NIH/NINDS
StrokeNet Thrombectomy Endovascular Platform Trial (STEP)

Jordan J Elm, PhD
Professor of Biostatistics
Medical University of South Carolina

2024
BOSTON

SCT | 45TH ANNUAL MEETING

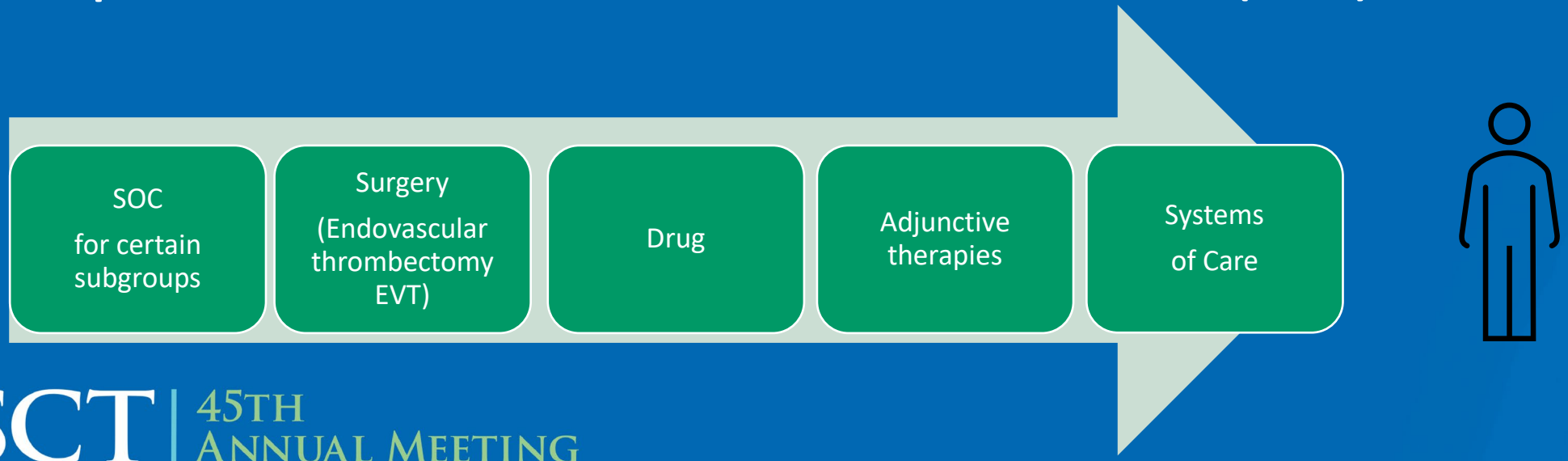
Disclosures

- NIH/NINDS grant funding StrokeNET NDMC
- Other Transaction Agreement OT2NS129366

STEP Platform

StrokeNet Thrombectomy Endovascular Platform Trial

Objective: To determine the optimal strategy for treatment of patients with Acute Ischemic Stroke (AIS)*

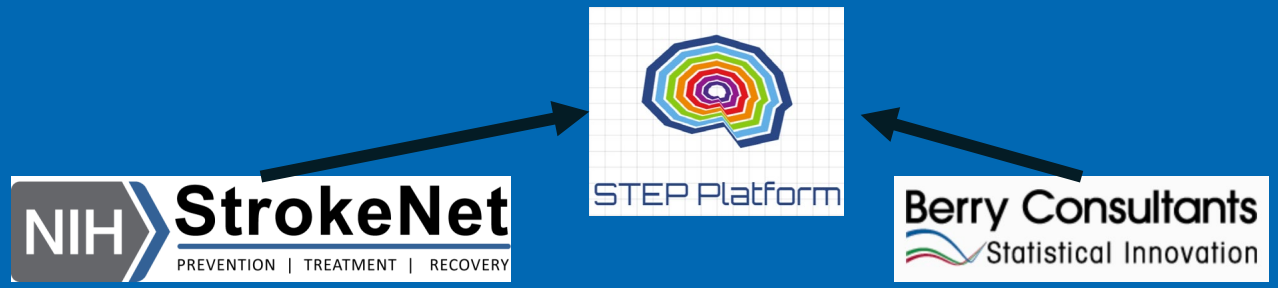


STEP

- Randomized Multifactorial Adaptive Platform Trial
- 38 US sites/ up to 10 in Canada
- Uses existing registries for data collection
  - American Heart Association Get with the Guidelines (GWTG-Stroke)
    - Quality improvement program
    - promotes adherence to treatment guidelines
  - NeuroVascular Quality Initiative-Quality Outcomes Database (NVQI-QOD)
    - neurovascular registry

Platform Trial

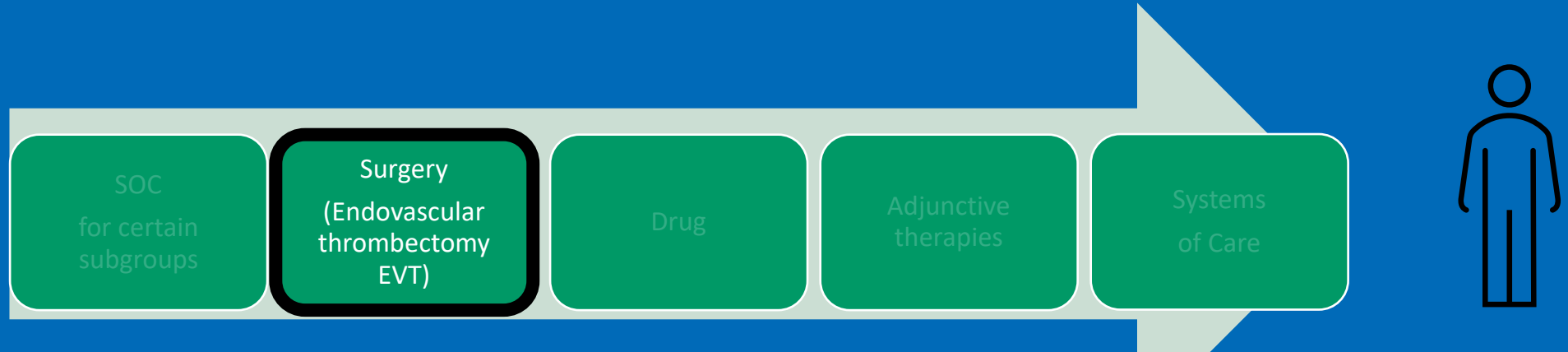
- Assess promising therapies simultaneously, rather than performing many, individuals trials
- Platform trials are designed to accelerate the pace of therapeutic development for a disease state: oncology (I-SPY), community acquired pneumonia (REMAP CAP), and covid-19 (ACTIV4A)
- In response to OTA-022-01 for NIH StrokeNET, the STEP Executive Team partnered with Berry Consultants to design the platform trial



Platform Domains

- The platform consists of multiple domains (sets of interventions being compared within a common population) that run simultaneously, with domains being opened/closed during the duration of the platform

- STEP Domain A Objective:
- To determine subsets of acute ischemic stroke patients, currently not treated with EVT according to guidelines, who do or do not benefit from EVT compared to Medical Management by having better functional outcome.



Master Protocol

Patients

- ✓ Acute ischemic stroke patients
- ✓ Intracranial large or medium vessel occlusion
- ❖ Contraindication to EVT
- ❖ Prisoners

Follow-Up

- ✓ Schedule of Assessments
- ✓ 90 days

Defines the largest Set of Inclusion/Exclusion Criteria to be studied

Broadly defines study procedures:

Baseline, 24 hr, Hospital discharge, 90 day

Specifies a single underlying statistical model (Bayesian hierarchical model of uw-mRS)

“Research Question” Domain Specific Appendix

Defines a set of patients eligible for the domain

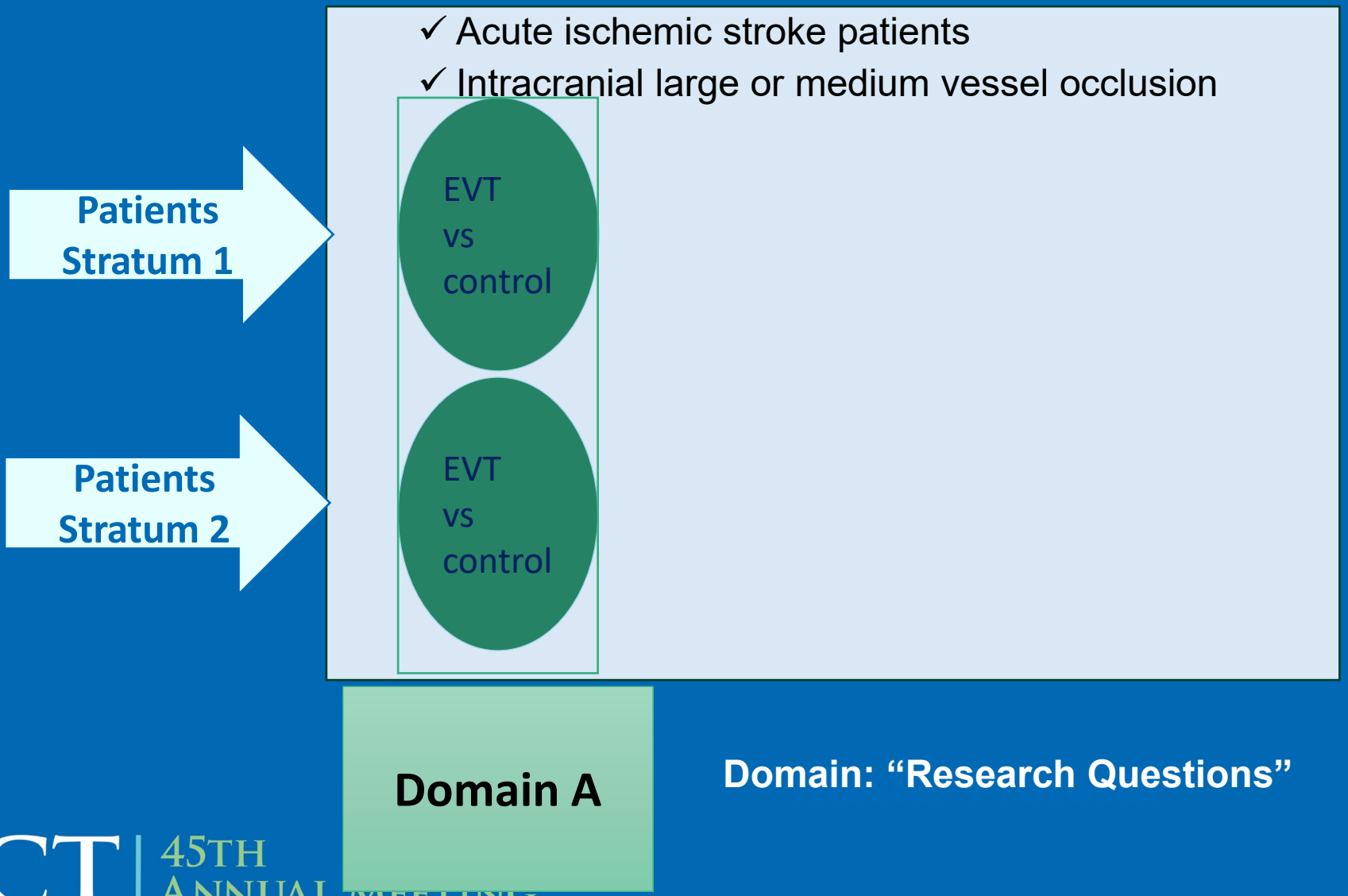
- Subset of Master Protocol I/E population

Details the type/delivery of intervention(s)

Details specific

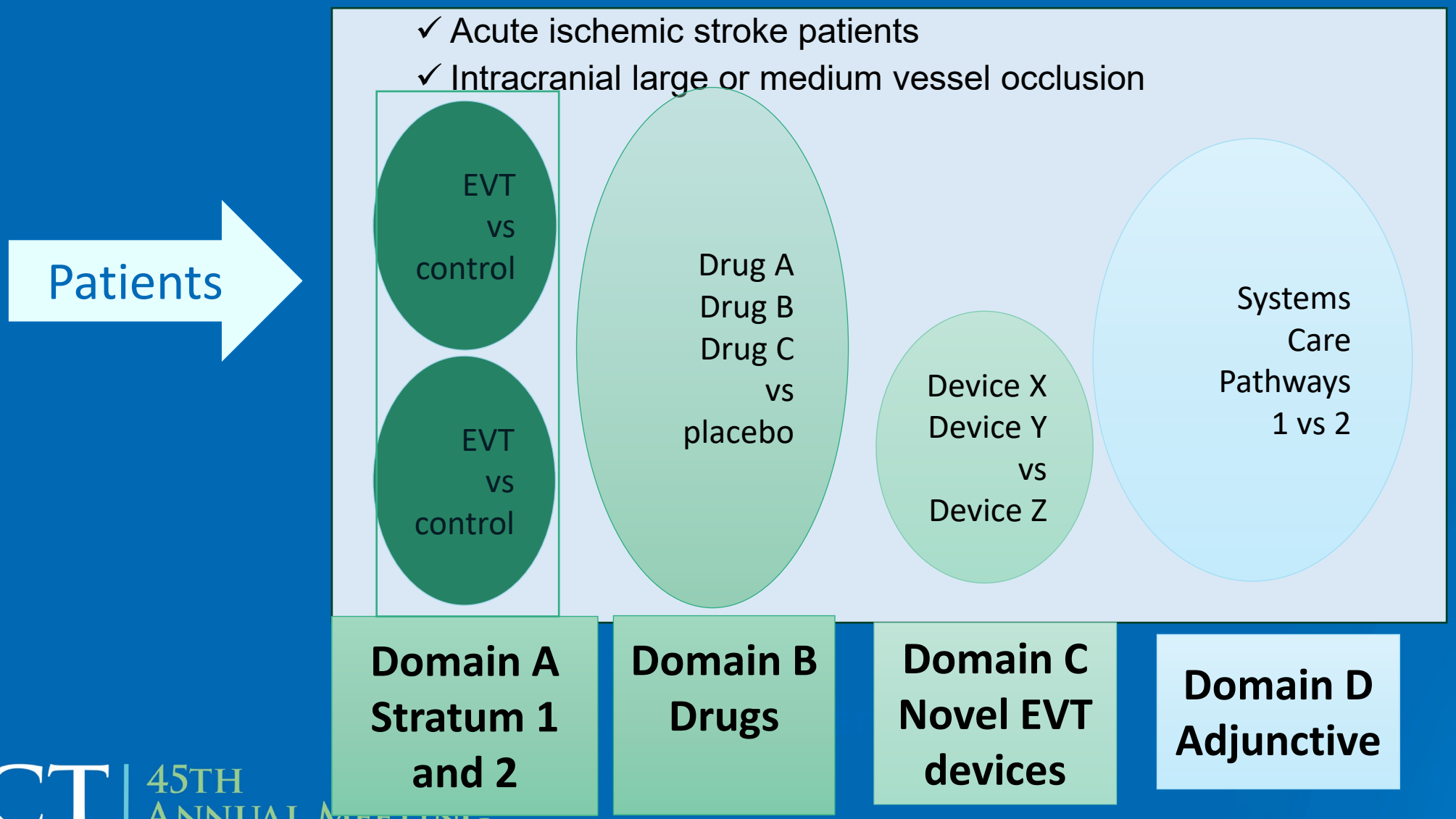
- Randomization/adaptations
- Analysis methods
- Additional research procedures
- Whether co-enrollment within other domains is allowable.
  - Whether “intervention by intervention” interactions will be modeled.

Master Protocol

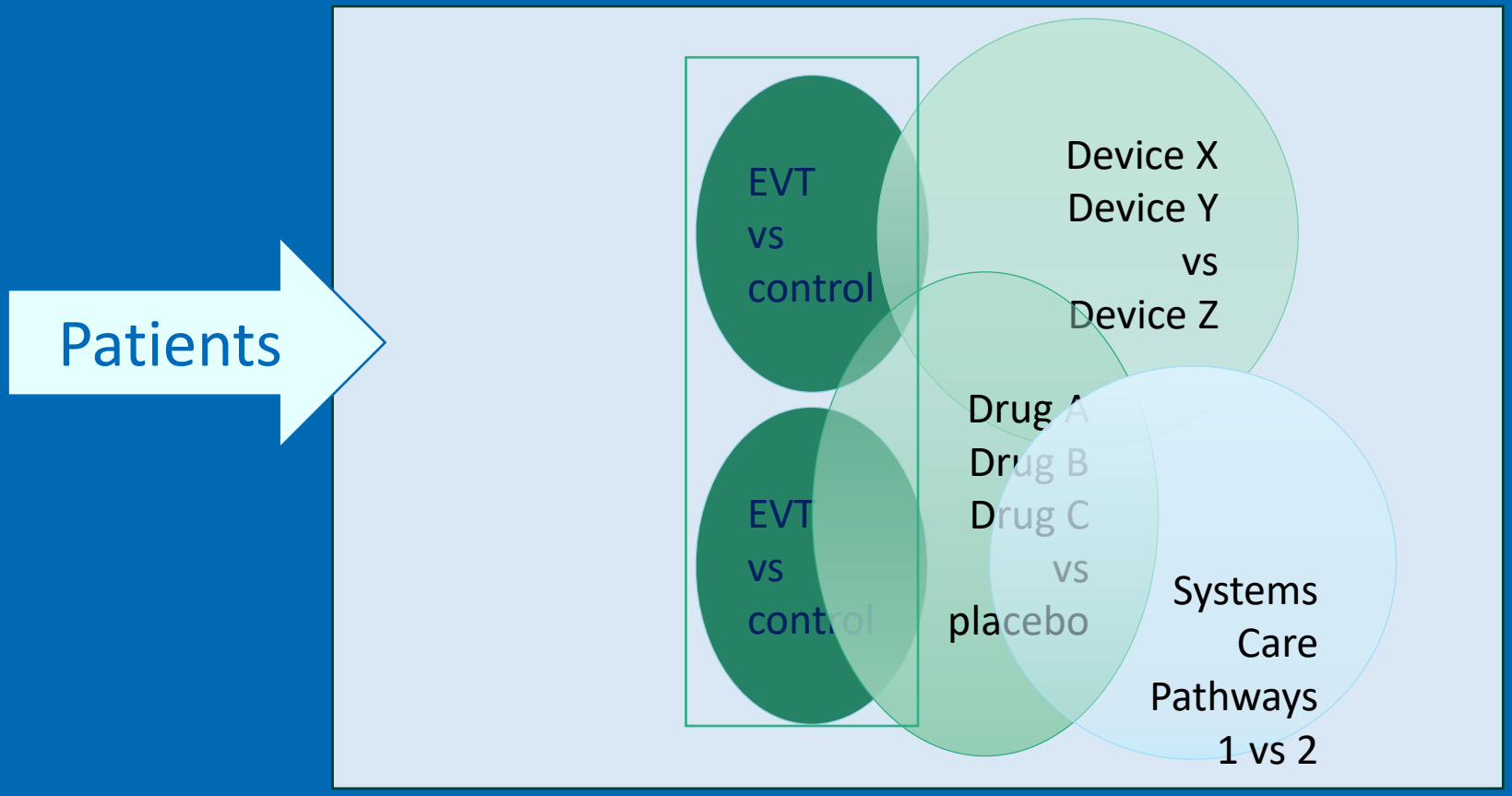


Domain: "Research Questions"

Domain: “Research Questions”

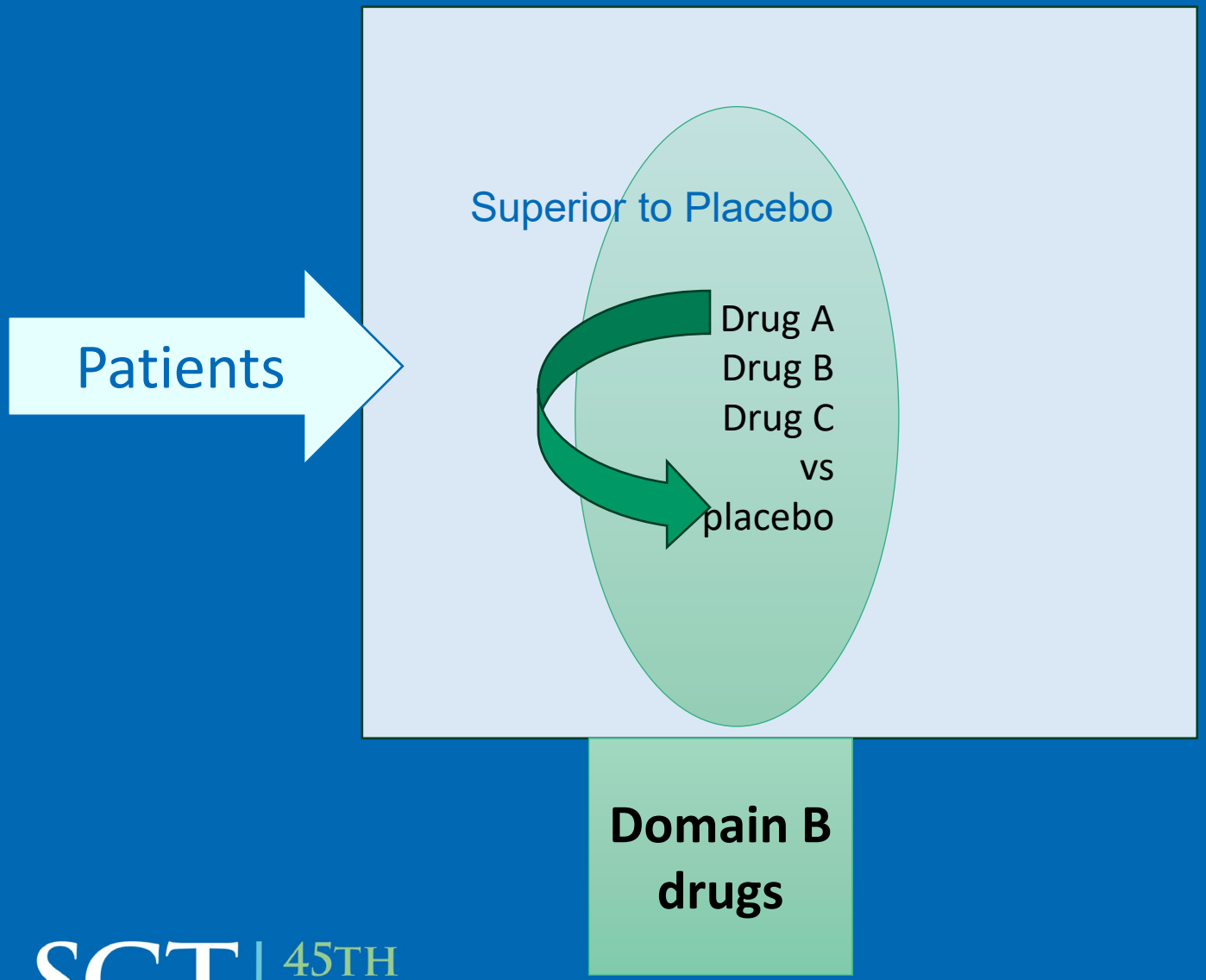


Master Protocol is Multifactorial



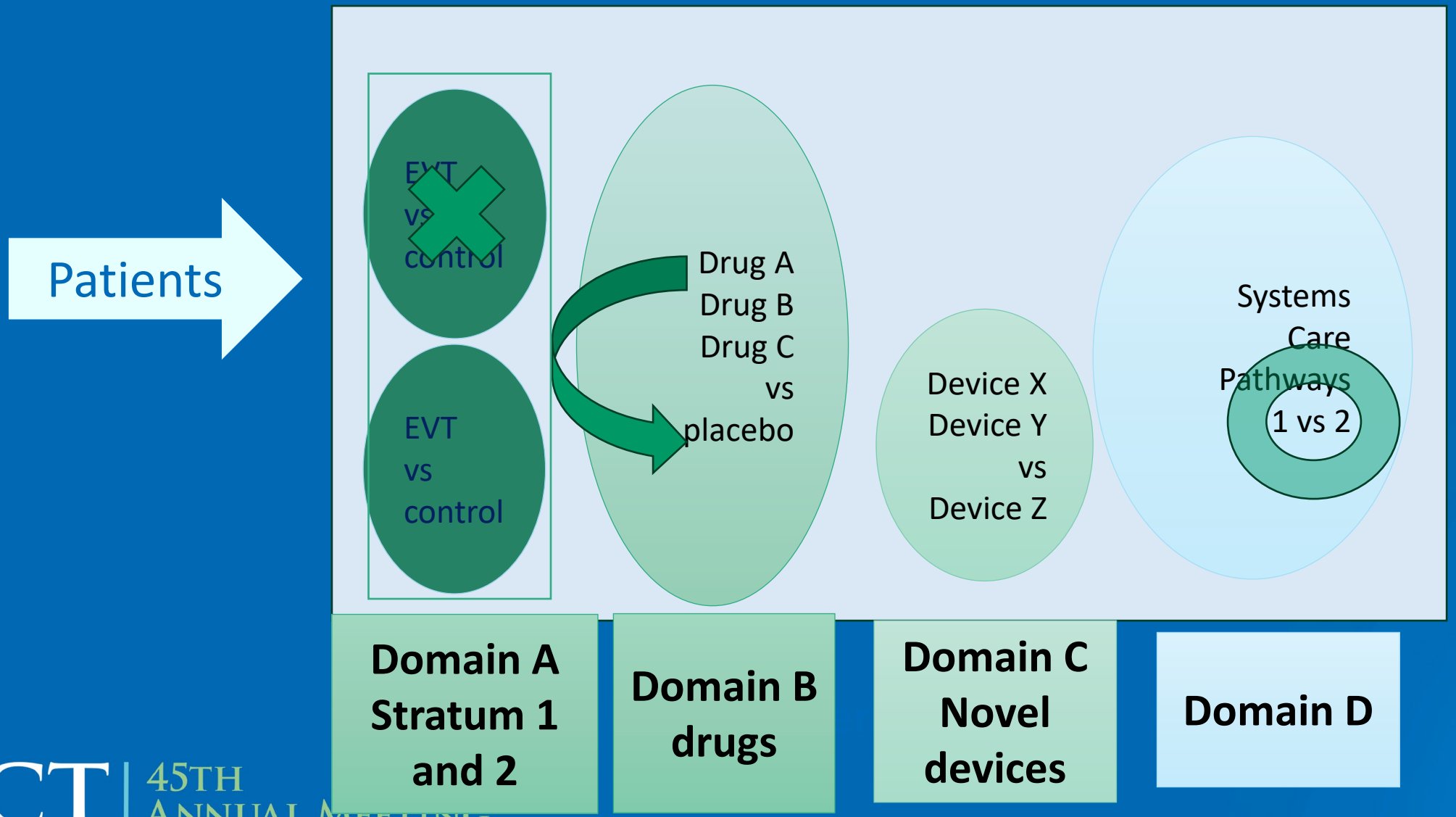
- Interventions within the domains are mutually exclusive
- Patient population can overlap between two domains
- Patients can be randomized within multiple domains (**multifactorial**)

Decisions

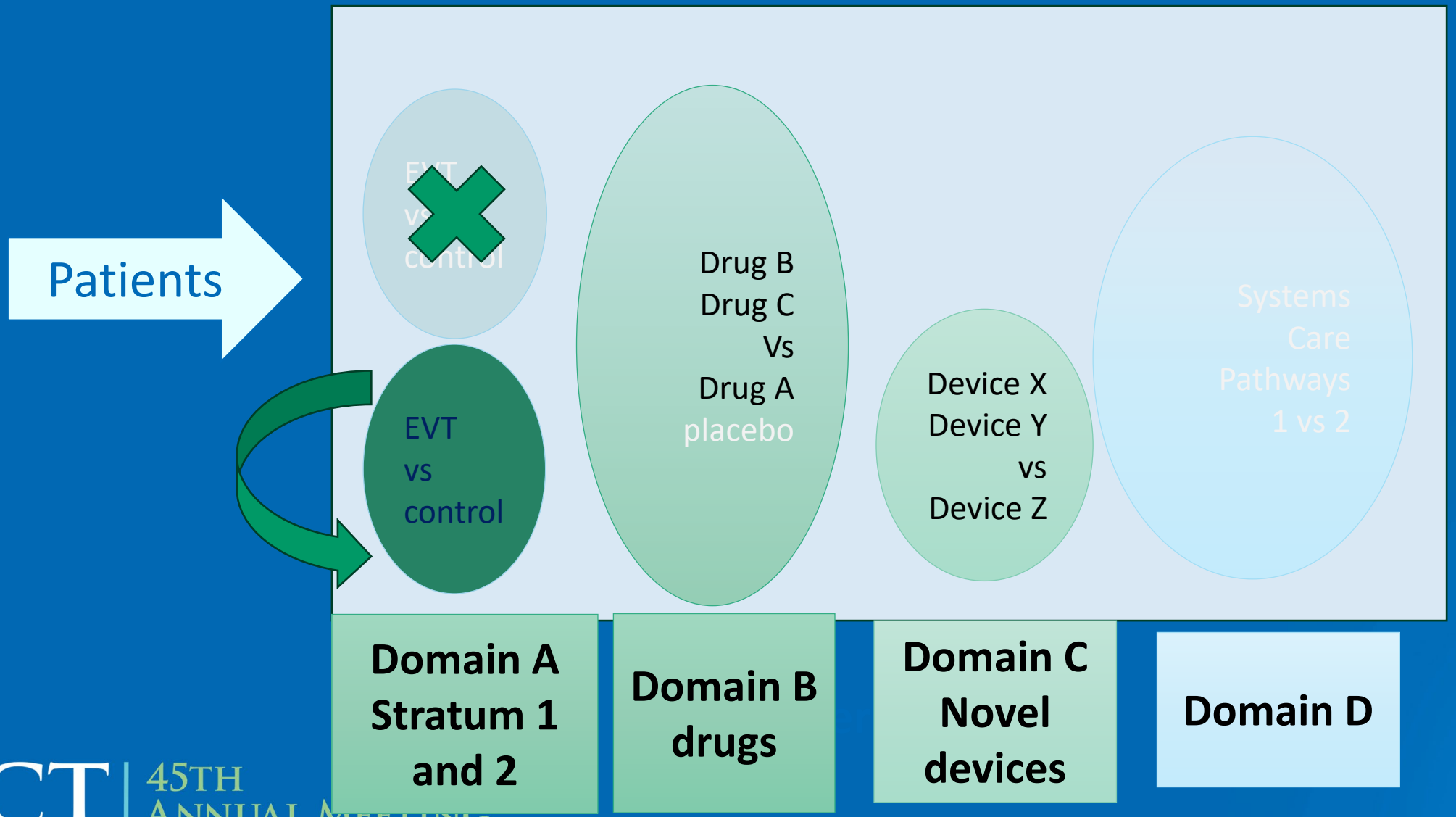


- Following types of decisions can be made for arm(s) or strata
  - ✓Superior (to control)
  - ✓Inferior
  - ✓Futile
  - ✓Equivalent
- Decisions are based on pre-defined statistical triggers
  - ✓Based on pre-defined analysis frequency
  - ✓Using platform statistical model

Decisions occur Quarterly (every 3 months)



Domain: “Research Questions”



Adaptations

- Interim analyses every quarter
- Domains added and dropped
- Interventions added/dropped within a domain
- Response Adaptive Randomization if more than 2 groups in a domain
  - randomization probabilities will be altered based on the updated posterior distribution
  - Increase randomization rate to the better performing intervention
  - Control allocation is fixed

Intent-to-treat

- The primary analysis set: all participants that are randomized to at least one intervention within at least one domain.
- The primary analysis set will analyze all participants by the interventions to which they were randomized.
- All participants in the perpetual trial will become a part of the accruing trial dataset and remain in the primary analysis set at adaptive analyses while the trial is running.
- The intent-to-treat group for a domain:
  - The analysis of an intervention within a domain is informed only by participants randomized to the respective domain (effect for domain) although covariates can be informed by all participants.
  - A patient not randomized within a domain is not a control for the respective domain.

Primary Endpoint
modified Rankin Score (mRS) at 90 days

mRS	0	1	2	3	4	5	6
UW-mRS	1	0.91	0.76	0.65	0.33	0	0

0 = No symptoms

1 = No significant disability;

……

6 = Dead

Ordinal scale 7 points is assigned values.

The mean score for a population or intervention will be modeled as normally distributed.

STEP Primary Analysis Model

- **Single inferential model:** model the primary outcome, Y = UW-mRS, as a function of baseline covariates, randomization to interventions within a domain, potentially interactions between interventions and baseline populations (strata), and potentially interactions between interventions in different domains.

- $Y = [\text{covariates}] + [\text{intervention effects}] + [\text{intervention} * \text{stratum}] + [\text{intervention} * \text{intervention}] + [\text{error}]$
- The error term of *Y* is modeled as normally distributed with a mean of 0 and a standard deviation of σ,

$$\epsilon \sim N(0, \sigma^2).$$

- The covariate effects will have a prior distribution of $\alpha_c \sim N(0,1)$. Weak.
- Adjusts for time period (year) of randomization (Effects for each previous era are estimated relative to the most recent era with a first-order normal dynamic linear model (NDLM).)
- By default interaction between interventions in different domains will NOT be modeled, but a given domain may specify an interaction effect across domains
- Domains may have specific analyses.

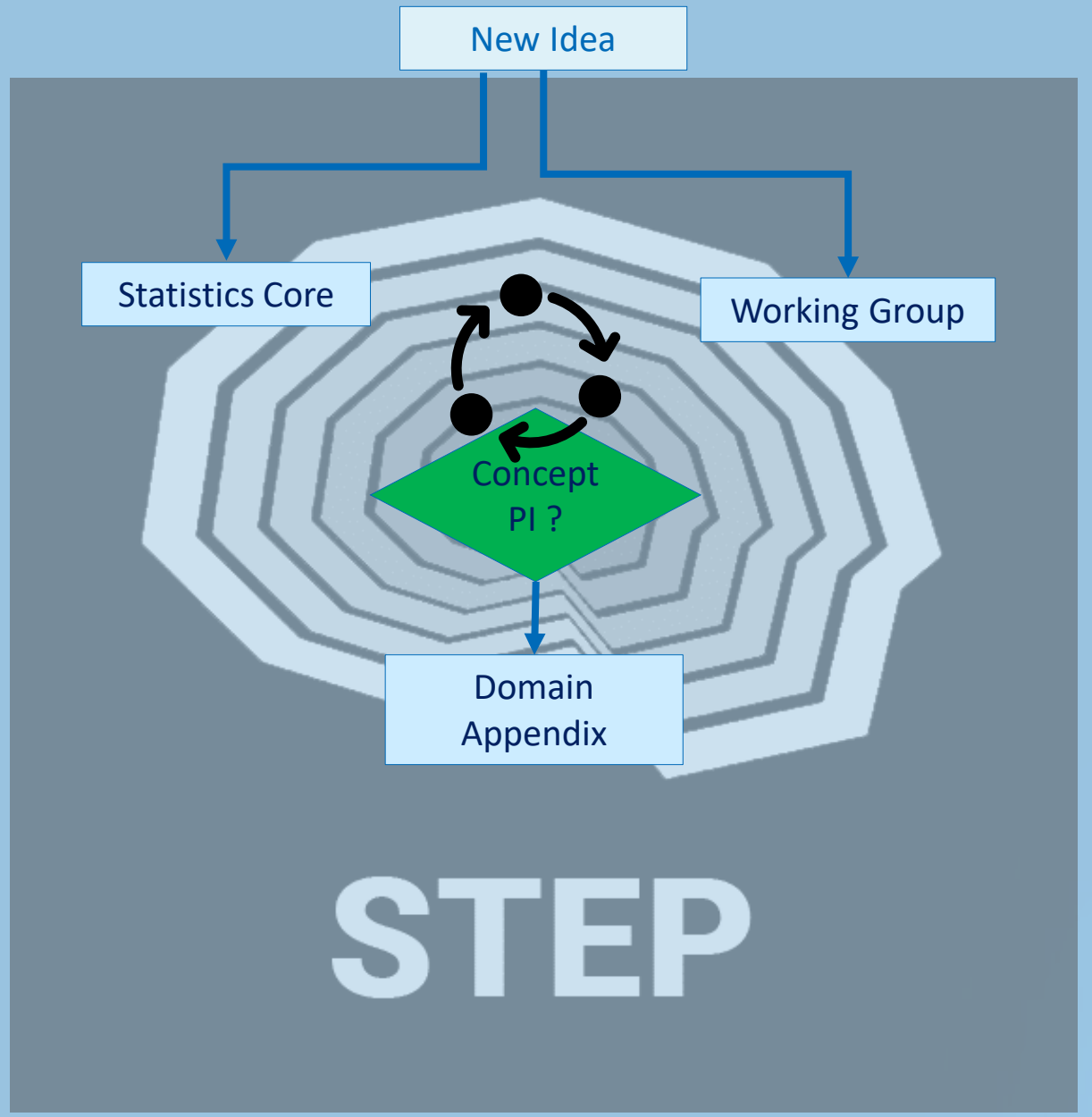
STEP Statistical Model

- The primary analysis within a domain will be based on the posterior distribution for the relative effects of the interventions within that domain.
- Superiority: At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being the optimal domain therapy, then that intervention will be deemed as being superior to control in that target population.
- Inferiority: If an intervention has less than a 0.01 posterior probability of being the optimal domain therapy then that intervention will be deemed as being inferior for that target population.

STEP- Consent Procedures

- Domain specific consent forms:
  - Electronic consent is required (unless participant or LAR prefers paper consent)
  - Domain specific consents are shown according to specific inclusion/exclusion criteria for given domains
  - As a participant becomes eligible for more domains, consent forms specific to those can be presented
  - Master protocol participant information sheet
    - Two-page sheet explaining the concept of platform in lay language
    - Does not need to be signed

New Concept Development Work Flow



Thank you! NIH/NINDS! Acknowledgements:

STEP Executive Committee	
Eva Mistry**	Pooja Khatri**
Jeffrey Saver**	J Mocco**
Raul Nogueira**	Adnan Siddiqui**
Tudor Jovin**	David Fiorella**
Colin Derdeyn**	Scott Janis
Roger Lewis	Mariam Afzal

**MPIs

Statistical Design Core
Scott Berry
Byron Gajewski
Karen Johnston
Amy Crawford
Liz Lorenzi
Nathan James
Jonathan Beall

Path To Prevention (P2P) Therapeutics Platform Trial

Christopher Coffey

on behalf of the P2P Working Group

SCT Annual Meeting

May 20, 2024

Parkinson's Progression Markers Initiative

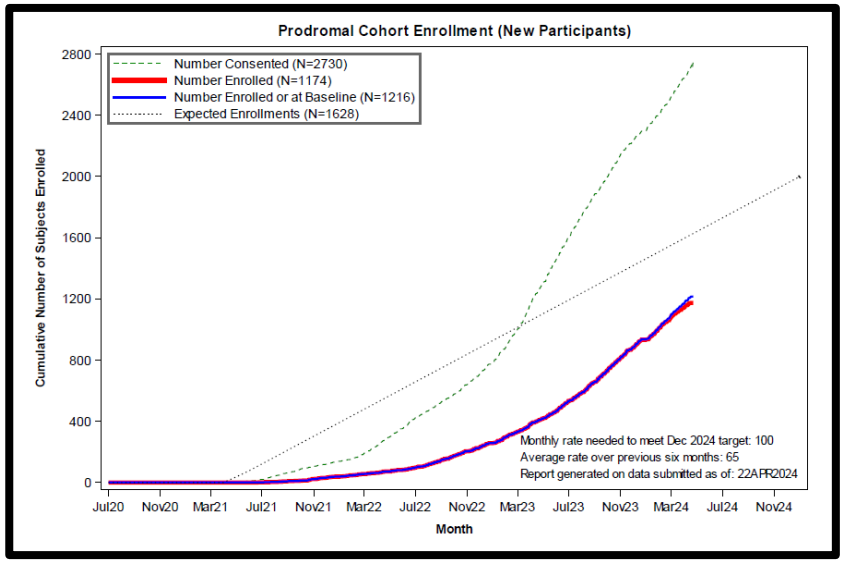
The Parkinson's Progression Markers Initiative (PPMI)

Enrollment as of 06May2024

Total Participants: 3379

- **PD:** 1391
- **Prodromal:** 1696
- **Healthy Controls:** 292

Over 50% of all prodromal participants enrolled in last 12 months



Parkinson's Progression Markers Initiative

PPMI 2023 Highlights: A New Biomarker!

'Big step forward': New lab tests may accelerate Parkinson's diagnosis and research

By Brenda Goodman, CNN
6 minute read · Published 6:37 PM EDT, Thu April 13, 2023

Michael J. Fox: Do you have Parkinson's? New test is 'breakthrough' in diagnosing disease.

I'm involved with the work of The Michael J. Fox Foundation in many ways, but I come to this breakthrough first and foremost as a patient.

Michael J. Fox Opinion contributor
Published 5:14 a.m. ET May 2, 2023

PARKINSONS DISEASE

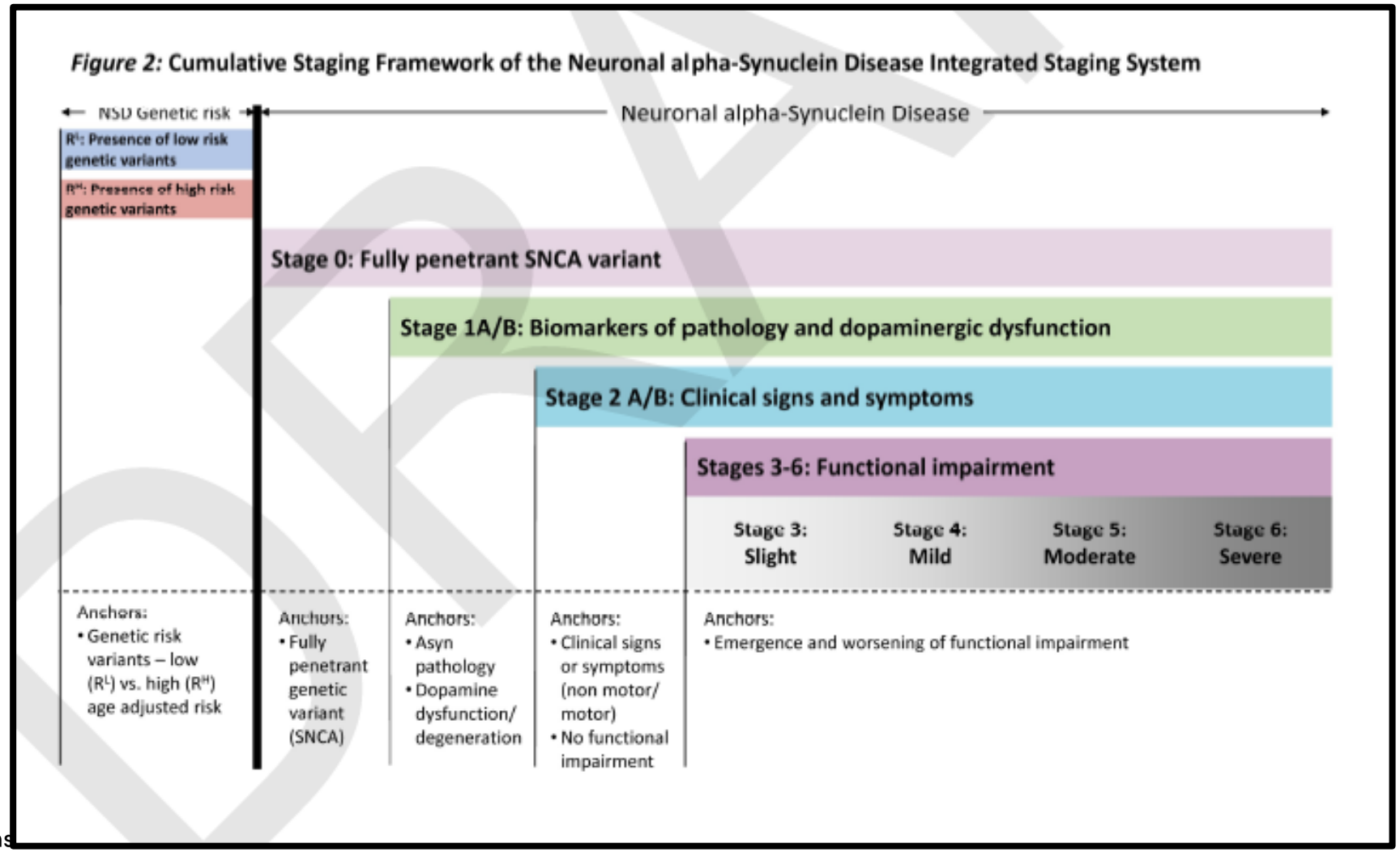
Parkinson's researchers discover disease biomarker in key breakthrough

Research revealed 93% of participants with Parkinson's had an abnormal test

By Julia Musto · Fox News
Published April 13, 2023 3:25pm EDT

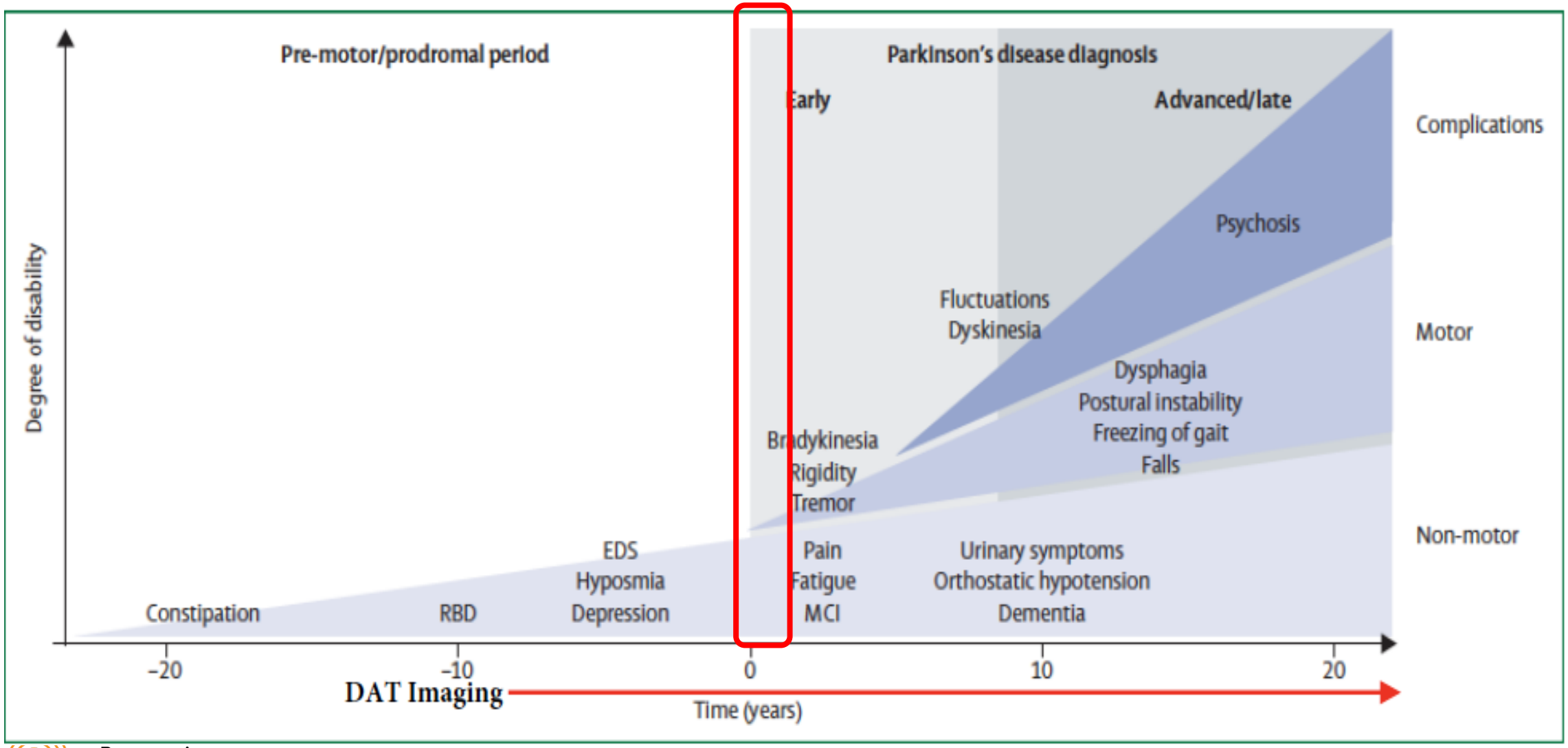
Parkinson's Progression Markers Initiative

PPMI 2024 Highlights: NDS-ISS Staging



Parkinson's Progression Markers Initiative

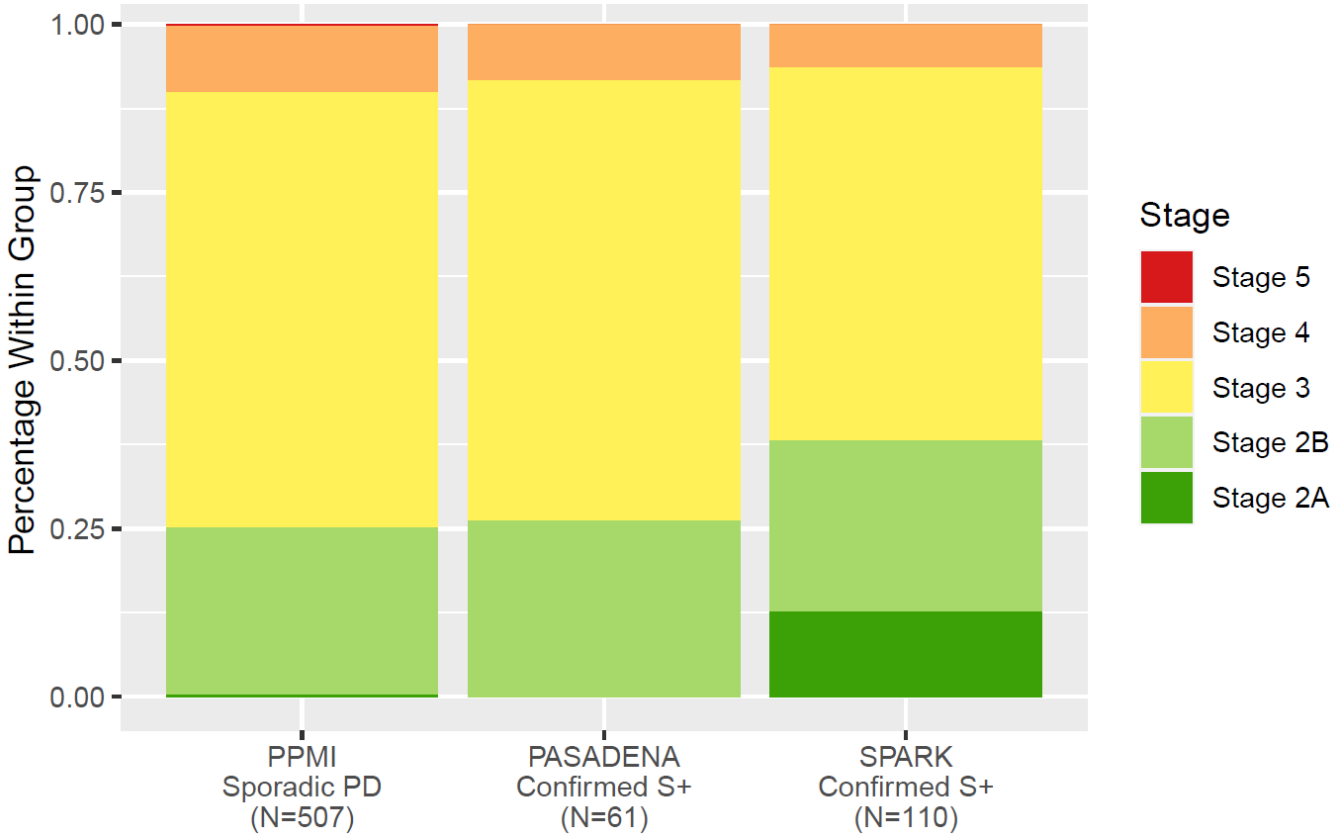
Current Disease Modification Trials



Progression Markers Initiative

Kalia LV, Lang AE et al, Lancet 2015

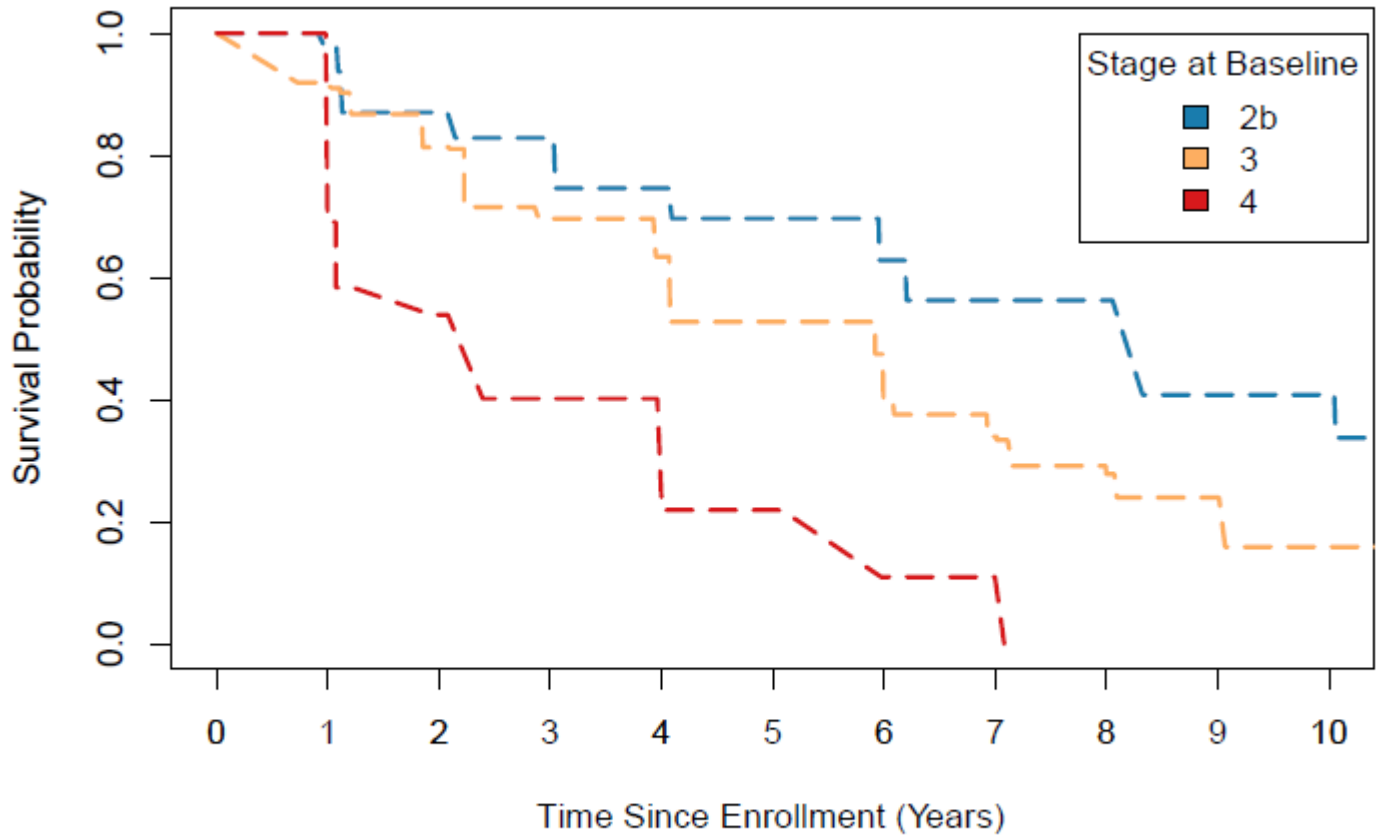
Baseline Staging: PPMI vs Recent Interventional Studies that Recruited De Novo PD Population



Stage	PPMI SPD (N=507)	PASADENA Conf. S+ (N=61)	SPARK Conf. S+ (N=110)
2A	2 (<1%)	0	14 (13%)
2B	126 (25%)	16 (26%)	28 (25%)
3	328 (65%)	40 (66%)	61 (55%)
4	50 (10%)	5 (8%)	7 (6%)
5	1 (<1%)	0	0

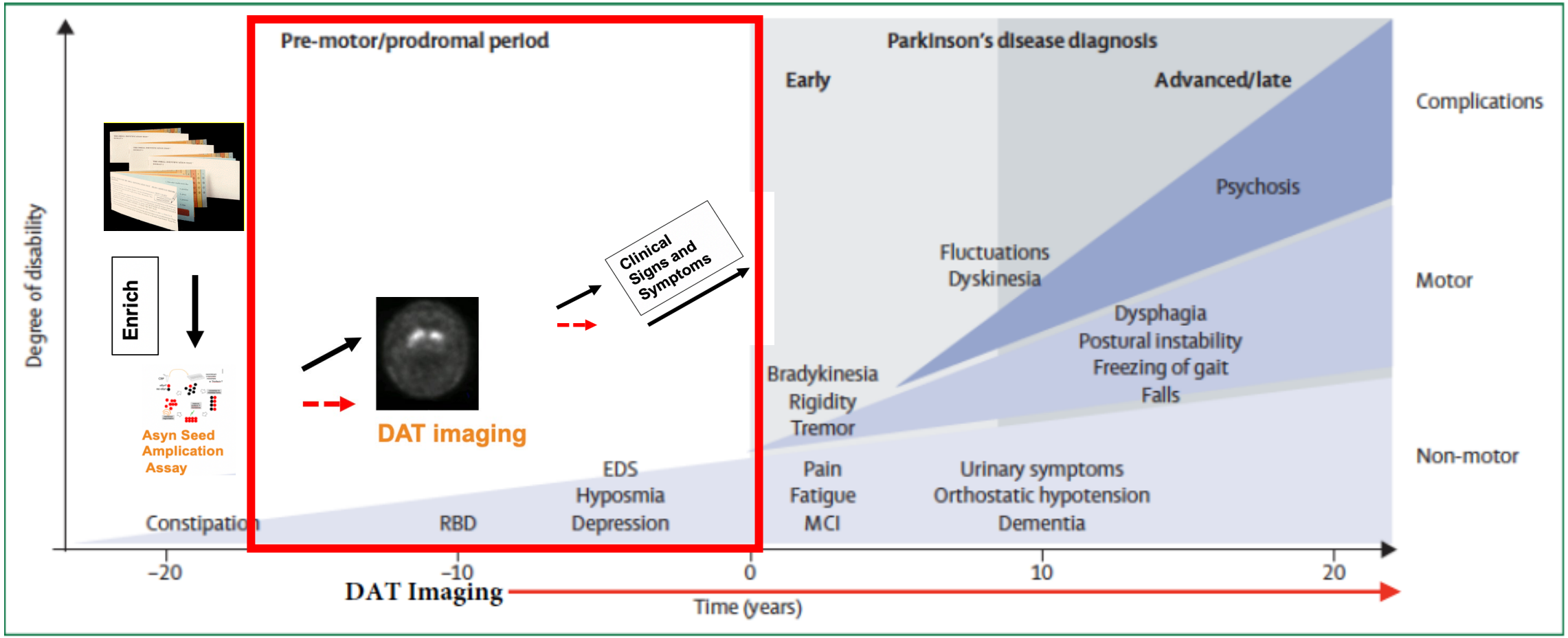
Parkinson's Progression Markers Initiative

Baseline Staging is Predictive of Disease Progression



Parkinson's Progression Markers Initiative

Secondary Prevention Trials Now Possible



Parkinson's Progression Markers Initiative

P2P: A Platform Trial Embedded in PPMI

Most efficient way to test a number of therapeutics/mechanisms under a master protocol

Enables **rapid** testing with more flexible study designs

Established success in other disease areas offers value to industry partners invested in PD

PPMI's prodromal cohort offers a **unique target population** that is otherwise challenging for individual sponsors to recruit

Parkinson's Progression Markers Initiative

Study Objectives

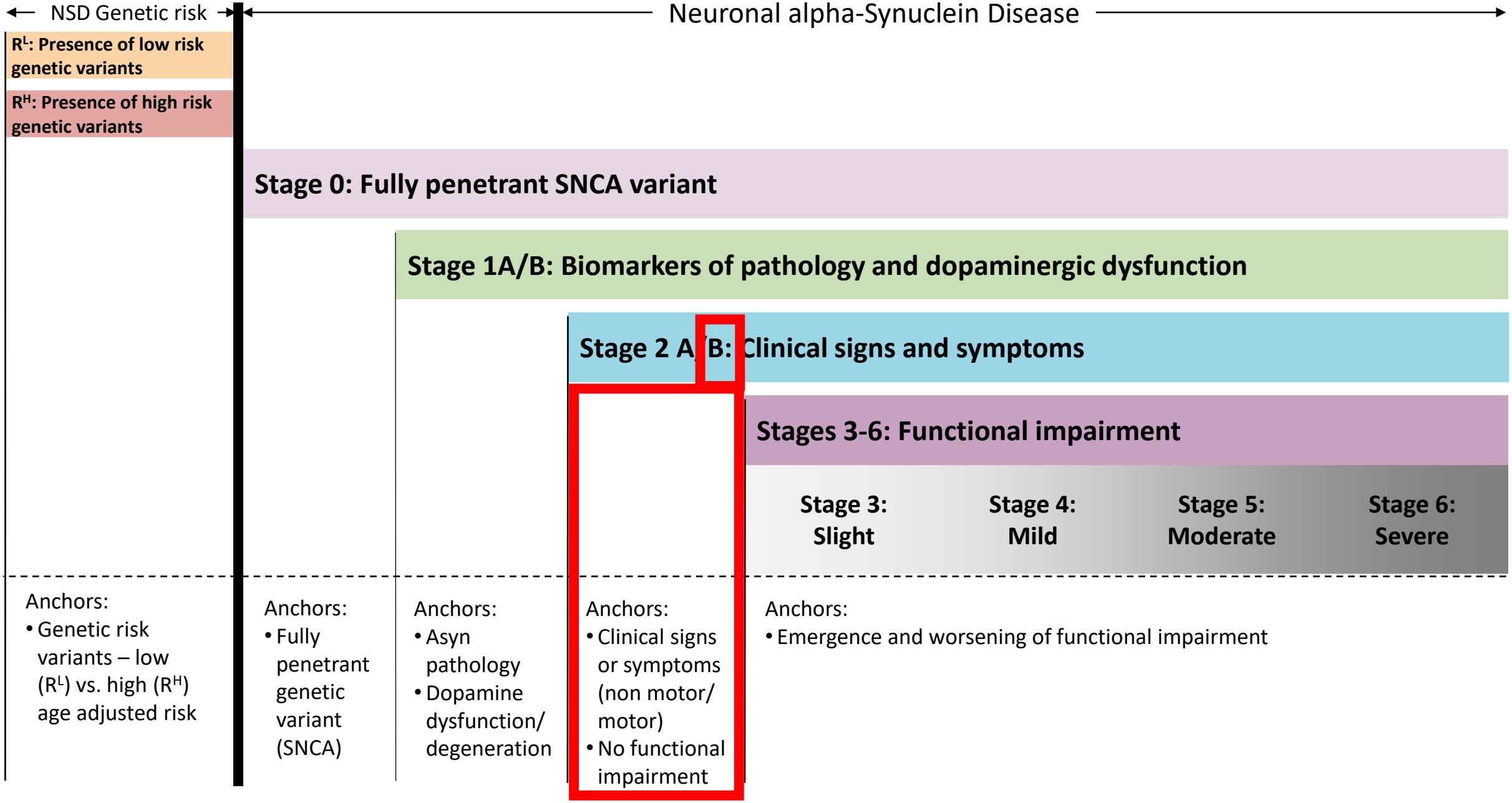
- Proof of concept learning Phase 2A randomized double blind study to assess impact of putative NSD therapies in participants with Early Stage NSD on DAT SPECT imaging, clinical measures of symptom worsening, feasibility, safety, and tolerability.

Study Population

- **Neuronal α-Synuclein Disease** Stage 2B with a high risk of further progression
- Stage 2b is defined by presence of:
  - A-SYN as measured by a validated biomarker (currently CSF SAA)
  - Dopaminergic dysfunction as measured by DAT imaging
  - Clinically detectable premotor/ subtle motor abnormalities but no functional impairment

Parkinson's Progression Markers Initiative

P2P target population: Biologically defined cohort | Stage 2B of the NSD-ISS



Investigational Products

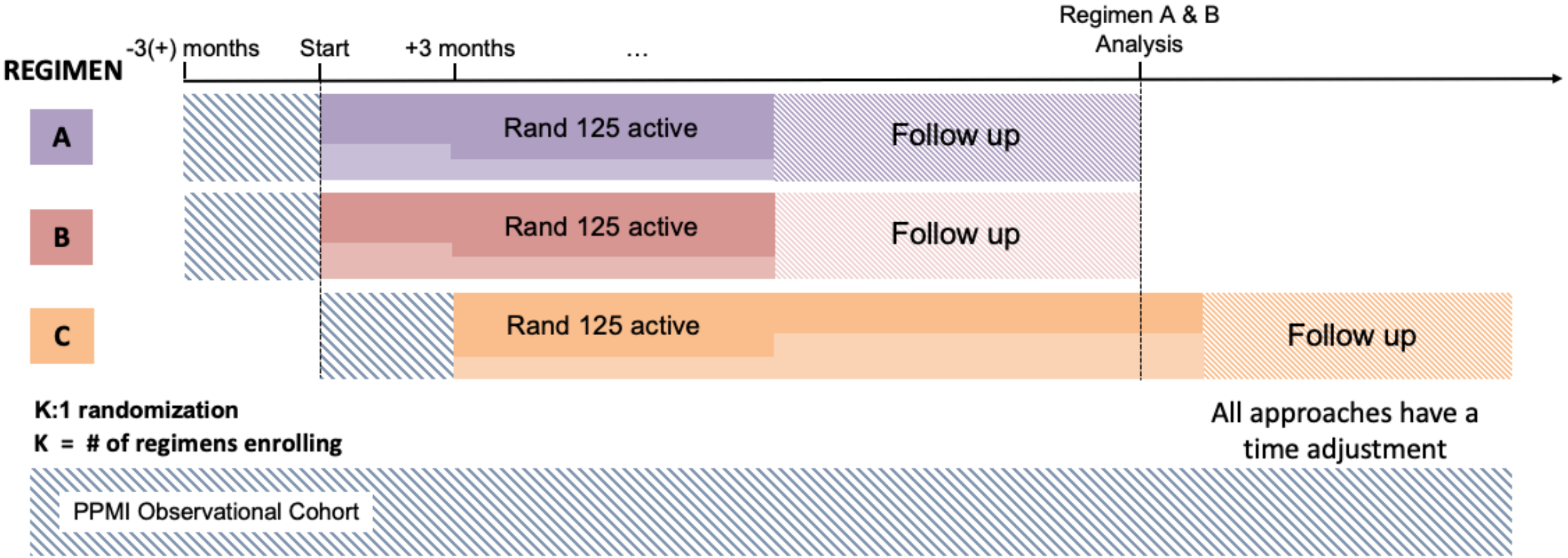
- Multiple investigational products (i.e., interventions, or active agents, from different regimen partners) will be tested in this Platform Trial
- Each investigational product will have an associated RSSP with the complete description of the tested product. Each active agent will have a matching placebo
- The platform can test investigational products with different modes of delivery
- Placebo arm will be shared across active regiments

Duration of Treatment per Arm

- All participants will remain on the originally assigned regimen-specific arm for a minimum of 24 months (until the last participant randomized to that RSSP has completed 24 months of follow-up on intervention).
- After randomization to a regimen specific arm, participants will be randomized to an active arm or placebo in a K:1 ratio with K denoting the number of active interventions.

Parkinson's Progression Markers Initiative

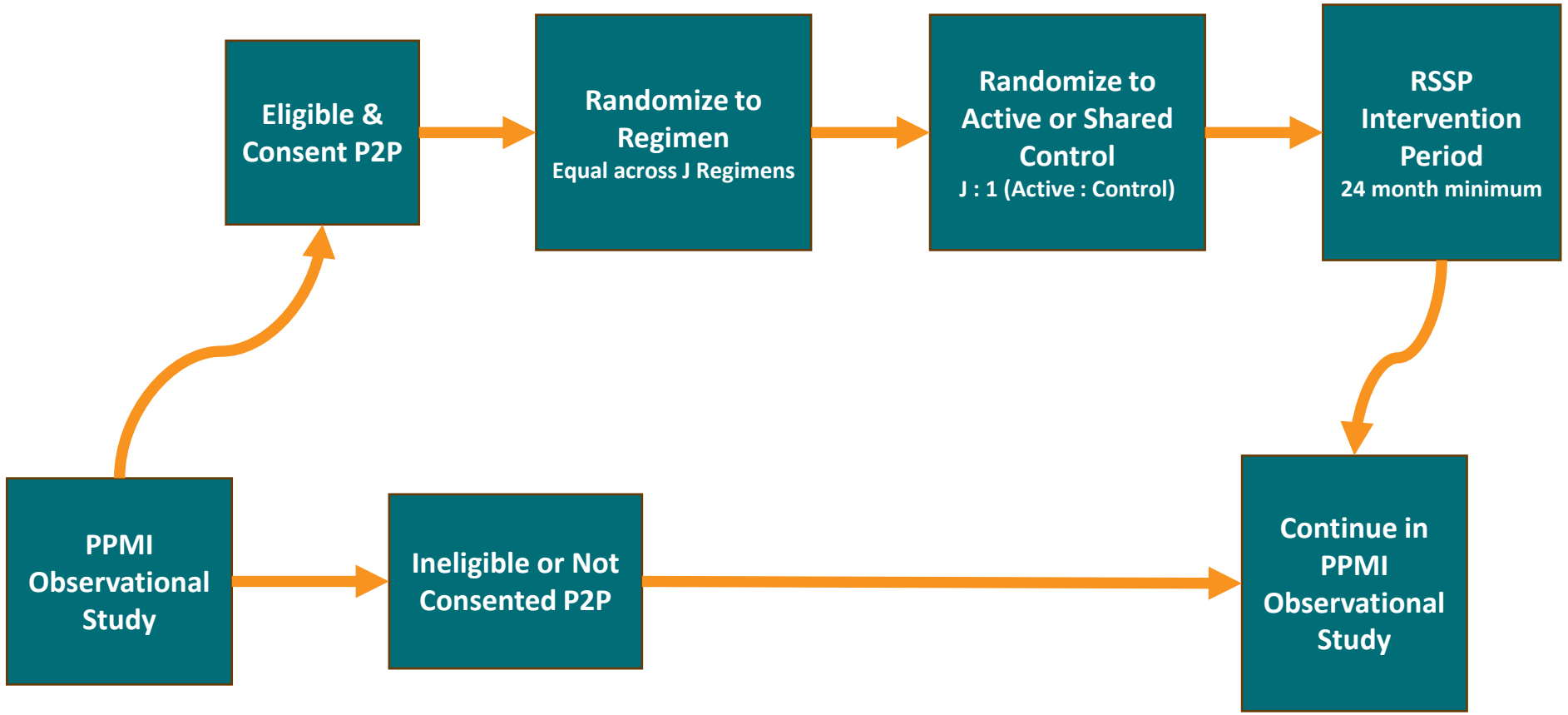
P2P Study Design: Perpetual Platform Trial



All controls: used for current power calculations.

All approaches include time adjustment to minimize potential bias

Participant Flow



Parkinson's Progression Markers Initiative

K = number of active regimens
J = number of active regimens a participant is eligible for

Multiple Primary Endpoints

Biomarker: Impact of interventions on DAT imaging

- As measured by a difference in the rate of progression in the mean striatum Specific Binding Ratio (SBR) in the active treatment arm versus placebo from baseline through follow-up.

Clinical: Impact of interventions on the clinical outcome

- As defined by a difference in the rate of progression in MDS-UPDRS parts III in the active treatment arm versus placebo from baseline through follow-up.

Parkinson's Progression Markers Initiative

Population Considered for Modeling

102 P2P Eligible Participants (59 recruited in PD & 43 recruited in prodromal cohort):

- 100 Stage 2B at baseline
- 2 Stage 2B at baseline, but under 60 (baseline is first visit after turning 60)

Only participants with P2P baseline and at least one annual follow-up within 3 years of baseline for both endpoints were included

One SWEDD participant was included in prodromal and overall models

Parkinson's Progression Markers Initiative

Estimated 2-Year Change by Cohort

Outcome	PD cohort [1]	Prodromal cohort [1]
Mean Striatum SBR		
n	59	43
Estimated 2-year change	-0.25	-0.14
St. Dev.	0.15	0.22
MDS-UPDRS-III		
n	59	43
Estimated 2-year change	7.4	3.3
St. Dev.	8.4	4.2

[1] Cohort at enrollment into PPMI

Estimates based on linear mixed effects models with random slope and intercept terms and adjusted for age and sex

Parkinson's Progression Markers Initiative

SCENARIOS CONSIDERED:

For each of the co-primary endpoints, power computed for 30%, 40%, & 50% reduction with planned sample size of 125 per group under three scenarios:

- Only prodromal participants enrolled
- 10% sporadic PD / 90% prodromal
- 50% sporadic PD / 50% prodroma

Univariate Power: DAT Endpoint

	100% Prodromal	10% Sporadic PD / 90% Prodromal	50% Sporadic PD / 50% Prodromal
30% Reduction	32%	39%	66%
40% Reduction	52%	61%	88%
50% Reduction	70%	80%	98%

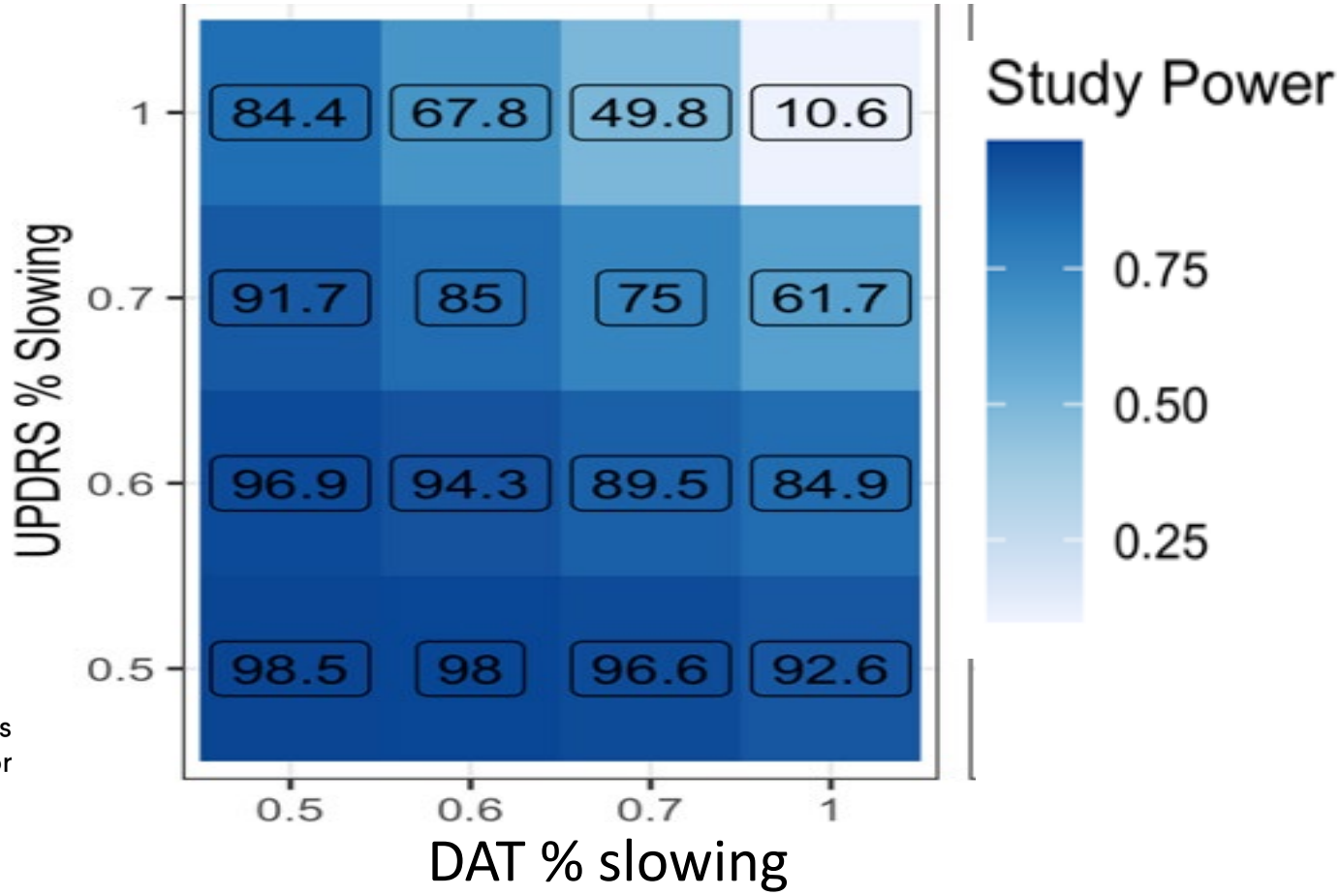
Parkinson's Progression Markers Initiative

Univariate Power – MDS-UPDRS Part II

	100% Prodromal	10% Sporadic PD / 90% Prodromal	50% Sporadic PD / 50% Prodromal
30% Reduction	47%	47%	52%
40% Reduction	70%	73%	79%
50% Reduction	87%	89%	92%

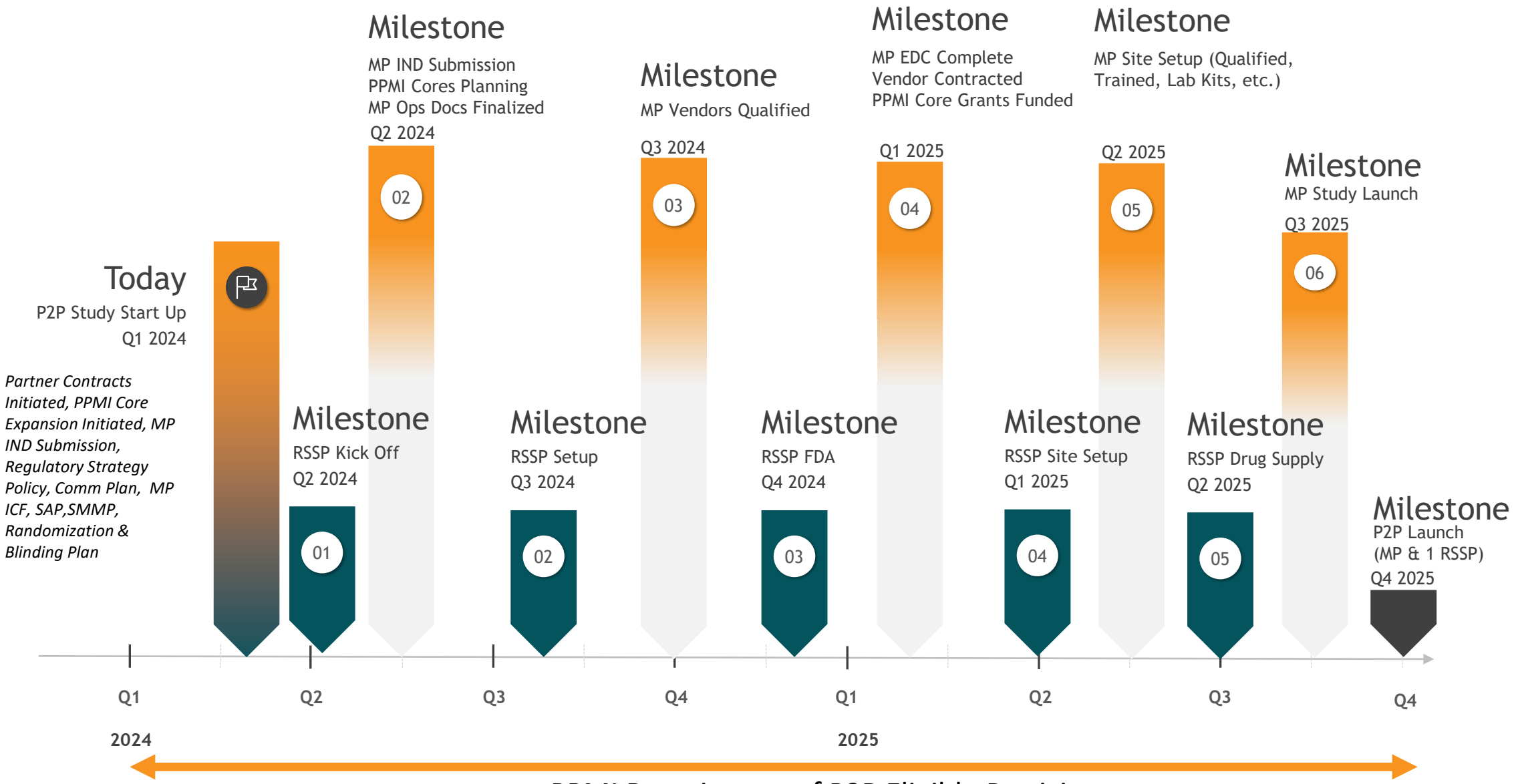
Parkinson's Progression Markers Initiative

"Success": Defined as Achieving Statistical Significance on Either Endpoint – Increases power to detect effect of intervention



Parkinson's Progression Markers Initiative

P2P High-Level Timeline



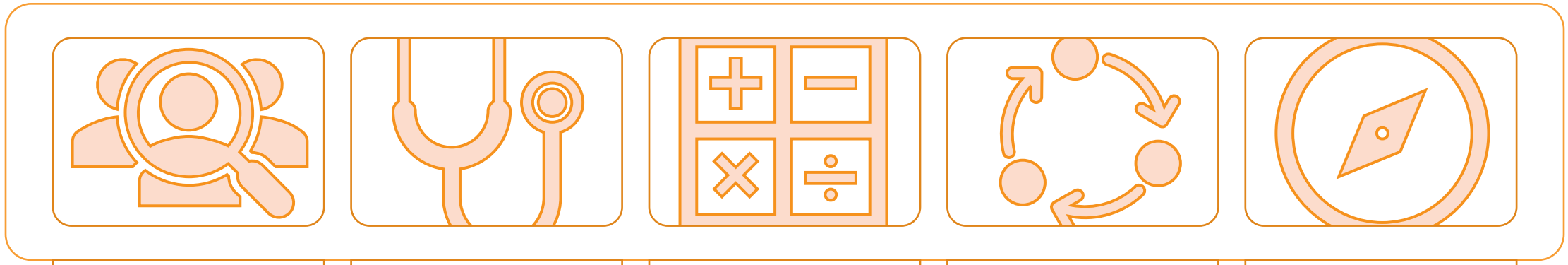
Note: ~3-6 mo between RSSP Launch

Connectivity Between PPMI and P2P Leads to Increased efficiencies

- P2P interventional cohorts recruited from PPMI
- P2P participants will continue contributing key data to PPMI (per PPMI cadence of visits)
- P2P can leverage additional natural history data from PPMI cohorts to inform progression modeling
- Upon completion of P2P interventional protocol, participants will continue to be followed in PPMI enabling long-term follow up
- PPMI will offset costs of P2P assessments aligned with core PPMI SOA

Parkinson's Progression Markers Initiative

P2P Development Team



PI:

Tanya Simuni

Clinical Experts:

Ken Marek

Karl Kieburtz

Carlie Tanner

Statistical Experts:

University of Iowa

Berry Consulting

Clinical Operations:

IND

Sponsor:

MJFF

Parkinson's Progression Markers Initiative

Industry partners

Identification and estimation of causal effects using non-concurrent controls in platform trials

Michele Santacatterina
Federico Macchiavelli

Iván Díaz
Xinyi Zhang

May 20, 2024

Disclosures

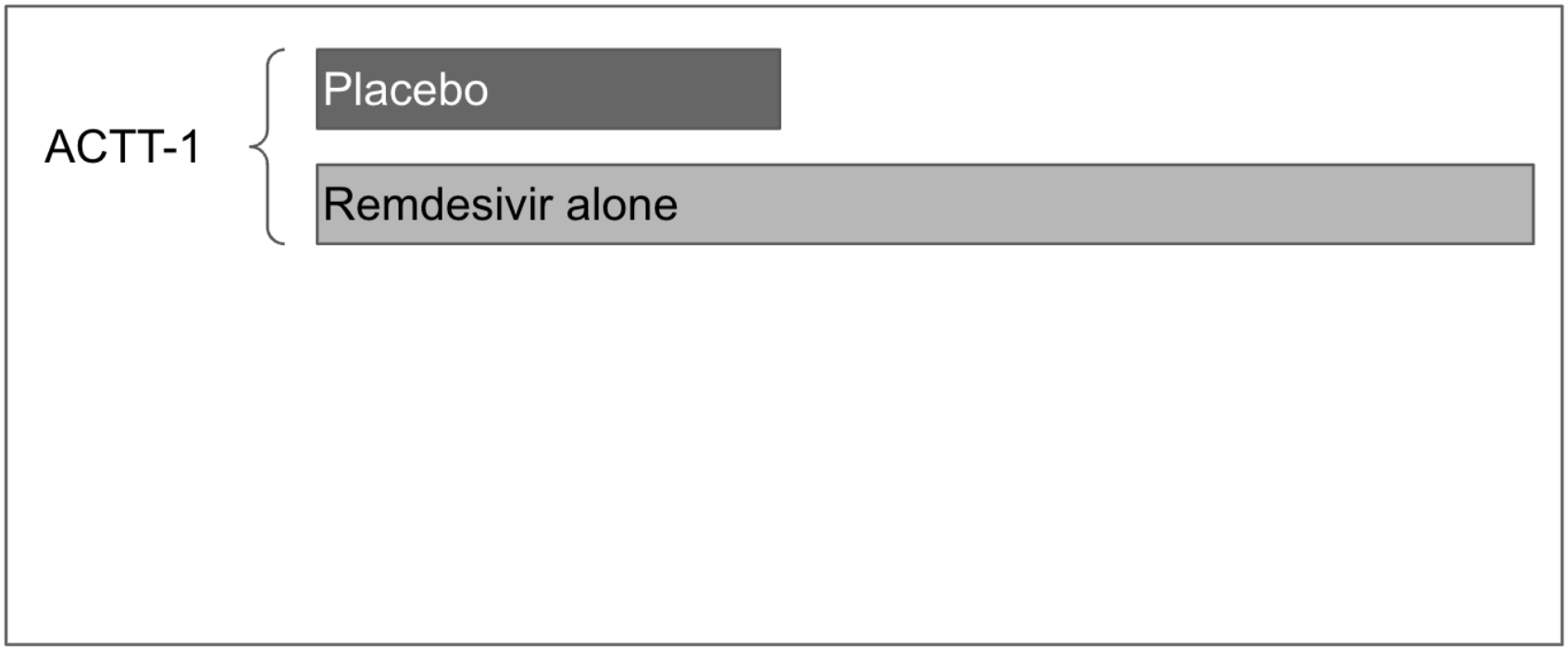
No relevant disclosures.

Platform trials

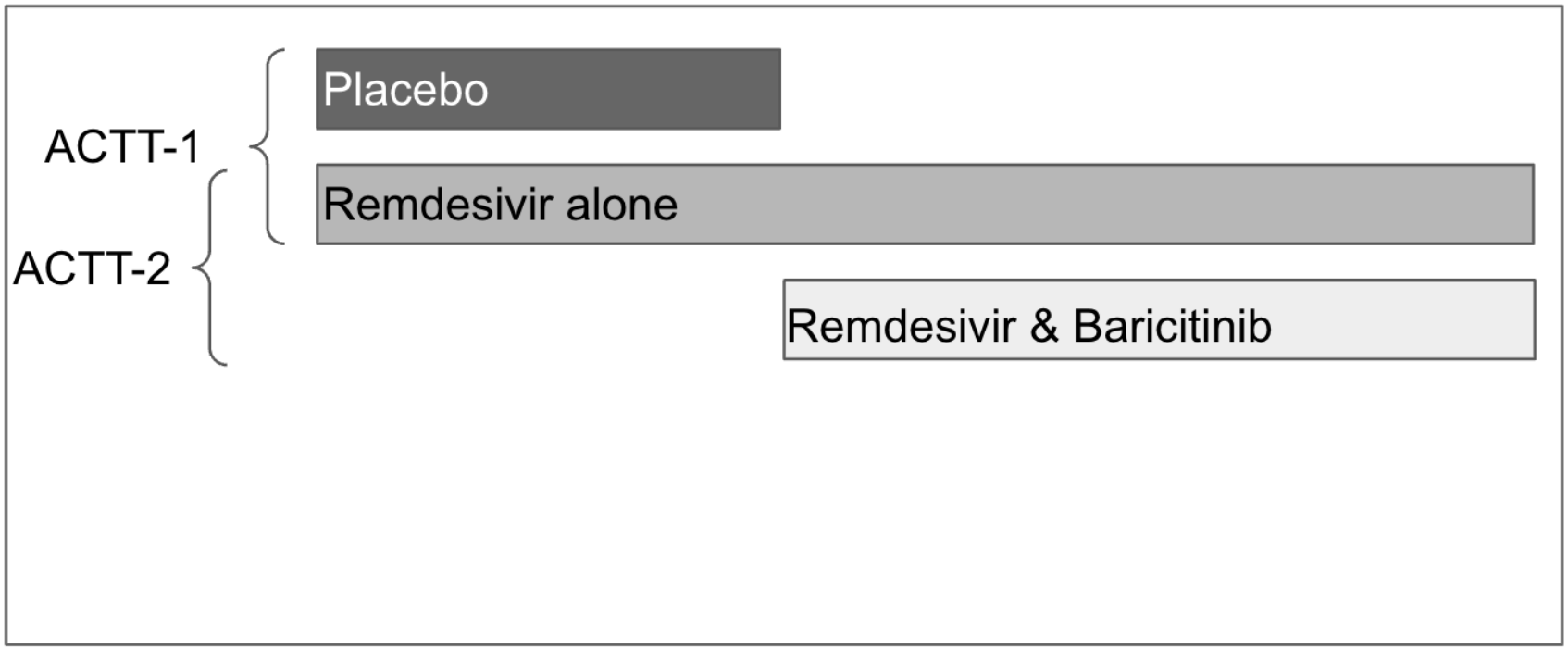
Platform trials: multi-arm designs that simultaneously evaluate multiple treatments for a single disease within the same overall trial structure.

- allow treatment arms to enter and exit the trial at distinct times while maintaining a (shared) arm throughout

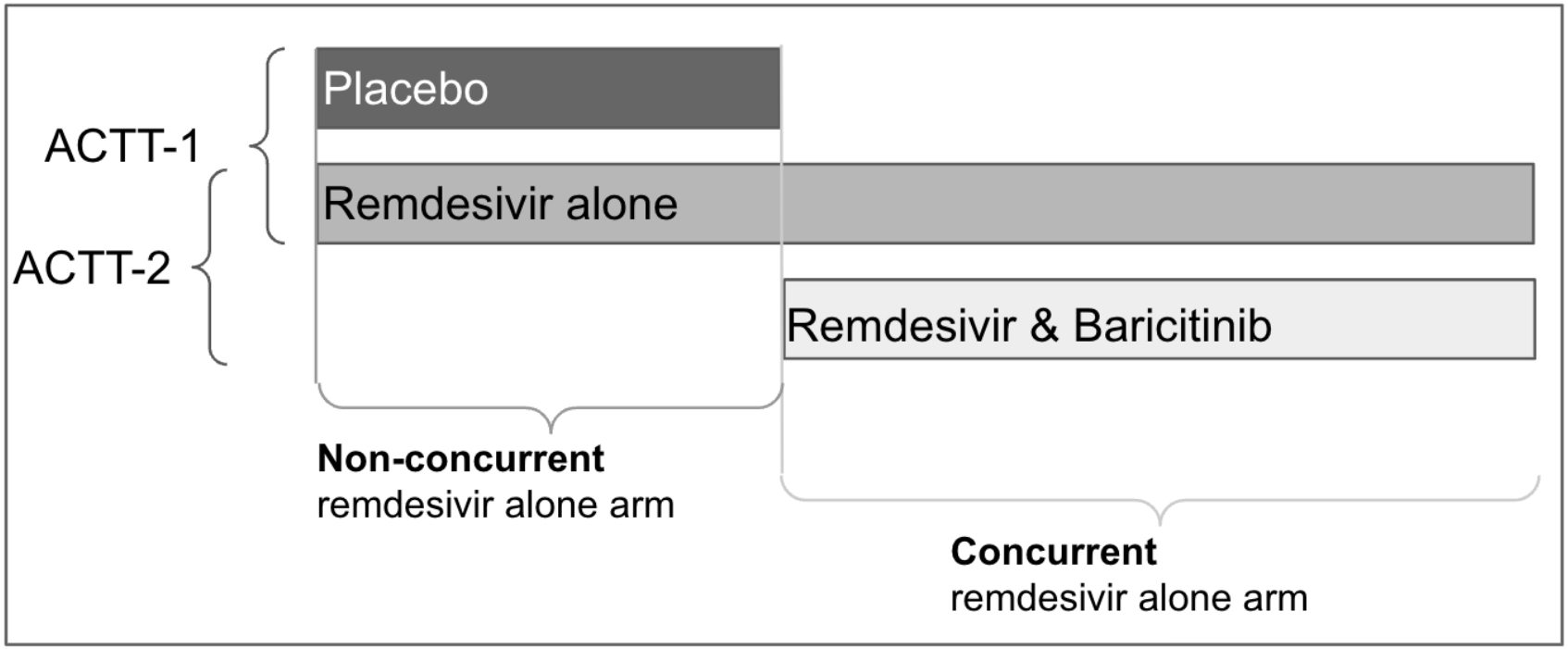
Case study
The Adaptive COVID-19 Treatment Trial (ACTT)



Case study
The Adaptive COVID-19 Treatment Trial (ACTT)



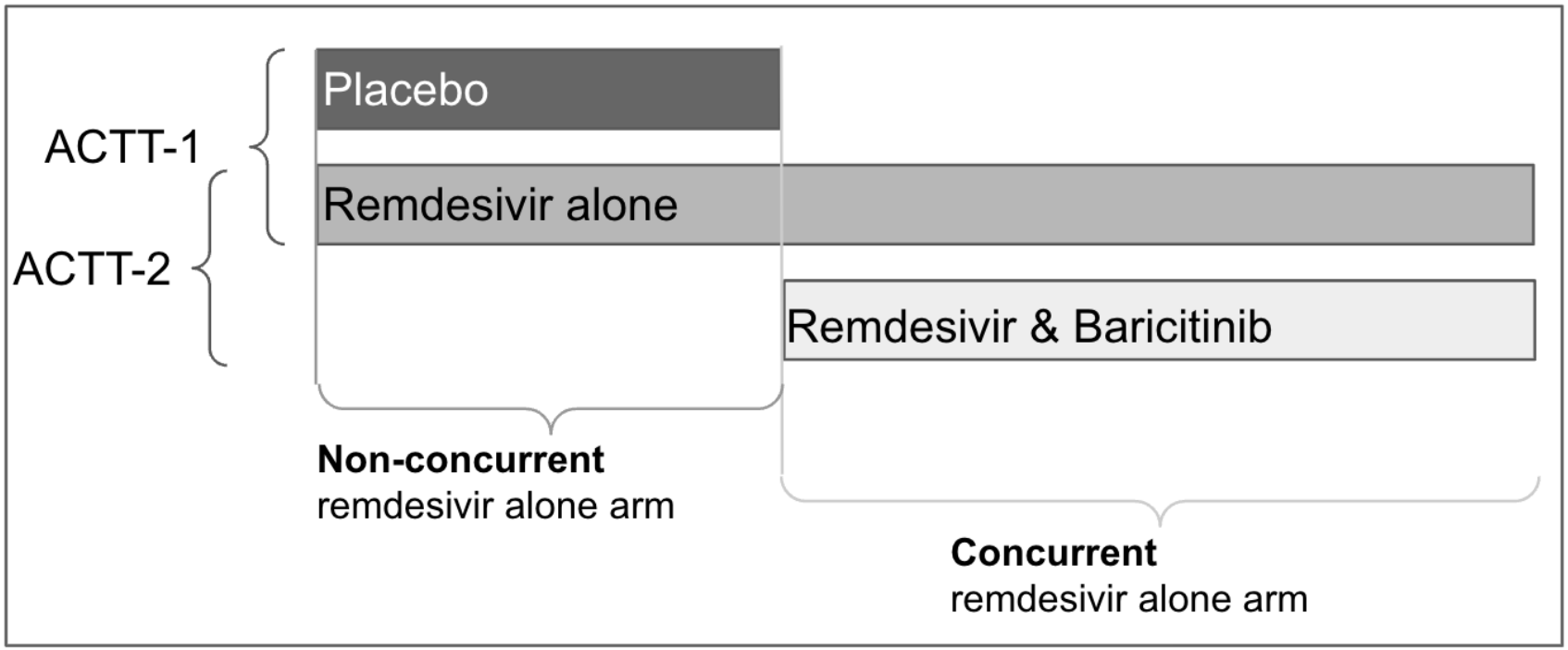
Case study
The Adaptive COVID-19 Treatment Trial (ACTT)



Non-concurrent: who enter the trial when the treatment arm under study is unavailable.

Concurrent: participants are randomized concurrently to either the treatment or control arm,

Question
The Adaptive COVID-19 Treatment Trial (ACTT)



Q: How do we efficiently utilize non-concurrent arm information to estimate the effect of Remdesivir & Baricitinib compared to Remdesivir alone?

Questions
On the use of non-concurrent controls in platform trials

Q: How do we efficiently utilize non-concurrent controls to estimate the effect of Remdesivir & Baricitinib compared to Remdesivir alone?

- What estimands should be used to evaluate the causal effect of a treatment versus control?
- Under what assumptions can these estimands be identified and estimated?
- Do we achieve any efficiency gains?

Questions
On the use of non-concurrent controls in platform trials

Q: How do we efficiently utilize non-concurrent controls to estimate the effect of Remdesivir & Baricitinib compared to Remdesivir alone?

- What estimands should be used to evaluate the causal effect of a treatment versus control?
- Under what assumptions can these estimands be identified and estimated?
- Do we achieve any efficiency gains?

Questions
On the use of non-concurrent controls in platform trials

Q: How do we efficiently utilize non-concurrent controls to estimate the effect of Remdesivir & Baricitinib compared to Remdesivir alone?

- What estimands should be used to evaluate the causal effect of a treatment versus control?
- Under what assumptions can these estimands be identified and estimated?
- Do we achieve any efficiency gains?

Our contribution

We contribute to the literature of platform trials by:

1. postulating a general structural causal model that describes the use of non-concurrent controls in platform trials;
2. defining causal estimands and providing non-parametric identification results;
3. developing estimators with desirable properties; and
4. discussing efficiency considerations.

Our contribution

We contribute to the literature of platform trials by:

1. postulating a general structural causal model that describes the use of non-concurrent controls in platform trials;
2. defining causal estimands and providing non-parametric identification results;
3. developing estimators with desirable properties; and
4. discussing efficiency considerations.

Our contribution

We contribute to the literature of platform trials by:

1. postulating a general structural causal model that describes the use of non-concurrent controls in platform trials;
2. defining causal estimands and providing non-parametric identification results;
3. developing estimators with desirable properties; and
4. discussing efficiency considerations.

Our contribution

We contribute to the literature of platform trials by:

1. postulating a general structural causal model that describes the use of non-concurrent controls in platform trials;
2. defining causal estimands and providing non-parametric identification results;
3. developing estimators with desirable properties; and
4. discussing efficiency considerations.

Structural causal model

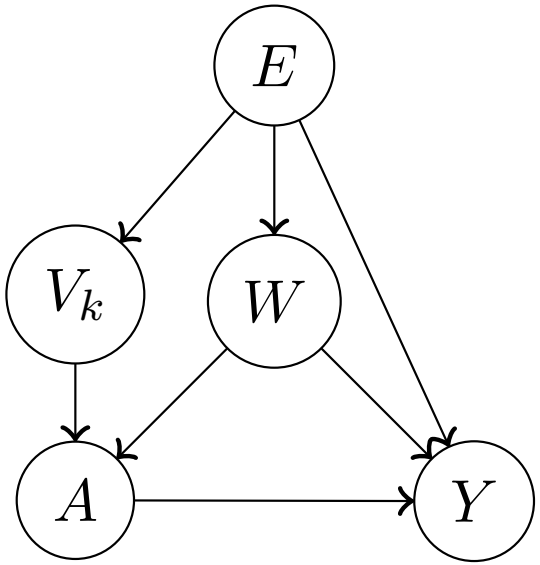


Figure: DAG associated to the structural equation model in equation (1).

$$
\begin{aligned}
E_i &= \text{entry time}, \\
W_i &= \text{covariates}, \\
V_{k,i} &= \text{trt k availability}, \quad (1) \\
A_i &= \text{treatment allocation}, \\
Y_i &= \text{primary endpoint}.
\end{aligned}
$$

Causal estimands
FDA estimand framework

From the FDA estimand framework

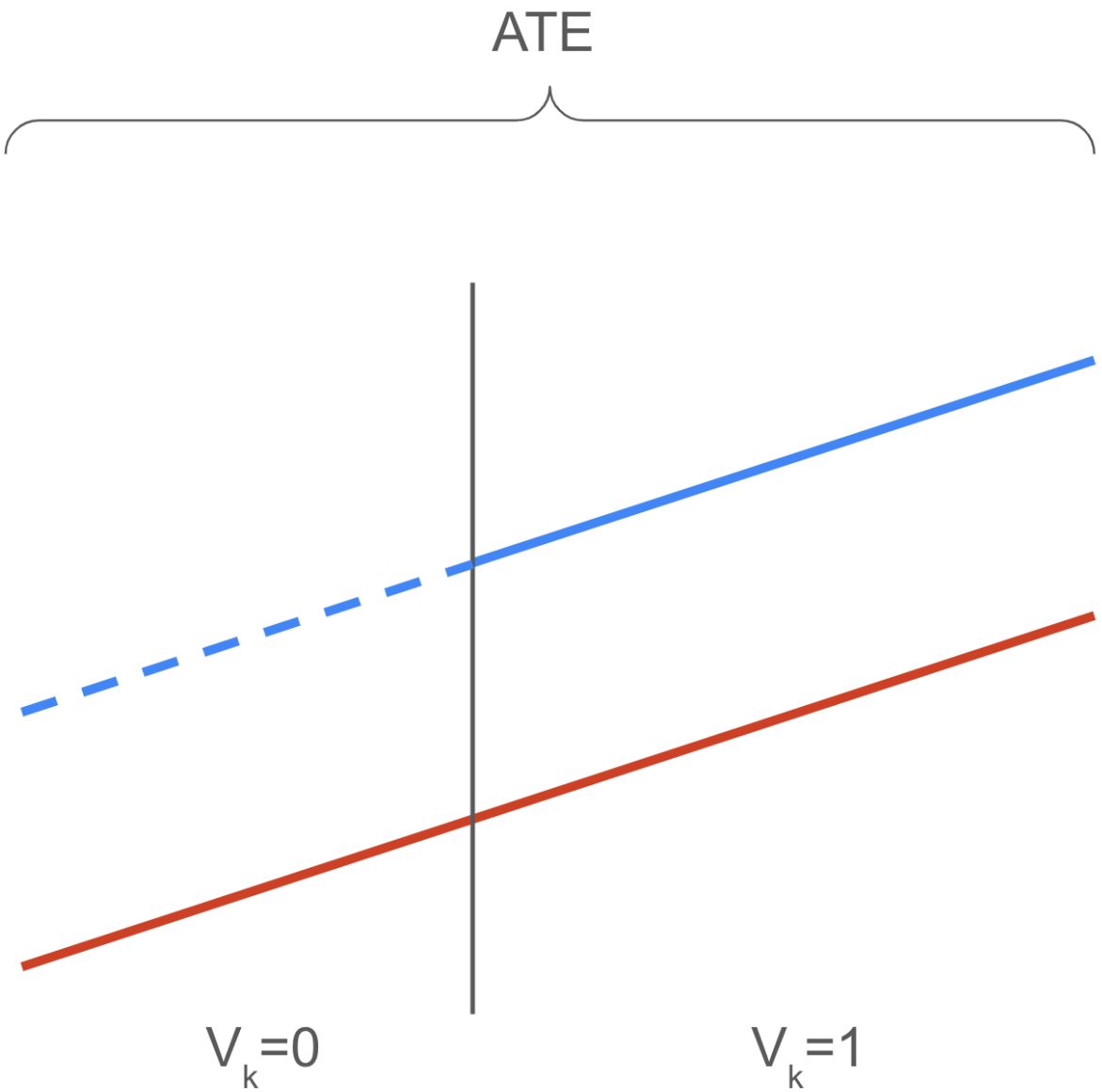
- A (causal) estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective.
- It summarizes at a population level what the outcomes would be in the same patients under different treatment conditions being compared

Causal estimands

Definition (Conditional and marginal average treatment effect of treatment arm k compared to control)

$$\mathsf{CATE}(k, w, e) = \mathsf{E}[Y(k) - Y(0) \mid W = w, E = e]$$
$$\mathsf{ATE}(k) = \mathsf{E}[\mathsf{CATE}(k, W, E)].$$

ATE

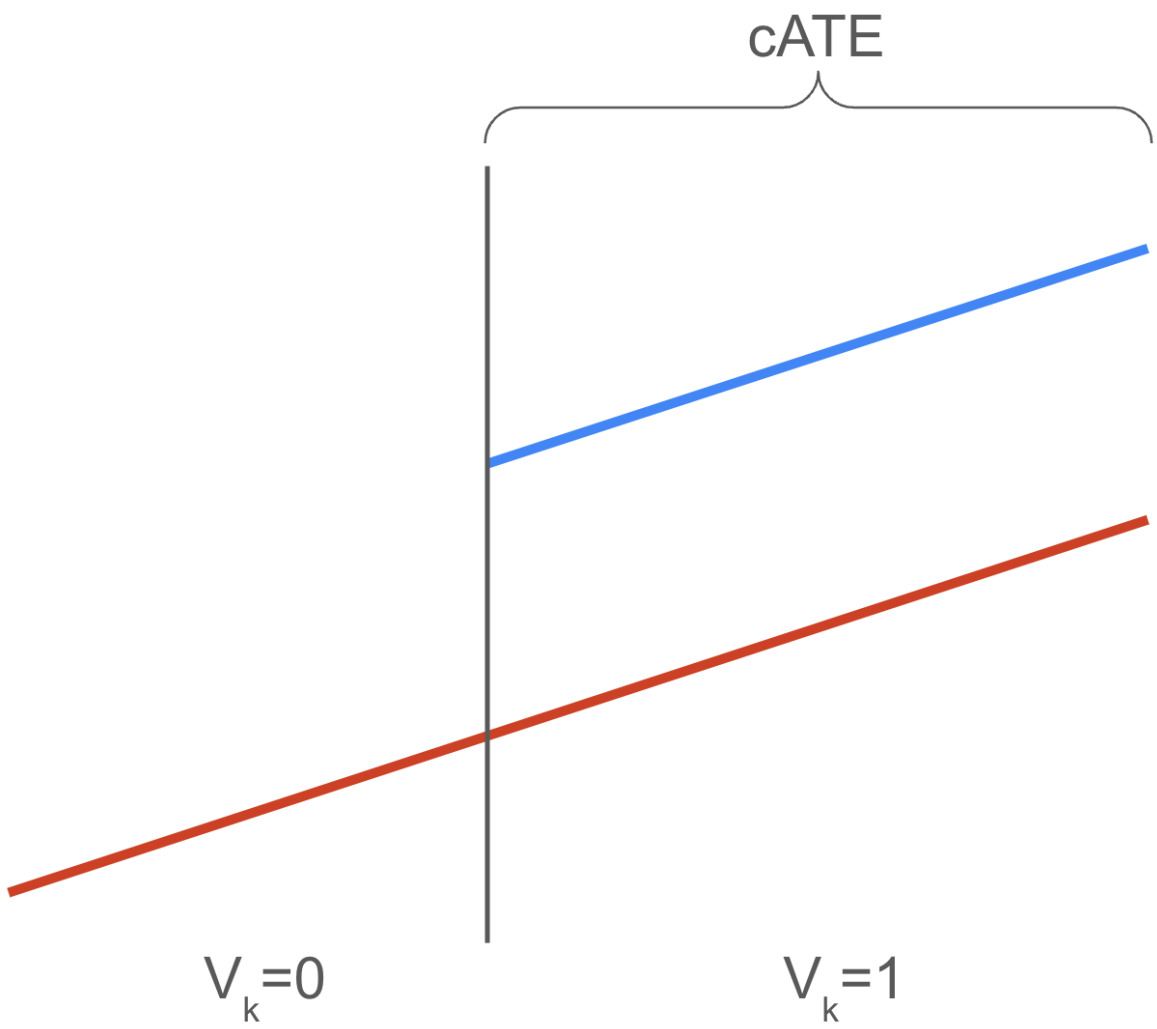


Causal estimands

Definition (Conditional and marginal average treatment effect of treatment arm k compared to control among concurrent population)

$$\mathsf{cCATE}(k, w, e) = \mathsf{E}[Y(k) - Y(0) \mid W = w, E = e, V_k = 1]$$
$$\mathsf{cATE}(k) = \mathsf{E}[\mathsf{cCATE}(k, W, E) \mid V_k = 1].$$

concurrent ATE



On identification

- Causal estimands are functions of counterfactual (potential) outcomes
- counterfactuals are not observable
- we need assumptions to link observable data to counterfactual quantities

Happy to chat offline if you want to learn more!

On identification

- Causal estimands are functions of counterfactual (potential) outcomes
- counterfactuals are not observable
- we need assumptions to link observable data to counterfactual quantities

Happy to chat offline if you want to learn more!

On identification

- Causal estimands are functions of counterfactual (potential) outcomes
- counterfactuals are not observable
- we need assumptions to link observable data to counterfactual quantities

Happy to chat offline if you want to learn more!

On identification

- Causal estimands are functions of counterfactual (potential) outcomes
- counterfactuals are not observable
- we need assumptions to link observable data to counterfactual quantities

Happy to chat offline if you want to learn more!

Assumptions

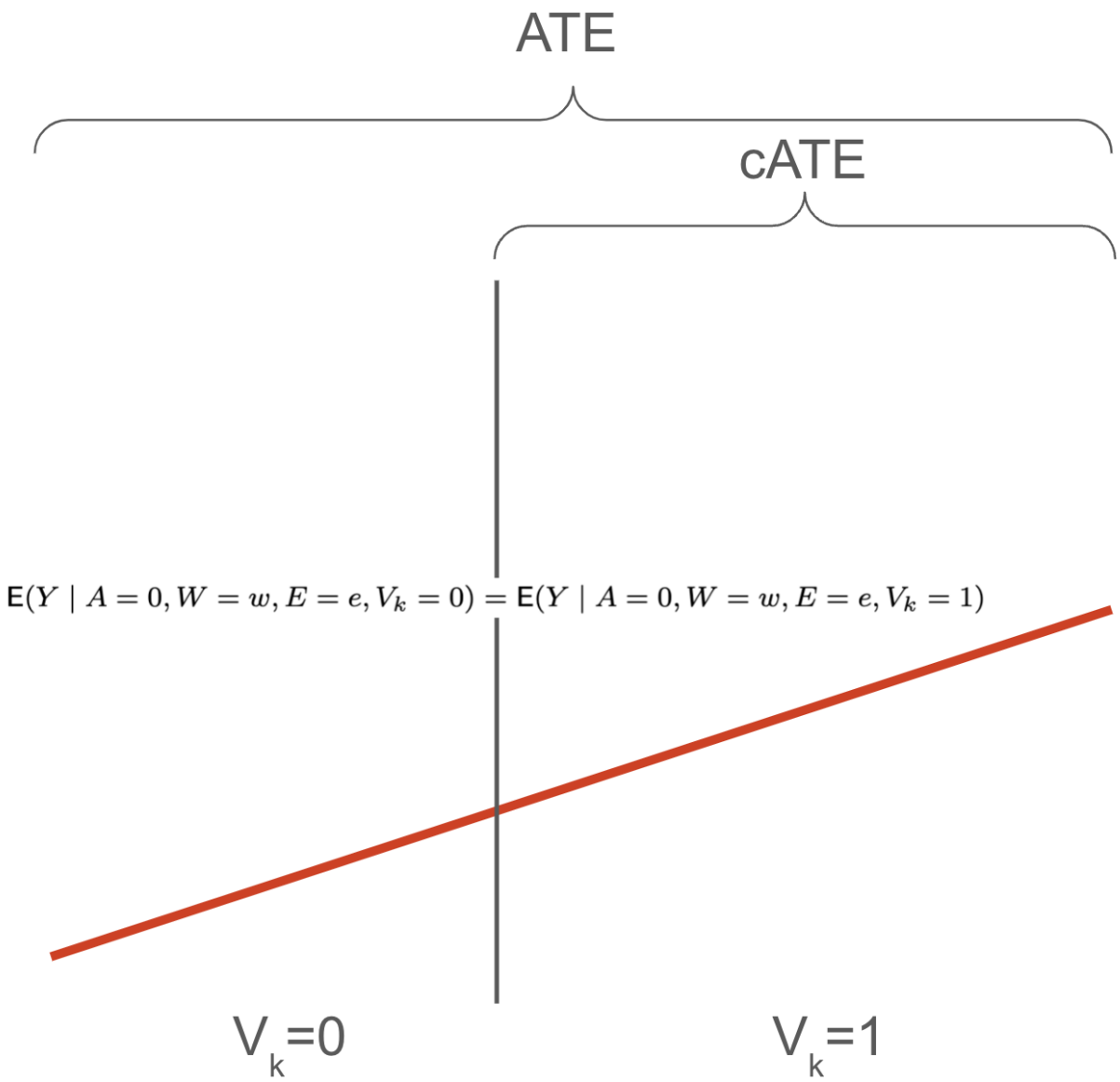
In addition to standard, ignorability, positivity, and consistency assumptions we assume:

(A1: Conditional exchangeability of outcome mechanism among controls)

$\mathsf{E}(Y \mid A = 0, W = w, E = e, V_k = 0) = \mathsf{E}(Y \mid A = 0, W = w, E = e, V_k = 1) = \mathsf{E}(\mathsf{Y}| A = 0, W = w, E = e)$.

A1 is a testable assumption that can be empirically checked.

Assumption A1



Assumptions

In addition to standard, ignorability, positivity, and consistency assumptions we assume:

(A2: Conditional exchangeability of outcome mechanism among the treated)

$\mathsf{E}(Y \mid A = k, W = w, E = e, V_k = 0) = \mathsf{E}(Y \mid A = k, W = w, E = e, V_k = 1) = \mathsf{E}(Y \mid A = k, W = w, E = e)$.

- A1 is a testable assumption that can be empirically checked.
- A2 is an **untestable, extrapolation** assumption. It requires assuming that the conditional outcome expectation observed in patients who could hypothetically be randomized to treatment k can be used to *extrapolate* to those who could not.

Assumptions

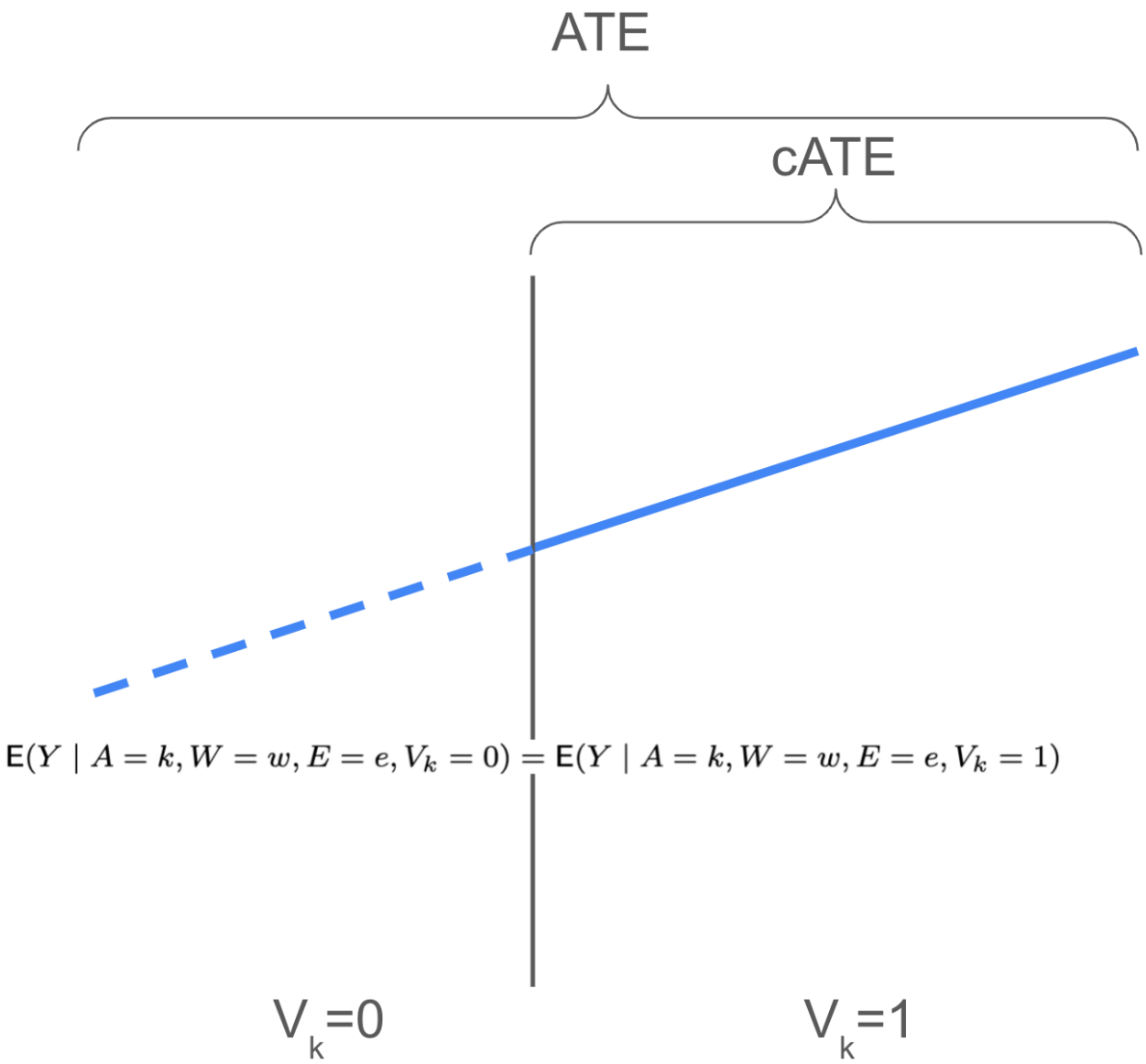
In addition to standard, ignorability, positivity, and consistency assumptions we assume:

(A2: Conditional exchangeability of outcome mechanism among the treated)

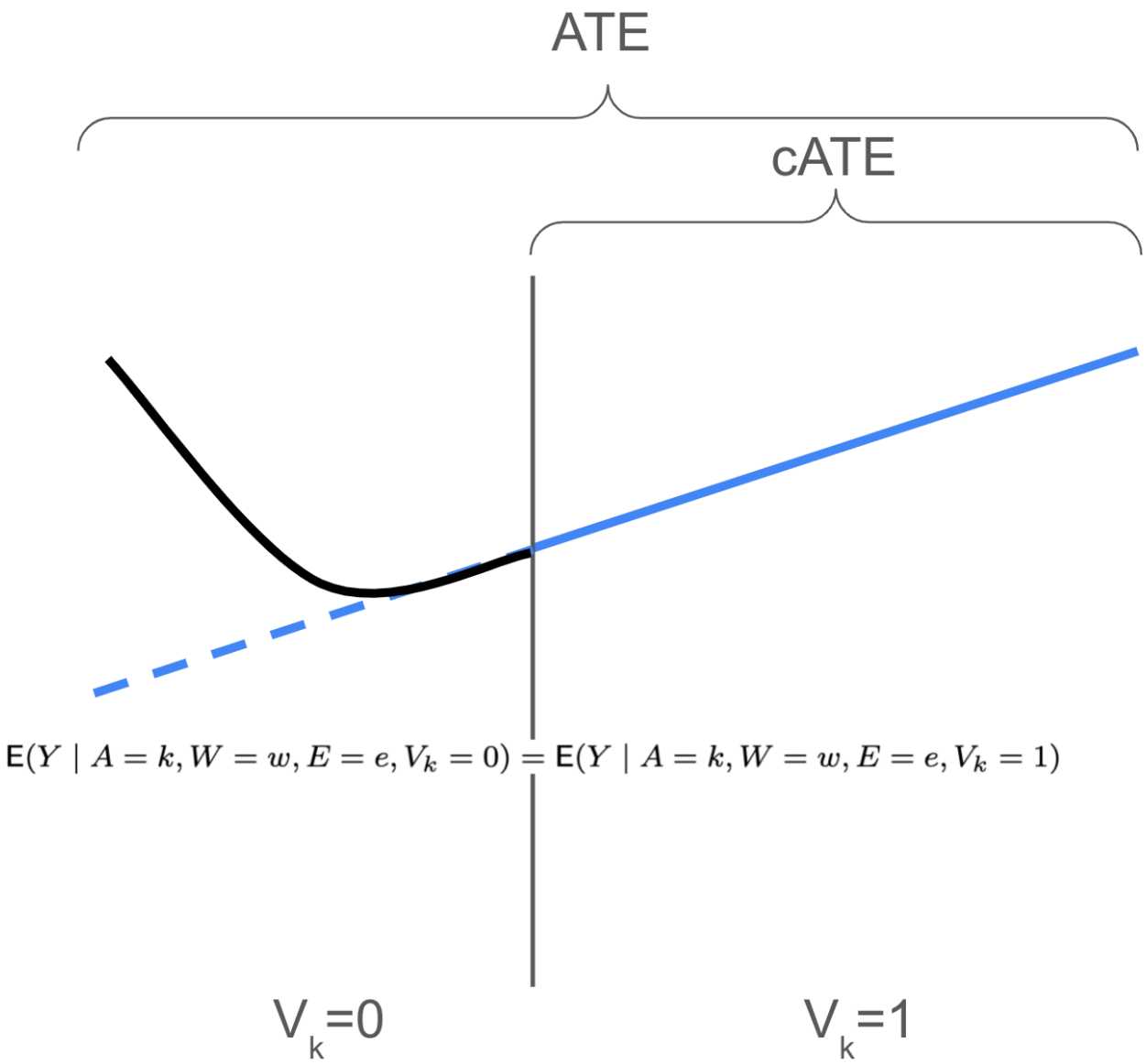
$\mathsf{E}(Y \mid A = k, W = w, E = e, V_k = 0) = \mathsf{E}(Y \mid A = k, W = w, E = e, V_k = 1) = \mathsf{E}(\mathrm{Y}| A = k, W = w, E = e)$.

- A1 is a testable assumption that can be empirically checked.
- A2 is an **untestable, extrapolation** assumption. It requires assuming that the conditional outcome expectation observed in patients who could hypothetically be randomized to treatment k can be used to *extrapolate* to those who could not.

Assumption A2



Assumption A2 - What can go wrong??



Identification

- ATE *requires* A2 (the extrapolation assumption) - this might be dangerous!!
- Concurrent (cATE) can be identified under a testable assumption
  - these results show that non-concurrent control can be used to improve efficiency, i.e., under A1, we can use **all** controls (concurrent plus non-concurrent)
    $\mathsf{E}(Y \mid A = 0, W = w, E = e)$ to identify and estimate
    $\mathsf{E}(Y \mid A = 0, W = w, E = e, V_k = 1)$.

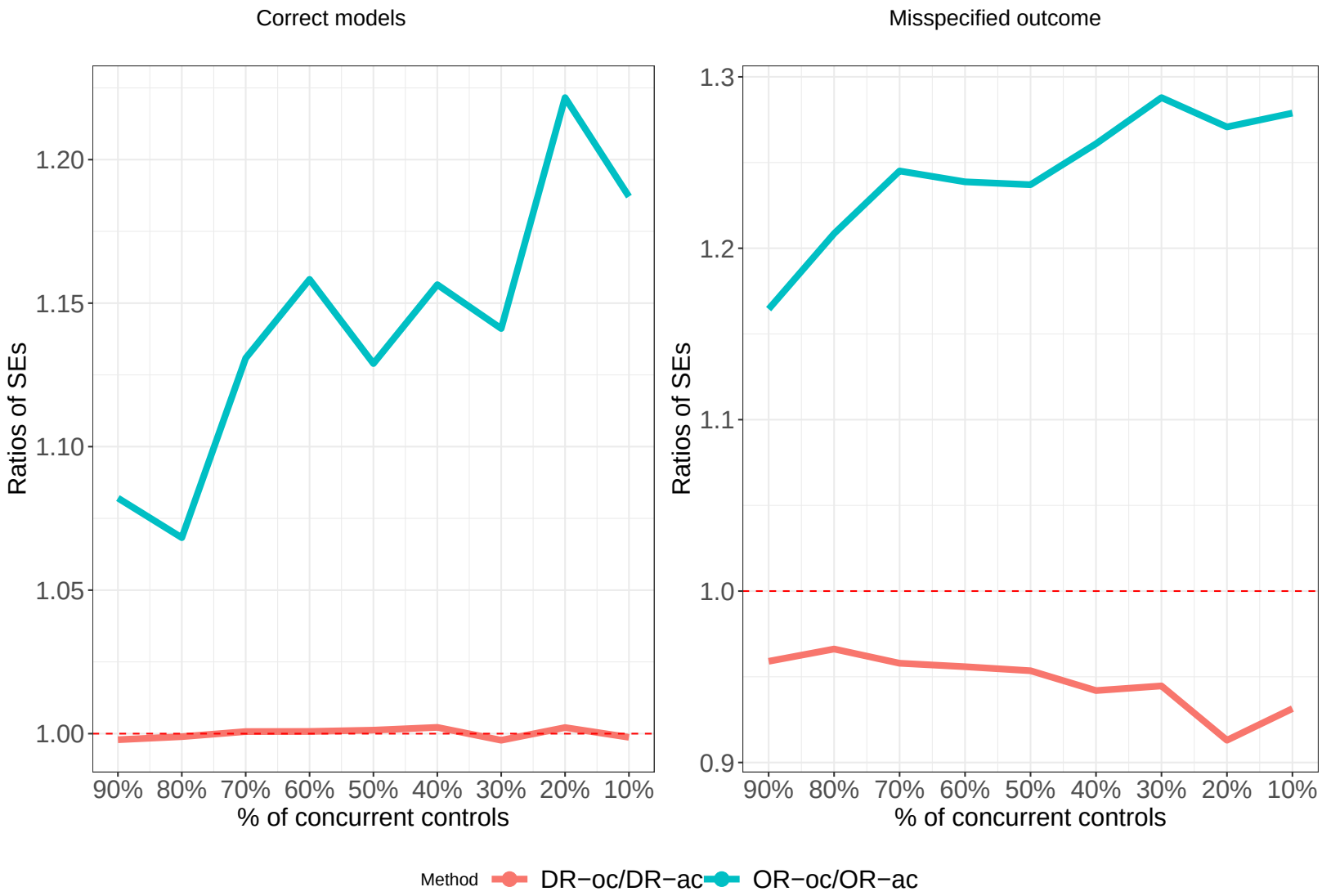
Identification

- ATE *requires* A2 (the extrapolation assumption) - this might be dangerous!!
- Concurrent (cATE) can be identified under a testable assumption
  - these results show that non-concurrent control can be used to improve efficiency, i.e., under A1, we can use **all** controls (concurrent plus non-concurrent)
    $\mathsf{E}(Y \mid A = 0, W = w, E = e)$ to identify and estimate
    $\mathsf{E}(Y \mid A = 0, W = w, E = e, V_k = 1)$.

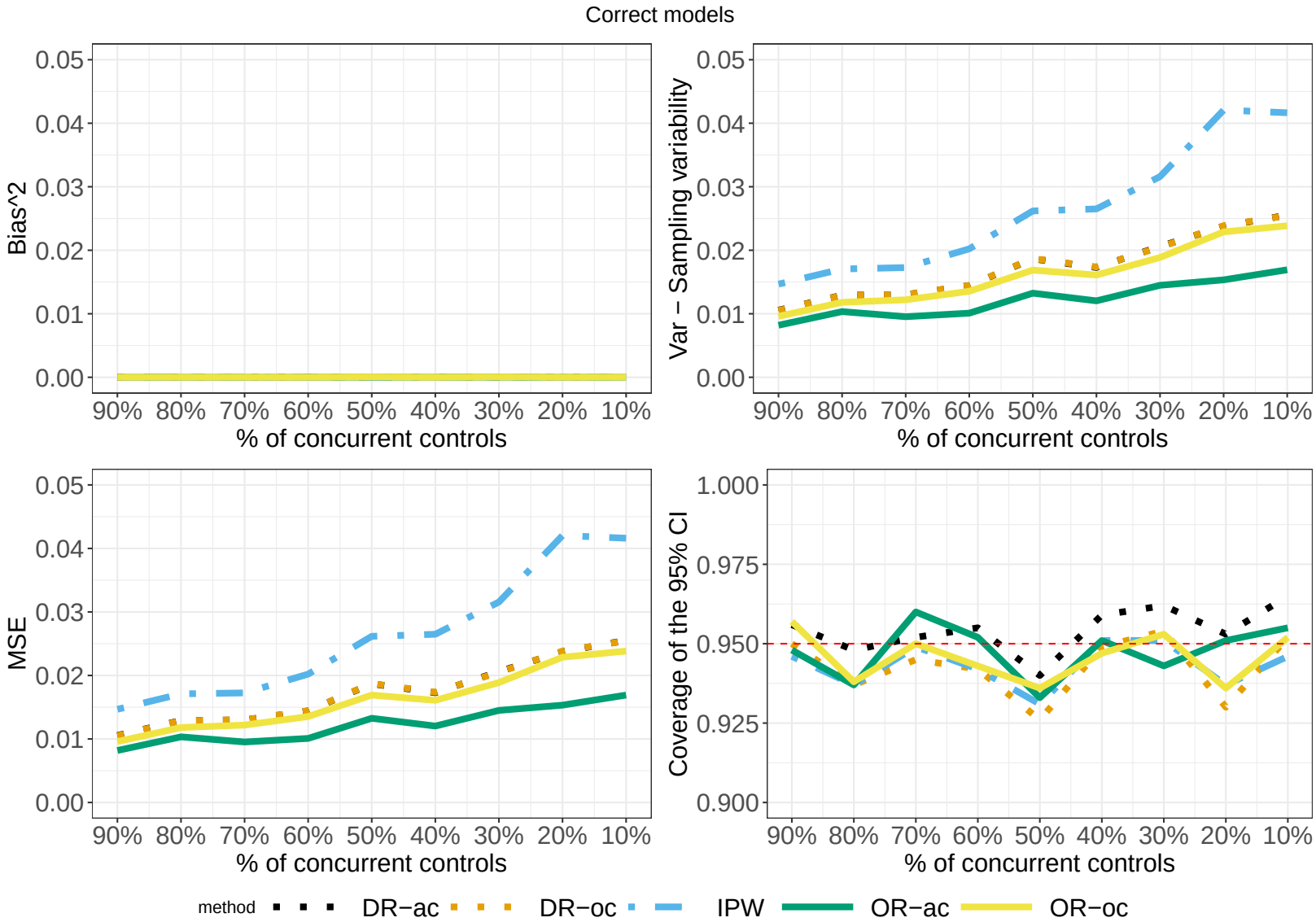
Estimators

Method	Acronym	
	cATE(k)	ATE(k)
Outcome regression using only concurrent data, ($\hat{\text{cATE}}^{\text{oc}}_{\text{OR}}$)	OR-oc	-
Outcome regression using all data, ($\hat{\text{cATE}}^{\text{all}}_{\text{OR}}$, $\hat{\text{ATE}}_{\text{OR}}$)	OR-ac	OR-ad
Weighting using only concurrent data ($\hat{\text{cATE}}^{\text{oc}}_{\text{IPW}}$)	IPW	-
Doubly robust using only concurrent data ($\hat{\text{cATE}}^{\text{oc}}_{\text{DR}}$)	DR-oc	-
Doubly robust using all data ($\hat{\text{cATE}}^{\text{all}}_{\text{DR}}$)	DR-ac	-

Simulations
Efficiency considerations

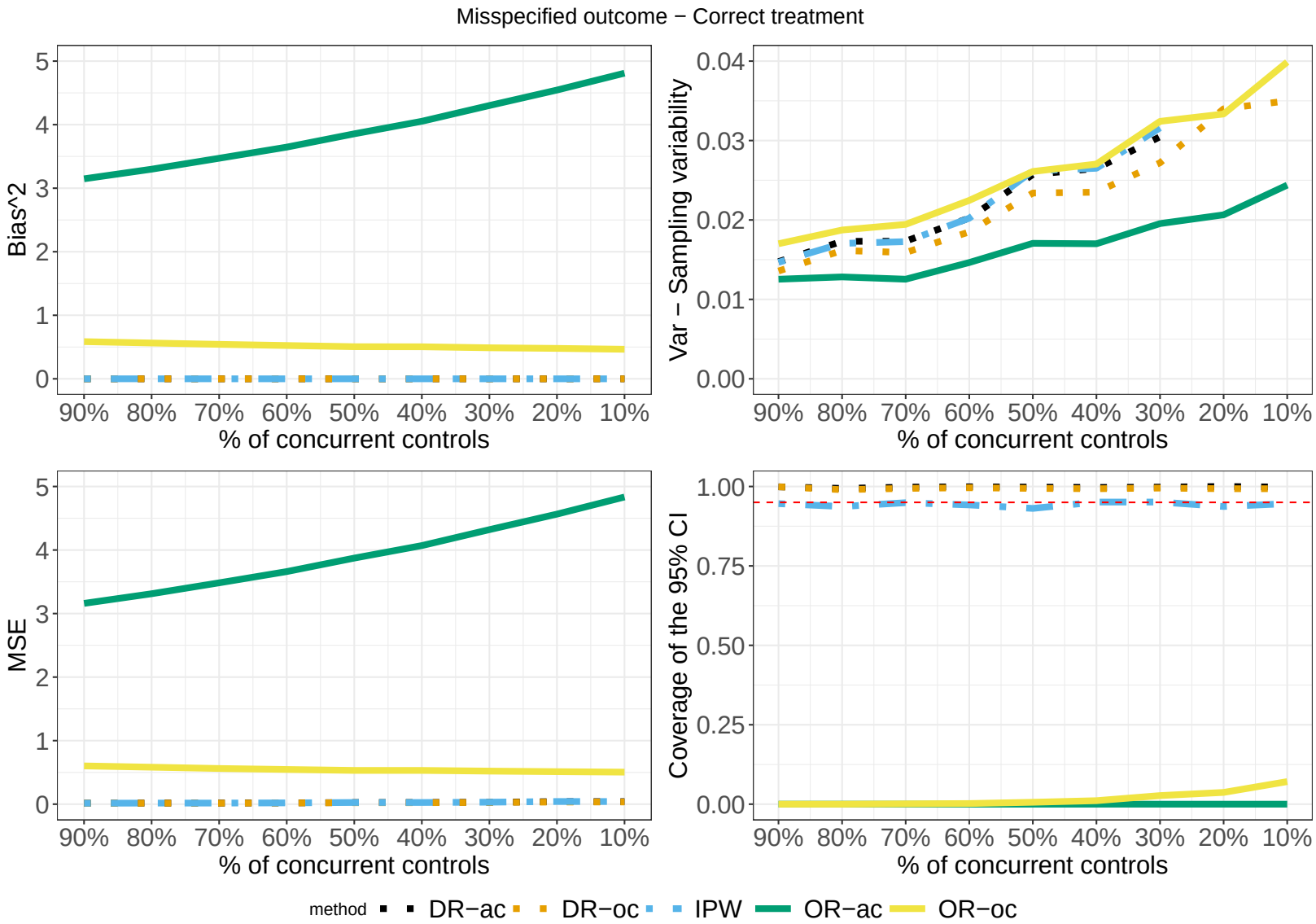


Simulations
Correct models



Simulations

Misspecified outcome - Correct treatment



Simulations
Summary

- Methods based on outcome regression improve efficiency when using non-concurrent controls.
- However, they introduce bias when misspecified.
- In contrast, doubly robust estimators provide consistent estimates with relatively small variance when either the treatment or outcome model is correctly specified.

Practical considerations

- Target cATE(k)
- If you are interested in ATE(k) consider discussing how valid your extrapolation assumption is and please disclose this in your SAP!
- Compare point estimate and standard error of proposed methods with "naive" estimator
- Leverage prognostic baseline predictors, if present
- Conduct sample size calculation as without non-concurrent control, conduct secondary analysis including them
- Conduct standard adjustment for multiple comparisons

Practical considerations

- Target cATE(k)
- If you are interested in ATE(k) consider discussing how valid your extrapolation assumption is and please disclose this in your SAP!
- Compare point estimate and standard error of proposed methods with "naive" estimator
- Leverage prognostic baseline predictors, if present
- Conduct sample size calculation as without non-concurrent control, conduct secondary analysis including them
- Conduct standard adjustment for multiple comparisons

Practical considerations

- Target cATE(k)
- If you are interested in ATE(k) consider discussing how valid your extrapolation assumption is and please disclose this in your SAP!
- Compare point estimate and standard error of proposed methods with "naive" estimator
- Leverage prognostic baseline predictors, if present
- Conduct sample size calculation as without non-concurrent control, conduct secondary analysis including them
- Conduct standard adjustment for multiple comparisons

Practical considerations

- Target cATE(k)
- If you are interested in ATE(k) consider discussing how valid your extrapolation assumption is and please disclose this in your SAP!
- Compare point estimate and standard error of proposed methods with "naive" estimator
- Leverage prognostic baseline predictors, if present
- Conduct sample size calculation as without non-concurrent control, conduct secondary analysis including them
- Conduct standard adjustment for multiple comparisons

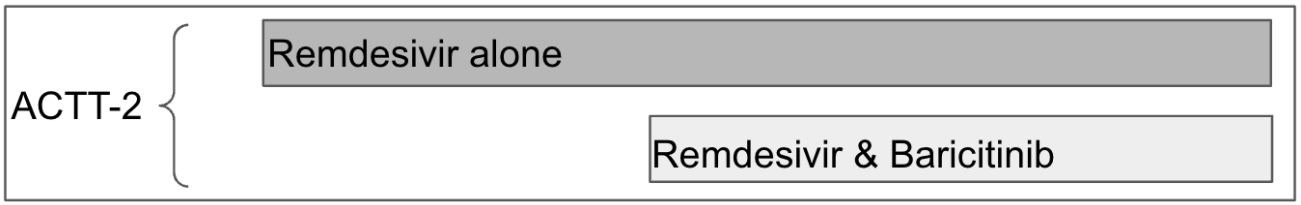
Practical considerations

- Target cATE(k)
- If you are interested in ATE(k) consider discussing how valid your extrapolation assumption is and please disclose this in your SAP!
- Compare point estimate and standard error of proposed methods with "naive" estimator
- Leverage prognostic baseline predictors, if present
- Conduct sample size calculation as without non-concurrent control, conduct secondary analysis including them
- Conduct standard adjustment for multiple comparisons

Practical considerations

- Target cATE(k)
- If you are interested in ATE(k) consider discussing how valid your extrapolation assumption is and please disclose this in your SAP!
- Compare point estimate and standard error of proposed methods with "naive" estimator
- Leverage prognostic baseline predictors, if present
- Conduct sample size calculation as without non-concurrent control, conduct secondary analysis including them
- Conduct standard adjustment for multiple comparisons

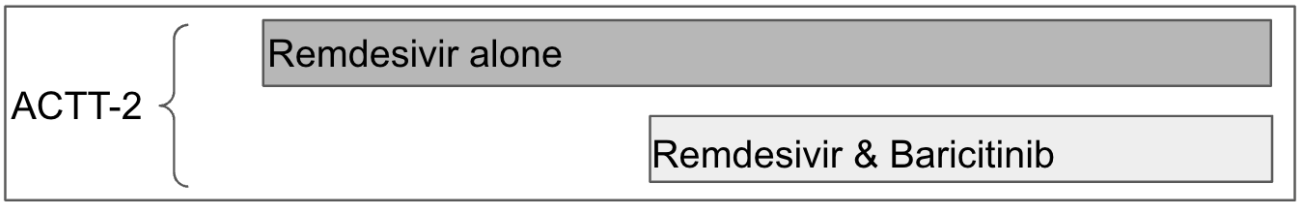
Application to the ACTT platform trial



Method	cÂTE	ÂTE	se	95% ci	p-value	Ratio
OR-oc	-1.29	-	0.47	(-2.21;-0.37)	<0.01	1.22
OR-ac	-0.75	-	0.45	(-1.63;0.13)	0.10	1.28
IPW	-1.28	-	0.47	(-2.20;-0.36)	<0.01	1.22
DR-oc	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.22
DR-ac	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.21
naive	-1.33	-	0.58	(-2.47;-0.19)	0.02	1.00
OR-ad	-	0.45	0.35	(1.15;-0.24)	0.19	-

Standard linear regression models regressing the outcome on 1) entry time and baseline covariates, and 2) entry time alone, resulted in (-0.46 0.52) and (-1.31; 0.57*).

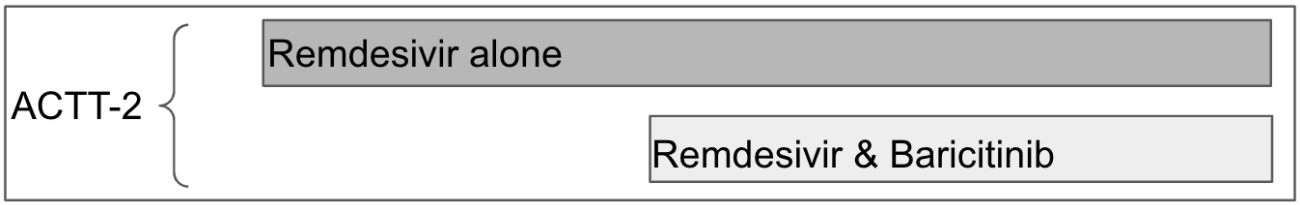
Application to the ACTT platform trial



Method	$\widehat{\text{cATE}}$	$\widehat{\text{ATE}}$	**se**	**95% ci**	**p-value**	**Ratio**
OR-oc	-1.29	-	0.47	(-2.21;-0.37)	<0.01	1.22
OR-ac	-0.75	-	0.45	(-1.63;0.13)	0.10	1.28
IPW	-1.28	-	0.47	(-2.20;-0.36)	<0.01	1.22
DR-oc	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.22
DR-ac	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.21
naive	-1.33	-	0.58	(-2.47;-0.19)	0.02	1.00
OR-ad	-	0.45	0.35	(1.15;-0.24)	0.19	-

Standard linear regression models regressing the outcome on 1) entry time and baseline covariates, and 2) entry time alone, resulted in (-0.46 0.52) and (-1.31; 0.57*).

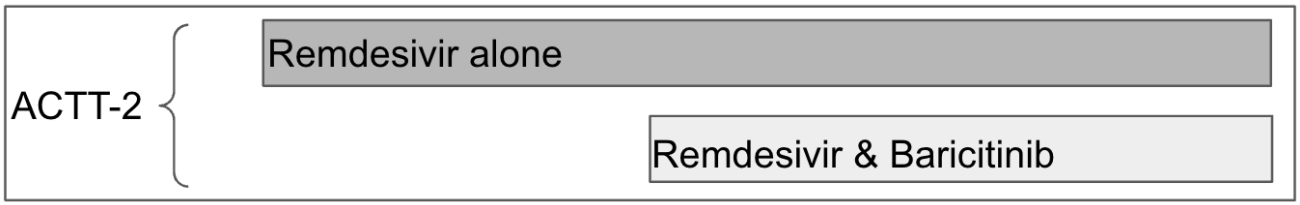
Application to the ACTT platform trial



Method	$\widehat{\text{cATE}}$	$\widehat{\text{ATE}}$	**se**	**95% ci**	**p-value**	**Ratio**
OR-oc	-1.29	-	0.47	(-2.21;-0.37)	<0.01	1.22
OR-ac	-0.75	-	0.45	(-1.63;0.13)	0.10	1.28
IPW	-1.28	-	0.47	(-2.20;-0.36)	<0.01	1.22
DR-oc	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.22
DR-ac	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.21
naive	-1.33	-	0.58	(-2.47;-0.19)	0.02	1.00
OR-ad	-	0.45	0.35	(1.15;-0.24)	0.19	-

Standard linear regression models regressing the outcome on 1) entry time and baseline covariates, and 2) entry time alone, resulted in (-0.46 0.52) and (-1.31; 0.57*).

Application to the ACTT platform trial



Method	$\widehat{\text{cATE}}$	$\widehat{\text{ATE}}$	**se**	**95% ci**	**p-value**	**Ratio**
OR-oc	-1.29	-	0.47	(-2.21;-0.37)	<0.01	1.22
OR-ac	-0.75	-	0.45	(-1.63;0.13)	0.10	1.28
IPW	-1.28	-	0.47	(-2.20;-0.36)	<0.01	1.22
DR-oc	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.22
DR-ac	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.21
naive	-1.33	-	0.58	(-2.47;-0.19)	0.02	1.00
OR-ad	-	0.45	0.35	(1.15;-0.24)	0.19	-

Standard linear regression models regressing the outcome on 1) entry time and baseline covariates, and 2) entry time alone, resulted in (-0.46 0.52) and (-1.31; 0.57*).

Conclusions

In this project, we provided

- SCM to clarify the role of entry time and non-concurrent controls in platform trials
- non-parametric identification results
- efficiency consideration
- new estimators

Next:

- machine learning, parametric and nonparametric Bayesian methods,
- extension to binary endpoints, time-to-event data,
- interim analysis, adaptive platform trials (I/E, randomization, etc)

Conclusions

In this project, we provided

- SCM to clarify the role of entry time and non-concurrent controls in platform trials
- non-parametric identification results
- efficiency consideration
- new estimators

Next:

- machine learning, parametric and nonparametric Bayesian methods,
- extension to binary endpoints, time-to-event data,
- interim analysis, adaptive platform trials (I/E, randomization, etc)

Questions?

Contact me at **santam13@nyu.edu**

https://arxiv.org/pdf/2404.19118

Visit my website **https://michelesantacatterina.github.io/**

Platform Trials: Experience in Design, Conduct, and Interpretation for NIH and Foundation Clinical Trial Networks

Discussant - Michelle A. Detry, PhD

Director Adaptive Trial Execution & Senior Statistical Scientist

Disclosures

- Employee of Berry Consultants, LLC, a statistical consulting firm that specializes in the design, implementation, oversight, and analysis of adaptive clinical trials.

Session Discussion

- Goal of session to share design, conduct, and interpretation experiences

- 3 Platform trials:
  - STEP NINDS StrokeNET acute ischemic stroke
  - P2P participants from the PPMI Michael J. Fox Foundation study
  - ACTT-1 and ACTT-2 from NIAID

Session Discussion -

- Platform trials began in oncology
- Expanded use in COVID-19
- Now in a variety of clinical indications:
  - Acute Ischemic Stroke
  - Parkinson's Disease
  - Other areas ALS, etc.

Session Discussion

- Platform trials are flexible for investigating different types of questions
- STEP – multifactorial, i.e. participants can be randomized to combinations of treatments, one treatment from each domain
- P2P – embedded trial within a cohort of participants to investigate therapies to slow progression
- ACTT-1 examined specific COVID-19 intervention remdesivir vs. placebo then ACTT-2 added a combination therapy to compare to remdesivir after it completed the comparison to placebo

Session Discussion

- All 3 trials meet the 2017 NEJM Woodcock and LaVange definition of platform master protocols:
  - *To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm*

- STEP and P2P continually enroll a control/SOC while new therapies enter and leave

- ACTT-1 and ACTT-2 is more sequential with a single therapy compared to control then the therapy becomes a comparator to a combination therapy

Common Threads

- Sharing infrastructure – sites, database, common data collection standards, etc.
- Adaptive clinical trials – decision criteria for stopping, response adaptive randomization, randomization ratios based on active arms, sample size re-estimation
- Sharing of control populations

- Goal of efficient use of trial participant contributions

Common Thread – Trial Simulation

- Designs are simulated to understand design performance and ensure scientifically sound operating characteristics
- Identify strengths and weaknesses of the design
- Investigate robustness of assumptions
- Allow for examination of “example trials”

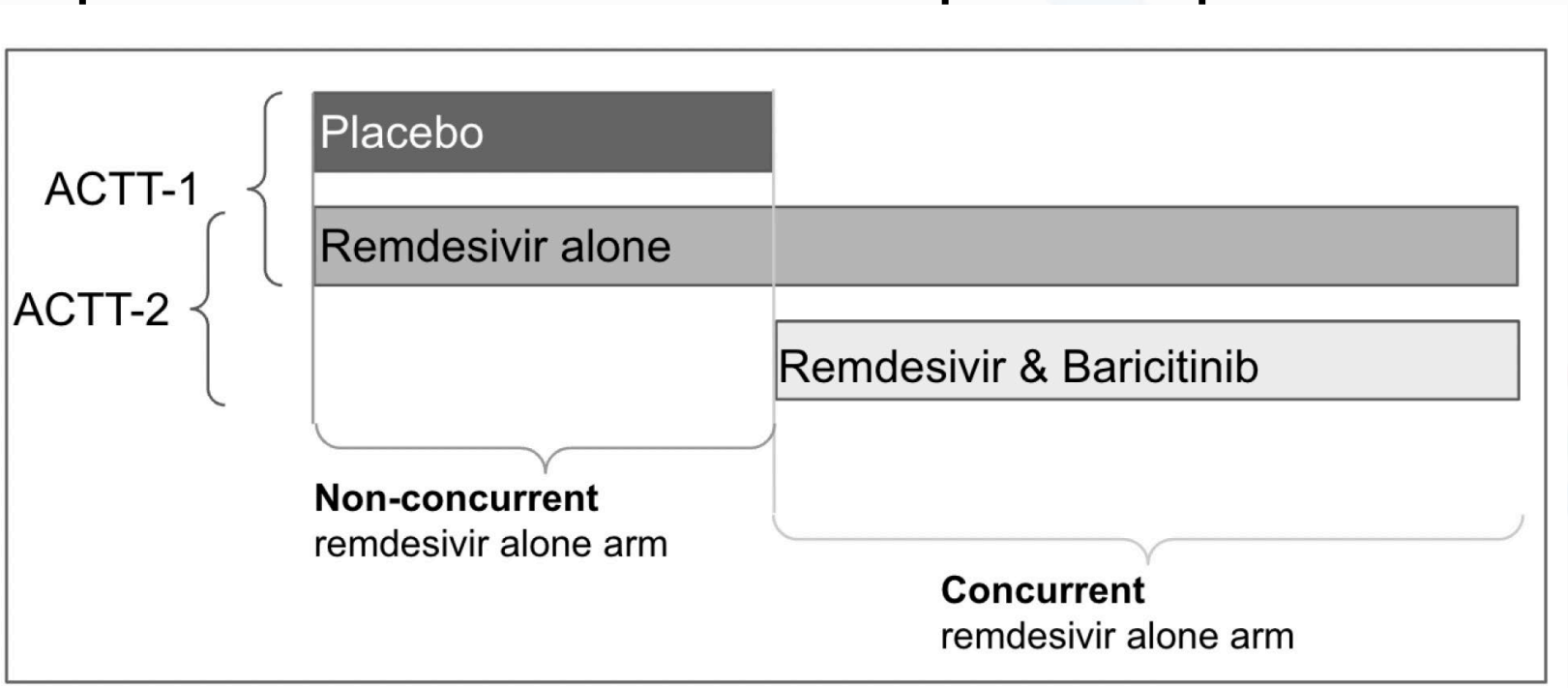
Common Thread – Thoughtful Consideration of Control Population

- Use of concurrent and non-concurrent controls
- All speakers agreed their designs need to adjust for, or consider, possible time trends in the controls

- STEP and P2P have primary analysis based on both concurrent and non-concurrent control population and both adjust for time
- Dr. Santacatterina proposed:
  - Primary analysis sample size be based on concurrent control population
  - Comparisons using non-concurrent controls as a secondary analysis

Common Thread – Thoughtful Consideration of Control Population

- More common situation is to have concurrently randomized controls in addition to non-concurrent controls
- Case study ACTT-1 and ACTT-2 did not have both
- Was the question for ACTT-2 to compare to placebo



Common Thread – Thoughtful Consideration of Control Population

- Use of non-concurrently randomized controls is an area of much research and debate
- Should be considered in the context of the specific platform and specific research questions
- Should consider how to effectively and appropriately use information learned during the perpetual platform trial

Summary

- Speakers shared experiences on design and interpretation
- Look forward to future sessions on implementation of their designs
- Platform trial implementation requires additional considerations for infrastructure, communication channels, data access plans, and dissemination of results
- Platform clinical trials may create unique challenges compared to other clinical trial designs
- But the challenges are being embraced, and solutions proposed, as demonstrated in this session and other sessions during SCT 2024

Berry Consultants

Statistical Innovation

CONTACT INFORMATION

info@berryconsultants.com | (512) 213-6428

WEBSITE
berryconsultants.com

YOUTUBE
youtube.com/berryconsultants

TWITTER
@berryconsultant