
Interactive Research Design Consultation

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Disclosures

- Academic Affiliation and Employment
 - Berry Consultants, LLC (multiple clients)
 - David Geffen School of Medicine at UCLA
 - Lundquist Institute for Biomedical Innovation
 - Retired: County of Los Angeles, Department of Health Services
- Special Government Employee
 - US Food and Drug Administration
- Other
 - Senior Statistical Editor, *JAMA*

A Toolset Rather than a Bookshelf

- Adaptive design is ideally a creative process of matching methodological solutions to specific threats to trial success, considering
 - Available resources, patient population
 - Acceptable error rates, potential threats to validity
 - Whether trial results are intended to influence future research efforts, regulatory decision making, or clinical practice
- While specific examples can illustrate benefits of adaptive design, anchoring on specific examples can erroneously suggest adaptive trials are just another limited set of inflexible options

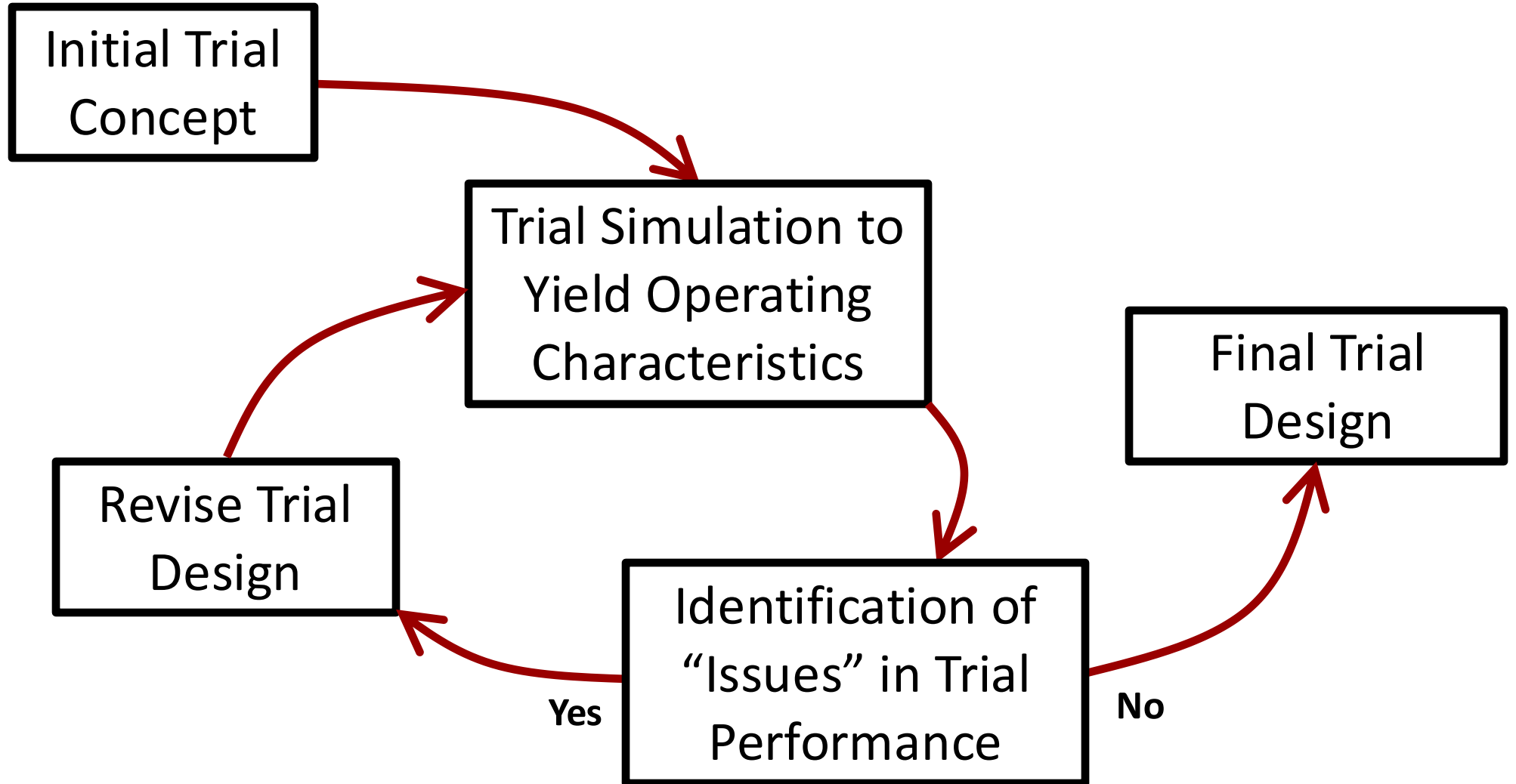
Avoiding Anticipated Regret

- A substantial fraction of all confirmatory trials fail despite promising “learn phase” results
- Investigators can anticipate the design decisions they are most likely to want to “take over” if the trial were to fail
- Areas of “anticipated regret” are promising targets for adaptations

Potential Adaptive Strategies

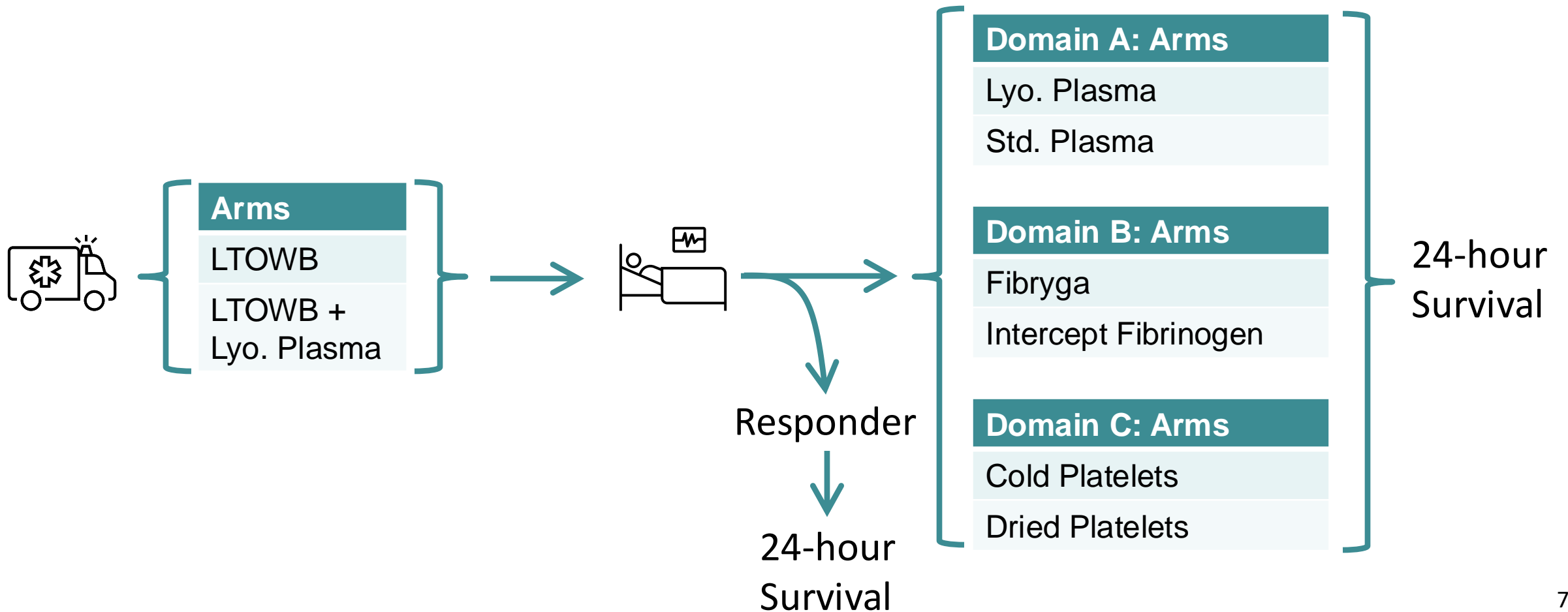
- Frequent interim analyses at which adaptations are possible
- Response-adaptive randomization (RAR)
 - Includes adding or dropping of arms or even groups of treatment options
- Explicit decision rules based on Bayesian predictive probabilities at each interim analysis
 - Early stopping for success
 - Early stopping for futility
- Sample size re-estimation
- Enrichment of study population
- Seamless transition from a phase II to a phase III comparison

The Adaptive Trial Design Process



Trial Structure

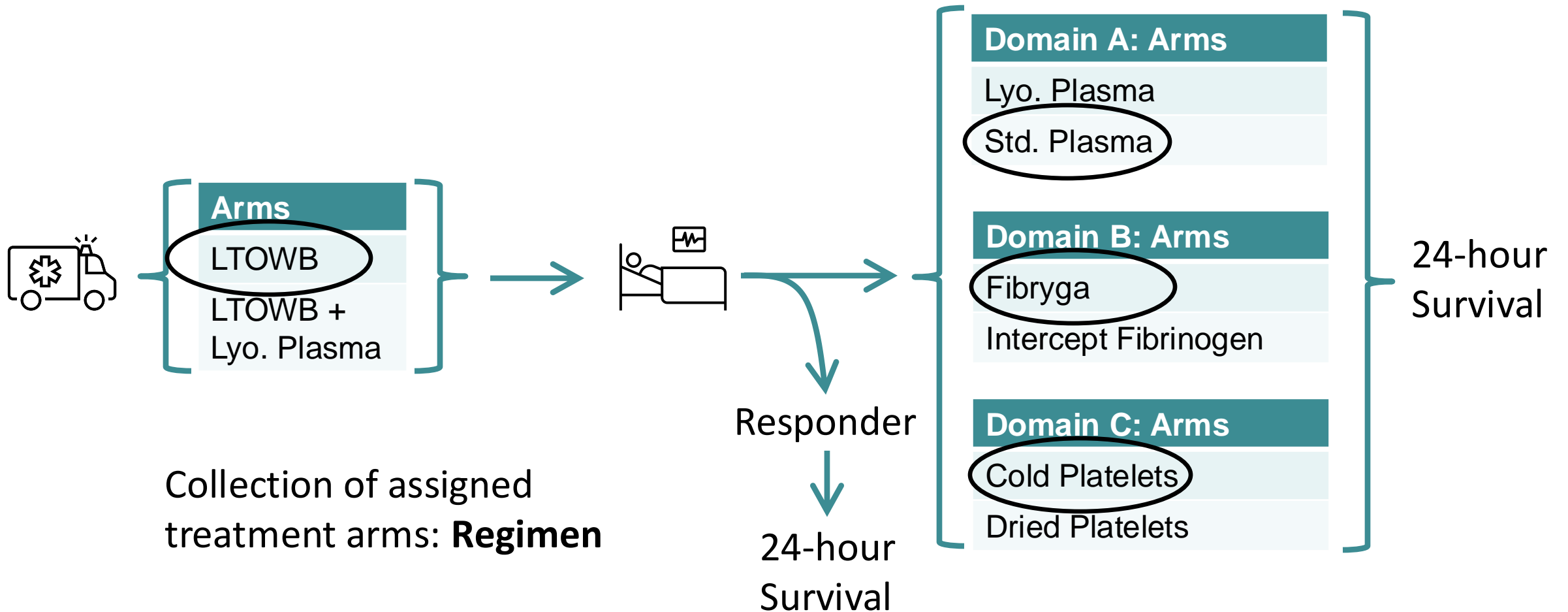
- People often over-simplify things when designing clinical trials
- Doesn't seem to be the case with Phil



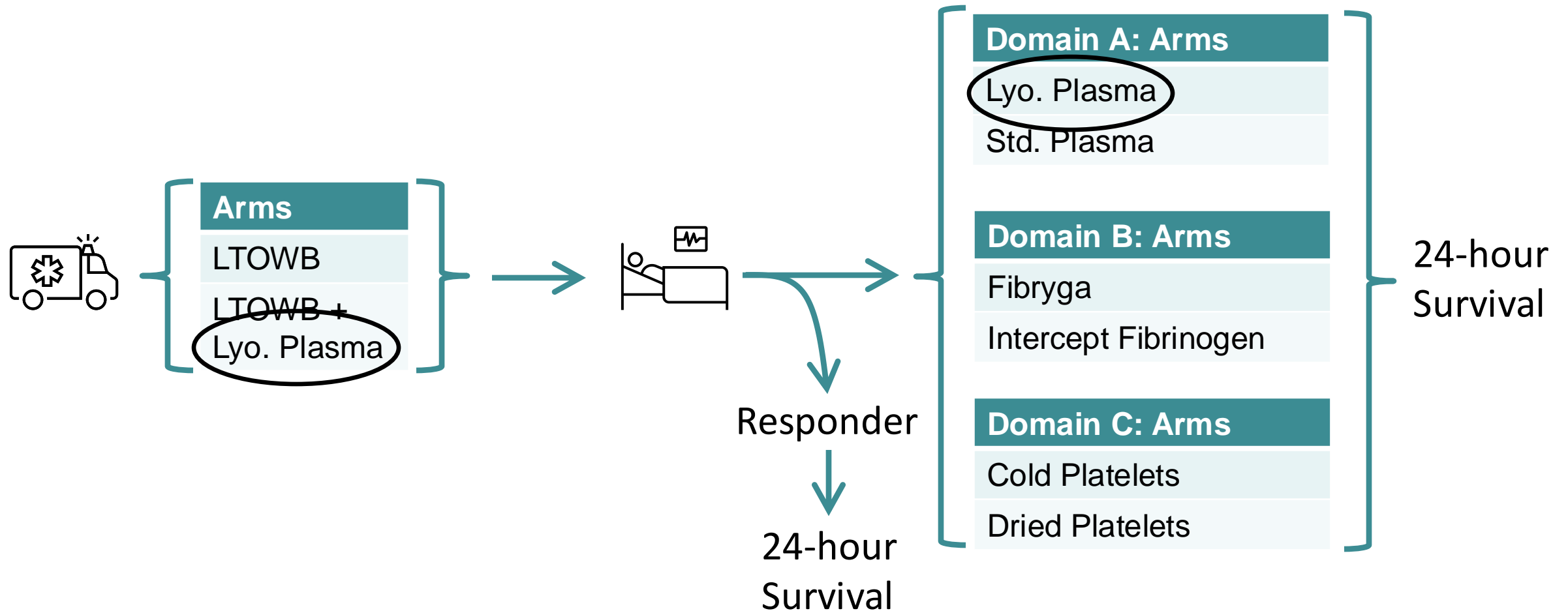
Multifactorial Platform Trial Terminology

- Domain
 - A domain of treatment
 - E.g., Fibrinogen supplementation, platelet replacement
- Factor
 - One particular treatment or arm within a domain
 - E.g., Fibryga, Intercept Fibrinogen Complex
- Regimen
 - The assigned collection of factors from multiple domains

Multifactorial Trial Structure

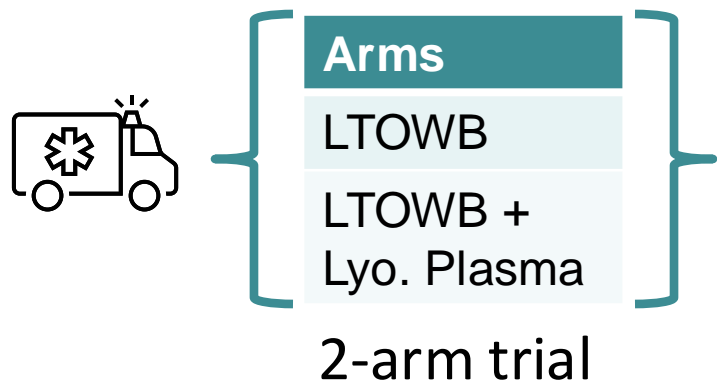


SMART Multifactorial Platform Trial Structure

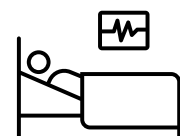


SMART Multifactorial Platform Trial Structure

Patients may be eligible for one or multiple treatment domains.

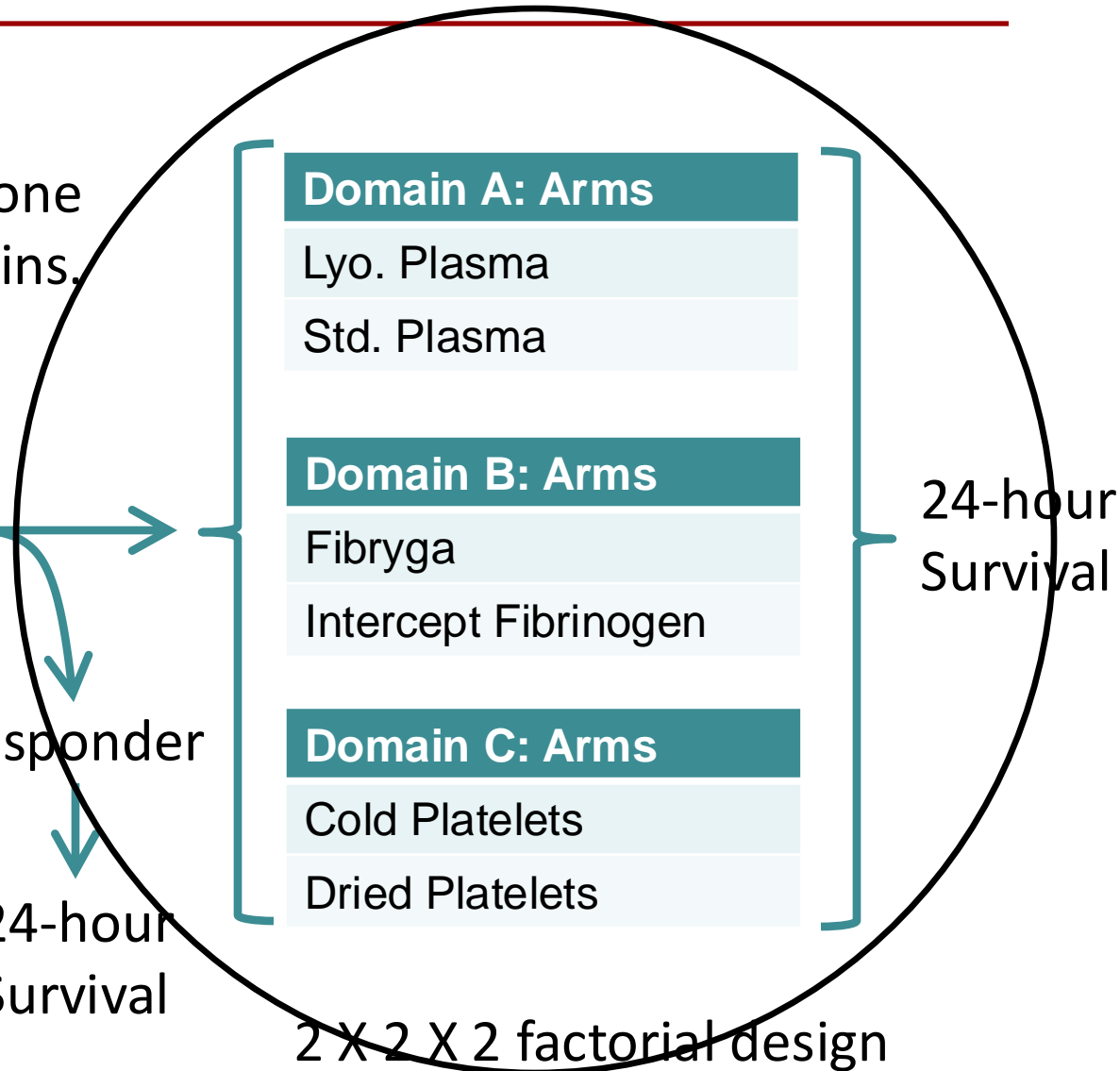


Randomization to any arm or domain may stop for demonstration of superiority, non-inferiority, futility, or harm.



Responder

24-hour Survival



Decision Rules

- Decision rules to be applied at interim analyses
- For each domain/comparison, calculate the probability:
 - That each arm is superior or non-inferior relative to the appropriate comparator(s); or that each arm is best of those in the domain
 - Compare probabilities to decision thresholds, e.g.,
 - $\text{Pr}(\text{SUP or NI}) > 0.9XX \rightarrow$ Stop randomization to arm for success
 - $\text{Pr}(\text{SUP or NI}) < 0.XXX \rightarrow$ Stop randomization for futility/lack of efficacy

Design Process: Choosing Thresholds

The screenshot displays the FACTS™ v7.0 software interface. The window title is "FACTS™ v7.0" and the menu bar includes "File", "Settings", and "Help". The main heading is "Fixed and Adaptive Clinical Trial Simulator (FACTS™)".

Select Design Type

- Enrichment Design
 - Continuous
 - Dichotomous
 - Time to Event
- Core Design
 - Continuous
 - Dichotomous**
 - Multiple Endpoint
 - Time to Event
- Staged Core Design
 - Create from existing Core Design project
 - Continuous
 - Dichotomous
 - Multiple Endpoint
 - Time to Event
- Platform Trial Design
 - Continuous
 - Dichotomous
- Dose Escalation Design
 - 3 + 3
 - mTPI
 - N-CRM
 - 2D-CRM
 - CRM(Toxicity)
 - CRM(Ordinal)

Design Engine Information

Design Name: Core Design Dichotomous Engine

Design Family: Core Design

Version: 7.0.0.0

Description: The "Core Design Engine for a Dichotomous Endpoint" is a highly flexible trial simulation engine for designing Phase 2 and 3 trials with dichotomous endpoints. Study designers can explore the effects of various simulated subject responses (either supplied or simulated with the tool) and different accrual and subject dropout profiles. Different trial designs can be explored with a variety of standard statistical analyses as well as Bayesian models for fitting response data and evaluating trial outcomes. Fixed and adaptive trial designs can be compared, with a variety of options for the method, timing and frequency of the adaptation.

Recent Work

Recent Projects: Select recent project



Recent Folders: Select recent folder

Design Process: Choosing Thresholds

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis

Explicitly Defined External Files

Dose Response

 Add  Delete

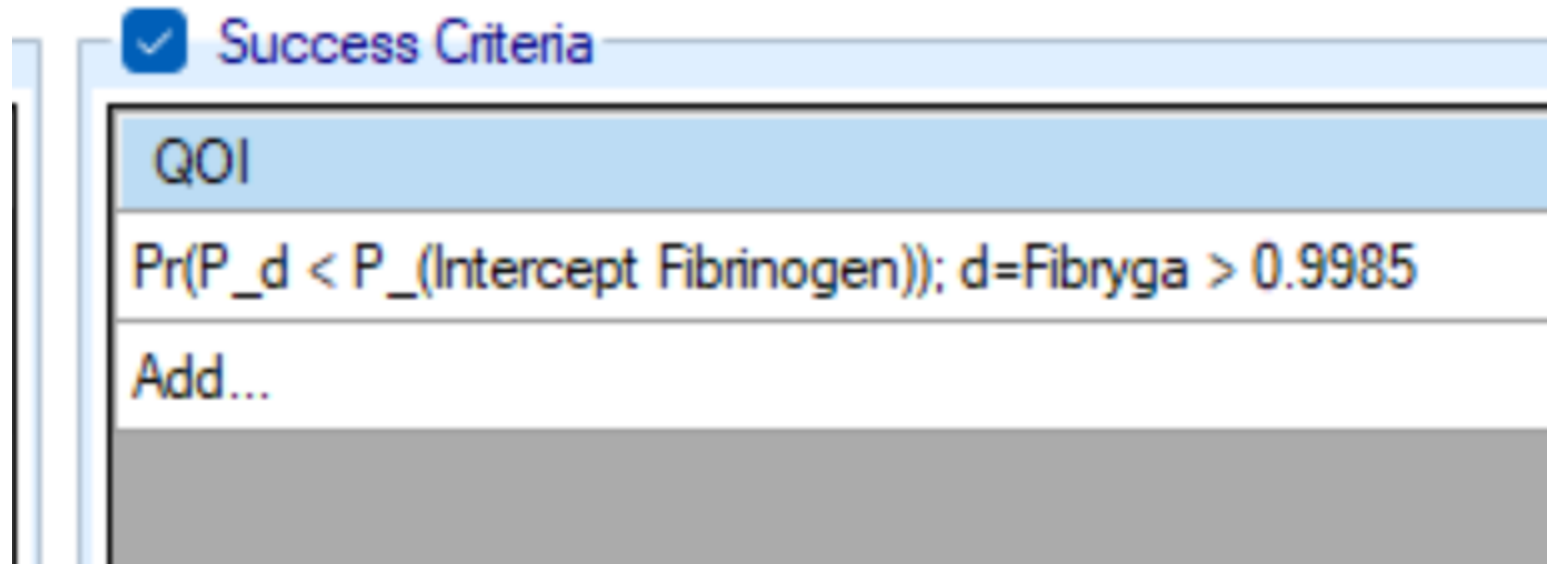
Profiles

- Null 0.20
- Fibryga Better**
- Fibryga Worse

Endpoint Values

Index	Dose	Dose Level	Response rate	Should succeed
1	Intercept Fibrinog...	0	0.2	<input type="checkbox"/>
2	Fibryga	1	0.15	<input checked="" type="checkbox"/>

Design Process: Choosing Thresholds



A screenshot of a software interface showing a list of success criteria. The list is titled "Success Criteria" and is checked. The criteria listed are "QOI" and "Pr(P_d < P_(Intercept Fibrinogen)); d=Fibryga > 0.9985". There is also an "Add..." option.

Success Criteria

- QOI
- Pr(P_d < P_(Intercept Fibrinogen)); d=Fibryga > 0.9985
- Add...

Design Process: Choosing Thresholds

Study Virtual Subject Response Execution Quantities of Interest Design Simulation Analysis


Simulation

Run Configuration


Number of simulations: 10000

Parallelization packet size: 1000

Subject Simulation Parameters:

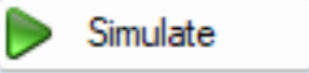
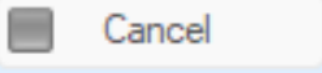
Random seed:  3500




Start at simulation: 1

 MCMC Settings

Run Simulations:

Locally On Grid Simulations completed: 30000/30000

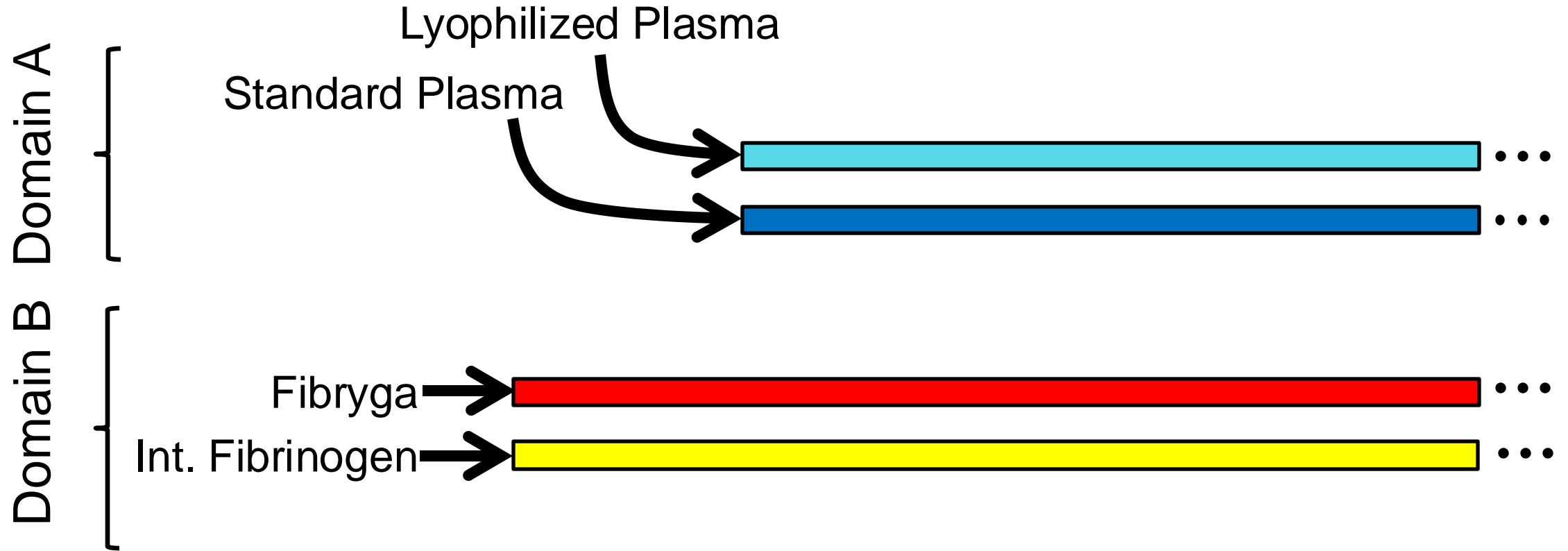
 

Select All	Settings	Status	Scenario	Num Sims
<input type="checkbox"/>		Completed (10/07/2024 20:33:55)	10 per week_Drop1_Null 0.20	10000
<input type="checkbox"/>		Completed (10/07/2024 20:36:10)	10 per week_Drop1_Fibryga Better	10000
<input type="checkbox"/>		Completed (10/07/2024 20:36:39)	10 per week_Drop1_Fibryga Worse	10000

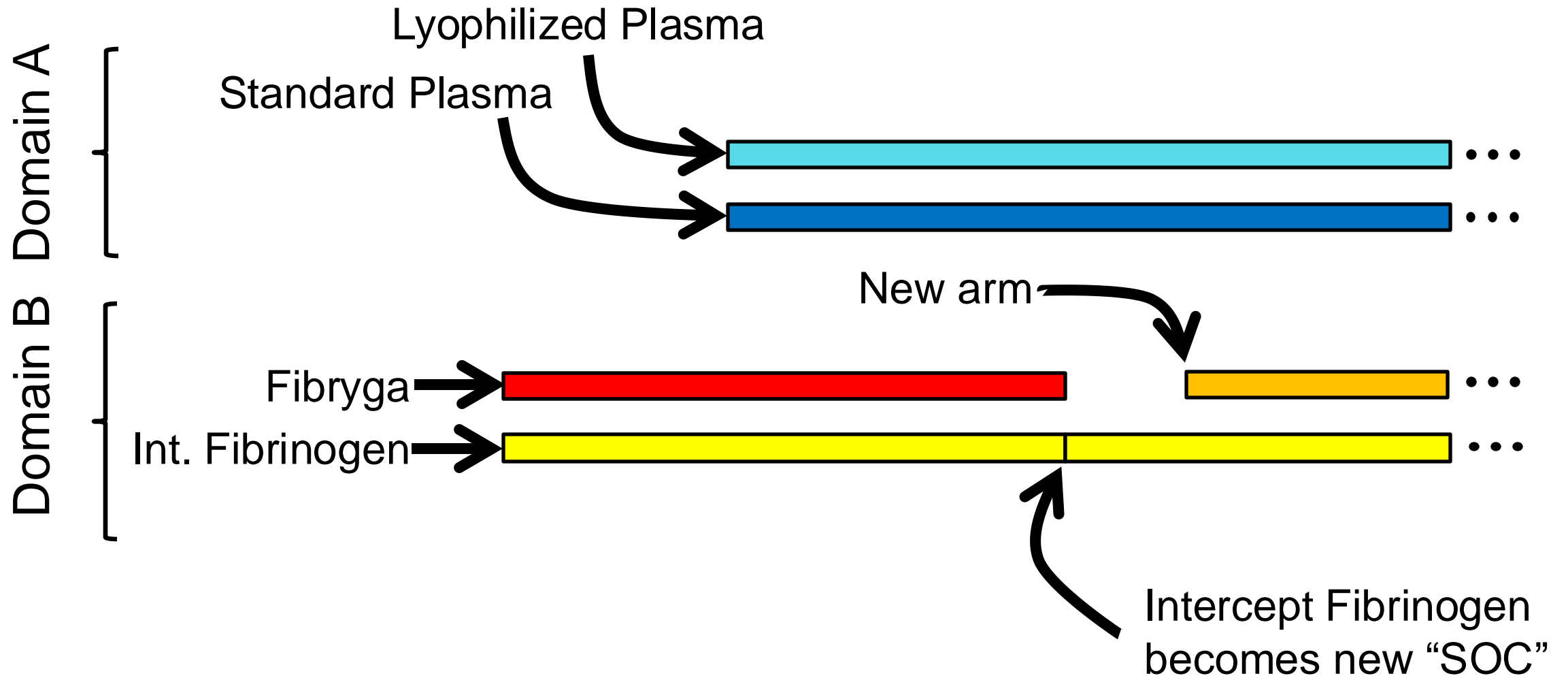
Design Process: Choosing Thresholds

	Num Sims	Mean Subj.	Ppn Early Success	Ppn Late Success	Ppn Late Futility	Ppn Early Futility
_Null 0.20	10000	1287.0192	0.0124	0.0141	0	0.1964
Fibryga Better	10000	1187.0524	0.4563	0.2425	0	0.0171
_Fibryga Worse	10000	680.9396	0.0005	0	0	0.8504

Multifactorial Platform (2 of 3 domains)



Multifactorial Platform





Key Elements in the Design of a Platform Trial (1)

- Overall Patient Population: Should generally be broadly defined to avoid overly limiting the population, given long time horizon
- Subpopulations/Strata: Exhaustive but mutually-exclusive subgroups, based on baseline characteristics, that define the smallest groups in which you may want to draw different conclusions regarding efficacy
- Initial Interventions: May be limited at the start of the trial
 - *Domains*: A group of therapeutic options sharing a common goal or mechanism (e.g., transfusion strategies, treatment or coagulopathy)
 - *Factors*: The set of mutually exclusive options within each domain (e.g., the choice of whole blood vs components, type of PCC)
 - *Combinations*: Must consider what combinations of factors across domains, if any, are excluded from consideration

Key Elements in the Design of a Platform Trial (2)

- Trial Endpoint: A single primary endpoint is generally chosen to “drive” the adaptive design
 - *Proximate outcomes*: more proximate outcomes can be used to inform interim decision-making allowing use of information from patients who have not yet reaching the primary endpoint
- Decisions Rules: The set of prespecified rules that comprise the adaptive design
 - *Stopping*: Criteria for stopping an arm (e.g., for harm or efficacy)
 - *Randomization*: Criteria for modifying randomization (e.g, RAR)
 - *Enrichment*: Criteria for restricting the randomization to selected subgroups of patients due to futility or harm in other subgroups
 - *Phase II/III transition*: Bringing a single treatment strategy forward to testing against control in a confirmatory setting

An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: Rationale and proposal

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Deborah J. Del Junco^{5,6} | Jason T. McMullan⁶ | Francis X. Guyette⁷ |
Henry Wang⁸ | Jan O. Jansen^{9,10}  | William J. Meurer^{3,11,12} |
Shraddha Mainali¹³ | Kabir Yadav^{1,2}  | Roger J. Lewis^{1,2,3}




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ADAPTIVE PLATFORM TRIAL DESIGN

An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: Planning and execution

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An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: Ethical and US regulatory considerations

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Thank you!
