Appendix A: Models for Analyzing Data from a Hybrid Experimental Design (HED)

Here, we propose models for analyzing data from the HED in Figure 6 to answer 4 types of scientific questions: (1) questions about the main effect of JITAI options on a proximal outcome, averaging over ADI options (e.g., question A1; Table 3A); (2) questions about the interaction between JITAI and ADI options in relation to a proximal outcome (e.g., questions A2-A4; Table 3A); (3) questions about the main effects of adaptive intervention (ADI) options on a distal outcome, averaging over just-in-time adaptive intervention (JITAI) options (e.g., questions B1-B2; Table 3B); and (4) questions about the interaction between ADI options and JITAI options in relation to a distal outcome (e.g., questions B3-B4; Table 3B).

Models

Notation

Time: Let $t = 1, \dots, T$ be the JITAI decision points at which individuals are micro-randomized; in the current example, there is one JITAI decision point per day over 16 weeks: $T = 7 \times 16 = 112$ days.

Baseline covariates: Let $\boldsymbol{X}_{i0}$ be the baseline covariates for individual i, which could include a column of 1's for the intercept.

ADI options: Let Z_{i1} represent the effect-coded first-stage ADI options for individual i, with possible levels $+1$ (for the digital intervention combined with coaching) and -1 (for the digital intervention alone). Let Z_{i2} represent the effect-coded second-stage ADI options for individual i, with levels +1 (for step-up among non-responders), -1 (for continue among non-responders) and 0 (for responders). In the current example individuals are randomized to first- and second-stage ADI options with probability ½.

Response status: Let $R_i = 1$ if individual i is classified as an early (week 4) responder, and $R_i = 0$ otherwise.

JITAI options: Let A_{it} represent the effect-coded JITAI options for individual i, at time t, with levels $+1$ (for a message) and -1 (for no message). In the current example individuals are randomized to JITAI options with probability ½ at each JITAI decision point.

Proximal Outcome: Let $Y_{it+\Delta}$ represent the proximal outcome (e.g., next-day number of drinks) for individual i, at time $t+\Delta$. It is important to note that Δ here is not intended to represent a separate model parameter; it is used as a heuristic notation to indicate that the proximal outcome is measured at some time Δ after A_{it} is assigned, but before A_{it+1} is assigned, so that A_{it} may affect $Y_{it+\Delta}$. For simplicity, we assume the proximal outcome is continuous and that a linear model (identity link function) is being used, but the models proposed here can be extended to other types of outcomes (e.g., binary and count) by using the appropriate link-function (i.e., generalized linear models).

Distal outcome: Let Y_i^* represent the distal outcome (here, substance use measured at the week 16 follow up) for individual i. As before, we assume for simplicity that the distal outcome is continuous and that a linear model is being used, but the models proposed here can be extended to other types of outcomes (e.g., binary and count) by using the appropriate link-function.

Model for the Proximal Outcome

The following models can be used to answer questions of types (1) and (2) above, which concern the effects of JITAI options on the proximal outcome. Specifically, these questions concern the *main effect* of JITAI options on the proximal outcome (averaging over ADI options) and their *moderated effects*—whether the effect of JITAI options on the proximal outcome varies by ADI options.

Here, an important challenge relates to the temporal ordering of JITAI decision points in relation to the ADI decision points. For example, prior to week 4, the effect of delivering a daily message (vs. no message) on next-day substance use can only be influenced by first-stage ADI options. After week 4, this effect may be influenced by both first-stage and second-stage ADI options. Failure to respect such ordering may lead to bias and incorrect conclusions (Dziak et al., 2019; Lu et al., 2016; Nahum-Shani et al., 2020).

Assuming that the baseline covariates do not interact with treatment, the model for $Y_{it+\Delta}$ can be written as follows:

$$\begin{aligned} E(Y_{it+\Delta}|\boldsymbol{X}_{i0},\boldsymbol{Z}_i,A_{it}) = \boldsymbol{X}_{i0}\boldsymbol{\beta}_0 + \beta_1 Z_{i1} + \beta_2 C_{it} Z_{i2} + \beta_3 C_{it} Z_{i1} Z_{i2} \\ +\gamma_0 A_{it} + \gamma_1 Z_{i1} A_{it} + \gamma_2 Z_{i2} C_{it} A_{it} + \gamma_3 Z_{i1} Z_{i2} C_{it} A_{it} \end{aligned} \quad (1)$$

where C_{it} is an indicator for whether ($C_{it} = 1$) or not ($C_{it} = 0$) the second-stage ADI options Z_{i2} were assigned by time t. In our example this would be $C_{it} = 1\{t > K\}$, where K=28 days. Notice that all terms involving Z_{i2} are multiplied by C_{it}. Because of the coding of Z_{i2} as 0 for responders, and the coding of C_{it} as 0 prior to the assignment of second-stage ADI options, γ_2 and γ_3 are relevant only for non-responders and only after time K.

Note that Model 1 can be extended to include time-varying effects. For example, the effect of ADI options Z_{i1} or Z_{i2} can be allowed to start at zero and then to accumulate linearly. This linear accumulation could be expressed by multiplying Z_{i1} by t or Z_{i2} by $t^* = \max(0, t-K)$, as follows

$$\begin{aligned} E(Y_{it+\Delta}|\boldsymbol{X}_{i0},\boldsymbol{Z}_i,A_{it}) = \boldsymbol{X}_{i0}\boldsymbol{\beta}_0 + \beta_1 Z_{i1} t + \beta_2 Z_{i2} t^* + \beta_3 Z_{i1} Z_{i2} t^* \\ +\gamma_0 A_{it} + \gamma_1 Z_{i1} A_{it} t + \gamma_2 Z_{i2} A_{it} t^* + \gamma_3 Z_{i1} Z_{i2} A_{it} t^*. \end{aligned}$$

More complicated trajectories are possible; for example, a constant plus a linear increase, or a quadratic function which rises as a treatment takes effect and then falls as the participant becomes bored or habituated. Model 1 can also be extended by multiplying the JITAI options A_{it} by t, allowing the average effect of the JITAI options to accumulate linearly with time.

Model for the Distal Outcome

The following model can be used to answer questions of types (3) and (4) above, which concern the effects of ADI options on the distal outcome. Specifically, these questions concern the *main effect* of ADI options on the distal outcome (averaging over JITAI options) and their *moderated effects*—whether the effect of ADI options on the distal outcome varies by the intensity (i.e., rate) of JITAI options delivered over the course of the study.

If it is assumed that the baseline covariates do not interact with ADI options, and that the effect of JITAI options on the distal outcome is equal and cumulative over time, then a reasonable parametric model for Y_i^* would be

$$E(Y_i^* | \boldsymbol{X}_{i0}, \boldsymbol{Z}_i, \bar{A}_i) = \boldsymbol{X}_{i0}\boldsymbol{\theta}_0 + \theta_1 Z_{i1} + \theta_2 Z_{i2} + \theta_3 Z_{i1} Z_{i2} + \theta_4 \bar{A}_i + \theta_5 Z_{i1} \bar{A}_i + \theta_6 Z_{i2} \bar{A}_i^{(2)} + \theta_7 Z_{i1} Z_{i2} \bar{A}_i^{(2)} \quad (2)$$

where $\bar{A}_i$ is the average JITAI options (here, the rate of message delivery) over all JITAI decision points for individual i, and $\bar{A}_i^{(2)}$ is the average over only those points after time *K*.

Estimands

Here, we explain how the coefficients from Models 1 and 2 can be used to answer each of the scientific questions outlined in Tables 3A (regarding the proximal outcome) and 3B (regarding the distal outcome) of the main manuscript.

Questions About the Effects of JITAI Options on a Proximal Outcome

A1 (Table 3A): What is the difference between JITAI options in terms of the proximal outcome, averaging over ADI options? This question concerns the *main effect* of JITAI options on the proximal outcome, averaging over ADI options. Under Model 1, assuming that participants are assigned to each level of Z_1 with equal probability and that non-responders are assigned to each level of Z_2 with equal probability, independently of Z_1, then $E(Z_{i1}) = 0$, $E(Z_{i2}) = 0$, and $E(Z_{i1}Z_{i2}) = 0$. Therefore

$$E(Y_{it+\Delta} | A_{it} = +1) - E(Y_{it+\Delta} | A_{it} = -1) = 2\gamma_0.$$

A2 (Table 3A): Does the effect of (i.e., difference between) JITAI options on the proximal outcome varies by first-stage ADI options? This question concerns the *interaction* between JITAI options and first-stage ADI options in relation to the proximal outcome. Using Model 1 and assuming that $E(Z_{i2}) = 0$,

$$\begin{array}{l} \left(E(Y_{it+\Delta}|A_{it} = +1, Z_{i1} = +1) - E(Y_{it+\Delta}|A_{it} = -1, Z_{i1} = +1)\right) \\ -\left(E(Y_{it+\Delta}|A_{it} = +1, Z_{i1} = -1) - E(Y_{it+\Delta}|A_{it} = -1, Z_{i1} = -1)\right) \end{array} = 4\gamma_1.$$

A3 (Table 3A): Does the effect of JITAI options on the proximal outcome vary by second-stage ADI options among non-responders? This question concerns the *interaction* between JITAI options and second-stage ADI options in relation to the proximal outcome. Using Model 1 and assuming that $E(Z_{i1}) = 0$,

$$\begin{array}{l} \left(E(Y_{it+\Delta}|A_{it} = +1, Z_{i2} = +1) - E(Y_{it+\Delta}|A_{it} = -1, Z_{i2} = +1)\right) \\ -\left(E(Y_{it+\Delta}|A_{it} = +1, Z_{i2} = -1) - E(Y_{it+\Delta}|A_{it} = -1, Z_{i2} = -1)\right) \end{array} = 4\gamma_2.$$

This is an estimate of the moderating effect of the second-stage ADI options, once they become operational, i.e., after time *K*; Model 1 assumes that this moderating effect is 0 before then.

A4 (Table 3A): Does the effect (i.e., the difference between) JITAI options on the proximal outcome vary by embedded ADIs? This question concerns the *interaction* between JITAI options, first-stage ADI options and second-stage ADI options in relation to the proximal outcome. Using Model 1, contrasts in proximal outcomes of the JITAI options between two embedded ADI's (z_1, z_2) and (z_1', z_2'), can be compared as follows:

$$\begin{array}{rl} & \left(E(Y_{it+\Delta}|A_{it} = +1, Z_{i1} = z_1, Z_{i2} = z_2) - E(Y_{it+\Delta}|A_{it} = -1, Z_{i1} = z_1, Z_{i2} = z_2)\right) \\ & -\left(E(Y_{it+\Delta}|A_{it} = +1, Z_{i1} = z_1', Z_{i2} = z_2') - E(Y_{it+\Delta}|A_{it} = -1, Z_{i1} = z_1', Z_{i2} = z_2')\right) \\ = & 2\gamma_1(z_1 - z_1') + 2C_{it}\gamma_2(z_2 - z_2') + 2C_{it}\gamma_3(z_1 z_2 - z_1' z_2') \\ = & 2\gamma_1(z_1 - z_1') + 2\gamma_2(z_2 - z_2')1\{t > K\} + 2\gamma_3(z_1 z_2 - z_1' z_2')1\{t > K\} \end{array}$$

Questions About the Effects of ADI Options on a Distal Outcome

B1 (Table 3B): What is the difference between first-stage ADI options in terms of the distal outcome, averaging over JITAI options? This question concerns the *main effect* of the first-stage ADI options on the distal outcome, averaging over JITAI options. Under Model 2, assuming participants were assigned to JITAI options with equal probability at each decision point such that $E(\bar{A}_i) = 0$ and $E\left(\bar{A}_i^{(2)}\right) = 0$,

$$E(Y_i^* | Z_{i1} = +1) - E(Y_i^* | Z_{i1} = -1) = 2\theta_1.$$

B2 (Table 3B): What is the difference between second-stage ADI options among non-responders, in terms of the distal outcome, averaging over JITAI options? This question concerns the *main effect* of the second-stage ADI options among non-responders on the distal outcome, averaging over JITAI options. Under Model 2, assuming participants were assigned to JITAI options with equal probability at each decision point such that $E(\bar{A}_i) = 0$ and $E\left(\bar{A}_i^{(2)}\right) = 0$

$$E(Y_i^* | Z_{i2} = +1) - E(Y_i^* | Z_{i2} = -1) = 2\theta_2.$$

B3 (Table 3B): Does the effect of (i.e., difference between) first-stage ADI options on the distal outcome vary by the intensity of JITAI options? This question concerns the *interaction* between first-stage ADI options and JITAI options in relation to the distal outcome. Based on Model 2, subtracting the conditional effects of first-stage ADI options on the distal outcome, given two $\bar{A}_i$ values of interest, can be interpreted as an interaction. For example, if $\bar{A}_i$ is, say, 0.6, then the conditional effect of the first-stage ADI options is $\left(E(Y_i^* | Z_{i1} = +1, \bar{A}_i = .6) - E(Y_i^* | Z_{i1} = -1, \bar{A}_i = .6)\right) = (\theta_1 + 0.6\theta_5) - (-\theta_1 - 0.6\theta_5) = 2(\theta_1 + 0.6\theta_5)$, and if $\bar{A}_i$ is 0.4, then the conditional effect is $2(\theta_1 + 0.4\theta_5)$. The difference between these two conditional effects is $2 * 0.2\theta_5$.

B3 (Table 3B): Does the difference between embedded ADIs in terms of the distal outcome, vary by the intensity of the JITAI options? This question concerns the *interaction* between first-stage

ADI options, second-stage ADI options and JITAI options in relation to the distal outcome. Using Model 2, the difference between any given ADI's (z_1, z_2) and (z_1', z_2') in terms of the distal outcome can be quantified and compared between different values of $\bar{A}_i$ and $\bar{A}_i^{(2)}$. For example, for $\bar{A}_i = \bar{A}_i^{(2)} = 0.3$,

$$\left(E\left(Y_i^* \middle| Z_{i1} = z_1, Z_{i2} = z_2\,, \bar{A}_i = \bar{A}_i^{(2)} = .3\right) - E\left(Y_i^* \middle| Z_{i1} = z_1', Z_{i2} = z_2', \bar{A}_i = \bar{A}_i^{(2)} = .3\right)\right)$$

$$= \theta_1(z_1 - z_1') + \theta_2(z_2 - z_2') + \theta_3(z_1 z_2 - z_1' z_2') + 0.3\theta_5(z_1 - z_1') + 0.3\theta_6(z_2 - z_2') + 0.3\theta_7(z_1 z_2 - z_1' z_2')$$

The difference between this conditional effect, and the conditional effect given another value of $\bar{A}_i$ and $\bar{A}_i^{(2)}$, can be interpreted as an interaction.

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