A sample size calculator for *SMART* pilot studies

Abstract

In clinical practice, as well as in other areas where interventions are provided, a sequential individualized approach to treatment is often necessary, whereby each treatment is adapted based on the object′s response. An *adaptive intervention* is a sequence of decision rules which formalizes the provision of treatment at critical decision points in the care of an individual. In order to inform the development of an *adaptive intervention*, scientists are increasingly interested in the use of *sequential multiple assignment randomized trials* (*SMART*), which is a type of multi-stage randomized trial where individuals are randomized repeatedly at critical decision points to a set treatment options. While there is great interest in the use of *SMART* and in the development of *adaptive interventions*, both are relatively new to the medical and behavioral sciences. As a result, many clinical researchers will first implement a *SMART* pilot study (i.e., a small-scale version of a *SMART*) to examine feasibility and acceptability considerations prior to conducting a full-scale *SMART* study. A primary aim of this paper is to introduce a new methodology to calculate minimal sample size necessary for conducting a *SMART* pilot.

1 Introduction

In the medical and behavioral health sciences, researchers have successfully established evidence-based treatments for a variety of health disorders. However, even with evidence-based treatments, there is heterogeneity in the type of individuals who respond and do not respond to treatment. Treatment effects may also vary over time (within the same individual): a treatment that improves outcomes in the short-run for an individual may not improve outcomes longer-term. Further, certain evidence based treatments may be too expensive to provide to all individuals; in such cases, health care providers may reserve these treatments for individuals who do not respond to less costly alternatives. The converse is also true: certain treatments are more ideally suited as maintenance treatments, and may be reserved for individuals who respond to earlier treatments in order to sustain improvements in outcomes. As a result, clinical researchers have recently shown great interest in developing sequences of treatments that are adapted over time in response to each individual's needs. This approach is promising because it allows clinicians to capitalize on the heterogeneity of treatment effect. An *adaptive intervention* offers a way to guide the provision of treatments over time, leading to such individualized sequence of treatments.

An *adaptive intervention* [1, 2, 3] is a sequence of decision rules that formalizes the provision of treatment at critical decision points in the course of care. In other words, an *adaptive intervention* is a guideline that can aid clinicians in deciding which treatment to use, for which individuals to use them, and when to use them. Figure 1 depicts a concrete example of an adaptive intervention for young children who are initially diagnosed with *pediatric anxiety disorder*.

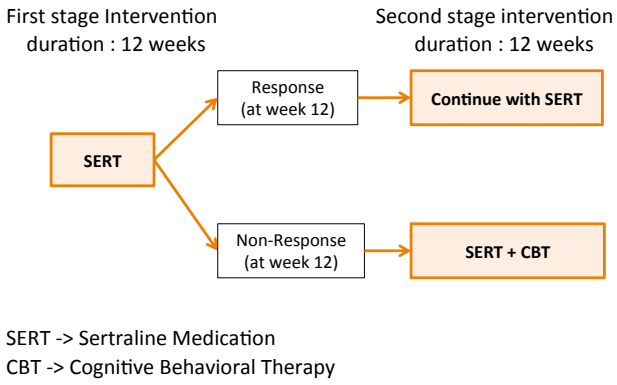

Figure 1: An example adaptive intervention for pediatric anxiety disorder patients

In this example *adaptive intervention*, first, clinicians offer the medication *sertraline* [4] for initial 12 weeks. If the child does not show an adequate response to the medication *sertraline* at the end of week 12, the clinician offers to augment the treatment with a combination of the medication *sertraline* and *cognitive behavioral therapy* [5] for additional 12 weeks. Otherwise if the child shows

an adequate response to initial medication, the clinician would continue the *sertraline* medication for another 12 weeks. In this *adaptive intervention*, response is defined based on a measure of improvement, for example, based on a cut-off of five or less on the *Clinical Global Impression-Improvement Scale* [6]. Change in the *Pediatric Anxiety Rating Scale* could also be used to define response/non-response [7]. An *adaptive intervention* is also known as an *adaptive treatment strategy* [8] or a *dynamic treatment regime* [9].

Recently, methodologists introduced a specific type of randomized trial design known as a *Sequential Multiple Assignment Randomized Trials* [1, 10, 11] to inform the development of high-quality, empirically-supported *adaptive interventions*. A *SMART* is a type of multi-stage trial where each subject is randomly (re)assigned to one of various treatment options at each stage. Each stage corresponds to a critical treatment decision point. And each randomization is intended to address a critical scientific question concerning the provision of treatment at that stage; together, the multiple randomizations and addressing these questions helps inform the development of a high-quality *adaptive intervention*. Lei et al. [1] reviews a number of *SMART* studies in behavioral interventions science. Also, see work by Almirall et al. [10]

An example *SMART* is provided in Figure 2. This example *SMART* could be used to develop an adaptive intervention for children who are diagnosed with *pediatric anxiety disorder*. At the first stage, there are two treatment options, *sertraline* medication or *cognitive behavioral therapy(CBT)*. Each subject is randomly assigned to one of the initial treatment options and the assigned treatment is conducted for the first 12 weeks. At the end of week 12, each subject's response to treatment is assessed based on *Clinical Global Impression-Improvement Scale* [4] and categorized as a responder or as a non-responder. Based on this, those who do not respond to the initial treatment are again randomly assigned to one of two secondary treatment options: One is a switch strategy whereby the child is switched to the stage 1 treatment option they were not offered at first. The second option is the combination of both *sertraline* medication and *cognitive behavioral therapy(CBT)*. For those who responded by the end of 12 weeks, continually initial intervention will be used. As with stage 1, both stage 2 treatments are provided for 12 weeks. Research outcomes, such as the *Pediatric Anxiety Rating Scale* [4], are collected at the end of week 24.

The *SMART* study described above can be used to address three key scientific questions in the development of an *adaptive intervention* for *pediatric anxiety disorder*: (1) 'Which treatment to use in stage 1, medication or *CBT*?' and (2) 'Which tactic is best for non-responders to stage 1 treatment, switch or augment?' Both of these questions involve randomized comparisons. Question (1) is addressed by comparing outcome measures of subgroup A, B and C in the Figure 2 with outcome measures of subgroup D,E and F in the Figure 2. Question (2) is addressed by comparing subgroup B and C when medication *sertraline* is stage 1 treatment and subgroup E and F when *CBT* is stage 1 treatment. Lastly, (3) This *SMART* design could also be used to compare the following four *adaptive interventions* contained within it.

1. First, offer *sertraline* medication for 12 weeks. If the patient does not respond well to initial medication at the end of week 12, augment by initiating a combination therapy (*sertraline*

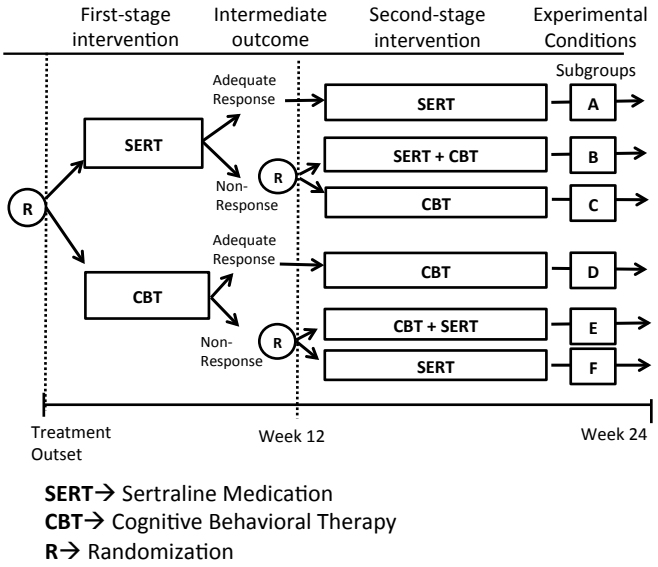

Figure 2: An example *SMART* for pediatric anxiety disorder patients

and *CBT*) for next 12 weeks. Otherwise continue with the medication *sertraline* for another 12 weeks. (Children in subgroups A and B provided data for this *adaptive intervention*.)

2. First, offer *sertraline* medication for 12 weeks. If the patient does not respond well to initial medication at the end of week 12, switch the treatment to *CBT* for next 12 weeks. Otherwise continue with the medication *sertraline* for another 12 weeks. (Children in subgroups A and C provided data for this *adaptive intervention*.)

3. First, offer *CBT* medication for 12 weeks. If the patient does not respond well to initial medication at the end of week 12, augment by initiating a combination therapy (*sertraline* and *CBT*) for next 12 weeks. Otherwise continue with the medication *CBT* for another 12 weeks. (Children in subgroups D and E provided data for this *adaptive intervention*.)

4. First, offer *CBT* medication for 12 weeks. If the patient does not respond well to initial medication at the end of week 12, switch the treatment to *sertraline* medication for next 12 weeks. Otherwise continue with the medication *CBT* for another 12 weeks. (Children in subgroups D and F provided data for this *adaptive intervention*.)

Note that the type of design used for *SMART* study described in Figure 2 is one of the most frequently used design. It has been used in *SMART* study of *adolescent marijuana use* [12], *cocaine dependence* [13, 14] and *youth with conduct disorders* [15]. For more recent ongoing *SMART* studies, visit the website: `http://methodology.psu.edu/ra/smart/projects`. For detailed data analysis method regarding *SMART*, see the work of Nahum-Shani et al. [11, 16].

Despite the advantages of *SMARTs*, it is fairly new to clinical research. Therefore, researchers may have concerns over the feasibility or acceptability of conducting a *SMART*. Feasibility refers to the capability of the investigators to perform the *SMART* and the ability of clinical staff (i.e., staff providing treatment) to treat subjects with the *adaptive interventions* in the *SMART*. For example, the psychologists or psychiatrists delivering the stage 1 treatments may have concerns about the way non-response is defined; it is important to work out these concerns prior to a full-scale *SMART* study. Acceptability refers to the tolerability of the *adaptive interventions* being studied from the perspectives of study participants, as well as the appropriateness of the decision rules from the perspective of the clinical staff. For instance, some parents may object to a switch strategy (they may, instead, prefer an augmentation or an intensification strategy). If this happens often, investigators may re-consider the acceptability of the switch strategy prior to conducting a full-scale *SMART*. In such cases, researchers may conduct *SMART pilot study* to resolve feasibility and acceptability concerns prior to performing the full-scale *SMART* study.

The design of any study (pilot or full-scale randomized trial) requires researchers to select an appropriate sample size in order to conduct the study. In full scale randomized trials (including *SMART*s), the sample size is typically determined to ensure sufficient statistical power to detect a minimally clinically significant treatment effect. For example, in a full scale *SMART* study, such as the one shown in Figure 1, the sample size could be determined to provide sufficient power (e.g., 80%) to detect a minimaly clinically significant treatment effect between any two of the four embedded adaptive interventions [17].

However, because the primary aim of pilot studies center on acceptability and feasibility considerations, the sample size for pilot studies are not based on statistical power considerations [18, 19, 20, 21]. For the *SMART* pilot study, the goal is to examine feasibility and acceptability of conducting a full-scale trial. One approach for selecting a sample size achieving this is to observe sufficient number of participants for each subgroup from A to E in Figure 2. This is because each subgroup corresponds to a particular sequence of treatments and if the investigator does not have an ample amount of participants in each group, they cannot detect potential problems regarding feasibility or acceptability of certain sequence of treatments prior to conducting full-scale *SMART*. The primary aim of this article is to introduce a new method which calculates a minimal sample size of *SMART* pilot study.

In section 2, we develop the methodology for calculating the minimal sample size for *SMART* pilot studies that are like the *pediatric anxiety disorder SMART* presented above. In section 3, we verify the result using simulation method. We also compare our proposed methodology with an existing method [22]. In section 4, we extend the method in section 2 to other types of *SMART* designs (the pediatric anxiety *SMART* described above represents just one type of S*SMART* design). In section 5, we provide a summary and discussions including areas for future work.

2 A method for calculating the sample size for a *SMART* pilot study

2.1 The Proposed Approach

In this section, we develop a sample size calculator for *SMART* pilot studies. We first develop an approach for the *SMART* study shown in Figure 2. Note that the method we will provide can be used in any area of *SMART* study whose design is identical to *SMART* study described in Figure 2. Later, in Section 4, we generalize the method for other types of *SMART* designs. The approach provides investigators planning a *SMART* pilot study a principled way to choose the sample size for the pilot study, such that a minimal number of participants are observed in subgroups A-F in Figure 2. This is important because if the investigators do not observe sufficient number of participants of one particular sequence of treatments, the investigator cannot judge whether the sequence of treatments is actually feasible or can be accepted. For example, suppose that to examine feasibility and acceptability concerns, an investigators wishes to observe at least three participants in each of the subgroups A-F in Figure 2: in this case, how many participants should the investigators recruit in the study? Because the exact number of non-responders is unknown ahead of the pilot study, a probabilistic argument is necessary to answer such a question.

To formalize these ideas we first define some notation. Let N denote the total sample size of the *SMART* pilot study. For simplicity, we assume N is always a multiple of two; later we discuss the implications of this. Let m denote the minimum number of participants that an investigator would like to observe in subgroups A-F. Let q_{j} denote the anticipated rate of non-response to stage 1 treatment where $\mathrm{j} = \mathrm{SERT}$ or $\mathrm{j} = \mathrm{CBT}$. And let $q = \min(q_{\mathrm{SERT}}, q_{\mathrm{CBT}})$, which will be used as a common non-response rate; the implications of using the minimum will also be discussed later. Lastly, a lower bound for the probability of the event that each subgroup will have at least m number of participants is denoted as k. Note that m, q and k are all provided by the investigator planning the *SMART* pilot. Hence, our goal is to provide a formulae for N as a function of m, q and k. More formally, the goal is to find a smallest N which satisfies

$$\mathbb{P}(\text{all subgroups A-F have more than } \mathrm{m} \text{ participants}) > k$$

Using our notation, the above is equivalent to

$$\mathbb{P}(M_{\mathrm{A}} > m, M_{\mathrm{B}} > m, M_{\mathrm{C}} > m, M_{\mathrm{D}} > m, M_{\mathrm{E}} > m \,\mathrm{and}\, M_{\mathrm{F}} > m) > k \tag{1}$$

where M_{A} stands for the number of participants who fall into subgroup A. M_{B},M_{C}, M_{D}, M_{E} and M_{F} are defined in same way, respectively. Note that $M_{\mathrm{A}}, M_{\mathrm{B}}, M_{\mathrm{C}}, M_{\mathrm{D}}, M_{\mathrm{E}}$ and M_{F} are all random variables. Next, we re-express equation (1) as

$$\mathbb{P}(M_{\mathrm{A}} > m, M_{\mathrm{B}} > m, M_{\mathrm{D}} > m \,\mathrm{and}\, M_{\mathrm{E}} > m) > k \tag{2}$$

This is because, by the design of *SMART* study in Figure 2, $M_{\mathrm{B}} = M_{\mathrm{C}}$ and $M_{\mathrm{E}} = M_{\mathrm{F}}$. In other words,

by block randomization [23] with equal probabilities there are as many participants in subgroup B as there are in subgroup C; similarly, there are as many participants in subgroup E as there are in subgroup F. Therefore an equation (2) is equivalent as (1).

Now let M_{NS} denote the number of non-responders out of $\frac{N}{2}$ who were initially assigned to *sertraline* medication; and, similarly, let M_{NC} denote the number of non-responders initially assigned to *CBT*. Then one can rewrite equation (2) as

$$\mathbb{P}\Big(\frac{N}{2} - M_{NS} > m, \quad \frac{M_{NS}}{2} > m, \quad \frac{N}{2} - M_{NC} > m, \quad \frac{M_{NC}}{2} > m\Big) > k \tag{3}$$

which is identical to

$$\mathbb{P}\Big(\frac{N}{2} - m > M_{NS} > 2m, \quad \frac{N}{2} - m > M_{NC} > 2m\Big) > k. \tag{4}$$

By design (i.e., random assignment of N individuals to *sertraline* or *CBT* with equal probability), M_{NS} and M_{NC} are independent random variables. Hence, we have

$$\mathbb{P}\Big(\frac{N}{2} - m > M_{NS} > 2m\Big) \cdot \mathbb{P}\Big(\frac{N}{2} - m > M_{NC} > 2m\Big) > k \tag{5}$$

Now note that

$$M_{NS} = \sum_{i=1}^{N/2} X_i \quad M_{NC} = \sum_{i=1}^{N/2} Y_i$$

where $X_i = 1$ if the nth participant assigned to *sertraline* medication did not respond well or $X_i = 0$ otherwise. Since the probability of non-response to *sertraline* is assumed to be q, we have that X_n has a Bernoulli distribution with probability q [24]. Similarly, Y_n has a Bernoulli distribution with probability q (recall the assumption that the probability of non-response is assumed to be q for both *sertraline* and *CBT*). Therefore, M_{NS} and M_{NC} have identical distributions, which we denote by the random variable M_q. Further, given the result that the sum of independent identically distributed Bernoulli random variables has a Binomial distribution [24], we have that

$$\mathbb{P}\Big(\frac{N}{2} - m > M_q > 2m\Big)^2 > k, \tag{6}$$

where $M_q \sim \text{Binomial}\left(\frac{N}{2}, q\right)$ or, equivalently,

$$\left(\mathbb{P}\Big(\frac{N}{2} - m - 1 \geqslant M_q\Big) - \mathbb{P}\Big(2m \geqslant M_q\Big)\right)^2 > k \tag{7}$$

holds as well.

As a side note, if we have a odd number of participants, it is impossible to assign an equal number of participants to both treatments. Therefore we set N to be a multiple of 2, this is because, by design of our *SMART* study in Figure 2, there is a block randomization in stage 1 [23].

Setting N as a multiple of 2 allows us to assign equal number of participants to two treatment options provided at the first stage. Additionally we use a minimum value of two non-response rate (q_{SERT},q_{CBT}) as a common non-response rate (q). This is because, by using a minimum value of two non-response rates, we will get a robust sample size which satisfies equation (7).

2.1.1 Implementation

For fixed values for m, k and q (i.e., provided by the scientists designing a *SMART* pilot), a suitable value of N can be found by searching for the smallest N such that equation (7) holds true. This is possible because equation (7) is just an inequality with respect to N assuming that m, k and q are given. This is easily accomplished using any computer program capable of calculating upper tail probabilities for random variables with Binomial distributions (e.g., the *pbinom* function in R [25]).

Using the implementation outlined above, Table 1 provides values of N for a range of values of m, k, and q. For example, suppose an investigator wishes that at least 3 participants are observed in each subgroup (m=3) with probability greater than 0.8 (k), and assumes that the common non-response rate is 0.30 (q). Based on the Table 1 below, the investigator needs to recruit at least 66 participants for the *SMART* pilot study.

Table 1: Minimal sample size of *SMART* pilot study using proposed method

	Range of q :	0.20	0.30	0.40	0.50	0.60	0.70	0.80
$k = 0.80$	$m = 3$	100	66	48	38	34	42	64
$k = 0.80$	$m = 4$	124	82	60	48	42	50	76
$k = 0.80$	$m = 5$	148	98	72	56	48	58	88
$k = 0.90$	$m = 3$	112	74	54	42	38	48	74
$k = 0.90$	$m = 4$	138	90	66	52	44	56	86
$k = 0.90$	$m = 5$	162	106	78	60	52	64	100

2.1.2 An Existing Approach

A similar approach to calculate the sample size for *SMART* pilot studies was first proposed by Almirall et al. [22]. Their proposal centered on finding the finding smallest sample size N which satisfies

$$\mathbb{P}(M_B > m, M_C > m, M_E > m, \text{and } M_F > m) > k.$$

This differs from our proposed approach, which requires that all six subgroups A-F have more than m participants with probability greater than k (see equation (1)). The use of this objective function was based on the argument that in typical *SMART* studies, the rate of non-response is often not very large (i.e less than equal to 0.60). Therefore, in such settings it is highly likely that if the condition that the number of participants in subgroups B, C, E and F are respectively greater

than m were required, the number of responders in subgroups A and D would also be greater m, respectively.

The problem with the existing approach is that when the common non-response rate is high (i.e greater than equal to 0.70), the assumption that the number of participants in subgroup B is greater than m guarantees that the number of participants in subgroup A is not necessarily true. Similarly the assumption is not valid for subgroup D. Therefore the sample size we get from the existing method may not guarantee that the investigator will observe at least m number of people for each subgroup with probability greater than k. In next section, we will conduct a simulation study to show that the existing method fails in the case when the common non-response rate(q) is sufficiently large (i.e greater than equal to 0.70) and compare the simulation result of existing method with that of the new method introduced in section 2.1.

3 Simulation

A simulation experiment is conducted (i) to verify that sample sizes obtained under the proposed approach satisfy equation (7) under a variety of realistic values for m, k and q, and (ii) to compare the performance of the proposed method with the existing method by Almirall et al. [22], described above.

The simulation experiment is conducted in the following way for each combination of values of m, k and q.

1. Firstly, the values m, k and q are used to calculate the minimum suggested sample size N based on the proposed methodology.

2. Secondly, using this sample size N, we simulate the flow of participants through one realization of the *SMART* shown in Figure 2. Specifically, we divide the total sample size(N) by 2. Then by *rbinom* function [25] in R, we obtain the number of responders and non-responders for each pilot *SMART* simulation, which allows us to get the number of participants in each of the subgroups A-E.

3. Thirdly, we check if the number of participants in each subgroup is greater than pre-specified m or not. If the condition is met, we count it as a successful *SMART* pilot study. This process is repeated for 2000 times. In the end, after 2000 simulations, we obtain the proportion of successes out of 2000. This represents an estimate of the left-hand side of equation (1), which we take it as a true proportion, denoted as ρ, since we are conducting 2000 times of *Monte Carlo* simulation.

4. Lastly, the proportion(ρ) obtained in previous step is compared with a pre-specified lower bound for the proportion(k). If this proportion(ρ) is greater than k value, we conclude the sample size obtained from proposed method is valid. Otherwise, the proposed sample size is invalid. The Table 2 provides the results of this experiment.

Notice that the number of non-responsers could be an odd number. In this case, we subtract one from the number of non-responsers and divide by two. Then we use this value to check if it is greater than *m* or not. This is to (i) to get a conservative sample size and (ii) to avoid having non integer value of participants in each subgroup. If both values are greater than *m*, then we count this trial *SMART* pilot as a successful *SMART* pilot study.

Table 2: Simulation table of the *SMART* pilot study for *pediatric anxiety disorder* using proposed method

	Range of q :	0.20	0.30	0.40	0.50	0.60	0.70	0.80
$k = 0.80$	$m = 3$	0.90	0.91	0.91	0.92	0.92	0.92	0.91
$k = 0.80$	$m = 4$	0.90	0.91	0.91	0.92	0.93	0.91	0.90
$k = 0.80$	$m = 5$	0.90	0.91	0.91	0.91	0.90	0.91	0.90
$k = 0.90$	$m = 3$	0.95	0.95	0.96	0.96	0.97	0.96	0.95
$k = 0.90$	$m = 4$	0.95	0.95	0.95	0.96	0.96	0.95	0.95
$k = 0.90$	$m = 5$	0.95	0.95	0.95	0.95	0.96	0.95	0.95

From the simulation result, we can assess if the sample sizes we get from the proposed method, which are in Table 1, are valid or not. For instance, when m = 3, k = 0.80 and q = 0.60, we need to have at least 34 participants to conduct a *SMART* pilot study based on the Table 1. And from Table 2, we can see that out of 2000 simulations, roughly in 1840 (2000·0.92) times, the condition that there are 3 or more people in each subgroup is satisfied. And since all the values we get from the simulation are greater than corresponding k value which is in left end column, we can say that the method developed in previous section is indeed valid.

To see whether the method discussed in section 2.1 is an improved version, a simulation study is also conducted, in a same manner, for existing method [22]. As one can see in Table 3, existing method failed when the value of q is greater than or equal to 0.70. Again, this is because of the assumption that if the number of participants in subgroup B is larger than m, a minimum size threshold for each subgroup, the number of participants in subgroup A is also larger than m, which is not true in the case when q is greater than equal to 0.70. However, in Table 2, all of the simulation results were greater than its corresponding k value on the left end. Therefore, the method discussed in section 2.1 indeed is an improved version of the existing method.

Table 3: Simulation table of the *SMART* pilot study for pediatric anxiety disorder using preexisting method

	Range of q :	0.20	0.30	0.40	0.50	0.60	0.70	0.80
$k = 0.80$	$m = 3$	0.90	0.91	0.91	0.92	0.81	0.53	0.12
$k = 0.80$	$m = 4$	0.90	0.91	0.91	0.92	0.84	0.49	0.00
$k = 0.80$	$m = 5$	0.90	0.91	0.91	0.91	0.86	0.45	0.00
$k = 0.90$	$m = 3$	0.95	0.95	0.96	0.96	0.92	0.63	0.12
$k = 0.90$	$m = 4$	0.95	0.95	0.95	0.96	0.93	0.58	0.09
$k = 0.90$	$m = 5$	0.95	0.95	0.95	0.95	0.94	0.55	0.07

4 Extensions to other *SMART* pilot studies

Not all *SMART* studies will be like the type shown in Figure 2. In the *SMART* in Figure 2, all non-responders were re-randomized at the second stage regardless of the initial treatment assignment; i.e., re-randomization to second-stage treatment depended only on response/non-response status. In a second type of commonly-used *SMART* design, re-randomization at the second stage depends on both initial treatment and response/non-response status. In a third type of commonly-used *SMART* design, both responders and non-responders are re-randomized at the second stage. In this section, we extend the methods of Section 2.1 to these two types of *SMART* designs.

4.1 Re-randomization depends on initial treatment and response status

In this section, we consider *SMART* studies where re-randomization to second-stage treatment depends on the choice of initial treatment as well as response/non-response status. As an

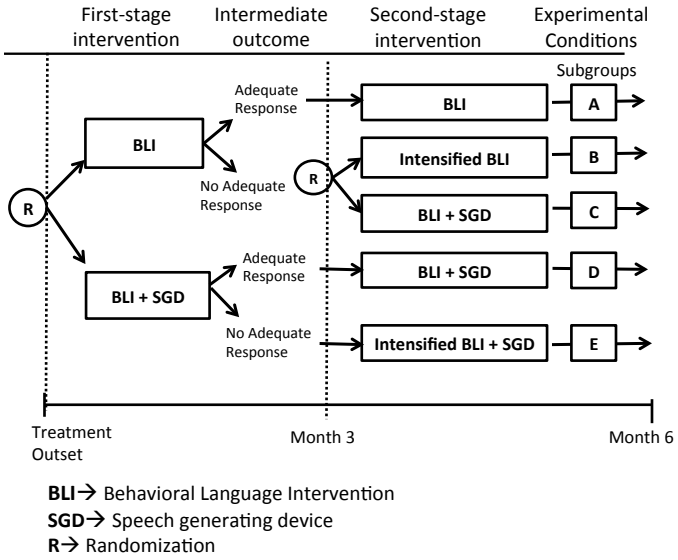

Figure 3: An example *SMART* for Children with Autism

example, consider the *SMART* shown in Figure 3. This *SMART* study was designed to develop adaptive interventions for improving linguistic and social communication outcomes among children with autism spectrum disorders who are minimally verbal [26]. Specifically, this *SMART* examined the effects of three different *adaptive interventions* involving different provisions of a speech generating device (SGD; a type of *Augmentative and Alternative Communication Interventions*) [27] by answering two scientific questions in the context of a behavioral language intervention (BLI)

for children with autism [28, 29]. Initially, all children were randomized at stage 1 to BLI versus BLI+SGD for 12 weeks to answer question (1): Is providing SGD more effective at initial stage? At the end of week 12, each participant is categorized as a responder or a non-responder to stage 1 treatment based on 14 measures including: 7 communication variables from *natural language sample* with blinded assessor and 7 communication variables from intervention transcripts [26]. All responders continued on stage 1 treatment for an additional 12 weeks. All non-responders to BLI+SGD received intensified BLI+SGD. Non-responders to BLI were re-randomized to intensified BLI versus BLI+SGD to answer question (2): For non-responders to BLI, is providing SGD with BLI as a rescue intervention more efficacious than intensifying the initial intervention?. Total number of spontaneous communicative utterances, primary outcome of the study, was collected at week 24 with a follow-up collection at week 36.

The derivation of the sample size formulae for a pilot study of a *SMART* of this type is similar to the derivation in Section 2.1. One difference in the notation is that in this *SMART* design, there are 5 subgroups, labeled A to E. Our goal is to determine the smallest N which guarantees that

$$\mathbb{P}(\text{all subgroups A-E have more than } \mathrm{m} \text{ participants}) > k$$

Using arguments similar to those used in section 2.1 (see Appendix A), one can show that this inequality is identical to

$$\left[\mathbb{P}\left(\frac{N}{2} - m - 1 \geqslant M_{\mathrm{q}}\right) - \mathrm{P}(2m \geqslant M_{\mathrm{q}})\right] \cdot \left[\mathbb{P}\left(\frac{N}{2} - m - 1 \geqslant M_{\mathrm{q}}\right) - \mathrm{P}(m \geqslant M_{\mathrm{q}})\right] > k \qquad (8)$$

Notice that, unlike with the inequality given in equation (7), the left-hand-side of equation (8) does not reduce to the square of a probability. This is due to the imbalance in the *SMART* design shown in Figure 3 (only non-responders to one of the initial treatments are re-randomized) relative to the design shown in Figure 2 (where all non-responders are re-randomized). Given k, q, and m, a solution for N in equation (8) can be found using an approach that is similar to the one described above to solve equation (7). Table 4 provides a minimal sample size for the type of *SMART* designs in Figure 3.

Table 4: Minimal sample size of *SMART* pilot study for nonverbal children with autism

	Range of q :	0.20	0.30	0.40	0.50	0.60	0.70	0.80
$\mathrm{k} = 0.80$	$\mathrm{m} = 3$	90	58	44	34	32	42	64
$\mathrm{k} = 0.80$	$\mathrm{m} = 4$	112	74	54	44	40	50	76
$\mathrm{k} = 0.80$	$\mathrm{m} = 5$	134	88	66	52	46	58	88
$\mathrm{k} = 0.90$	$\mathrm{m} = 3$	102	66	48	38	36	48	74
$\mathrm{k} = 0.90$	$\mathrm{m} = 4$	126	82	60	48	44	56	86
$\mathrm{k} = 0.90$	$\mathrm{m} = 5$	150	98	72	56	50	64	100

See the work of Kilbourne et al. [30], which employs a *SMART* of this type to enhance outcomes of a mental disorders program.

4.2 Both responders and non-responders are re-randomized

In this section, we consider a third type of *SMART* design where both responders and non-responders are re-randomized.

As an example of this type of design, we present a study of individuals with alcoholic use disorder which followed a design of this type. The example *SMART* design is shown in Figure 4. The goal of this *SMART* study, which is reviewed in greater detail in Lei et al. [1], was to develop *adaptive interventions* for individuals with alcoholic use disorders. This *SMART* was used to answer three scientific questions regarding the use of naltrexone medication (*NTX*) [31], an opioid receptor antagonist, for the management and prevention of relapse among individuals with alcohol use disorder. All participants were provided *NTX* medication as a stage 1 treatment. Non-response to *NTX* was measured on a weekly basis. However, participants were randomized initially to two different definitions for non-response to *NTX*–a lenient versus a more stringent definition–to answer the question (1): What extent of weekly drinking activity is best regarded as non-response? The lenient definition of non-response was defined as having five or more heavy drinking days per week, whereas the stringent definition of non-response was defined as having two or more heavy drinking days per week. Participants identified as non-responders to *NTX* were re-randomized to the combination of *combined behavioral intervention* (*CBI*) [32, 33], *medical management* (*MM*) [34] versus to the combination of *NTX*, *CBI* and *MM*. This randomization answers the question (2): What type of treatments would be useful for subjects who do not respond well to *NTX*? If participants had not been identified as non-responders by week 8, they were said to be responders to stage 1 intervention. Responders were re-randomized to the *NTX* versus to the combination of *NTX* and *telephone disease management* (*TDM*) to answer the question (3): What type of treatments would be effective for reducing the chance of relapse among people who responded well to *NTX*? Primary outcomes included the percentage of heavy drinking days and percentage of drinking days of the last two months of the study.

The variables *m, k*, and *q* are defined as in Section 2.1 (see the Appendix B). In this type of *SMART*, however, there are 8 subgroups, labeled A through H. In addition, in this type of *SMART*, randomization occurs both for responders and non-responders. Our goal is to find a smallest *N* which satisfies

$$\mathbb{P}(\text{all subgroups A-H have more than } \mathfrak{m} \text{ participants}) > k$$

In Appendix B we show that the above equation is true if and only if

$$\left[\mathbb{P}\Big(\frac{N}{2} - 2m - 1 \geqslant M_{\mathrm{q}}\Big) - \mathbb{P}(2\mathfrak{m} \geqslant M_{\mathrm{q}})\right]^2 > k, \tag{9}$$

As you can see in equation (9), unlike in equation (8), since the design is perfectly symmetric we have two identical probability terms multiplied each other. In addition, unlike equation (7), instead of m, $2m$ was subtracted from $\frac{N}{2}$. This is because for the type of *SMART* designs described in Figure 4, responders were also randomized. For more detailed explanation how this influences the method, see Appendix B. Again, given m, k and q, a solution for N in equation (9) can be

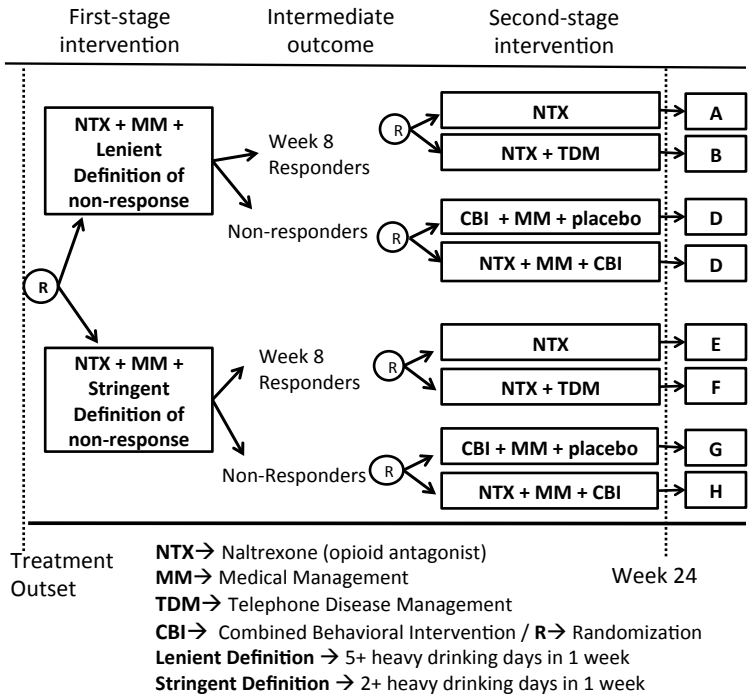

Figure 4: An example *SMART* for alcoholic patients

found using an approach that is similar to the one described above to solve equation (7). Table 5 provides a minimal sample size for the type of *SMART* design in Figure 4.

Table 5: Minimal sample size of *SMART* pilot study for alcoholic patient

	Range of q :	0.20	0.30	0.40	0.50	0.60	0.70	0.80
$k = 0.80$	$m = 3$	100	66	48	42	48	66	100
$k = 0.80$	$m = 4$	124	82	60	52	60	82	124
$k = 0.80$	$m = 5$	148	98	72	60	72	98	148
$k = 0.90$	$m = 3$	112	74	54	46	54	74	112
$k = 0.90$	$m = 4$	138	90	66	56	66	90	138
$k = 0.90$	$m = 5$	162	106	78	64	78	106	162

A number of other *SMART* studies are similar to the type shown in Figure 4. These studies include a *SMART* for developing an adaptive reinforcement-based behavioral intervention for woman who are pregnant and abusing drugs [35]; a *SMART* study aimed at developing an adaptive intervention involving individual and family-delivered cognitive behavioral therapy among children with depression; and a *SMART* designed to develop an adaptive intervention for children with autism spectrum disorders who are minimally verbal. All three of these studies are currently in the field.

5 Discussion

This manuscript presents pilot sample size calculators for 3 of the most common types of *sequential multiple assignment randomized trial (SMART)* designs. As stated in the introduction, researchers use *SMARTs* to inform the development of *adaptive interventions*. More specifically, *SMART* designs can be used to address critical scientific questions that need to be answered in order to construct high-quality *adaptive interventions*. Over the last 15 years, *SMART* designs have become more popular among clinical and health service researchers. However, some researchers may have concerns regarding the feasibility of conducting a full scale *SMART* or the acceptability of the treatments or adaptive interventions embedded in a *SMART* design. Such researchers may choose to conduct a smaller-scale pilot *SMART* prior to conducting a full-scale *SMART*. Specifically, a *SMART* pilot study is a small scale version of full scale *SMART* study, where the primary purpose is to examine the acceptability and feasibility issues. See the following papers for more detailed explanations and concrete examples of *SMART* pilot studies [15, 22, 36].

This paper develops an approach for determining the minimum sample size necessary for conducting a pilot *SMART*. The number of participants for *SMART* pilot study should be enough to address concerns in feasibility and acceptability of full-scale *SMART* study. The paper introduces one way to operationalize this, which is to ensure that each subgroup corresponding to sequence of treatments to observe some minimum number(m) of participants. This approach was used to select the sample sizes for two recent *SMART* pilot studies: 1) *SMART* for developing an adaptive intervention for adolescent depression [36], 2) *SMART* for adolescent conduct problems [15]. Further, the methods are developed for three of the most commonly used types of *SMART* designs. Finally, we compare our proposed method with an existing, related method for calculating the sample size for a *SMART* pilot [22] and explain how the proposed methodology is an improvement on the previous one. In addition, the characteristics of the methodologies developed in this paper were examined thoroughly via *monte carlo* simulation. Specifically, for each type of *SMART* design, 2000 simulation *SMART* pilot studies were conducted with different combinations of values of m,k and q via statistical software R. And, in all possible combinations of m,k and q, the simulation study supported that the condition imposed on the sample size(N) was met.

In general, our proposed approach is conservative in two aspects. First of all, our proposed approach is conservative in that we obtain significantly higher values of true proportion(ρ), compared to the given lower bound for the proportion(k). This is partly due to the discrete nature of sample size. Once the user provides sample size(N), common non-response rate(q), minimum number of participants for each subgroup(m), the simulation study provides the proportion(ρ) of successes out of 2000. And since the sample size(N) is a discrete quantity, the output from the simulation is also discrete. This may cause a large discrepancy between the values of ρ. For instance, if one gets simulation result of $\rho = 0.75$ for $m = 3$, $q = 0.6$ and $N = 30$, and $\rho = 0.90$ for $m = 3$, $q = 0.6$ and $N = 31$, the discrepancy between ρ values is 0.15. And this large discrepancy does not allow us to find a sample size which gives ρ close to the target k unless we treat the sample size as a

continuous quantity. (i.e sample size doesn't necessary need to be positive integers).

Secondly, the method is conservative in that we get larger sample size than the sample size we actually need to conduct a real world *SMART* pilot study. This is because our proposed approach uses the minimum value of two non-response rates as a common non-response rate. In other words, the method is based on one single value of non-response rate. And this will likely lead to conservative sample size relative to a method which may use both of two different non-response rates. Therefore, in future, one can possibly develop a new methodology to calculate minimum sample size for *SMART* pilot study using two non-response rates. Also one can further investigate, in which circumstances(i.e. which combinations of m, k and q), a method which uses two non-response rate values results in substantially small sample size than the method introduced in this paper.

Some suggestions on choosing values for m, k and q are provided in this paragraph. Concerning q: Existing data from previous studies (not necessarily a previous *SMART* study) are often used to obtain estimates of q. Typical values of non-response rates for *SMART* ranges from 0.3 to 0.7. Concerning m: In many cases, we have found that investigators are interested in observing between 3 and 5 participants for each subgroup of a pilot *SMART*. Note that for typical pilot studies, resources, including the maximum number of participants that could be afforded in a pilot study, are often limited. And observing between 3 to 5 people for each subgroup is typically enough to assess feasibility and acceptability issues regarding *adaptive interventions* . Concerning k: typical values range from 0.8 to 0.95.

This manuscript provides a way to choose the sample size for a pilot study *SMART*, to examine feasibility and acceptability concerns before conducting full scale *SMART* study. Another possible approach is to choose the sample size so that investigators may observe an estimate of response/non-response rate with pre-specified amount of precision. Researchers may want to adopt this approach to estimate non-response rate. By using the estimate of non-response rate, researchers can implement the methodologies described in the paper. For instance, suppose we want a sample size N which allows us to estimate non-response rate(q) within the margin of error of 0.1 with significance level 0.05. And we estimate q by the proportion of non-responders among total sample($\hat{q}$). Since the number of non-responders follows a Binomial distribution with parameters q and N [24, 37], after some calculation, we get $N = 100$. Note that the above example is just to illustrate another way to calculate sample size for pilot study. In this way, one can come up with an alternative way to develop a sample size calculator for *SMART* pilot study. For more detailed technical explanation, see Appendix C.

A Appendix A

Here, we provide mathematical derivation of equation (8). All the variables used here are defined in a similar way as in section 2.1. Recall that what we want to calculate is the smallest N such that

$$\mathbb{P}(\text{all subgroups A-E have more than } m \text{ participants}) > k$$

holds. In mathematical way, one can write it as

$$\mathbb{P}(M_{\mathrm{A}} > m, M_{\mathrm{B}} > m, M_{\mathrm{C}} > m, M_{\mathrm{D}} > m \text{ and } M_{\mathrm{E}} > m) > k$$

By design, we know that M_{B} is equal to M_{C}, therefore the above equation is equivalent to

$$\mathbb{P}(M_{\mathrm{A}} > m, M_{\mathrm{B}} > m, M_{\mathrm{D}} > m \text{ and } M_{\mathrm{E}} > m) > k$$

By the independence of each initial intervention group, above is same as

$$\mathbb{P}(M_{\mathrm{A}} > m, M_{\mathrm{B}} > m) \cdot \mathbb{P}(M_{\mathrm{D}} > m, M_{\mathrm{E}} > m) > k$$

One can re-write above as

$$\mathbb{P}(\frac{N}{2} - M_{\mathrm{q}} > m,\ M_{\mathrm{q}} > 2m) \cdot \mathbb{P}(\frac{N}{2} - M_{\mathrm{q}} > m,\ M_{\mathrm{q}} > m) > k$$

where M_{q} follows a Binomial distribution with size parameter $\frac{N}{2}$ and probability parameter q. Since we are using smaller value of non-response rates, the number of non-responders for each intervention will have same distribution. Therefore, in words, M_{q} represents the number of non-responders for each initial intervention. Then one can further simplify as

$$\mathbb{P}(\frac{N}{2} - m > M_{\mathrm{q}} > 2m) \cdot \mathbb{P}(\frac{N}{2} - m > M_{\mathrm{q}} > m) > k$$

And the above is analogous to

$$\Big[\mathbb{P}\Big(\frac{N}{2} - m - 1 \geqslant M_{\mathrm{q}}\Big) - \mathrm{P}(2m \geqslant M_{\mathrm{q}})\Big] \cdot \Big[\mathbb{P}\Big(\frac{N}{2} - m - 1 \geqslant M_{\mathrm{q}}\Big) - \mathrm{P}(m \geqslant M_{\mathrm{q}})\Big] > k$$

B Appendix B

Here, we provide mathematical derivation of equation (9). All the variables used here are defined in a similar way as in section 2.1. Recall that what we want to calculate is the smallest N such that

$$\mathbb{P}(\text{all subgroups A-H have more than } m \text{ participants}) > k$$

holds. In mathematical way, one can write it as

$$\mathbb{P}(M_{\mathrm{A}} > m, M_{\mathrm{B}} > m, M_{\mathrm{C}} > m, M_{\mathrm{D}} > m, M_{\mathrm{E}} > m, M_{\mathrm{F}} > m, M_{\mathrm{G}} > m \text{ and } M_{\mathrm{H}} > m) > k$$

By design, we know that $M_{\mathrm{A}} = M_{\mathrm{B}}$, $M_{\mathrm{C}} = M_{\mathrm{D}}$, $M_{\mathrm{E}} = M_{\mathrm{F}}$ and $M_{\mathrm{G}} = M_{\mathrm{H}}$, therefore the above equation is equivalent to

$$\mathbb{P}(M_{\mathrm{A}} > m, M_{\mathrm{C}} > m, M_{\mathrm{E}} > m \text{ and } M_{\mathrm{F}} > m) > k$$

By the independence of each initial intervention group, above is same as

$$\mathbb{P}(M_{\mathrm{A}} > m, M_{\mathrm{C}} > m) \cdot \mathbb{P}(M_{\mathrm{E}} > m, M_{\mathrm{G}} > m) > k$$

One can re-write above as

$$\mathbb{P}(\frac{N}{2} - M_{\mathrm{q}} > 2m,\ M_{\mathrm{q}} > 2m) \cdot \mathbb{P}(\frac{N}{2} - M_{\mathrm{q}} > 2m,\ M_{\mathrm{q}} > 2m) > k$$

where M_{q} follows a Binomial distribution with size parameter $\frac{N}{2}$ and probability parameter q. Then one can further simplify as

$$\mathbb{P}(\frac{N}{2} - 2m > M_{\mathrm{q}} > 2m) \cdot \mathbb{P}(\frac{N}{2} - 2m > M_{\mathrm{q}} > 2m) > k$$

And the above is equivalent to

$$\left[\mathbb{P}\left(\frac{N}{2} - 2m - 1 \geqslant M_{\mathrm{q}}\right) - \mathrm{P}(2m \geqslant M_{\mathrm{q}})\right]^2 > k$$

C Appendix C

In this section, we provide technical explanation of finding sample size using margin of error. Recall that the number of non-responders follows a Binomial distribution with parameters q and N [24, 37]. One can show that $\hat{q}$, a proportion of non-responders among total sample, is an unbiased estimate of q and its variance and standard deviation are below [38]:

$$\mathrm{Var}(\hat{q}) = \frac{q(1-q)}{N} \Rightarrow \mathrm{sd}(\hat{q}) = \sqrt{\frac{q(1-q)}{N}}$$

Then the goal is to find a sample size N which satisfies

$$2 \cdot \sqrt{\frac{q(1-q)}{N}} = 0.1$$

However, since we do not know the true value of q, we instead use $\frac{1}{2}$ as a value of q to find conservative sample size of N [37, 39]. By solving above formula after plugging in $\frac{1}{2}$ to q, we have

$$\frac{1}{\sqrt{N}} = 0.1 \Rightarrow N = 100$$

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