Adaptive design 101

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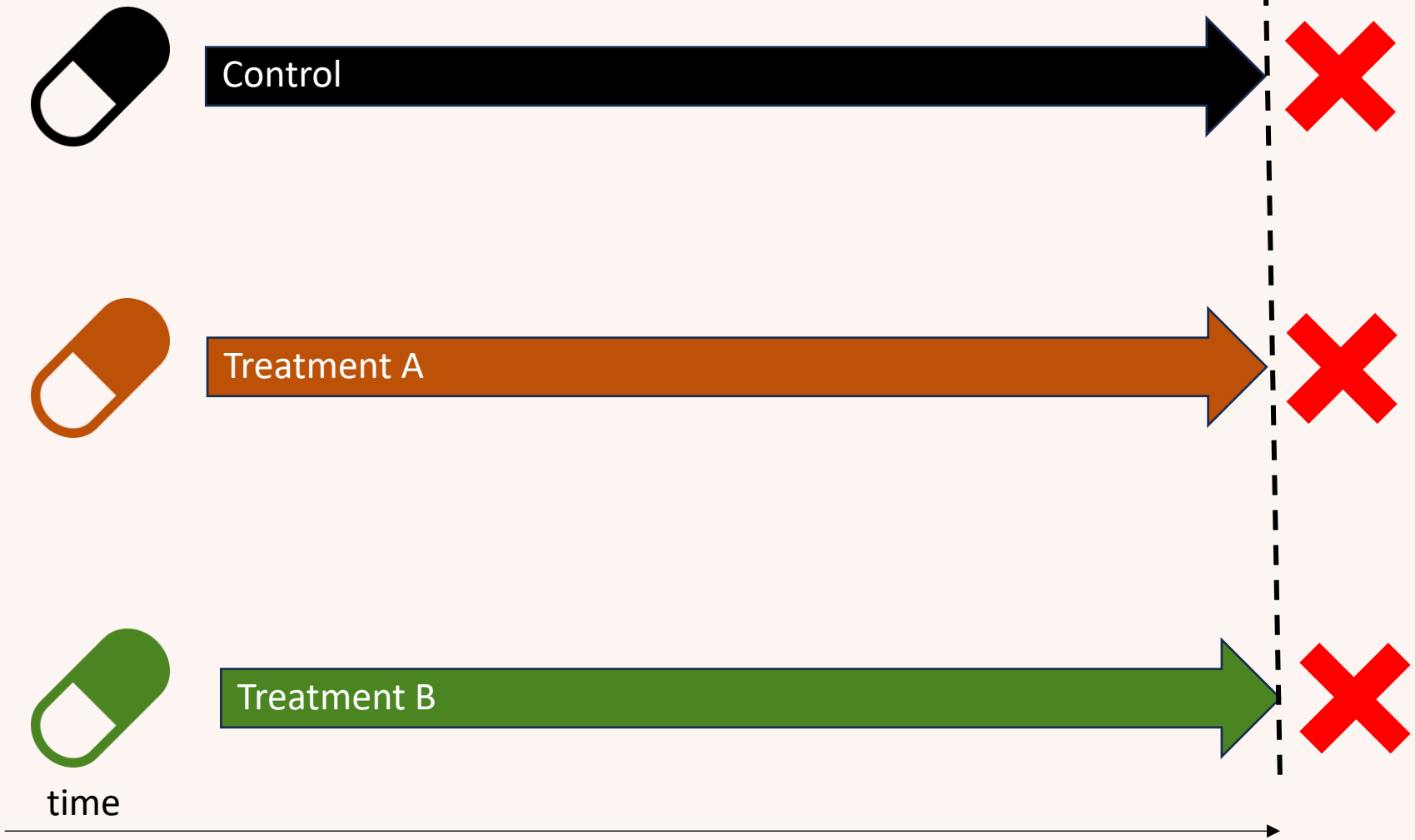
Traditional RCT



Traditional RCT

1. Unexpected result
   - Too good/ too bad
2. Futility
   - Not show difference
3. Guideline change

Control

Treatment A

Treatment B

time

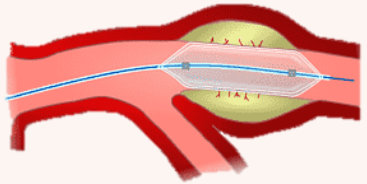
Traditional RCT

Adaptive designs

The Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PHOENIX trial

Patients undergone
1. Urgent PCI
2. Elective PCI

Planned for 10,900



1:1 randomization

Cangrelor

Clopidogrel

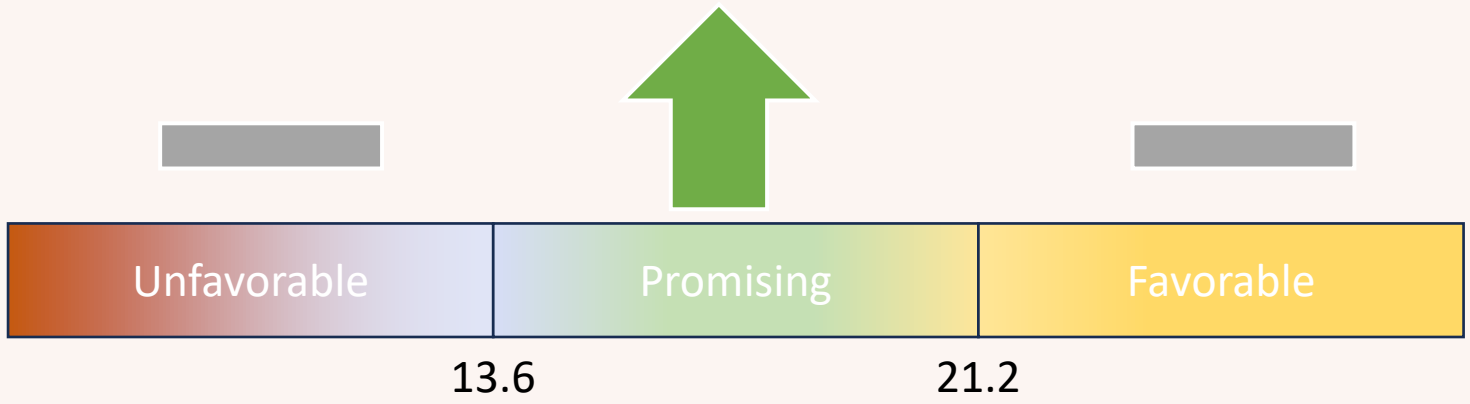
Primary endpoint:

- Composite of
  - Death
  - myocardial infarction
  - ischemia-driven revascularization
  - stent thrombosis within 48 hours after PCI

Permitted possible sample size re-estimation at interim analysis

CHAMPION PHOENIX TRIAL

- Adaptive trial design
  - 70% of enrollment interim analysis
    - Possible early stopping: gamma (−5) alpha spending function defines by O'Brien–Fleming boundaries provided the study with 86% power to detect a 24% lower relative risk, from an event rate of 5.1% in the control group to an event rate of 3.9% in the experimental-therapy group.
    - Sample size re-estimation:
      - Observed percentage lowering in relative risk



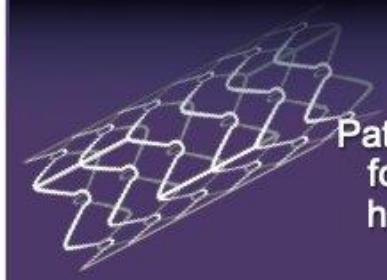
UNIVERSITÀ degli STUDI di CATANIA

CHAMPION-PHOENIX

RCT

Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events

INDUSTRY-FUNDED, DOUBLE-BLIND, MULTICENTER, SUPERIORITY RANDOMIZED TRIAL



10,942 Patients undergoing PCI for CCS or ACS who had not been treated with clopidogrel

	Cangrelor (clopidogrel 600 mg at the end of the infusion)	**Clopidogrel** (300/600 mg before or after the start of PCI)
	N=5,472	N=5,470
Death, MI, or ischemia-driven revascularization or ST (48 hours)	**4.7%**	**5.9%**
	Odds ratio 0.78; 95% CI 0.66 to 0.93; P=0.005 (mITT)	
Severe bleeding	**0.2%**	**0.1%** P=0.44

Cangrelor significantly reduced the rate of ischemic events with no significant increase in severe bleeding

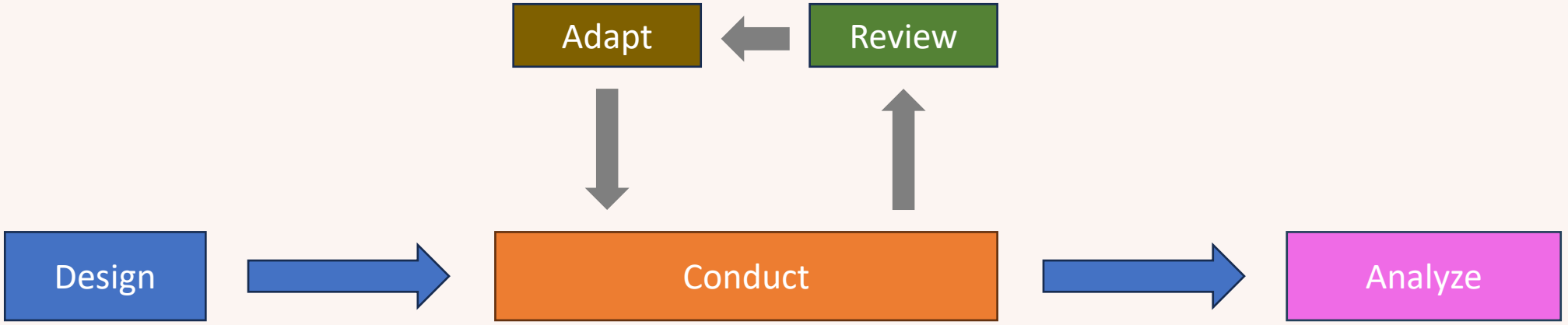
Bhatt DL, et al. N Engl J Med 2013; 368:1303-1313

Adaptive design

- Clinical trial that allow modification to trial or statistical procedures
- “Planning to be Flexible”
- More flexible, efficient and fast
- Pre plan changed

Traditional design

Adaptive design



Pre-planned changes

- Refining the sample size
- Abandoning treatments or doses
- Changing the allocation ratio of patients to trial arms
- Identifying patients most likely to benefit and focusing recruitment efforts on them
- Stopping the whole trial at an early stage for success or lack of efficacy.

- (But not limit to these)

Major type of adaptive designs

1. Group Sequential Design
2. Adaptive Dose-Finding Design
3. Adaptive Randomization Design
4. Multi-Arm Multi-Stage (MAMS) Design
5. Bayesian Adaptive Design

Group Sequential Designs

Definition

This design allows the trial to be stopped early at interim stages for efficacy, futility, or safety concerns.

How it work?

Pre-planned interim analyses are conducted at multiple stages to evaluate the trial’s progress.

Uses statistical methods like the O'Brien–Fleming or Pocock boundaries to determine if the trial should continue or stop.

Stopping rules!!

Group Sequential Designs

- **Definition:** This design allows the trial to be stopped early at interim stages for efficacy, futility, or safety concerns.
- **How It Works:** Pre-planned interim analyses are conducted at multiple stages to evaluate the trial’s progress.
- **Stopping Rules:** Uses statistical methods like the O'Brien–Fleming or Pocock boundaries to determine if the trial should continue or stop.

Group Sequential Designs

Pro

- Faster access to results.
- Ethical (fewer patients exposed to ineffective or harmful treatments).
- Reduces trial duration and costs

Con

- Requires careful planning of interim analyses.
- Potential for misleading results if not well-designed.

Adaptive Dose-Finding Designs

- Definition: Primarily used in Phase I/II trials to determine the optimal dose of a drug. The dose is adjusted based on accumulating safety and efficacy data.

- How It Works: This design uses data from early participants to modify the doses given to later participants.

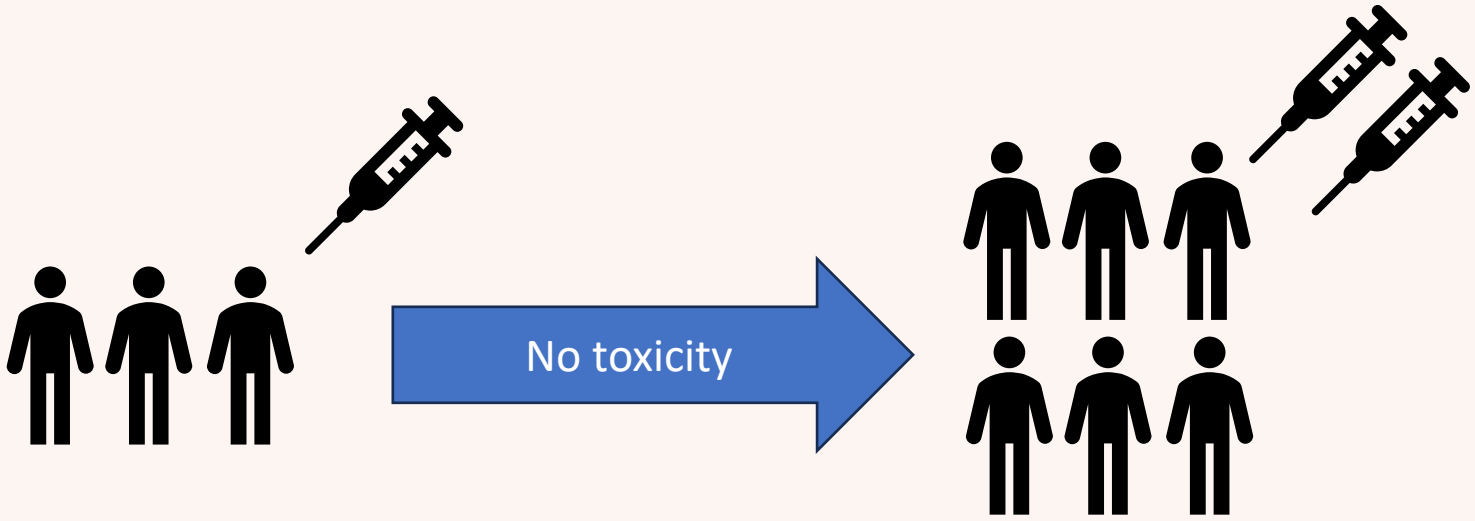
- Methods: The 3+3 dose-escalation method and model-based approaches like the Continual Reassessment Method (CRM).

Rule-based

Model-based

3+3 dose-escalation method

- A traditional, rule-based approach used in early-phase trials to find the maximum tolerated dose



3+3 dose-escalation method

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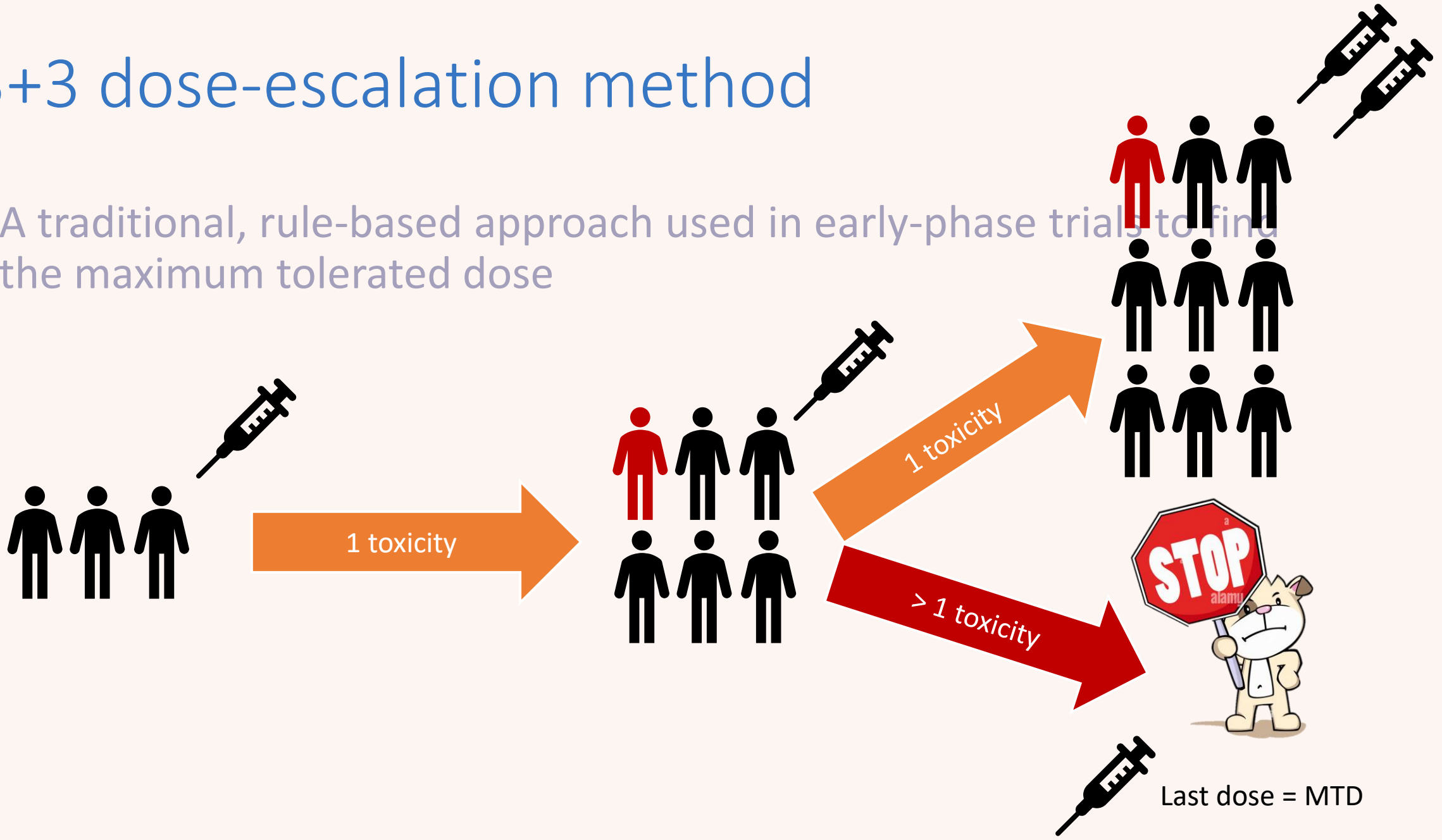
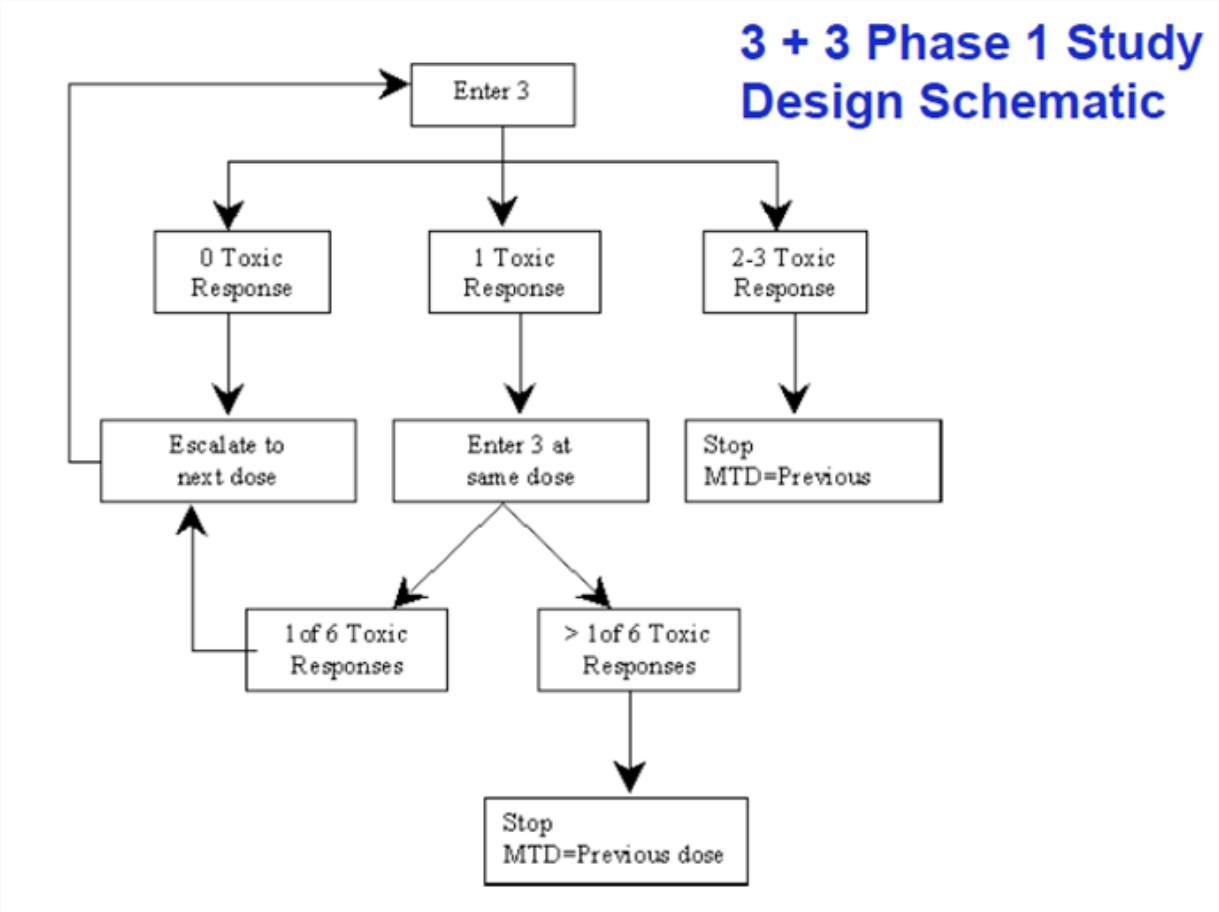


3+3 dose-escalation method

- A traditional, rule-based approach used in early-phase trials to find the maximum tolerated dose

Last dose = MTD

3+3 dose-escalation method



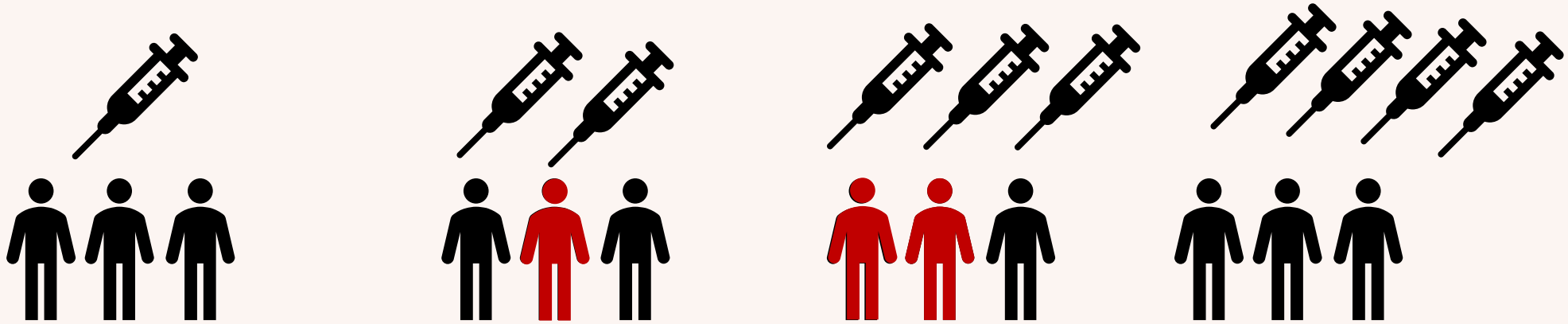
3+3 dose-escalation method

- Advantages:
  - Simplicity: Easy to implement and widely used in oncology and early drug development.
  - Safety-Oriented: Reduces the risk of exposing too many patients to high, potentially toxic doses.

- Disadvantages:
  - Inefficiency: It may take many cycles to find the correct dose, prolonging the trial.
  - Dose-Finding Limitations: It does not provide much information about the relationship between dose and efficacy/toxicity. The dose escalation decisions are based on a small number of patients, which can lead to variability and suboptimal dose selection.

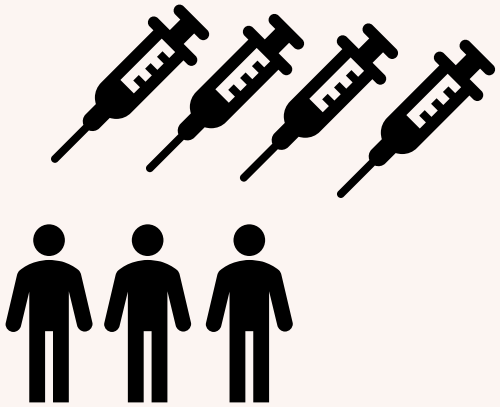
Continual Reassessment Method

- CRM itself is an adaptive design
- Statistical method



Continual Reassessment Method

- model is updated with the observed outcomes
- Based on the updated data, the CRM recalculates the DLT probability for each dose level.
- The next cohort of patients is assigned the dose that the model predicts is closest to the MTD, with the goal of efficiently finding this dose with fewer patients exposed to suboptimal doses.



Continual Reassessment Method Compare to 3+3

- Efficiency:
  - CRM is more efficient than traditional methods like the 3+3 design because it continuously refines the dose-toxicity relationship.
  - It can more quickly home in on the MTD, reducing the number of patients needed and minimizing their exposure to unsafe or ineffective doses.

- Flexibility:
  - CRM can adapt as the trial progresses, meaning the dose escalation or de-escalation decisions are made dynamically based on real-time data rather than rigid rules.

Adaptive Dose-Finding Designs

- 3+3 method
- And use data from 3+3 to construct model of CRM

Pro

- Quickly identifies the optimal dose.
- Reduces exposure to harmful doses.
- Improves patient outcomes by refining doses during the trial

Con

- May require more complex statistical models.
- More logistical planning for real-time dose adjustments

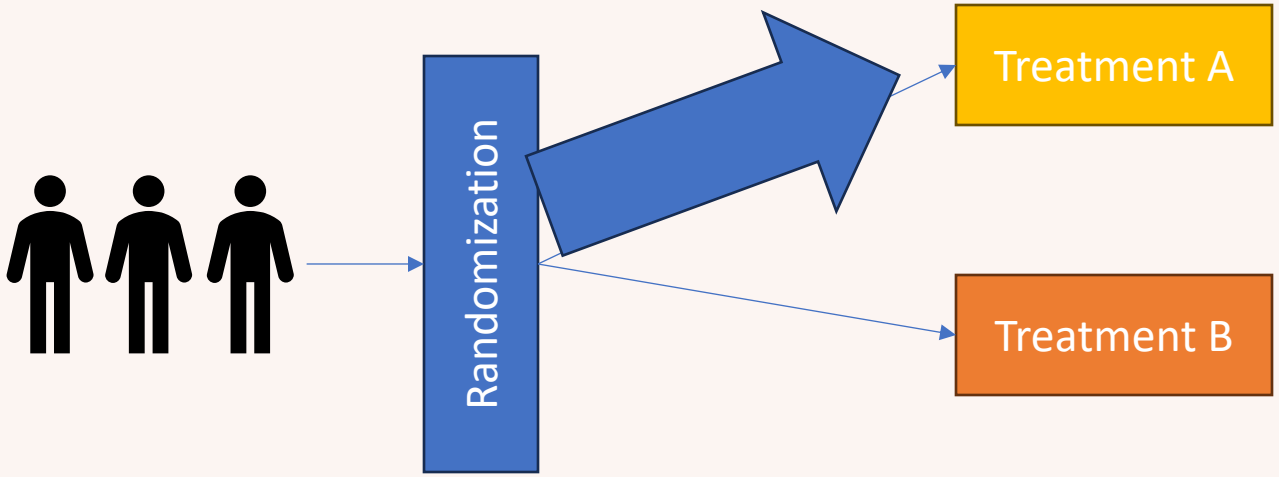
Adaptive Randomization Designs

- **Definition:** Adjusts the randomization ratio based on the ongoing results, favoring more effective treatments.

- **How It Works:** As data accumulates, patients are preferentially assigned to treatment arms that are showing greater efficacy. Methods include Response-Adaptive Randomization (RAR) and Covariate-Adaptive Randomization (CAR).

Response-Adaptive Randomization (RAR)

- Adaptive design



Response-Adaptive Randomization (RAR)

Pro

- Increases the likelihood that participants receive the more effective treatment.
- Ethically preferable (more patients benefit from better treatments).
- More efficient use of trial resources.

Con

- Complex to manage and analyze.
- May introduce bias if not carefully controlled.

Covariate-Adaptive Randomization (CAR)

- Adaptive design
- randomization based on specific baseline characteristics, or covariates, such as age, gender, disease severity, or genetic markers

- Continuous Adjustment:
  - If one group becomes imbalanced with respect to a certain covariate

Covariate-Adaptive Randomization (CAR)

Pro

- Balanced Treatment Groups
  - Ensures that important covariates are evenly distributed
- Enhanced Statistical Power
  - Controlling for confounding variables
- Customizable: CAR allows the trial to be tailored to the specific needs of the population being studied

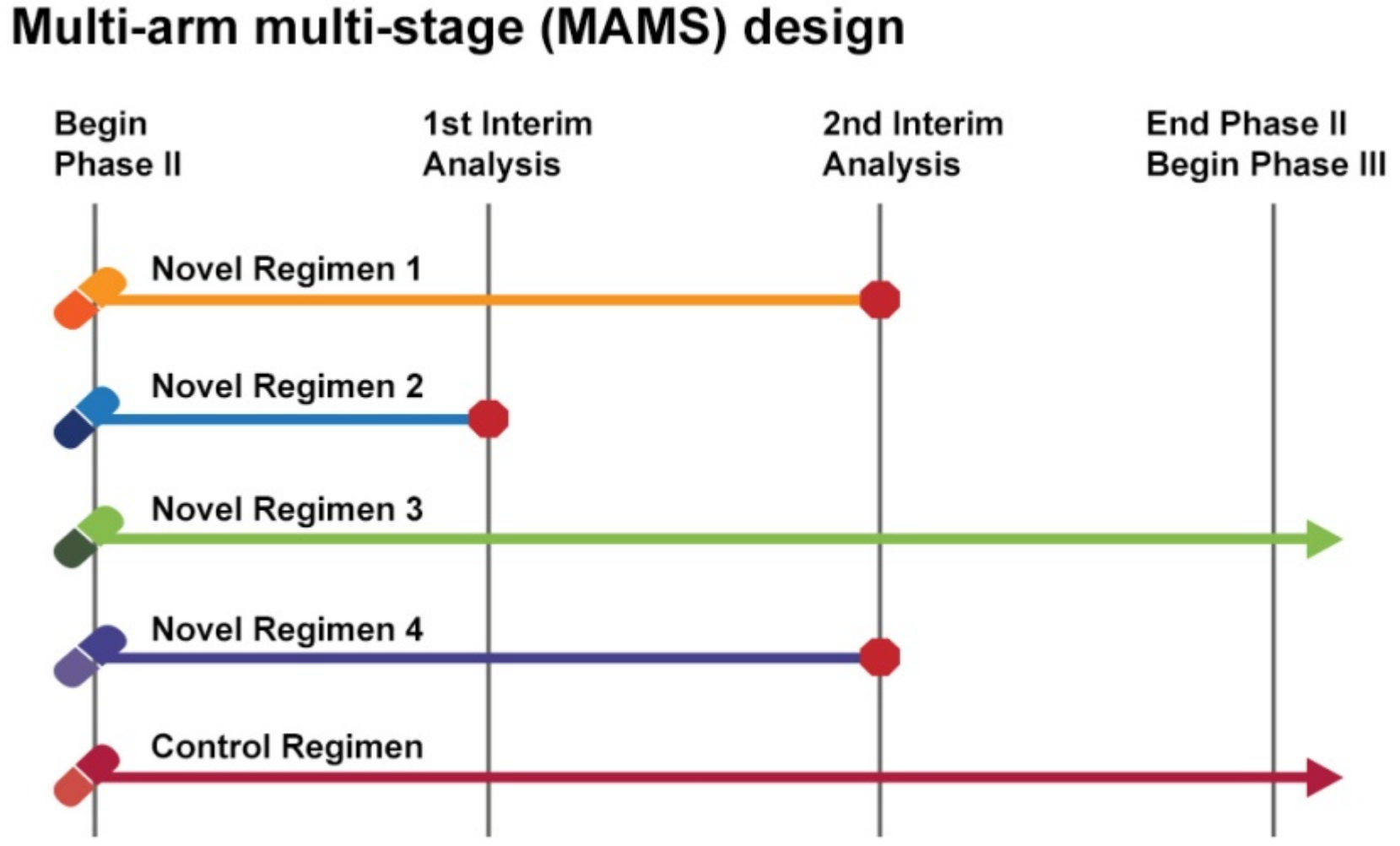
Con

- Increased Complexity: More complex than simple randomization, requiring careful planning and analysis to ensure covariate balance is achieved.
- Potential Overfitting: If too many covariates are used, it could lead to overfitting and reduce the generalizability of the trial results.

Multi-Arm Multi-Stage (MAMS) Design

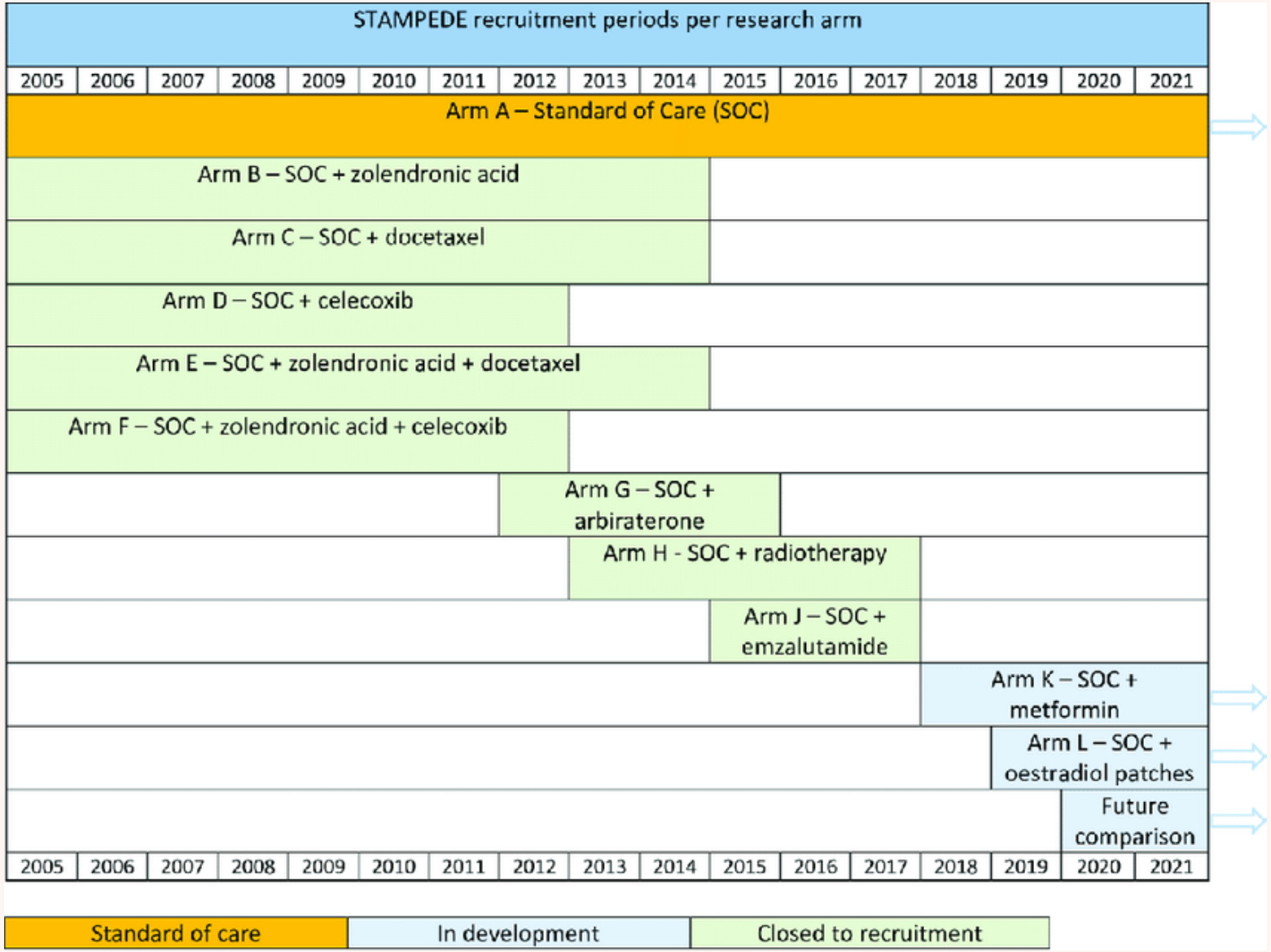
- adaptive trial design
- allows multiple treatments to be tested simultaneously (multi-arm)
- evaluated at interim stages (multi-stage) to drop, add, or continue treatments based on the results.

Multi-Arm Multi-Stage (MAMS) Design



Example

STAMPEDE trial




THANK
YOU