Design and analysis considerations for a sequentially randomized HIV prevention trial

David Benkeser†,1, Keith Horvath2, Cathy J. Reback3, Joshua Rusow3, Michael Hudgens4
1Department of Biostatistics and Bioinformatics, Emory University
2Department of Psychology, University of California, San Diego
3Friends Research Institute
4Department of Biostatistics, University of North Carolina, Chapel Hill

Abstract
TechStep is a randomized trial of a mobile health interventions targeted towards transgender adolescents. The interventions include a short message system, a mobile-optimized web application, and electronic counseling. The primary outcomes are self-reported sexual risk behaviors and uptake of HIV preventing medication. In order that we may evaluate the efficacy of several different combinations of interventions, the trial has a sequentially randomized design. We use a causal framework to formalize the estimands of the primary and key secondary analyses of the TechStep trial data. Targeted minimum loss-based estimators of these quantities are described and studied in simulation.

1 Introduction
Transgender individuals are estimated to make up between 0.39% and 0.53% of the US population [7, 14], with higher percentages of high school students identifying as transgender [9]. Transgender, gender non-conforming, and gender non-binary (referred to here collectively as trans) demonstrate elevated rates of risky sexual behaviors relative to their cisgender peers, leaving this population vulnerable to infection with human immunodeficiency virus (HIV) [21]. A potential avenue for improvement in the health of trans youth is through mobile technology-based interventions. Such interventions circumvent the face-to-face interaction required for traditional health care delivery, and are therefore highly scalable. Moreover, technology-based interventions may be extremely low cost, confidential, and can cultivate communication amongst users, which may be important to trans youth who face high levels of stigma in healthcare and employment settings [20, 18]. It is therefore of interest to design mobile interventions tailored to trans youth, and to evaluate the efficacy of these interventions in preventing HIV infection.

The TechStep study is an ongoing randomized controlled trial (RCT) of mHealth interventions in high-risk HIV-negative trans youths and young adults (15–24 years old).
Three trans-specific mHealth interventions were developed for TechStep: a short messaging service (SMS or text), a mobile-optimized webapp, and an eCoaching intervention, which offers one-on-one risk behavior counseling administered through a mobile video conferencing service \cite{13, 30}. The goal of the trial is to evaluate the efficacy of these interventions for reducing sexual risk behaviors (e.g., condomless anal or vaginal intercourse, engagement in sex work, sex while feeling the effects of alcohol or drugs) and increasing uptake of pre-exposure prophylaxis (PrEP). The trial will have a total of nine months of follow-up with clinical assessments on participants taken at baseline and at three-, six-, and nine months after enrollment.

The availability of multiple intervention modalities complicates the design of an RCT to evaluate its efficacy. We must consider whether the mHealth interventions should be offered individually, all together, or in a sequential fashion. A priori eCoaching might be expected to be the most effective intervention of the three; however, from an implementation perspective, scalability may be limited due to its cost. These and other considerations led to a sequential multi-arm randomized trial (SMART) design for the TechStep trial.

SMARTs randomize participants to an initial intervention and monitor participants after receipt of the intervention \cite{12, 15, 2, 16, 17, 6}. Based on interim data, participants may become eligible for re-randomization to a new intervention. After receipt of the intervention, participants are monitored again. Based on these new data (and all previous data), participants may again become eligible for re-randomization to a new intervention. This process of monitoring and re-randomizing to different interventions continues until a pre-specified timepoint. The data generated from such a trial can be used to evaluate the efficacy of one or several treatment rules, that is, rules for how participants should be assigned treatment at each time.

SMART trials have great potential to advance HIV prevention science. Results of such trials can move researchers closer to personalized care for individuals, and enable evaluation of interventions that are feasible to implement. This is highly relevant in the field of HIV prevention, where competing prevention modalities are emerging and must be evaluated head-to-head in randomized trials. This is true not just of behavioral interventions, like the ones considered here, but also when considering pharmacological interventions such as pre-exposure prophylaxis (PrEP) or preventive HIV vaccines. Current thinking in the HIV prevention field is that some prevention modalities will be acceptable and effective in some individuals, but not in others. Thus, utilizing trial designs that can aid our understanding of which interventions are effective for which individuals may help improve comprehensive efforts at HIV prevention \cite{8}. Nevertheless, in spite of the potential benefits of SMART designs, their usage in the context of HIV prevention is extremely limited. In this paper, we discuss the motivation for a SMART design in the TechStep trial, the statistical methods needed to provide a robust and efficient analysis of the trial, and a simulation study to assess the power of the design to answer key questions of interest. We hope that this work will provide researchers with a better understanding for the motivation of SMART HIV prevention trials, as well as some ideas for how such trials can be planned and analyzed in practice.
2 Scientific questions and implications for design

2.1 Primary questions

To identify a primary question of interest, we first define our outcomes and interventions of interest. For the outcome, we focus on the cumulative number of risky sexual encounters, defined as acts of condomless anal intercourse, engagement in sex work, or sex while feeling the effects of alcohol or drugs. We will consider an intervention effective if it reduces the average number of risky sexual encounters over the duration of the trial.

Ideally, a primary analysis should assess an intervention that is feasible to implement in a broader clinical setting [5]. We reasoned that many clinics could offer either a the text- or an webapp-based intervention, but not both. Moreover, such low intensity interventions may be sufficiently efficacious for many participants in reducing risky sexual behaviors. However, there may be individuals for whom the low intensity interventions would be insufficient to change risk behaviors. These individuals may derive greater benefit from the more intensive and personalized eCoaching intervention. For these reasons, we are motivated to compare three interventions: (i) control intervention consisting of a static website with trans-specific HIV and risk reduction information and local and national trans resources, (ii) text + eCoaching, where participants receive text messaging for ninety days and those who do not improve their risk behaviors receive three months of eCoaching in addition to text messaging, and (iii) webapp + eCoaching, where participants receive access to a webapp for ninety days and those who do not improve receive eCoaching for three months in addition to the webapp. The primary goal of the trial is to compare average number of risky encounters for participants who receive intervention (ii) vs. (i) and who receive intervention (iii) vs. (i).

2.2 Secondary questions

Some health clinics may be unable to staff trained eCoaching counselors, and thus interventions (ii) and (iii) may be infeasible to implement in some clinical settings. However, clinics could likely support either a text message system or a webapp, since these interventions are extremely low cost. Thus, there is good motivation to evaluate two additional interventions: (iia) text messaging only, where participants receive text messaging for six months and (iiia) webapp only, where participants receive access to a mobile-optimized webapp for six months. A key secondary goal of the trial is to compare the average number of risky encounters for participants who receive intervention (iia) vs. (i) and who receive intervention (iiia) vs. (i).

While an eCoaching intervention is the most intensive and costly mHealth intervention we considered, it is also hypothesized a-priori to be the most effective. Thus, it is also relevant to assess the marginal benefit of offering eCoaching to participants whose behavior does not improve under other mHealth interventions. To this end, another key secondary goal of the trial is to compare the average number of risk encounters for participants who receive intervention (ii) vs. (iia) and (iii) vs. (iiia). Such information could be provided to key stakeholders weighing the benefits of implementing a more intensive and expensive eCoaching intervention on top of a low intensity, first line mobile health intervention.
3 Causal Estimands

In this section, we detail the design of the TechStep trial that enables us to answer the questions above. We introduce notation that describes data collected in trial and translate the primary and secondary questions into formal causal estimands. Finally, we establish identifiability of these estimands based on the observed trial data.

Figure 1 illustrates the design of the TechStep study. At the baseline visit, participant information is collected, which we denote by \( L_0 = (Y_0, W_0) \), where \( Y_0 \) denotes sexual risk behaviors and \( W_0 \) other (e.g., demographic) information collected. While in the actual TechStep trial, \( Y_0 \) will consist of multiple measures of risk behaviors, for simplicity, here we consider that \( Y_0 \) is scalar-valued. We use \( A_0 \) to denote the intervention randomly assigned with equal probability to participants at enrollment, with \( A_0 = 0 \) denoting that standard of care was assigned, \( A_0 = 1 \) denoting that a first-line text intervention was assigned, and \( A_0 = 2 \) denoting that a first-line webapp intervention was assigned. We use \( C_1 \) to denote whether a participant attends the three-month clinic visit, so that \( C_1 = 0 \) denotes that the participant did not attend the visit, and \( C_1 = 1 \) denotes that the participant did attend the visit. For participants who attend the three-month visit, we measure additional information on sexual risk behaviors over the last three months. In particular, \( L_1 = (Y_1, W_1) \) denotes a vector of participant information collected at the three-month visit, where, as above, we use \( Y_1 \) to denote sexual risk behaviors over the first three months of the study, and \( W_1 \) denotes other information collected on participants. Based on this information, participants may become eligible for re-randomization. For simplicity, here we consider that participants with \( Y_1 \geq Y_0 \) and \( Y_1 \neq 0 \), i.e., those who have at least some risky behaviors and whose behaviors do not improve under the first-line intervention, are re-randomized 2:1 to either “step-up” to eCoaching or to maintain their current intervention. Individuals who have improved risk behaviors \( Y_1 < Y_0 \) or \( Y_1 = 0 \) are not eligible for re-randomization and so maintain their current intervention with probability one. We use \( A_1 \) to denote the intervention assigned to participants at the three-month visit and set \( A_1 = 3 \) if a participant is chosen to step-up to eCoaching, while \( A_1 = A_0 \) otherwise. Continuing on, \( C_2 \) denotes whether a participant attends the six month clinic visit and \( L_2 = (Y_2, W_2) \) to denote information collected at this visit. Similarly, \( C_3 \) and \( Y_3 \) are used to denote the same quantities collected at the nine month clinic visit. We denote by \( Y = Y_1 + Y_2 + Y_3 \) the cumulative outcome over the duration of the study. Thus, the time-ordered data for a typical study participant can be represented as a random variable \( O = (L_0, A_0, C_1, L_1, Y_1, A_1, C_2, L_2, Y_2, C_3, Y_3) \). We denote by \( \mathbb{P} \) the distribution of the observed data unit \( O \) and assume a nonparametric model for \( \mathbb{P} \).

To formalize our causal question of interest, we use a nonparametric structural equation model (NPSEM). This model assumes that each observed variable is a function of its parent variables and an exogenous error term. We adopt a model that assumes the parents of a given observed variable are all variables that temporally precede it. For example, \( L_0 \) has no parent variables, the parent of \( A_0 \) is \( L_0 \), the parent of \( C_1 \) is \( A_0 \) and \( L_0 \), and so on. We define interventions on this NPSEM that correspond to interventions (i), (ii), (iia), (iii), and (iiia) above. In addition to intervening on the mHealth variables \((A_0, A_1)\), these interventions enforce that participants attend each clinic visit. We define a function \( d \) that maps \( A_0, Y_0, Y_1 \) to \( \{0,1,2,3\} \), and defines our rules for stepping people up to the eCoaching intervention,
The interventions of interest are shown in Table 1. We denote by $Y^{(i)}$, $Y^{(ii)}$, $Y^{(iia)}$, $Y^{(iii)}$, and $Y^{(iia)}$ the counterfactual outcomes generated by interventions (i), (ii), (iia), (iii), and (iia), respectively. For example, $Y^{(i)}_j$ represents the total number of reported risky sexual behaviors over the duration of the trial, if, possibly counter to fact, individual $j$ received standard of care throughout the trial. We use $Y^{(·)}$ to generically denote one of these counterfactual outcomes. The distribution of the counterfactual variable $Y^{(·)}$ is denoted by $P^{(·)}$. We are interested in $\psi(·) = E[Y^{(·)}] = \int y dP^{(·)}(y)$ for each intervention. Our primary and secondary questions can be answered using statistical inference about parameters of the counterfactual outcome distributions. In particular, we quantify intervention effects in terms of additive differences in the average number of mean outcome over the duration of the trial. The causal estimands of interest pertaining to each of our primary and secondary questions are shown in Table 2.

In this section, we discuss identification of $E[Y^{(ii)}]$ using $P$, the distribution of the observed data. Nearly identical arguments can be used to establish identifiability of the other causal estimands. We use the longitudinal G-formula to establish identifiability; see [22, 1, 11] for more on the assumptions under which this identification result holds. We draw particular attention to the assumption of sequential randomization of intervention and missingness, referred to colloquially as the assumption of no unmeasured (time-varying) confounding. The SMART design of the trial ensures that intervention rules are randomly assigned and thus that observed intervention values are independent of counterfactual outcomes. However, as with any clinical trial, we expect that participants will miss clinic visits. Thus, in order that the sequential randomization assumption is satisfied, we require that amongst those participants who receive intervention (ii), $C_t$ is independent of $Y^{(ii)}$ given $L_{t-1}$, the covariate information collected up to time $t-1$. That is, the covariate history $L_{t-1}$ should include all individual characteristics that are related both to participants’ propensity for risky sexual behaviors and for attending future clinic visits. We will adopt this bar notation throughout to denote a collection past measurements of particular variables. For example, $\bar{C}_t = (C_1, \ldots, C_t)$ for $t = 1,2,3$. We will sometimes write $\bar{T}$ to denote a unit vector, the length of which will be apparent from the context. For example, $\bar{C}_3 = \bar{T}$ denotes the event that $C_1 = 1, C_2 = 1, C_3 = 1$, while $\bar{C}_2 = \bar{T}$ denotes the event that $C_1 = 1, C_2 = 1$, and so on.

If the assumptions described above are satisfied, then $E[Y^{(ii)}]$ can be written as a functional of $P$, for which we require the following definitions. We define $Q_3(y, \bar{z}_2)$ as the conditional cumulative distribution function (CDF) of $Y$ given $A_0 = 1, A_1 = d(1, y_0, y_1), \bar{C}_3 = \bar{T}$, and $\bar{E}_2 = \bar{z}_2$ evaluated at $y$. In words, $Q_3(y, \bar{z}_2)$ describes the probability of having fewer than or equal to $y$ risky sexual encounters over the duration of the trial, amongst the participants in
intervention arm (ii) that attended each of the three follow-up visits and had observed covariate history $\mathbf{\ell}_2$. Similarly, we define $Q_2(\mathbf{\ell}_2)$ as the conditional CDF of $L_2$ given $A_0 = 1, A_1 = d(1,y_0,y_1), \bar{C}_2 = 1, \bar{L}_1 = \bar{\mathbf{e}}_1$ evaluated at $\mathbf{e}$, and we define $Q_1(\mathbf{\ell}_1)$ as the conditional CDF of $L_1$ given $A_0 = 1, C_1 = 1$, and $L_0 = \mathbf{e}$. Finally, we define $Q_0(\mathbf{\ell}_0)$ as the conditional CDF of $L_0$ evaluated at $\mathbf{\ell}_0$. The G-formula for the causal estimand of interest is

$$E(Y^{(ii)}) = \int Q_1(\mathbf{\ell}_0) dQ_0(\mathbf{\ell}_0).$$

where $Q_1$ is recursively defined as follows,

$$Q_1(\mathbf{\ell}_0) = \int Q_2(\mathbf{\ell}_1) dQ_1(\mathbf{\ell}_1) \quad (1)$$

$$Q_2(\mathbf{\ell}_1) = \int Q_3(\mathbf{\ell}_2) dQ_2(\mathbf{\ell}_2) \quad (2)$$

$$Q_3(\mathbf{\ell}_2) = \int y dQ_3(y, \mathbf{\ell}_2). \quad (3)$$

4 Statistical Methodology

Well-controlled randomized trials generally allow researchers to utilize covariate-unadjusted statistical methods to draw inference on causal effects, since, by virtue of the randomized design, counterfactual outcomes are marginally independent of intervention assignment. However, the same is not true in SMART trials, as sequential randomization probabilities depend on past covariates. Thus, these covariates must be accounted for by the estimator in order to draw valid inference. A more challenging issue is that typically at least some follow-up data are missing in randomized trials, for example, due to participants moving out of the study region. Simple strategies, such as complete-case analysis, run the risk of incurring bias due to informative missingness. To draw more robust inference, we can utilize estimators that account for all measured covariates, not just those that are used to determine re-randomization probabilities. If the measured covariates are rich enough to satisfy the sequential randomization assumption on missingness, then we should be able to draw valid inference about intervention effects, in spite of the informative nature of the missingness.

We will analyze the TechStep trial using targeted minimum loss-based estimation (TMLE) [28, 26, 27]. TMLE is a general framework for generating plug-in estimators that solve a set of user-selected equations [24]. In the present problem, we sequentially generate estimates of the parameters of the G-formula (1)–(3) that solve the efficient influence function estimating equation. We refer interested readers to [19, 23] for technical derivations of the underpinnings of TMLE in the present context. We provide a detailed description of the implementation of the estimator in the appendix.
From a high level, our estimator is built in several stages. In the first stage, we obtain estimates of randomization probabilities and the probability of a participant attending each clinic visit. Collectively, we refer to these probabilities as the propensity scores. These propensity scores, in particular, the components pertaining to missingness probabilities are used in the procedure to control for the possibility of time-varying confounding based on measured participant characteristics. With estimates of the propensity scores in hand, we proceed to estimating the outcome process using a sequence of regressions and starting at the final timepoint. Each of these outcome regressions involves two steps: obtaining an initial regression estimate and augmenting this estimate using so-called fluctuation submodels. The purpose of the first step is to obtain an estimator that adjusts for potential time-varying confounders of the outcome and missingness process, while the second step ensures that the efficient influence function estimating equation is satisfied. This latter step endows the TMLE with desirable robustness and efficiency properties. Notably, the TMLE controls for potential time-varying confounding through estimation of propensity scores and through sequential estimation of the outcome process. The augmentation step is the crucial step in wedding these two approaches. In particular, this step ensures that, so long as either the outcome process or the propensity scores are consistently estimated, the resultant TMLE is consistent. That is, the TMLE is doubly robust. For more on double-robustness in the present context, see [1, 11].

5 Simulation

We performed extensive simulations to determine the sample size required to detect clinically meaningful differences in average risk behaviors in the TechStep trial. We designed a data generating process that mimicked the design of the trial and analyzed the simulation data using the proposed statistical methodology. Simulated data were generated as follows. For simplicity, we assumed $W_0$ was scalar-valued and drawn from a Bernoulli($1/2$) distribution. Baseline sexual risk behaviors $Y_0$ were drawn from a Poisson($\exp(\gamma_0)$) distribution, where $\gamma_0$ is the log-average number of risk behaviors. Using estimates from published data [10, 21], we set $\gamma_0 = \log(1.5)$. The treatment $A_0$ was assigned randomly with $1/3$ probability of control, text-, and webapp-based interventions. Data for the 3, 6, and 9-month visits were generated as follows. For $t = 1, 2, 3$, we drew $C_t$ from Bernoulli($\logit^{-1}(\alpha_0)$) distribution; thus, $\alpha_0$ controls the level of participant dropout. Given $C_t = 1$ (i.e., that the participant attended clinic visit $t$), we drew $Y_t$ from a Poisson distribution with conditional mean

$$Y_t - 1 \lor \frac{1}{2} \exp \left[ \gamma_A, 1 \mathbf{1}(A_{t-1} \land 1 = 1) + \gamma_A, 2 \mathbf{1}(A_{t-1} \land 1 = 2) + \gamma_A, 3 \mathbf{1}(A_{t-1} \land 1 = 3) + \gamma_W W_0 \right].$$

Here, $x_1 \lor x_2$ and $x_1 \land x_2$ denote the smaller and larger of two real-valued numbers $x_1, x_2$, respectively. Note that this corresponds to a Markov model, where the only factors of participants’ history that influence their risk behaviors are their most recently measured risk behaviors ($Y_{t-1}$), their most recent treatment ($A_{t-1} \land A_1$), and baseline covariate $W_0$. We consider a wide range of scenarios by selecting different values of simulation parameters (Table 3). For each combination of simulation parameters, we analyzed five hundred data sets. Power for each choice of $n$ and for each of the comparisons shown in Table 2 was estimated by the proportion of simulations in which the two-sided level 0.05 Wald test rejected the null hypothesis of no difference in average number of risky behaviors. To
estimate the conditional probability of censoring, we used main terms logistic regression. To estimate the sequential outcome regression, we used the super learner based on five-fold cross-validation with a library of candidate regressions that consisted of an intercept-only model, a Poisson regression model, a negative binomial regression model, and the highly adaptive LASSO \[^3\]. The latter is a flexible semiparametric regression estimator.

For the primary analysis, we found that type I error rate was adequately controlled for each sample size considered (Figure 2). Across a wide range of settings, we estimated that we have 80\% power to detect a difference in 1.60 average risk behaviors comparing text+step versus control at \( n = 300 \), 1.75 at \( n = 250 \), and 1.90 at \( n = 200 \). These results seem to be robust across situations where the majority of the benefit is derived from the text versus from the eCoaching component of the intervention. Increasing censoring from 5\% to 10\% (left versus right column of Figure 2) tended to decrease power by 3–5\%. For the secondary analysis examining the effect of text+step versus text-only interventions we found that type I error rates were slightly higher than the nominal level in the smallest sample size (Figure 3). We found similar power curves for this secondary analysis as with the primary analysis. There tended to be higher power to detect differences when there was a small effect of the text intervention \((\gamma_1 = -0.11)\) relative to no effect of the text intervention \((\gamma_1 = 0)\). Results for the simulation studying the secondary analysis that compares efficacy of text-only versus app-only are included in the appendix. These results were similar to the primary analysis with 80\% power to detect differences in average number of risk behaviors of between 1.60 and 1.90. Results for comparing text-only versus app-only interventions are shown in Figure 4. We found a minor increase in type I error for this comparison using the proposed test. Across the various settings, there is 80\% power to detect an average difference of about two risk behaviors between the text-only and app-only interventions.

6 Discussion

Based on these simulation results and other criteria, a target of \( n = 250 \) was set for enrollment in the TechStep trial. Our simulation results suggest this sample size will afford sufficient power to detect clinically meaningful differences between interventions, and balances power appropriately between the primary analyses and key secondary analyses.

Further research is warranted in several areas. First, our Wald tests were slightly anti-conservative for testing differences between the text+step versus text condition. We will explore alternative standard error estimators including cross-validated influence function-based standard errors. Second, we may wish to evaluate whether and how to adjust for intervention engagement (e.g., webapp para-data) in the primary and secondary analyses. If such information is predictive of risky behaviors, then incorporating such information may lead to improved power to detect differences amongst the interventions. Finally, we will explore different techniques for time-varying confounder selection. Extensive surveys will be collected at each clinic visit, so \( W_0, W_1, W_2 \) are all potentially high-dimensional vectors. We will evaluate different strategies for selecting components to include in the primary and secondary analyses.
Acknowledgments

Supported by United States National Institute of Health Grant 5U19HD089881 and U24HD089880

Appendix

To provide a concrete example of how to implement a TMLE in the present problem, we consider estimation of $E(Y^{(ii)})$ in a setting where $W_0, W_1,$ and $W_2$ are scalar-valued.

Estimating propensity scores

Our first task is to estimate the randomization probabilities for the text + step-to-eCoaching intervention. Specifically, we require estimates of

$$g_{A, 0} = P(A_0 = 1)$$

and

$$g_{A, 1} = P(A_1 = d(1, Y_0, Y_1)|A_0 = 1, C_1 = 1, L_0 = \ell_0, Y_1 = y_1).$$

While these probabilities are known by design, our estimators will utilize empirical estimates to account for chance imbalances between intervention arms. To that end, we define

$$g_{A, 0n} = \frac{1}{n} \sum_{i=1}^{n} \mathbb{1}(A_{0i} = 1)$$

and

$$g_{A, 1n}(0, y_1) = \left\{ \begin{array}{ll}
\frac{\sum_{i=1}^{n} \mathbb{1}(A_{0i} = 1, C_1i = 1, A_{1i} = 3)}{\sum_{i=1}^{n} \mathbb{1}(A_{0i} = 1, C_1i = 1)} & \text{if } y_1 \geq y_0 \text{ and } y_1 \neq 0 \\
1 & \text{else}
\end{array} \right.$$

Note that the latter estimator accounts for our step-up criteria. If a participant’s sexual risk behaviors do not improve, then they are eligible for step up and may be re-randomized to the eCoaching intervention. We estimate this re-randomization probability using an empirical proportion. If, on the other hand, a participant’s sexual risk behaviors improve, then that participant is not eligible for step up and stays on the text intervention with probability 1.

The second step is to estimate the probability of missing each clinic visit as a function of past covariates. In particular, for each covariate history $\overline{z}_2$, we require an estimate of

$$g_{C, 1}(\ell_0) = P(C_1 = 1|A_0 = 1, L_0 = \ell_0),$$

$$g_{C, 2}(\overline{z}_1) = P(C_2 = 1|A_0 = 1, C_1 = 1, A_1 = d(1, Y_0, Y_1), L_1 = \overline{z}_1),$$

and

$$g_{C, 3}(\overline{z}_2) = P(C_3 = 1|A_0 = 1, C_1 = 1, A_1 = d(1, Y_0, Y_1), C_2 = 1, L_2 = \overline{z}_2).$$

These estimates can be obtained, for example, using logistic regression. Considering estimation of $g_{C, 1}$, we could posit a logistic regression model, and regress the binary outcome $C_1$ onto basis functions of $L_0$ amongst participants randomized to the text intervention. Alternatively, we could posit a logistic regression model for the probability of attending the first clinic visit as a function of $A_0$ and $L_0$, and regress $C_1$ onto basis functions...
of $L_0$ and $A_0$ amongst all participants. As a concrete example, consider the main-terms logistic regression model for $\tilde{g}_{C,1}(a_0, \ell_0) = \mathbb{P}(C_1 = 1 | A_0 = a_0, L_0 = \ell_0)$,

$$\text{logit}\{\tilde{g}_{C,1}(a_0, \ell_0)\} = \gamma_0 + \gamma_1 \mathbb{1}(a_0 = 1) + \gamma_2 \mathbb{1}(a_0 = 2) + \ell_0 \gamma_L, \gamma \in \mathbb{R}^5,$$

where $\gamma = (\gamma_0, \gamma_1, \gamma_2, \gamma_L)^T$ and $\gamma_L$ is a two-dimensional vector of parameters associated with $W_0$ and $Y_0$. We note that this regression pools across interventions to estimate the conditional probability of attending the first clinic visit. An estimate $\hat{\gamma}$ of $\gamma$ can be obtained via maximum likelihood. We use $\tilde{g}_{C,1}(a_0, \ell_0)$ to denote the fitted value from this regression for an observation with $A_0 = a_0$ and $L_0 = \ell_0$. For any $\ell_0$ our estimate of $\tilde{g}_{C,1}$ is

$$\tilde{g}_{C,1}(a_0, \ell_0) = \tilde{g}_{C,1}(1, \ell_0) = \text{logit}^{-1}(\hat{\gamma}_0 + \hat{\gamma}_1 + \ell_0 \hat{\gamma}_L).$$

To estimate $\tilde{g}_{C,2}$ we take a similar approach. For example, we could posit a logistic regression model for the probability of attending the second clinic visit as a function of $A_0$ and $L_1$, and regress $C_2$ onto basis functions of $A_0$ and $L_1$ using data from all participants who attended the first clinic visit. As a concrete example, consider the main-terms logistic regression model for $\tilde{g}_{C,2}(a_0, a_1, \ell_1) = \mathbb{P}(C_2 = 1 | A_0 = a_0, C_1 = 1, L_1 = \ell_1)$,

$$\text{logit}\{\tilde{g}_{C,2}(a_0, a_1, \ell_1)\} = \eta_0 + \eta_1 \mathbb{1}(a_0 = 1, a_1 = 1) + \eta_2 \mathbb{1}(a_0 = 2, a_1 = 2) + \eta_3 \mathbb{1}(a_0 = 1, a_1 = 3) + \eta_4 \mathbb{1}(a_0 = 2, a_1 = 3) + \ell_1 \eta_L, \eta \in \mathbb{R}^7.$$

where $\eta = (\eta_0, \eta_1, \ldots, \eta_4, \eta_L)$ and $\eta_L$ is a four-length vector of regression parameters associated with $Y_0, W_0, Y_1,$ and $W_1$. An estimate $\hat{\eta}$ of $\eta$ can be obtained via maximum likelihood, and similarly as above, we use $\tilde{g}_{C,2}(a_0, a_1, \ell_1)$ to denote the fitted value from this regression for an observation with $A_0 = a_0, A_1 = a_1$, and $L_1 = \ell_1$. For any $\ell_1$ our estimate of $\tilde{g}_{C,2}$ is

$$\tilde{g}_{C,2}(\ell_1) = \tilde{g}_{C,2}(1, d(1, y_0, y_1), \ell_1) = \text{logit}^{-1}(\hat{\eta}_0 + \hat{\eta}_1 d(1, y_0, y_1) = 1) + \hat{\eta}_3 d(1, y_0, y_1) = 3) + \ell_1 \hat{\eta}_L.$$ 

Finally, we estimate the conditional probability of attending the third clinic visit similarly as with the second to obtain $\tilde{g}_{C,3}$, an estimate of $\tilde{g}_{C,3}$.

**Estimating sequential outcome regressions**

We now turn to obtaining an estimate of $\tilde{g}_3$, the conditional mean of the cumulative number of risky sexual behaviors amongst participants in the text + step-to-eCoaching who attended each clinic visit given their sexual risk behaviors and covariates measured through the second clinic visit. We can write (3) as
\[Q_3(\tilde{z}_2) = E(Y_3 | A_0 = 0, A_1 = 1, \tilde{y}, \tilde{z}_3 = \overline{1}, \tilde{L}_2 = \tilde{z}_2)\]

\[\equiv y_1 + y_2 + E(Y_3 | A_0 = 0, A_1 = 1, \tilde{y}, \tilde{z}_3 = \overline{1}, \tilde{L}_2 = \tilde{z}_2)\]

\[\equiv y_1 + y_2 + Q_3(1, d(1, y_0, y_1), \tilde{z}_2).\]

where we defined \(Q_3(a_0, a_1, \tilde{z}_2) = E(Y_3 | A_0 = a_0, A_1 = a_1, \tilde{z}_3 = \overline{1}, \tilde{L}_2 = \tilde{z}_2)\). The second equality follows from the fact that we are conditioning on \(\tilde{L}_2 = \tilde{z}_2\), which includes past sexual risk behaviors \(y_1\) and \(y_2\). Thus, in order to estimate \(Q_3\), it suffices to estimate \(\tilde{Q}_3\). For example, since \(Y_3\) is a count variable, we could posit a generalized linear model with Poisson family and log link function for \(Q_3\). As with estimation of missingness probabilities, we will use regressions that pool over intervention groups, by regressing the outcome \(Y_3\) onto basis functions of \(\tilde{A}_2\) and \(\tilde{L}_2\). To provide a concrete example, we consider the following pooled, log-linear regression model for \(Q_3\),

\[
\log\{Q_3(a_0, a_1, \tilde{z}_2)\} = \beta_0 + \beta_1 (a_0 = 1, a_1 = 1) + \beta_2 (a_0 = 2, a_1 = 2) + \beta_3 (a_0 = 1, a_1 = 3) + \beta_4 (a_0 = 2, a_1 = 3) + \tilde{z}_2 \beta_L,
\]

\[\beta \in \mathbb{R}^{12}.
\]

An estimate \(\hat{\beta}\) of \(\beta\) can be obtained via maximum likelihood, and we denote by \(\tilde{Q}_3n(a_0, a_1, \tilde{z}_2)\) the fitted value from this regression for an observation with \(\tilde{A}_1 = \overline{a}_1\) and \(\tilde{L}_2 = \tilde{z}_2\). For any \(\tilde{z}_2\) an estimate of \(\tilde{Q}_3(\tilde{z}_2)\) is

\[
\tilde{Q}_3n(\tilde{z}_2) = y_1 + y_2 + \tilde{Q}_3n(1, d(1, y_0, y_1), \tilde{z}_2)
\]

\[\equiv y_1 + y_2 + \exp\{\hat{\beta}_0 + \hat{\beta}_1 (d(1, y_0, y_1) = 1)
\]

\[+ \hat{\beta}_3 (d(1, y_0, y_1) = 3) + \tilde{z}_2 \hat{\beta}_L\}.
\]

Next, we augment our initial estimate of \(\tilde{Q}_3\) by estimating the parameter of a fluctuation submodel associated with the augmentation covariate

\[
H_{3n}(a_0, a_1, \tilde{z}_3, \tilde{z}_2) = \frac{1(a_0 = 1, a_1 = d(1, y_0, y_1), \tilde{z}_3 = \overline{1})}{\delta_{A_0} \delta_{A_1} (y_0, y_1) \prod^n = 1 \delta_{C, t_n (\tilde{z}_3 - 1)}}.
\]

Recall, that TMLE is a general purpose tool for generating estimators that solve user-specified equations. In the current problem, we need an estimate \(\tilde{Q}_3n\) of \(Q_3\) that satisfies

\[
\frac{1}{n} \sum^n_{i = 1} H_{3n}(A_{0i}, A_{1i}, \tilde{C}_{3i}, \tilde{L}_{2i})\{Y_i - \tilde{Q}_3n(\tilde{L}_{2i})\} = 0.
\]

This can be achieved as follows. First, we compute maximum observed value of \(Y_3\), denoted by \(s_{3[0]}\) and we scale \(Y_3\) to the unit interval, \(Y_3^3 = Y_3/s_{3[0]}\). Next, we define the augmented regression model,
logit\(Q_3(a_0, a_1, \bar{T}_2)/s_3[\bar{a}_1]\) = logit\(Q_3^n(a_0, a_1, \bar{T}_2)/s_3[\bar{a}_1]\) + \(\epsilon_3 H_3n(a_0, a_1, \bar{a}, \bar{T}_2)\). \(\epsilon_3 \in \mathbb{R}\).

Estimating the parameter \(\epsilon_3\) corresponds to fitting a logistic regression in subset of participants \(\mathcal{C}_2 = \bar{T}\), where the outcome is \(Y_2\), the regressor is \(H_3n\) and the model includes an offset equal to the logit of the scaled fitted value. Denoting by \(e_3n\) the estimate of \(\epsilon_3\), the augmented estimate of \(\bar{Q}_3\) is

\[\bar{Q}_3^{sn}(a_0, a_1, \bar{T}_2) = e_3[n]\logit^{-1}[\logit[\bar{Q}_3^n(\bar{T}_2)/s_3[\bar{a}_1]] + e_3 H_3n(a_0, a_1, \bar{T}_2)].\]

Thus, for a given \(\bar{T}_2\), the augmented estimate of \(\bar{Q}_3(\bar{T}_2)\) is

\[\bar{Q}_3^{sn}(\bar{T}_2) = y_1 + y_2 + \bar{Q}_3^n(1, d(1, \bar{y}_0, \bar{y}_1), \bar{T}_2).\]

It is straightforward to show that \(\bar{Q}_3^{sn}\) satisfies equation (5), as required.

Our next task it to obtain an estimate of \(\bar{Q}_2\), the conditional mean of \(\bar{Q}_3\) amongst participants in the text + step-to-eCoaching intervention who attended clinic visits one and two, and given covariate-history measured through the first follow-up clinic visit. We can write (2) as

\[\bar{Q}_2(\bar{T}_1) = \mathbb{E}\{\bar{Q}_3(\bar{T}_2) | A_0 = 1, A_1 = d(1, \bar{y}_0, \bar{y}_1), \bar{C}_2 = \bar{T}, L_1 = \bar{T}_1\} = \mathbb{E}\{y_2 + \bar{Q}_3(\bar{T}_2) | A_0 = 1, A_1 = d(1, \bar{y}_0, \bar{y}_1), \bar{C}_2 = \bar{T}, L_1 = \bar{T}_1\} = y_1 + \bar{Q}_2(1, d(1, \bar{y}_0, \bar{y}_1), \bar{T}_1),\]

where we defined \(\bar{Q}_2(a_0, a_1, \bar{T}_1) = \mathbb{E}\{\bar{Q}_3(a_0, A_1, \bar{L}_2) | A_0 = a_0, A_1 = a_1, \bar{C}_2 = \bar{T}, L_1 = \bar{T}_1\}\). Thus, to estimate \(\bar{Q}_2\), it suffices to estimate \(\bar{Q}_2\). This quantity could be estimated, as above, using a pooled log-linear regression model,

\[
\logit\{\bar{Q}_2(a_0, a_1, \bar{T}_1)\} = v_0 + v_1 I\{a_0 = 1, a_1 = 1\} + v_2 I\{a_0 = 2, a_1 = 2\} + v_3 I\{a_0 = 1, a_1 = 3\} + v_4 I\{a_0 = 2, a_1 = 3\} + \bar{T}_1^T v L, \ v \in \mathbb{R}^9.
\]

We could estimate the parameters of this regression as follows. First, the fitted value \(\bar{Q}_3^{sn}(A_0, A_1, \bar{L}_1)\) is computed for \(i = 1, \ldots, n\) and these values are used to create the regression outcome \(Y_2 + \bar{Q}(A_0, A_1, \bar{L}_1)\). The regression model is fit using observations with \(\bar{C}_2 = \bar{T}\).

We denote by \(\bar{Q}_2n(a_0, a_1, \bar{T}_1)\) the fitted value from this regression for a given observation of \(O\) with \(\bar{X}_1 = \bar{a}_1\) and \(\bar{L}_1 = \bar{T}_1\). The initial estimate of \(\bar{Q}_2\) for this observation is thus

\[\bar{Q}_2n(\bar{T}_1) = y_1 + \bar{Q}_2n(1, d(1, \bar{y}_0, \bar{y}_1), \bar{T}_1) = y_1 + \exp\{\hat{v}_0 + \hat{v}_1 I(d(1, \bar{y}_0, \bar{y}_1) = 1) + \hat{v}_2 I(d(1, \bar{y}_0, \bar{y}_1) = 2) + \hat{v}_3 I(d(1, \bar{y}_0, \bar{y}_1) = 3) + \bar{T}_1^T \hat{v} L\}.\]
As above, the next step is to augment the initial estimate of $\mathcal{Q}_2$ using an appropriate fluctuation submodel. To that end, we define the augmentation covariate

$$H_{2n}(a_0, a_1, \tilde{c}_2, \tilde{r}_1) = \frac{1(q_0 = 1, a_1 = d(1, y_0, 1), \tilde{c}_2 = \tilde{r}_1)}{\mathbb{E}_{A_0, 0n} \mathbb{E}_{A_1, n}(y_0, 1) \prod_{i=1}^n \mathbb{E}_{C_i, 0n}(\tilde{r}_i - 1)}.$$

The goal of this augmentation step is to generate an estimate $\mathcal{Q}^*_2$ of $\mathcal{Q}_2$ that satisfies

$$\frac{1}{n} \sum_{i=1}^n \left( H_{2n}(a_0, A_1, \tilde{c}_2, \tilde{r}_1) \{ \mathcal{Q}^*_n(\tilde{L}_2) - \mathcal{Q}_n^*(\tilde{L}_1) \} \right) = 0. \quad (6)$$

This can be achieved using a similar strategy as above. First, we compute the maximum observed value of $Y_2 + \mathcal{Q}^*_n(1, d(1, Y_0, Y_1), \tilde{L}_2)$, say $s_{2n}$. We then generate a scaled outcome $Y^*_2 = \{ Y_2 + \mathcal{Q}_n(1, d(1, Y_0, Y_1), \tilde{L}_2) \} / s_{2n}$. Next, we define an augmented regression model for $\mathcal{Q}_2$

$$\text{logit} \{ \mathcal{Q}_2(a_0, a_1, \tilde{r}_1) / s_{2n} \} = \text{logit} \{ \mathcal{Q}_n(a_0, a_1, \tilde{r}_1) / s_{2n} \} + \epsilon_2 \mathcal{H}_{2n}(a_0, a_1, \tilde{c}_2, \tilde{r}_1). \quad \epsilon_2 \in \mathbb{R}.$$ 

Estimating the parameter $\epsilon_2$ corresponds with fitting a logistic regression in the subset of participants with $C_2 = 1$, where the regression outcome is $Y^*_2$, the single covariate is $\mathcal{H}_{2n}$ and the model includes an offset equal to the logit of the scaled fitted value. Denoting by $e_{2n}$ the estimate of $\epsilon_2$, the augmented estimate of $\mathcal{Q}_2$ is

$$\mathcal{Q}^*_2(a_0, a_1, \tilde{r}_1) = s_{2n} \text{logit}^{-1} \left[ \text{logit} \{ \mathcal{Q}_n(a_0, a_1, \tilde{r}_1) / s_{2n} \} + \epsilon_2 \mathcal{H}_{2n}(a_0, a_1, \tilde{c}_2, \tilde{r}_1) \right].$$

Thus, the augmented estimate of $\mathcal{Q}_2(\tilde{r}_1)$ is $\mathcal{Q}^*_2(\tilde{r}_1) = \mathcal{Q}_1(\tilde{r}_1) + \mathcal{Q}_2(\tilde{r}_1) = y_1 + \mathcal{Q}_2(\tilde{r}_1) \text{logit}^{-1} \left[ \text{logit} \{ \mathcal{Q}_n(a_0, a_1, \tilde{r}_1) / s_{2n} \} + \epsilon_2 \mathcal{H}_{2n}(a_0, a_1, \tilde{c}_2, \tilde{r}_1) \right]$. It is straightforward to show that $\mathcal{Q}^*_2$ and $\mathcal{Q}^*_n$ together satisfy equation (6).

Our next task is to obtain an estimate of $\mathcal{Q}_1$, the baseline-covariate-conditional mean of $\mathcal{Q}_2$ amongst participants initially in the text intervention who attended clinic visit one. We can write (1) as

$$\mathcal{Q}_1(\epsilon_0) = \mathbb{E} \{ \mathcal{Q}_2(\tilde{L}_1) | A_0 = 1, C_1 = 1, L_0 = \epsilon_0 \}$$
$$= \mathbb{E} \{ Y_1 + \mathcal{Q}_2(1, d(1, Y_0, Y_1), \tilde{L}_1) | A_0 = 1, C_1 = 1, L_0 = \epsilon_0 \}$$
$$\equiv \mathcal{Q}_1(1, \epsilon_0).$$

where we defined $\mathcal{Q}_1(a_0, \epsilon_0) = \mathbb{E} \{ Y_1 + \mathcal{Q}_2(1, d(1, Y_0, Y_1), \tilde{L}_1) | A_0 = a_0, C_1 = 1, L_0 = \epsilon_0 \}$.

Obtaining an initial, and subsequently, an augmented estimate of $\mathcal{Q}_1$ proceeds similarly as with $\mathcal{Q}_2$. We first obtain an initial estimate of $\mathcal{Q}_1$, e.g., through log-linear regression of the outcome $Y_1 + \mathcal{Q}^*_n(a_0, d(1, Y_0, Y_1), \tilde{L}_1)$ on $A_0, W_0, Y_0$ amongst observations with $C_1 = 1$. Given an observation of $O$ with $L_0 = 1$, our estimate of $\mathcal{Q}_1(\epsilon_0)$ is $\mathcal{Q}_1(\epsilon_0) = \mathcal{Q}^*_1(1, \epsilon_0)$. 

*Stat Biosci.* Author manuscript; available in PMC 2021 December 01.
We augment \( \bar{Q}_{1n} \) using the covariate

\[
H_{1n}(\epsilon_0, c_1, \epsilon) = \frac{1(a_0 = 1, c_1 = 1)}{\mathbb{E}_{A_0, B_0, C, 1n(\epsilon_0)}},
\]

with the goal generating an estimate \( \bar{Q}_{1n}^\delta \) of \( \bar{Q}_1 \) that satisfies

\[
\frac{1}{n} \sum_{i=1}^{n} H_{1n}(A_0, C_1, L_0) \{ \bar{Q}_{2n}^\delta(L_{1i}) - \bar{Q}_{1n}^\delta(L_{0i}) \} = 0.
\] (7)

We again use logistic regression to this end. The scaled outcome is

\[ Y_1^s = Y_1 + \bar{Q}_{2n}(A_0, d(1, Y_0, Y_1), L_2), \]

where \( s_{1n} \) is the maximum observed value of \( Y_1 + \bar{Q}_{2n}(1, d(1, Y_0, Y_1), L_1) \). As in previous steps, we regress the scaled outcome \( Y_1^s \) onto the covariate \( H_{1n} \) with offset equal to logit\((\bar{Q}_{1n}/s_{1n})\) amongst observations with \( C_1 = 1 \).

Denoting by \( \epsilon_{1n} \) the estimate of \( \epsilon_1 \), the augmented estimate of \( \bar{Q}_1(\epsilon_0) \) is

\[ \bar{Q}_{1n}(\epsilon_0) = s_{1n} \text{logit}^{-1} \left[ \text{logit} \left( \bar{Q}_{1n}(\epsilon_0)/s_{1n} \right) + \epsilon_{1n} H_{1n}(1, 1, \epsilon_0) \right]. \]

It is straightforward to show that \( \bar{Q}_{2n}^\delta \) and \( \bar{Q}_{1n}^\delta \) together satisfy equation (6).

The final step is to plug-in the estimate \( \bar{Q}_{1n}^\delta \) into right-hand-side of equation (3). To evaluate this plug in estimator, we also need an estimate of \( Q_0 \), the CDF of \( L_0 \). For this, we use the empirical distribution \( Q_n(\epsilon_0) = \frac{1}{n} \sum_{i=1}^{n} 1(L_{0i} \leq \epsilon_0) \). The final TMLE estimator is thus

\[ \psi_n^* = \int \bar{Q}_{1n}^\delta(\epsilon_0) dQ_n(\epsilon_0) = \frac{1}{n} \sum_{i=1}^{n} \bar{Q}_{1n}^\delta(L_{0i}). \]

**Note on propensity score and outcome regression estimators**

In the above description of TMLE, we used initial estimators based on parametric models to illustrate key ideas. However, TMLE methodology is in no way limited to such estimators. In particular, we may wish to consider more flexible regression techniques in order to mitigate the risk of residual bias incurred by regression model misspecification. To that end, it may be propitious to utilize super learning \([25]\), a generalization of regression stacking \([29, 4]\). A super learner can build estimators of regression quantities by considering all possible convex combinations of a library of pre-specified regression estimators. That is to say, a fitted value from a super learner regression is a weighted combination of fitted values from various candidate regression estimators. The candidate regression estimators can range from parametric regression estimators to highly data-adaptive estimators. The super learner selects weights assigned to each candidate estimator by finding the convex weights that minimize a cross-validated risk criteria, for example, cross-validated mean squared-error. The use of super learner is particularly appealing in the context of randomized trials in that...
the method can be fully pre-specified and is essentially a nonparametric method so long as sufficiently flexible regressions are included in the library. For these reasons, in the analysis of the TechStep trial, we will use the super learner to estimate the conditional probabilities of missingness and the sequential outcome regressions described in the previous paragraph.

**Confidence intervals and hypothesis tests based on influence functions**

We note that our specific labeling of interventions (e.g., \( A_0 = 1 \) corresponds to text, \( A_0 = 2 \) to app, etc…) is arbitrary. Moreover, by redefining the rule \( d(a_0, y_0, y_1) \) (e.g., to equal a constant for any value of \( a_0 \)), then we can directly apply the methodology described above to estimate the counterfactual outcome under any of the interventions of interest. Let \( \psi_n^{(\cdot)} \) denote the TMLE of \( E[Y(\cdot)] \). Similarly, let \( \tilde{Q}_{tn}^{(\cdot)} \) denote the augmented sequential outcome regression estimate and \( H_{tn}^{(\cdot)} \) the augmentation covariate. Define the estimated influence function of \( \psi_n^{(\cdot)} \) evaluated on observation \( i \) as

\[
D_{ti}^{(\cdot)} = H_{3n}^{(\cdot)}(A_{0i}, A_{1i}, C_{3i}, L_{2i}) \left( Y - \tilde{Q}_{tn}^{(\cdot)}(I_{2i}) \right)
\]

\[
D_{2i}^{(\cdot)} = H_{2n}^{(\cdot)}(A_{0i}, A_{1i}, C_{2i}, L_{1i}) \left( \tilde{Q}_{3n}^{(\cdot)}(I_{2i}) - \tilde{Q}_{2n}^{(\cdot)}(I_{1i}) \right)
\]

\[
D_{1i}^{(\cdot)} = H_{1n}^{(\cdot)}(A_{0i}, C_{1i}, L_{0i}) \left( \tilde{Q}_{2n}^{(\cdot)}(I_{1i}) - \tilde{Q}_{1n}^{(\cdot)}(I_{0i}) \right)
\]

\[
D_{0i}^{(\cdot)} = \tilde{Q}_{1n}^{(\cdot)}(I_{0i}) - \int \tilde{Q}_{1n}^{(\cdot)}(\epsilon) dQ_{n}(\epsilon).
\]

An estimate of the standard error of \( n^{1/2} \psi_n^{(\cdot)} \) is

\[
\sigma_n^{(\cdot)} = \left[ \frac{1}{n} \sum_{i=1}^{n} \sum_{t=0}^{3} D_{ti}^{(\cdot)} \right]^{1/2}
\]

and the confidence interval \( \psi_n^{(\cdot)} \pm z_{1 - a/2} \sigma_n^{(\cdot)} / n^{1/2} \), where \( z_{1 - a/2} \) is the \( 1 - a/2 \) quantile of a standard Normal distribution, will have asymptotic coverage no smaller than \( 1 - a \).

Similar influence function-based standard error estimates can be used to describe the asymptotic covariance between any two TMLEs. For example, the asymptotic covariance of \( n^{1/2} \langle \psi_n^{(i)}, \psi_n^{(ii)} \rangle \) is consistently estimated by

\[
\Sigma_n^{(i)(ii)} = \begin{bmatrix} \sigma_n^{(i)} & \sigma_n^{(i)(ii)} \\ \sigma_n^{(i)(ii)} & \sigma_n^{(ii)} \end{bmatrix}^2
\]

where

\[
\sigma_n^{(i)(ii)} = \frac{1}{n} \sum_{i=1}^{n} \left\{ \sum_{t=0}^{3} D_{ti}^{(i)} \sum_{t=0}^{3} D_{ti}^{(ii)} \right\}
\]

Thus, by the Delta method, an estimate of the standard error of \( n^{1/2} (\psi_n^{(ii)} - \psi_n^{(i)}) \) is

\[
\tau_n = \left[ \sigma_n^{(i)} + \sigma_n^{(ii)} - 2 \sigma_n^{(i)(ii)} \right]^{1/2}
\]
A Wald test that rejects the null hypothesis $E(Y^{(ii)}) = E(Y^{(i)})$ whenever

$$\frac{n^{1/2}(\psi_n^{(ii)} - \psi_n^{(i)})}{\tau_n} > z_1 - \alpha/2$$

will have asymptotic level $\alpha$.

References

[1]. Bang H, Robins JM: Doubly robust estimation in missing data and causal inference models. Biometrics 61(4), 962–973 (2005) [PubMed: 16401269]

[2]. Bembom O, van der Laan MJ: Analyzing sequentially randomized trials based on causal effect models for realistic individualized treatment rules. Statistics in Medicine 27(19), 3689–3716 (2008) [PubMed: 18407580]

[3]. Benkeser D, van der Laan MJ: The highly adaptive LASSO estimator. In: 2016 IEEE International Conference on Data Science and Advanced Analytics (DSAA), pp. 689–696. IEEE (2016)

[4]. Breiman L: Stacked regressions. Machine learning 24(1), 49–64 (1996)

[5]. Brown CH, Curran G, Palinkas LA, Aarons GA, Wells KB, Jones L, Collins LM, Duan N, Mittman BS, Wallace A, et al.: An overview of research and evaluation designs for dissemination and implementation. Annual Review of Public Health 38, 1–22 (2017)

[6]. Chakraborty B, Moodie E: Statistical methods for dynamic treatment regimes. Springer (2013)

[7]. Crissman HP, Berger MB, Graham LF, Dalton VK: Transgender demographics: a household probability sample of US adults, 2014. American Journal of Public Health 107(2), 213–215 (2017) [PubMed: 27997239]

[8]. Janes H, Donnell D, Gilbert PB, Brown ER, Nason M: Taking stock of the present and looking ahead: envisioning challenges in the design of future HIV prevention efficacy trials. The Lancet HIV 6(7), e475–e482 (2019) [PubMed: 31078451]

[9]. Johns MM, Lowry R, Andrejewski J, Barrios LC, Demissie Z, McManus T, Rasberry CN, Robin L, Underwood JM: Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students – 19 states and large urban school districts, 2017. Morbidity and Mortality Weekly Report 68(3), 67 (2019) [PubMed: 30677012]

[10]. Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Queen B, Lowry R, Chyen D, Whittle L, Thornton J, et al.: Youth risk behavior surveillance – United States, 2017. MMWR Surveillance Summaries 67(8), 1 (2017)

[11]. van der Laan MJ, Gruber S: Targeted minimum loss based estimation of causal effects of multiple time point interventions. The International Journal of Biostatistics 8(1), 1–34 (2012). DOI 10.1515/1557-4679.1370

[12]. Lavori PW, Dawson R: A design for testing clinical strategies: biased adaptive within-subject randomization. Journal of the Royal Statistical Society: Series A (Statistics in Society) 163(1), 29–38 (2000)

[13]. Lentferink AJ, Oldenhuis HK, de Groot M, Polstra L, Veltuijsen H, van Gemert-Pijnen JE: Key components in eHealth interventions combining self-tracking and persuasive ecoaching to promote a healthier lifestyle: a scoping review. Journal of Medical Internet Research 19(8), e277 (2017) [PubMed: 28765103]

[14]. Meerwijk EL, Sevelius JM: Transgender population size in the United States: a meta-regression of population-based probability samples. American Journal of Public Health 107(2), e1–e8 (2017)

[15]. Murphy SA: An experimental design for the development of adaptive treatment strategies. Statistics in Medicine 24(10), 1455–1481 (2005) [PubMed: 15586395]

[16]. Murphy SA, Bingham D: Screening experiments for developing dynamic treatment regimes. Journal of the American Statistical Association 104(485), 391–408 (2009) [PubMed: 20589222]
[17]. Nahum-Shani I, Qian M, Almirall D, Pelham WE, Gnagy B, Fabiano GA, Waxmonsky JG, Yu J, Murphy SA: Experimental design and primary data analysis methods for comparing adaptive interventions. Psychological Methods 17(4), 457 (2012) [PubMed: 23025433]

[18]. Perez-Brumer A, Nunn A, Hsiang E, Oldenburg C, Bender M, Beauchamps L, Mena L, MacCarthy S: “we don’t treat your kind”: Assessing HIV health needs holistically among transgender people in Jackson, Mississippi. PLoS One 13(11), e0202389 (2018) [PubMed: 30383751]

[19]. Petersen M, Schwab J, Gruber S, Blaser N, Schomaker M, van der Laan M: Targeted maximum likelihood estimation for dynamic and static longitudinal marginal structural working models. Journal of Causal Inference 2(2), 147–185 (2014) [PubMed: 25909047]

[20]. Reisner SL, Hughto JMW, Dunham EE, Heflin KJ, Begeny JBG, Coffey-Esquivel J, Cahill S: Legal protections in public accommodations settings: A critical public health issue for transgender and gender-nonconforming people. The Milbank Quarterly 93(3), 484–515 (2015) [PubMed: 26219197]

[21]. Reisner SL, Jadwin-Cakmak L, Sava L, Liu S, Harper GW: Situated vulnerabilities, sexual risk, and sexually transmitted infections’ diagnoses in a sample of transgender youth in the United States. AIDS Patient Care and STDs 33(3), 120–130 (2019) [PubMed: 30844303]

[22]. Robins JM: Robust estimation in sequentially ignorable missing data and causal inference models. In: Proceedings of the American Statistical Association Section on Bayesian Statistical Science, pp. 6–10 (1999)

[23]. Schnitzer ME, van der Laan MJ, Moodie EE, Platt RW: LTMLE with clustering. In: Targeted Learning in Data Science, pp. 233–251. Springer (2018)

[24]. van der Laan MJ, Benkeser D, Sofrygin O: Targeted minimum loss-based estimation. Wiley StatsRef: Statistics Reference Online pp. 1–8 (2018)

[25]. van der Laan MJ, Polley EC, Hubbard AE: Super learner. Statistical Applications in Genetics and Molecular Biology 6(1) (2007)

[26]. van der Laan MJ, Rose S: Targeted learning: causal inference for observational and experimental data. Springer Science & Business Media (2011)

[27]. van der Laan MJ, Rose S: Targeted learning in data science: causal inference for complex longitudinal studies. Springer (2018)

[28]. van der Laan MJ, Rubin D: Targeted maximum likelihood learning. The International Journal of Biostatistics 2(1) (2006)

[29]. Wolpert DH: Stacked generalization. Neural Networks 5(2), 241–259 (1992)

[30]. Yousuf H, Reintjens R, Slipszenko E, Blok S, Somsen G, Tulevski I, Hofstra L: Effectiveness of web-based personalised e-Coaching lifestyle interventions. Netherlands Heart Journal 27(1), 24–29 (2019) [PubMed: 30488381]
Figure 1:
A design schematic for the TechStep trial. Randomization probabilities are shown beneath A. labels. At each study visit, we note intervention label for participants along each path. Censoring variables are also shown along paths with the question mark denoting that the probability of censoring is unknown and must be estimated from the data.
Figure 2:
Probability of rejecting $H_0 : E[y^{(ii)}] = E[y^{(i)}]$ (no effect of text-step versus control) as a function of the size of the effect, $E[y^{(ii)}] - E[y^{(i)}]$. Dotted lines indicate the nominal type I error rate of the Wald test (0.05) and power of 80%.
Figure 3:
Probability of rejecting $H_0 : \mathbb{E}[\gamma^{(ii)}] = \mathbb{E}[\gamma^{(iia)}]$ (no effect of text + step versus text-only) as a function of the size of the effect, $\mathbb{E}[\gamma^{(ii)}] - \mathbb{E}[\gamma^{(iia)}]$. Dotted lines indicate the nominal type I error rate of the Wald test (0.05) and power of 80%.
Figure 4:
Probability of rejecting $H_0 : \mathbb{E}[Y^{(ii)}] = \mathbb{E}[Y^{(iii)}]$ (no effect of text-only versus app-only) as a function of the size of the effect, $\mathbb{E}[Y^{(ii)}] - \mathbb{E}[Y^{(iii)}]$. Dotted lines indicate the nominal type I error rate of the Wald test (0.05) and power of 80%.
Table 1:
Hypothetical interventions on nonparametric structural equation model.

| Label | NPSEM intervention | Description |
|-------|--------------------|-------------|
| (i)   | $A_0 = 0, C_1 = 1, A_1 = 0, C_2 = 1, C_3 = 1$ | standard of care for 6 months and attend each visit |
| (ii)  | $A_0 = 1, C_1 = 1$  
$A_1 = d(1, Y_0, Y_1)$  
$C_2 = 1, C_3 = 1$ | text messages for 3 months, step up to eCoaching if no improvement at 6 months and attend each visit |
| (iiia)| $A_0 = 1, C_1 = 1, A_1 = 1, C_2 = 1, C_3 = 1$ | text messages for 6 months and attend each clinic visit |
| (iii) | $A_0 = 2, C_1 = 1$  
$A_1 = d(2, Y_0, Y_1)$  
$C_2 = 1, C_3 = 1$ | webapp for 3 months, step up to eCoaching if no improvement at 6 months and attend each visit |
| (iiia)| $A_0 = 2, C_1 = 1, A_1 = 2, C_2 = 1, C_3 = 1$ | webapp for 6 months and attend each clinic visit |
Table 2:
Causal estimands used to answer primary and secondary questions of interest.

| Question | Causal estimand | Description |
|----------|----------------|-------------|
| Primary  | $E(Y^{ii}) - E(Y^{i})$ | difference in mean outcome under text + step intervention versus standard of care |
|          | $E(Y^{iii}) - E(Y^{i})$ | difference in mean outcome under webapp + step intervention versus standard of care |
| Secondary| $E(Y^{iia}) - E(Y^{i})$ | difference in mean outcome under text-only versus standard of care |
|          | $E(Y^{iia}) - E(Y^{i})$ | difference in mean outcome under webapp-only versus standard of care |
|          | $E(Y^{ii}) - E(Y^{iia})$ | difference in mean outcome under text + step versus text only |
|          | $E(Y^{iii}) - E(Y^{iia})$ | difference in mean outcome under webapp + step intervention versus webapp only |
Table 3:
Simulation parameter values and descriptions. Values of $\gamma_j$ are log rate ratios.

| Parameter | Values                      | Notes                        |
|-----------|-----------------------------|------------------------------|
| $n$       | 200, 250, 300               | Sample size                  |
| $\gamma_1$ | 0, −0.11, −0.22, −0.36      | Text eff. on risky behaviors |
| $\gamma_2$ | 0, −0.22, −0.51             | Webapp eff. on risky behaviors |
| $\gamma_3$ | 0, −0.11, −0.22, −0.36, −0.69, *−0.92, *−1.20, *−1.61 | ECoaching eff. on risky behaviors |
| $\alpha_0$ | −4.06, −3.35               | Loss-to-followup of 5% and 10% |

* denotes that simulations were performed only when $\gamma_1 = 0,−0.11$. 