A spectrum of causal estimands – differences in dose adherence patterns

- **Presenter: Anna Menacher (Novo Nordisk)**
- Nerissa Nance (Novo Nordisk)
- Yi Li (UC Berkeley)
- Mark van der Laan (UC Berkeley)
- Maya Petersen (UC Berkeley)

Why this matters:

moving beyond general adherence

From measuring dose adherence to understanding what treatment effects mean under realistic use.

01

Why does it matter?

Dose adherence can change the question a trial is able to answer.

02

What did we find?

Estimands and data-adaptive thresholds show how results shift across assumptions.

03

How can it be used?

Use as an exploratory tool alongside standard trial estimands.

Key idea: go beyond “did patients adhere?” and evaluate treatment effects under realistic dose adherence regimes.

Spectrum of Longitudinal Treatment Estimands

ITT
(Treatment Policy / Treatment Regime)

Effect of assigning a treatment strategy

Hypothetical Estimand
(Trial Product / Efficacy)

Effect if everyone followed the assigned treatment perfectly

Dynamic Estimands
(Adaptive)

Effect of strategies that adapt to patient characteristics or responses over time

Static Estimand
(While on Treatment)

Effect while patients remain on the assigned treatment

Least control — Increasing control over post-baseline treatment — Most control

Let’s talk trial estimands …

Treatment policy / regime estimand (ITT)

The estimand addresses the difference in mean change in body weight from baseline to end of treatment in participants with overweight or obesity **regardless of adherence to randomised treatment** or initiation of anti-obesity rescue intervention.

Hypothetical estimand (trial product / efficacy estimand)

The estimand addresses the treatment effect in the hypothetical scenario in which **all participants remain on their randomised treatment** without initiating anti-obesity rescue intervention prior to the time of evaluation.

For FDA the primary statistical analysis will be based on the treatment policy estimand and for all other purposes the primary analysis will be based on the hypothetical estimand.

… maybe we can do better

Static estimand

The estimand addresses the treatment effect in the hypothetical scenario in which **all participants remain on their randomised treatment and their intended targeted dose** after dose escalation while accounting for time-varying confounding and censoring.

Dynamic estimand(s)

The estimand addresses the treatment effect in the hypothetical scenario in which **all participants remain on their randomised treatment and their intended targeted dose** after dose escalation while accounting for time-varying confounding and censoring **except if their propensity for treatment is low** (tolerability estimate).

… maybe we can do better

Static estimand

Causal estimand:

$$\mathrm{E}\left[Y_{R=Treatment,\, C=0,\, A=Dose\ XX\ at\ Week\ YY}\right] - \mathrm{E}\left[Y_{R=Placebo,\, C=0,\, A=any}\right]$$

Dynamic estimand(s)

The estimand addresses the treatment effect in the hypothetical scenario in which **all participants remain on their randomised treatment and their intended targeted dose** after dose escalation while accounting for time-varying confounding and censoring **except if their propensity for treatment is low** (tolerability estimate).

$C = 0$: Remain uncensored. Censoring occurs after initiation of rescue intervention.

… maybe we can do better

Static estimand

Causal estimand:

$$\mathrm{E}\left[Y_{R=Treatment,\, C=0,\, A=Dose\ XX\ at\ Week\ YY}\right] - \mathrm{E}\left[Y_{R=Placebo,\, C=0,\, A=any}\right]$$

Dynamic estimand(s)

Causal estimand:

$$\mathrm{E}\left[Y_{R=Treatment,\, C=0,\, A=d_{G>\alpha}(\bar{a})}\right] - \mathrm{E}\left[Y_{R=Placebo,\, C=0,\, A=any}\right]$$

Realistic treatment policy for each individual based on thresholding the cumulative longitudinal product of propensity scores

$C = 0$: Remain uncensored. Censoring occurs after initiation of rescue intervention.

… maybe we can do better

Static estimand

Stay on the max dose no matter what!

Dynamic estimand(s)

Causal estimand:

$$\mathrm{E}\left[Y_{R=Treatment,\, C=0,\, A=d_{G>\alpha}(\bar{a})}\right] - \mathrm{E}\left[Y_{R=Placebo,\, C=0,\, A=any}\right]$$

Realistic treatment policy for each individual based on thresholding the cumulative longitudinal product of propensity scores

$C = 0$: Remain uncensored. Censoring occurs after initiation of rescue intervention.

… maybe we can do better

Static estimand

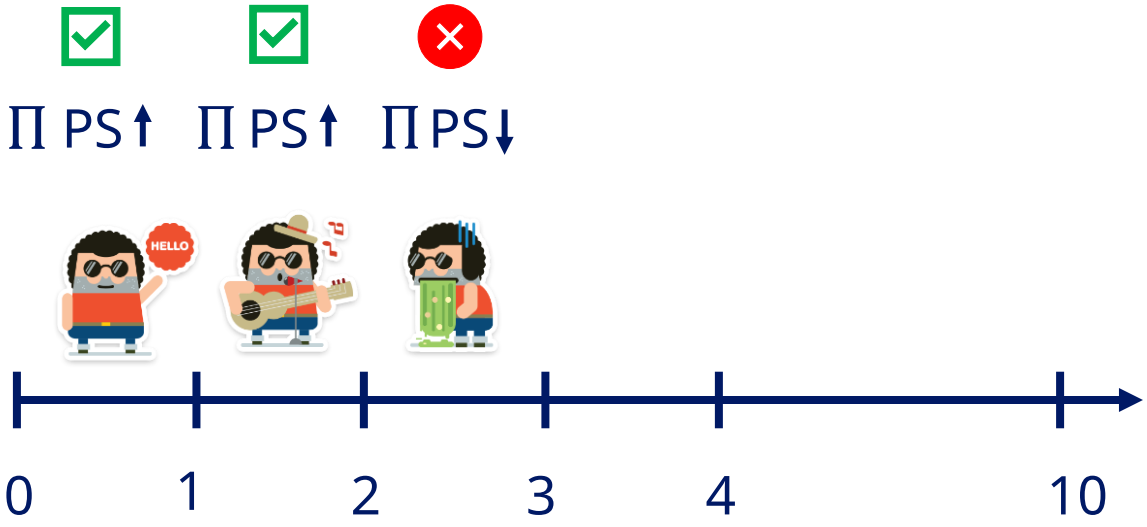
Stay on the max dose
no matter what!

Dynamic estimand(s)

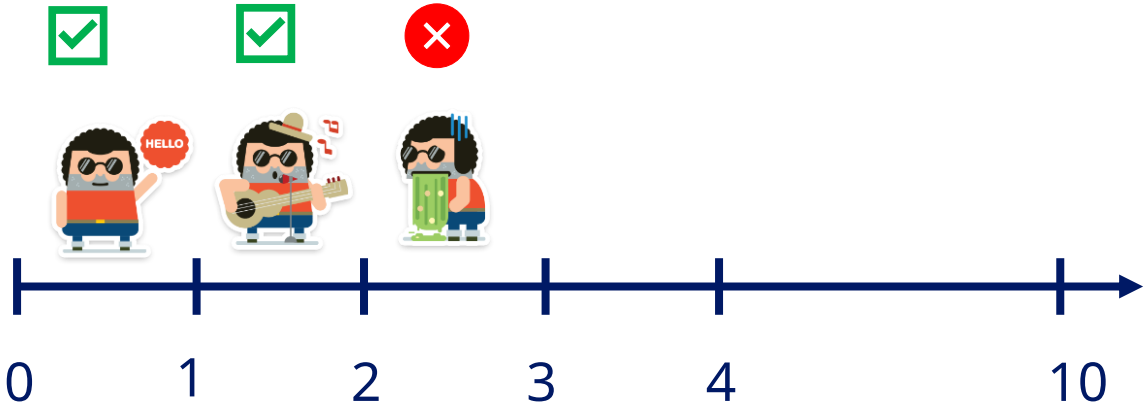
Stay on the max dose
unless you have a low probability to
receive treatment!

Differences between the two dynamic regimes

Simple thresholding regime

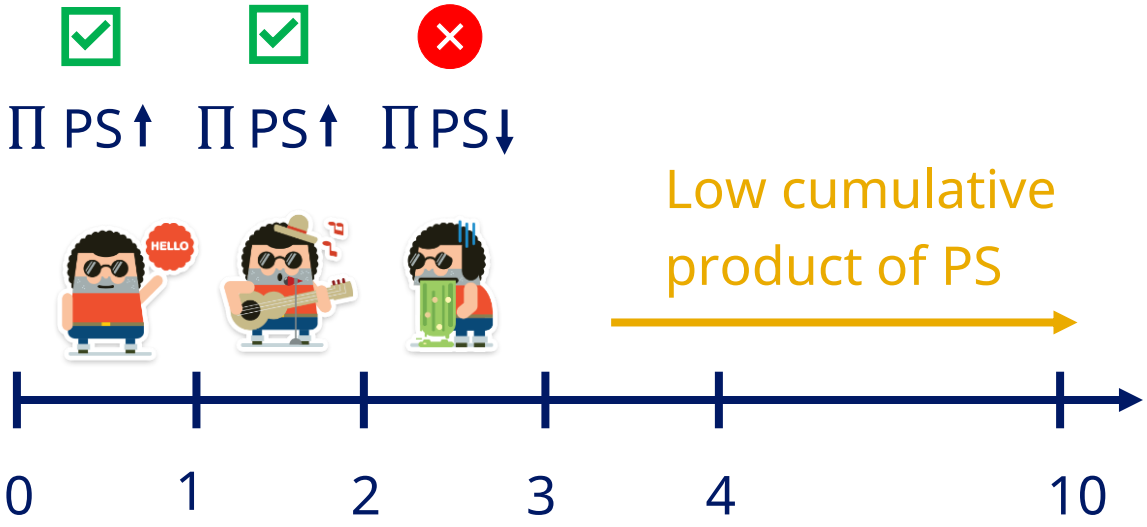


Sticky thresholding regime

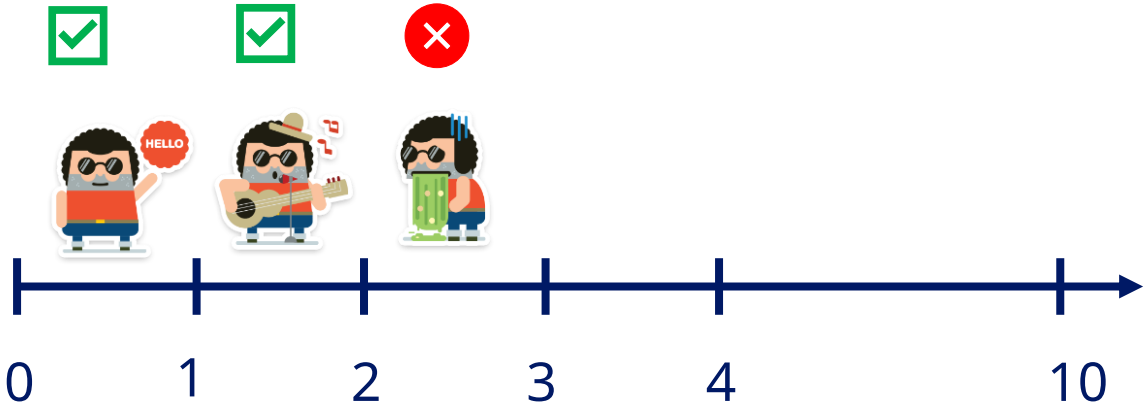


Differences between the two dynamic regimes

Simple thresholding regime

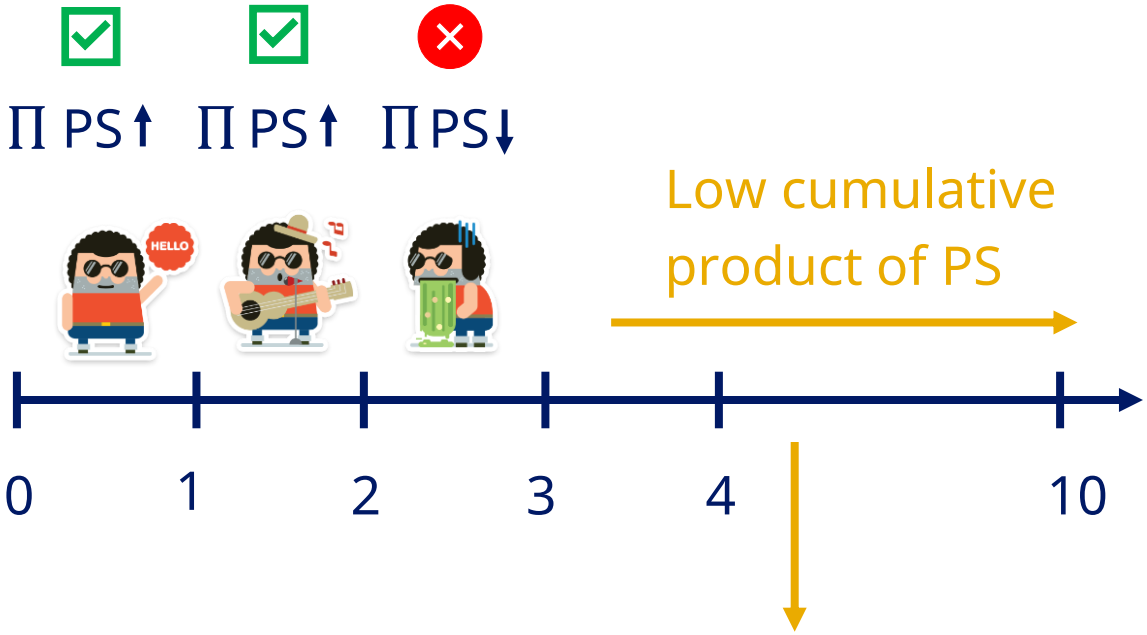


Sticky thresholding regime



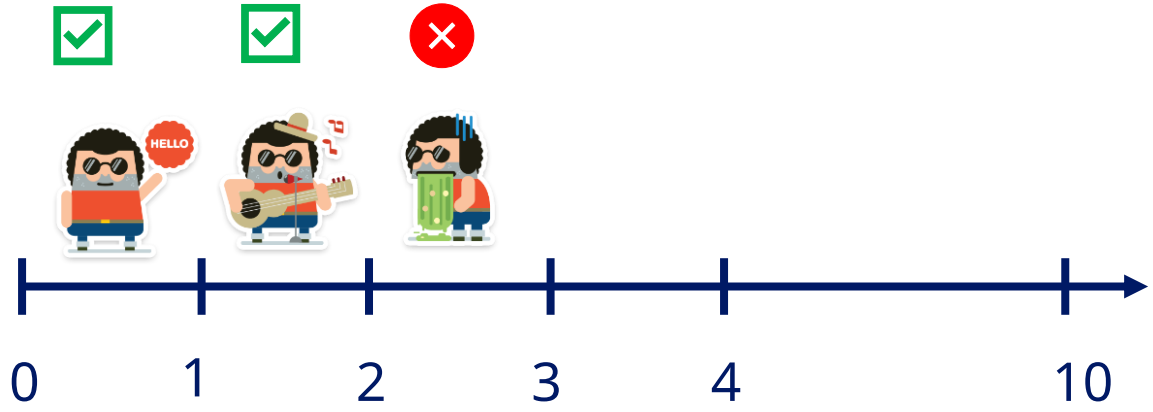
Differences between the two dynamic regimes

Simple thresholding regime



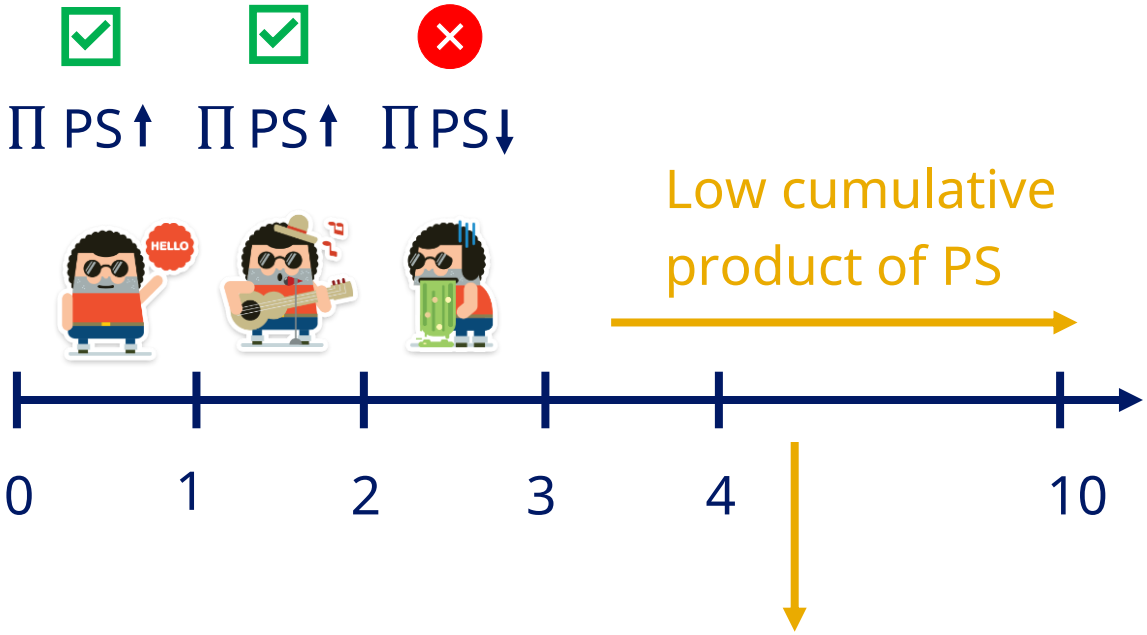
No intervention → observed value for regime after dip in cumulative product of PS $\leq \alpha$ for individual

Sticky thresholding regime



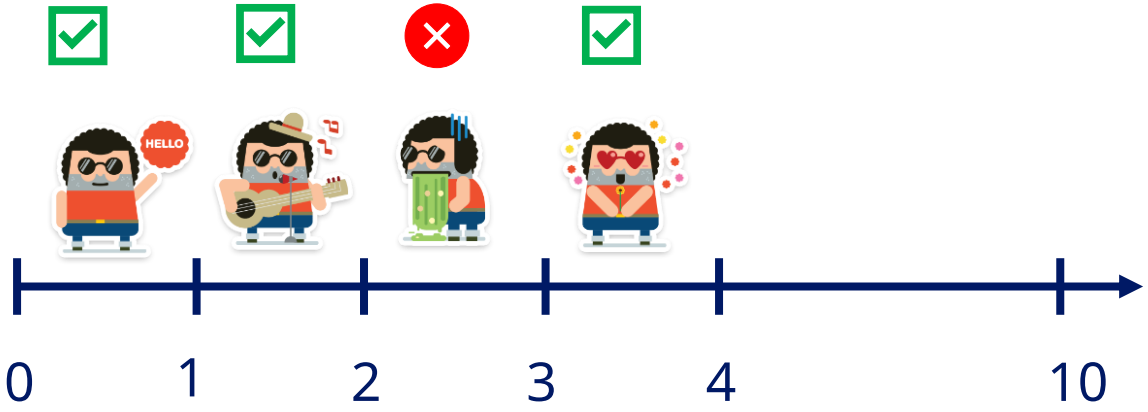
Differences between the two dynamic regimes

Simple thresholding regime



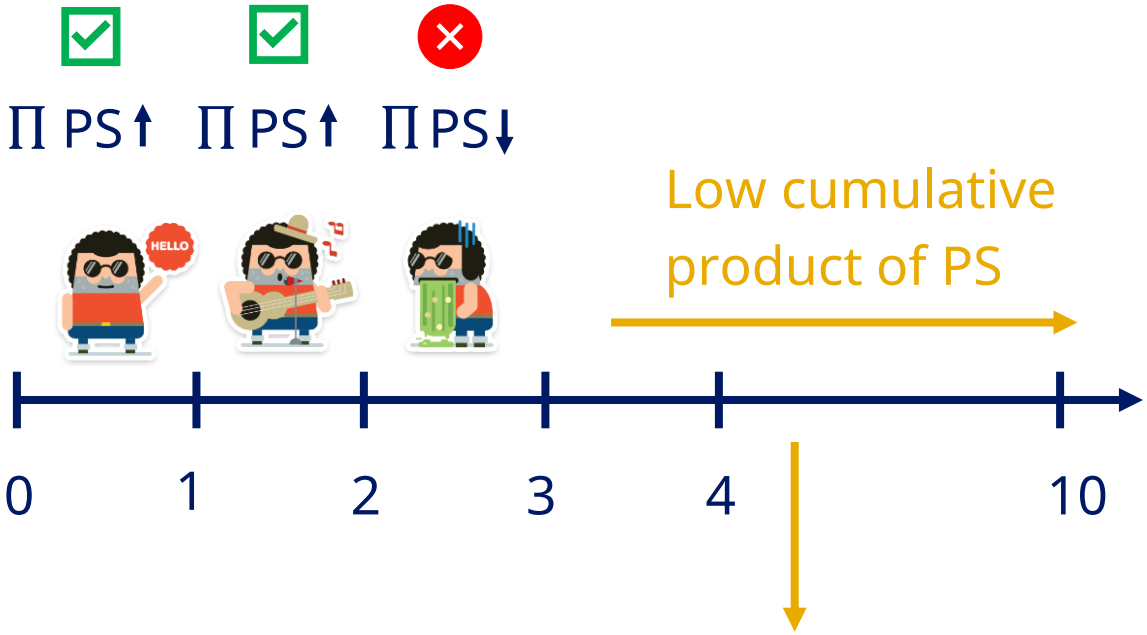
No intervention → observed value for regime after dip in cumulative product of PS $\leq \alpha$ for individual

Sticky thresholding regime



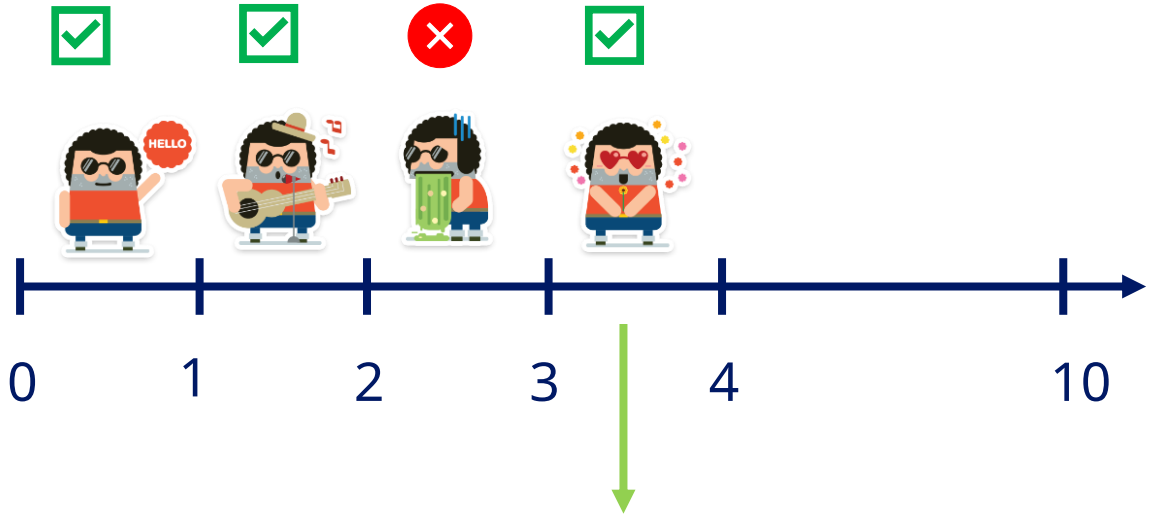
Differences between the two dynamic regimes

Simple thresholding regime



No intervention → observed value for regime after dip in cumulative product of PS $\leq \alpha$ for individual

Sticky thresholding regime



Sticky cumulative product of PS that only updates if threshold is exceeded → prevents cumulative product of PS from becoming arbitrarily small

Dynamic regime with **thresholding** of cumulative treatment propensity

Simple

Sticky

Cumulative treatment propensity

$$G_t = \prod_{t's=1}^{t} g_s(1|\mathcal{H}_s, C_{s-1} = 1)$$

Thresholding regime

Dynamic regime with **thresholding** of cumulative treatment propensity

Simple

Sticky

Cumulative treatment propensity

$$G_t = \prod_{t's=1}^{t} g_s(1|\mathcal{H}_s, C_{s-1} = 1)$$

Thresholding regime

$$d_\alpha^{simple}(a_t, h_t) = \begin{cases} 1, & \text{if } G_t > \alpha, \\ a_t, & \text{otherwise.} \end{cases}$$

Dynamic regime with **thresholding** of cumulative treatment propensity

Simple

Sticky

Cumulative treatment propensity

$$G_t = \prod_{t's=1}^{t} g_s(1|\mathcal{H}_s, C_{s-1} = 1)$$

For t = 1:

$$\tilde{G}_1 = \begin{cases} g_1(1|h_1), & \text{if } g_1(1|h_1) > \alpha, \\ 1, & \text{otherwise.} \end{cases}$$

For t > 1:

$$\tilde{G}_t = \begin{cases} \tilde{G}_{t-1} \cdot g_t(1|h_t, C_{t-1} = 0), & \text{if } \tilde{G}_{t-1} \cdot g_t(1|h_t, C_{t-1} = 0) > \alpha, \\ \tilde{G}_{t-1}, & \text{otherwise.} \end{cases}$$

Thresholding regime

$$d_\alpha^{simple}(a_t, h_t) = \begin{cases} 1, & \text{if } G_t > \alpha, \\ a_t, & \text{otherwise.} \end{cases}$$

Dynamic regime with **thresholding** of cumulative treatment propensity

Simple

Cumulative treatment propensity

$$G_t = \prod_{t's=1}^{t} g_s(1|\mathcal{H}_s, C_{s-1} = 1)$$

Thresholding regime

$$d_\alpha^{simple}(a_t, h_t) = \begin{cases} 1, & \text{if } G_t > \alpha, \\ a_t, & \text{otherwise.} \end{cases}$$

Sticky

Cumulative treatment propensity

For t = 1:

$$\tilde{G}_1 = \begin{cases} g_1(1|h_1), & \text{if } g_1(1|h_1) > \alpha, \\ 1, & \text{otherwise.} \end{cases}$$

For t > 1:

$$\tilde{G}_t = \begin{cases} \tilde{G}_{t-1} \cdot g_t(1|h_t, C_{t-1} = 0), & \text{if } \tilde{G}_{t-1} \cdot g_t(1|h_t, C_{t-1} = 0) > \alpha, \\ \tilde{G}_{t-1}, & \text{otherwise.} \end{cases}$$

Thresholding regime

For t = 1:

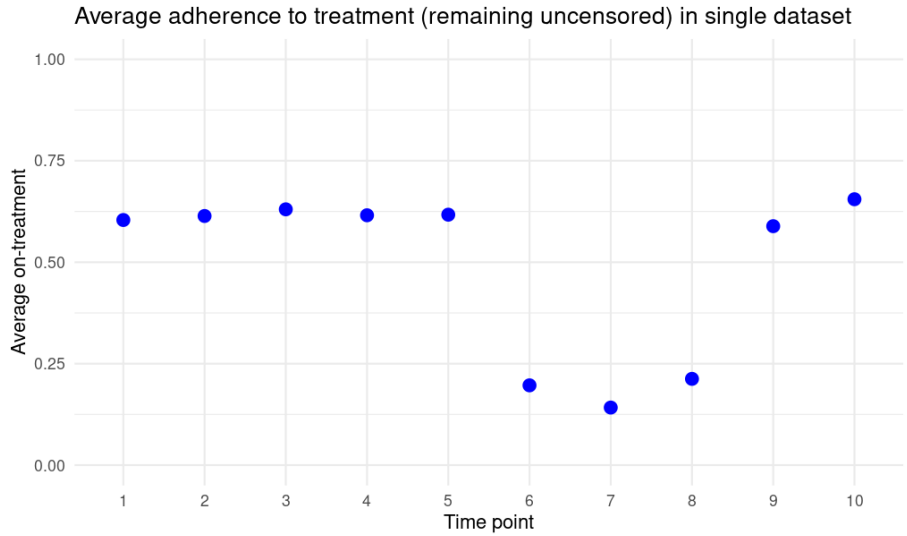
$$d_\alpha^{sticky}(a_1, h_1) = \begin{cases} 1, & \text{if } g_1(1|h_1) > \alpha, \\ a_1, & \text{otherwise.} \end{cases}$$

For t > 1:

$$d_\alpha^{sticky}(a_t, h_t) = \begin{cases} 1, & \text{if } \tilde{G}_{t-1} \cdot g_t(1|h_t, C_{t-1} = 0) > \alpha, \\ a_t, & \text{otherwise.} \end{cases}$$

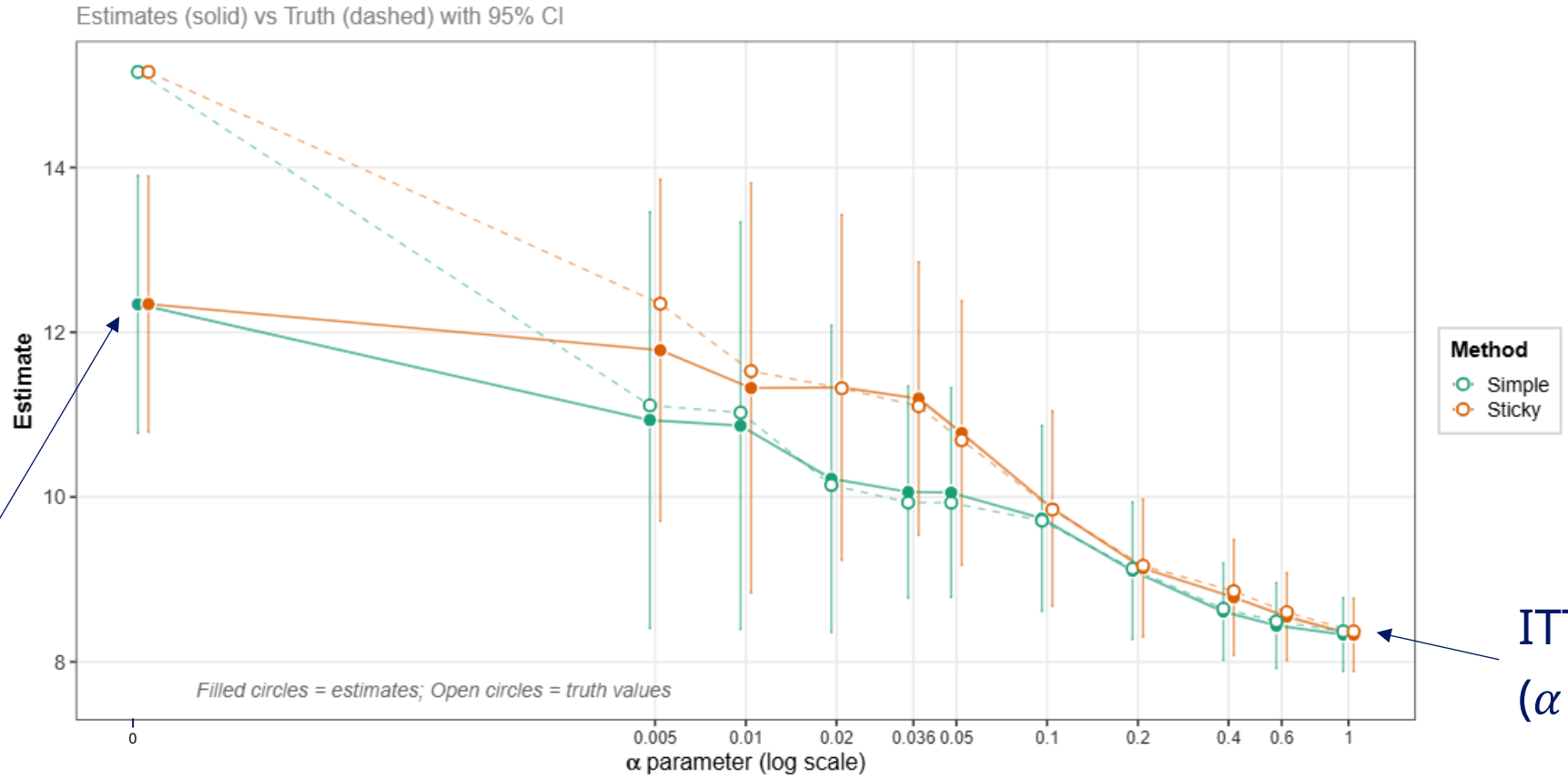
Simulation study: data generating process

Time t = 1-5	Time t = 6-8	Time t = 9-10
High propensity	Low propensity	High propensity
60% probability of treatment	10% probability of treatment	60% probability of treatment



Simulation studies performed by Yi Li (PhD Student at UC Berkeley)

Simulation study: estimated vs truth – varying thresholding parameters



Static
$(\alpha = 0)$

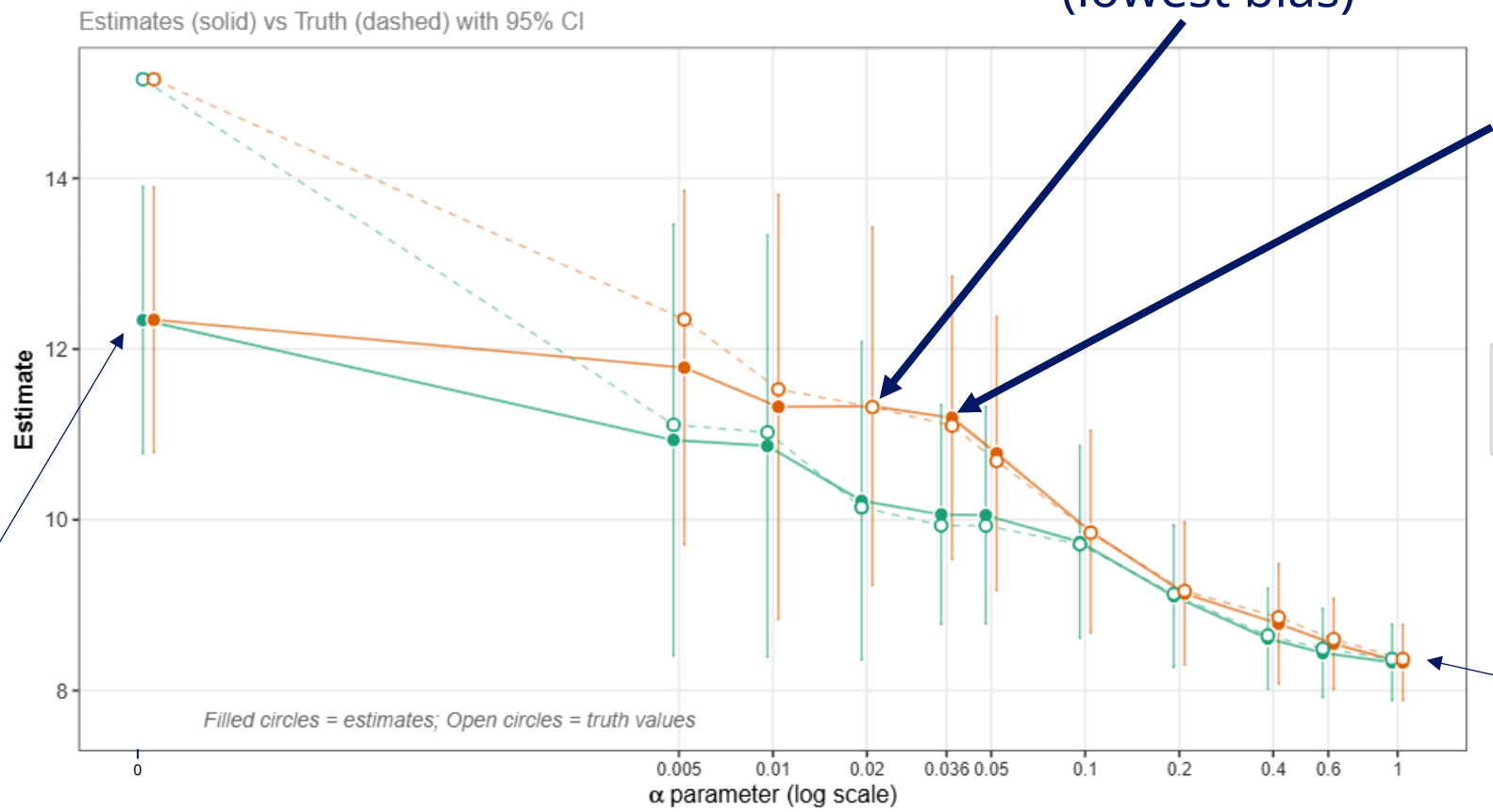
ITT
$(\alpha = 1)$

Simulation studies performed by Yi Li (PhD Student at UC Berkeley)

Simulation study: estimated vs truth – varying thresholding parameters

α=0.02
(lowest bias)

$\alpha=\frac{5}{\sqrt{n}\log(n)}$ ≈0.04
(control the $\prod_{t=1}\frac{g_t^*}{g_t}$ in the EIC/clever covariate by $\frac{1}{\alpha}$)



Static
($\alpha = 0$)

ITT
($\alpha = 1$)

Simulation studies performed by Yi Li (PhD Student at UC Berkeley)

Simulation study: results

Method	Mean Estimate	Mean Truth	Bias	Variance	MSE
Static (α=0)	12.34	15.16	-2.82	0.63	8.56
Dynamic (simple, α=0.036*)	10.06	9.93	0.13	0.43	0.44
Dynamic (simple, α=0.1)	9.74	9.71	0.03	0.33	0.32
Dynamic (sticky, α=0.036*)	11.20	11.10	0.09	0.71	0.64
Dynamic (sticky, α=0.1)	9.86	9.85	0.01	0.37	0.35
ITT (α=1)	8.33	8.37	-0.04	0.05	0.05

$*\alpha = \frac{5}{\sqrt{n}\log n} \approx 0.036$ *for n = 500.*

Simulation studies performed by Yi Li (PhD Student at UC Berkeley)

Simulation study: results

Method	Mean Estimate	Mean Truth	Bias	Variance	MSE
Static (α=0)	12.34	15.16	-2.82	0.63	8.56
Dynamic (simple, α=0.036*)	10.06	9.93	0.13	0.43	0.44
Dynamic (simple, α=0.1)	9.74	9.71	0.03	0.33	0.32
Dynamic (sticky, α=0.036*)	11.20	11.10	0.09	0.71	0.64
Dynamic (sticky, α=0.1)	9.86	9.85	0.01	0.37	0.35
ITT (α=1)	8.33	8.37	-0.04	0.05	0.05

$*\alpha = \frac{5}{\sqrt{n}\log n} \approx 0.036$ *for n = 500.*

Simulation studies performed by Yi Li (PhD Student at UC Berkeley)

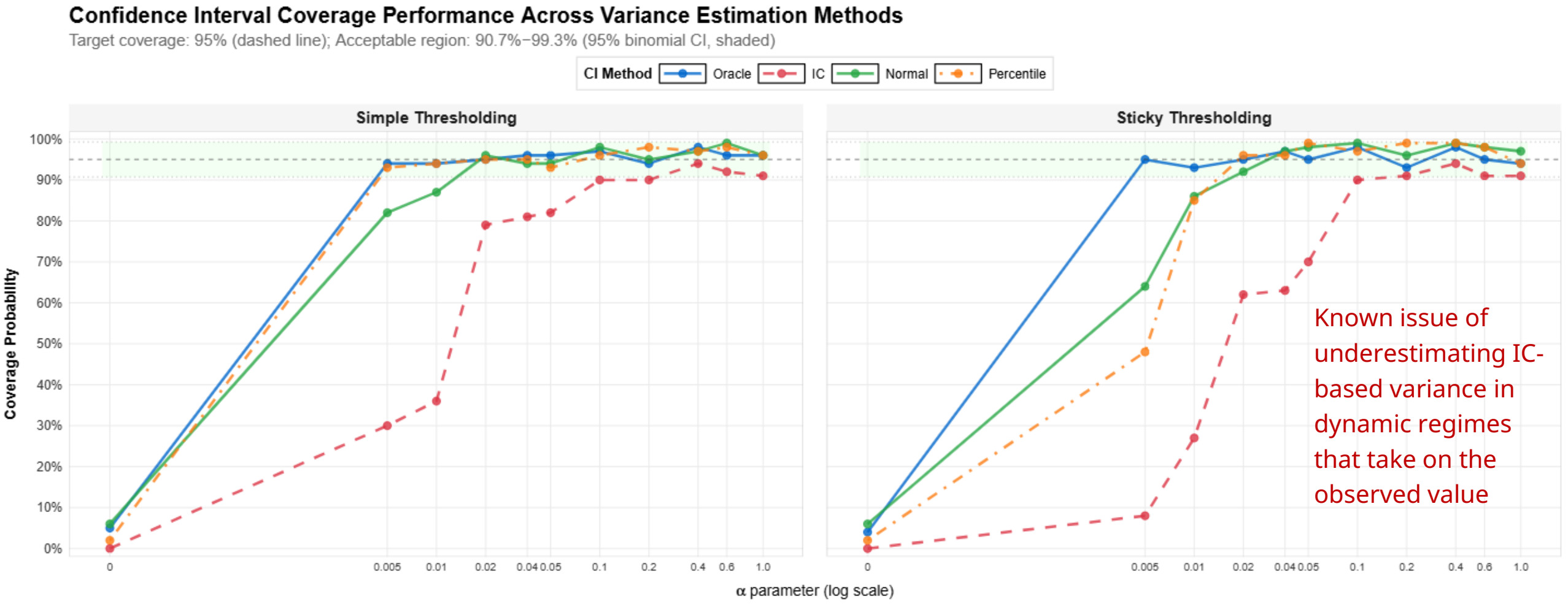
Simulation study: results

Method	Mean Estimate	Mean Truth	Bias	Variance	MSE
Static (α=0)	12.34	15.16	-2.82	0.63	8.56
Dynamic (simple, α=0.036*)	10.06	9.93	0.13	0.43	0.44
Dynamic (simple, α=0.1)	9.74	9.71	0.03	0.33	0.32
Dynamic (sticky, α=0.036*)	11.20	11.10	0.09	0.71	0.64
Dynamic (sticky, α=0.1)	9.86	9.85	0.01	0.37	0.35
ITT (α=1)	8.33	8.37	-0.04	0.05	0.05

$*\alpha = \frac{5}{\sqrt{n}\log n} \approx 0.036$ *for n = 500.*

Simulation studies performed by Yi Li (PhD Student at UC Berkeley)

Simulation study: coverage



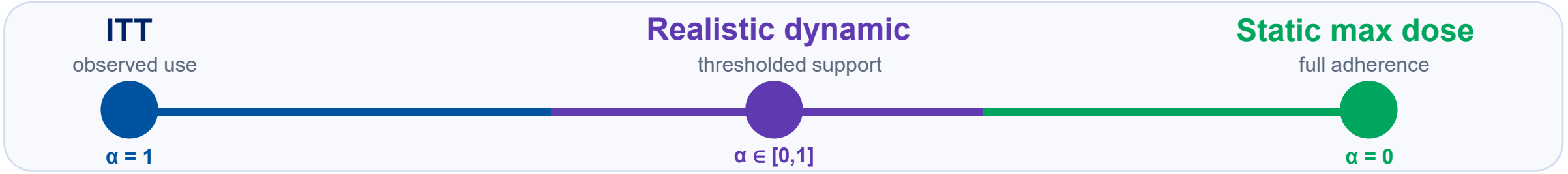
Known issue of underestimating IC-based variance in dynamic regimes that take on the observed value

Simulation studies performed by Yi Li (PhD Student at UC Berkeley)

Novo Nordisk®

Take-home: beyond dose adherence

Choose the estimand that answers a realistic clinical question and is supported by the trial data.



01 Why it matters

Adherence changes what the treatment effect means.

02 What we found

Thresholding moves toward effects the data can support.

03 How to use it

Exploratory sensitivity tool alongside standard estimands.

Other approaches

Longitudinal IV method

- Extends Bowden et al. (2025) accounting for dose adherence
- Adherence defined as actual / planned dose
- Parametric decay model includes a dose-response component

Jack Bowden · Aske Iversen · Jesper Madsen

References

- ICH E9(R1) addendum on estimands and sensitivity analysis (2019)
- van der Laan & Petersen (2007): realistic individualized treatment rules
- Kennedy (2019): incremental propensity score interventions
- Bowden et al. (2025): longitudinal IV methods for hypothetical estimands

Thank you!

Contact: iaam@novonordisk.com

Yi Li
UC Berkeley

Maya Petersen
UC Berkeley

Mark van der Laan
UC Berkeley

Nerissa Nance
Novo Nordisk

Anna Menacher
Novo Nordisk