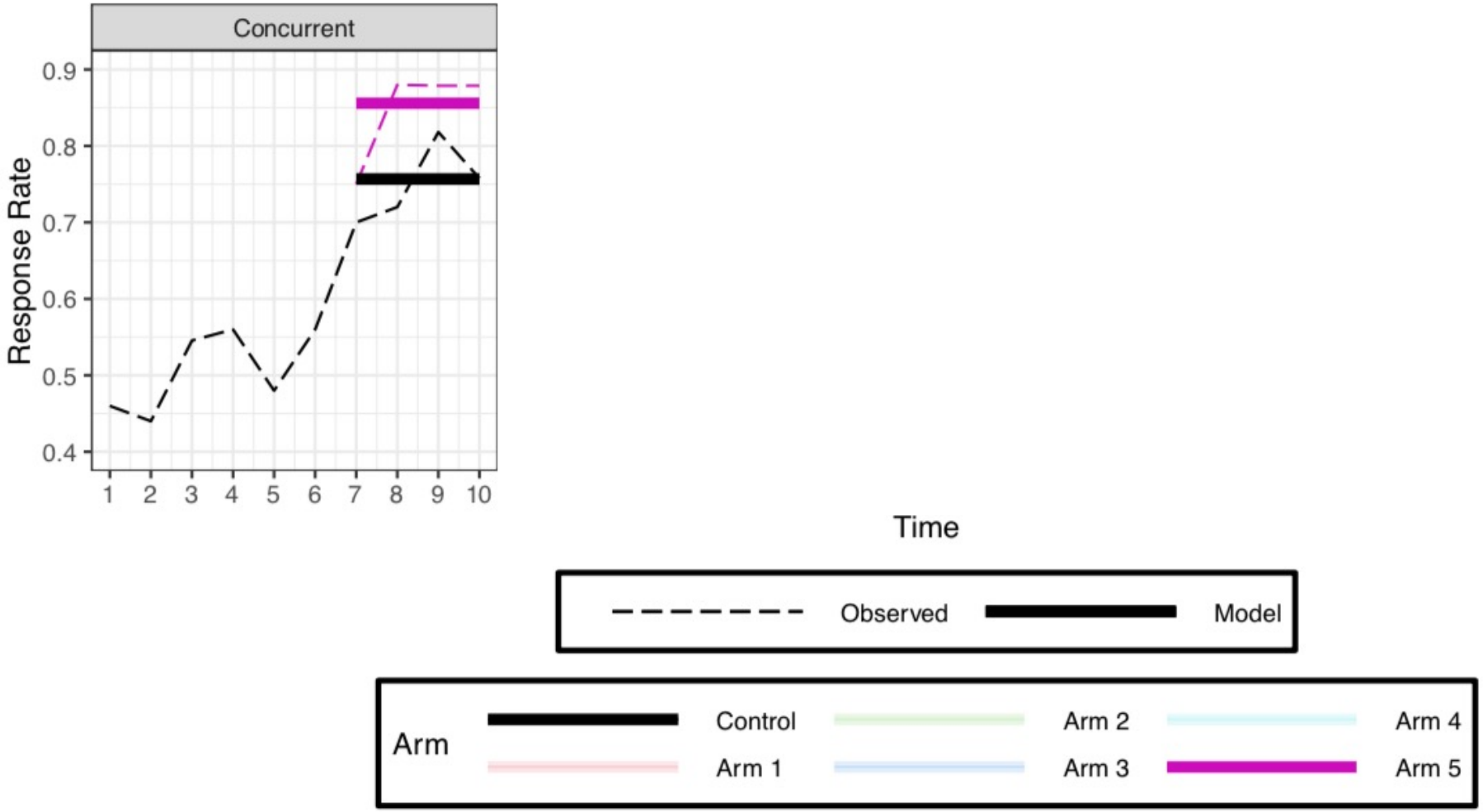
Historical Controls

- “Historical Controls” is a generally a *pejorative* term (to some)
- Non-Concurrent controls in platform trials are randomized
  - in the same protocol
  - same inclusion/exclusion
  - same visits
  - same procedures
  - same data quality
  - overlapping treatment arms
- The only difference is **TIME**!!

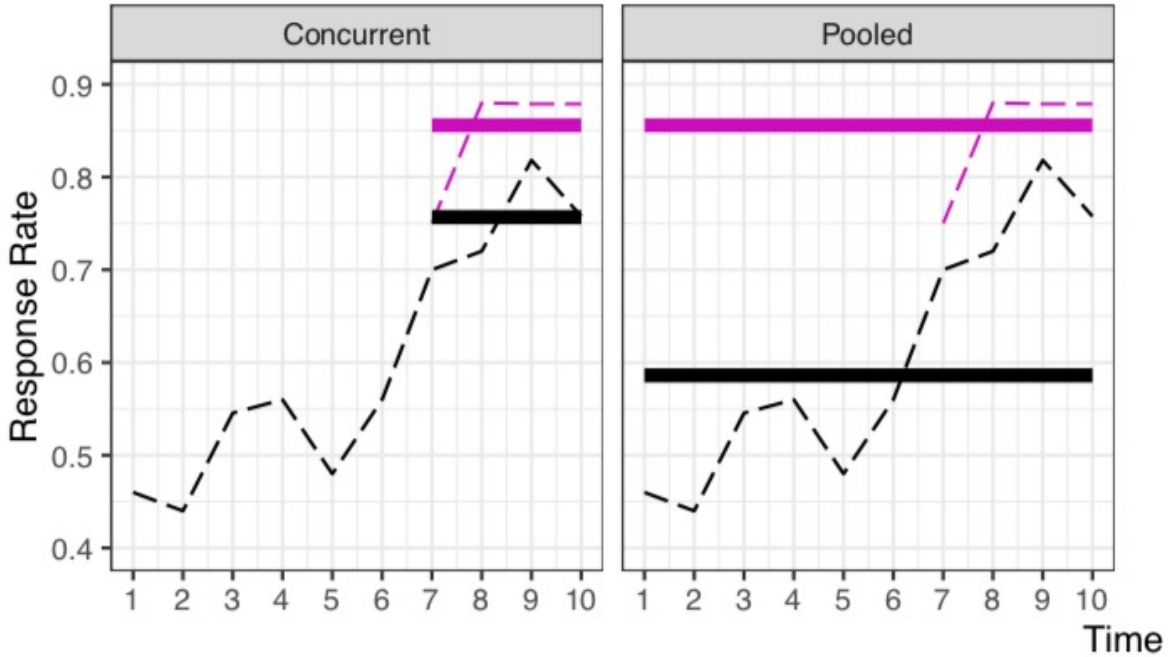
How to Model?

- What is the best way to estimate effect of Arm 5?





Method	Log Odds Ratio	Standard Error	Odds Ratio (95% CI)	One–sided P–value	Posterior Prob
1) Concurrent Controls	0.646	0.349	1.91 (0.96,3.78)	0.032	–



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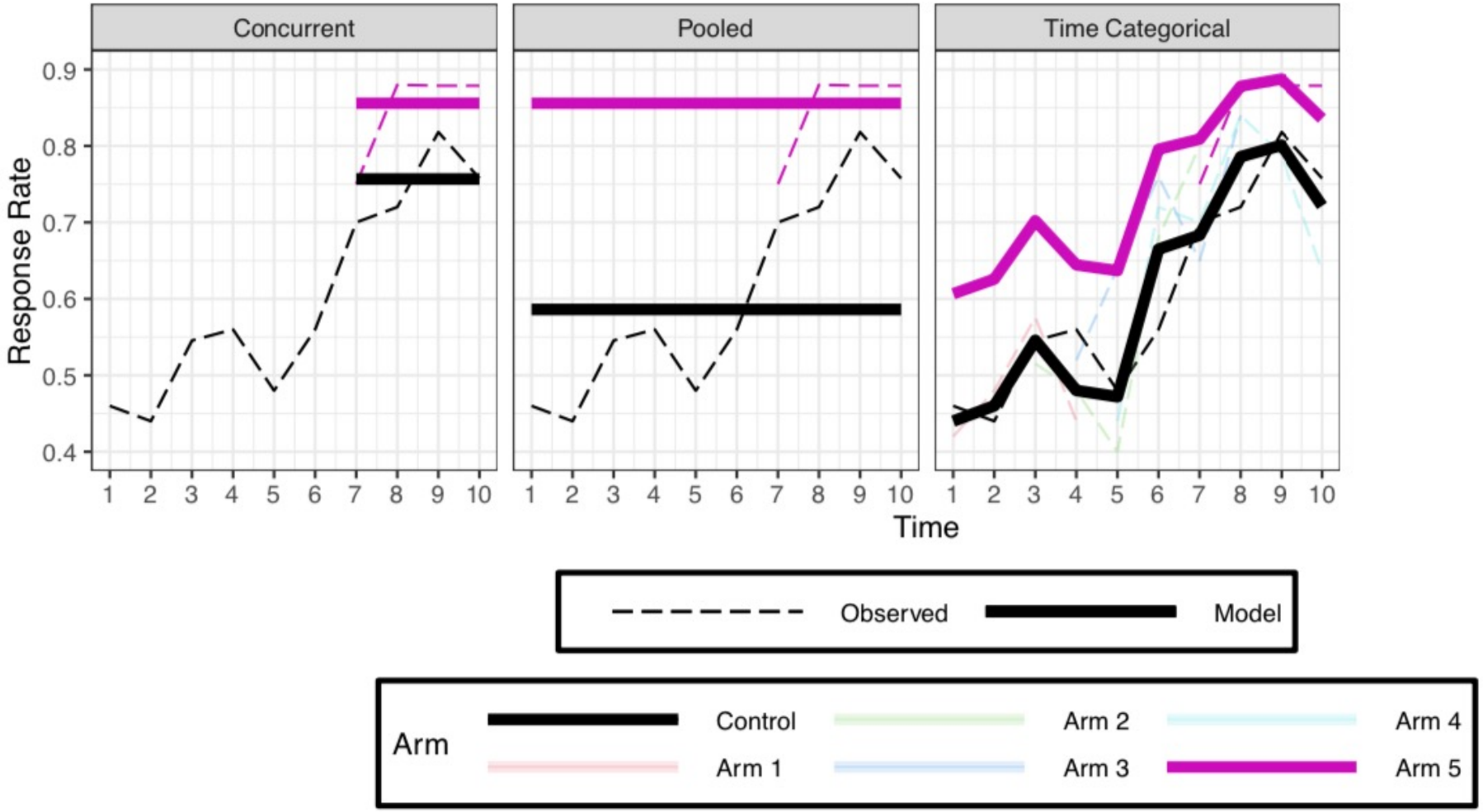
1) Concurrent Controls	0.646	0.349	1.91 (0.96,3.78)	0.032	–
2) Pooled Controls	1.433	0.293	4.19 (2.36,7.45)	0	–



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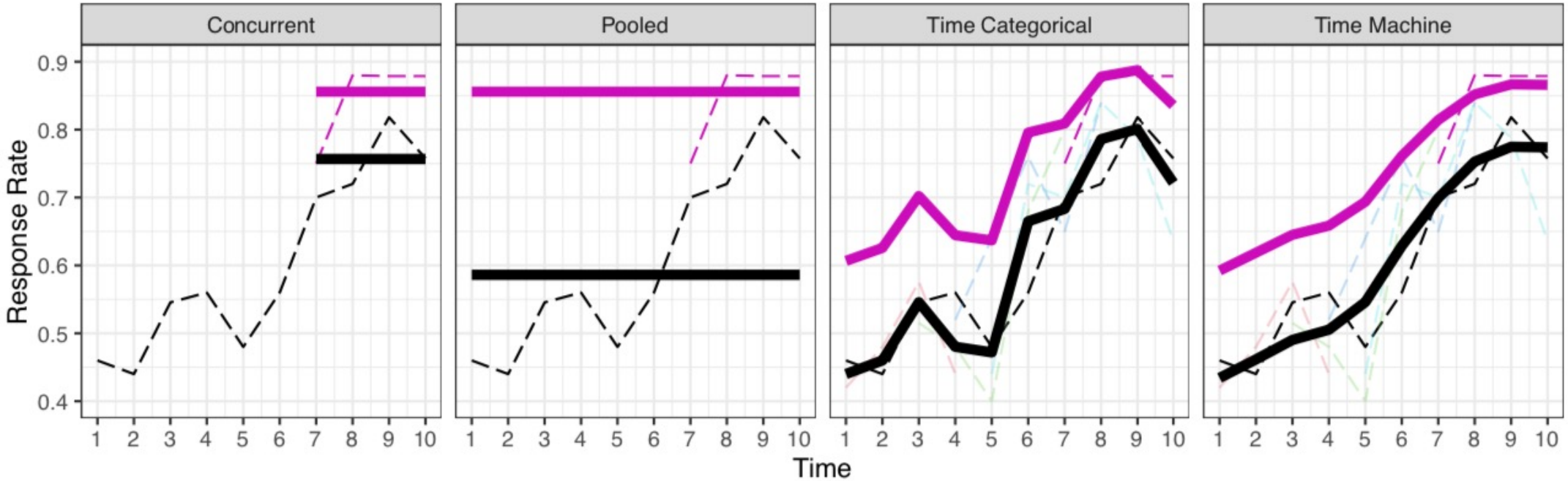
3) Time Categorical	0.674	0.328	1.96 (1.03,3.73)	0.02	–



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3) Time Categorical	0.674	0.328	1.96 (1.03,3.73)	0.02	–
4) Time Machine	0.653	0.315	1.92 (1.04,3.56)	–	0.981

Bayesian Time Machine

- Second-order normal dynamic linear model (NDLM)

$$E(Y_i) = \mu_i$$
$$g(\mu_i) = \gamma + \theta_{j(i)} + \boldsymbol{x}_i'\boldsymbol{\beta} + \alpha_{t(i)}$$

- Y_i: response for subject i
- γ: model intercept
- $\theta_{j(i)}$: increment in linear predictor for treatment arm j
- $\alpha_{t(i)}$: increment in linear predictor for time interval t
- $\boldsymbol{x}$: vector of covariates with parameters $\boldsymbol{\beta}$
- Non-informative priors for γ, $\theta_{j(i)}$, $\boldsymbol{\beta}$

Temporal Drift

- Divide time since start of trial into T buckets
  - Count backwards from most recent time interval $(t = 1)$ to beginning of trial $(t + 1, t + 2, \dots, T)$

$$\alpha_1 = 0 \text{ for identifiability}$$

$$\alpha_2 \sim N(0, 1/\tau)$$

$$\alpha_t \sim N(2\alpha_{t-1} - \alpha_{t-2}, 1/\tau), t \geq 3$$

- τ: Drift parameter that determines amount of "smoothing"

Dynamic Smoothing

- Use observed data to determine degree of smoothing
- Hyperprior for τ

$$\tau \sim \text{Gamma}(a, b)$$

- Weight of $2a$ intervals of data centered at a/b

- Centering τ at large values with large variance allows flexible and dynamic smoothing
  - Estimated drift determined by observed data

Simulation Study

Objective

- Simulate a platform trial ***with*** and ***without*** temporal trends, and compare different analysis strategies

Assumptions/Setting

- Binary endpoint
- 5 treatment arms vs. control (focus on Arm 5)
- Staggered entry and exit of treatment arms
- 10 distinct time intervals
- 100 patients randomized within each time interval
- No lag between randomization and primary outcome measurement

Data Assumptions (Base)

- Control response rate: 50% at start of trial
  1. Rate constant
  2. Rate increases to a peak; then decreases (inverted-U)
  3. Rate has linear increase

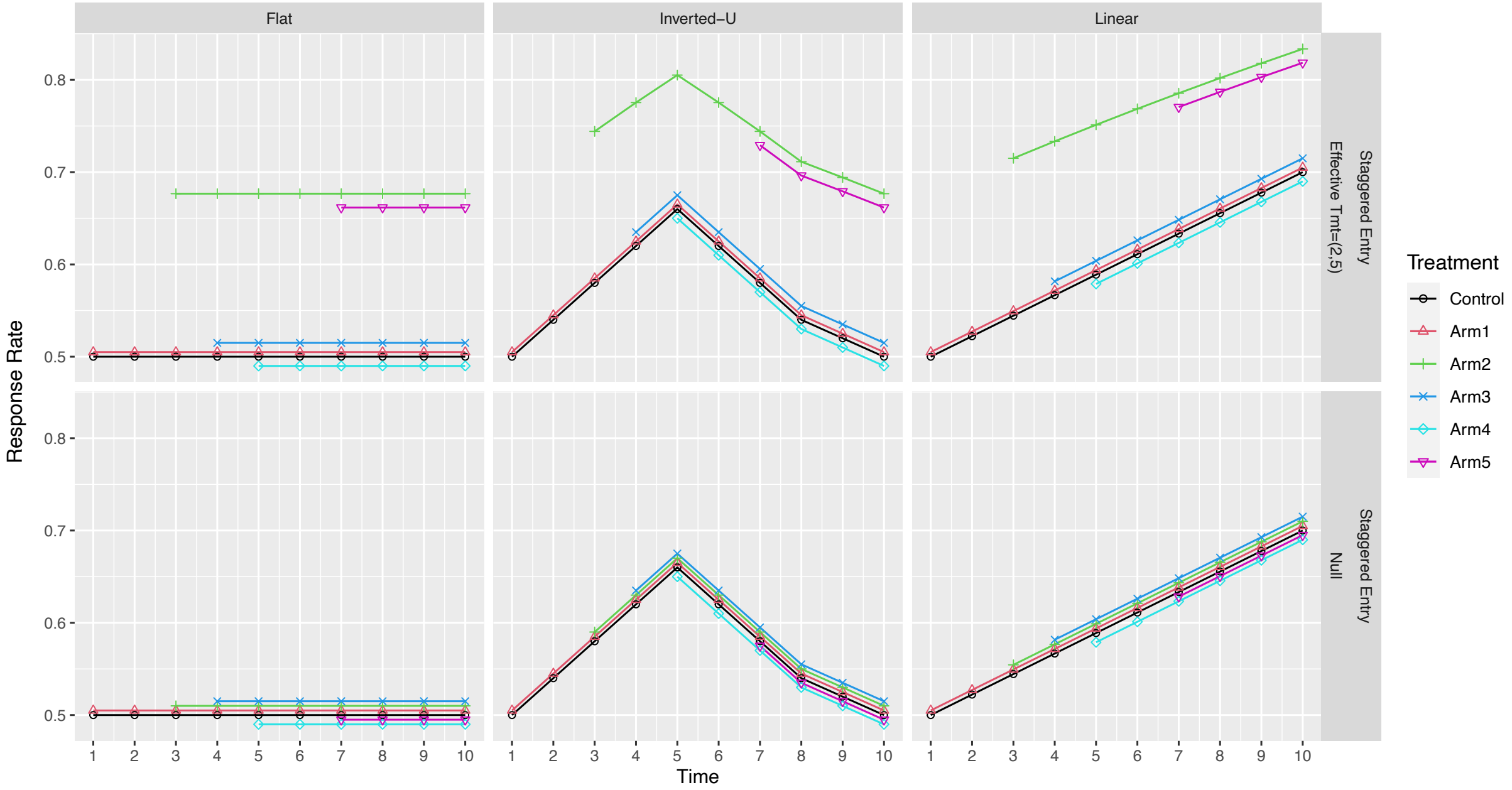
- Treatment response rates
  1. No benefit vs. control: Odds ratio =1.0
  2. Superior vs. control: Odds ratio = 2.0

- Staggered entry (& exit) of treatment arms

Number of Subjects by time (Base)

Table 1. Scenarios: Number of subjects by arm and time.

Staggered	Treatment	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6	Time 7	Time 8	Time 9	Time 10
Entry	Control	50	50	33	25	20	20	17	17	17	17
	Arm 1	50	50	33	25	20	20	17	17	17	17
	Arm 2			33	25	20	20	17	17	17	17
	Arm 3				25	20	20	17	17	17	17
	Arm 4					20	20	17	17	17	17
	Arm 5							17	17	17	17


Flat
Inverted−U
Linear
Staggered Entry
Effective Tmt=(2,5)
Staggered Entry
Null
Response Rate
Time
0.5
0.6
0.7
0.8
1
2
3
4
5
6
7
8
9
10
Treatment
Control
Arm1
Arm2
Arm3
Arm4
Arm5

Analysis Methods for Arm 5 vs. Control

1. Concurrent Controls Analysis
   - Logistic regression for Arm 5 vs. concurrent controls
2. Pooled Controls Analysis
   - Logistic regression for Arm 5 vs. pooled controls
3. Time Categorical Analysis
   - Logistic regression for Arm 5 vs. all controls
   - Covariate adjustment for time (categorical bins)
   - Includes all treatment arms
4. Bayesian Time Machine
   - Bayesian logistic regression for Arm 5 vs. all controls
   - Adjustment for time via Bayesian smoothing
   - Includes all treatment arms

Analysis Methods: Assumptions

1. Concurrent Controls Analysis
   - Assumes non-concurrent controls have no useful information
2. Pooled Controls Analysis
   - Assumes control response rate is constant across time
3. Time Categorical Analysis
   - Assumes independent bins for control response across time
4. Bayesian Time Machine
   - Assumes smoothing control response across time is appropriate
   - $\tau^2 \sim \text{Gamma}(a = 0.1, b = 0.01)$

All strategies assume treatment effects are constant across time

Metrics

1. Bias and standard error (SE) of treatment effects
2. Mean square error (MSE) ratio of each method compared to Bayesian Time Machine
3. Statistical Power
   - H_0: log-odds of Arm 5 vs. control ≤ 0
   - H_1: log-odds of Arm 5 vs. control > 0
   - Use one-sided alpha = 0.025 for p-values; Bayes posterior prob 0.975

Results

Table 2. Treatment Arm 5 vs. Control

			Avg Bias log(OR)				Average SE				MSE Ratio vs. TimeMachine (smaller is better)				Statistical Power			
Stag	Eff	Drift	ConC	PoolC	Time Cat	Time Mach	ConC	PoolC	Time Cat	Time Mach	ConC	PoolC	Time Cat	Time Mach	ConC	PoolC	Time Cat	Time Mach
E	Null	Flat	0.00	0.00	0.00	0.00	0.35	0.27	0.30	0.29	1.44	0.91	1.08	1	0.022	0.023	0.026	0.024
		Lin	0.00	0.41	0.00	0.02	0.37	0.29	0.31	0.31	1.44	2.64	1.08	1	0.023	0.274	0.024	0.027
		InvU	0.00	-0.10	0.00	-0.02	0.35	0.27	0.30	0.29	1.42	0.99	1.07	1	0.028	0.010	0.026	0.022
	2,5	Flat	0.01	0.01	0.01	-0.01	0.36	0.29	0.31	0.30	1.42	0.93	1.08	1	0.493	0.693	0.631	0.631
		Lin	0.02	0.43	0.03	0.03	0.41	0.33	0.36	0.35	1.37	2.43	1.10	1	0.409	0.954	0.524	0.565
		InvU	0.01	-0.08	0.02	-0.01	0.36	0.29	0.32	0.31	1.39	0.99	1.08	1	0.478	0.536	0.613	0.598

Results

Table 2. Treatment Arm 5 vs. Control

Stag	Eff	Drift
E	Null	Flat Lin InvU
	2,5	Flat Lin InvU

Results

Table 2. Treatment Arm 5 vs. Control

			Avg Bias log(OR)			
Stag	Eff	Drift	ConC	PoolC	Time Cat	Time Mach
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	2,5	Flat	0.01	0.01	0.01	-0.01
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		InvU	0.01	-0.08	0.02	-0.01

Results

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		Lin	0.02	0.43	0.03	0.03	0.41	0.33	0.36	0.35
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Results

Table 2. Treatment Arm 5 vs. Control

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Results

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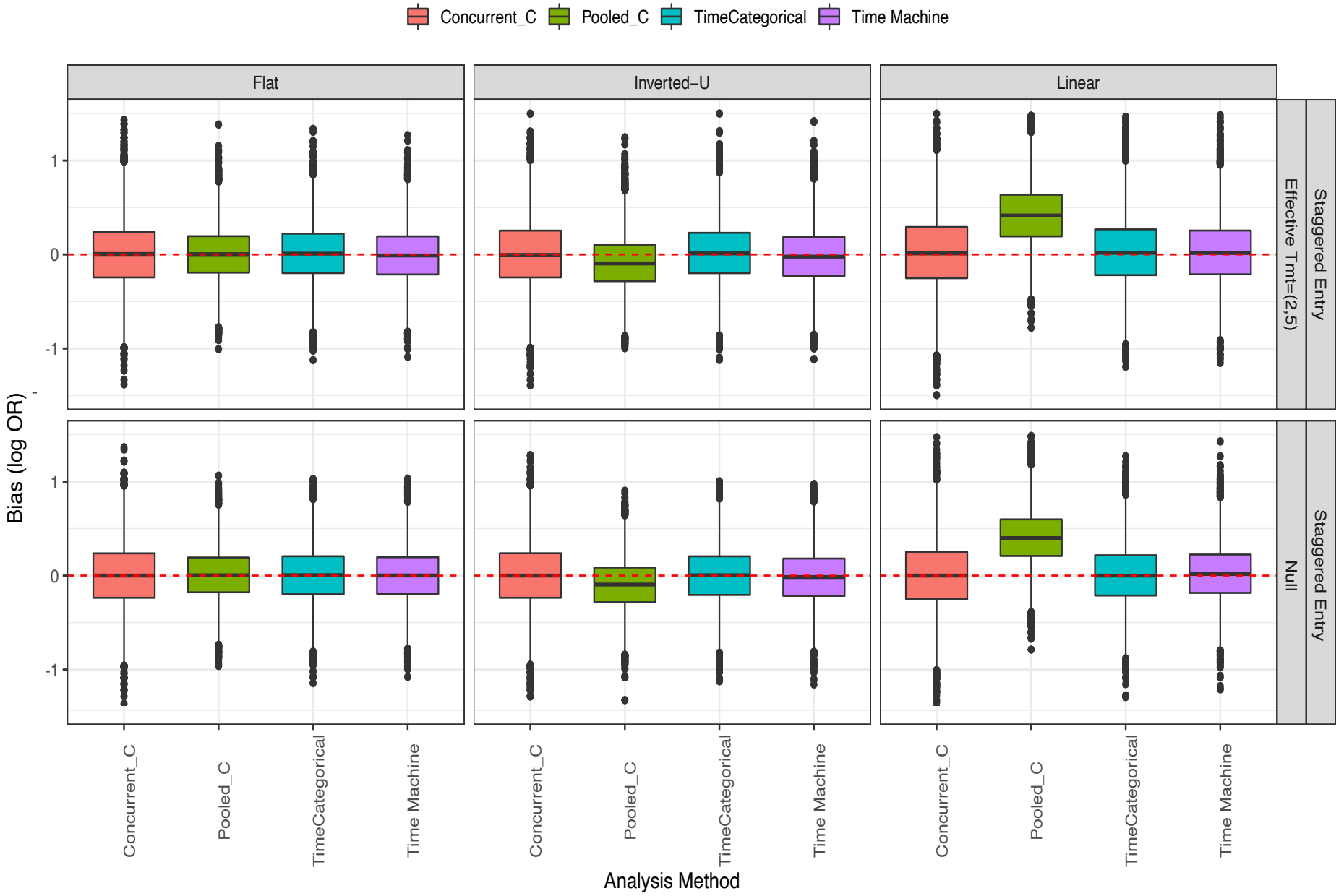
Concurrent_C
Pooled_C
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Time Machine
Flat
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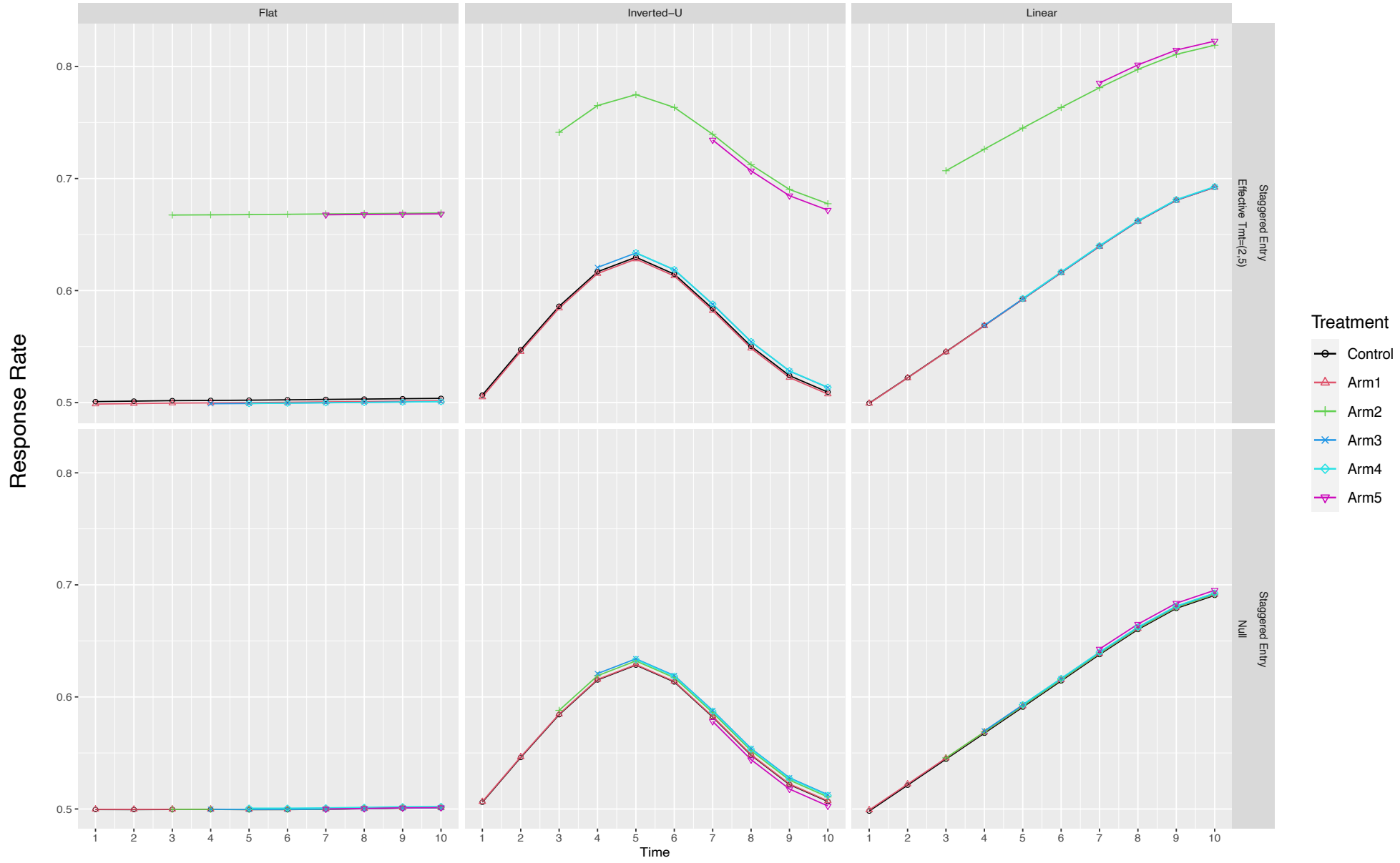
Staggered Entry
Effective Tmt=(2,5)
Staggered Entry
Null
Bias (log OR)
1
0
-1
Concurrent_C
Pooled_C
TimeCategorical
Time Machine
Analysis Method

Average Estimates: Time Machine



Simulation Results

- Time Machine inferential improvements
  - Power, MSE: 20% improvement vs concurrent controls
  - Improvement applies to EACH arm in the platform!
- Time Machine nearly unbiased
  - Smoothed estimates across time more plausible
- Time Categorical also outperforms pooled and concurrent controls
  - Adjusting for time is superior to either extreme

PRINCIPLE
Platform Randomised trial of INterventions against COVID-19 In older peoPLE

The PRINCIPLE Adaptive Platform Trial for Community Treatment of COVID-19: Innovation in Trial Design and Delivery

PRINCIPLE: COVID-19 in Primary Care

- Most people with COVID-19 are managed in the community
  - Community treatments may have the widest reach and impact
- PRINCIPLE objective: Evaluate whether re-purposed drugs can make a difference with early intervention
- Needed a rapidly initiated trial with adaptive features
  - Ability to evaluate treatments quickly (early superiority/futility)
  - Flexibility to add treatments
- Urgency: First patient randomized < 3 weeks from initial contact with Oxford collaborators!

PRINCIPLE: COVID-19 in Primary Care

Participants:

- Presenting **in primary care** within 14 days since onset of cough and/or fever during time of prevalent COVID-19 infections

Randomized among multiple interventions or Usual Care

- Frequent interim analyses
- Response adaptive randomization

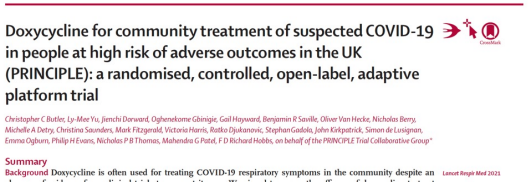
Primary endpoints:

1. Time to self-reported recovery within 28 days
2. Hospitalization/Death (binary) within 28 days

Intervention Timeline in PRINCIPLE


Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Ly-Mee Yu*, Mona Bafadhel*, Jienchi Dorward*, Gail Hayward, Benjamin R Saville, Oghenekome Gbinigie, Oliver Van Hecke, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, Duncan Richards, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Milensu Shanyinde, Simon de Lusignan, Monique I Andersson, Peter J Barnes, Richard E K Russell, Dan V Nicolau Jr, Sanjay Ramakrishnan, F D Richard Hobbs†, Christopher C Butler†, on behalf of the PRINCIPLE Trial Collaborative Group‡

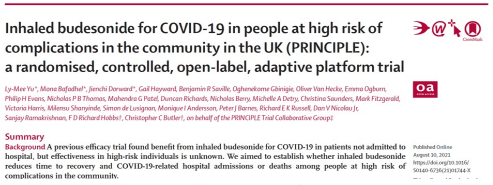

Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Christopher C Butler, Ly-Mee Yu, Jienchi Dorward, Oghenekome Gbinigie, Gail Hayward, Benjamin R Saville, Oliver Van Hecke, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Ratko Djukanović, Stephan Gadola, John Kirkpatrick, Simon de Lusignan, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, F D Richard Hobbs, on behalf of the PRINCIPLE Trial Collaborative Group*

Summary

Background Doxycycline is often used for treating COVID-19 respiratory symptoms in the community despite an

Lancet Respir Med 2021


Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Ly-Mee Yu*, Mona Bafadhel*, Jienchi Dorward*, Gail Hayward, Benjamin R Saville, Oghenekome Gbinigie, Oliver Van Hecke, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, Duncan Richards, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Milensu Shanyinde, Simon de Lusignan, Monique I Andersson, Peter J Barnes, Richard E K Russell, Dan V Nicolau Jr, Sanjay Ramakrishnan, F D Richard Hobbs†, Christopher C Butler†, on behalf of the PRINCIPLE Trial Collaborative Group‡

Summary

Background A previous efficacy trial found benefit from inhaled budesonide for COVID-19 in patients not admitted to hospital, but effectiveness in high-risk individuals is unknown. We aimed to establish whether inhaled budesonide reduces time to recovery and COVID-19-related hospital admissions or deaths among people at high risk of complications in the community.

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Ivermectin

23 Jun 2021

Favipiravir

8 Apr 2021

Colchicine

4 Mar 2021 — 26 May 2021

Inhaled Budesonide

1 Dec 2020 — 31 March 2021

Doxycycline

24 Jul 2020 — 14 Dec 2020

Azithromycin

22 May 2020 — 30 Nov 2020

Hydroxychloroquine

2 Apr 2020 — 22 May 2020

Apr 2020 | Jun | Aug | Oct | Dec | Feb 2021 | Apr | Jun | Aug | ... | July 2022

Intervention Timeline in PRINCIPLE

Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Christopher C Butler, Ly-Mee Yu, Jienchi Dorward, Oghenekome Gbinigie, Gail Hayward, Benjamin R Saville, Oliver Van Hecke, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Ratko Djukanović, Stephan Gadola, John Kirkpatrick, Simon de Lusignan, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, F D Richard Hobbs, on behalf of the PRINCIPLE Trial Collaborative Group*

Summary

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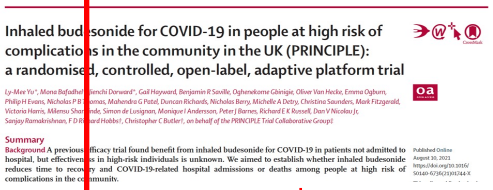

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Summary

Background A previous efficacy trial found benefit from inhaled budesonide for COVID-19 in patients not admitted to hospital, but effectiveness in high-risk individuals is unknown. We aimed to establish whether inhaled budesonide reduces time to recovery and COVID-19-related hospital admissions or deaths among people at high risk of complications in the community.

Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

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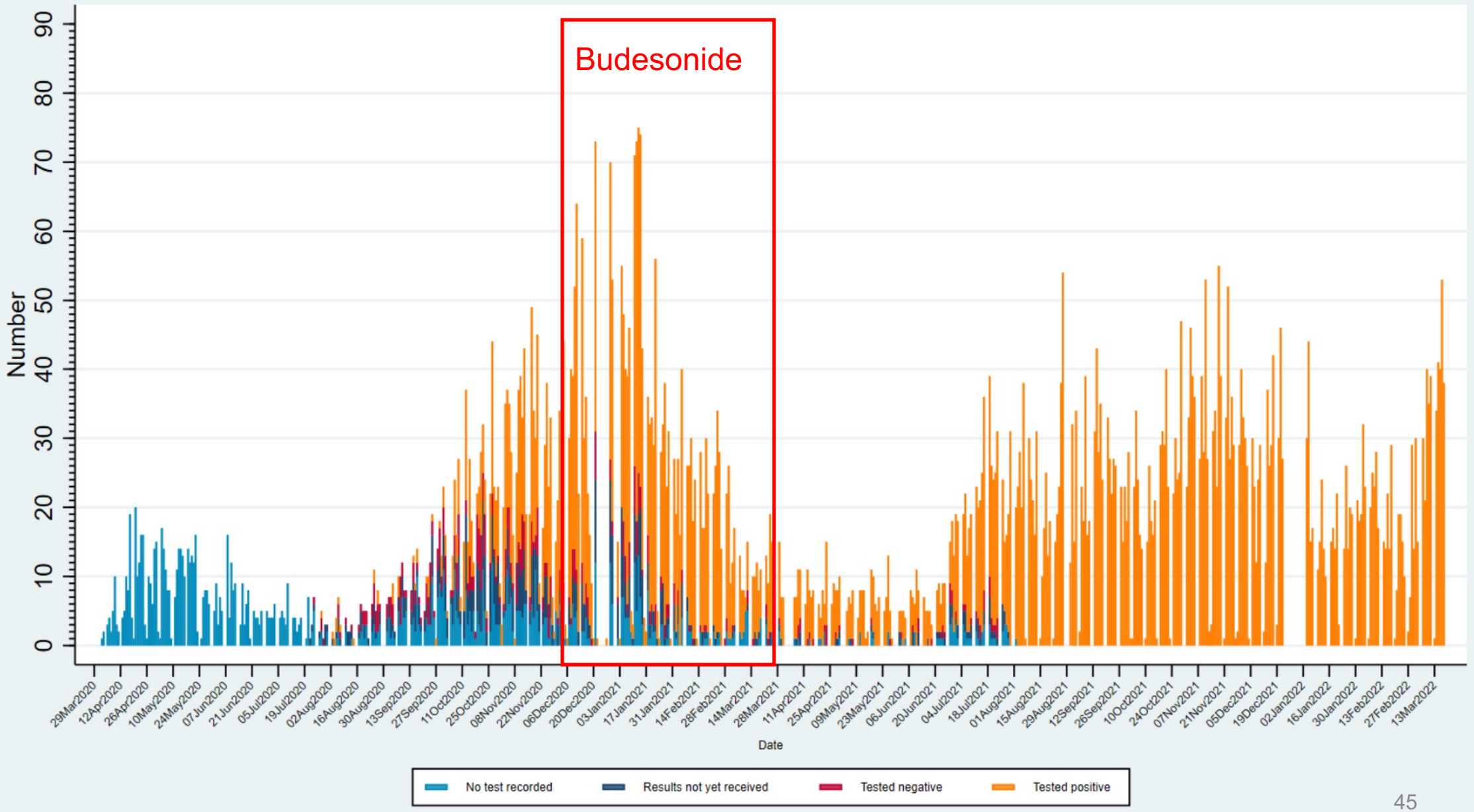
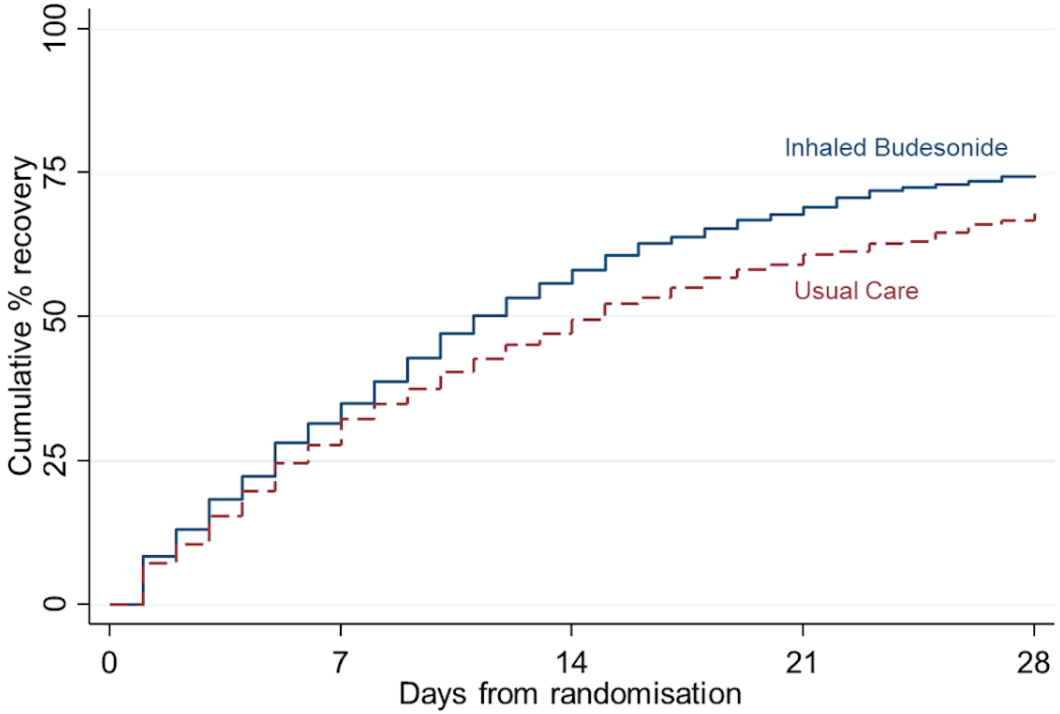
Daily Randomization



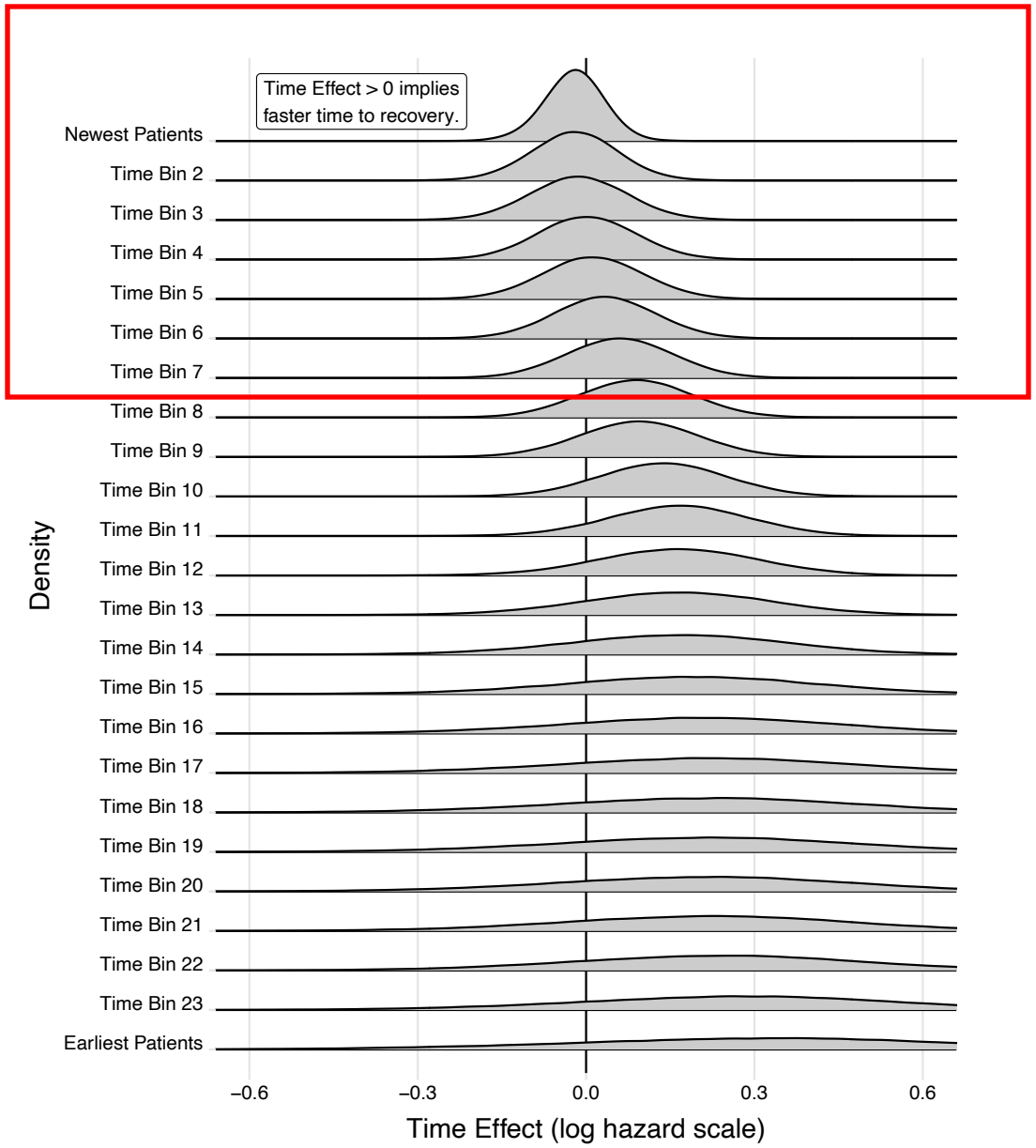
Budesonide

- ~3 day benefit (Median TTR 12 vs. 15 days)
- ~2% reduction in hospitalization rate (7% vs. 9%)



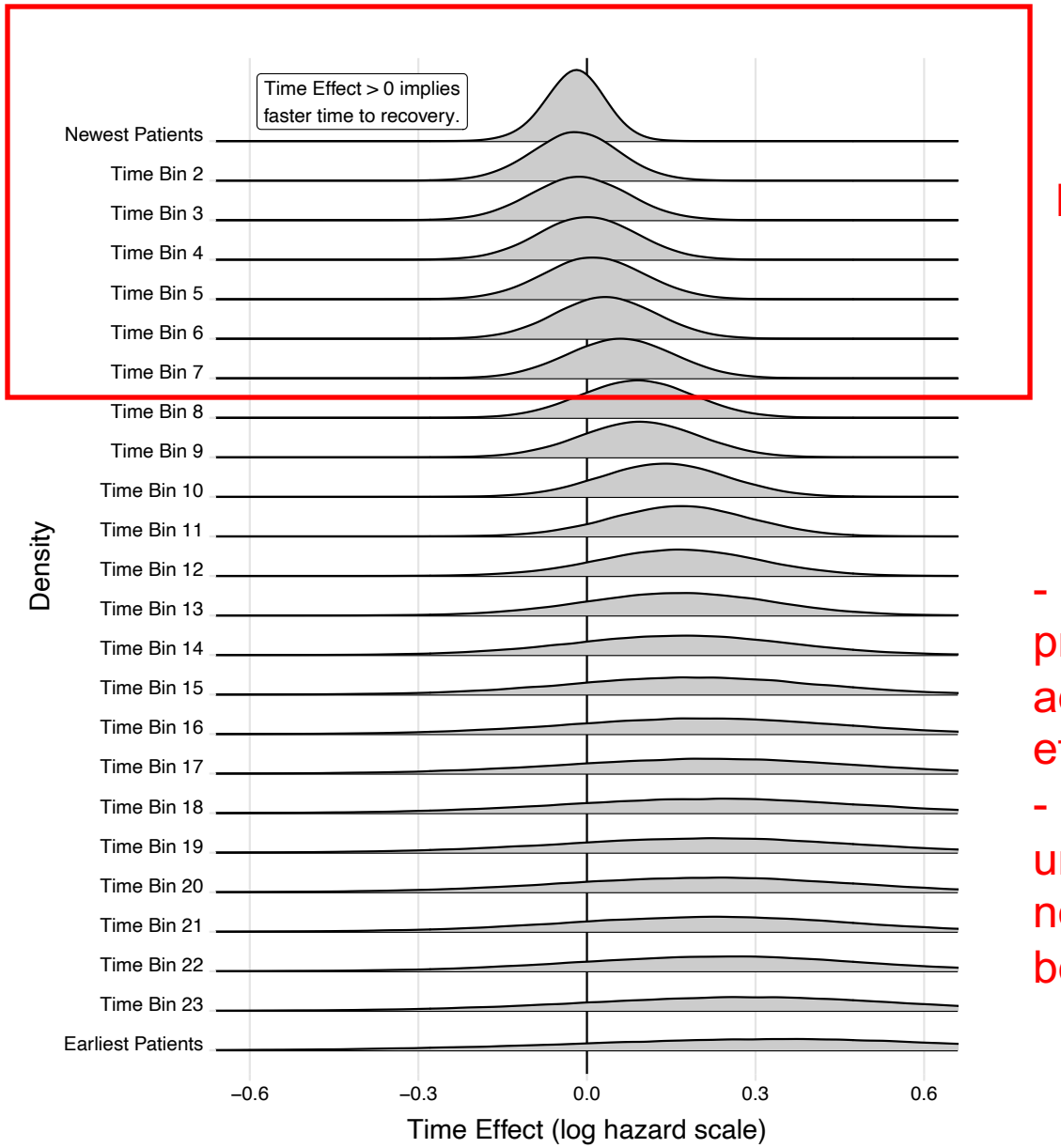
	Inhaled budesonide (95% BCI)	Usual care (95% BCI)	Estimated benefit median time to recovery or hospital admission or death rate (95% BCI)	Hazard ratio or odds ratio (95% BCI)	Probability of superiority
Primary analysis—SARS-CoV-2-positive participants					
Number of participants	787	1069	..	..	..
Time to first reported recovery, days*	11·8 (10·0 to 14·1)	14·7 (12·3 to 18·0)	2·94 (1·19 to 5·11)	1·21 (1·08 to 1·36)	>0·999
Hospital admission or death at 28 days†	6·8% (4·1 to 10·2)	8·8% (5·5 to 12·7)	2·0% (–0·2 to 4·5)	0·75 (0·55 to 1·03)	0·963
Sensitivity analysis—concurrent randomisation population					
Number of participants	787	838	..	..	..
Time to first reported recovery, days*	11·7 (9·8 to 14·2)	15·0 (12·5 to 18·3)	3·26 (1·46 to 5·43)	1·24 (1·10 to 1·39)	>0·999
Hospital admission or death at 28 days†	6·6% (3·8 to 10·1)	8·9% (5·2 to 13·1)	2·2% (0·0 to 4·9)	0·73 (0·53 to 1·00)	0·975

Bayesian Time Machine



Budesonide

Bayesian Time Machine



Budesonide

- Pre-specified Time Machine provided opportunity for additional precision of treatment effect
- Budesonide: Too much uncertainty of temporal drift and non-concurrent controls to benefit (small N, overlap, etc.)

Bayesian Time Machine

- Incorporates ALL available data
  - Non-concurrent controls and other treatment arms
  - Generally better estimates, precision, and power
- Real-world applications
  - I-SPY2, GBM AGILE, Precision Promise, Healey ALS, REMAP-CAP, PRINCIPLE, etc.
- Platform trials are novel and complex!
  - Why do we insist on simple “unbiased” analyses?
    - Cost of lower precision and statistical power
  - Better estimation via modeling that leverages ALL platform trial data

Modern analysis methods for modern trials!