

SMARTp: A SMART design for non-surgical treatments of chronic periodontitis with spatially-referenced and non-randomly missing skewed outcomes

October 15, 2019

SMARTp: A SMART design for non-surgical treatments of chronic periodontitis with spatially-referenced and non-randomly missing skewed outcomes

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Received zzz, revised zzz, accepted zzz

This paper proposes dynamic treatment regimes (DTRs) as effective individualized treatment strategies for managing chronic periodontitis. The proposed DTRs are studied via SMARTp – a two-stage sequential multiple assignment randomized trial (SMART) design. For this design, we propose a statistical analysis plan and a novel cluster-level sample size calculation method that factors in typical features of periodontal responses, such as non-Gaussianity, spatial clustering, and non-random missingness. Here, each patient is viewed as a cluster, and a tooth within a patient's mouth is viewed as an individual unit inside the cluster, with the tooth-level covariance structure described by a conditionally autoregressive structure. To accommodate possible skewness and tail behavior, the tooth-level clinical attachment level (CAL) response is assumed to be skew- t , with the non-randomly missing structure captured via a shared parameter model corresponding to the missingness indicator. The proposed method considers mean comparison for the regimes with or without sharing an initial treatment, where the expected values and corresponding variances or covariance for the sample means of a pair of DTRs are derived by the inverse probability weighting and method of moments. Simulation studies are conducted to investigate the finite-sample performance of the proposed sample size formulas under a variety of outcome-generating scenarios. An R package SMARTp implementing our sample size formula is available at the Comprehensive R Archive Network for free download.

Key words: Dynamic treatment regimes; inverse probability weighting; method of moments; periodontitis; skew-normal; skew- t ; SMART

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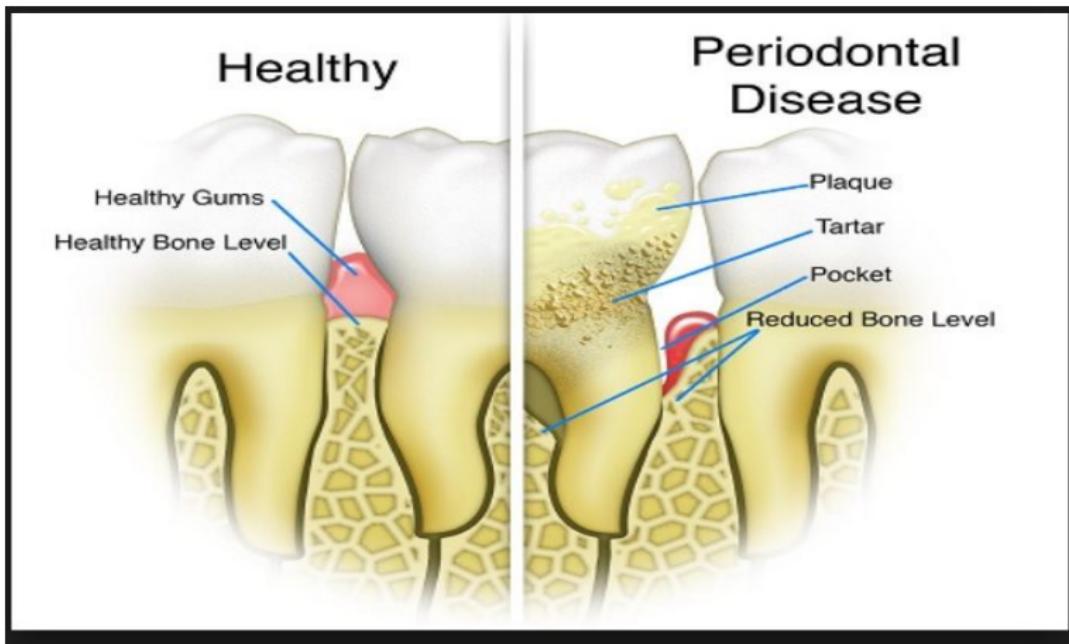
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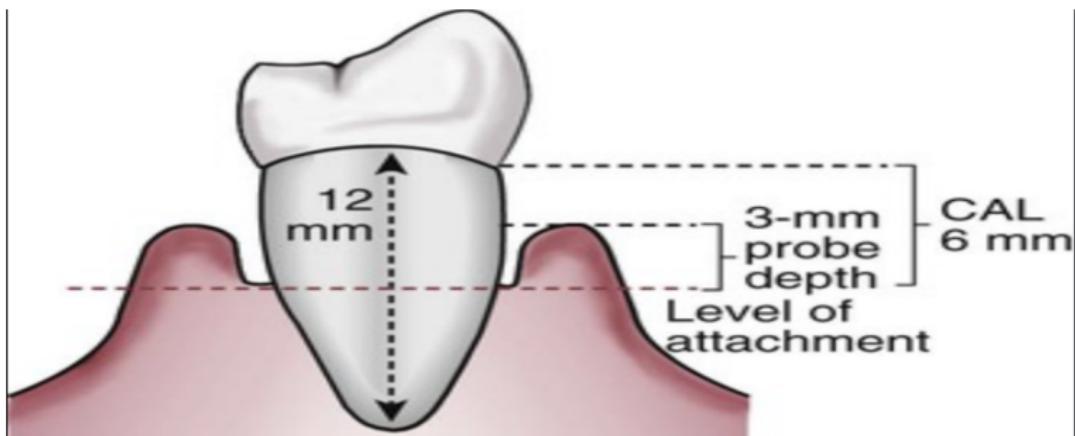
Periodontitis

- Inflammation due to bacteria in the mouth
- Affects the tissues surrounding the teeth, gums pull away, teeth bone loss and teeth falling



Periodontitis

- Severity measure based on clinical attachment level (CAL)
(i.e. Mild: 1-2mm, Moderate: 3-4mm, Severe: $\geq 5\text{mm}$),
refers to the amount of lost periodontal ligament fibers



Periodontitis

- Causes diabetes, cardiovascular complications, respiratory illnesses, etc
- Affects almost half of the US adults (≥ 30 yrs)

Periodontitis

Treatments

- Oral hygiene
- Scaling and root planing (SRP)/with adjunctive treatment
- Laser therapy
- Surgery

Periodontitis

Scaling and root planing (SRP)

- Improved CAL by 0.5mm, i.e. Smiley et al (2015)

Periodontitis

Scaling and root planing (SRP) with adjunctive treatment

- Improved CAL by 0.2-0.6mm than SRP alone, i.e. Smiley et al (2015)
- None of them to be statistically superior to the other, and SRP with local antimicrobial as the best, i.e. John et al (2017).

Periodontitis

Laser therapy

- Effective for some patients according to the American Academy Periodontology(AAP), but inconclusive

Dynamic Treatment Regime

- Precision medicine
- Multi-stage, adaptive interventions according to the patients' response in order to achieve optimal treatment effect
- Managing chronic diseases that require long-term care

Dynamic Treatment Regime

Examples

- Alcoholism, Breslin et al (1998)
- Smoking, Chakraborty et al (2010)
- Drug abuse, Brooner and Kidorf (2002)
- Depression, Untzer et al (2001)
- Hypertension, Glasgow et al (1989)
- Immuno-oncology research, Kidwell et al (2017)
- Oral health, NOVEL

Dynamic Treatment Regime

Existing Treatments for Periodontitis

- Oral hygiene instruction (1)
- Education on risk reduction (2)
- Scaling and root planing (SRP) (3)
- SRP with adjunctive:
 - Local antimicrobial therapy (4)
 - Systemic antimicrobial therapy (5)
 - Photodynamic therapy (this uses lasers, but only to activate an antimicrobial agent) (6)
 - Systemic subantimicrobial-dose doxycycline (SDD) (7)
- Laser therapy (8)

Dynamic Treatment Regime

Proposal Treatment Regimes

- Regime 1 (d_1): 1 and 2→3→ 3^R or 4^{NR}
- Regime 2 (d_2): 1 and 2→3→ 3^R or 5^{NR}
- Regime 3 (d_3): 1 and 2→3→ 3^R or 6^{NR}
- Regime 4 (d_4): 1 and 2→3→ 3^R or 7^{NR}
- Regime 5 (d_5): 1 and 2→8→ 8^R or 4^{NR}
- Regime 6 (d_6): 1 and 2→8→ 8^R or 5^{NR}
- Regime 7 (d_7): 1 and 2→8→ 8^R or 6^{NR}
- Regime 8 (d_8): 1 and 2→8→ 8^R or 7^{NR}

Note that 'R' stands for response and 'NR' stands for non-response.

Sequential Multiple Assignment Randomized Trial (SMART)

- Popularly used to study dynamic treatment regimes (DTRs),
i.e. Murphy (2005), Chakraborty and Moodie (2013)
- Randomization at the initial stage, followed by
re-randomization at subsequent stage(s), depending on
patients' intermediate response

Sequential Multiple Assignment Randomized Trial (SMART)

Biometrical Journal **60** (2019) 10

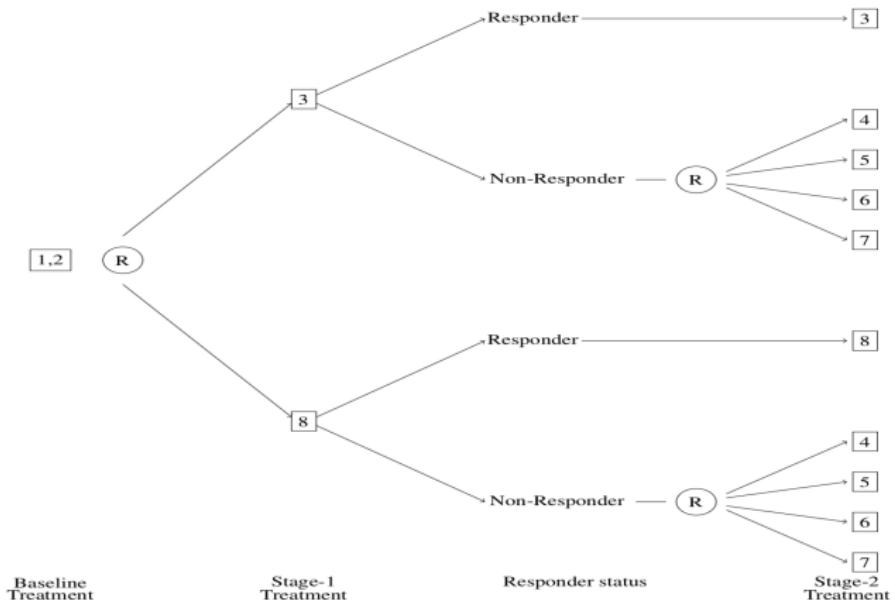


Figure 2 A SMART design schematic diagram for developing DTRs for treating chronic periodontitis. R = randomization, 1 = oral hygiene instruction, 2 = education on risk reduction, 3 = scaling and root planing (SRP), 4 = SRP with local antimicrobial therapy, 5 = SRP with systemic antimicrobial therapy, 6 = SRP with photodynamic therapy, 7 = SRP with systemic sub-antimicrobial-dose doxycycline (SDD), 8=laser therapy.

Sequential Multiple Assignment Randomized Trial (SMART)

Advantages of SMART over Single-Stage Trials

- Single-stage trials may fail to detect delayed effects
- SMARTs offer better options at the second stage in case an initial treatment is not effective.
- Non-responders may drop out of single-stage trials, but less likely to drop out of a SMART because they expect to receive possibly better treatments at the next stage if the initial treatment is ineffective for them.

Analysis Plan and Sample Size Calculation

Hypothesis Tests

- Hypothesis 1: Detecting a single regime effect, e.g., Regime 1
- Hypothesis 2: Comparing a pair of regimes with same initial treatment, e.g., Regime 1 vs Regime 3
- Hypothesis 3: Comparing a pair of regimes with different initial treatment, e.g., Regime 1 vs Regime 5
- Hypothesis 4: Testing whether a particular regime (e.g. Regime 1) is the best

Analysis Plan and Sample Size Calculation

Sample Size Calculation

- Hypotheses 1-3:

$$\Pr\left(\frac{\hat{\delta}}{2\sigma/\sqrt{N}} \geq z_{\alpha/2}\right) = \text{Power}$$

- Hypothesis 4:

$$\Pr\left(\frac{\hat{\delta}_{d_1-d_2}}{2\sigma_{d_1-d_2}/\sqrt{N}} \geq z_{\alpha}, \dots, \frac{\hat{\delta}_{d_1-d_8}}{2\sigma_{d_1-d_8}/\sqrt{N}} \geq z_{\alpha}\right) = \text{Power},$$

where, e.g.,

$$\hat{\delta}_{d_1-d_3} = \hat{\mu}_{d_1} - \hat{\mu}_{d_3}$$

and

$$\frac{1}{N} 2\sigma_{d_1-d_3}^2 = \text{VAR}(\bar{Y}^{d_1} - \bar{Y}^{d_3})$$

Analysis Plan and Sample Size Calculation

Outcome measure of Regime 1

- Inverse probability weighting and method of moment
- $\bar{Y}^{d_1} = \frac{1}{N} \sum_{i=1}^N W_i^{d_1} \bar{Y}_i = \hat{\mu}^{d_1}$
- $W_i^{d_1} = \frac{I(i \in d_1)}{\Pr(i \in d_1)} = \frac{I(A_{i1} = a_{1i}^{d_1}, A_{i2} = [a_{2i}^{d_1 R}]^{R_i} [a_{2i}^{d_1 NR}]^{1-R_i})}{\pi_{1i}^{d_1} [\pi_{2i}^{d_1 R}]^{R_i} [\pi_{2i}^{d_1 NR}]^{1-R_i}}$
- A_{i1} : treatment at stage-I of individual i
- R_i : responding status at stage-I of individual i
- $\pi_{2i}^{d_1 R}$: allocation probability of stage-II treatments for individual i who responses (R) at stage-I under regime 1 (d_1)

Analysis Plan and Sample Size Calculation

Outcome measure of each patient

- Average of CAL change over the available teeth

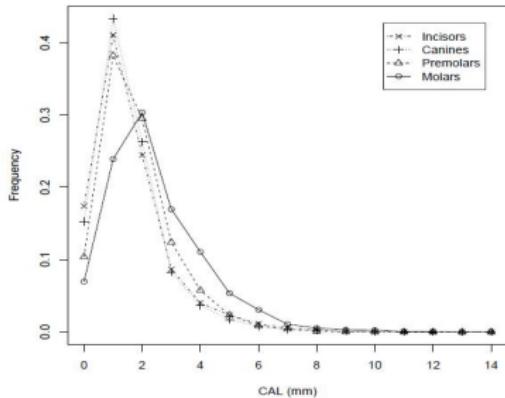
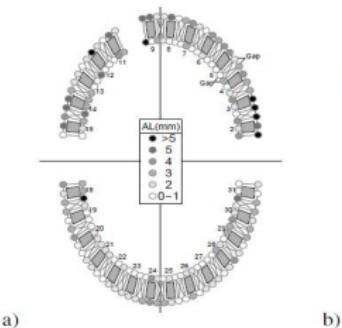
- $\bar{Y}_i = \frac{\sum_{t=1}^{28} Y_{it}(1 - M_{it})}{\sum_{t=1}^{28} (1 - M_{it})}$

Note that estimating $E(\bar{Y}_i)$ and $\text{VAR}(\bar{Y}_i)$ require Monte Carlo method.

Analysis Plan and Sample Size Calculation

Change of Clinical Attachment Level (CAL)

- $Y_{it} = \mu_i + Q_{it} + \epsilon_{it1}, i = 1 \dots, N \text{ and } t = 1, \dots, 28,$
 - $Q_i \sim MVN(\mathbf{0}, \text{spatial}(\boldsymbol{\Sigma}))$
 - $\epsilon_{it1} \sim ST(0, \sigma_1^2, \lambda, \nu)$



Analysis Plan and Sample Size Calculation

Tooth Missing

- $M_{it} = I(a_0 + b_0 Q_{it} + \epsilon_{it0} > 0)$, where
 - $Q_i \sim MVN(\mathbf{0}, spatial(\Sigma))$
 - $\epsilon_{it0} \sim N(0, \sigma_0^2)$
 - Reich and Bandyopadhyay (2010), Ann Appl Stat, “A Latent Factor Model for Spatial Data with Informative Missness”

Analysis Plan and Sample Size Calculation

Assumptions:

1. Random vectors $(\bar{Y}_i, W_i^{d_1}, W_i^{d_3})$, $0 \leq i \leq N$ are independent and identically distributed, and distribution of \bar{Y}_i is independent of $W_i^{d_1}$ and $W_i^{d_3}$.
2. Let μ_{d_10} , μ_{d_30} , and $\delta_{(d_1-d_3)0}$ denote the true values of μ_{d_1} , μ_{d_3} , and $\delta_{d_1-d_3}$, respectively. Assume unbiased estimators $\frac{1}{N} \sum_{i=1}^N W_i^{d_1} \bar{Y}_i$ and $\frac{1}{N} \sum_{i=1}^N W_i^{d_3} \bar{Y}_i$ for μ_{d_1} and μ_{d_3} , respectively, i.e., $E(W_i^{d_1} \bar{Y}_i - \mu_{d_1}) = 0$ only when $\mu_{d_1} = \mu_{d_10}$ and $E(W_i^{d_3} \bar{Y}_i - \mu_{d_3}) = 0$ only when $\mu_{d_3} = \mu_{d_30}$. Hence, $E(\hat{\delta}_{d_1-d_3} - \delta_{d_1-d_3}) = 0$ only for $\delta_{d_1-d_3} = \delta_{(d_1-d_3)0} = \mu_{d_10} - \mu_{d_30}$.

Analysis Plan and Sample Size Calculation

Theorem

The Inverse Probability Weighting and Method of Moment estimator $\hat{\delta}_{d_1-d_3}$ is a consistent estimator of $\delta_{d_1-d_3}$. Under moment conditions and the above assumptions, we have asymptotic property of normality $\sqrt{N}(\hat{\delta}_{d_1-d_3} - \delta_{(d_1-d_3)0}) \rightarrow \text{Normal}(0, 2\sigma_{d_1-d_3}^2)$.

Simulation

- Hypothesis 1-4
- Power: 80%
- Level of significance: 5%

Simulation

Table: Hypothesis 1: $H_0 : \mu_{d_1} = 0$ vs $H_1 : \mu_{d_1} \neq 0$

Absolute Effect Size	Skewness	DF	Response Rate d_1	Standardised Effect Size	Sample Size	Power
1.28	0	Inf	0.25	0.43	84	0.80
0.78			0.5	0.29	189	0.79
1.28		8	0.25	0.43	84	0.80
0.78			0.5	0.29	190	0.81
1.28		3	0.25	0.43	86	0.81
0.78			0.5	0.28	196	0.79
2.03	10	Inf	0.25	0.51	60	0.79
1.53			0.5	0.43	87	0.80
2.11		8	0.25	0.52	59	0.79
1.61			0.5	0.44	83	0.79
2.31		3	0.25	0.53	57	0.80
1.82			0.5	0.46	76	0.80

Simulation

Table: Hypothesis 2: $H_0 : \mu_{d_1} = \mu_{d_3}$ vs $H_1 : \mu_{d_1} \neq \mu_{d_3}$

Absolute Effect Size	Skewness	DF	Response Rate d_1	Standardised Effect Size	Sample Size	Power
1.12	0	Inf	0.25	0.35	127	0.80
0.75			0.5	0.26	229	0.79
1.12		8	0.25	0.35	128	0.79
0.75			0.5	0.26	233	0.80
1.12		3	0.25	0.35	132	0.80
0.75			0.5	0.26	238	0.80
1.13	10	Inf	0.25	0.25	257	0.80
0.75			0.5	0.18	465	0.81
1.13		8	0.25	0.24	277	0.80
0.75			0.5	0.18	498	0.80
1.12		3	0.25	0.22	333	0.79
0.75			0.5	0.16	593	0.80

Simulation

Table: Hypothesis 3: $H_0 : \mu_{d_1} = \mu_{d_5}$ vs $H_1 : \mu_{d_1} \neq \mu_{d_5}$

Absolute Effect Size	Skewness	DF	Response Rate d_1	Standardised Effect Size	Sample Size	Power
0.63	0	Inf	0.25	0.19	420	0.78
0.75			0.5	0.25	244	0.80
0.62		8	0.25	0.19	432	0.81
0.74			0.5	0.25	249	0.80
0.63		3	0.25	0.19	444	0.80
0.75			0.5	0.25	257	0.80
0.63	10	Inf	0.25	0.14	842	0.79
0.75			0.5	0.18	484	0.81
0.63		8	0.25	0.13	909	0.80
0.75			0.5	0.17	524	0.81
0.62		3	0.25	0.12	1097	0.80
0.75			0.5	0.16	623	0.80

Simulation

Table: Hypothesis 4: $H_0 : \mu_{d_1} \leq \mu_{d_2} \text{ or } \dots \text{ or } \mu_{d_1} \leq \mu_{d_8}$ vs
 $H_1 : \mu_{d_1} > \mu_{d_2} \text{ & } \dots \text{ & } \mu_{d_1} > \mu_{d_8}$

Absolute Effect Size	Skewness	DF	Response Rate d_1	Standardised Effect Size	Sample Size	Power
1.50	0	Inf	0.25	0.48	95	0.79
1.00			0.5	0.35	179	0.80
1.50		8	0.25	0.48	96	0.80
1.00			0.5	0.35	180	0.80
1.50		3	0.25	0.47	101	0.80
1.00			0.5	0.34	189	0.80
1.50	10	Inf	0.25	0.35	172	0.78
1.00			0.5	0.26	316	0.79
1.50		8	0.25	0.34	186	0.79
1.00			0.5	0.25	344	0.80
1.50		3	0.25	0.31	229	0.79
1.00			0.5	0.23	418	0.79

R Implementation

- Package: SMARTp
- Sample size calculation function: SampleSize_SMARTp

```
SampleSize_SMARTp(mu, st1, dtr, regime, pow, a,  
rho, tau, sigma1, lambda, nu, sigma0, Num, p_i,  
c_i, a0, b0, cutoff)
```

R Implementation

```
SampleSize_SMARTp(mu, st1, dtr, regime, pow, a,  
rho, tau, sigma1, lambda, nu, sigma0, Num, p_i,  
c_i, a0, b0, cutoff)
```

```
#The packages required  
library("SMARTp")  
library("mvtnorm")  
library("sn")
```

R Implementation

```
SampleSize_SMARTp(mu, st1, dtr, regime, pow, a,  
rho, tau, sigma1, lambda, nu, sigma0, Num, p_i,  
c_i, a0, b0, cutoff)
```

```
#The SMART Design  
mu = matrix( 0, 10, 28 )  
mu[ 2, ] = rep( 0.5, 28 )  
mu[ 4, ] = rep( 2, 28 )  
mu[ 7, ] = rep( 5, 28 )  
st1 = cbind( c( 1,1 ), c( 4, 4 ), c( 0.25, 0.5  
, 1 : 2 )  
dtr = cbind( 1 : 8,  
c( rep( 1, 4 ), rep( 6 , 4 ) ),  
c( 2, 3, 4, 5, 7, 8, 9, 10 ),  
c( rep( 1, 4 ), rep( 2, 4 ) ) )
```



R Implementation

```
SampleSize_SMARTp(mu, st1, dtr, regime, pow, a,  
rho, tau, sigma1, lambda, nu, sigma0, Num, p_i,  
c_i, a0, b0, cutoff)
```

```
#Hypothesis Test 3,  
#with power and Type-1 error rates to be 80%  
#and 5% respectively  
regime=c(1,5)  
pow = 0.8  
a = 0.05
```

R Implementation

```
SampleSize_SMARTp(mu, st1, dtr, regime, pow, a,  
rho, tau, sigma1, lambda, nu, sigma0, Num, p_i,  
c_i, a0, b0, cutoff)
```

```
# Parameter values given by Reich and  
Bandyopadhyay (2010)  
cutoff=0;  
sigma1=0.95; sigma0=1;  
lambda=0; nu=Inf;  
b0=0.5; a0=-1.0;  
rho=0.975;tau=0.85;
```

R Implementation

```
SampleSize_SMARTp(mu, st1, dtr, regime, pow, a,  
rho, tau, sigma1, lambda, nu, sigma0, Num, p_i,  
c_i, a0, b0, cutoff)
```

```
#Iteration size  
Num = 1000000
```

R Implementation

The R code to compute

- Sample Size: N.
- Effect Size: Del.
- Standardised Effect Size: Del_std.

R Implementation

```
SampleSize = SampleSize_SMARTp( mu = mu, st1 =  
st1, dtr = dtr, regime = regime, pow = pow, a =  
a, rho = rho, tau = tau, sigma1 = sigma1, lambda  
= lambda, nu = nu, sigma0 = sigma0, Num = Num,  
a0 = a0, b0 = b0, cutoff = cutoff );  
  
N = ceiling(SampleSize$N); print(N);  
  
Del = SampleSize$Del; print(Del);  
  
Del_std = SampleSize$Del_std; print(Del_std);
```

R Implementation

Absolute Effect Size	Skewness	DF	Response Rate d_1	Standardised Effect Size	Sample Size	Power
2.12	0	Inf	0.25	0.28	196	0.79

Conclusion

- This paper proposes some novel DTRs for periodontitis.
- These DTRs can be studied under a SMART design.
- The proposed sample size calculation method has been validated in terms of Monte Carlo power.
- To compare with existing method of clustered SMART design, i.e. Ghosh (2015) and NeCamp (2017), the proposed method considers informative missingness, spatial associations and non-normal outcomes.
- R package “SMARTp” is available in CRAN

Further Direction

- Sample size calculation to select the optimal treatment regime, e.g., Artman, et al (2017)
- Sample size calculation that include covariates using Q-learning approach
- Run a study, collect the data and perform data analysis, then update the experimental design, statistical analysis plan and sample size method

Acknowledgement

- Dr Chakraborty's AcRF Tier 2 grant from the Ministry of Education, Singapore
- Dr Chakraborty's start-up grant from Duke-NUS, Singapore
- Dr Bandyopadhyay's grant from the National Institutes of Health, United States
- Comments from editors and reviewers of Biometrical Journal