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Short communication

Sequential Multiple Assignment Randomized Trials (SMART) Designs for COVID-19 Clinical Studies

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ABSTRACT

The impact of COVID-19 has been felt across the whole world. Economies of many countries have suffered yet there is still no cure for the pandemic. A novel approach of conducting a clinical trial that may be employed in COVID-19 clinical trials is presented. This approach can help in identifying a treatment policy or policies which can result in quicker recovery.

Keywords: *COVID-19; Clinical trials; SMART designs; Treatment policies.*

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INTRODUCTION

The coronavirus, the virus that causes COVID-19, has caused over a million deaths with total number of cases of surpassing 45 million worldwide. In Africa, there have been over 1.7 million reported cases and with over 40 thousand deaths (Worldometers, 2020). The coronavirus is thought to spread from person to person through respiratory droplets produced when an infected person coughs or sneezes. The spread is more likely when people are in close proximity with one another. Respiratory droplets can lend on surfaces, touching surfaces contaminated with the coronavirus can also lead to the spread of COVID-19. Some infections can be spread through airborne transmission (Centers for Disease Control (CDC), 2020; World Health Organization, 2020). The World Health organization declared COVID-19 a pandemic in March 2020, this lead to various measures to limit the spread of the pandemic (World Health Organization, 2020). These measures included lockdowns in many countries which have, in turn, affected the economies of many countries in the developing world and sub-Saharan Africa in particular (Fernandes, 2020).

At present, there is no cure or vaccine for COVID-19 with proven efficacy in randomized controlled studies. Several drugs have been experimented but there is still no approved treatment for this pandemic (Sheahan et al., 2020). One of these drugs is remdesivir which demonstrated some efficacy against COVID-19 (Song et al., 2020). Many of the studies done in testing different treatments for COVID-19 have investigated one treatment or a combination of treatments but only using one stage of randomization (Song et al., 2020). Is it possible that there can be treatment policy or policies that can shorten the recovery time of patients? To our knowledge there has been no study that utilized two stages of randomization.

Dynamic Treatment Regimes: In the treatment of chronic diseases such as HIV, treatment is usually individualized according to the patients' needs. Clinicians treat patients in multiple stages, individualizing treatment type or dosage according to adverse events, response of patient to the treatment, burden and preference. For example, in HIV patients, clinicians may switch a patient from one drug to another if the patient does not respond or experiences serious side effects. The primary reasons in considering sequences of treatments are high interpatient variability in response to treatment, presence of co-morbidities and time-varying severity of side effects (Chakraborty, 2011).

A dynamic treatment regime (DTR), also known as adaptive treatment strategies or treatment policy, is a sequence of decision rules applied at different stages. A DTR comprises of treatment options, critical decision points at which a patient is assessed and treatment decisions are made. At each stage or decision point, a tailoring variable allows for the personalization of the intervention. Individual and intervention level information can be used as tailoring variables. Treatment policies are developed to define the sequence of treatments that will result in the most favourable clinical outcome possible, a DTR is said to optimal if it

optimizes the mean long term outcome of interest (Chakraborty & Murphy, 2014).

This paper suggests an innovative design that can be used in COVID-19 clinical trials where the primary objective is to identify empirically treatment sequences that can lead to favourable outcomes in COVID-19 patients. These outcomes can be, for example, shortened recovery time (quick recovery) or any other desirable outcomes. Focus shall be on survival endpoint, that is, time to recovery. Sequential multiple assignment randomized trial (SMART) designs are well suited for developing optimal DTRs.

Sequential Multiple Assignment Randomized Trial (SMART) Designs: In SMART designs patients are initially randomized to first-stage treatments followed by re-randomization at each subsequent stage of some or all of the patients to treatment actions available at those stages. Re-randomization after the first stage may depend on information collected in previous stages such as information on how well the patient responded to prior treatments. SMART designs have been used in cancer clinical trials and in behavioural sciences (Kidwell et al., 2018).

The general SMART design is where all individuals or patients are re-randomized, that is, in the case where response is the tailoring variable; both the responders and non-responders are re-randomized at the second-stage. In most cancer studies which utilize SMART designs, only responders are randomized after the first-stage, for example, in the CALGB 19808 study (Kolitz et al., 2014). For purposes of this paper and also looking at suitability to Covid-19, the focus is on two stage randomization designs where both responders and non-responders are re-randomized. Figure 1 shows an example of a two- stage randomization design which may be applicable in COVID-19 clinical trials. As an illustration, we denote the available treatments in each stage by uppercase letters. Let A_1 and A_2 denote the first stage available treatments and also let B_1 and B_2 represent the second stage treatments available to responders, finally denote by B_{1NR} and B_{2NR} the second stage treatments available to non-responders. The treatment policy, A_1B_1, means treat with treatment A_1 followed by B_1 if the patient is a responder. This is shown pictorially.

Practical Considerations and Sample Size Calculation: Many authors recommend that the design of SMARTs should not be complicated (Chakraborty & Murphy, 2014; Kidwell et al., 2018). There should not be any unnecessary restrictions on the class of treatment options at each stage. For instance, it is advisable to use low dimensional summary criterion (e.g. responder non-responder status) instead of all intermediate outcomes like adherence, adverse events, improvement of symptom severity etc.

Sometimes, the primary hypothesis in some SMARTs concerns the main effect of the initial stage treatments. In this case, the question of interest would be "marginalizing over second stage treatments, on average, what is the best initial treatment? It is also possible that the primary hypothesis concerns the main effect of second stage treatments; in this case the research question could be "on average, what is the best secondary treatment, a switch or augmentation, for non-responders to the first stage treatment? In the above cases, the sample size formulae are standard and can easily be derived (Chakraborty & Murphy, 2014).

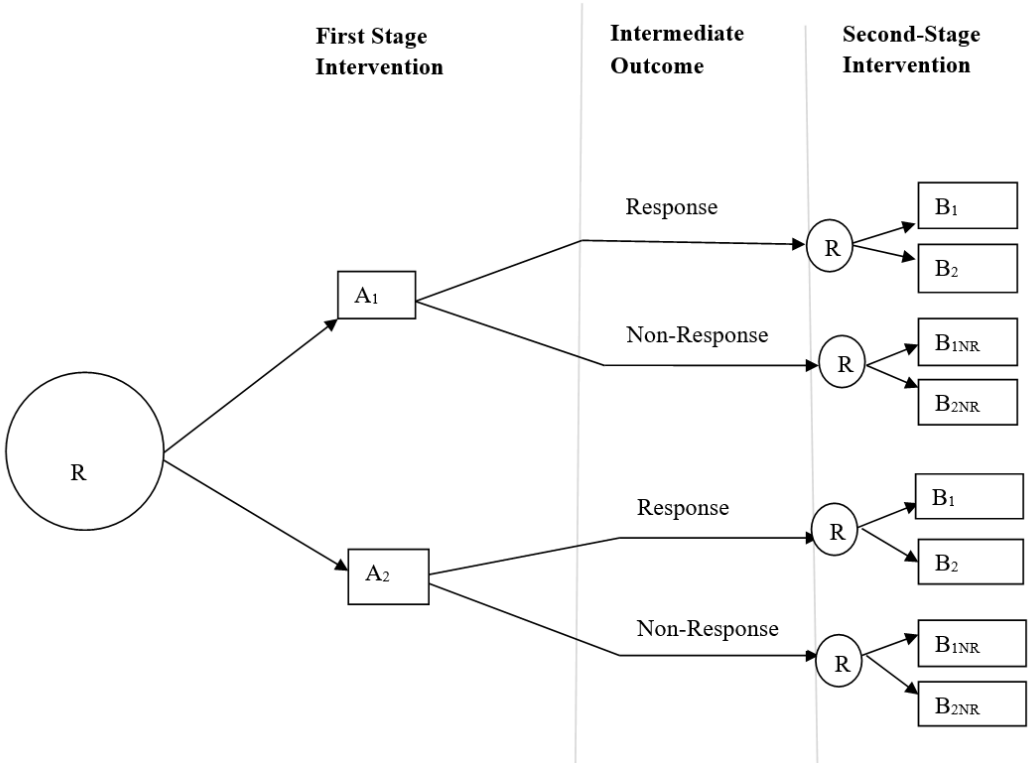

Figure 1
An example of a SMART design with 8 embedded DTRs. R denotes randomization.

In some instances, however, the primary research lies on the comparison of two or more treatment policies embedded in a SMART (Kidwell et al., 2018). In this case, interest is on identifying the best treatment policy or policies, for example, in Covid-19 studies would be to identify a treatment policy that can lead to quick recovery of patients. For such studies, the sample size formulae for continuous endpoints have been developed (Murphy, 2005). Some studies have survival endpoints and the sample size for these studies can be found in (Lunceford & Tsiatis, 2002; Feng & Wahed, 2008) . A web application is also available from the authors.

Analysis of Data from SMART Designs: The main goal from SMART designs with survival endpoints is the estimation of survival distributions and comparing of different treatment policies embedded in the SMART. For this purpose, several methods have been developed (Lunceford & Tsiatis, 2002; Kidwell & Waheed, 2012; Tang & Wahed, 2014; Vilakati & Cortese, 2019; Vilakati & Cortese, 2020). Inverse probability weights are used in the analysis and the problem is formulated using counterfactuals or potential outcomes (Rubin, 1974). The methods mentioned above cannot be used in COVID-19 SMARTs with a survival endpoint where for an example the outcome of interest is time to recovery. The problem arises because of competing risks. An individual entering the study may have his recovery time observed or may die before recovery. In this case death is a competing risk. An individual who does not recover at the end of the study is censored (right censoring).

Competing risk censoring occurs when individuals in a study are exposed to more than one possible failure and the specific event of interest is unobservable owing to the occurrence of competing events. In the presence of competing risks, interest is usually on the instantaneous failure rate of one cause, that is, the cause specific hazard or the probability of the occurrence of the target event by a specific time point, the cumulative incidence function (CIF). The CIF is easy to interpret and it is non-parametrically identifiable and for these reasons it has been commonly used (Yavuz et al., 2018). In the presence of competing risks in SMART study, the objective then becomes finding a regime which results in a higher (or reduced) probability of occurrence desired (undesired) event of interest. In the case of employing SMART studies in covid-19 trials, the event of interest could be time to recovery. The estimation of the CIF can be done following the methodology developed in this paper (Yavuz et al., 2018). The estimation of the CIF can be done using fixed weights or time-dependent weights. Confidence intervals can also be constructed for the two case cases of fixed weights and time-dependent weights. The comparison of treatment policies can also be done using CIFs (Yavuz et al., 2018).

Conclusion

In this paper, a novel approach of conducting a clinical trial that may be employed in COVID-19 clinical trials is presented. This approach can help in identifying a treatment policy or policies which can result in quicker recovery. This is important in keeping our hospitals not overwhelmed by many patients. This study does not suggest which interventions can be tested in a covid-19 SMART but leaves this to clinicians who have knowledge of potential treatment policies which can be tested

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