Design of clustered sequential multiple assignment randomized trial (cSMART)

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Abstract

In behavioral intervention research, group/community based clinical trials are quite common. In recent times, sequential multiple assignment randomized trials (SMART) are being used to develop optimal treatment strategies for patients based on their medical history. In this work, we design clustered SMART (cSMART) for group/community based intervention. Assuming the outcome variable is continuous and introducing intra-class correlation, the sample size formula for cSMART has been derived. A simulation study shows estimated power corresponding to the derived sample size formulae.

Key words: Intra-class correlation, SMART design, sample size, clustered data.

1 Introduction

Community based clinical trials are quite common in behavioral intervention research. In this type of trials, interventions are provided at a group or family or other community level instead of individual level. Xiong et al. (1994) discussed a family based randomized controlled trial for schizophrenic patients in China. Other examples of community/family based study can be found in obsessive compulsive disorder (Storch et al., 2010), obesity (White et al., 2004), prevention and treatment of drug abuse (Liddle et al., 2008), family bereavement programs (Sandler et al., 2010; Hagan et al., 2012) and in a school-based problem behavior prevention programs (Flay and Collins, 2005). A different approach is needed to conduct a community based study as in this case the unit is a group/family rather than an individual.

In recent years, in different medical fields, more in behavioral science, multiple treatments are given to a patient over the different stages of treatment process. A related question, different from the context of conventional clinical trial: what is the optimum sequence of different treatment components for a particular individual? A sequential multiple assignment randomized trial (SMART) is used to develop optimal treatment strategy for each patient based on his/her medical history. In a SMART, randomization is used in each of the different stages of the trial for allocation of treatments among the patients rather than only once in a conventional clinical trial. In general, at the beginning of a SMART, a randomization is done to allocate the available treatment options, followed by re-randomization at each subsequent stage considering some or all the patients to the treatment options corresponding to a stage (Lavori and Dawson, 2004; Murphy, 2005).

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In this work, we consider design issues of a SMART for clustered data. Consider a hypothetical family based education reinforcement study to reduce the risk of stroke. Changes in lifestyle can make a big impact to reduce the risk of stroke. The proposed hypothetical study involves multiple interventional components to address the various risk factors of stroke. The unit of interest is a family (cluster). Assume, there are m number of members from each family with high risk of stroke, are to attend six didactic sessions over a 12-month period, and in each session one of the two intervention components nutrition (NU) and physical activity (PA) or both are given to modify the risk factors related to stroke. Guidelines on social cognitive theory (Bandura, 2004) are followed to develop the sequence of sessions. Figure 1 illustrate the randomization scheme for the SMART design to be used in this study. There are two stages of the proposed SMART design. The study begins with N number of families. At the start of the first stage, each family (cluster) is randomized between the two interventional components: NU and PA. These interventions will be given over three sessions. Note that, the primary outcome of this study is the reduction in blood pressure level. After six months, i.e., end of the first stage, a family will be a responder if the average blood pressure level of the family decrease; otherwise the family will be a non-responder. As shown in the figure 1, at the second stage, a responder family will continue with same intervention and a non-responder family will be re-randomized to either switch to other component or to the combined components ($NU + PA$). In the next section, we present the sample size formula for this study.

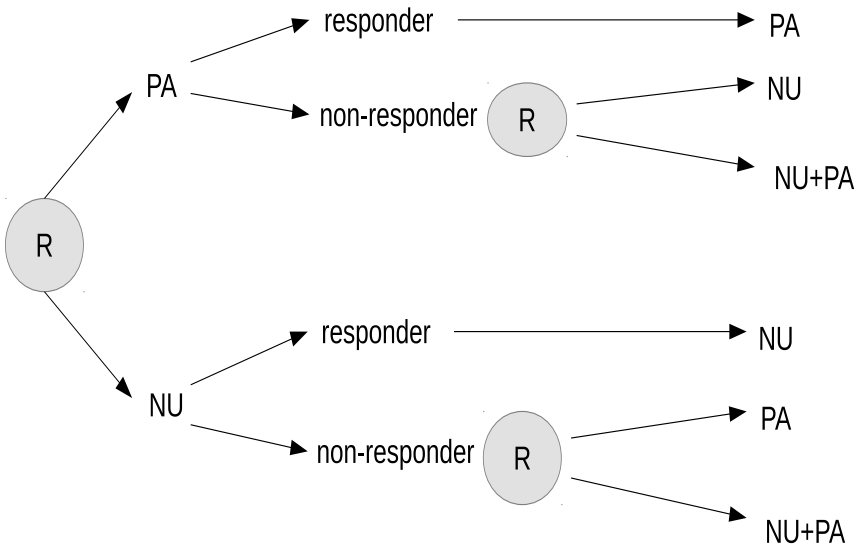

Figure 1: A diagram of a SMART design for the family based education reinforcement study. Here, "R" in a circle represents randomization.

2 Primary Analysis for clustered SMART

In this section, we consider the goal of the primary analysis for a SMART (Oetting et al., 2011) design to compare two or more embedded regimes in the study that starts with different initial treatments. We assume that outcome variable is continuous. Then the primary analysis compares two or more regime means. To conduct a study, we need to estimate the mean of an embedded regime d. In the context of a SMART design, the regime mean is essentially a weighted average of the outcomes of subjects whose treatment trajectories are consistent with d (Oetting et al., 2011; Nahum-Shani et al., 2012; Chakraborty and Murphy, 2014). The weighting follows from the fact that in the SMART design that we are considering here (Figure 1), there is a structural imbalance between responders and non-responders, e.g., the non-responders are re-randomized at stage 2

whereas the responders are not. The responders have a probability of $\frac{1}{2}$ of receiving the treatment sequence they actually received, whereas the non-responders have a probability of $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$ of receiving the treatment sequence they actually received. Thus, the weight associated with the ith subject $W_i = \frac{1}{1/2} = 2$ for responders, and likewise $W_i = \frac{1}{1/4} = 4$ for non-responders. In general, the weight can be written as $W_i = 2(2 - R_i)$ where R_i is the response indicator, taking value 1 for responders and 0 for non-responders. The same weighting technique has been widely used in many areas of statistics, namely, the *inverse probability weighted* estimator in causal inference (Hernán et al., 2000).

In case of clustered SMART, intra-class correlation (ICC), the correlation present between the members of the same group or cluster (e.g., members of the same family in a family-based study, or members of a community in a community-based study) makes the study more complicated.

3 Sample Size Calculation

Let X_i, $i = 1, \ldots, N_d$ denote the primary outcome for the ith subject for a given regime d, where N_d is the number of subjects in the trial whose treatment trajectories are consistent with d. We assume that X is continuous; for example, in a blood pressure reduction intervention trial as described in Section 1, X could be the change in blood pressure level from baseline. Suppose $E(X_i) = \mu$ and $\text{Var}(X_i) = \sigma^2$, for all $i = 1, \ldots, N_d$. Then the observed mean of the regime d is $\overline{X}_d = \sum_{i=1}^{N_d} W_i X_i / \sum_{i=1}^{N_d} W_i$, where W_i is as defined above. Then, $E(\overline{X}_d) = \sum_{i=1}^{N_d} W_i E(X_i) / \sum_{i=1}^{N_d} W_i = \mu$, and $\text{Var}(\overline{X}_d) = \sigma^2 \sum_{i=1}^{N_d} W_i^2 / (\sum_{i=1}^{N_d} W_i)^2$. Using the weights derived from the definition of the regime d, the variance can be computed. For example, let us consider $d = (PA, PA^R, NU^{NR})$, denoting the set of rules, "provide treatment PA at stage 1; continue PA at stage 2 if the person is a responder (R) at the end of stage 1, or switch to NU at stage 2 if the person is a non-responder (NR) at the end of stage 1". Consider there are N subjects at the beginning of the trial and that the response rate to the initial treatment PA is γ, according to some pre-specified definition of response (e.g., whether there has been a reduction in blood pressure from baseline by a pre-specified amount). Half of the original N subjects are expected to get randomized to PA. Then the expected number of responders to PA is simply $\frac{N}{2} \times \gamma$. Similarly, the expected number of non-responders to PA are $\frac{N}{2} \times (1 - \gamma)$. Note that only half of these non-responders get re-randomized to NU, and thus their treatment trajectories become consistent with d. Hence the expected number of people in the trial whose treatment trajectories are consistent with d are given by $E(N_d) = \frac{N}{2} \times \gamma + \frac{N}{2} \times (1-\gamma) \times \frac{1}{2} = \frac{N}{4}(1+\gamma)$. Now, recall that $W_i = 2$ for responders and $W_i = 4$ for non-responders. Hence, for a fixed N_d, $\sum_{i=1}^{N_d} W_i = 2 \times (\frac{N}{2} \times \gamma) + 4 \times \frac{N}{2} \times (1 - \gamma) \times \frac{1}{2} = N$ and $\sum_{i=1}^{N_d} W_i^2 = 2^2 \times (\frac{N}{2} \times \gamma) + 4^2 \times \frac{N}{2} \times (1 - \gamma) \times \frac{1}{2} = 2(2 - \gamma)N$. It follows that $\text{Var}(\overline{X}_d) = \frac{2(2-\gamma)}{N} \sigma^2$.

Furthermore, the members within a group are correlated, i.e. $\text{corr}(X_{ij}, X_{i'j}) = \rho$ for $i \neq i'$ within a fixed j, which amounts to $\text{Cov}(X_{ij}, X_{i'j}) = \rho\sigma^2$; however, members from different groups are uncorrelated, i.e. $\text{corr}(X_{ij}, X_{i'j'}) = 0$ for $j \neq j'$ for any i, i'. As mentioned before, in a group-randomized trial, the unit of intervention and analysis is a group. We take the overall group outcome to be an average of all the members' outcomes in the group, i.e., $\overline{X}_j = \frac{1}{m} \sum_{i=1}^{m} X_{ij}$, as is often the case. In general, one can think of other choices of the group outcome. It follows that $E(\overline{X}_j) = \mu$ and

$$\text{Var}(\overline{X}_j) \;=\; \frac{1}{m^2} \Big[\sum_i \text{Var}(X_{ij}) + \sum_{i \neq i'} \text{Cov}(X_{ij}, X_{i'j}) \Big] = \frac{1}{m^2} \Big[m\sigma^2 + m(m-1)\rho\sigma^2 \Big] = \frac{\sigma^2}{m} [1 + (m-1)\rho].$$

Now for a given regime d, the observed regime mean is a weighted average of the group outcomes of all the N_d groups whose treatment trajectories are consistent with d, and the weights W_j are

determined by the structure of the SMART design. Thus the observed mean of the regime is $\overline{X}_d = \sum_{j=1}^{N_d} W_j \overline{X}_j / \sum_{j=1}^{N_d} W_j$. Then, $E(\overline{X}_d) = \sum_{j=1}^{N_d} W_j E(\overline{X}_j) / \sum_{j=1}^{N_d} W_j = \mu$, and $\text{Var}(\overline{X}_d) = \sum_{j=1}^{N_d} W_j^2 / (\sum_{j=1}^{N_d} W_j)^2 \cdot \frac{\sigma^2}{m}[1 + (m-1)\rho]$. Note that, the stage one of both the regimes have identical number of patients.

The hypothesis under consideration is $H_0 : \mu_1 = \mu_2$, and the unscaled test statistic, $\overline{X}_{d_1} - \overline{X}_{d_2}$, for large samples, follows $\mathcal{N}(\delta, \frac{2\sigma^2}{mN}(4-\gamma_1-\gamma_2)(1+(m-1)\rho))$ under $H_1 : \mu_1 \neq \mu_2$, where $\delta = (\mu_1 - \mu_2)/\sigma$ is the postulated scaled effect size. It can be easily shown, the required number of groups (families)

Table 1: Calculated sample size and the Monte Carlo estimate of power when the nominal power is 80%, type I error $\alpha = 0.05$, common initial response rate $\gamma_1 = \gamma_2 = \gamma = 0.2$, and postulated difference in mean $\mu_2 - \mu_1 = 0.4$.

m	σ	ρ	scaled effect size	required $E(N_{d_1}) = E(N_{d_2})$	required total N	estimated power
	2.0	0.01	0.2	144	480	80.50%
3	0.8	0.01	0.5	23	77	79.49%
	0.5	0.01	0.8	9	30	80.83%
	2.0	0.05	0.2	155	518	80.99%
3	0.8	0.05	0.5	25	83	81.51%
	0.5	0.05	0.8	10	32	80.90%
	2.0	0.10	0.2	170	565	80.63%
3	0.8	0.10	0.5	27	90	80.78%
	0.5	0.10	0.8	10	35	78.36%
	2.0	0.01	0.2	46	154	81.05%
10	0.8	0.01	0.5	8	25	83.69%
	0.5	0.01	0.8	3	10	82.30%
	2.0	0.05	0.2	62	205	80.94%
10	0.8	0.05	0.5	10	33	82.78%
	0.5	0.05	0.8	4	13	84.89%
	2.0	0.10	0.2	80	268	80.47%
10	0.8	0.10	0.5	13	43	81.90%
	0.5	0.10	0.8	5	17	77.30%

5 Discussion

In this work, we have provided the sample size formula for clustered SMART designs. We have also discussed how to construct the weights appearing in the definition of a regime mean. This may be helpful defining regime means in more complex SMART designs. This methodology can be extended to other outcome types; see Ghosh et al. (2015) for details.

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