A Checklist for Planning Simulations When Designing a Bayesian Adaptive Randomized Controlled Trial

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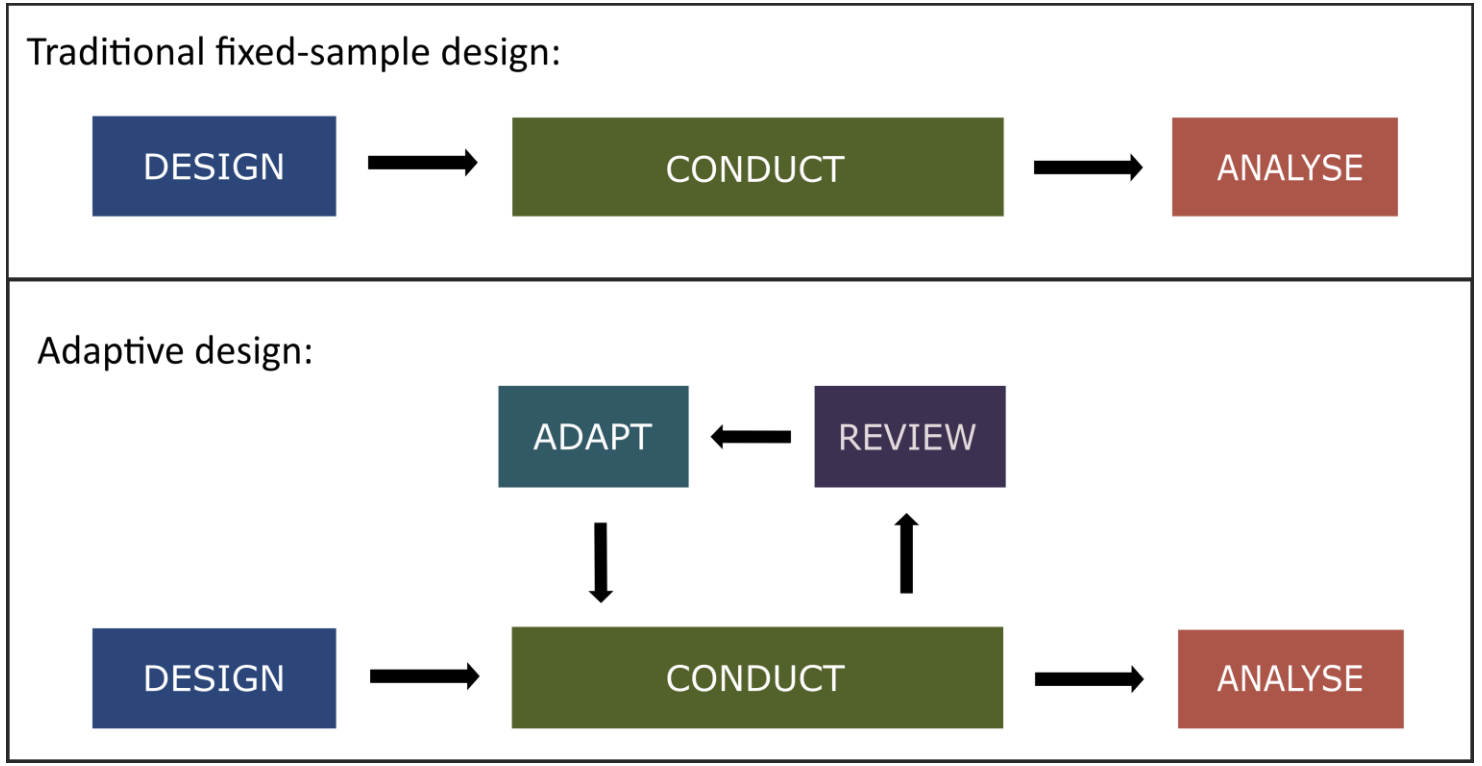
Outline

- Adaptive Randomized Controlled Trials (RCTs)
- A checklist for planning simulations of a Bayesian Adaptive RCT
- Application: Planning RCT of a flu vaccine

Adaptive RCTs

- Adaptive RCTs are growing in popularity.
  - Improved efficiency
  - Increased chance that participants receive an efficacious intervention



(Pallmann et al., 2018)

Adaptive RCTs are still not widely applied

Statistics
in Medicine

Special Issue Paper

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Bayesian adaptive clinical trials: a dream for statisticians only?

Sylvie Chevret[a,b,c*†]

- Perceived complexity of methods
- Absence of established standards for design, analysis and reporting
- Requires extensive simulations to calculate Type I and Type II errors

Chevret, Sylvie. “Bayesian adaptive clinical trials: a dream for statisticians only?.” Statistics in medicine vol. 31,11-12 (2012): 1002-13.

A checklist for planning simulations

1	Identify the interventions and outcomes of interest
2	Define the criteria to be evaluated to answer the objectives of the trial
3	Specify the number of interim analyses and the decision rules to be used
4	Enumerate possible outcomes at each interim analysis and the final analysis
5	Determine the prior distributions for each unknown parameter
6	Determine the range of the feasible sample size and the initial allocation ratio
7	Specify the definition of the Type I and Type II errors and their desired values
8	Specify the simulation settings and statistics to be monitored

Application of checklist to DEFINE trial

Objective: Compare 3 influenza vaccines

- Standard Dose (SD) vs High Dose (HD) vs Adjuvant (ADJ) in people with rheumatoid arthritis

Previous study: (Colmegna et al., 2020)

- Efficacy: HD > SD
- Safety: HD = SD

Motivation:

- SD is covered by the public health system. The cost of HD is significant.
- Adjuvant vaccine would be less expensive than HD

Colmegna, Inés, et al. "Immunogenicity and safety of high-dose versus standard-dose inactivated influenza vaccine in rheumatoid arthritis patients: a randomised, double-blind, active-comparator trial." *The Lancet Rheumatology* 2.1 (2020): e14-e23.

#1. Identify the interventions and outcomes of interest

- 3 interventions → 3 arms at the start of the trial
  - SD vs HD vs ADJ

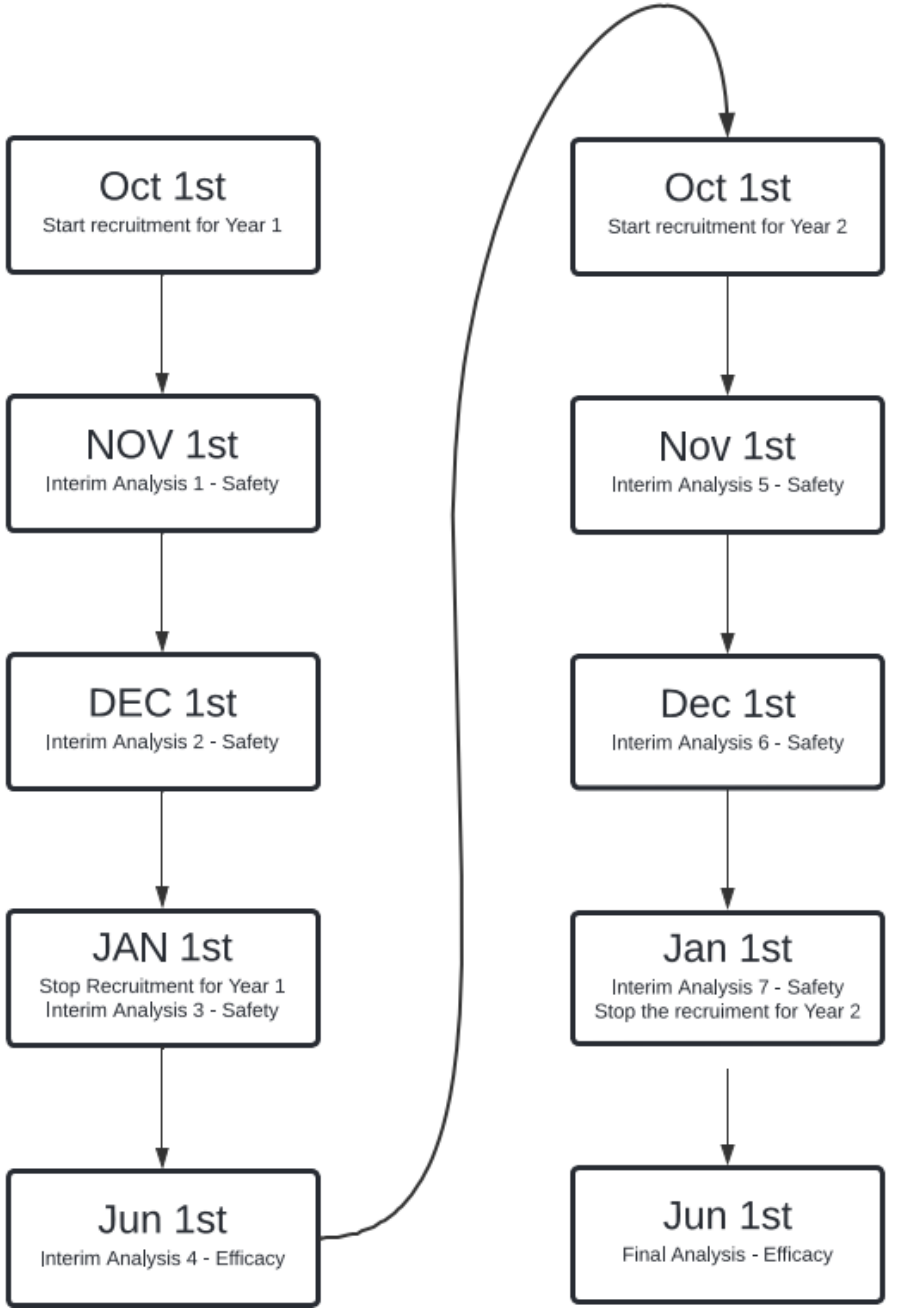
- 2 outcomes of interest
  - Safety was measured in terms of the risk of flares
  - Efficacy was measured in terms of the risk of seroconversion
    - Superiority of ADJ vs SD
    - Non-inferiority of ADJ vs HD

#2. Define the criteria to be evaluated to answer the objectives of the trial

Outcome	Success	Futility
Safety	$P(p_{Flares,ADJ}/p_{Flares,SD} \geq 3) < 0.025$ $P(p_{Flares,ADJ}/p_{Flares,HD} \geq 3) < 0.025$	$P(p_{Flares,ADJ}/p_{Flares,SD} \geq 3) > 0.975$ $P(p_{Flares,ADJ}/p_{Flares,HD} \geq 3) > 0.975$
Efficacy - Superiority (ADJ vs. SD)	$P(p_{SCR,ADJ} - p_{SCR,SD} > 0) > 0.975$	$P(p_{SCR,ADJ} - p_{SCR,SD} > 0) < 0.025$
Efficacy - Non-inferiority (ADJ vs. HD)	$P(p_{SCR,ADJ} - p_{SCR,HD} > -0.1) > 0.975$	$P(p_{SCR,ADJ} - p_{SCR,HD} > -0.1) < 0.025$

- Efficacy criteria are inspired by CBER guidelines for vaccine RCTs, which are specified in terms of 95% confidence intervals.
- The probabilities are estimated using posterior distributions available at the interim or final analysis.

#3. Specify the number of interim analyses and the decision rules to be used



#3. Specify the number of interim analyses and the decision rules to be used (Continued)

- If Safety ADJ < Safety SD or Safety HD

  => ADJ arm dropped

- If Efficacy ADJ > Efficacy SD at Year 1 interim analysis

  => SD arm dropped for Year 2

- If Safety and Efficacy criteria are not met in Year 2

  => Trial inconclusive

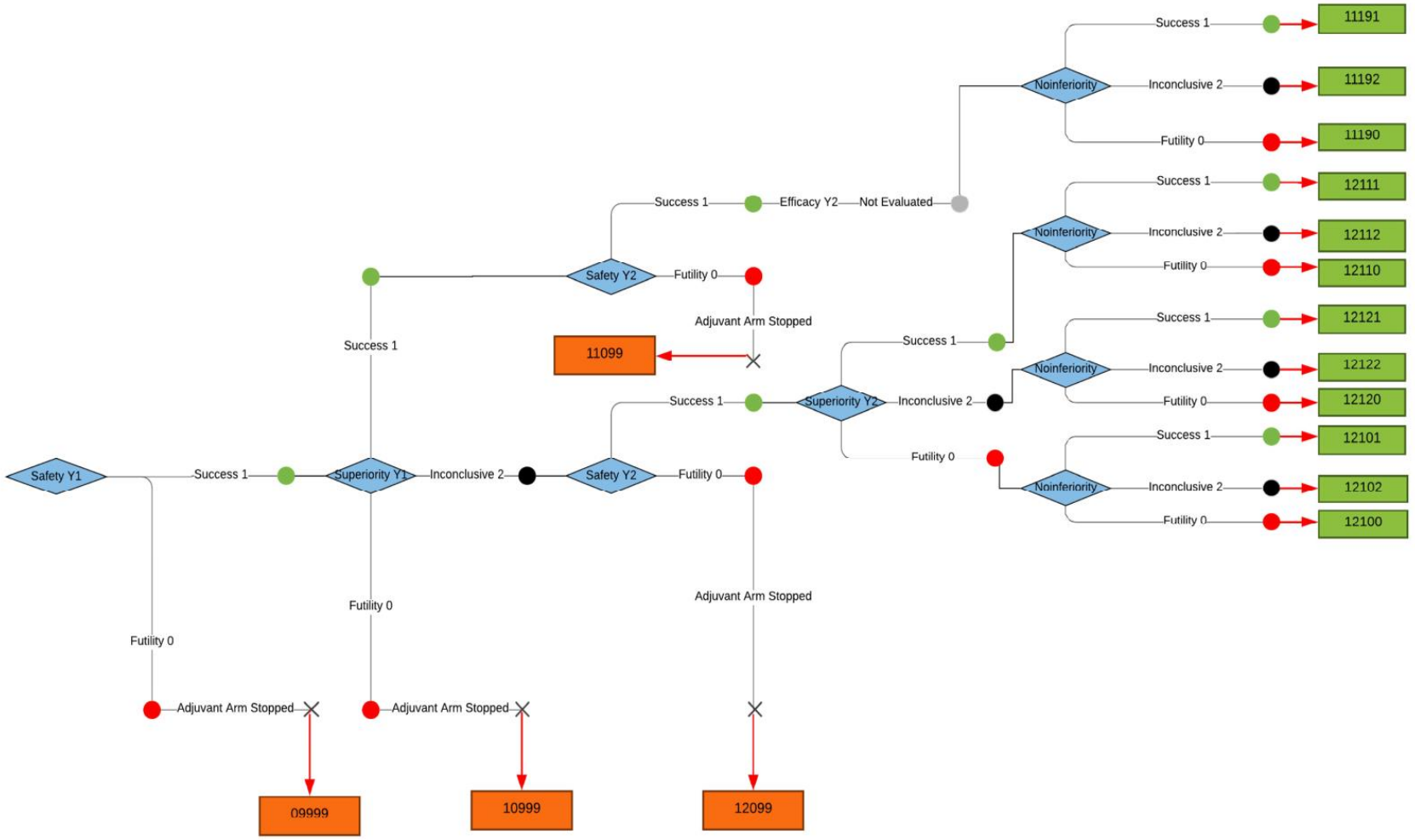
#4. Enumerate possible outcomes at each interim analysis and the final analysis

- A 5-dimensional vector was defined to capture outcomes among interim analyses
- Each element in the vector can take 4 values:
  - Futility (0), Success (1), Inconclusive (2), Not evaluated (9)

$$V_{outcome} = \begin{pmatrix} \text{Safety}_{\text{Y1}} \\ \text{Superiority}_{\text{Y1}} \\ \text{Safety}_{\text{Y2}} \\ \text{Superiority}_{\text{Y2}} \\ \text{Noninferiority} \end{pmatrix}$$

#4. Flow diagram all possible outcomes (Continued)

- We found that our 5-dimensional vector can take 16 possible values considering the different possible adaptations.
- Of these 16 possible values, 4 involve dropping the ADJ arm.



#5. Determine the prior distribution for each unknown parameter

- To limit the influence of previous study results, we used a mixture prior for the efficacy parameters with equal weight for
  - Information from the previous study.
  - Low-information prior distributions.
- For other parameters, we used low-information prior distributions.

		High dose	**Standard dose**
Efficacy	Seroconversion risk	22.5% (15.8%, 30.3%)	8.8% (4.6%, 14.9%)
	Beta distribution	Beta (28.6, 97.7)	Beta (10.6, 106.2)
Safety	Flares risk	5% (1%, 9%)	5% (1%, 9%)
	Beta distribution	Beta (3.5, 84.1)	Beta (3.5, 84.1)

#6. Determine the range of the feasible sample size and specify the allocation ratio

- The feasible sample size may be determined by budget, ease of recruitment, etc.
  - Frequentist sample size calculation is a useful starting point.
  - It was expected that each participating centre contributed 100 subjects. We set a Minimum sample size=100.
  - We set a Maximum sample size=1000 to respect the budget.
- The planned allocation ratio in the 1st year was 1:1:1 for SD: HD: ADJ

#7. Define the Type I and Type II errors and their desired values

- Defining Type I error for ADJ vs SD (superiority):

  P(ADJ > SD | ADJ = SD)
  = P(ADJ > SD | ADJ = SD = 0.08)

- Defining Type II error for ADJ vs SD (superiority):

  P(ADJ <= SD | ADJ > SD)

  = P(ADJ <= SD | ADJ = 0.15, SD = 0.08)

- Desired values
  - Type I error = 0.05, Type II error = 0.2

#8. Specify the simulation settings and the statistics to be monitored

- # of simulated adaptive RCTs (N_S) = 1000
- # of posterior samples in each RCT (N_P) = 10000
- Statistics to be monitored
  - Is the criterion for superiority met in a given trial?

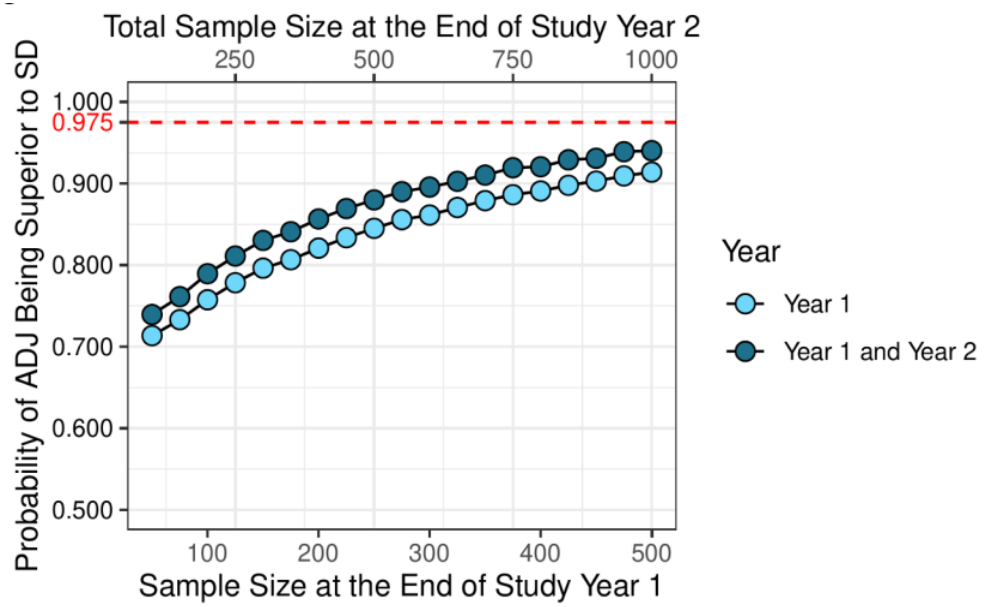
$$\frac{\#\ of\ posterior\ samples\ with\ p_{SCR,ADJ} > p_{SCR,SD}}{N_P} > 0.975$$

- Type I or Type II error?

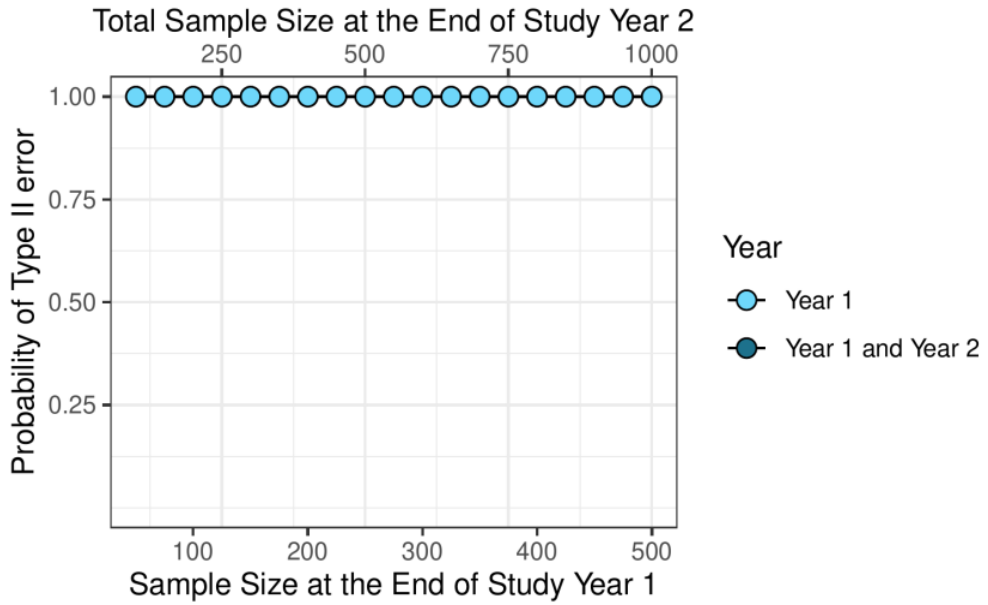
$$\frac{\#\ of\ trials\ satisfying\ criterion\ of\ superiority}{N_S}$$

Results of DEFINE trial simulations

$p_{SCR,SD}$ =0.08, $p_{SCR,ADJ}$ =0.15, $p_{SCR,HD}$ =0.22



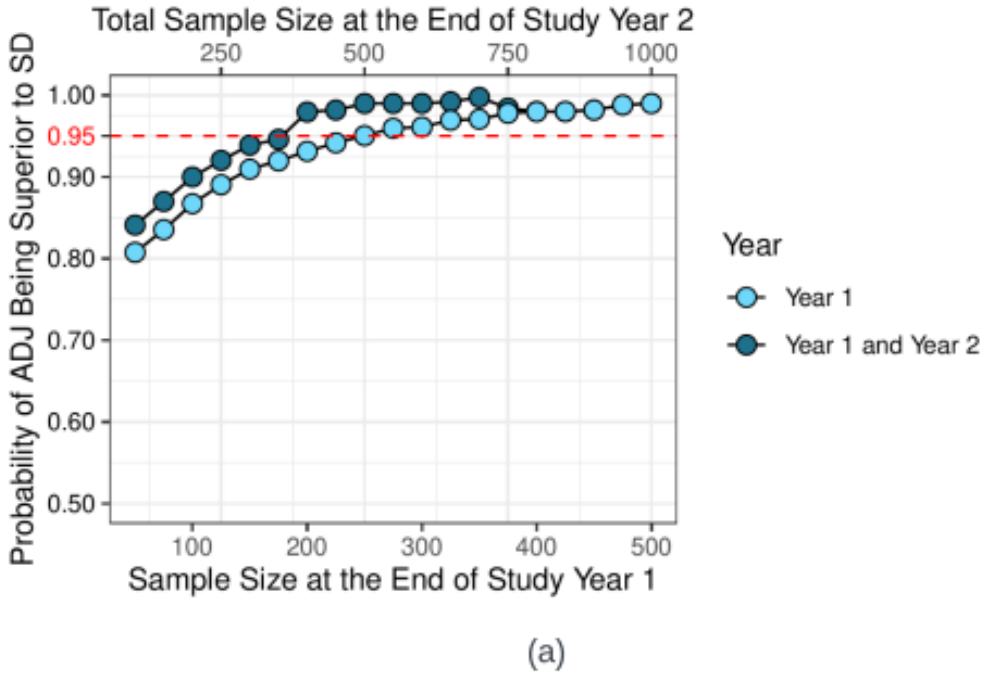
(a)



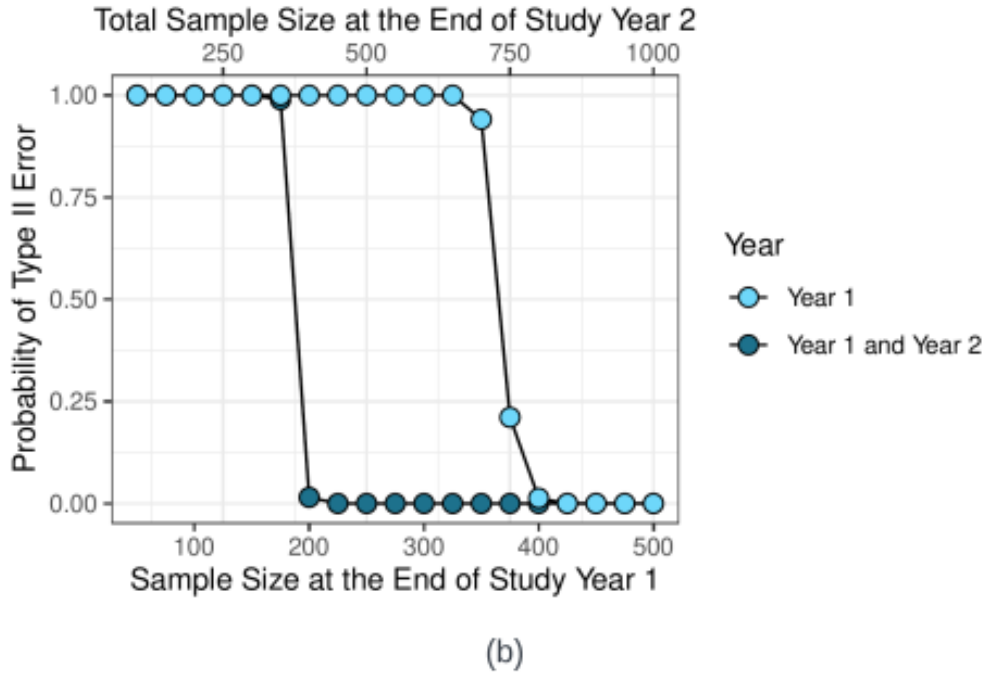
(b)

Results of DEFINE trial simulations

$p_{SCR,SD}$ =0.08, $p_{SCR,ADJ}$ =0.2, $p_{SCR,HD}$ =0.22 with a less stringent superiority criteria

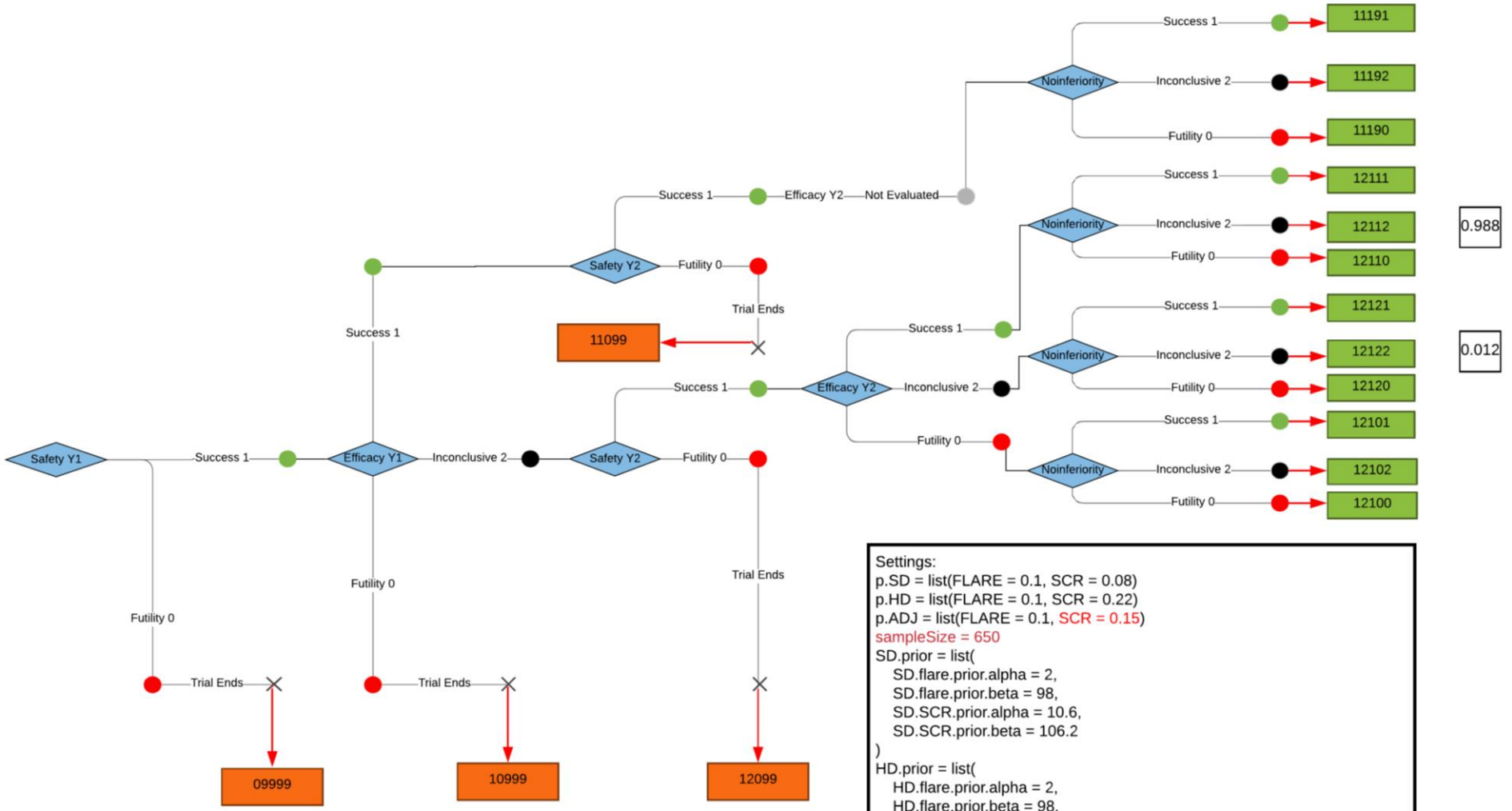


(a)



(b)

Possible Outcomes



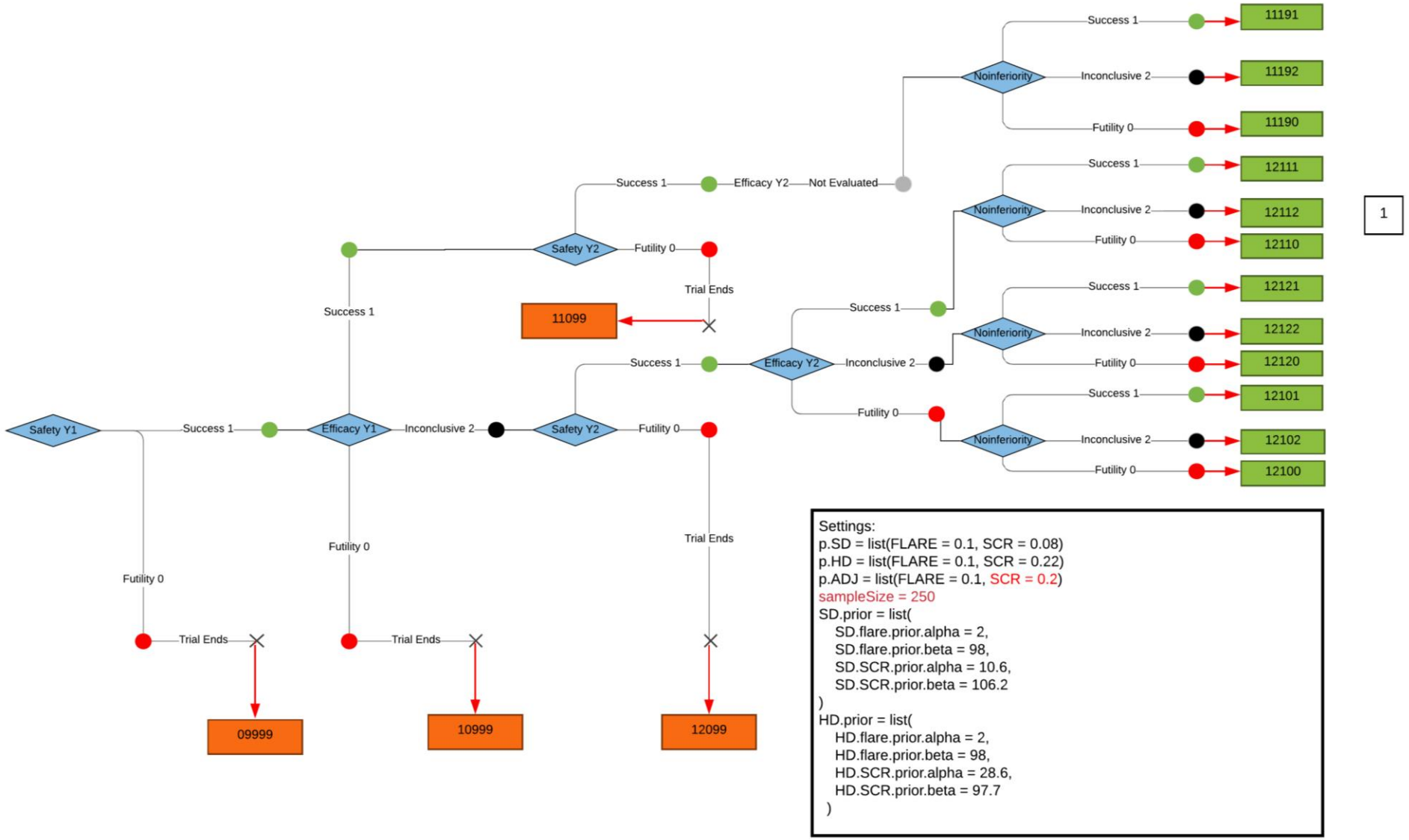
p.SD=0.08,

p.ADJ=0.15,

p.HD=0.22,

sample size = 650

Possible Outcomes



p.SD=0.08,

p.ADJ=0.2,

p.HD=0.22,

sample size = 650

Discussion

- We have illustrated how the checklist can be used to design simulations that help to design a good trial.
- This checklist can also be used as a reporting guideline.
- Next steps
  - Apply the checklist to more complex trials, e.g. platform trials, basket trials, umbrella trials and trials with more complex adaptations.

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Thank you