When is it appropriate to combine phases

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Calls for “New tools to get

- fundamentally ***better*** answers about how the safety and effectiveness of new products can be demonstrated,
- in ***faster*** time frames,
- with ***more certainty***,
- and ***at lower costs***”

Seamless Phase II/III designs offer great potential for achieving these objectives

PhRMA WGAD White Paper

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Adaptive Seamless Phase II/III Designs— Background, Operational Aspects, and Examples

Seamless Designs: Definition

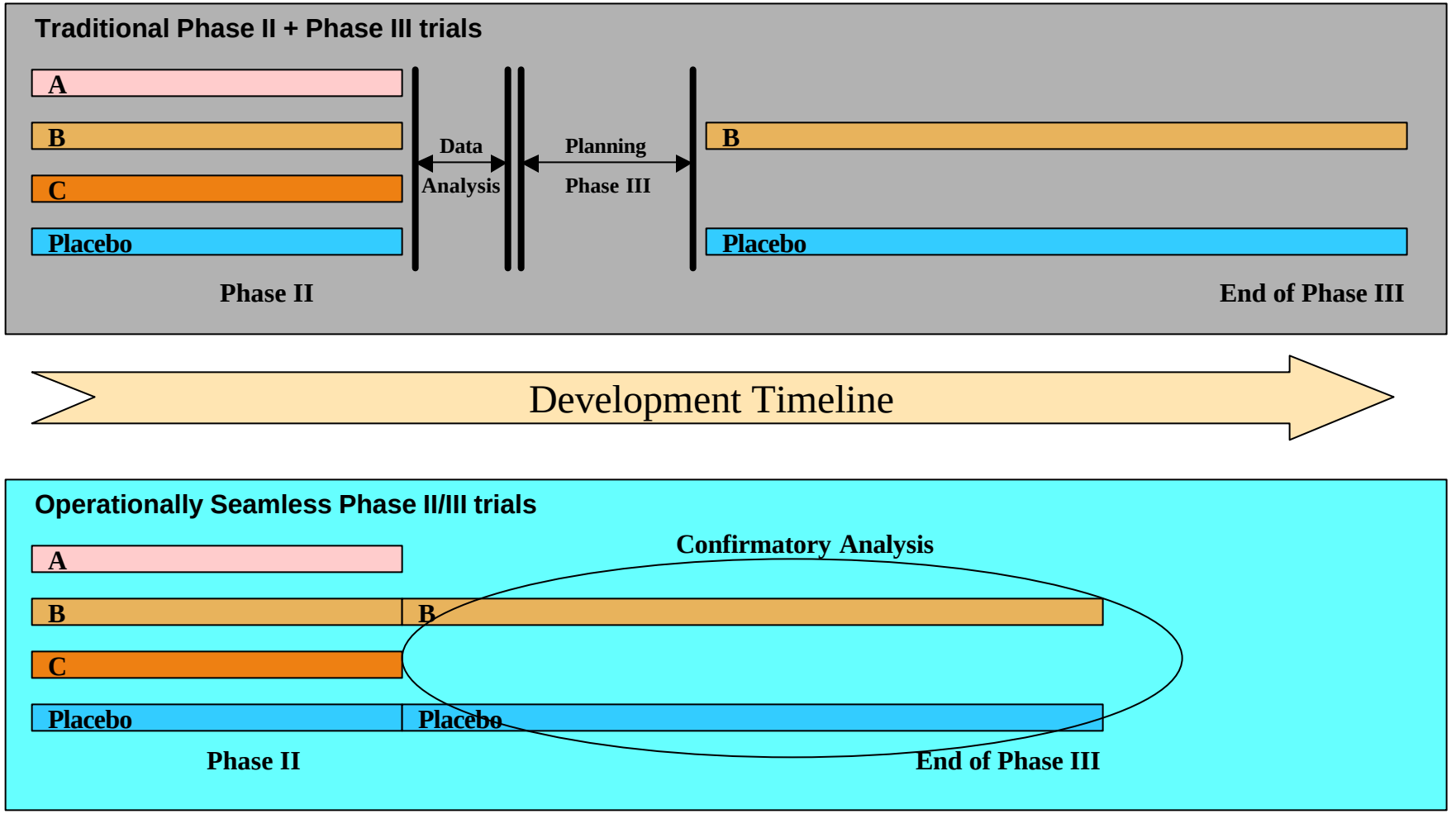
Seamless design

- A clinical trial design that combines into a single trial objectives which are traditionally addressed in separate trials (*operationally* seamless)

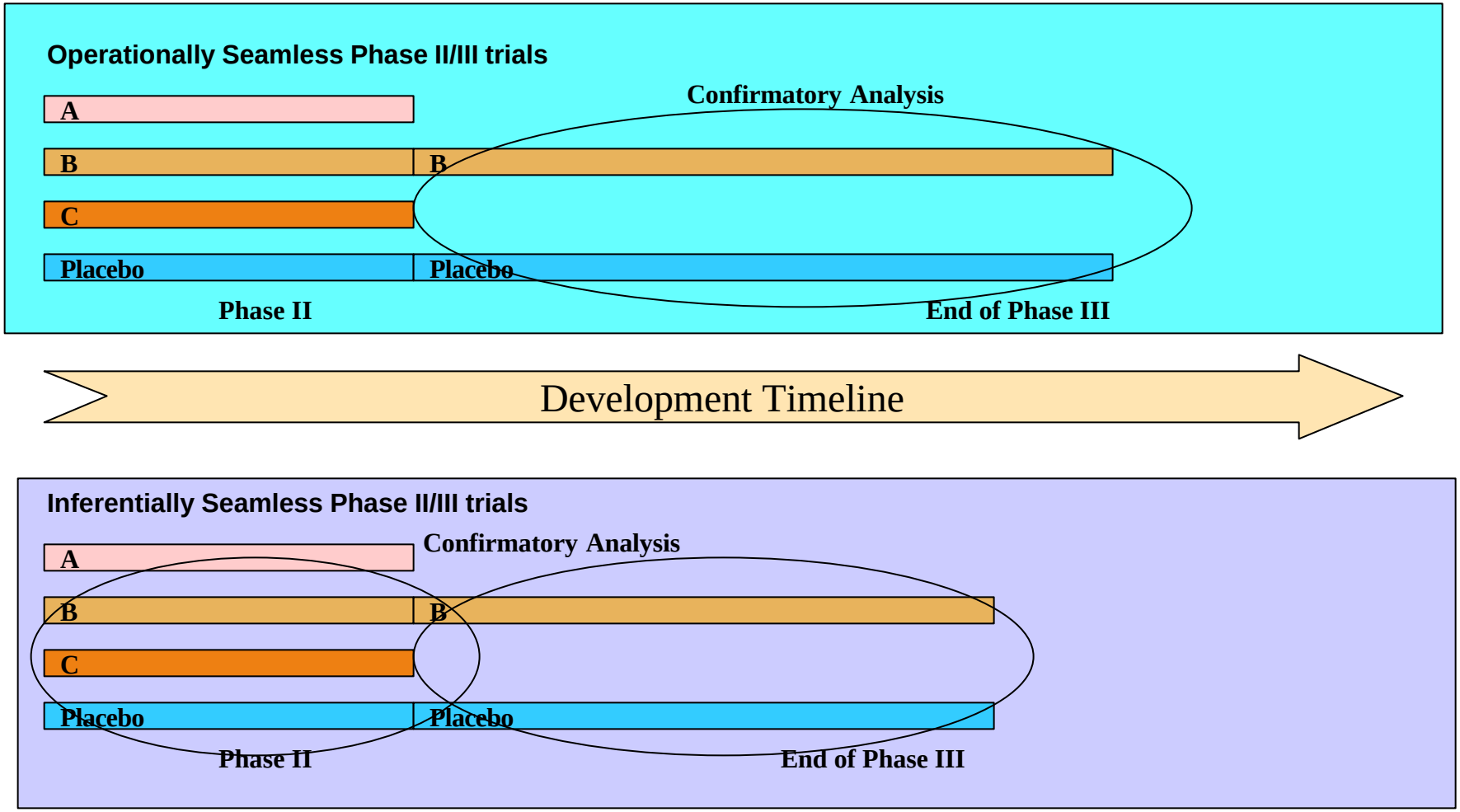
Adaptive Seamless design

- A seamless trial in which the final analysis will use data from patients enrolled before and after the adaptation (*inferentially* seamless)

Faster: Operationally Seamless



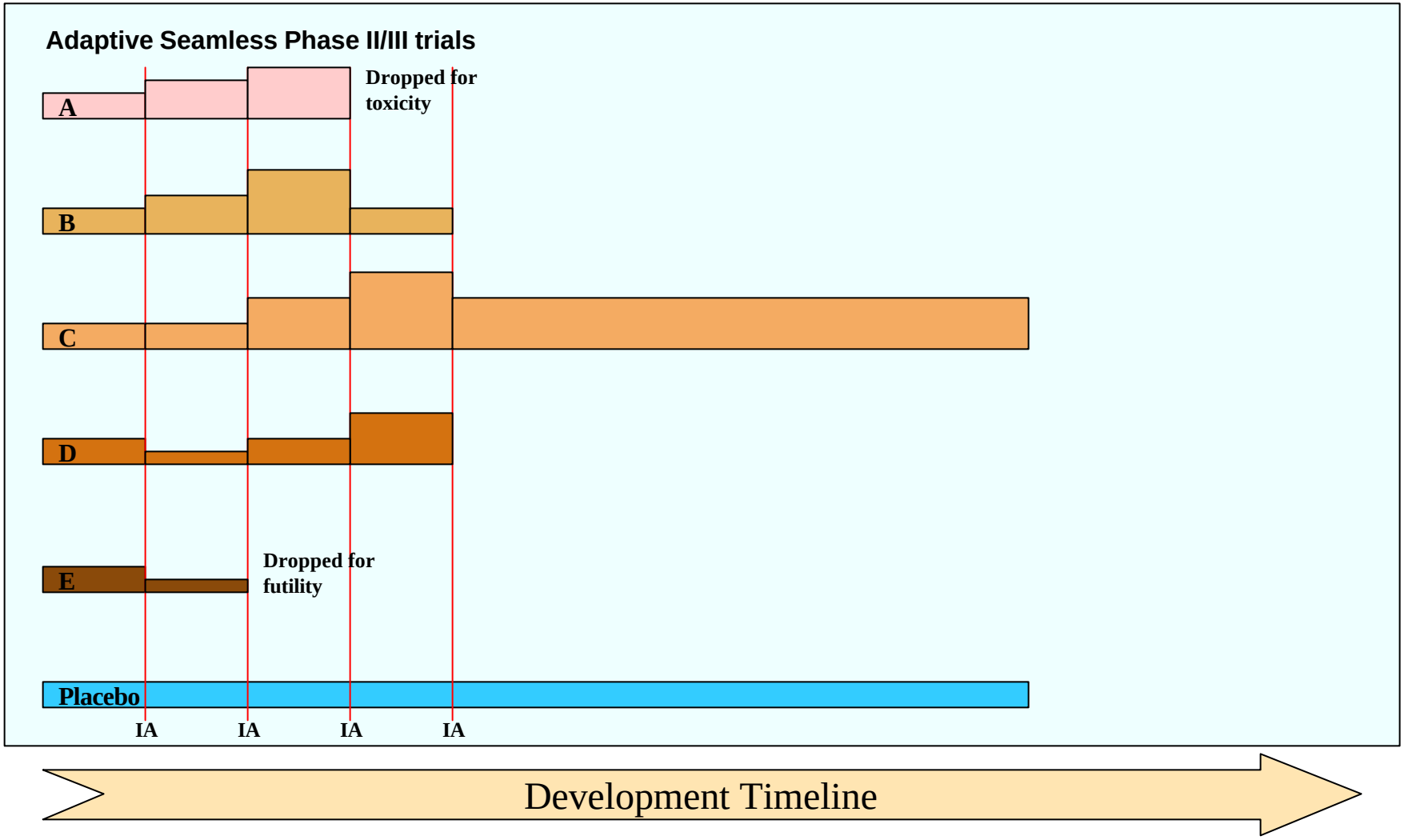
At lower costs: Inferentially Seamless



At lower costs: Inferentially Seamless

- Combining data from the ‘learning’ stage with data from the confirmation stage
  - adds efficiency in using patient data
  - draws stronger conclusions with the same number of exposed patients
  - reduces development time
- 2nd Stage data and the relevant groups from 1st Stage data should be combined in a way that
  - Guarantees the Type I error rate for the comparison with control
  - Produces efficient unbiased estimates and confidence intervals with correct coverage probability

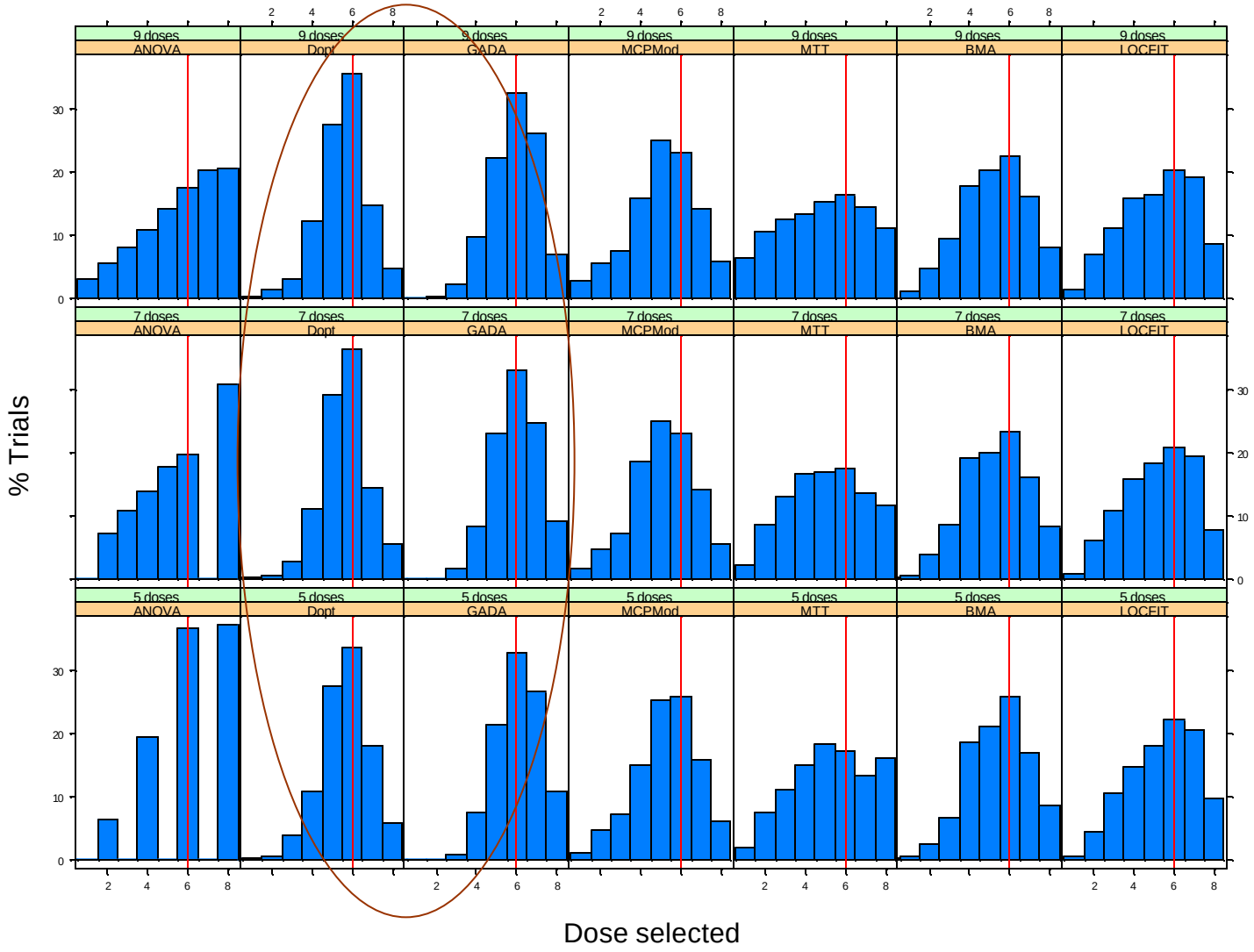
Better: Adaptive Seamless



Better: Adaptive Seamless

- More doses than in traditional Phase II can be used
- Phase II part uses target population
- Treatment selection may be based on a short-term endpoint X, while confirmation stage uses a long-term (clinical) endpoint Y
- Complex relationship between X and Y may improve decision making
  - Include direct effects of treatment on Y not mediated through X
  - And effects of patient covariates on both Y and X
- Adaptive model-based designs in Stage I may improve selection of the target dose for Stage II

More Certainty: Adaptive Dose Ranging



Adaptive dose-ranging methods lead to:

- gains in power to detect DR
- precision to select target dose, and
- to estimate DR

PhRMA ADRS WG White Paper JBS 2007, v 17(6)

Adaptive Seamless Designs

Primary objective – combine "dose selection" and "confirmation" into one trial

- Although dose is most common Phase IIb objective, other choices could be made, e.g. population
- After dose selection, the only change is to new enrollments (patients are generally not re-randomized)
- Patients on terminated treatment groups could be followed
- All data from the chosen group and comparator is used in the final analysis. Appropriate statistical methods must be used

Potential Benefits

- More efficacy/dose information prior to triggering Phase III
  - by response-adaptive treatment allocation, dropping treatment arms
- Reduced development timelines and cost
  - by cutting out the 'white space' between Ph II and Ph III, using the same operational infrastructure
- More safety information on longer term patient exposure
  - by allowing for longer follow-up on patients enrolled in the 1st Stage
- Higher chance of patients within the trial to be treated with efficacious and safe doses
  - by making timely use of available information in the interest of patient benefit

New Challenges

- Drug supply and drug packaging could be more challenging
- Need the final formulation available at the start of the seamless trial
- Challenges regarding data review at the end of ‘learning’ stage
- Decision process may require additional expertise and/or perspective not usually represented on DMCs
- Sponsor involvement in decision making
- Information inferable from the selection decision may impact the operational bias