snSMART Design in Rare Disease Research: Motivated by ARAMIS

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Other Members of the Team

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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 the first stage

• Drugs involved effective in 1 stage period, no carryover effects
ARAMIS: A RAnomized Multicenter study for Isolated Skin 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

- **Goal:** to compare treatments within person
- **Sequential randomization**
- **Find 1 overall best treatment**
- **Washout period is required**
- **All individuals receive (a different) treatment in second stage regardless of response to previous treatment**

- **Goal:** to compare treatments between patients
- **No washout period is required**
- **Only individuals who do not respond to previous treatment receive a different subsequent treatment**
SMART vs. snSMART

**SMART**
- *Goal:* to construct or compare dynamic treatment regimens (tailored sequences of treatments)
- *Any sample size, often larger*
- *Re-randomization endpoint is an intermediate endpoint; does not have to be overall outcome*

**snSMART**
- *Goal:* to compare treatments by pooling data from all stages to find 1 superior treatment
- *Small sample size (e.g. <200)*
- *Re-randomization endpoint is the same as the overall outcome*

*Sequential randomization*
- *Subsequent randomization depends on response to previous treatment*
Primary Goal: 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?

Outcome: 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

\[ Y_{i1k} \sim \text{Bernoulli}(\pi_k) \]
\[ Y_{i2k'} | Y_{i1k}, \pi_k \sim \text{Bernoulli}(\beta_1 \pi_k^{Y_{i1k}} (\beta_0 \pi_k)^{1-Y_{i1k}}) \]

• Response rate for treatment k: \( \pi_k \); \( i \)th patient at the \( j \)th stage

• \( \beta_0 \leq 1 \) is the \textit{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 \textit{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

- $\pi_k \sim \text{Beta}(0.4, 1.6)$
  - ARAMIS investigators felt an ineffective treatment would have spontaneous response rate of 0.20
  - Prior sample size = 2
- $\beta_0 \sim \text{Beta}(1,1)$
  - Equivalent to Unif(0,1)
  - On average the stage 2 response rate for non-responders is $\frac{1}{2}$ times as large as stage 1 response rate
- $\beta_1 \sim \text{Pareto}(3,1)$
  - 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

![Graph showing BIAS and RMSE for JointStageBayes and JointStageGee](image)

- BIAS:
  - πA: JointStageBayes
  - πB: JointStageBayes
  - πC: JointStageGee

- RMSE:
  - πA: JointStageBayes
  - πB: JointStageGee
  - πC: JointStageGee
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/](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


Under Review

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