The Sequential Multiple Assignment Randomized Trial for Controlling Infectious Diseases: A Review of Recent Developments

Xinru Wang, MS, and Bibhas Chakraborty, PhD

See also Vaughan, p. 35, Seewald, p. 37, Bauer et al., p. 40, and Liu et al., p. 60.

Infectious diseases have posed severe threats to public health across the world. Effective prevention and control of infectious diseases in the long term requires adapting interventions based on epidemiological evidence. The sequential multiple assignment randomized trial (SMART) is a multistage randomized trial that can provide valid evidence of when and how to adapt interventions for controlling infectious diseases based on evolving epidemiological evidence.

We review recent developments in SMARTs to bring wider attention to the potential benefits of employing SMARTs in constructing effective adaptive interventions for controlling infectious diseases and other threats to public health. We discuss 2 example SMARTs for infectious diseases and summarize recent developments in SMARTs from the varied aspects of design, analysis, cost, and ethics.

Public health investigators are encouraged to familiarize themselves with the related materials we discuss and collaborate with experts in SMARTs to translate the methodological developments into preeminent public health research. (*Am J Public Health*. 2023;113(1):49–59. https://doi.org/10.2105/AJPH.2022.307135)

Infectious diseases have posed severe threats to public health throughout human history. In recent years, the COVID-19 pandemic has inflicted enormous human suffering and in tandem has attracted considerable research attention. To slow the spread of COVID-19 and to reduce the morbidity and mortality rates, numerous interventions have been imposed to control the spread of the disease (e.g., limiting group size of social gatherings, promoting vaccine uptake, and issuing stay-at-home orders).[1] However, to minimize the negative impact on people's livelihood while also effectively controlling the diseases, decision-makers are required to find the precise ways to adapt health promotion and disease prevention programs based on evolving epidemiological evidence, instead of sticking to "one-size-fits-all" interventions.

Such sequences of decision-making about when and how to adapt interventions based on evolving epidemiological evidence have been widely applied to the prevention of infectious diseases and can be referred to as "adaptive interventions," also known as "dynamic treatment regimens" or "adaptive treatment strategies" in the field of biostatistics.[2] The main components of an adaptive intervention are (1) intervention options, such as different types of interventions, delivery approaches, and dosage levels; (2) decision points, that is, the prespecified time points to recommend interventions based on baseline characteristics or intermediate tailoring variables; (3) tailoring variables, that is, variables that can be used to identify which intervention should be recommended and for whom (e.g., mediators, moderators, or early surrogates for longer-term outcomes of interest); and (4) decision rules, that is, prespecified rules that can recommend

interventions based on previous historical data.

One example of an adaptive intervention for treating COVID-19–positive patients with mild symptoms is the following: First, treat the patients at community care facilities with general medical care. Then, assign patients who respond adequately, according to prespecified criteria, to the community recovery facilities before discharging them, and hospitalize nonresponders and provide intensified medical care.[3]

With the increasing popularity of adaptive interventions, there appears to be a wave of interest in developing a promising evidence-based adaptive intervention to maximize patient gains.[4] When faced with life-threatening infectious diseases, researchers rely primarily on historical experiences and observational data to inform decision-making procedures, given that explanatory randomized controlled trials (RCTs) are time consuming and may fail to generate up-to-date conclusions to guide the implementation of public health interventions. However, the validity of such an analysis based on observational data depends on the untestable ignorable intervention assignment assumption, that is, the assumption that receiving the intervention or not is independent of the potential outcomes.[5]

At the outset of the COVID-19 pandemic, observational studies were essential to provide evidence for prompt public policies. However, as the increasing level of COVID-19 vaccine coverage has significantly decreased the morbidity and mortality rates, proactive research (e.g., pragmatic study designs) is needed to move to the next-generation epidemiological prevention measures and further identify evidence-based interventions for future public health practice for infectious diseases.

The sequential multiple assignment randomized trial (SMART) is an experimental design consisting of multiple randomization stages.[2] This type of design serves as a promising tool to address scientific questions about constructing effective adaptive interventions for controlling infectious diseases. SMARTs have been implemented in various health domains, including diet and weight control,[6] HIV infection,[7] mental health,[8] and behavioral sciences.[9] This recent surge in the prevalence of SMARTs can be attributed to the increasingly ripened methodology in the design and analysis aspects and the availability of some good tutorial articles providing blow-by-blow guidance to help practitioners gain a better understanding of SMARTs.[10–16] However, to the best of our knowledge, except for the setting of HIV infection, there are far fewer SMARTs in the field of infectious diseases, likely on the grounds that contagious diseases require a rapid real-time response at the early stage of the outbreak. Furthermore, SMARTs may be relatively uncommon to many public health researchers; thus, researchers may hesitate to choose a SMART design when constructing evidence-based adaptive interventions for controlling infectious diseases.

We aim to facilitate the implementation of SMARTs for infectious diseases by summarizing the recent developments in SMARTs with a special focus on infectious diseases. We first review 2 SMARTs for infectious diseases to help readers gain a better grasp of employing SMARTs to improve public health. We then provide details about associated data analysis and cost and ethical considerations in SMARTs. We also summarize the existing software for designing and analyzing SMARTs to build a bridge between methodological developments and practical implementation. Although we focus on infectious diseases, our discussion is sufficiently general to apply SMARTs to a wide range of other fields.

EXAMPLE SMARTS FOR INFECTIOUS DISEASES

In this section, we provide 2 example SMARTs for controlling infectious diseases.

Example 1

Despite the high global capacity to produce COVID-19 vaccines and the increasing clinical trial data demonstrating their effectiveness, some people still hesitate to get vaccinated because they fear potentially severe side effects or simply lack the conviction that the vaccines are useful. Governments have taken public measures (e.g., mounting public media programs) to dispel the rumors about COVID-19 vaccines. However, such measures can reach only a limited audience. More efforts are needed to further promote vaccine uptake and speed up the process of herd immunity.

There is a large-scale SMART, each stage of which was planned as a separate RCT for investigating the effect of digital interventions on the uptake of COVID-19 vaccines.[17] The investigators in this SMART considered several first-line interventions to motivate people to get vaccinated and second-line interventions to further remind those who have not received the first vaccine dose in a prespecified period because of having received the first-line intervention. A simplified version of the design is presented in Figure 1. Participants who had not already taken the first dose at the starting point of the trial

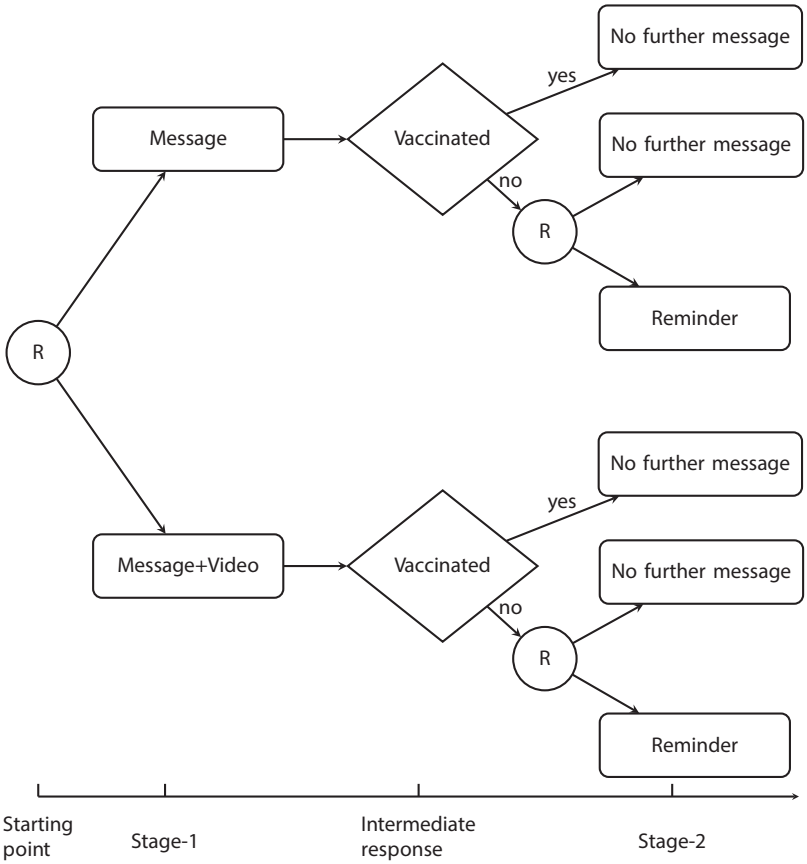

FIGURE 1— A SMART for Developing Digital Adaptive Interventions to Facilitate the Uptake of COVID-19 Vaccines

Note. R = randomization.

were equally randomized to either the message group or the message plus video group. After 8 days, those who still had not received the first dose were randomized to either the no further message group or the reminder group, with a reminder message that could help clear potential barriers to vaccination, such as forgetfulness, hassle, costs, and procrastination. The primary outcome of interest was whether a participant has made the appointment for the first vaccine dose. There were 4 adaptive interventions embedded in this SMART: (1) first send a motivating message, then send a basic reminder message if not vaccinated; (2) send a motivating message only at the starting point; (3) first send a motivating message plus explanatory video, then send a reminder message if not vaccinated; and (4) send a motivating message plus explanatory video only at the starting point.

Example 2

Malaria, a potentially serious infectious disease transmitted by a specific type of mosquito, can be effectively controlled by the use of long-lasting insecticide-treated nets (LLIN), indoor residual spraying (IRS), and larval source management (LSM).[18] The high cost of implementing IRS and LSM is a major concern that needs to be considered when constructing an effective adaptive intervention for malaria control, and more scientific evidence is required to guide the prevention interventions, such as when and how to employ IRS and LSM while ensuring efficient harnessing of the resources for malaria control.

An ongoing cluster-randomized SMART (Figure 2) was designed to collect evidence for constructing an effective adaptive intervention for malaria control in western Kenya.[18] By "cluster randomized," we mean that the interventions are randomly administered at the cluster level (e.g., a village or several neighboring villages), whereas the outcomes are collected at the individual level (i.e., residents in the randomly selected households). The enrolled clusters are randomized to receive LLIN, piperonyl butoxide (PBO) LLIN (the next-generation LLIN combining the synergist piperonyl butoxide with pyrethroids), or the combination of LLIN and IRS. After 15 months, clusters will be evaluated for the response status based on the change in clinical malaria incidence when using PBO LLIN or LLIN + IRS compared with LLIN alone. Responders will continue with their initial intervention, whereas nonresponders to PBO LLIN are randomized to the combination of PBO LLIN + LSM or the intervention determined by a reinforcement learning algorithm developed to generate unbalanced randomization probabilities in favor of the estimated superior intervention for each cluster, and nonresponders to LLIN + IRS are randomized to LLIN + IRS + LSM or PBO LLIN + IRS. The primary outcome of interest is the clinical malaria incidence. The primary aim of this trial is to compare first-line interventions PBO LLIN and LLIN + IRS in terms of the effectiveness of reducing malaria incidence after 36 months, and the secondary aim is to identify the

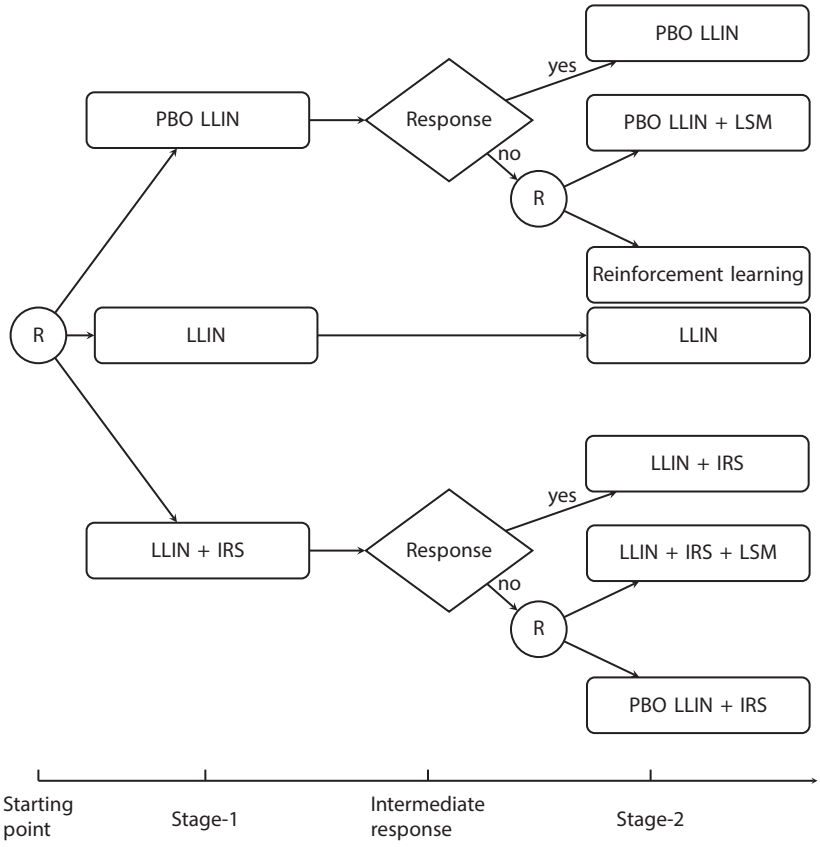

FIGURE 2— A SMART for Developing Optimal Adaptive Interventions for Malaria Control

Note. IRS = indoor residual spraying; LLIN = long-lasting insecticide-treated nets; LSM = larval source management; PBO = piperonyl butoxide; R = randomization.

most effective intervention to reduce malaria incidence.

In addition to these 2 examples, there is another ongoing SMART for developing an optimal adaptive intervention to facilitate COVID-19 testing and adherence to the Centers for Disease Control and Prevention recommendations among high-risk people in an urban community.[19] We have not presented details here because of space limitations.

WHEN TO USE SMARTS

There have been tremendous improvements in the experimental designs for constructing interventions with multiple components, such as factorial designs,[20] SMARTs, and microrandomized trials.[21] Given that the concepts of these designs are somewhat entangled, researchers may be confused about when to use SMARTs at the beginning of the design stage, which limits the broader use of SMARTs. With this backdrop, Nahum-Shani et al.[22] proposed a practical framework to provide valuable insights into choosing the most appropriate design among all these candidate designs. To briefly summarize, a SMART design is a proper choice when (1) the interventions of interest are multicomponent interventions, (2) the researchers aim to select multiple effective components out of all candidates to be included in the final intervention, (3) there are research interests in the timing of intervention components, and (4) the conditions are changing slowly.

It is important to note that, in cases in which all 4 conditions for choosing SMARTs are met, multiple single-stage RCTs may serve as an alternative way to examine the effect of the initial and subsequent interventions.[23] Single-stage RCTs, however, have some inevitable disadvantages compared with SMARTs.[11] First, single-stage RCTs do not allow researchers to investigate either the synergetic effect between the initial and subsequent interventions in the long term or the potential tailoring variables for more tailored adaptive interventions.

In addition, it can be argued that participants in SMARTs may be less likely to drop out because alternative interventions are provided in cases of insufficient early response. In other words, SMARTs provide participants with a "safety net" (i.e., a second chance to get a different, potentially beneficial intervention when the current intervention is not working). By contrast, with single-stage RCTs, participants with apparently ineffective interventions have no choice but to discontinue the intervention or drop out. SMARTs can also be replaced by an up-front randomized trial,[24] which randomizes patients to candidate adaptive interventions at the beginning of the study. Compared with SMARTs, the rationale and statistical methods in up-front randomized trials are easier to understand. However, several studies have demonstrated that the estimators from SMARTs are more efficient (with smaller variance) than are those from up-front randomized trials.[24,25] Moreover, rerandomizations in SMARTs allow restratification, which may be useful in achieving balanced distributions of

covariates in rerandomizations, whereas up-front randomized trials do not allow this.

SAMPLE SIZE CALCULATIONS IN SMARTS

The required sample size in a SMART is dictated by its primary research questions.

Table 1 summarizes the most common primary goals of SMARTs, and some illustrative applications and software are provided for each case when applicable. Briefly, there are mainly 4 primary research goals in SMARTs: (1) performing the pilot evaluation, (2) estimating the main effects of first-line and second-line interventions, (3) comparing embedded adaptive interventions, and (4) developing the optimization goal (i.e., more deeply tailored adaptive interventions).

The evaluation of feasibility is often the intended goal in a pilot SMART, in which researchers assess the acceptability and the rationale of the embedded adaptive interventions as well as the fidelity of the study staff to implement the specified adaptive interventions in preparation for a future full-scale SMART. Almirall et al.[12] described in detail how to design a pilot SMART and proposed a feasibility-based method to determine the required sample size that ensures sufficient participants in each intervention sequence, allowing researchers to gather comprehensive information about the feasibility of a planned SMART. Building on this, Yan et al.[26] presented a precision-based method to size a pilot SMART with various types of outcomes, by which the SEs of estimates of interest are confined in a prespecified range.

TABLE 1— Sample Size Calculations for Different Primary Research Questions in SMARTs

Primary Goal	Method	Cluster/Individual	Primary Outcome	Example Trials	Software
Pilot evaluation	Precision based	Individual	Continuous/binary/count[26]	Yan et al.[27]	https://bit.ly/3zyktU7
	Feasibility based	Both	All[12]	Lambert et al.[28]	https://bit.ly/3Nqq3gY
Main effect	Effect of first-line treatments	Similar to RCTs	Similar to RCTs[29]	Zhou et al.[18]	https://bit.ly/3SUgcRG
	Effect of second-line treatments	Similar to RCTs	Similar to RCTs[29]	Sherwood et al.[6]	https://bit.ly/3SUgcRG
Compare adaptive interventions	Select optimal adaptive interventions	Individual	Continuous[29]		
	Pairwise superiority testing	Individual	Continuous[29–31]		https://bit.ly/3SUgcRG https://bit.ly/3Fx1blQ[32]
			Continuous/binary[33]		
			Binary[34]		https://bit.ly/3SUgcRG
			Survival[35]		
			Continuous longitudinal[36]		
			Ordinal[37]		https://bit.ly/3NmHeQA
		Cluster	Continuous/binary[33]	Quanbeck et al.[38]	
			Continuous[39]		
			Continuous (skew-t, MNAR)[40]		https://bit.ly/3zwLTtA[41]
	Pairwise noninferiority testing	Individual	Continuous[42]		https://bit.ly/3Wnd7gf
	MCB testing	Individual	Continuous[43]		https://bit.ly/3DK1EyT[44]
			Binary[45]		https://bit.ly/3Nluw4R, https://bit.ly/3NvA1Os[46]
Optimization	Normality based or projection based	Individual	Continuous[47]		

Note. MCB = multiple comparisons with the best; MNAR = missing not at random; RCT = randomized controlled trial; SMART = sequential multiple assignment randomized trial.

For a full-fledged SMART, one of the most common primary research goals that drive sample size calculation is to investigate the effect of individual components. Oetting et al.[29] gave a detailed illustration of deriving the required sample size for comparing stage-specific intervention effects with continuous primary outcomes. Briefly, the calculation procedure is similar to that used in RCTs, except that the response rate of initial interventions should be incorporated when investigating the intervention effect of subsequent interventions for responders and nonresponders. Practitioners can follow the same principles for other types of primary outcomes.

A sizable literature focuses on comparing embedded adaptive interventions as a whole, comparing 2 or more embedded adaptive interventions,[29–31] or screening out the inferior set of adaptive interventions.[43] Ghosh et al.[42] further extended the framework by emphasizing the importance of noninferiority testing between 2 embedded adaptive interventions to construct an almost equally effective adaptive intervention with lower cost, less burden, or fewer side effects and developed the analysis and sample size calculation formulas for the noninferiority testing. All the aforementioned sample size calculation methods are suitable for individual-level SMARTs with continuous primary outcomes. Recently there has been tremendous progress in deriving the sample size calculation formulas for comparing embedded adaptive interventions in individual-level SMARTs with binary,[34] survival,[35,48–50] ordinal,[37] and continuous longitudinal[36] outcomes; for cluster-level SMARTs with binary and continuous outcomes[33,39]; and for cluster-level SMARTs with various features of outcomes, including spatial clustering, non-Gaussianity, and missing not at random.[40]

Investigators may also be interested in constructing more tailored adaptive interventions (i.e., sequences of decision rules that recommend intervention options based on additional observed information; e.g., baseline characteristics or intermediate potential tailoring variables). The research question is thus to explore an optimal tailored adaptive intervention that is expected to maximize the overall effectiveness of interventions if applied to the entire study population. Although optimization is a possible primary goal, it often serves as a bonus on top of investigating main effects and comparing embedded adaptive interventions when conducting a SMART.

When a SMART is designed with the optimization objective, the sample size calculation involves technical issues posed by estimating and evaluating an optimal adaptive intervention using the same data. Rose et al.[47] proposed normality-based and projection-based sample size calculation methods to ensure enough power for comparing the estimated optimal deeply tailored adaptive intervention with the fixed standard intervention. Note that the required sample size for comparing embedded adaptive interventions or optimization is often higher than that for comparing stage-specific interventions. Researchers are advised to define the primary goals of SMARTs based on the research budget for recruiting participants and the major research questions of interest.

Although significant strides have been made in statistical methodology, to the best of our knowledge, these sample size calculation methods for comparing adaptive interventions or optimizations are scarcely used in real practice. The reason for this may be that both the scientific investigators and the statisticians are more familiar with the statistical methods in standard trials, so they are inclined to sizing SMARTs based on the main effect, with the additional goal of comparing embedded adaptive interventions or optimization to provide complementary information for future confirmatory trials. More efforts are needed to translate the developed methodologies to real clinical and public health practice by lucidly explaining the concepts of SMARTs and the statistical tools to a broader audience.

DATA ANALYSIS IN SMARTS

When the research question concerns examining the main effects in a SMART, standard statistical methods in RCTs can be used to analyze the SMART data. However, when the goal is to discern the effectiveness of 2 or more embedded adaptive interventions, adjustments to the standard methods are required to account for the sequential randomizations in SMARTs. The weighted and replicated regression[51] can provide valid inferences of the mean outcomes of all the embedded adaptive interventions simultaneously, by weighting and replicating observations to account for the underrepresentation of certain subgroups because of the design of the trial. Nahum-Shani et al.[52] presented a thorough guideline on how to use this method to analyze data from SMARTs with end-of-study continuous outcomes. This method holds the promise of being straightforward and accessible to practitioners as it is akin to standard regression

TABLE 2— R Packages for Data Analysis in SMART

Package Name	Objective	Outcome	Method	Software
SMARTAR[32]	Comparisons between embedded adaptive interventions	Continuous, binary	Global/pairwise testing	https://bit.ly/3Fx1blQ
DTR[60]	Comparisons between embedded adaptive interventions	Survival	Weighted logrank tests	https://bit.ly/3NvMyBl
DTRlearn2[61]	Optimization	Continuous, binary	Q-learning, other outcome-weighted learning methods	https://bit.ly/3zxCwK5
DTRreg[62]	Optimization	Continuous, binary, survival	Q-learning, G-estimation, dynamic weighted ordinary least squares (dWOLS)	https://bit.ly/3zypg83
DynTxRegime[63]	Optimization	Continuous, binary	Q-learning, interactive Q-learning, weighted learning, value-search methods	https://bit.ly/3WlZGx2

Note. SMART = sequential multiple assignment randomized trial.

methods and can be executed using standard software. The method has been extended to analyze data from SMARTs with continuous longitudinal outcomes,[53] binary outcomes,[34] and continuous outcomes in cluster-level SMARTs,[39] and it has been employed in real practice for primary, secondary, and exploratory analyses.[6,54,55]

Q-learning, a stage-by-stage regression-type procedure,[56] can be used to identify an optimal deeply tailored adaptive intervention (as opposed to the embedded adaptive interventions) based on SMART data. The letter Q stands for the quality of an intervention (e.g., a desired clinical outcome), conditional on the observed information and subsequent interventions. Intuitively, Q-learning begins by estimating the optimal decision rule at the last stage and moves backward successively to construct an optimal decision rule at each stage, assuming the use of optimal decision rules at the subsequent stages. Nahum-Shani et al.[56] provide a detailed illustration of implementing Q-learning to construct more tailored adaptive interventions in SMARTs. Other notable statistical learning–based and tree-based methods[57–59] can also be applied to develop optimal adaptive interventions. Table 2 lists several user-friendly R packages to compare embedded adaptive interventions or develop more tailored adaptive interventions.

Missing data problems pose a significant challenge to data analysis in SMARTs. Standard imputation methods cannot be directly applied to deal with missing data in SMARTs because of the nonstandard multistage randomization procedure. However, researchers can alleviate the impact of missing data on the validity of analysis from both design and analysis perspectives. First, as stated by Almirall et al.,[12] pilot SMARTs can provide valuable insights for future full-scale SMARTs in terms of strategies to reduce the dropout rate and to treat early dropout patients. Liu et al.[64] presented a SMART with enrichment to improve design efficiency when the dropout rate is high by augmenting the trial sample with new patients who have received previous stages' interventions. In terms of analysis, Shortreed et al.[65] proposed a multiple imputation strategy to tackle the unique missing data problems arising in SMARTs. Researchers are encouraged to employ these tactics to achieve more reliable inferences from SMARTs and perform sensitivity analysis to check the validity of the missing at random assumption.

COST-EFFECTIVE ADAPTIVE INTERVENTIONS

Effective control of infectious diseases requires the involvement of a variety of communities and stakeholders. Efficient use of scarce medical and financial resources is one of the major challenges when implementing large-scale prevention and intervention programs.[66] When intervention resources are limited for conducting a SMART, the optimal allocation of interventions with a fixed budget constraint is desired. Morciano and Moerbeek[67] proposed an optimal allocation strategy for simultaneously comparing embedded adaptive interventions in SMARTs with a fixed sample

size or a fixed budget and provided an easy to use Web app to facilitate the use of this optimal allocation strategy.

Although the efficacy of improving outcomes is often the main focus when developing optimal adaptive interventions, the cost of an intervention is another important factor to consider in health economics. When an intervention is more effective and less costly than another, it is deemed to be the strictly superior intervention. However, if the more effective intervention costs more, to select the adaptive interventions that can be both effective and sustainable in practice, policymakers are expected to weigh their options between health efficacy and the additional cost per unit outcome improvement. Xu et al.[68] proposed a decision tree–based algorithm to develop a cost-effective adaptive intervention with the net monetary benefit as the primary outcome. This cost-effectiveness analysis method is recognized as a promising way to analyze SMART data and develop more tailored cost-effective adaptive interventions. As it has been widely acknowledged that cost effectiveness is a major concern during clinical practice, researchers are encouraged to collect cost-related data for a future cost-effectiveness analysis.

ETHICAL CONSIDERATIONS IN SMARTS

Even though SMARTs can potentially unpack the black box of sequenced multicomponent interventions, they may require more time to implement than do standard RCTs. For infectious diseases, however, the earlier the intervention is delivered, the more benefits it will provide for public health. With the aim of reducing the time for conducting SMARTs, Wu et al.[69] proposed a SMART with interim monitoring, in which the global hypothesis testing of all embedded adaptive interventions is conducted at each interim monitoring time, and early stopping of the trial is permitted if the evidence of efficacy is sufficient.

When faced with emerging infectious diseases that threaten millions of human lives, it is imperative to conduct trials to select effective interventions for future patients while minimizing the infection and mortality rate of enrolled participants. Several extensions of SMARTs can be potentially applied to increase the number of participants receiving the optimal intervention in SMARTs for controlling infectious diseases. Cheung et al.[70] provided a SMART with adaptive randomization based on Q-learning. Roughly speaking, it estimates the parameters of the stage-specific conditional mean outcomes based on the data from previous patients and updates the assignment probabilities in favor of the interventions with higher values of the predicted stage-specific conditional mean outcomes. Wang et al.[71] presented a response-adaptive SMART to incorporate the short-term intervention efficacy shown from previous patients when randomizing the stage 2 interventions. So far, very few adaptive SMARTs have been implemented in practice; for example, Ruppert et al.[72] presented a trial protocol for a SMART with an interim analysis targeting older patients with chronic lymphocytic leukemia, in which rerandomization will be discontinued if the adaptive intervention to be randomized has proven to be inferior to the others.

At the early stage of an infectious disease outbreak, the information regarding potentially effective interventions accumulates continuously, and as a result, a more flexible trial design that allows adding new interventions and removing inferior interventions may be a better choice to save on costs and time. One of the most notable examples is the RECOVERY (Randomized Evaluation of COVid-19 ThERapY) trial,[73] a platform trial to discover effective interventions to reduce the mortality rate in hospitalized COVID-19 patients. Future work could extend SMARTs to have such flexibility and compare its statistical properties with other types of SMARTs, which may be useful in planning for future pandemic control.

CONCLUSIONS

We sought to facilitate the application of SMARTs in the area of infectious diseases by familiarizing interested investigators with the general framework of SMARTs and the recent developments in SMARTs in terms of methodology and practical guidelines. Despite our best efforts to find related literature for a thorough review, there may be some publications that we have missed. Although we do not provide an exhaustive list of related articles, we cover the most important aspects of conducting a SMART, from identifying scenarios in which SMARTs are applicable and summarizing design and analysis methods for SMARTs to addressing the costs and ethical issues in such trials. Note that we did not intend to provide step-by-step guidance on implementing a SMART; instead, we attempted to provide comprehensive resources for potential designers of SMARTs for infectious diseases, including example SMART designs for controlling infectious diseases and easy to use software for sample size calculation and data analysis in SMARTs.

Although SMARTs may seem conceptually complex to some readers, they

can shift the fixed interventions to the more realistic interventions in which modifying interventions is allowed according to the early response status, which mimics what public health practitioners do in practice. We hope that investigators will draw inspiration from this review and translate it into practice to improve public health in the face of life-threatening infectious diseases as well as other potential health-related challenges. AJPH

ABOUT THE AUTHORS

Xinru Wang and Bibhas Chakraborty are with the Centre for Quantitative Medicine, Duke-NUS Medical School, Singapore. Bibhas Chakraborty is also with the Department of Statistics and Data Science, National University of Singapore, Singapore.

CORRESPONDENCE

Correspondence should be sent to Bibhas Chakraborty, the Centre for Quantitative Medicine and the Program in Health Services and Systems Research, Duke-NUS Medical School, 8 College Rd, Level 6, #06-31, Singapore 169857 (e-mail: bibhas.chakraborty@duke-nus.edu.sg). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

PUBLICATION INFORMATION

Full Citation: Wang X, Chakraborty B. The sequential multiple assignment randomized trial for controlling infectious diseases: a review of recent developments. *Am J Public Health*. 2023;113(1):49–59.

Acceptance Date: September 19, 2022.

DOI: https://doi.org/10.2105/AJPH.2022.307135

CONTRIBUTORS

X. Wang drafted and revised the article.
B. Chakraborty helped write and critically revise the article.

ACKNOWLEDGMENTS

B. Chakraborty would like to acknowledge research support from a Khoo Bridge Funding Award (Duke-NUS-KBrFA/2021/0040) and a start-up grant from Duke-NUS Medical School, National University of Singapore.

We wish to acknowledge helpful comments from Roger Vaughan, DrPH, MS, and the anonymous reviewers.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

HUMAN PARTICIPANT PROTECTION

No protocol approval was needed for this study because no human participants were involved.

REFERENCES

1. Brauner JM, Mindermann S, Sharma M, et al. Inferring the effectiveness of government interventions against COVID-19. *Science.* 2021;371(6531):eabd9338. https://doi.org/10.1126/science.abd9338
2. Murphy SA. An experimental design for the development of adaptive treatment strategies. *Stat Med.* 2005;24(10):1455–1481. https://doi.org/10.1002/sim.2022
3. Zhang J, Chua QHA, Shen XM, Viseikumaran JA, Teoh T, Tan NG. A Systematic implementation of telemedicine in Singapore's COVID-19 community recovery facilities. *Telemed E-Health.* 2022; Epub ahead of print. https://doi.org/10.1089/tmj.2021.0466
4. Lavori PW, Dawson R, Rush AJ. Flexible treatment strategies in chronic disease: clinical and research implications. *Biol Psychiatry.* 2000;48(6):605–614. https://doi.org/10.1016/S0006-3223(00)00946-X
5. Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized studies. *J Educ Psychol.* 1974;66(5):688–701. https://doi.org/10.1037/h0037350
6. Sherwood NE, Crain AL, Seburg EM, et al. BestFIT sequential multiple assignment randomized trial results: a SMART approach to developing individualized weight loss treatment sequences. *Ann Behav Med.* 2022;56(3):291–304. https://doi.org/10.1093/abm/kaab061
7. Mustanski B, Moskowitz DA, Moran KO, et al. Evaluation of a stepped-care eHealth HIV prevention program for diverse adolescent men who have sex with men: protocol for a hybrid type 1 effectiveness implementation trial of SMART. *JMIR Res Protoc.* 2020;9(8):e19701. https://doi.org/10.2196/19701
8. Schoenfelder EN, Chronis-Tuscano A, Strickland J, Almirall D, Stein MA. Piloting a sequential, multiple assignment, randomized trial for mothers with attention-deficit/hyperactivity disorder and their at-risk young children. *J Child Adolesc Psychopharmacol.* 2019;29(4):256–267. https://doi.org/10.1089/cap.2018.0136
9. Morgenstern J, Kuerbis A, Shao S, et al. An efficacy trial of adaptive interventions for alcohol use disorder. *J Subst Abuse Treat.* 2021;123:108264. https://doi.org/10.1016/j.jsat.2020.108264
10. Collins LM, Murphy SA, Strecher V. The multiphase optimization strategy (MOST) and the sequential multiple assignment randomized trial (SMART): two novel evaluation methods for developing optimal training programs. *Am J Prev Med.* 2007;32(5, suppl):S112–S118. https://doi.org/10.1016/j.amepre.2007.01.022
11. Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SAA. "SMART" design for building individualized treatment sequences. *Annu Rev Clin Psychol.* 2012;8:21–48. https://doi.org/10.1146/annurev-clinpsy-032511-143152
12. Almirall D, Compton SN, Gunlicks-Stoessel M, Duan N, Murphy SA. Designing a pilot sequential multiple assignment randomized trial for developing an adaptive treatment strategy. *Stat Med.* 2012;31(17):1887–1902. https://doi.org/10.1002/sim.4512
13. Kidwell KM, Postow MA, Panageas KS. Sequential, multiple assignment, randomized trial designs in immuno-oncology research. *Clin Cancer Res.* 2018;24(4):730–736. https://doi.org/10.1158/1078-0432.CCR-17-1355
14. Kidwell KM, Hyde LW. Adaptive interventions and SMART designs: application to child behavior research in a community setting. *Am J Eval.* 2016;37(3):344–363. https://doi.org/10.1177/1098214015617013
15. Almirall D, Nahum-Shani I, Sherwood NE, Murphy SA. Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research. *Transl Behav Med.* 2014;4(3):260–274. https://doi.org/10.1007/s13142-014-0265-0
16. Chakraborty B. Dynamic treatment regimes for managing chronic health conditions: a statistical perspective. *Am J Public Health.* 2011;101(1):40–45. https://doi.org/10.2105/AJPH.2010.198937
17. Dai H, Saccardo S, Han MA, et al. Behavioural nudges increase COVID-19 vaccinations. *Nature.* 2021;597(7876):404–409. https://doi.org/10.1038/s41586-021-03843-2
18. Zhou G. Adaptive interventions for optimizing malaria control: an implementation study protocol for a block-cluster randomized, sequential multiple assignment trial. *Trials.* 2020;21(1):665. https://doi.org/10.1186/s13063-020-04573-y
19. Windsor L, Benoit EM, Pinto R, Sarol J. Optimization of a new adaptive intervention using the SMART design to increase COVID-19 testing among people at high risk in an urban community. *Trials.* 2022;23:310. https://doi.org/10.1186/s13063-022-06216-w
20. Baker TB, Smith SS, Bolt DM, et al. Implementing clinical research using factorial designs: a primer. *Behav Ther.* 2017;48(4):567–580. https://doi.org/10.1016/j.beth.2016.12.005
21. Walton A, Nahum-Shani I, Crosby L, Klasnja P, Murphy S. Optimizing digital integrated care via micro-randomized trials. *Clin Pharmacol Ther.* 2018;104(1):53–58. https://doi.org/10.1002/cpt.1079
22. Nahum-Shani I, Dziak JJ, Wetter DW. MCMTC: a pragmatic framework for selecting an experimental design to inform the development of digital interventions. *Front Digit Health.* 2022;4:798025. https://doi.org/10.3389/fdgth.2022.798025
23. Almirall D, Nahum-Shani I, Wang L, Kasari C. Experimental designs for research on adaptive interventions: singly and sequentially randomized trials. In: Collins LM, Kugler KC, eds. *Optimization of Behavioral, Biobehavioral, and Biomedical Interventions: Advanced Topics.* Cham, Switzerland: Springer International; 2018:89–120. https://doi.org/10.1007/978-3-319-91776-4_4
24. Ko JH, Wahed AS. Up-front versus sequential randomizations for inference on adaptive treatment strategies. *Stat Med.* 2012;31(9):812–830. https://doi.org/10.1002/sim.4473
25. Yan X, Matchar DB, Sivapragasam N, Ansah JP, Goel A, Chakraborty B. Sequential multiple assignment randomized trial (SMART) to identify optimal sequences of telemedicine interventions for improving initiation of insulin therapy: a simulation study. *BMC Med Res Methodol.* 2021;21(1):200. https://doi.org/10.1186/s12874-021-01395-7

26. Yan X, Ghosh P, Chakraborty B. Sample size calculation based on precision for pilot sequential multiple assignment randomized trial (SMART). *Biom J.* 2021;63(2):247–271. https://doi.org/10.1002/bimj.201900364
27. Yan X, Dunne DM, Impey SG, et al. A pilot sequential multiple assignment randomized trial (SMART) protocol for developing an adaptive coaching intervention around a mobile application for athletes to improve carbohydrate periodization behavior. *Contemp Clin Trials Commun.* 2022;26:100899. https://doi.org/10.1016/j.conctc.2022.100899
28. Lambert SD, Grover S, Laizner AM, et al. Adaptive web-based stress management programs among adults with a cardiovascular disease: a pilot sequential multiple assignment randomized trial (SMART). *Patient Educ Couns.* 2022;105(6):1587–1597. https://doi.org/10.1016/j.pec.2021.10.020
29. Oetting AI, Levy JA, Weiss RD, Murphy SA. Statistical methodology for a SMART design in the development of adaptive treatment strategies. In: Shrout P, Keyes K, Ornstein K, eds., *Causality and Psychopathology: Finding the Determinants of Disorders and Their Cures.* New York, NY: Oxford University Press; 2011:179–205. https://doi.org/10.1093/oso/9780199754649.003.0013
30. Ogbagaber SB, Karp J, Wahed AS. Design of sequentially randomized trials for testing adaptive treatment strategies. *Stat Med.* 2016;35(6):840–858. https://doi.org/10.1002/sim.6747
31. Zhong X, Cheng B, Qian M, Cheung YK. A gatekeeping test for selecting adaptive interventions under general designs of sequential multiple assignment randomized trials. *Contemp Clin Trials.* 2019;85:105830. https://doi.org/10.1016/j.cct.2019.105830
32. Zhong T, Wang X, Cheng B, Cheung YK. SMARTAR: sequential multiple assignment randomized trial and adaptive randomization. R Package version 1.1.0. Available at: https://CRAN.R-project.org/package=SMARTAR. Accessed October 28, 2022.
33. Ghosh P, Cheung YK, Chakraborty B. Sample size calculations for clustered SMART designs. In: Kosorok MR, Moodie EEM, eds., *Adaptive Treatment Strategies in Practice.* Philadelphia, PA: Society for Industrial and Applied Mathematics; 2015:55–70. https://doi.org/10.1137/1.9781611974188.ch5
34. Kidwell KM, Seewald NJ, Tran Q, Kasari C, Almirall D. Design and analysis considerations for comparing dynamic treatment regimens with binary outcomes from sequential multiple assignment randomized trials. *J Appl Stat.* 2018;45(9):1628–1651. https://doi.org/10.1080/02664763.2017.1386773
35. Li Z, Murphy SA. Sample size formulae for two-stage randomized trials with survival outcomes. *Biometrika.* 2011;98(3):503–518. https://doi.org/10.1093/biomet/asr019
36. Seewald NJ, Kidwell KM, Nahum-Shani I, Wu T, McKay JR, Almirall D. Sample size considerations for comparing dynamic treatment regimens in a sequential multiple-assignment randomized trial with a continuous longitudinal outcome. *Stat Methods Med Res.* 2020;29(7):1891–1912. https://doi.org/10.1177/0962280219877520
37. Ghosh P, Yan X, Chakraborty B. A novel approach to assess dynamic treatment regimes embedded in a smart with an ordinal outcome. April 2022. Available at: http://arxiv.org/abs/1808.07287. Accessed June 25, 2022.
38. Quanbeck A, Almirall D, Jacobson N, et al. The balanced opioid initiative: protocol for a clustered, sequential, multiple-assignment randomized trial to construct an adaptive implementation strategy to improve guideline-concordant opioid prescribing in primary care. *Implement Sci.* 2020;15(1):26. https://doi.org/10.1186/s13012-020-00990-4
39. Necamp T, Kilbourne A, Almirall D. Comparing cluster-level dynamic treatment regimens using sequential, multiple assignment, randomized trials: regression estimation and sample size considerations. *Stat Methods Med Res.* 2017;26(4):1572–1589. https://doi.org/10.1177/0962280217708654
40. Xu J, Bandyopadhyay D, Salehabadi SM, Michalowicz B, Chakraborty B. SMARTp: a SMART design for nonsurgical treatments of chronic periodontitis with spatially referenced and nonrandomly missing skewed outcomes. *Biom J.* 2020;62(2):282–310. https://doi.org/10.1002/bimj.201900027
41. Xu J, Bandyopadhyay D, Azevedo D, Chakraborty B. SMARTp: sample size for SMART designs in non-surgical periodontal trials. R package version 0.1.1. Available at: https://CRAN.R-project.org/package=SMARTp. Accessed October 28, 2022.
42. Ghosh P, Nahum-Shani I, Spring B, Chakraborty B. Noninferiority and equivalence tests in sequential, multiple assignment, randomized trials (SMARTs). *Psychol Methods.* 2020;25(2):182–205. https://doi.org/10.1037/met0000232
43. Artman WJ, Nahum-Shani I, Wu T, Mckay JR, Ertefaie A. Power analysis in a SMART design: sample size estimation for determining the best embedded dynamic treatment regime. *Biostatistics.* 2020;21(3):432–448. https://doi.org/10.1093/biostatistics/kxy064
44. Artman W. Smartsizer: power analysis for a SMART design. R package version 1.0.3. Available at: https://CRAN.R-project.org/package=smartsizer. Accessed October 28, 2022.
45. Artman WJ, Johnson BA, Lynch KG, McKay JR, Ertefaie A. Bayesian set of best dynamic treatment regimes: construction and sample size calculation for SMARTs with binary outcomes. *Stat Med.* 2022;41(9):1688–1708. https://doi.org/10.1002/sim.9323
46. Artman W. SMARTbayesR: Bayesian set of best dynamic treatment regimes and sample size in SMARTs for binary outcomes. R package version 2.0.0. Available at: https://CRAN.R-project.org/package=SMARTbayesR. Accessed October 28, 2022.
47. Rose EJ, Laber EB, Davidian M, Tsiatis AA, Zhao YQ, Kosorok MR. Sample size calculations for SMARTs. June 2019. Available at: http://arxiv.org/abs/1906.06646. Accessed June 24, 2022.
48. Kidwell KM, Wahed AS. Weighted log-rank statistic to compare shared-path adaptive treatment strategies. *Biostatistics.* 2013;14(2):299–312. https://doi.org/10.1093/biostatistics/kxs042
49. Jiang R, Lu W, Song R, Davidian M. On estimation of optimal treatment regimes for maximizing t-year survival probability. *J R Stat Soc Series B Stat Methodol.* 2017;79(4):1165–1185. https://doi.org/10.1111/rssb.12201
50. Chao YC, Tran Q, Tsodikov A, Kidwell KM. Joint modeling and multiple comparisons with the best of data from a SMART with survival outcomes. *Biostatistics.* 2022;23(1):294–313. https://doi.org/10.1093/biostatistics/kxaa025
51. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes. Part I: main content. *Int J Biostat.* 2010;6(2):8. https://doi.org/10.2202/1557-4679.1200
52. Nahum-Shani I, Qian M, Almirall D, et al. Experimental design and primary data analysis methods for comparing adaptive interventions. *Psychol Methods.* 2012;17(4):457–477. https://doi.org/10.1037/a0029372
53. Lu X, Nahum-Shani I, Kasari C, et al. Comparing dynamic treatment regimes using repeated-measures outcomes: modeling considerations in SMART studies. *Stat Med.* 2016;35(10):1595–1615. https://doi.org/10.1002/sim.6819
54. Kasari C, Kaiser A, Goods K, et al. Communication interventions for minimally verbal children with autism: a sequential multiple assignment randomized trial. *J Am Acad Child Adolesc Psychiatry.* 2014;53(6):635–646. https://doi.org/10.1016/j.jaac.2014.01.019
55. Pelham WE, Fabiano GA, Waxmonsky JG, et al. Treatment sequencing for childhood ADHD: a multiple-randomization study of adaptive medication and behavioral interventions. *J Clin Child Adolesc Psychol.* 2016;45(4):396–415. https://doi.org/10.1080/15374416.2015.1105138
56. Nahum-Shani I, Qian M, Almirall D, et al. Q-learning: a data analysis method for constructing adaptive interventions. *Psychol Methods.* 2012;17(4):478–494. https://doi.org/10.1037/a0029373
57. Zhao Y, Zeng D, Rush AJ, Kosorok MR. Estimating individualized treatment rules using outcome weighted learning. *J Am Stat Assoc.* 2012;107(449):1106–1118. https://doi.org/10.1080/01621459.2012.695674
58. Laber EB, Zhao YQ. Tree-based methods for individualized treatment regimes. *Biometrika.* 2015;102(3):501–514. https://doi.org/10.1093/biomet/asv028
59. Zhou X, Mayer-Hamblett N, Khan U, Kosorok MR. Residual weighted learning for estimating individualized treatment rules. *J Am Stat Assoc.* 2017;112(517):169–187. https://doi.org/10.1080/01621459.2015.1093947
60. Tang X, Melguizo M. DTR: an R package for estimation and comparison of survival outcomes of dynamic treatment regimes. *J Stat Softw.* 2015;65(7):1–28. https://doi.org/10.18637/jss.v065.i07
61. Chen Y, Liu Y, Zeng D, Wang Y. DTRlearn2: statistical learning methods for optimizing dynamic treatment regimes. R package version 1.1. Available at: https://CRAN.R-project.org/package=DTRlearn2. Accessed October 28, 2022.
62. Wallace M, Moodie EEM, Stephens DA, Schulz GS, Rreg JDT. DTR estimation and inference via G-estimation, dynamic WOLS, Q-Learning, and dynamic weighted survival modeling (DWSurv). R package version 1.7. Available at: https://CRAN.R-project.org/package=DTRreg. Accessed October 28, 2022.
63. Holloway ST, Laber EB, Linn KA, Zhang B, Davidian M, Tsiatis AA. DynTxRegime: methods for estimating optimal dynamic treatment regimes. R package version 4.10. Available at: https://CRAN.R-project.org/package=DynTxRegime. Accessed October 28, 2022.
64. Liu Y, Wang Y, Zeng D. Sequential multiple assignment randomization trials with enrichment design. *Biometrics.* 2017;73(2):378–390. https://doi.org/10.1111/biom.12576

65. Shortreed SM, Laber E, Scott Stroup T, Pineau J, Murphy SA. A multiple imputation strategy for sequential multiple assignment randomized trials. *Stat Med.* 2014;33(24):4202–4214. https://doi.org/10.1002/sim.6223
66. Matrajt L, Eaton J, Leung T, Brown ER. Vaccine optimization for COVID-19: who to vaccinate first? *Sci Adv.* 2021;7(6):eabf1374. https://doi.org/10.1126/sciadv.abf1374
67. Morciano A, Moerbeek M. Optimal allocation to treatments in a sequential multiple assignment randomized trial. *Stat Methods Med Res.* 2021; 30(11):2471–2484. https://doi.org/10.1177/09622802211037066
68. Xu Y, Greene TH, Bress AP, et al. Estimating the optimal individualized treatment rule from a cost-effectiveness perspective. *Biometrics.* 2022;78(1):337–351. https://doi.org/10.1111/biom.13406
69. Wu L, Wang J, Wahed AS. Interim monitoring in sequential multiple assignment randomized trials. *Biometrics.* 2021; Epub ahead of print. https://doi.org/10.1111/biom.13562.
70. Cheung YK, Chakraborty B, Davidson KW. Sequential multiple assignment randomized trial (SMART) with adaptive randomization for quality improvement in depression treatment program. *Biometrics.* 2015;71(2):450–459. https://doi.org/10.1111/biom.12258
71. Wang J, Wu L, Wahed AS. Adaptive randomization in a two-stage sequential multiple assignment randomized trial. *Biostatistics.* 2022;23(4):1182–1199. https://doi.org/10.1093/biostatistics/kxab020
72. Ruppert AS, Yin J, Davidian M, et al. Application of a sequential multiple assignment randomized trial (SMART) design in older patients with chronic lymphocytic leukemia. *Ann Oncol.* 2019;30(4): 542–550. https://doi.org/10.1093/annonc/mdz053
73. National Library of Medicine. Randomised evaluation of COVID-19 therapy (RECOVERY). May 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04381936. Accessed September 13, 2022.