Interactive Research Design Consultation

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Berry Consultants
Statistical Innovation

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

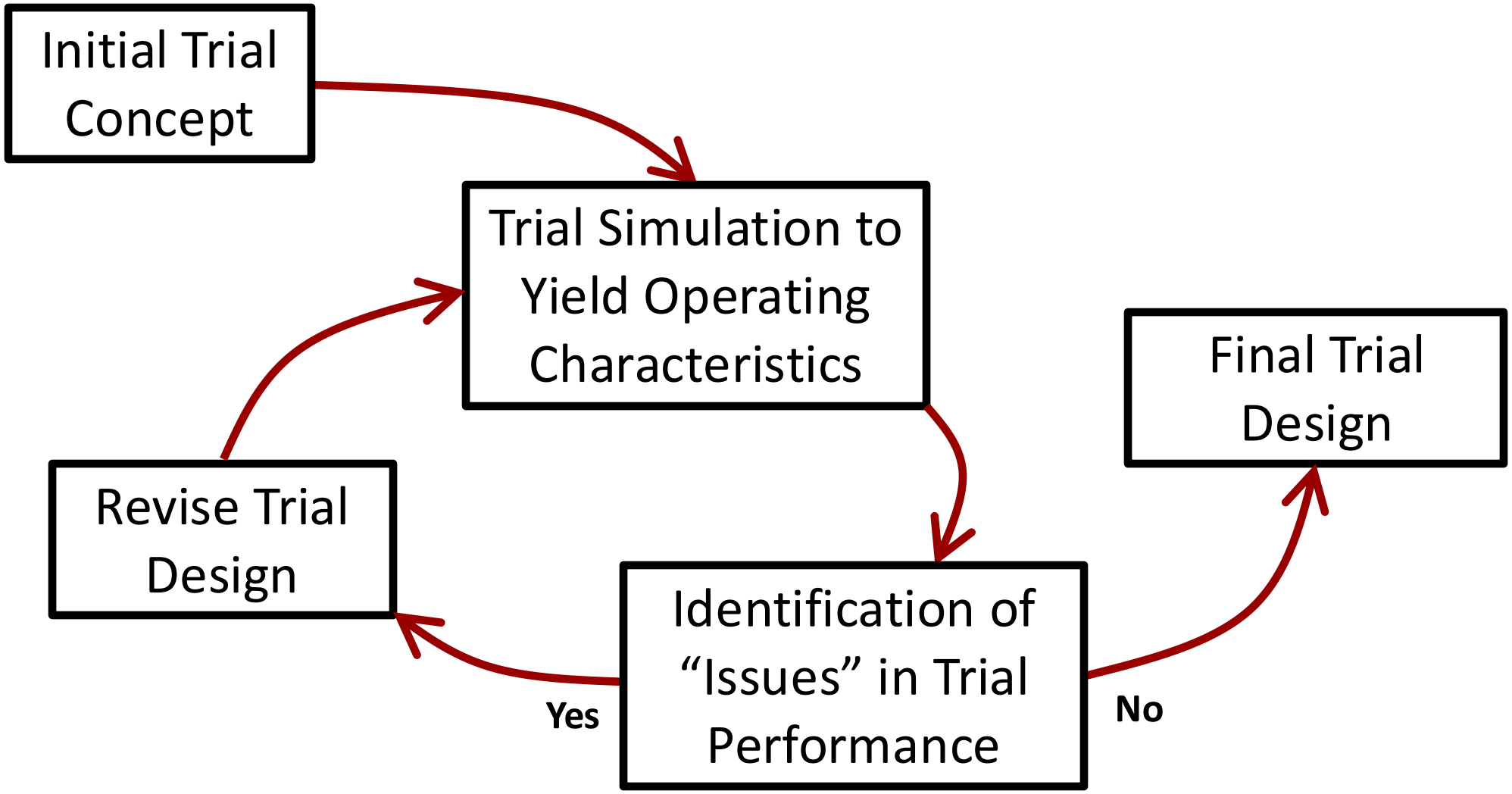
Avoiding Anticipated Regret

- 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

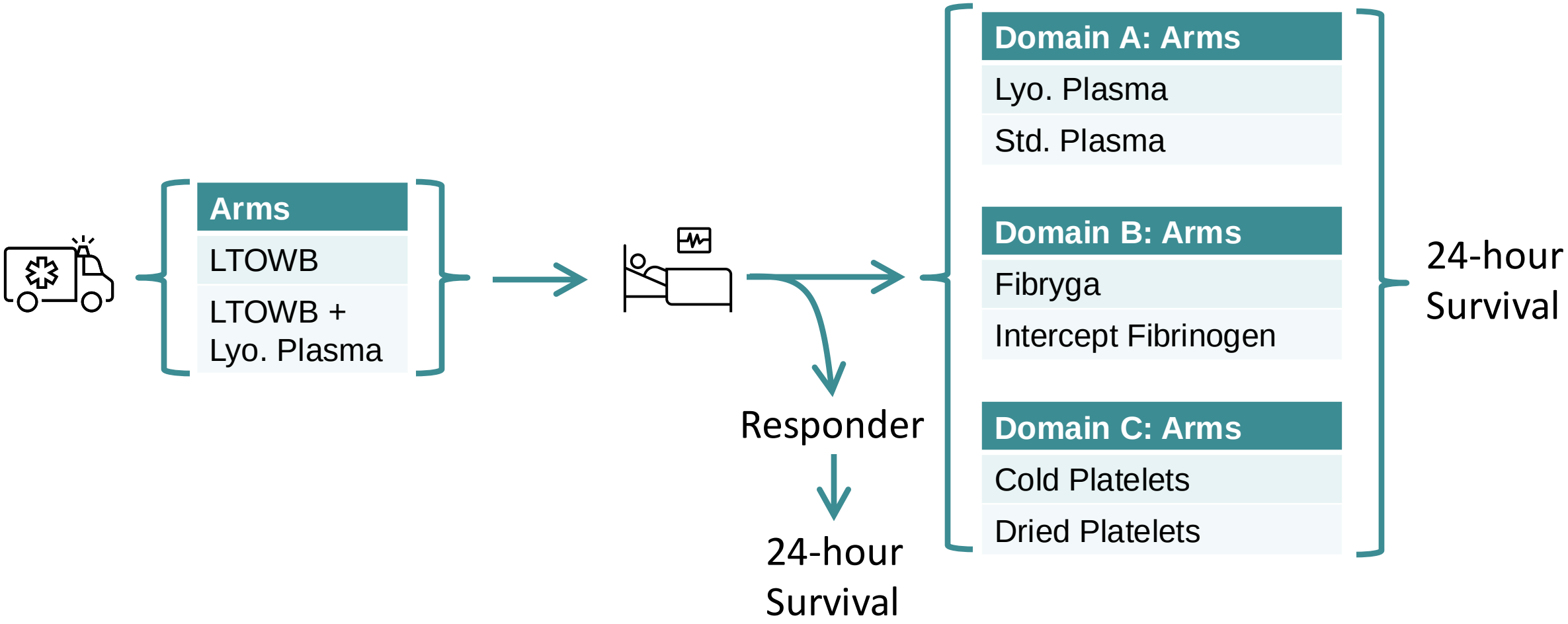
- Frequent interim analyses at which adaptations are possible
- Response-adaptive randomization (RAR)
  - Includes adding or dropping of arms or even groups of treatment options
- Explicit decision rules based on Bayesian predictive probabilities at each interim analysis
  - Early stopping for success
  - 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

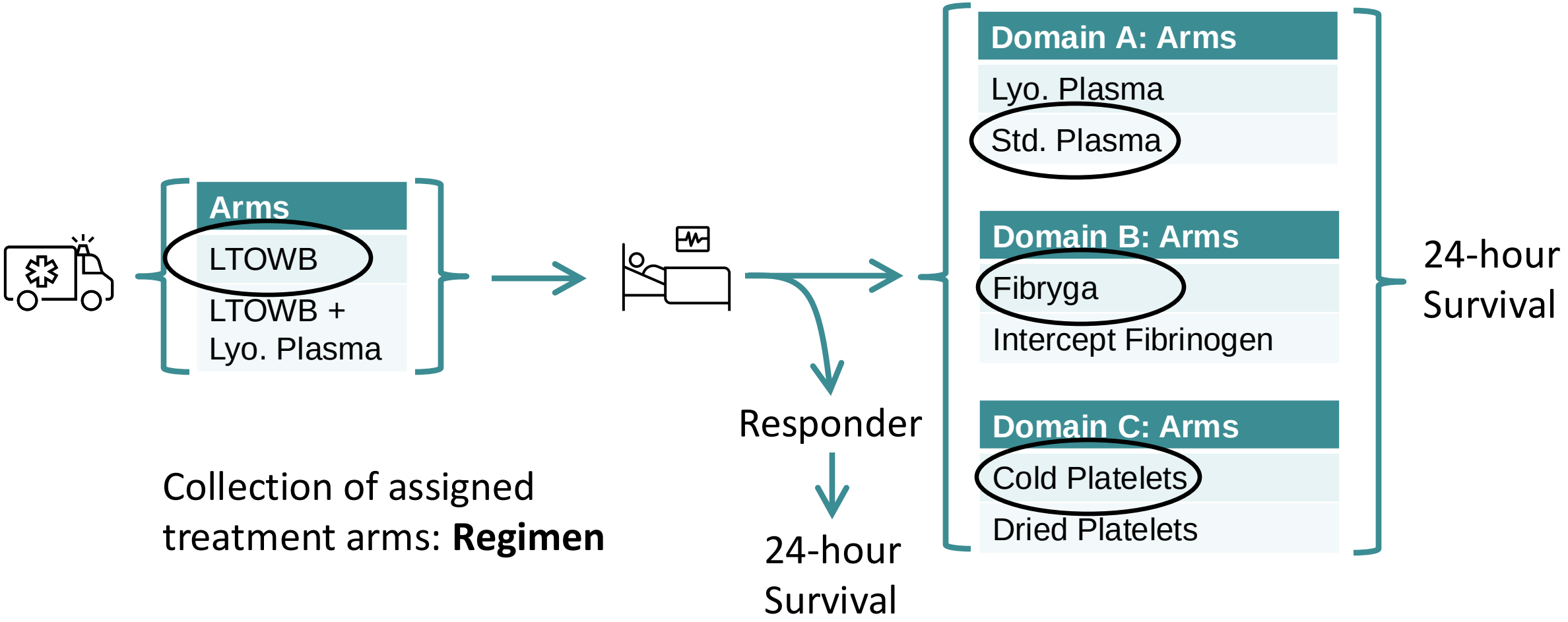
- People often over-simplify things when designing clinical trials
- Doesn't seem to be the case with Phil



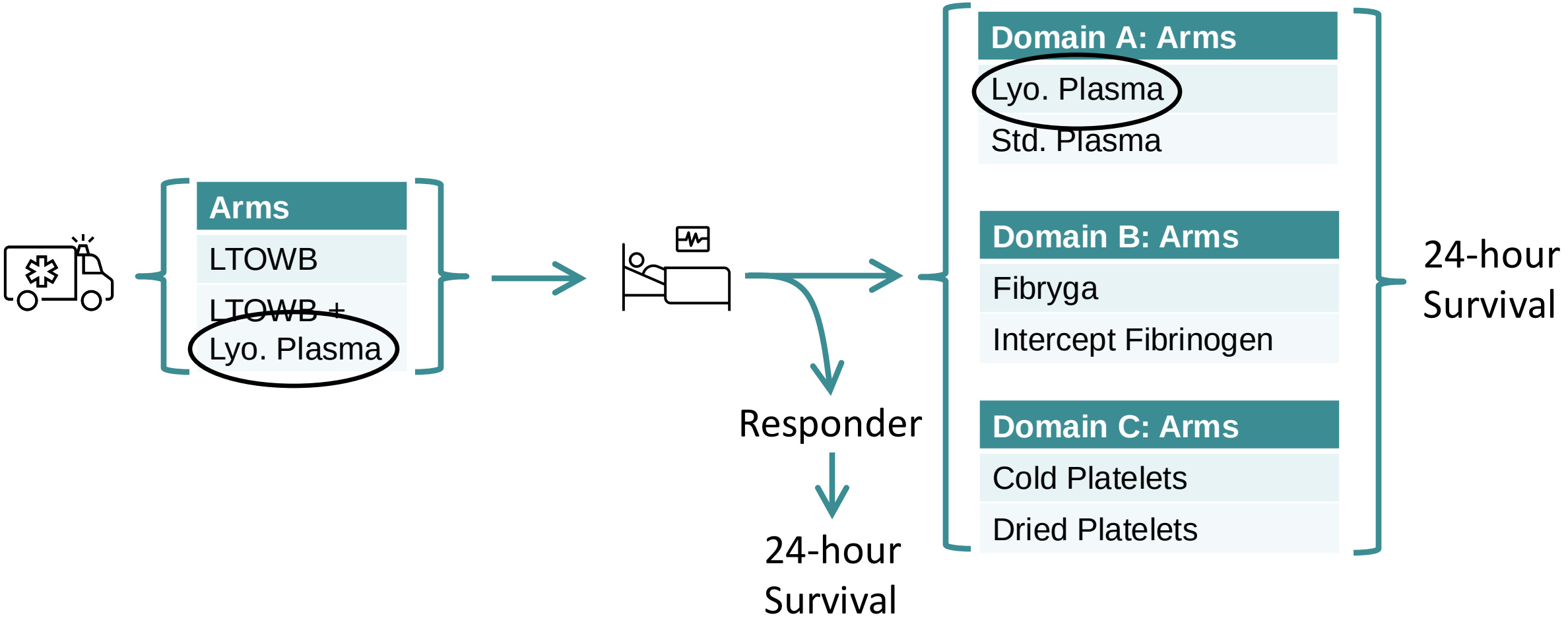
Multifactorial Platform Trial Terminology

- 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

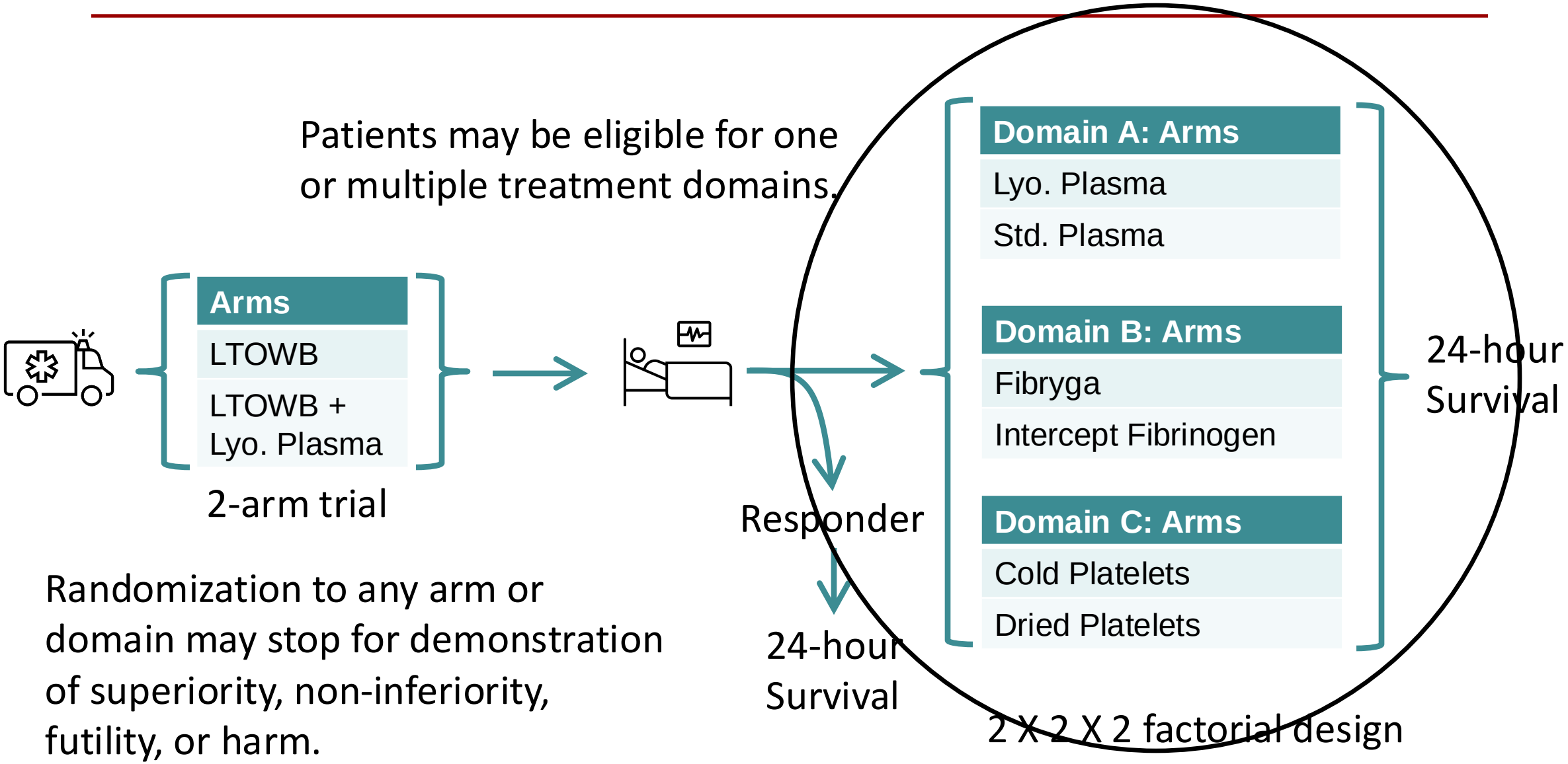
Multifactorial Trial Structure



SMART Multifactorial Platform Trial Structure



SMART **Multifactorial Platform** Trial Structure

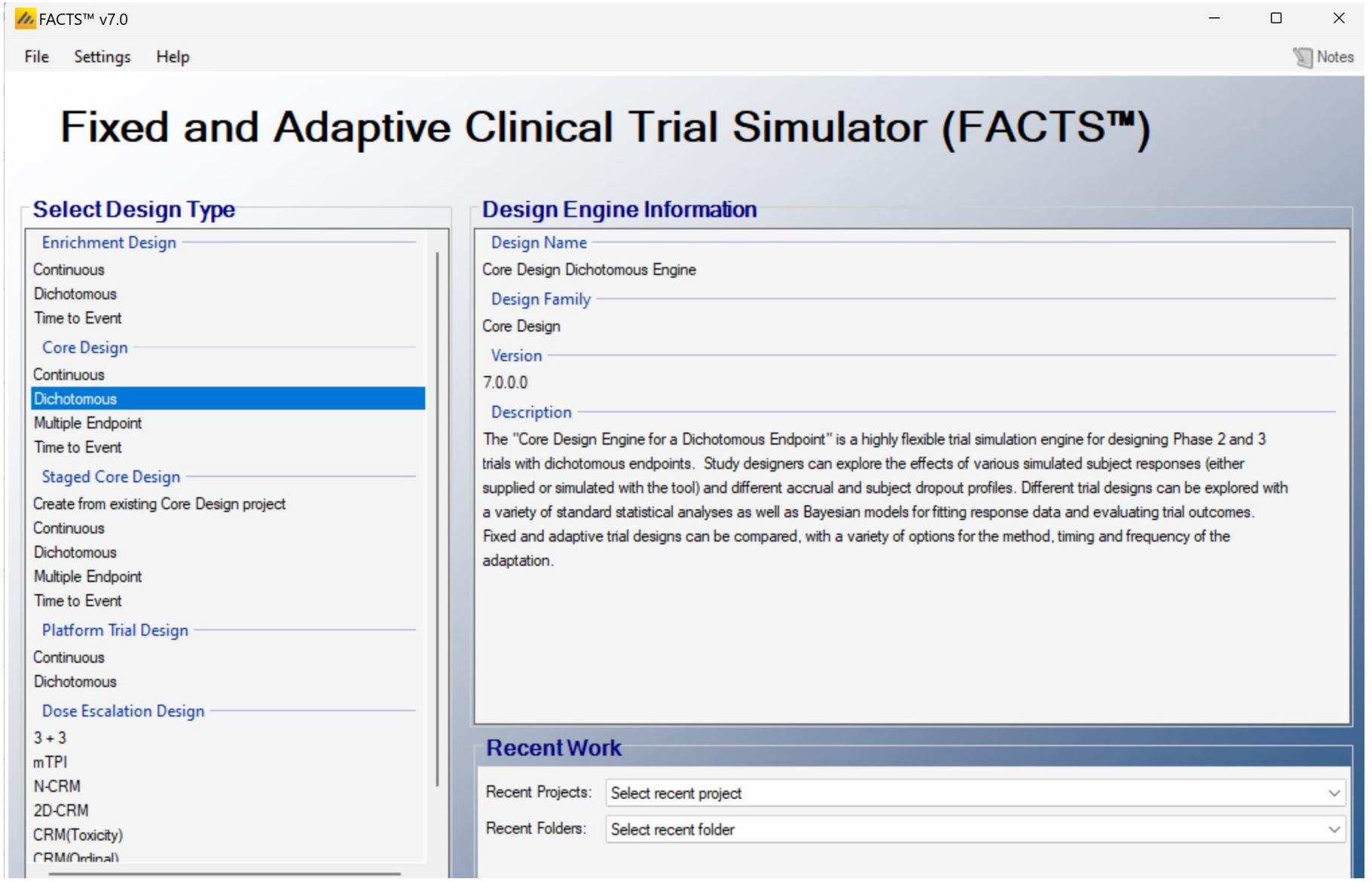


Randomization to any arm or domain may stop for demonstration of superiority, non-inferiority, futility, or harm.

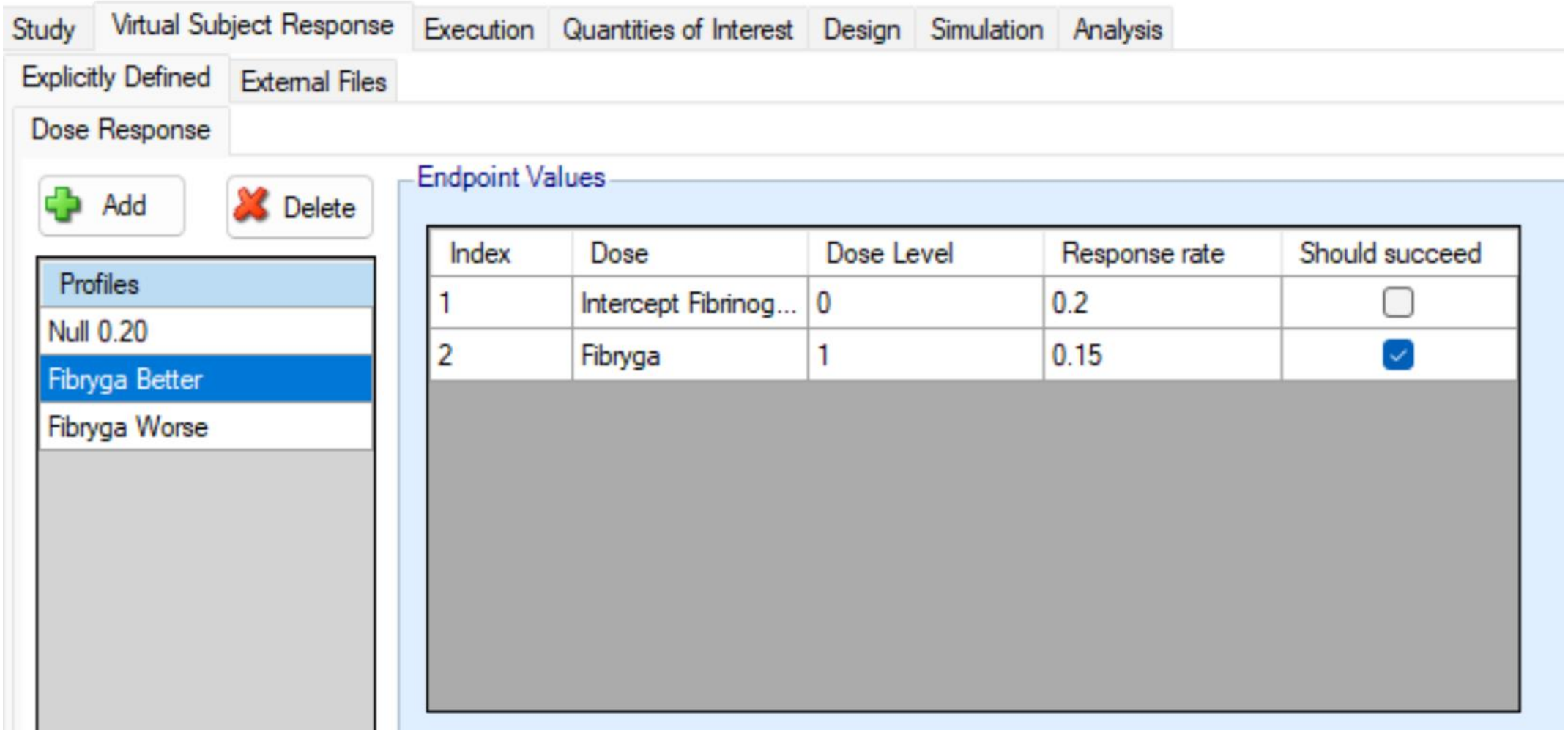
Decision Rules

- 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.,
    - Pr(SUP or NI) > 0.9XX → Stop randomization to arm for success
    - Pr(SUP or NI) < 0.XXX → Stop randomization for futility/lack of efficacy

Design Process: Choosing Thresholds



Design Process: Choosing Thresholds



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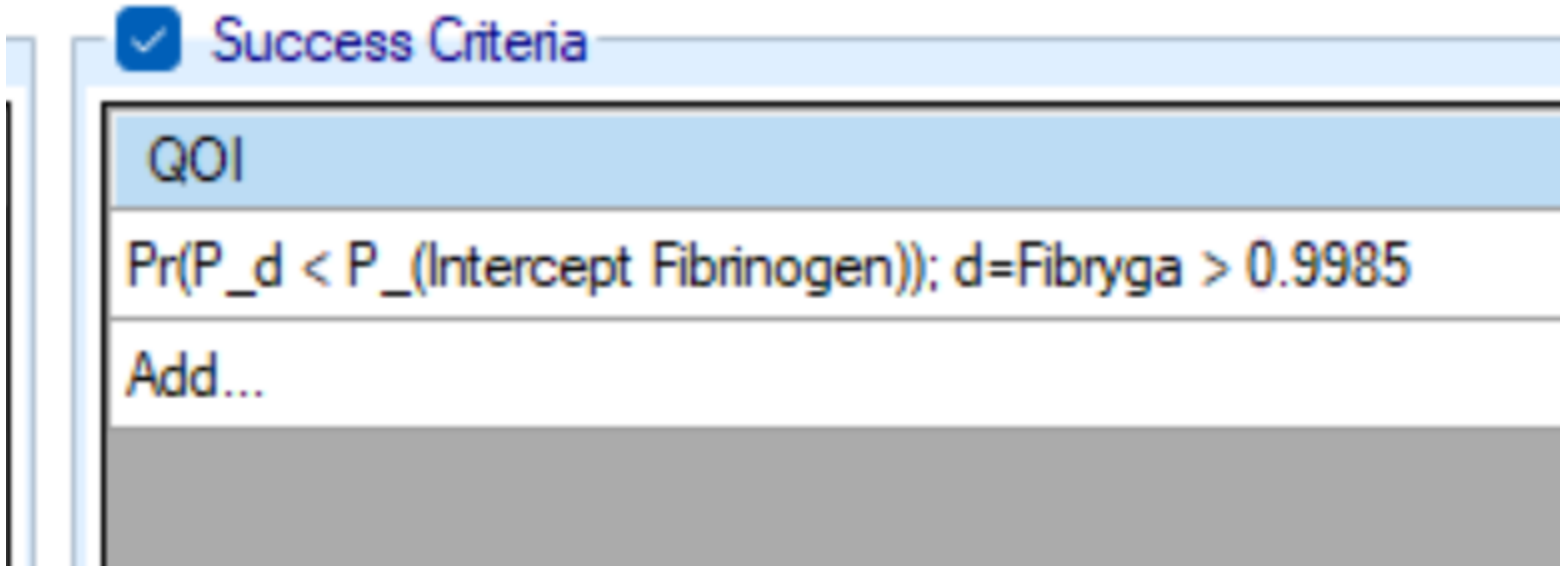
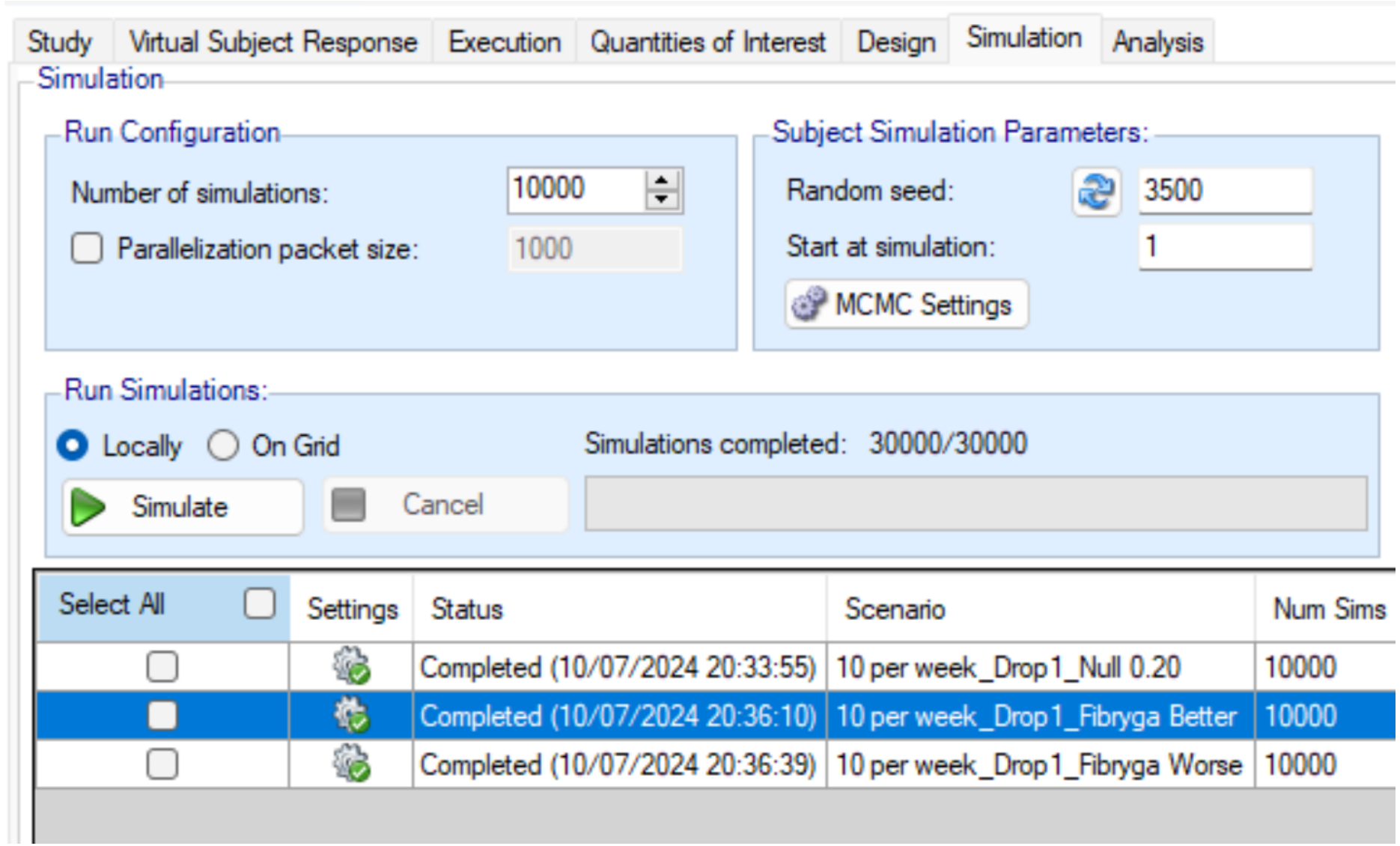


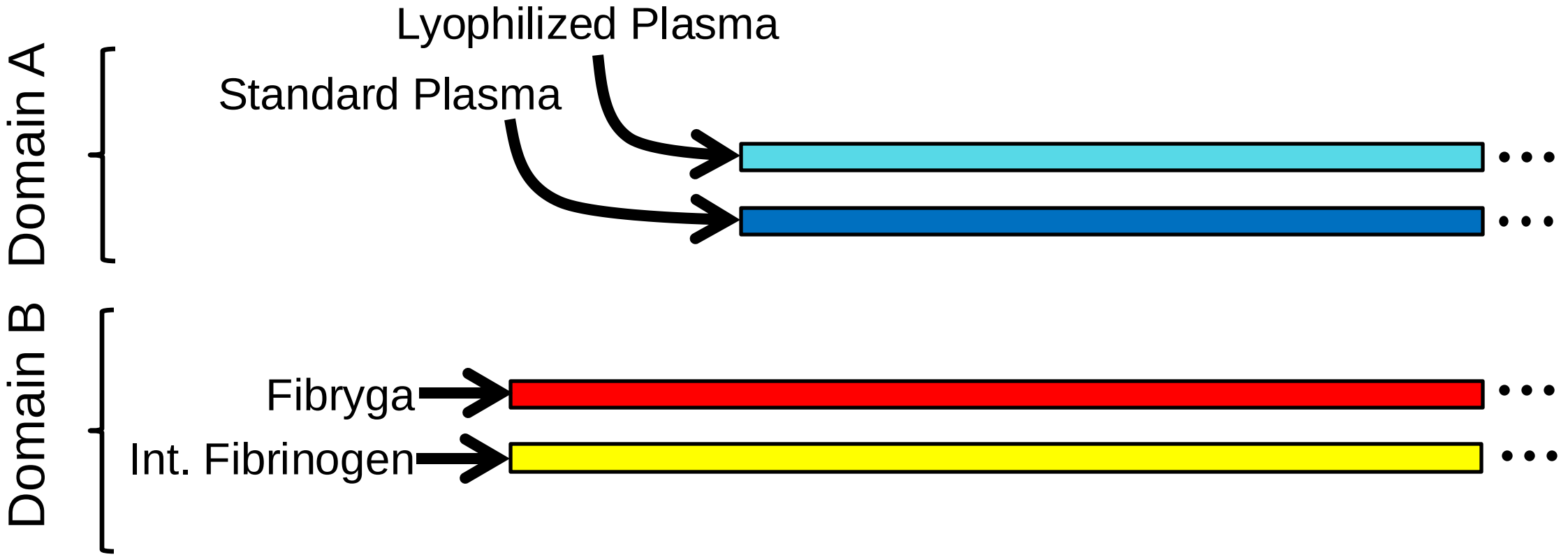
Design Process: Choosing Thresholds



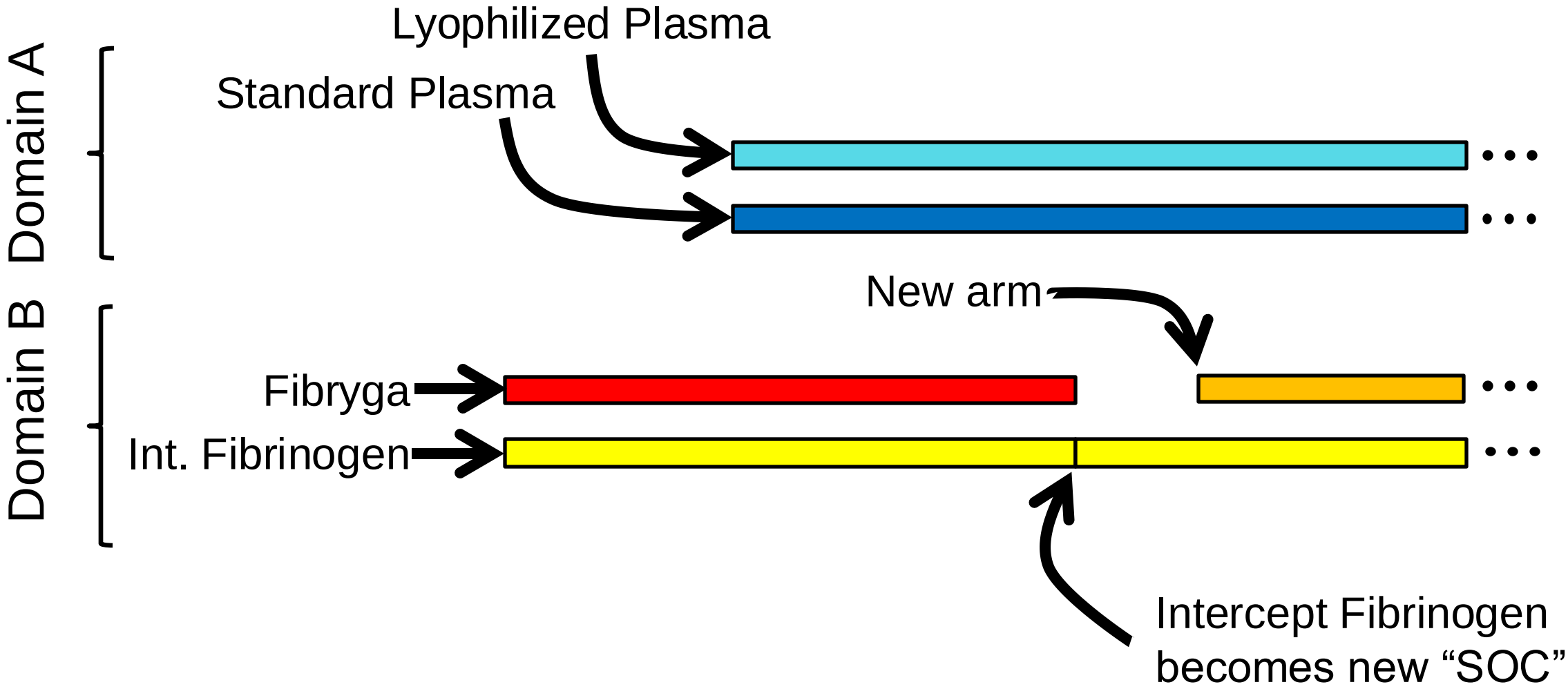
Design Process: Choosing Thresholds

	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

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ADAPTIVE PLATFORM TRIAL DESIGN

TRANSFUSION

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

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Tolles J, Beiling M, Schreiber MA, et al. Transfusion. 2022 Aug;62 Suppl 1:S231-S241.

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ADAPTIVE PLATFORM TRIAL DESIGN

TRANSFUSION

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

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ADAPTIVE PLATFORM TRIAL DESIGN

TRANSFUSION

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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Goldkind SF, Brosch LR, Lewis RJ, et al. Transfusion. 2022 Aug;62 Suppl 1:S255-S265.

Thank you!