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Review Article:

An Integrative Review of Multistage Clinical Trials

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Abstract

Introduction: Clinical trials have long been vital to advancing how to prevent, diagnose, and treat diseases. However, traditional clinical trials are limited to one-stage interventions and therefore have little flexibility. With application of precise medicine, new concepts in terms of design can increase the flexibility of clinical trials, which in turn augment the likelihood that a trial will benefit the most people who participate.

Materials and Methods: In today's world, we are facing the spread of various diseases. Thus, physicians have to make numerous treatment decisions in different stages of the disease. In practice, such decisions represent the way physicians treat patients, but this is statistically a dynamic treatment regimen (DTR). Effective DTRs can be developed and studied in clinical trials called Sequential Multiple Assignment Randomized Trials (SMART).

Results: A total of 30 studies were extracted from reliable databases and websites, and research related to SMART was reviewed.

Conclusion: Considering that most experiments are performed in one step, and intermediate events are ignored and that focus is on the final event, introducing SMART plans and the concept of DTRs is important for researchers and clinical colleagues; treatment guidelines must encompass entire treatment regimens in order for them to be useful for clinicians and patients.

Keywords: Dynamic treatment regimen, SMART, Two-step design

1. Introduction

In today's world, we are facing the spread of chronic diseases such as cardiovascular diseases, anemia, cancer, diabetes, obesity, to name but a few, which are the main causes of death and disability of people all over the world. These diseases are among the most costly and common health problems [1].

Clinical trials have long been vital to advancing how to prevent, diagnose, and treat diseases. However, traditional clinical trials are limited to one-stage interventions and therefore have little flexibility. With application of precise medicine, new concepts in terms of design can increase the flexibility of clinical trials, which in turn augment the likelihood that a trial will benefit the most people who participate [2].

Most randomized clinical trials have a one stage parallel design. In such studies, each group of participants is exposed to one of the study interventions. In the cross-over design, each participant has to receive all study interventions in consecutive periods. Yet, if adaptive interventions are used for clinical trials, i.e., interventions in which the type or dose offered to patients is determined based on patient characteristics or individual clinical manifestations and then iteratively adjusts over time in

response to their ongoing performance, it will be a very useful approach for trials.

Sequential Multistage Assignment Randomized Trial (SMART) is a Randomized Clinical Trial (RCT) design that randomly assigns a set of DTRs to patients. SMART is usually considered as a clinical trial design to compare multi-step treatment strategies for chronic diseases [3].

SMART design is a natural choice for the treatment of chronic diseases because most patients require consecutive treatments. They provide the timing, sequencing, and adjustment of treatments and offer guidelines to inform clinical judgment. SMARTs effectively use information from all subjects, and may reach clinical decisions in less time than single-step tests, while answering more complex and relevant treatment questions [4].

The figure 1 shows two of the most common two-stage SMART designs [5].

In design 1, eight Dynamic Treatment Regimens (DTR) are included, which are as follows:

$\{A_1 B_1 C_1\}$, $\{A_1 B_1 C_2\}$, $\{A_1 B_2 C_1\}$, $\{A_1 B_2 C_2\}$, $\{A_2 B_1 C_1\}$, $\{A_2 B_1 C_2\}$, $\{A_2 B_2 C_1\}$, $\{A_2 B_2 C_2\}$

where each set includes a first-stage treatment ($A_1 or\ A_2$) and a second-stage treatment for responders (B_1or B_2) and a second-stage treatment for non-responders (C_1 or C_2) [5-8].

Design 2: A variant of the SMART design where randomization for the second stage is assigned only to responders, resulting in four DTRs:

$\{A_1 B_1 C_1\}$, $\{A_1 B_2 C_1\}$, $\{A_2 B_1 C_1\}$, $\{A_2 B_2 C_1\}$

SMART is an efficient design for clinical trials when we are interested in evaluating a set of DTRs because we can identify treatments, primary variables, and their interactions.

There are many designs for SMART; as the number of treatment steps increases, the complexity of SMART also rises. One of these designs is the three-stage design for SMART, which can be referred to the article by which has been used in Fernandez et al.'s study to increase the access and effectiveness of smoking cessation treatment in American community health centers. This is shown in figure 2 [9].

Our goal in this article is to review SMART features and we will also introduce examples of SMART plans so that the concept of SMART and DTR is well clarified for researchers and clinical colleagues. Moreover, current research in this vibrant and growing field will be discussed.

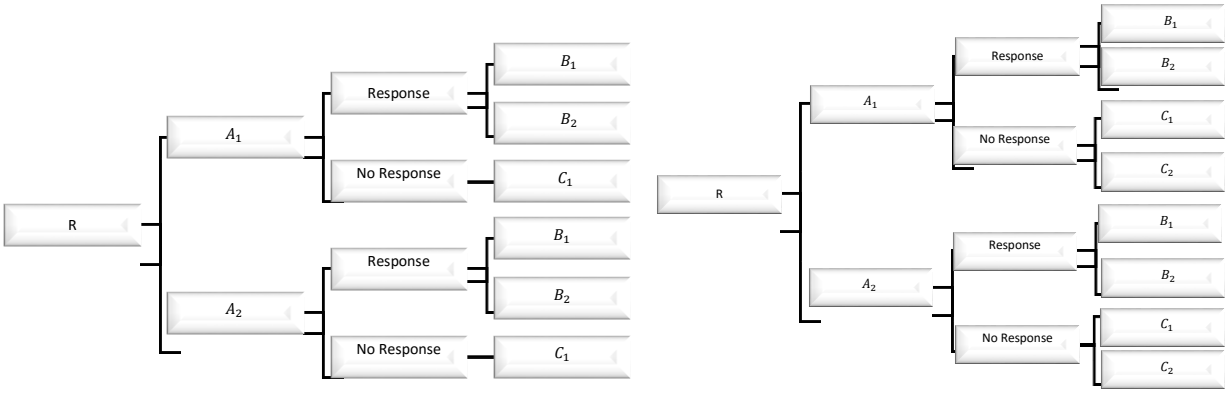
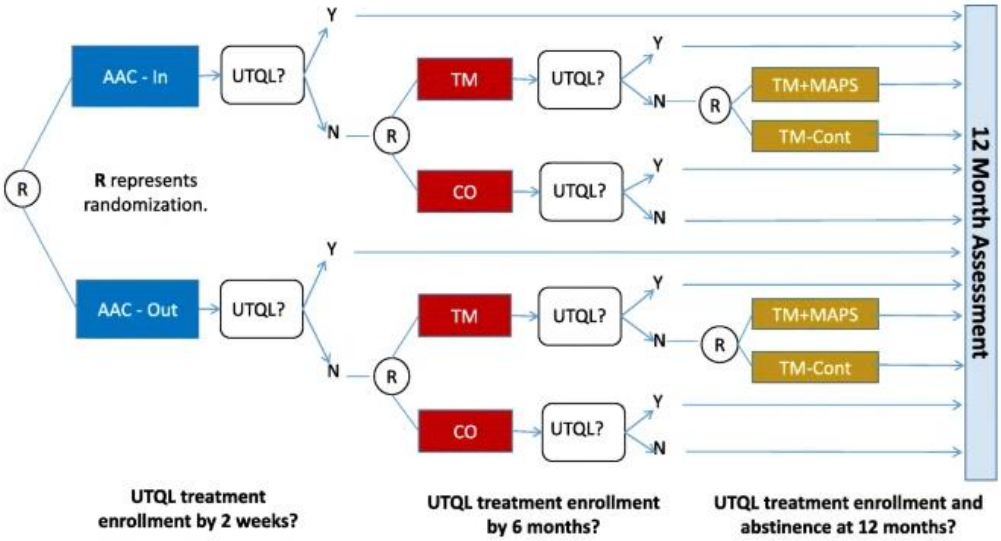


Figure 1. Two of the most common two-stage SMART designs



UTQL = Utah Tobacco Quit Line; Y = yes; N = no; AAC-In = Ask-Advise-Connect Opt-In; AAC-Out = Ask-Advise-Connect Opt-Out; TM = Text message; CO = Continued AAC; TM+MAPS = Text message + Motivation And Problem Solving; TM-Cont = Continued text message

Figure 2. An example of a three-step SMART design

2. Materials and Methods

Physicians make several treatment decisions for patients with chronic diseases at important stages of the disease. In practice, such decisions represent how physicians treat patients, but this is statistically a Dynamic Treatment Regimen (DTR or adaptive interventions). Effective DTRs can be developed and studied in clinical trials called SMART. SMART is a multistage experimental design that allows subjects to be randomized in two or more stages based on intermediate results to inform the DTR construct [5].

In many diseases, most patients need consecutive treatments; thus, SMART design can be used for many clinical trials. SMARTs provide the timing, sequencing, and adjustment of treatments and offer guidelines to inform clinical judgment.

Advantages

Considering the increasing progress of medical science and the development of new treatment methods, new concepts in the design of clinical trials are very important. In SMART designs, there is a lot of variety; the right and appropriate design can be selected in the light of the disease type.

Another attractive feature of SMART is that it provides sequential randomization of the data to allow the examination of multiple research questions.

Unlike many trials that ignore intermediate events and focus on the final event, SMARTs effectively use information from everyone. In SMARTs, they check the condition of the patients in each of the treatment stages and determine the next treatments for them accordingly.

Another advantage of SMART is the introduction of different types of DTRs where DTRs can be compared in order to choose the best one.

Challenges

One of the limitations of SMART is the reduction of statistical power due to sequential randomization of data. For this reason, it is recommended not to use more than two steps for randomization.

Another challenge in SMART compared to traditional trial designs is its higher cost.

Besides, SMARTs have a more complex structure, and to increase the statistical power, we should use a larger sample size in comparison with that of the traditional trials.

3. Results

First, we compare SMART and several RCT designs that more or less share some common features with SMART. The similarities between SMART and these designs sometimes cause confusion for clinical trials.

By making these comparisons, we further demonstrate the unique features of SMART within the family of RCT designs.

A crossover design is a repeated measures RCT design in such a way that subjects receive different treatments at its different stages [10].

Operationally, the sequential feature makes SMART somewhat similar to the crossover design. However, the motivation behind SMART is quite different from that of the crossover design. A cross-over design is performed with the aim of increasing the efficiency and reducing the sample size, as well as comparing the non-adaptive interventions of a study. By contrast, the purpose of SMART is to compare adaptive interventions. Also, treatment assignment in a cross-over study depends only on randomization results at baseline; in SMART, however, sequential random-ization of data is performed.

A factorial design decomposes the variability of the primary outcome into main effects and possible interaction effects of one or more factors. Factorial design is a classic experimental design that has been widely used not only in clinical trial research, but also in various fields such as agriculture, engineering, and marketing. Experience with factorial design can help us better understand the SMART design. We can view SMART as a factorial design based on which time and treatment decisions play a fundamental role [11-14].

Adaptive design uses intermediate data from a study to modify some aspects of the design, e.g., the randomization design of the trial, during the study without undermining the validity and integrity of the study. Compared with SMART, adaptive design is a broader concept that covers a family of RCT designs parallel to SMART. The objective of the adaptive design is to improve the overall quality of care for the trial participants in favor of treatments that show better efficacy or less toxicity in the initial period of the trial, and thus intrasubject information is matched. On the other hand, patient treatment assignment in SMART is adapted to within-subject information, whereas common design elements (e.g., sample size, random-ization scheme, etc.) are predetermined for the trial and will not be modified during the study [15].

The Sequential Multistage Assignment Randomized Trial with Adaptive Randomization (SMART-AR) is a design that can improve the quality of patient care by adapting some design parameters in the SMART framework. In SMART-AR, subjects receive treatments based on sequential randomization like the SMART, and the entire study is designed in several phases so that some design parameters (such as randomization probability) can be modified based on interim analysis within the same clinical trial [16].

In what follows, we will examine the research related to SMART.

Modeling of response to dynamic treatment regimens can be seen in the works of Robbins (1986, 1989, 1993, 1997). In these articles, using nested structure models, Robbins tried to estimate various treatment effect parameters. Also, Robbins discussed the parameters in a non-random dynamic treatment regimen with censoring in the data [17,18].

In the study of Murphy et al. in 2001, according to observational longitudinal data or data in which there is level selection, they proposed a method that allowed the estimation of the average response to a dynamic treatment regimen, assuming sequential random-ization [19].

In a 2002 study by Lunsford et al., survival outcomes were evaluated on a dataset of leukemia clinical trials in the SMART literature. In their study, Lunsford et al. proposed fixed estimators for the survival distribution and limited survival time for each treatment policy in two-stage studies, and constructed the survival estimators based on the Inverse Probability Weight (IPW) framework [20].

Using several clinical examples, Lavery and Dawson (2004) tried to provide the simplest randomized trial designs to compare and describe DTR.

They began by considering an initial treatment A and a second treatment B and discussed how a dynamic treatment regimen starting with A and (sometimes) leading to B would compare with a fixed treatment of A or B. Besides, finding the best sequence of treatments in DTR was discussed. In their study, two methods of combining randomization, i.e., primary randomization among DTRs versus randomization at decision points (sequential randomized designs), were proposed [21].

Goa and Tsiatis (2005) presented an approach to improving the efficiency of estimators for the survival distribution of treatment methods for two-stage randomized designs with censored survival data. The approach they used, with the concepts of risk pooling and the counting process, made it possible to use data from patients who either not used any treatments or used other ones.

WRSE is a natural format of the Nelson Allen

estimator for the survival curve, which makes it more understandable. Compared with other existing estimators, such as the estimators proposed by Lunsford et al., the improved estimator is not only more efficient but also easier to implement [22].

In 2007, Thal et al. presented a Bayesian framework for a clinical trial comparing two-stage strategies for the treatment of metastatic renal cell carcinoma; they proposed a Bayesian combinatorial model that reduced overall survival time in the mean response time, but Weiball distribution considers a relatively limited assumption for both time points [23].

In 2012, Shortread and Moody presented an analysis comparing DTRs for antipsychotic treatments in the CATIE schizophrenia study using marginal structural models and IPW [24].

Zhao et al. (2014) introduced robust double estimation methods of DTRs for survival data, but these methods are only applicable to one-stage treatment [25].

In 2015, Chong et al. proposed the SMART-AR scheme, which can improve the quality of patient care by adapting some design parameters in the SMART framework. In SMART-AR, subjects receive treatments based on sequential randomization like a SMART, and the entire study is designed in several phases so that some design parameters (such as the probability of randomization) can be analyzed based on an interim analysis within the same clinical trial [26].

In 2017, Tamura et al introduced an snSMART (for small data) scheme to be used in rare disease research and demonstrated the sample size estimation and performance characteristics of snSMART in this scheme [27].

Hager et al (2018) presented a method to identify and estimate the optimal DTR in a SMART. However, their method on treatments, covariates or interaction effects cannot make inferences to make optimal DTR [28].

Yan Cheng Chao in 2022 presented a two-stage SMART design for patients with acute bone marrow leukemia using a joint modeling framework and multiple comparisons with the best of data from a SMART with survival outcome, and identified an optimal DTR for patients with acute bone marrow leukemia [5].

4. Discussion

Clinical trials are important because they determine the safety and effectiveness of drugs and treatment regimens intended for humans. Clinical trials may be used to prevent, treat, analyze, or alleviate the symptoms of a disease [29]. On the other hand, statistics is an important aspect of clinical trials, because the range of statistical issues covers the entire spectrum of clinical trials [30].

In this research, we first introduced SMART and presented examples of SMART plans, so that the concept of SMART and DTR is well clarified for researchers and clinical colleagues. As previously mentioned, there are many designs for SMART that increase the complexity of SMART as the number of treatment steps increases, thus reducing statistical power. For this reason, researchers recommend not using more than two steps for randomization. However, the most important feature of SMART is that according to the condition of the patients, further treatment instructions are considered for them; that is, intermediate events are not ignored. Everyone's information is effectively used.

Next, we compared SMART and several RCT designs that more or less share some common features with SMART. The similarities between SMART and these designs sometimes cause confusion for clinical trials. By making these comparisons, we further demonstrated the unique features of SMART in the family of RCT designs.

This was followed by examining the research related to the topic of SMART in which Robbins proposed the concept of DTR for the first time, and later, researchers expanded this topic in different fields. Under the rubric of survival, the topic of SMART was also given a lot of attention. Researchers used different methods for survival estimators, including IPW, WRSE. Last but not least, the most recent research in the topic of survival is related to the study of Yang Cheng Chao who proposed a combined modeling tool to evaluate DTRs, which is a very efficient method for data with survival results [5].

5. Conclusion

In this research, we first introduced SMART and then compared SMART and several RCT designs that more or less share some common features with SMART. The similarities between SMART and these designs sometimes cause confusion for clinical trials. By making these comparisons, we showed more clearly the unique features of SMART in the family of RCT

designs and then attempted to review the research related to the topic of SMART.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences, Iran.(IR.SBMU.RETECH.REC.1399.076)

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Author's contributions

The authors equally contributed to preparing this article.

Conflict of interest

The authors have declared no conflict of interest.

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