

NOVEL STATISTICAL METHODS

Microrandomized Trial Design for Evaluating Just-in-Time Adaptive Interventions Through Mobile Health Technologies for Cardiovascular Disease

ABSTRACT: Smartphone and wearable device use is rising broadly and can be leveraged for chronic disease management. Just-in-time adaptive interventions promise to deliver personalized, dynamic interventions directly to patients through use of push notifications from mobile devices. Although just-in-time adaptive interventions are a powerful tool for shaping health behavior, their application to cardiovascular disease management has been limited as they can be challenging to design. Herein, we provide a general overview and conceptual framework for microrandomized trials, a novel experimental study design that can be used to optimize just-in-time adaptive interventions. Microrandomized trials leverage mobile devices to sequentially randomize participants to types or levels of an intervention to determine the effectiveness of an intervention and time-varying moderators of those effects. Microrandomized trials are an efficient study design that can be used to determine which intervention components to include in just-in-time adaptive interventions and to optimize their decision rules while maintaining the strength of causal inference associated with traditional randomized controlled trials.

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Use of mobile health technology is expanding at an outstanding rate. More than 8 in 10 Americans owned a smartphone in 2019¹ with adoption rates increasing across the spectrum of age,² race,³ and socioeconomic groups.¹ Nearly 70% of Baby Boomers own a smartphone,² and the proportion of users is largely equivalent across Black, Hispanic, and White adults.³ This growth in mobile health technologies has clinical implications as an increasing number of American adults use smartphones and other wearable devices to digitally track at least one health behavior.⁴

Given such widespread adoption, there is great hope that mobile health technologies can deliver personalized, dynamic interventions directly to patients in real-time to assist with management of chronic diseases.^{5–8} Just-in-time adaptive interventions (JITAs, pronounced as Jedis) use contextual information from mobile devices (location, calendar, etc) to determine when to provide interventions to individuals.⁹ Specifically, JITAs aim to provide support at optimal times to shape health behaviors, such as sending a planning intervention when the user is cognitively available to engage in planning or a suggestion for low-sodium food options when the system detects the user has entered a fast-food restaurant.⁶ Unlike static pull interventions—in-app feedback, psychoeducation, etc—which require users to be

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aware of their need for support and to reach for an intervention, JITAs use push notifications to deliver interventions when the system detects states of risk or opportunity, with the goal of modifying health behaviors in the moment and over time in a participant's natural environment.⁹ To determine when to intervene, JITAs rely both on passively sensed data, such as step counts, location, and blood alcohol levels sensed via a transdermal alcohol monitor¹⁰; and data collected actively via short mobile questionnaires, termed ecological momentary assessments, to assess psychosocial measures, such as mood or anxiety.⁶ Intervention components delivered as part of a JITAI may be based on any number of behavior change techniques such as goal-setting, feedback, and implementation intentions to promote long-term behavior change.¹¹⁻¹⁴ To date, JITAs have been applied to states of physical inactivity^{15,16}; chronic medical conditions, such as obesity,¹⁷ alcohol abuse,¹⁸ and nicotine addiction¹⁹; and mental health disorders.²⁰

While JITAs hold promise, their application to cardiovascular disease management has been limited by the lack of experimental methods that can empirically inform their design: decisions on which components to include in a JITAI and rules (termed decision rules) for when and how often those components should be delivered to maximize their effectiveness. We highlight limitations of commonly used experimental designs for informing JITAI design and then present microrandomized trials as a unique approach for optimizing JITAs.

CHALLENGES WITH DESIGNING JITAS

Traditional randomized controlled trials (RCTs) refer to an experimental design in which participants are randomized to one of two or more groups, an experimental group and a control group in which participants received placebo or the prior standard of care, and then are compared on one or more outcomes. These, however, have 3 key shortcomings as a method for JITAI optimization. First, due to resource constraints, RCTs typically have a limited number of study arms and are thus best suited for determining the efficacy of an intervention rather than the efficacy of individual components in a multicomponent intervention.⁹ Second, given that intervention assignment is randomized at baseline, RCTs cannot rigorously assess the effect of intervention components moderated by time-varying factors such as changing levels of patient motivation or self-efficacy, or the context (eg, location) in which an intervention component is delivered. Such information is essential for determining decision rules for the provision of JITAs. Third, analyses of RCTs are traditionally based on a relatively small number of prespecified time points (eg, 1 and 3 years). JITAI design provides detailed information about how the effectiveness of an intervention

component changes over time. For example, the effect of a reminder to go for a walk may rapidly decrease over a few weeks, making such a component a poor match for a JITAI designed for long-term behavior modification. RCTs provide no rigorous ways of studying such issues empirically.

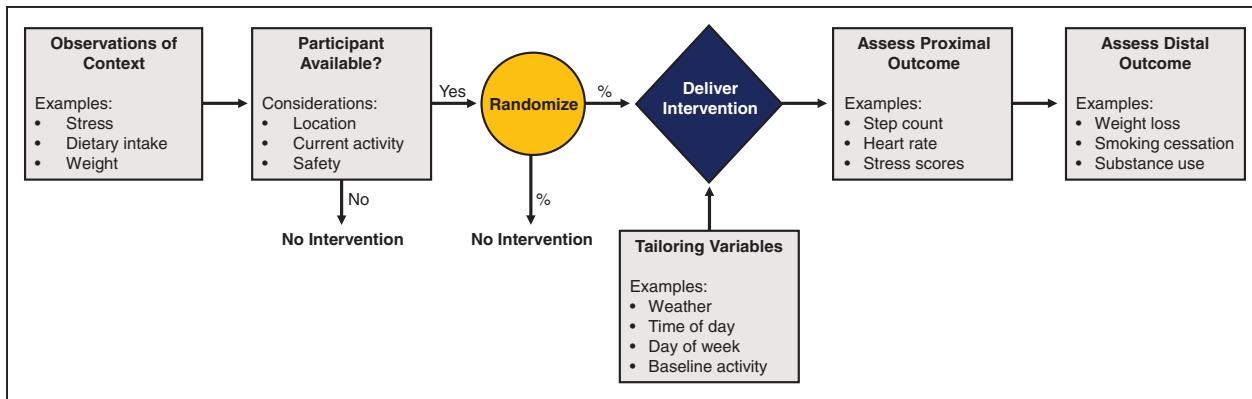
A key limitation of RCTs—namely the inability to efficiently study the efficacy of individual intervention components—can be addressed through the use of factorial experiments. Factorial experiments are a study design in which participants are randomized to different combinations of a multicomponent intervention, and the efficacy of each component is assessed, averaging across the other intervention components. Like RCTs, however, factorial designs are limited in their ability to study the effect of time-varying moderators on intervention effectiveness.

OVERVIEW OF MICRORANDOMIZED TRIALS

The microrandomized trial is an experimental design to aid in constructing empirically based JITAs through the serial randomization of participants to different types of interventions and different levels of an intervention. Researchers can use microrandomized trials to decide whether to include a time-varying component in a multicomponent intervention and in which contexts delivering a component is most effective. These trials are not confirmatory studies designed to evaluate an intervention package; instead, they are focused on selecting and optimizing intervention components for use in a JITAI. For the remainder of this article, we focus on the development and execution of microrandomized trials, providing a general overview of the design, illustrating key concepts through a case example, and closing with important statistical considerations.

Microrandomization refers to the process of sequential randomized assignment to one or several intervention components throughout the conduct of the trial.²¹ Microrandomized trials are unique with respect to the time scale over which they operate, potentially randomizing a single individual at multiple time points—termed decision points—over the course of a day (Figure 1). Decision points are guided by tailoring variables, which are individual-level or contextual characteristics used to determine when a participant is most likely to benefit from an intervention component. In a microrandomized trial with multiple intervention components (eg, medication reminders and planning of activity), each component will be associated with its own decision points and decision rules that operationalize intervention delivery.

At each decision point, participants are randomized to levels of an intervention component: to receive or not receive the intervention or to receive different forms

**Figure 1.** Sample microrandomized trial design.

In this example, participants would be randomized to receive the intervention or no intervention based on prespecified probabilities. In an alternative study design, participants could be randomized to different forms or levels of an intervention.

of the intervention (eg, framing of a motivational message). When provided, interventions are typically delivered through push notifications. In a microrandomized trial, intervention effectiveness is assessed via repeated short-term assessments of near-term outcomes, termed the proximal outcome. By repeatedly randomizing participants, microrandomized trials can interrogate the dynamic effects of intervention components and investigate psychosocial, temporal, and contextual factors that moderate effectiveness. By leveraging within-person contrasts over time (ie, instances in which a participant receives versus does not receive an intervention component), microrandomized trials are a statistically and temporally efficient study design that can add to our understanding of causal effects.²² Table 1 lists the types of research questions that microrandomized trials can help answer.^{22,23} A JITAI that was optimized based on the data from a microrandomized trial can then be tested for overall efficacy in a confirmatory trial, such as a standard RCT.

CASE STUDY

To date, microrandomized trials have been leveraged for primary cardiovascular disease prevention, such as the promotion of physical activity,¹⁵ weight loss,²⁴ and smoking cessation, though applications to secondary cardiovascular disease prevention are lacking.²⁵ To illustrate how microrandomized trials could be used for cardiovascular disease management and provide a framework by which to present important design concepts, we describe a hypothetical study, termed the HEART study (Heart Failure With Preserved Ejection Fraction Diet and Activity Microrandomized Trial).

The HEART study would be a microrandomized trial for patients with heart failure with preserved ejection fraction in which participants would receive a smartwatch and a mobile application that delivers

microrandomized notifications (Figure 2). The application would allow for tracking of activity parameters, such as step count and distance walked, but also proximity to fast-food restaurants through geofencing, a location-based smartphone feature which tracks crossings of defined geographic boundaries. The study would have 2 synergistic intervention components designed to promote weight loss and improve functional capacity through (1) promotion of physical activity and (2) avoidance of fast-food restaurants.

The first goal of the HEART study would be to encourage participants' to be more physically active (Figure 2A). Participants on enrollment would identify 5 times of day¹⁵ at Heart Failure with Preserved Ejection Fraction Diet and Activity Microrandomized which they are typically sedentary. At each of these time points (ie, decision points), their activity level would be assessed. If sedentary, as determined by their step count in the prior 30 minutes, participants would be randomized, with 60% probability, to receive a notification promoting physical activity, or to no notification (at 40% probability). The probabilities chosen are arbitrary and would be selected by the investigators based on their clinical knowledge of the setting. Messages would be selected from a message bank and tailored to contextual factors, such as season, weather, and day of the week. Short-term intervention effectiveness would be determined through step count over the 1 hour following randomization (the proximal outcome; see Table 2 for this and other key terms).

The second goal of the HEART study would be to support participants in minimizing consumption of high-fat foods through avoidance of fast-food restaurants (Figure 2B). Close proximity to a fast-food restaurant, determined through geofencing, would trigger an ecological momentary assessment containing 2 questions on stress and anxiety, capturing information on the user more difficult to measure passively.⁹ With

Table 1. Sample Research Questions That Can Be Answered by a Well-Designed Microrandomized Trial^{22,23}

Study questions	Example
Does an intervention component impact its intended proximal outcome?	Does receiving a notification encouraging walking result in more steps in an hour following the randomization than not receiving a notification?
How is the effect of an interaction component impacted by other intervention components?	Are patients more likely to act on notifications encouraging a low-sodium diet by choosing a low-sodium meal when they receive a morning reminder of their commitment to their heart health?
Is treatment effectiveness context-dependent?	In participants with PAD, are notifications encouraging them to walk more effective when received at home or at work?
How does the effect of an intervention component change over time?	Do participants become less responsive over time to notifications reminding them to choose low-sodium meals?
How frequently should an intervention component be delivered?	For secondary MI prevention, are walking notifications more effective for increasing step count if delivered one or 3 times per day?

MI indicates myocardial infarction; and PAD, peripheral arterial disease.

50% probability, participants would receive a notification promoting a low-sodium diet, tailored to stress and anxiety scores. The other 50% of times, participants would receive a generic notification not tailored to their current state. Fifteen minutes after a decision point, participants would receive a survey to ascertain whether they entered the restaurant and what they ordered. The proximal outcome would be entry into the restaurant.^{18,26} After 1 month, percent weight loss (the distal outcome) would be assessed.

DESIGN CONSIDERATIONS FOR MICRORANDOMIZED TRIALS

Proximal and Distal Outcomes

A microrandomized trial design requires selecting a long-term clinical outcome, termed the distal outcome,^{13,14} which guides the intervention design and is analogous to the primary outcome in an RCT (Table 2). The distal outcome also serves to guide the choice of proximal outcomes, a short-term version, or hypothesized mediator of the distal outcome.¹³ A proximal outcome should capture short-term progress towards adopting and maintaining a target behavior. It should be measurable passively or actively at a low burden to the participant after each decision point.²⁷ For example, exercise minutes are a measurable outcome and clear mediator in an intervention designed to promote weight loss. For an intervention component designed to reduce addiction, proximal outcomes may include reduction in cravings or an increase in sobriety motivation. The proximal outcome should also be one that can be measured consistently and with sufficient temporal granularity to link it to an intervention component. In the HEART study, both intervention components would be assessed within an hour of randomization, linking them temporally to the intervention (Table 2). Both also represent intermediates in the weight loss pathway (ie, increased activity and decreased consumption of high-fat foods).

Decision Points and Decision Rules

Decision points denote times at which an intervention component may be delivered and are chosen based on the dynamics (anticipated or actual) of the state that the intervention component is targeting (eg, sedentary behavior or fast-food consumption). These may be prespecified time points or may arise rapidly and ecologically in response to the interaction between dynamic and static factors. Fixed decision points afford greater control over the frequency with which notifications are delivered, ensuring alignment between the time frame over which the tailoring variable and proximal outcome are expected to change.¹² In contrast, this lack of flexibility may lead to missed opportunities for facilitating behavior change, and notifications may be delivered at times when participants are unreceptive, such as activity notifications during vacations or illness. While dynamic decision points avoid many of these limitations, they require high-frequency monitoring and wearable device signals which can be measured with sufficient reliability and fidelity to ensure intervention components are appropriately timed. Dynamic decision points are also analytically more complex²⁸ and afford less control over the frequency of decision points.

Decision points are paired with decision rules to operationalize the provision of support, establishing levels, ranges, or thresholds for treatment delivery¹³; these may be modified over time in response to participant behavior. When selecting decision rules, researchers must balance the complex interplay between participant engagement and intervention fatigue to maintain adherence and retention.

For the dietary intervention in the HEART study, decision points would arise once participants crossed a virtual fence surrounding a fast-food restaurant. In contrast, for the activity intervention, decision points would be preselected with the decision rule specifying that participants would be randomized if they walked <200 steps in the 30 minutes before a decision point. Fixed time points ensure that participants would receive

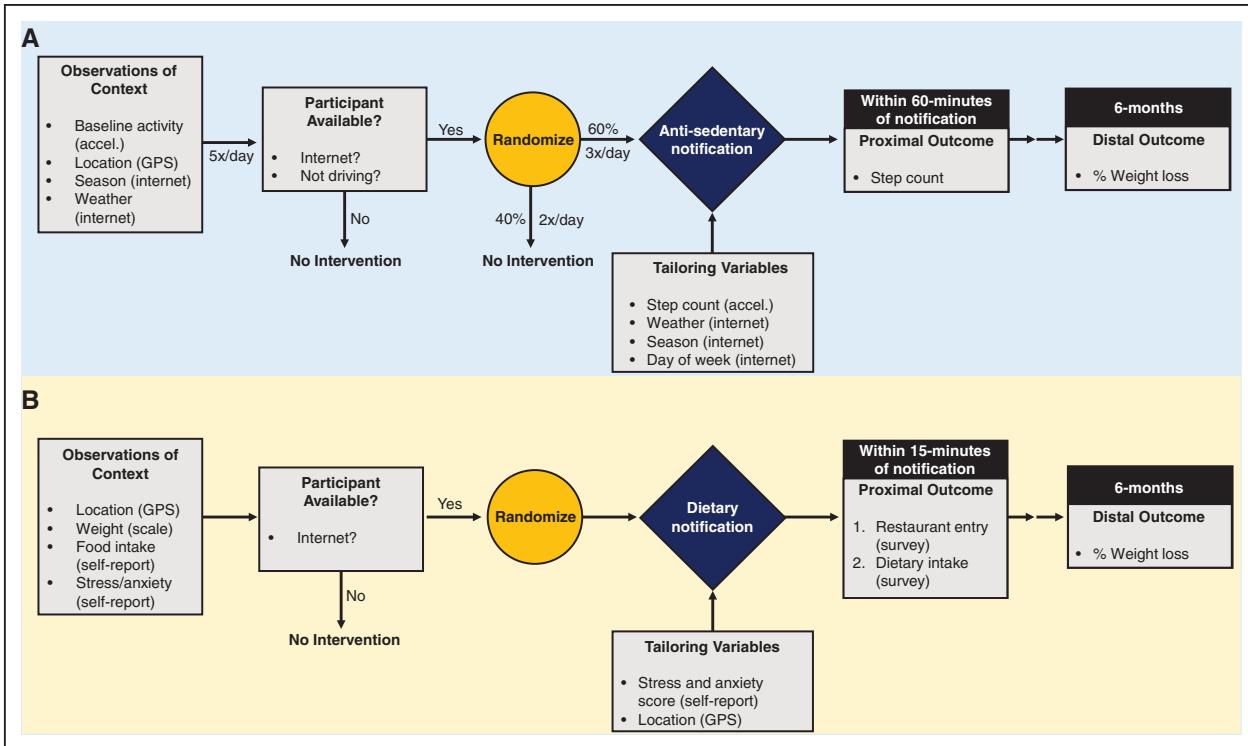


Figure 2. Visual representation of the HEART study (Heart Failure with Preserved Ejection Fraction Diet and Activity Microrandomized Trial); (A) activity and (B) dietary interventions.

accel indicates accelerometer; and GPS, global positioning system.

notifications with sufficient frequency to promote weight loss though not so frequently as to lead to burnout in this relatively inactive population. The burden to participants could be reduced by decreasing the overall frequency of notifications delivered, either by altering the decision rules or by reducing the probability of receiving a notification at each decision point. Minimizing the burden to participants by increasing the threshold for notifications must be balanced, however, against the risk of decreased intervention effectiveness. Additionally, in this study design, the least active individuals would receive the greatest number of activity notifications yet their response burden would be greatest. As an alternative design, participants could be stratified on baseline activity levels and different decision rules implemented for each activity quartile. These decision rules could then be modified over time as participants become more active.

Tailoring Variables

Tailoring variables are individual-level and contextual characteristics used to identify conditions in which a participant may benefit from an intervention component, denoting periods of opportunity or vulnerability.¹² Tailoring variables are used as part of decision rules to operationalize the intervention provision protocol. Tailoring variables can be measured passively by sensors,

such as step count, or actively via ecological momentary assessment. These actively or passively collected measures may be intrinsically informative (ie, step count for identifying states of inactivity) or may require aggregation with other variables to form composite scores for intervention-relevant states.^{12,13} For example, in patients with opioid use disorders, a machine-learning model was trained to predict heroin and cocaine cravings using global positioning system data and participant-level demographic characteristics.²⁹ Such predictors can be used as tailoring variables to determine when to intervene (eg, when the risk of heroin use is above a threshold). Tailoring variables should be able to be assessed reliably and with sufficient granularity to identify meaningful changes in states of interest (eg, risk of drug use).^{12,13}

In the HEART study, the tailoring variables in the activity intervention would be time of day and step count before decision points; in the dietary intervention, stress and anxiety scores, and distance from a fast-food restaurant. The latter leverages stress-vulnerability theory which reflects the transient tendency of individuals to experience adverse health outcomes or to engage in maladaptive behaviors during periods of heightened anxiety or stress.^{11,13} Step count, in contrast, is designed to leverage the impact of shaping on attainment of the target behavior.

Table 2. Key Terms in Microrandomized Trial Design and Their Application to the HEART Study

	Definition	HEART study: activity intervention	HEART study: dietary intervention
Proximal outcome	Short-term impact of an intervention component	Step count in the 60 min following a decision point	Entry into fast-food restaurant
Distal outcome	Target behavior	Percent weight loss	Percent weight loss
Tailoring variable	Participant-level and contextual characteristics determining treatment selection and timing	Step count Season Weather Day of week	Stress and anxiety scores Location
Decision points	Times when a participant may be randomized to receive levels of a treatment	Five preselected time points each day	When a participant is within Y distance of a fast-food restaurant
Decision rules	Operationalizes the provision of support by establishing levels, ranges, or thresholds for treatment delivery	If step count <200 in the 30 min before a decision point Then randomize provision of activity notification Else no notification	If <Y-feet from a fast-food restaurant Then randomize provision of dietary notification Else no notification
Randomization probability	Likelihood of receiving a treatment at each decision point	60% activity notifications 40% no notification	50% dietary notification tailored on stress and anxiety 50% generic notification
Participant availability	Rules governing when a participant will not be randomized at a decision point	Unavailable when: No internet connection Driving Recently active (step count ≥200 in prior 30 min)	Unavailable when: No internet connection
Intervention options	Treatments or actions at a decision point	Notification recommending activity within current context No notification	Notification promoting a heart-healthy diet No notification

HEART indicates Heart Failure With Preserved Ejection Fraction Diet and Activity Microrandomized Trial.

Participant Availability

Participant availability to receive an intervention at each decision point encapsulates rules for when it is safe and appropriate to deliver an intervention. Participant availability may change from one decision points to another, and the rules governing availability will differ based on the target behavior. For example, activity notifications are inappropriate when a participant is driving or is currently physically active and, potentially, for a certain period thereafter. Definitions of unavailability may significantly impact how frequently a component of an intervention can be delivered and should be considered during the study design phase given its impact on sample size calculations. Participant availability may also change systematically over the course of a study. An effective physical activity intervention may lead to greater unavailability if participants can only receive treatment when sedentary.²¹ During times of both availability and unavailability, the same participant data should be collected to allow interrogation of sources of unavailability during the analytic phase of the study.²¹

For the dietary intervention in the HEART study, participants would be considered unavailable only when they lacked an internet connection. More complex rules could be incorporated to determine exactly when participants are available, although

these would come at the cost of increased burden to participants. One could imagine a trial in which participants would only be considered available to receive a notification if they had already exceeded their daily recommendations for trans and saturated fat consumption.

Intervention Options

Finally, when designing a microrandomized trial, one must consider the form of intervention delivery (eg, smartwatch notifications, text messages, or phone calls) and which treatments or actions should be randomized. Participants may be randomized to receive or not receive an intervention, or to receive one of 2 or more forms of an intervention, as in the dietary intervention of the HEART study. Intervention components should be selected which actuate the psychosocial mechanisms mediating behavior change with the amount, type, and source of support guided by prior digital health research, behavioral health theory, and technical and logistical considerations. Intervention components should be randomized if there is uncertainty as to the (1) best intervention or combination of interventions; (2) appropriate intervention dose; or (3) how context of delivery impacts intervention effectiveness.^{9,22}

STATISTICAL CONSIDERATIONS FOR MICRORANDOMIZED TRIALS

We now detail several important statistical considerations when designing and analyzing microrandomized trials. While we focus herein on sample size calculations, the same techniques can be applied when analyzing microrandomized trial data to determine causal effects. The following section focuses on estimating the time-varying effects of an intervention component on the proximal outcome. While the study could be powered based on the distal outcome, this is typically avoided as microrandomized trials focus on the selection and optimization of time-varying intervention components and are not confirmatory studies. Sample size calculations are thus designed to assess the proximal effects of the time-varying component. An intervention package containing the time-varying components from a microrandomized trial can subsequently be evaluated in a confirmatory trial. Herein, we demonstrate sample size calculations for the HEART study. For ease of demonstration, we focus on the activity intervention in which decision points are fixed and opportunities to receive an intervention component are the same for all participants, contingent on availability. In this example, the intervention would be notifications promoting low-level physical activity, and the proximal outcome would be step count in the hour after a randomization. Moreover, we may be only interested in the effect if the participant is currently sedentary.

Generally, let $t=1, \dots, T$ index the decision points with $A_t=1$ if the participant is sent a push notification and $A_t=0$ otherwise. These decision points may be fixed (eg, every minute or hour during the day), as in this example, or patient-dependent (eg, patient chooses exact timing of decision points within predefined 2-hour windows). Let Y_{t+1} denote the proximal outcome after decision point t . The effect of treatment at decision point t is the expected difference in Y_{t+1} between participants who receive the push notification and those who do not. Let $I_t=1$ if the participant is sedentary at time t and $I_t=0$ if not. A microrandomized trial aims to test a particular treatment effect denoted:

$$\beta(t) = E[Y_{t+1} | A_t = 1, I_t = 1] - E[Y_{t+1} | A_t = 0, I_t = 1]$$

See Dempsey et al²⁸ for a full derivation of $\beta(t)$ using causal inference notation. Of note, the proximal effect is defined with respect to treatment at decision point t . This is distinct from traditional longitudinal analyses in which the time-varying effect is with respect to a single treatment administered at baseline.

The next step is to calculate the study's sample size, for which we can leverage the publically available calculator at <https://CRAN.R-project.org/package=MRTSampleSize.30>. We wish to calculate a sample size with sufficient power to detect alternatives

to our null hypothesis that notifications have no effect on our proximal outcome, defined as $H_0: \beta(t)=0$ for every decision point $t=1, \dots, T$. Sample size calculations for microrandomized trials require 5 inputs: (1) study duration, (2) number of decision points per day, (3) randomization probability, (4) expected availability, and (5) standardized proximal treatment effect. In the HEART study, the study duration would be 1 month (30 days), the number of decision points 5 per day, and the probability of receiving a notification 60%. Expected availability at decision point $E[I_t]$ is the fraction of users available for treatment at each decision point t . As participants in the HEART study would only be available if sedentary (ie, $I_t=1$), availability may vary over the course of the study. For simplicity, we assume here a constant fraction of sedentary participants at each decision point. We consider several plausible values of expected availability as follows: 0.3, 0.4, 0.5, and 0.6 (Table 3). See Klasnja et al⁹ and Liao et al³⁰ for a further discussion of participant availability.

Finally, calculating expected power requires estimates of the standardized proximal treatment effect, which depends on (1) the proximal treatment effect $\beta(t)$ and (2) the population SD of Y_{t+1} , denoted $\sigma(t)$. Technically, the standardized effect at each decision point is as follows:

$$d(t) = \frac{\beta(t)}{\sigma(t)}$$

The standardized effect measures the magnitude of effect relative to the SD and is equivalent to Cohen d .³¹ For the numerator, we assume a simple functional form which can be constant, linear, or quadratic based on the predicted response to treatment. If, for example, we suspect that the treatment effect will decrease with time due to habituation than a linear form would be appropriate.²⁸ Alternatively, a quadratic form may be selected if the intervention's effectiveness is predicted to be low at the start of the study, increase as participants become familiar with the intervention, and then decrease with time due to habituation. While a less complex form has the advantage of requiring a smaller sample size, it may not reflect the true alternative. We thus suggest sizing a study using the least complex realistic alternative. Since in the HEART study, we would be interested in detecting linear trends in treatment effect, we size the study where the alternative is linear based on day-in-study with treatment effect, $\beta(t)$, decreasing with time t .

The magnitude of the standardized proximal effect may be informed by prior data³² if available. The numerator can be estimated by taking the difference between those who received treatment at decision point t and those who did not, ($\hat{\beta}(t) = \bar{Y}_{t+1,1} - \bar{Y}_{t+1,0}$); the denominator can be calculated using standard pooled variance calculations at each decision point. This is in

Table 3. Sample Size as a Function of Standardized Effect Size (\bar{d}) and Participant's Expected Availability $E[I_t]$

$\bar{d}, E[I_t]$	0.3	0.4	0.5	0.6
0.05	293	220	177	148
0.06	204	154	124	103
0.07	151	114	91	77
0.08	116	88	71	59
0.09	92	70	56	47
0.10	75	57	46	39

line with Cohen d which calculates the SD pooled over treatment groups.³² If prior data are unavailable, we may choose standardized effect sizes that are in line with prior sample size calculations. In Liao et al,³⁰ the average effect sizes $\bar{d} = \frac{1}{T} \sum_{t=1}^T d(t)$ ranged from 0.05 to 0.10 (Table 3).³⁰ Due to minimal prior data, we consider the same range in the HEART study.

Data from a microrandomized trial can also be used to assess moderation of a treatment effect given a time-varying covariate. In the HEART study, for example, scientists may be interested in assessing the intervention effect based on self-reported stress S_t . The moderated effect of treatment at decision point t is the expected difference in Y_{t+1} between participants who receive tailored push notifications while at stress level s and those who do not receive notifications at stress level s . Mathematically, the moderated treatment effect can be denoted³³:

$$\beta(t; s) = E[Y_{t+1} | A_t = 1, I_t = 1, S_t = s] - E[Y_{t+1} | A_t = 0, I_t = 1, S_t = s].$$

Similarly, one may be interested in assessing treatment effect only at at-risk times, as determined by the tailoring variables. In the HEART study, for example, the dietary intervention is only provided when a participant is within the virtual fence surrounding a fast-food restaurant. Let L_t denote a binary indicator that the individual is within the virtual fence at decision point t (ie, $L_t = 1$ if true and 0 otherwise). Then the effect of interest using the above notation is $\beta(t; 1)$ where L_t replaces S_t as the time-varying covariate. Note that in settings where the primary aim is assessment of effects at at-risk times, the randomization probabilities are often complex functions of participants' histories. When this occurs, the corresponding analytic methods and sample size calculations are more complex.²⁸

OPPORTUNITIES AND CHALLENGES

As microrandomized trials enrich our understanding of digital behavioral interventions through the provision of longitudinally dense data, additional questions

in the field may be broached. Should decision rules change over time once goals are achieved?²⁷ What factors dictate the timing over which new behaviors are developed? How are users' experiences impacted by their mobile interactions and by the form of goal attainment? Additional questions exist with respect to how best to analyze this data. These include how to (1) assess delayed effects under JITAI policies that differ from the microrandomization protocol, (2) handle missing data in the primary analysis, (3) evaluate proposed JITAI using the microrandomized trial data, and (4) update intervention components in real-time for future study participants.

Finally, while not unique to microrandomized trials, we must consider how we are keeping participant data safe. While digital data collected as part of a research study remains protected under the Health Information and Privacy Protection Act Privacy Rule, that same information collected by nonstudy applications can be sold to commercial entities.³⁴ There are numerous publications that discuss this issue in detail and readers are referred to those sources.³⁴⁻³⁶ It remains to be seen, however, whether these challenges to privacy will be addressed at the consumer level or through greater regulation of health-related information.

Herein, we presented microrandomized trials as a novel experimental design that can aide in optimizing JITAI while maintaining the strength of causal inference associated with traditional RCTs. By leveraging evolving mobile technology and behavior change strategies, JITAI promise to deliver interventions to users when and where they are most needed, helping them to implement behavior changes in their daily lives. Such an approach, we hope, will allow mobile health technologies to achieve their potential of facilitating long-term change and help users with cardiovascular disease manage their condition more effectively.

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REFERENCES

- Taylor K, Silver L. Smartphone Ownership Is Growing Rapidly Around the World, but Not Always Equally. 2019. <https://www.pewresearch.org/global/2019/02/05/smartphone-ownership-is-growing-rapidly-around-the-world-but-not-always-equally/>. Accessed March 12, 2020.
- Vogels EA. Millennials stand out for their technology use, but older generations also embrace digital life. 2019. <https://www.pewresearch.org/fact-tank/2019/09/09/us-generations-technology-use/>. Accessed March 12, 2020.
- Perrin A, Turner E. Smartphones help blacks, Hispanics bridge some – but not all – digital gaps with whites. 2019. <https://www.pewresearch.org/fact-tank/2019/08/20/smartphones-help-blacks-hispanics-bridge-some-but-not-all-digital-gaps-with-whites/>. Accessed March 12, 2020.
- Day S. Digital Health Consumer Adoption Report 2019. 2019. <https://rockhealth.com/reports/digital-health-consumer-adoption-report-2019/>. Accessed November 11, 2019.
- Wongvibulsin S, Martin SS, Saria S, Zeger SL, Murphy SA. An individualized, data-driven digital approach for precision behavior change. *Am J Lifestyle Med.* 2020;14:289–293. doi: 10.1177/1559827619843489
- Menictas M, Rabbi M, Klasnja P, Murphy S. Artificial intelligence decision-making in mobile health. *Biochemist.* 41:20–24.
- Zheng X, Spatz ES, Bai X, Huo X, Ding Q, Horak P, Wu X, Guan W, Chow CK, Yan X, et al. Effect of text messaging on risk factor management in patients with coronary heart disease: the CHAT randomized clinical trial. *Circ Cardiovasc Qual Outcomes.* 2019;12:e005616. doi: 10.1161/CIRCOUTCOMES.119.005616
- Huo X, Krumholz HM, Bai X, Spatz ES, Ding Q, Horak P, Zhao W, Gong Q, Zhang H, Yan X, et al. Effects of mobile text messaging on glycemic control in patients with coronary heart disease and diabetes mellitus: a randomized clinical trial. *Circ Cardiovasc Qual Outcomes.* 2019;12:e005805. doi: 10.1161/CIRCOUTCOMES.119.005805
- Klasnja P, Hekler EB, Shiffman S, Boruvka A, Almirall D, Tewari A, Murphy SA. Microrandomized trials: an experimental design for developing just-in-time adaptive interventions. *Health Psychol.* 2015;34S:1220–1228. doi: 10.1037/he0000305
- Businelle MS, Walters ST, Mun EY, Kirchner TR, Hébert ET, Li X. Reducing drinking among people experiencing homelessness: protocol for the development and testing of a just-in-time adaptive intervention. *JMIR Res Protoc.* 2020;9:e15610. doi: 10.2196/15610
- Nahum-Shani I, Hekler EB, Spruijt-Metz D. Building health behavior models to guide the development of just-in-time adaptive interventions: a pragmatic framework. *Health Psychol.* 2015;34S:1209–1219. doi: 10.1037/he0000306
- Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, Murphy SA. Just-in-Time Adaptive Interventions (JITAs) in mobile health: key components and design principles for ongoing health behavior support. *Ann Behav Med.* 2018;52:446–462. doi: 10.1007/s12160-016-9830-8
- Nahum-Shani S, Smith SN, Tewari A, Witkiewitz K, Collins LM, Spring B, Murphy SA. *Just-in-time adaptive interventions (JITAs): An organizing framework for ongoing health behavior support.* (Technical Report No. 14-126). University Park: The Methodology Center, Penn State; 2014.
- Klasnja P, Hekler EB. Rethinking evaluations of mhealth systems for behavior change. *GetMobile.* 2018;22:11–14. doi: 10.1145/3276145.3276149
- Klasnja P, Smith S, Seewald NJ, Lee A, Hall K, Luers B, Hekler EB, Murphy SA. Efficacy of contextually tailored suggestions for physical activity: a micro-randomized optimization trial of heartsteps. *Ann Behav Med.* 2019;53:573–582. doi: 10.1093/abm/kay067
- Hardeman W, Houghton J, Lane K, Jones A, Naughton F. A systematic review of just-in-time adaptive interventions (JITAs) to promote physical activity. *Int J Behav Nutr Phys Act.* 2019;16:31. doi: 10.1186/s12966-019-0792-7
- Thomas JG, Bond DS. Behavioral response to a just-in-time adaptive intervention (JITAI) to reduce sedentary behavior in obese adults: Implications for JITAI optimization. *Health Psychol.* 2015;34S:1261–1267. doi: 10.1037/he0000304
- Gustafson DH, McTavish FM, Chih MY, Atwood AK, Johnson RA, Boyle MG, Levy MS, Driscoll H, Chisholm SM, Dillenburg L, et al. A smartphone application to support recovery from alcoholism: a randomized clinical trial. *JAMA Psychiatry.* 2014;71:566–572. doi: 10.1001/jamapsychiatry.2013.4642
- Riley W, Obermayer J, Jean-Mary J. Internet and mobile phone text messaging intervention for college smokers. *J Am Coll Health.* 2008;57:245–248. doi: 10.3200/JACH.57.2.245-248
- Ben-Zeev D, Brenner CJ, Begale M, Duffecy J, Mohr DC, Mueser KT. Feasibility, acceptability, and preliminary efficacy of a smartphone intervention for schizophrenia. *Schizophr Bull.* 2014;40:1244–1253. doi: 10.1093/schbul/sbu033
- Seewald NJ, Smith SN, Lee AJ, Klasnja P, Murphy SA. Practical considerations for data collection and management in mobile health micro-randomized trials. *Stat Biosci.* 2019;11:355–370. doi: 10.1007/s12561-018-09228-w
- Walton A, Nahum-Shani I, Crosby L, Klasnja P, Murphy S. Optimizing digital integrated care via micro-randomized trials. *Clin Pharmacol Ther.* 2018;104:53–58. doi: 10.1002/cpt.1079
- Müller AM, Blandford A, Yardley L. The conceptualization of a Just-In-Time Adaptive Intervention (JITAI) for the reduction of sedentary behavior in older adults. *Mhealth.* 2017;3:37. doi: 10.21037/mhealth.2017.08.05
- Klasnja P, Rosenberg DE, Zhou J, Anau J, Gupta A, Arterburn DE. A quality-improvement optimization pilot of Barifit, a mobile health intervention to promote physical activity after bariatric surgery. *Transl Behav Med:iba040.* doi: 10.1093/tbm/iba040.
- Liao P, Dempsey W, Sarker H, Hossain SM, Al'absi M, Klasnja P, Murphy S. Just-in-Time but Not Too Much: Determining Treatment Timing in Mobile Health. *Proc ACM Interact Mob Wearable Ubiquitous Technol.* 2018;2:179. doi: 10.1145/3287057
- Dorsch MP, An LC, Hummel SL. A novel just-in-time contextual mobile app intervention to reduce sodium intake in hypertension: protocol and rationale for a randomized controlled trial (LowSalt4Life Trial). *JMIR Res Protoc.* 2018;7:e11282. doi: 10.2196/11282
- Klasnja P, Kendall L, Pratt W, Blondon K. Long-term engagement with health-management technology: a dynamic process in diabetes. *AMIA Annu Symp Proc.* 2015;2015:756–765.
- Dempsey W, Liao P, Kumar S, Murphy Susan A. The stratified micro-randomized trial design: sample size considerations for testing nested causal effects of time-varying treatments. *Ann Appl Stat.* 2020;14:661–684. doi: 10.1214/19-AOAS1293
- Epstein DH, Tyburski M, Kowalczyk WJ, Burgess-Hull AJ, Phillips KA, Curtis BL, Preston KL. Prediction of stress and drug craving ninety minutes in the future with passively collected GPS data. *NPJ Digit Med.* 2020;3:26. doi: 10.1038/s41746-020-0234-6

-
- 30. Liao P, Klasnja P, Tewari A, Murphy SA. Sample size calculations for micro-randomized trials in mHealth. *Stat Med*. 2016;35:1944–1971. doi: 10.1002/sim.6847
 - 31. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2 ed: Taylor & Francis; New York, NY. 1988.
 - 32. Luers B, Klasnja P, Murphy S. Standardized effect sizes for preventive mobile health interventions in micro-randomized trials. *Prev Sci*. 2019;20:100–109. doi: 10.1007/s11121-017-0862-5
 - 33. Boruvka A, Almirall D, Witkiewitz K, Murphy SA. Assessing time-varying causal effect moderation in mobile health. *J Am Stat Assoc*. 2018;113:1112–1121. doi: 10.1080/01621459.2017.1305274
 - 34. Golbus JR, Price WN 2nd, Nallamothu BK. Privacy gaps for digital cardiology data: big problems with big data. *Circulation*. 2020;141:613–615. doi: 10.1161/CIRCULATIONAHA.119.044966
 - 35. Price WN 2nd, Cohen IG. Privacy in the age of medical big data. *Nat Med*. 2019;25:37–43. doi: 10.1038/s41591-018-0272-7
 - 36. US Department of Health & Human Services. “Health Information Privacy Beyond HIPAA: A 2018 Environmental Scan of Major Trends and Challenges.” A Report for the National Committee on Vital and Health Statistics (NCVHS) and its privacy, Security, and Confidentiality Subcommittee. December 13, 2017. Accessed September 19, 2019. <https://ncvhs.hhs.gov/wp-content/uploads/2018/05/NCVH.pdf>