
# Bayesian & Emerging Approaches to Rare Disease Drug Development

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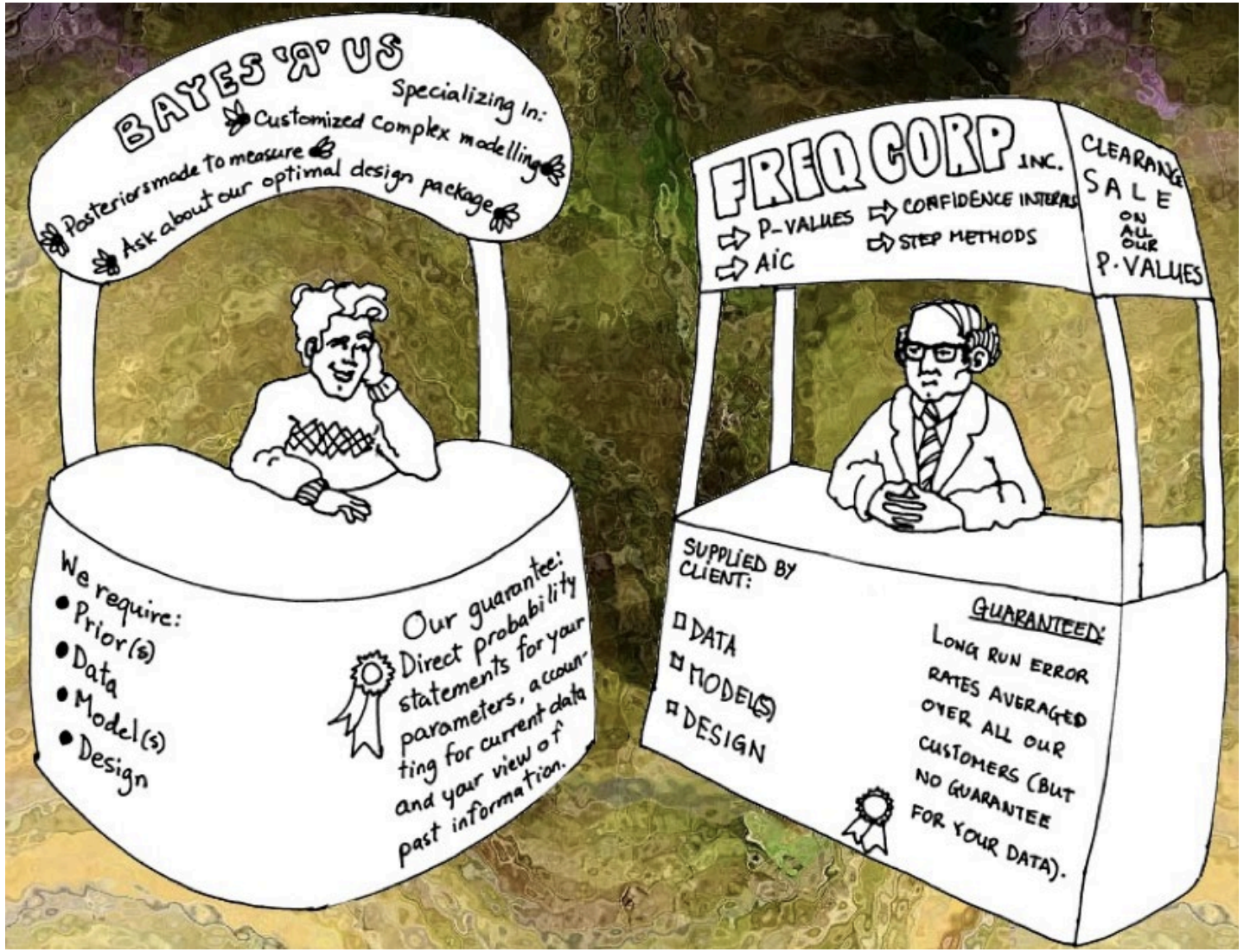
# Complex Innovative Designs Paired Meeting Program

- Established under PDUFA VI
- Facilitate and advance use of complex, adaptive, Bayesian and other novel clinical trial designs
- Increased interaction with FDA staff
- Extensive simulations and sensitivity analyses
- All submissions so far have used a **Bayesian** framework
  - 6 case studies




# Bayesian Toolkit

https://sofile.files.wordpress.com/2015/01/bayes-vs-frequentist.png

# Bayesian Framework

We don’t know what the population parameters/true values(e.g. response rates) are

random (they can change)

We take our best guess at the response rates based on our current knowledge (expert, registry, prior trials)

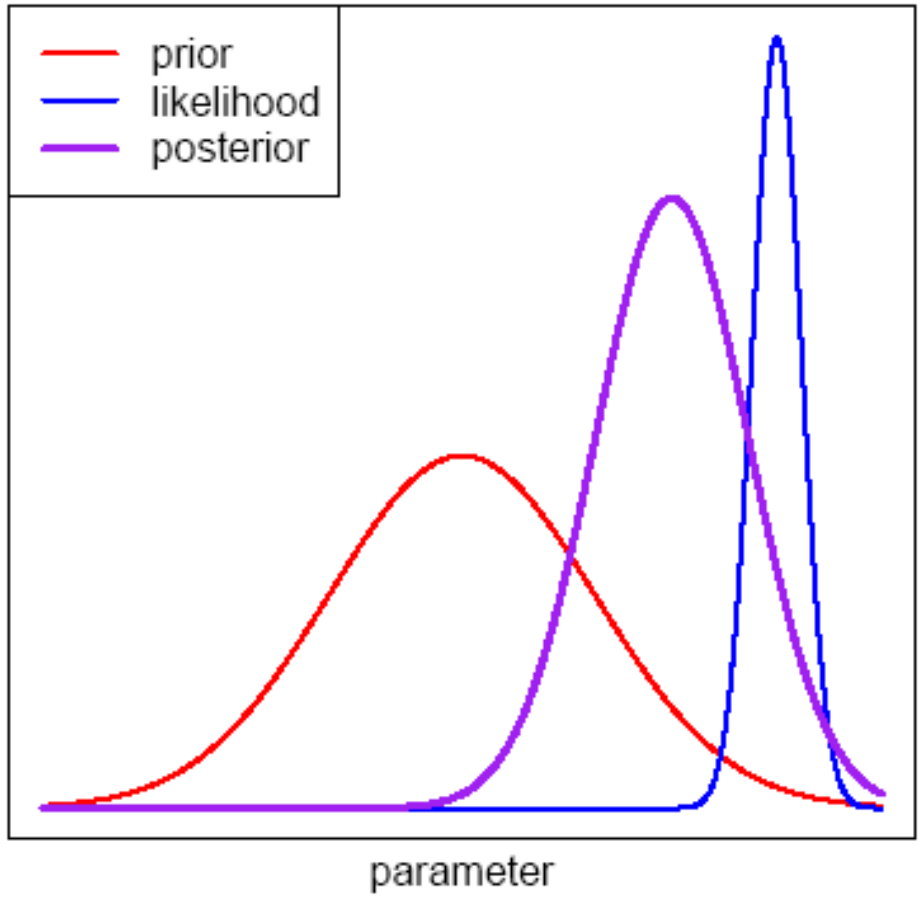
**PRIOR**

We collect data to observe the response rates (trial)

**LIKELIHOOD**

We combine our **PRIOR** & **LIKELIHOOD** for updated estimates of the response rates (results)

**POSTERIOR**

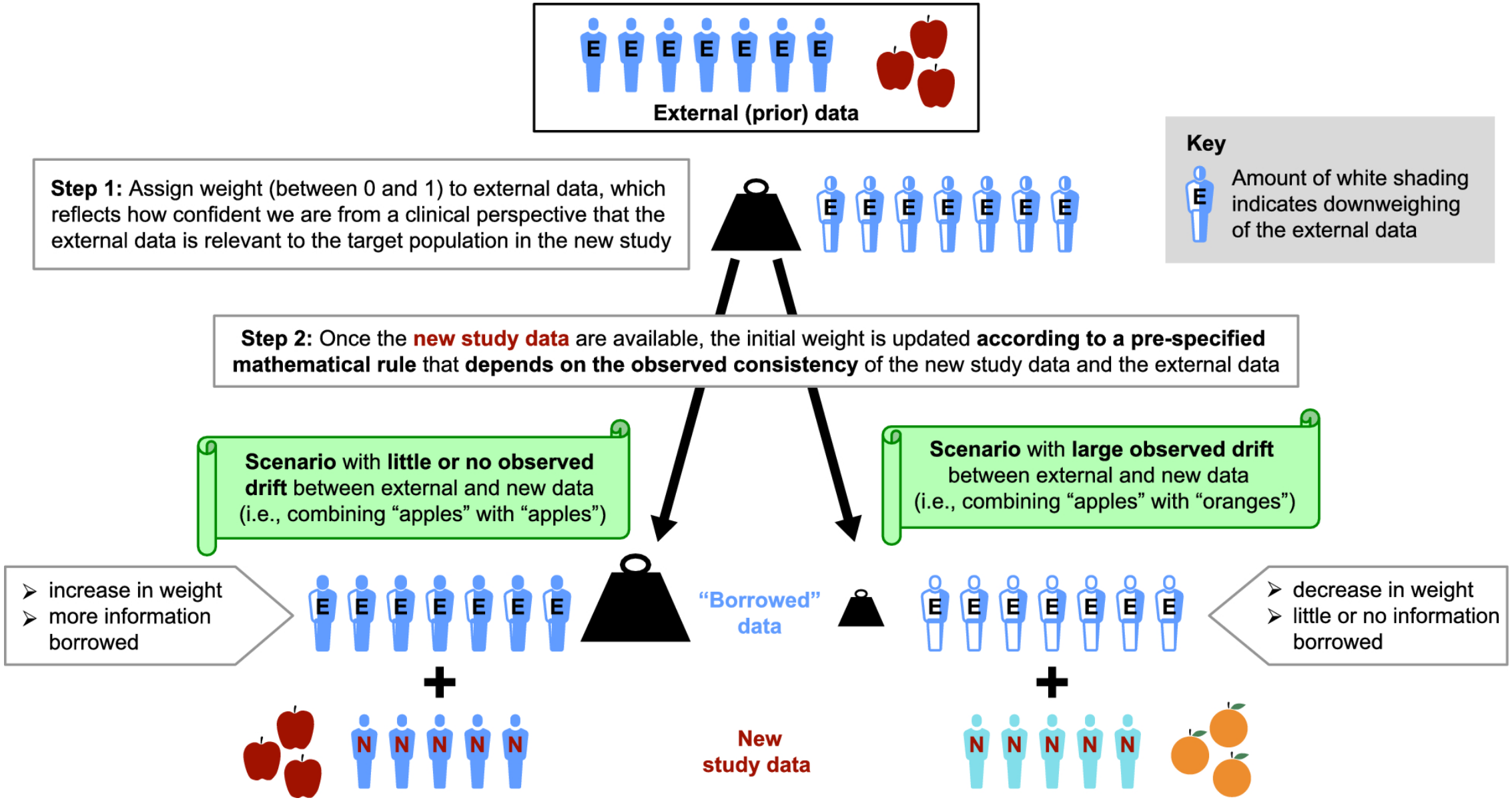


# Bayesian Approaches to Rare Disease Trials

- Incorporating External Control Data
  - Decrease number in trial
  - Decrease # on placebo
- Disease Progression Modelling
- Multi-stage Designs
- Platform Studies
- Seamless Phase II-III studies

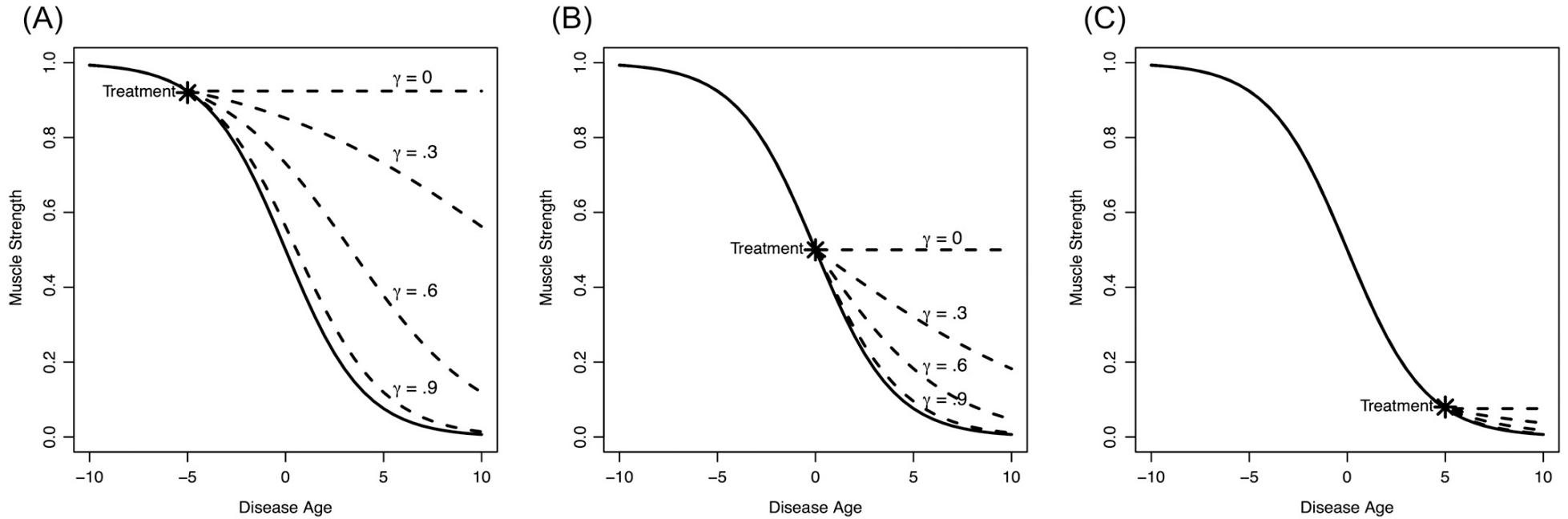
# Incorporating External Control Data

- Careful selection of external data (Pocock Criteria)
  - Previous/ongoing trial data, published literature, registry data, EHR, other RWE
  - Want high quality data - standards
- **Supplementation** or **replacement** of control arm
- Power Prior: estimates informative prior
- Meta-analytic or hierarchical modeling: places distribution on degree of borrowing across current and historical controls where variation is controlled by similarity of data


External (prior) data
Key
Amount of white shading indicates downweighing of the external data
Step 1: Assign weight (between 0 and 1) to external data, which reflects how confident we are from a clinical perspective that the external data is relevant to the target population in the new study
Step 2: Once the new study data are available, the initial weight is updated according to a pre-specified mathematical rule that depends on the observed consistency of the new study data and the external data
Scenario with little or no observed drift between external and new data (i.e., combining "apples" with "apples")
Scenario with large observed drift between external and new data (i.e., combining "apples" with "oranges")
increase in weight
more information borrowed
"Borrowed" data
decrease in weight
little or no information borrowed
New study data

# Disease Progression Modelling

- Use of natural history data to model disease progression
- Estimate trajectories over time, identify possible treatment responders
- Aid in trial design, simulations, power

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# Multi-stage Designs: snSMART

•small sample (n), Sequential, Multiple Assignment, Randomized Trial

•A type of **multi-stage,** randomized design where individuals are randomized to a set of treatment options and may be **re-randomized based on response** to initial treatment; Restricted crossover design

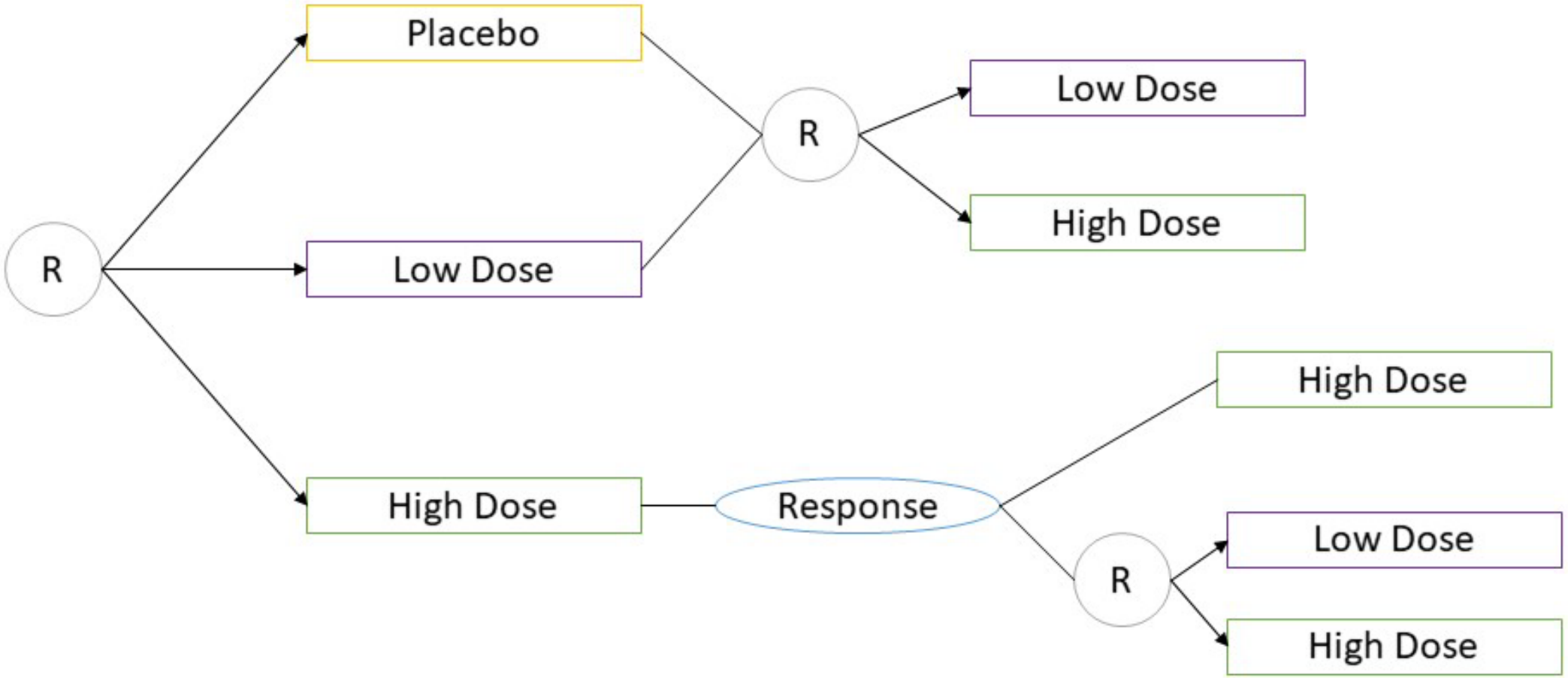
•**All** participants receive active (or some dose of) treatment

•Obtain **more information from smaller number** of participants

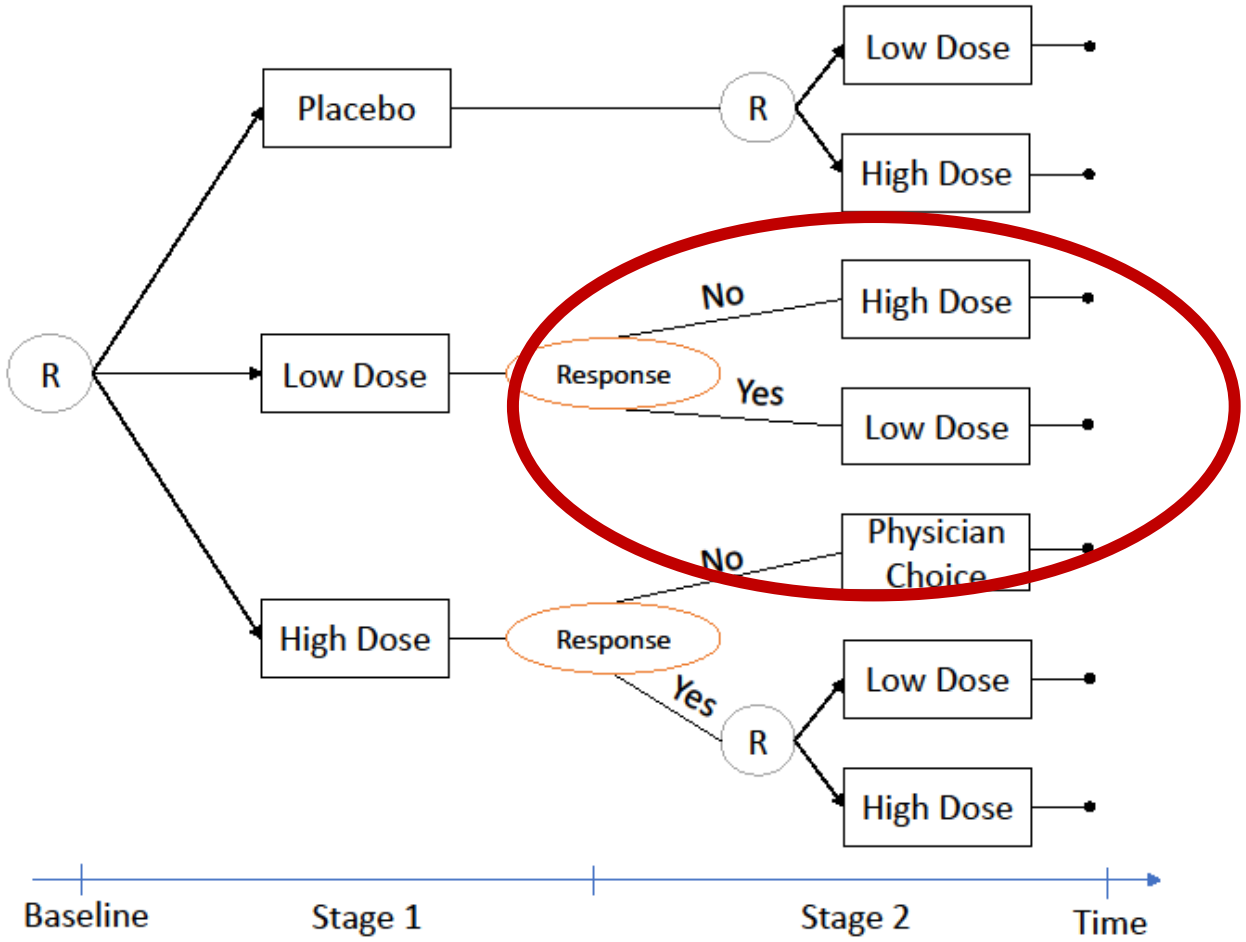
•Ability to **stay on treatment if responding**, **switch** to different treatment if not responding

•Appropriate for rare diseases or disorders that are **chronic, relatively stable** over the 2 stages of the trial

# snSMART Dose Design 1



# snSMART Dose Design 2




More patient-centered re-randomization

# snSMART Bayesian Analysis

| Goal | Provide | Shift | Incorporate |
| --- | --- | --- | --- |
| Estimate the first stage response rates (or mean outcomes) of each treatment by pooling data from both stages of the trial | Credible intervals of effect or difference between treatment effects: contain the true effect with some particular probability | Focus away from significance/p-values | Expert opinion, historical data, or co-data to increase precision |

**Sample size for an snSMART using the Bayesian Joint Stage Model reduces sample size from a 1 stage design by 15-60%**

# Regulatory Perspective

- **Detailed protocol**, critical features of design and analysis
  - Rationale
  - data sources
- **Statistical analysis plan** includes methodologic approach and **simulation** settings/results
  - Exchangeability
  - Broad parameter space explored
  - Sensitivity to prior specifications
  - Methods and use of borrowing
  - Pre-specification of adaptations

# Summary

- **Bayesian design and analyses** should be considered in available design and methods **toolkit** for rare disease drug discovery
  - Combine data sources
  - Increase study power
- Extensive development required
- **Early conversations** with regulatory agencies suggested
  - Complex Innovative Design Paired Program

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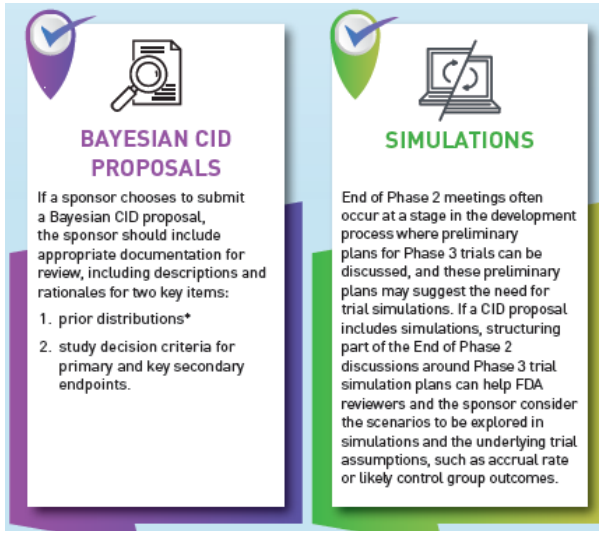
# Extra Slides

# Need for clinical trial innovation

## Design

- Minimal **size** while providing robust evidence
- **Benefit participants**
  - maximize chance of receiving therapy
  - minimize number receiving placebo
- Consider **more than 1 dose or treatment** and confirm its efficacy




## Analysis

- Provide estimates with **clinical interpretability**: probability of clinical meaningful treatment benefit
- Incorporate **external data** (natural history studies, previous trials)

# Results from Models

- Compared to one stage design analyses or joint stage frequentist analyses, our **Bayesian Joint Stage Models (BJSM)** provide treatment effects that
  - have low to no bias
  - are more efficient (lower variance)


- When assumptions are violated, BJSM are robust and maintain good results

- Can **test sensitivity of BJSM** to assumptions
  - via simulations in design phase
  - via comparing to Frequentist model in the analysis phase

# snSMART Bayesian Analysis Approach

## Prior Distributions: Informed by clinician investigators, historical data

- Informative, usually few people's worth of info
- Mixture approach: informative prior informed by expert & non-informative prior
- Test sensitivity of results given different prior distributions

## Likelihood: Joint Model of current snSMART trial data

- Model the first stage outcome simply
- Model the second stage outcome based on the first stage treatment and outcome and second stage treatment
  - Augment expected outcome from stage 1 – can add potential resistance to drug
  - Link the outcome from stage 1 to stage 2 using linkage parameters – induces within patient correlation

# How do investigators size an snSMART

For placebo, high and low doses and continuous outcome

- Rshiny Applet coming soon
- Find n such that the credible interval of the difference between low dose and placebo rules out 0 with desired probability (power)

| Scenario | One stage Design | | snSMART Design | | $N/N_{1Freq}$ | $N/N_{1Bayes}$ |
|---|---|---|---|---|---|---|
| | $N_{1Freq}$ | $N_{1bayes}$ | N | Power | | |
| 1 | 50 | 46 | 31 | 0.81 (0.80-0.82) | 0.62 | 0.67 |
| 2 (↑ correlation) | 50 | 46 | 20 | 0.80 (0.79-0.81) | 0.40 | 0.43 |
| 3 (↑ var on trt est) | 50 | 50 | 34 | 0.81 (0.80-0.82) | 0.68 | 0.68 |

**Sample size for an snSMART using the Bayesian Joint Stage Model reduces sample size from a 1 stage design by 15-60%**