snSMART Design in Rare Disease Research: Motivated by ARAMIS

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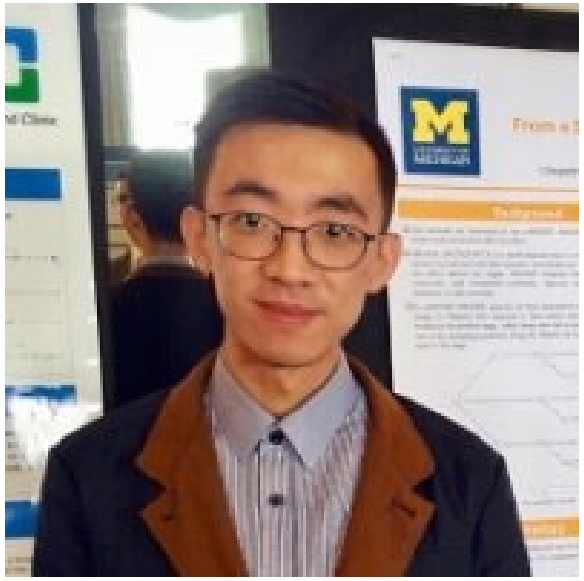
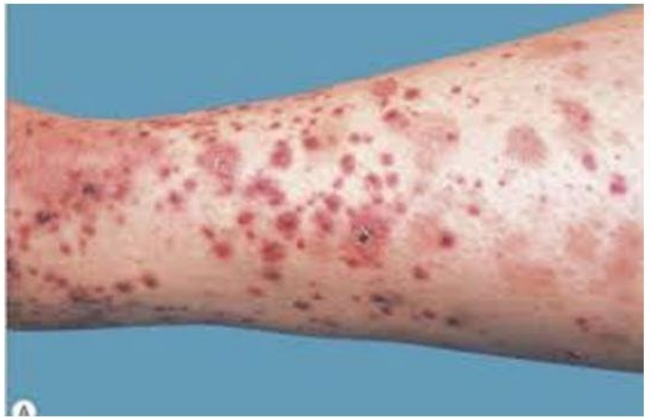


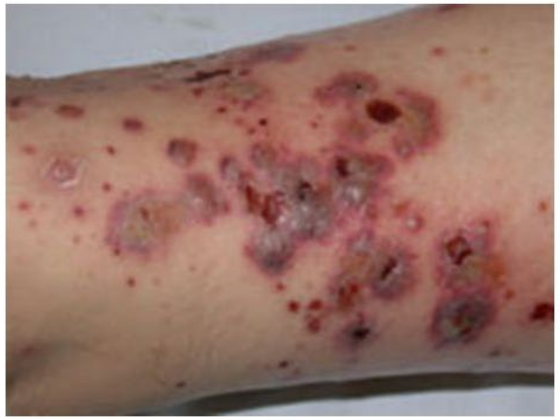
Boxian Wei

Yan-Cheng Chao

Motivating Setting: Isolated Skin Vasculitis

- Cutaneous vasculitis lesions can be pruritic, painful, and cosmetically disturbing
- Can ulcerate causing infection and scarring
- Associated with discomfort and psychosocial impact
- **Chronic**, relatively **stable** disease



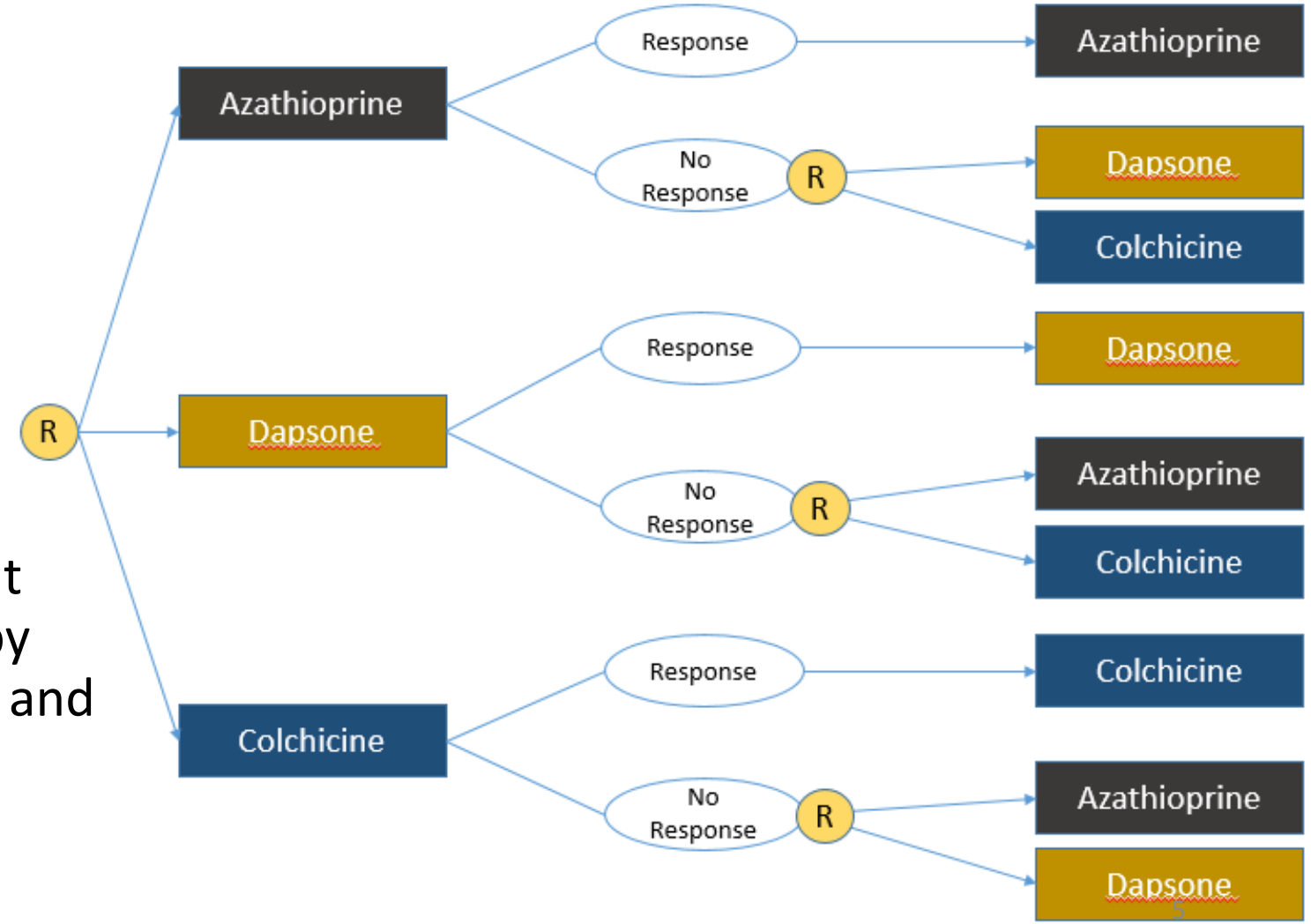


Motivation for Design

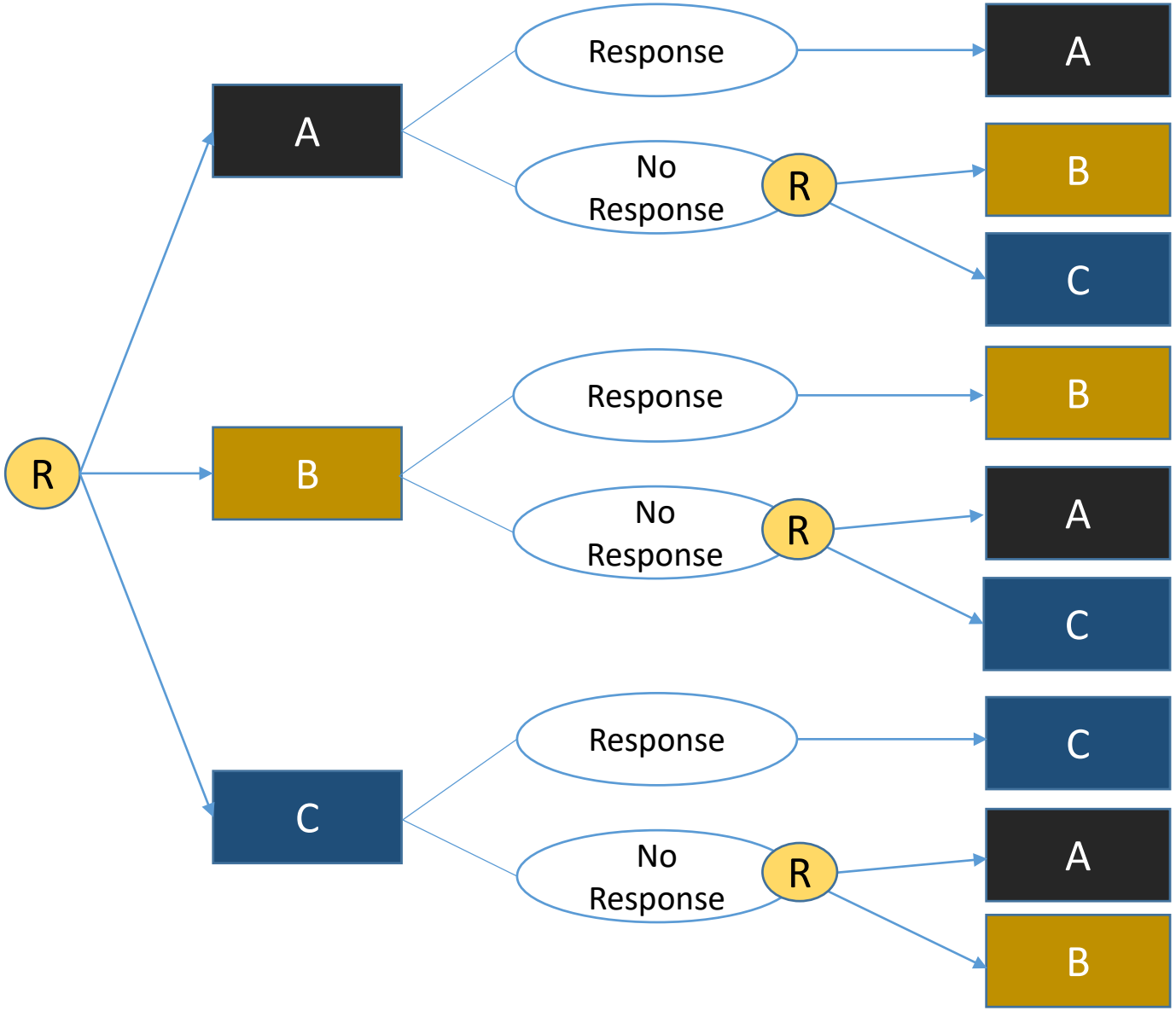
- **No placebo**: inability to enroll, difficulty blinding, no clear favorite drug
- Individuals are guaranteed to be on **at least 1 drug**
- Individuals **move to a different drug** if they do not respond to the first drug
- Individuals can **stay on a drug** if they respond to in in the first stage
- Drugs involved effective in 1 stage period, no carryover effects

ARAMIS: **A RA**ndomized **M**ulticenter study for Isolated **S**kin vasculitis

- NCT02939573
- 1/2017-present
- 1 stage = 6 month
- 90 participants
- International
- Outcome: complete or significant response to treatment defined by number of lesions and physician and patient scales



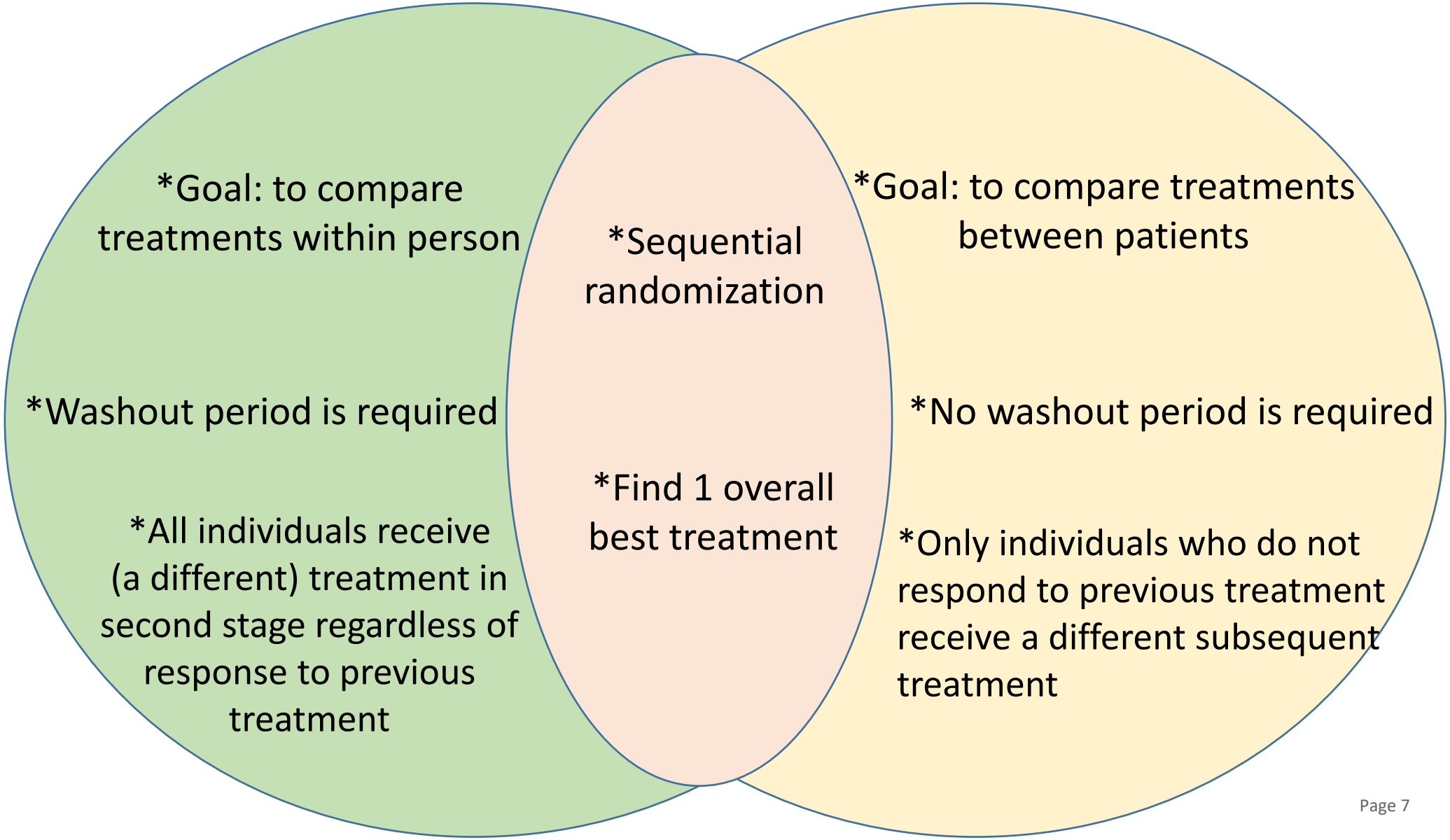
General Small n, Sequential, Multiple Assignment, Randomized Trial



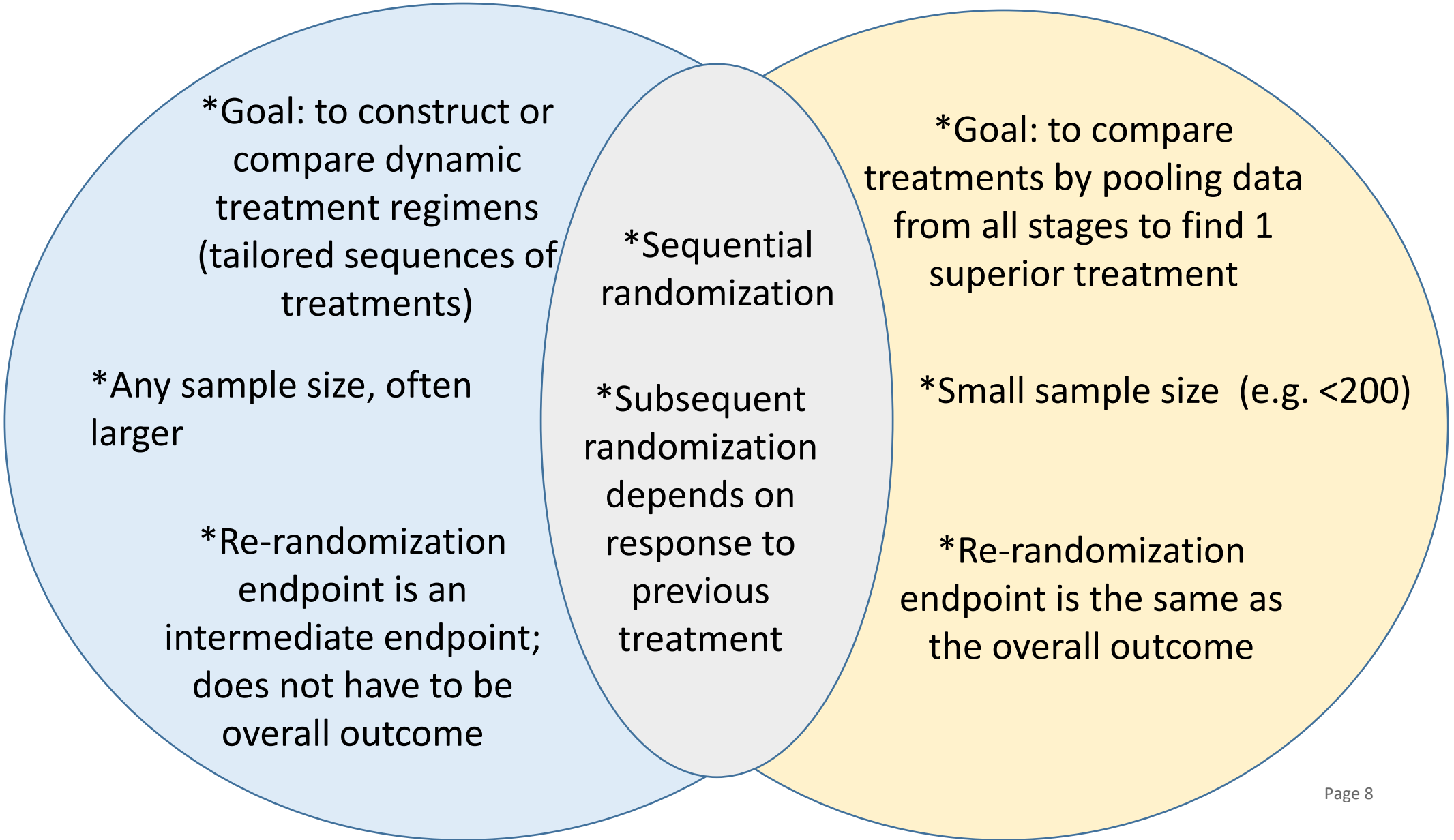
Assumptions

- 3 active treatments
- Primary Interest: Stage 1 outcome
- No carryover effects
- Binary Outcome
- Chronic, stable disease

Crossover vs. snSMART



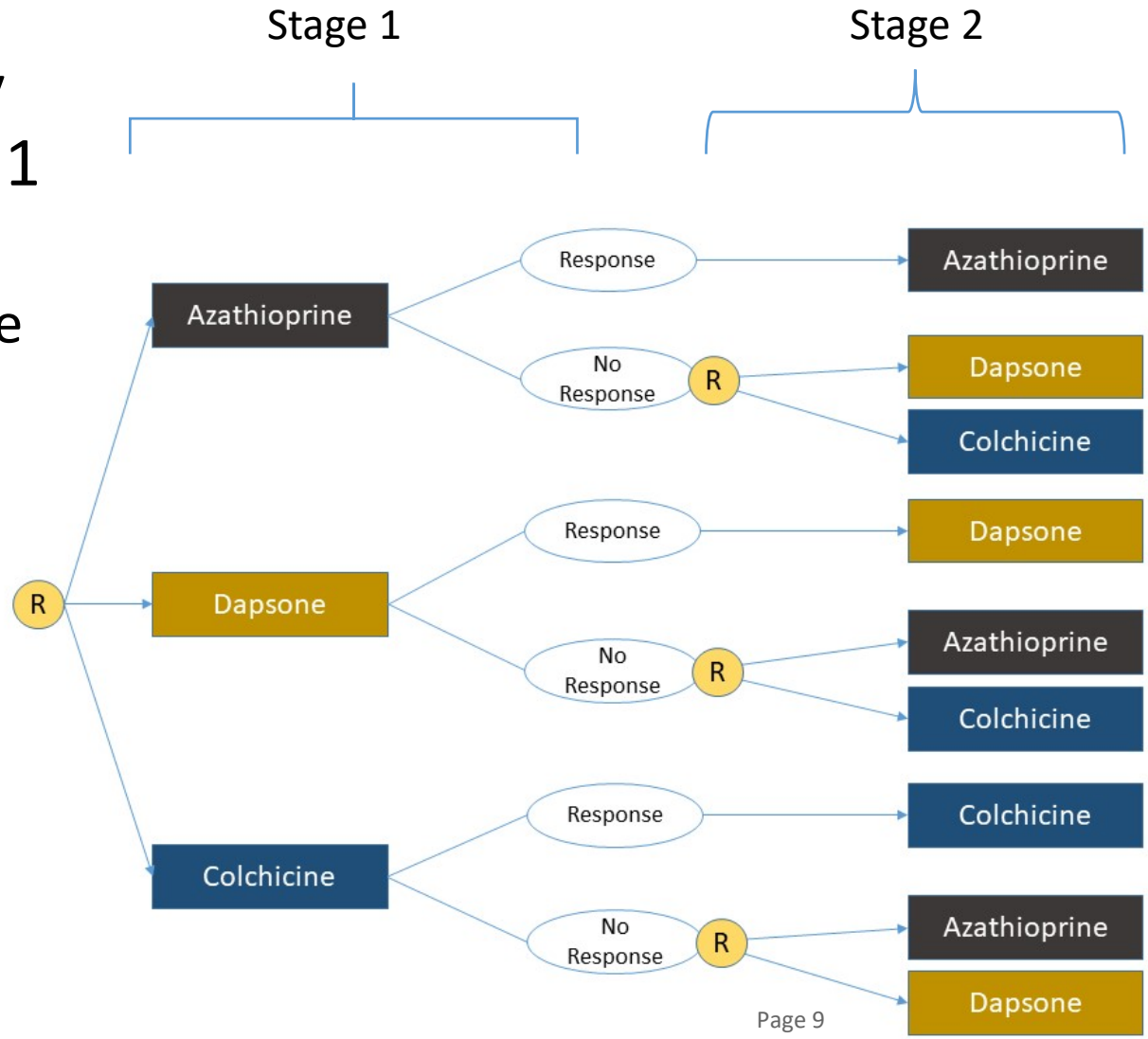
SMART vs. snSMART



ARAMIS setting

- <u>Primary Goal</u>: compare treatments by pooling data from both stages to find 1 optimal treatment
  - Does Azathioprine, Dapsone, or Colchicine have the best 6 month response rate?

- <u>Outcome</u>: Binary
  - Measured at the end of stage 1 (e.g., 6 months) and stage 2 (e.g., 12 months)



Bayesian Joint Stage Model

- Uses **all data** from both stage 1 and 2 in estimation and inference
- Incorporates **investigators' opinions** about response rates (prior distributions)
- **Links data** from stage 1 and 2 using "linkage parameters"- assumptions
- Stage 1 outcome is Bernoulli and stage 2 outcome is modeled conditionally on stage 1 outcome using "linkage parameters"

Bayesian Joint Stage Model

$$Y_{i1k} \sim \text{Bernoulli}(\pi_k)$$

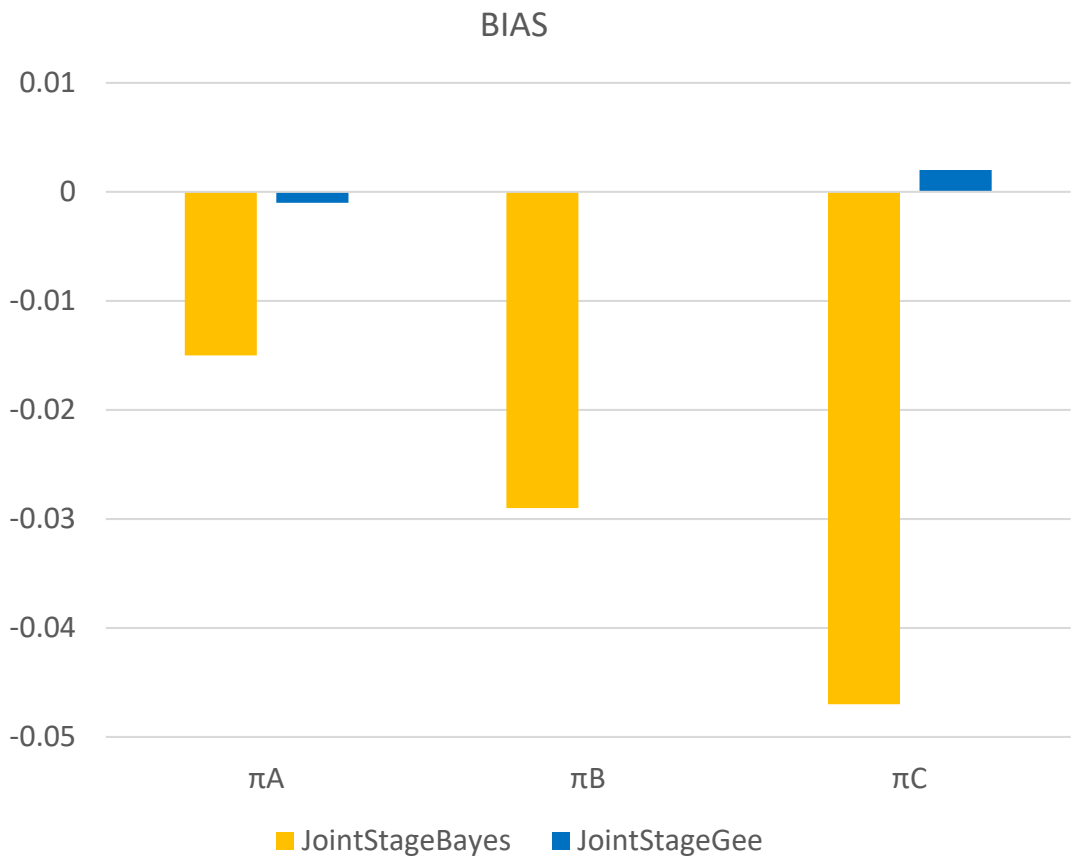
$$Y_{i2k'} \mid Y_{i1k}, \pi_k \sim \text{Bernoulli}((\beta_1 \pi_k)^{Y_{i1k}} (\beta_0 \pi_{k'})^{1-Y_{i1k}})$$

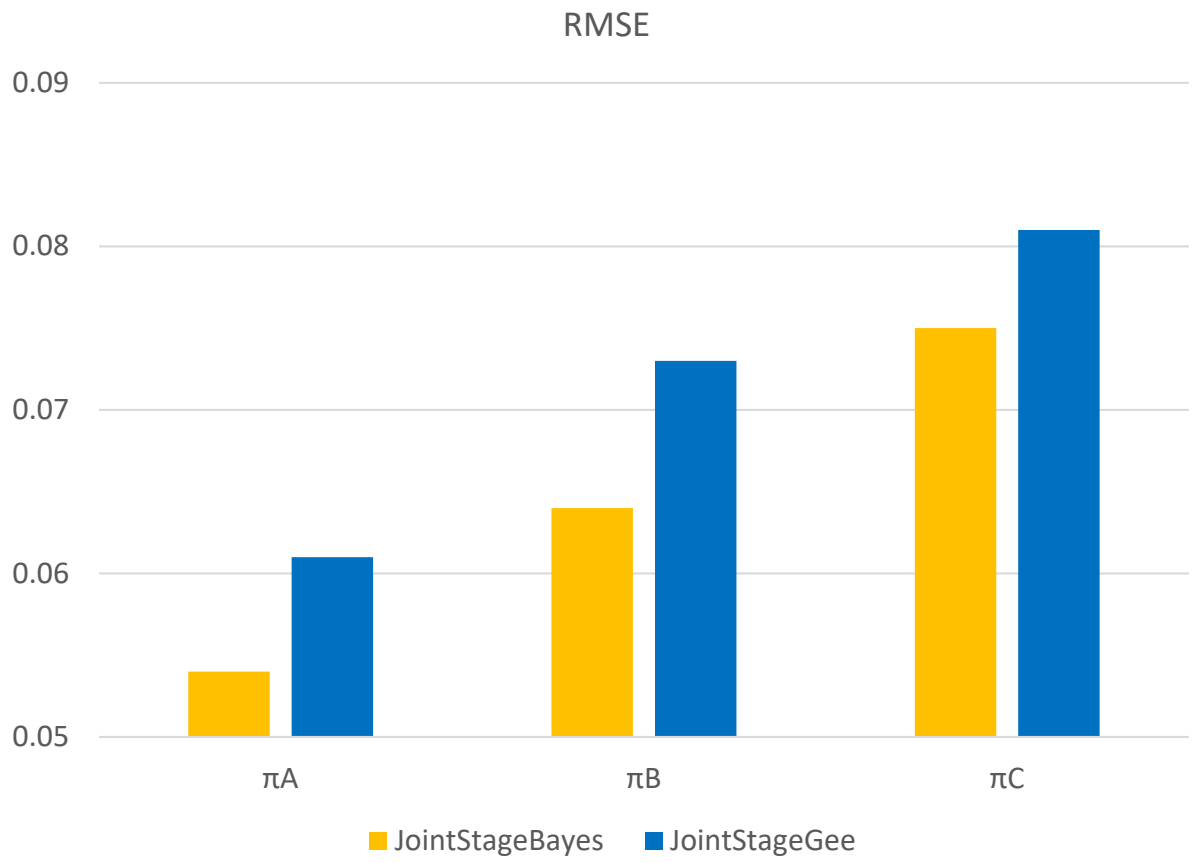
- Response rate for treatment k: π_k; i^{th} patient at the j^{th} stage
- $\beta_0 \leq 1$ is the **linkage parameter for non-responders** such that response rate for treatment k in stage 2 is lower than the response rate for treatment k in stage 1
- $\beta_1 \geq 1$ is the **linkage parameter for responders** such that response rate for treatment k in stage 2 is higher than the response rate for treatment k in stage 1

Choice of Prior Distributions

- π_k ~ Beta(0.4, 1.6)
  - ARAMIS investigators felt an ineffective treatment would have spontaneous response rate of 0.20
  - Prior sample size = 2
- β_0 ~ Beta(1,1)
  - Equivalent to Unif(0,1)
  - On average the stage 2 response rate for non-responders is ½ times as large as stage 1 response rate
- β_1 ~ Pareto(3,1)
  - On average the stage 2 response rate for responders is 1.5 times as large as the stage 1 response rate

BJSM Results vs. Log Poisson GEE model: **Efficiency**





Other snSMART Methods

- **Bayesian Joint Stage Model**
  - Unbiased and efficient estimation of treatment effects and **dynamic treatment regimens** (tailored sequences of treatments, start with A, continue if response, switch to B if not)
- **Sample Size Calculation and Applet**
  - Find n such that the credible interval of the difference in the 2 best treatment rules out 0 with desired power
  - https://umich-biostatistics.shinyapps.io/snsmart_sample_size_app/
- **Two Step Bayesian Dropping Rule**
  - Include interim analyses to drop the worst performing arm
- **Allowing for Continuous Intermediate and Overall Outcomes**

Overall research goal

APPROVED TREATMENTS ARE AVAILABLE FOR >> 5% OF ALL RARE DISEASES

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References

- Tamura et al.
  Small n sequential multiple assignment randomized trial design for use in rare disease research. (2016) Contemporary Clinical Trials. 46, 48-51.
- Wei B, Braun TM, Tamura RN, Kidwell KM. A Bayesian analysis of small n sequential multiple assignment randomized trials (snSMARTs). (2018) *Statistics in Medicine*. 37(26): 3723—3732.

Under Review

- Wei B, Braun TM, Tamura RN, Kidwell KM. Sample size considerations for a small n sequential multiple assignment randomized trial (snSMART) using Bayesian analysis.
- Chang YC, Braun TM, Tamura RN, Kidwell KM. A group sequential small n sequential multiple assignment randomized trial.
- Chao YC, Braun, TM, Trachtman H, Gipson DS, Spino C, Kidwell KM. Small n SMART design to efficiently develop personalized treatment regimens in rare disease: An application in Focal Segmental Glomerulosclerosis (FSGS).