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snSMART: An R Package for Small Sample, Sequential, Multiple Assignment, Randomized Trial Data Analysis

Sidi Wang [1], **Fang Fang** [1], **Roy Tamura**[2], **Thomas Braun** [1], **and Kelley M Kidwell** [1]

1 University of Michigan **2** University of South Florida

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Summary

Small sample, sequential, multiple assignment, randomized trials (snSMARTs) are multistage trials designed to estimate first stage treatment effects. By using data from all stages, snSMARTs provide more precise estimates of these effects. Additionally, the design may enhance participant recruitment and retention compared to standard rare disease trials. To support the application of snSMART statistical methods, we introduce the R package `snSMART`.

Statement of need

The design and methods of snSMARTs are applicable to any disorder or disease that affects a small group and remains stable over the trial duration. Recent advances include methods for snSMARTs with three active treatments (Chao, Trachtman, et al., 2020; Wei et al., 2018, 2020), group sequential designs (Chao, Braun, et al., 2020), placebo with two dose levels (Fang et al., 2021), and continuous outcomes (Hartman et al., 2021). Despite these developments, there is a lack of software to implement these methods. The `snSMART` R package addresses this need by providing sample size calculations and trial data analysis using both Bayesian and frequentist approaches. To our knowledge, no other R packages offer similar functionalities.

Functionality of the snSMART package

We have summarized the functionality of all the `snSMART` functions included in this package in Table 1. The `BJSM_binary`, `BJSM_c`, and `group_seq` functions implement the Bayesian Joint Stage Modeling (BJSM) methods to estimate treatment effects across all treatment arms in a snSMART design with binary outcomes, continuous outcomes, and in a group sequential trial design, respectively. The `LPJSM_binary` function serves as the frequentist equivalent to `BJSM_binary` and can be used for sensitivity analysis. The `sample_size` function performs Bayesian sample size calculations for a snSMART design with binary outcomes, ensuring that the trial is scientifically valid, ethically responsible, and resource-efficient.

snSMART comparing two dose levels with placebo

Table 1: Summary of the functionality of the snSMART package.

Function	Description
BJSM functions	
BJSM_binary	BJSM binary (3AT or P2D snSMART)
BJSM_c	BJSM (3AT snSMART with a mapping function and continuous outcome)
group_seq	BJSM (interim analysis and final analysis of group sequential 3AT snSMART)
Frequentist functions	
LPJSM_binary	LPJSM (3AT or P2D snSMART)
Sample size calculation	
sample_size	3AT snSMART sample size calculation
S3 summary and print methods	
for class 'BJSM_binary'	Summarize and print 'BJSM_binary' object
for class 'BJSM_binary_dose'	Summarize and print 'BJSM_binary_dose' object
for class 'BJSM_c'	Summarize and print 'BJSM_c' object
for class 'group_seq'	Summarize and print 'group_seq' object
for class 'LPJSM_binary'	Summarize and print 'LPJSM_binary' object
for class 'sim_group_seq'	Summarize and print 'sim_group_seq' object

This section details one of the snSMART designs, which investigates the response rate of an experimental treatment at low and high doses compared to placebo (Fang et al., 2021). In this design (Figure 1), participants are equally assigned to receive either placebo, low dose, or high dose in the first stage. They continue their initial treatment for a pre-specified duration until their responses are measured at the end of stage 1. In the second stage, all participants who initially received placebo or low dose are re-randomized to either low or high dose, regardless of their first stage response. Participants who responded to the high dose are re-randomized between low and high doses, while non-responders to the high dose continue with the high dose in the second stage. The main goal of this snSMART is to estimate and compare first stage response rates for low and high doses to placebo by modeling the pooled data from both stages.

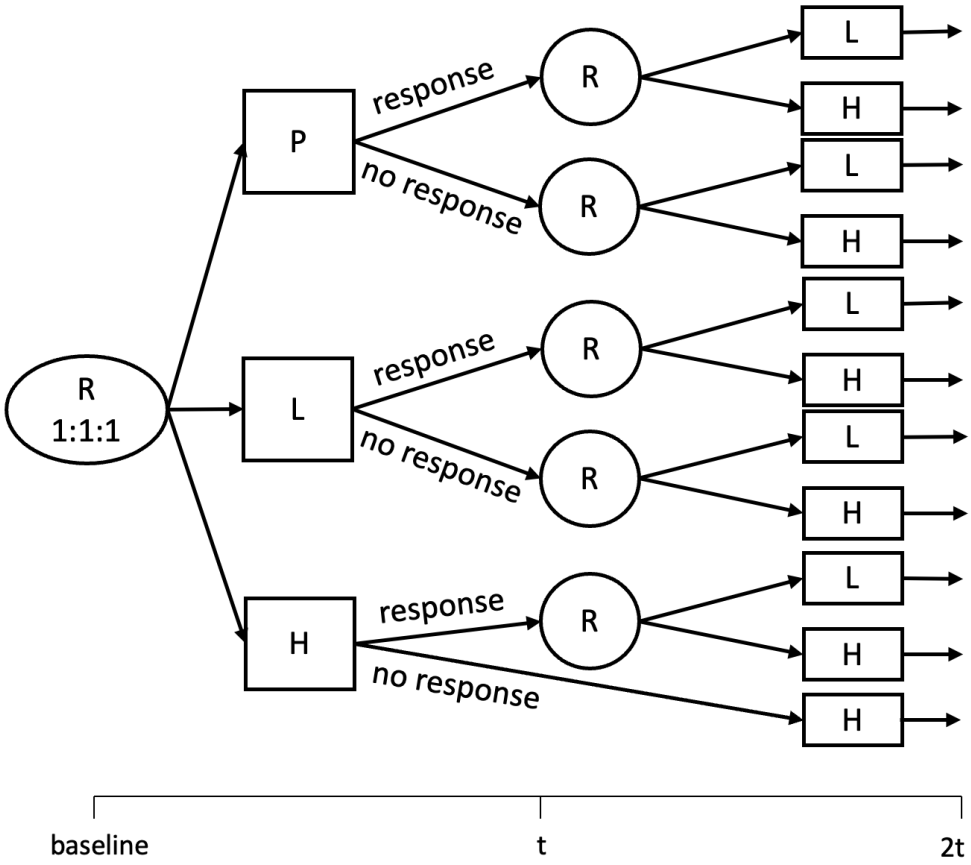

Figure 1: Study design of an snSMART with two dose levels and a placebo. In stage 1, participants are randomized (R) to treatment P (placebo), L (low dose), or H (high dose) with equal probability. At time t, response to stage 1 treatment is assessed. Non-responders to high dose stay on the same treatment in stage 2, while all the other participants are equally re-randomized to either low or high dose in stage 2. Interest is in the first stage response rate of placebo, low and high doses.

Fang et al. (2021) adapted the Bayesian joint stage model (BJSM) from Wei et al. (2018) in Equations 1 and 2. For this design, $m = P, L, H$ and $m' = L, H$, where P represents placebo, L low dose, and H high dose. The prior distribution for the response rate of placebo, π_P, may be informed by natural history studies or previous trials and specified as $\pi_P \sim Beta(\zeta_n, \eta_n)$. It is assumed that the drug doses have a weak tendency for higher response rates than placebo, modeled as $\log(\pi_L/\pi_P) \sim N(\mu, \sigma^2)$ and $\log(\pi_H/\pi_P) \sim N(\mu, \sigma^2)$. The prior distributions for the linkage parameters may vary, specified as $\beta_{0m}, \beta_{1m} \sim Gamma(\omega, \psi)$.

The BJSM is specified as follows:

$$Y_{i1m}|\pi_m \sim Bernoulli(\pi_m) \tag{1}$$

$$Y_{i2m'}|Y_{i1m}, \pi_{m'}, \beta_{1m}, \beta_{0m} \sim Bernoulli((\beta_{1m}\pi_m)^{Y_{i1m}}(\beta_{0m}\pi_{m'})^{1-Y_{i1m}}) \tag{2}$$

for $i = 1, ..., N$; and $j = 1, 2$; where Y_{ijm} is the outcome for participant i at stage j for treatment m and takes the value 1 for response to treatment and 0 for no response; N is the total sample size; β_{0m} and β_{1m} are the linkage parameters for non-responders and responders, respectively; π_m is the first stage response rate for treatment m; $\beta_{1m}\pi_m$ is the second stage response rate for first stage responders; and $\beta_{0m}\pi_{m'}$ is the second stage response rate for

non-responders to treatment m in the first stage who receive treatment m' in the second stage.

To conduct the analysis in R, we can use the `BJSM_binary` function. Users specify priors, MCMC details, and BJSM model type (six beta or two beta). Here, we assume the prior distribution of π_P as $Beta(3, 17)$, β_{jm} as $Gamma(2, 2)$, and the treatment effect ratio as $Normal(0.2, 100)$. Label placebo as 1, low dose as 2, and high dose as 3 in the dataset. The output is a `BJSM_dose_binary` object with posterior samples and estimates of linkage parameters, treatment response rates, and pairwise response rate differences.

```
BJSM_dose_result <- BJSM_binary(
  data = data_dose, prior_dist = c("beta", "gamma"),
  pi_prior = c(3, 17), normal.par = c(0.2, 100), beta_prior = c(2, 2),
  n_MCMC_chain = 2, n.adapt = 1000, BURN.IN = 10000,
  MCMC_SAMPLE = 60000, ci = 0.95
)
summary(BJSM_dose_result)
```

```
Treatment Effects Estimate:
       Estimate Std. Error C.I.     CI low   CI high
trtP 0.08606853 0.04004852 0.95 0.01694565 0.1618828
trtL 0.39969511 0.06130935 0.95 0.28185110 0.5202667
trtH 0.73414788 0.07501235 0.95 0.58710144 0.8763916

Differences between Treatments:
         Estimate  Std.Error C.I.     CI low    CI high
diffPL -0.3136266 0.07345504 0.95 -0.4577648 -0.1696336
diffLH -0.3344528 0.07967433 0.95 -0.4895912 -0.1785552
diffPH -0.6480794 0.08559511 0.95 -0.8071207 -0.4772492

Linkage Parameter Estimate:
           Estimate Std. Error C.I.     CI low   CI high
beta[1,1] 0.9763364  0.1640819 0.95 0.65222142 1.2973089
beta[2,1] 0.8560191  0.3257939 0.95 0.23204941 1.4280772
beta[1,2] 1.0749284  0.1869756 0.95 0.70435649 1.4426901
beta[2,2] 0.9872268  0.2503916 0.95 0.48669193 1.4458416
beta[1,3] 0.3824723  0.1899827 0.95 0.05813823 0.7529239
beta[2,3] 1.0703154  0.1657493 0.95 0.74952233 1.4055420
```

The response rates for placebo, low dose and high dose are estimated to be `trtP` 0.09 (95% credible interval (CI): 0.02 - 0.16), `trtL` 0.40 (95% CI: 0.28 - 0.52), and `trtH` 0.73 (95% CI: 0.59 - 0.88) respectively. Other estimated outcomes are also clearly presented in the R output above.

Discussion

We introduced and demonstrated the `snSMART` package for analyzing snSMART data using Bayesian methods. BJSM is often more efficient, but frequentist methods are recommended for sensitivity analysis. The package will be updated with new designs and methods to aid in finding effective treatments for rare diseases.

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