RESEARCH PROTOCOL

SIGNIFICANCE

A.1 This project targets dietary non-adherence, a major cause of poor outcomes during behavioral obesity treatment (BOT) - a first-line intervention for cardiovascular disease (CVD). BOT produces clinically significant weight losses and reduces CVD risk and severity.[1] Weight loss and maintenance depend on adherence to a specific eating plan, however non-adherence to this plan is common.[2] **Dietary lapses** are defined as specific instances of non-adherence to one or more BOT dietary goals or eating behaviors.[3,4] Our work shows that lapses during BOT are frequent (~3-4 times per week) and associated with poorer weight loss outcomes.[3,5] The ability to cope with temptation, and thus prevent lapses, is associated with BOT success.[6-11] Despite the clear potential for lapses to influence weight loss outcomes, there is insufficient evidence for how to intervene on lapses in BOT, which highlights the need for transformative research in this area.

A.2 Our team has pioneered innovative strategies that capitalize on mobile technology to overcome barriers that have made it difficult to assess and intervene on dietary lapses. Dietary lapses are difficult to simulate in the lab and vulnerable to inaccuracy when studied via retrospective self-report (e.g., questionnaires, interviews).[7,12] Ecological momentary assessment (EMA) enhances the reliability and validity of lapse assessment via real-time measurement.[12] EMA employs short surveys delivered via smartphone repeatedly throughout the day to capture changing behaviors, cognitive/emotional states, and environmental contexts.[13] To further enhance the scientific rigor of lapse assessment, we have supplemented EMA-reported lapses with objective monitoring of eating behavior. Wrist-watch devices (described below) now allow for passive sensing of eating by measuring the acceleration and rotation of dominant-hand wrist movement.[14] The PI's work (F32 HL143954) shows that this type of objective monitoring provides fine-grained information (e.g., rate, frequency, duration, estimated energy intake) about eating that can enhance characterization of lapses. Advances in mobile health (mHealth) technologies (e.g., EMA, passive sensing) can enhance timely intervention and/or improve measurement of intervention effects.[15,16]

A.3 Prior interventions for lapse are limited by reliance on patients' ability to independently maintain total vigilance of their behavior and its antecedents. Our pilot-tested just-in-time adaptive intervention (JITAI) monitors risk and intervenes *as needed*. A key limitation of BOT is that strategies to improve adherence (e.g., stimulus control, coping with temptation) require continuous awareness of triggers for lapse, as well as an ability to immediately formulate and implement an effective plan to avoid lapse. In contrast, just-in-time adaptive interventions (JITAI)[17] delivered via mobile device can improve adherence by monitoring lapse risk and providing support to prevent lapses in an adaptive manner in exact moments of need.[18] Through several rigorous feasibility tests, our team has developed a JITAI for dietary lapses that uses EMA to monitor lapse triggers.[5,19] The JITAI uses a machine learning algorithm to calculate an ongoing level of risk for lapsing and deliver preventative intervention to the participant as needed. Integrating machine learning allows the JITAI to efficiently personalize intervention, which even further reduces the need for constant vigilance by the participant.[20] While we have shown that this approach is feasible, we still know relatively little about the specific intervention strategies that are most effective for countering lapse when risk is high.

A.4 Micro-randomized trial (MRT) methods allows us to *empirically optimize* JITAI for dietary lapse very *efficiently* by evaluating the *immediate effects* of a range of intervention options on target behaviors.[21] To develop scientifically rigorous and maximally effective JITAIs, a data-driven approach to optimization is imperative. The goal of our JITAI is to have an *immediate, proximal effect* on dietary lapse. To formally evaluate intervention efficacy, we therefore need to employ an experimental design for examining *immediate, proximal effects*.[22] A traditional RCT design is insufficient to meet this need because it only assesses whether, on average (e.g., across weeks or months), an intervention affected behavior. As such, an RCT cannot determine which interventions are efficacious *at a given moment in time*, which is crucial to designing a data-driven JITAI.[23] An MRT design is the most methodologically sound approach to efficiently evaluate the efficacy

of interventions for reducing dietary lapse, which will ultimately serve to optimize our JITAI.[24] MRT is a well-established optimization design, similar to a Sequential, Multiple Assignment, Randomized Trial (SMART),[25] that capitalizes on sequential randomization.[22,23] Rather than randomizing an individual only once to a single treatment as is typical in an RCT, sequential randomization involves repeatedly randomizing at a specific instance based on participant's current state or context (referred to as *decision point).*[23] In our JITAI, the *decision point* is when an EMA survey is completed and our well-validated machine learning algorithm determines that lapse risk is elevated. In our MRT, participants will be randomized to an intervention option *at each decision point*. As a result, each participant can be randomized hundreds of times over the course of the study. This repeated randomization increases the efficiency of the research because it requires fewer participants to achieve sufficient power to detect the proximal main effect of an intervention.[22]

A.5 By testing theory-driven interventions, with established acceptability and feasibility, we will advance the behavioral science of dietary lapse etiology and prevention specifically, and non-adherence, more generally. Because dietary lapses are relatively understudied, it is not known which theory-driven approaches to behavior change will be most effective for preventing lapse during heightened risk.[26,27] To further advance our understanding of dietary lapses and how to address them, we will examine the impact of 4 theoretically distinct, yet compatible, empirically-supported interventions for adherence: Enhanced Education, Autonomous Motivation, Self-efficacy, and Self-regulation. The MRT will provide important data about the role of each theory-driven intervention in preventing lapse, and how these roles may change over time and throughout different contexts.[23] For example, if an intervention designed to foster motivation is effective in reducing the proximal outcome of dietary lapses and this effect is moderated by whether a participant is in active treatment or follow-up, we can determine that motivation is an important momentary factor contributing to adherence *especially during no-treatment follow-up*. In addition to informing a data-driven JITAI, results of this MRT will advance the science of adherence more generally by directly comparing the immediate effects of multiple behavior change theories repeatedly over the course of a behavioral (obesity) treatment.[17]

Design and Overview.

We will conduct a MRT to evaluate the effects of 4 theory-driven interventions, generic risk alerts, or no intervention, on the immediate occurrence of dietary lapse (primary outcome) over 6 mos. All participants (N=159) will receive 3 mos of online BOT+JITAI followed by 3 mos of JITAI-only. This allows us to test the JITAI both during active BOT treatment and no-treatment follow-up. Up to 275 participants will be recruited to account for possible drop-out and unusable data, thus ensuring that we obtain 159 evaluable participants. The use of MRT, with hundreds of randomizations and observations of the outcome per participant, allows us to compare the effects of each intervention condition on the outcome with full statistical power. This would not be feasible in a traditional RCT with between-subjects randomization to 6 conditions and many fewer observations of the outcome.

Data from the MRT will inform an optimized JITAI that selects the theory-driven approach most likely to counter lapse risk in a given moment, to be tested in a future RCT that will establish the efficacy of the JITAI for improving clinical outcomes (e.g., weight, diet, eating behaviors and CVD risk/severity).

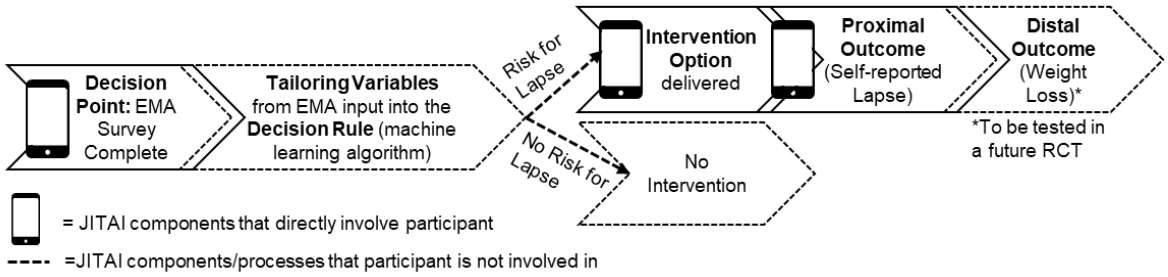
Rx Weight Loss (RxWL): The Online Behavioral Obesity Treatment Used to Test the JITAI. We define dietary lapse as "specific instances of non-adherence to one or more BOT dietary goals or eating behaviors." Thus, interventions targeting lapse must be tested within the context of BOT. Our well-established RxWL program will serve as the BOT in this study. The RxWL program has already been refined and validated in multiple prior NIH-funded trials (e.g., RC1 HL100002; R18 DK114715; R18 DK083248) and can be used in this project at low cost with no further development. The RxWL program is based on self-regulation theory, which promotes behavior change via goal setting, monitoring of progress, problem-solving, and self-incentives.[43] RxWL consists of: (a) 12 weekly multimedia lessons for training in behavioral weight loss skills; (b) online tools for self-monitoring weight, diet, and physical activity; and (c) weekly automated text-based feedback on progress to date. Participants are given a goal of losing 1-2lbs per week to achieve a total weight loss of ≥10%

of initial body weight. Participants are prescribed a calorie goal of 1200-1800 kcal/day tailored on initial weight. Participants are given guidelines to follow a low-fat or Mediterranean diet to meet the prescribed calorie goal.[44-46] Participants are given a physical activity goal tailored on initial activity level that gradually increases to 200 min/wk of activity, emphasizing brisk walking as the primary form of activity.[47] They also receive a primer in self-monitoring weight, diet, and physical activity. Participants are instructed to self-monitor and follow the prescribed diet for the 6-month study period.

RxWL teaches behavioral strategies for healthy eating and physical activity (based on the approached used in the DPP and Look AHEAD trials) via weekly 10-15 minute interactive multimedia lessons. Lessons are interactive to improve patient engagement; they incorporate video, animation, audio, quizzes, and exercises for goal setting, planning, and problem-solving.[48] Example topics include restaurant eating, changing the home environment, and obtaining social support.[49,50] Participants submit daily values for weight, caloric, and physical activity minutes at least weekly to the RxWL platform. In response, participants will receive a weekly automated feedback (delivered in the form of text appearing on the platform). The RxWL feedback messages are generated automatically by comparing participants' self-reported values to their goals for weight loss, caloric intake, and physical activity minutes. Participants receive praise for meeting goals; if goals are not met they receive strategies to improve weight loss, along with encouragement. Because dietary feedback is based on *average weekly caloric intake*, RxWL feedback is distinct from intervention provided within the JITAI, which focuses on specific dietary lapses triggers occurring at specific moments in time. To provide an integrated treatment experience, mentions of the JITAI, it's importance, and how best to benefit from it (e.g., timely completion of EMA surveys and use of interventions delivered via JITAI during times of heightened lapse risk) have been added to the online lessons and feedback messages. To ensure adequate engagement with RxWL, automated email reminders are sent to participants who have not visited the platform on a given week.

JITAI for Dietary Lapses. Our JITAI for dietary lapses follows the conceptual framework by Nahum-Shani and colleagues.[51] Per their framework, the components of a JTAI include decision points (times at which an intervention decision is made; in this case, when an EMA survey is completed and lapse risk is heightened), tailoring variables (information that is used at a decision point to decide when and how to intervene; in this case information on lapse triggers submitted via EMA), decision rules (algorithms of deciding which intervention option to offer, for whom, and when), intervention options (in this case, one of 4 theory-informed interventions, a generic risk alert, or no intervention), proximal outcomes (behaviors targeted by the JITAI, in this case dietary lapse) and distal outcomes (health conditions that are expected to improve as a result of targeting proximal outcomes, in this case, weight control, CVD risk/severity, to be evaluated in a future RCT). Below we describe the components of our JITAI in greater detail. See Figure 1 for a conceptual model of JITAI components and how they work together to provide real-time adaptive intervention.

Figure 1. Conceptual Model of Just-in-time Adaptive Intervention (JITAI) Components



C.4.a Decision Points. A decision point is a time at which an intervention decision is made.[51] In our JITAI, an intervention decision is made following the completion of each EMA survey. EMA is well-suited to inform the decision points within our JITAI because measurements of tailoring variables (see **Tailoring Variables C.4.b**) can be repeated over time in the changing context of everyday life,[12] thus informing multiple opportunities for assessment and intervention. PiLR Health will prompt participants via vibration and audible tone to complete self-report EMA surveys. Participants will be prompted to complete a survey semi-randomly near 6 anchor times throughout the day (9:00am, 11:30pm, 2:00pm, 4:30pm, 6:00pm, 8:30pm). Participants are given 90 minutes to respond to an EMA survey before it expires. Based on prior studies,

participants will complete approximately 4 surveys per day, lasting no more than 60-90 seconds each (~70% of EMA surveys). Participants find this protocol to be tolerable, and it provides sufficient information to predict the majority of lapses.[19,20] Given that there are 6 daily EMA surveys, there are 6 decision points each day in which an intervention *could be provided*. However, randomization to an intervention option will only be triggered at a subset of decision points in which an EMA survey is completed *and* lapse risk is judged to be elevated.

C.4.b Tailoring Variables. A JITAI tailoring variable is participant information that is used to decide (a) when to intervene (i.e., help define the decision point), and/or (b) how to intervene (i.e., which type of intervention to administer).[51] The tailoring variables used to determine *when* to intervene in our JITAI have been identified and tested across 3 prior studies. Specifying tailoring variables began with an extensive literature review that revealed 21 hypothesized behavioral, psychological, and physiological triggers for dietary lapse.[20] These 21 tailoring variables were assessed via EMA in 2 pilot tests of our protocol.[5,19] We then used variable selection procedures to identify tailoring variables that meaningfully contribute to lapse prediction. These analyses identified 17 tailoring variables that were necessary for predicting dietary lapse.[40] A third pilot study confirmed that these 17 tailoring variables are feasible to assess via EMA and suitable for predicting lapse within our proposed JITAI (see **Measures**).[40] Our Exploratory Aim seeks to identify other tailoring variables (e.g., contextual moderators) to refine our JTIAI by explaining *how* to intervene under specific risk conditions.

C.4.c Decision Rule. The decision rule identifies a current state of vulnerability and specifies when it is appropriate to offer intervention.[51] The decision rule is enacted at each decision point and is based on the tailoring variables (triggers for dietary lapse). Our prior work has revealed that it would be nearly impossible to employ a static, simple decision rule for all individuals (e.g., if cravings > [threshold], then recommend intervention) because there is substantial individual variability in which tailoring variables, at which thresholds, and at which times indicate a heightened state of lapse risk.[3,5,52] We therefore chose to utilize machine learning to inform our decision rule because of it can accommodate the highly personalized, and swiftly changing nature of associations between the identified tailoring variables and dietary lapse.[20,53,54]

Using Machine Learning to Inform the Decision Rule: Machine learning involves the development of computational systems (e.g., algorithms) that can learn from their experiences over time.[55] There are many different machine learning approaches that can be used depending on the research question. Below we describe the key features of our algorithm that enable a data-based and personalized JITAI decision rule.

- The decision rule for our JITAI is data-based, i.e., informed by our prior work on factors that predict dietary lapses. We used supervised machine learning, a type of machine learning in which an algorithm uses previously collected data on tailoring variables to predict lapse by modeling the function of these tailoring variables.[56] We used our data to train several different algorithms to predict dietary lapse and tested their accuracies on a previously unexamined validation data subset.[55] This process revealed that ensemble classifiers,[57] a series of C4.5 decision tree algorithms,[58] predicted the likelihood of reporting a lapse at the next EMA survey (in approximately 2-3 hours) with high levels of accuracy. Supervised machine learning is a powerful tool because it built our algorithm from existing data, thus allowing a data-based JITAI decision rule despite the lack of theoretical models to guide in-the-moment lapse prediction.
- The decision rule for our JITAI is capable of individual personalization because the algorithm adapts to new data entered by the participant. Our prior research indicates that lapse behavior and its antecedents are highly variable across participants,[5] which may necessitate personalized intervention.[51,59] Specifically, we found that an algorithm based on data from the group tends to poorly predict a single participant's lapses.[5] However, entirely individualized algorithms tend to take a long time to learn based on a single participant's behavior and once they do there is concern for overfitting.[5] The solution we have developed and evaluated is to combine group- and participant-level data, allowing the JITAI to start with a base algorithm comprised of data from our previous trials, and then continuously adapt itself to the individual via incoming participant data.[19,20]

Application of the Decision Rule: The machine learning algorithm that drives the JITAI decision rule is written using R code and embedded into the PiLR Health server. At the decision point, the tailoring variables from a participant's EMA survey are uploaded to the PiLR Health server that processes the data using the above-described algorithm. The algorithm then predicts, based on these data, whether or not a user will lapse in the following 2-3 hours. If the prediction for lapse is "yes", then the participants will be randomized to one of 6 intervention conditions in the MRT (i.e., 4 theory-driven interventions, generic risk alert, and no intervention). If the prediction for lapse is "no", then nothing will be done at that time because the participant is not in a state

of heightened lapse risk. The algorithm-informed decision rule, and the procedures for applying the decision rule have been evaluated across three pilot studies and are therefore ready for use in the proposed study.

C.4.d Intervention Options. In the proposed MRT, a participant is randomized to 1 of 6 intervention options (4 theory-driven interventions, generic risk alert, and no intervention). The intervention options in a JITAI should be theoretically and/or empirically driven and target the proximal outcome.[51] A major limitation in our work to date is that our intervention options have not been based on a priori selected theories that are specific to models of adherence behavior. This has precluded us from using theory or empirical data to guide *which type* of intervention should be delivered *in a specific moment* to have the greatest possible effect on risk of dietary lapse. We propose to improve upon our prior work by using an underlying conceptual model of adherence behavior to guide the theory-driven intervention options to be evaluated in this MRT.

Conceptual model underlying selection of the theory-driven intervention options: The intervention options in the proposed JITAI are based on the Information-Motivation-Strategy (IMS) model, which takes a simple but comprehensive approach to exploring factors that influence adherence behavior.[60] The IMS model extends and is grounded in several health behavior models (e.g., Health Belief Model, Theory of Planned Behavior);[61] it has also been validated for explaining adherence behavior via meta-analytic reviews and large-scale trials.[60,61] The IMS model offers three broad categories of intervention to improve adherence: **Information** (i.e., providing education on factors that influence adherence and treatment goals), **Motivation** (i.e., motivating participants to carry out treatment recommendations via self-efficacy and aligning personal values), and **Strategy** (i.e., strategizing with participants to ensure capability and ability to adhere). We selected the IMS model to guide the intervention options for the proposed JITAI because IMS: a) has been empirically validated for adherence behavior; b) can flexibly incorporate theory-driven interventions with empirical support for dietary adherence specifically; c) encourages tailoring within the categories, making it consistent with the JITAI framework; and d) is practical and easy to interpret. Figure 2 illustrates how the IMS model informed the intervention options to be tested in our JITAI.[60] Intervention options met several important criteria to be selected for inclusion. Criterion #1: The intervention option could be implemented on a momentary basis (i.e., distilled into a few minutes' worth of intervention delivered via mobile phone). Criterion #2: There was prior literature showing that the intervention option has been associated with dietary adherence. Criterion #3: The intervention option was compatible with the base RxWL program; Criterion #4: The intervention options could not involve contradictory recommendations due to sequential randomization.

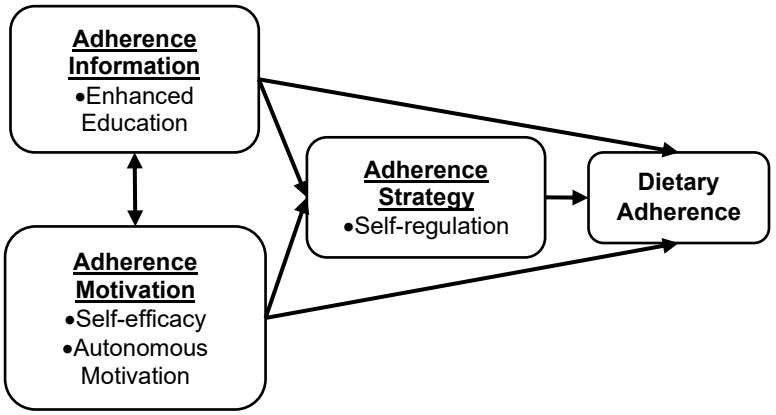


Figure 2. Information-Motivation-Strategy Model informs JITAI Intervention Options

Description of theory-driven intervention options and comparators: Each intervention option is designed to have the highest impact while minimizing burden. The content is brief, and interactive where possible (i.e., prompting participant responses, presenting video content, etc).[18] Intervention options are pushed to the participants via PiLR Health platform and available through the participant's personal smartphone. The BOT program (RxWL) teaches participants the basic skills required for dietary adherence (i.e., facilitating self-monitoring, creating dietary goals, teaching basic skills for self-regulation, problem-solving, goal-setting).[62] Therefore, these intervention options are meant to remind participants to employ skills that they have already been taught and/or use easy-to-digest new strategies to facilitate engagement in behavioral skills. Each category lends itself to a variety of specific intervention strategies, and we have therefore created a **library of brief intervention "modules"** that can be administered in any order when a participant is randomized to receive a theory-driven intervention. Varied modules presented to the participant will facilitate long-term engagement via reduced repetition and encourage well-rounded skill development.[63,64] If a participant is randomized to a theory-driven intervention option, a module will be randomly selected from that option.

- **Enhanced Education (Information).** The *Information* category of the IMS model highlights the importance of participant knowledge.[60,65] Providing education, particularly on dietary recommendations and the health-

behavior link, has improved dietary adherence among participants with CVD risk.[66,67] In particular, the "Teach-back" method,[68] which has been shown to improve dietary adherence,[69,70] aims to increase participant understanding of disease information by asking them to repeat back key points. Therefore, our Enhanced Education intervention option seeks to: 1) enhance understanding of personal health-behavior links, 2) improve health literacy by checking the adequacy of participant understanding, and 3) remind participant of important elements of BOT dietary goals. Each module consists of three parts. First, participants are notified of the top three tailoring variables that are contributing to heightened lapse risk according to the JITAI's machine learning algorithm. This is possible through variable selection techniques in which our algorithm selects a subset of the most relevant predictors used within a predictive model.[20] While it has not been used this way previously, no additional development is necessary to provide this level of personalization in the proposed project. Second, the module reminds participants of their dietary goals (i.e., "Remember that the experiences that you have during the day can contribute to off-track eating that can take you over your daily calorie goal"). Third, the module finishes with a 3-question quiz (with response feedback) related to important elements of dietary adherence and the health-behavior link. We have designed 5 different modules with rotating dietary goals messages with accompanying quizzes. This intervention option is expected to improve dietary adherence by enhancing participant insight into their own behavior and reminding them of important health goals.

- **Self-Efficacy (Motivation).** The *Motivation* category in the IMS model posits that participants' confidence in their ability to change behavior (i.e., self-efficacy) is essential for adherence.[60] This is consistent with the large body of obesity research, including Dr. Lora Burke's self-efficacy-based BOT,[71] that shows self-efficacy is associated with improved weight loss[72] and adherence to dietary recommendations.[73] This intervention option is based on Dr. Burke's approach, which is a multi-component intervention for increasing self-efficacy. To provide variety in this intervention option and limit time spent in a single intervention, we split the components into independent modules that either prompt: 1) attainable intention setting related to dietary adherence (e.g., "I will focus on eating mostly fruits/vegetables in my next meal/snack in order to take back control of my eating"); 2) barrier identification for adhering to dietary goals along with a brief problem-solving exercise; 3) devising a small self-reward; OR 4) self-assessment of thoughts/behaviors that could interfere with dietary adherence in the next several hours with coping strategies (e.g., stimulus control, social support). Each independent module is sufficiently impactful because it builds on strategies already covered in the RxWL program. This intervention option is expected to facilitate dietary adherence by improving self-efficacy in moments of heightened lapse risk, which will enhance motivation and ability to engage in adherence strategies.
- **Autonomous Motivation (Motivation).** Another central tenant of the *Motivation* category is beliefs about the value of engaging in a behavior (e.g., risks, benefits, and efficacy).[74-76] Motivational Interviewing (MI) is an effective and widely used strategy for improving and maintaining motivation for health behavior change,[77] including dietary adherence.[78] This intervention capitalizes on core components of the brief MI intervention used by Dr. Delia West to improve outcomes in BOT.[79] To provide variety in this intervention option and limit time spent in a single intervention, we split the components into independent modules that either: 1) guide participants in identifying values related to weight control (e.g., longevity, quality of life, being a role model) and connect those values to their behavior in the current moment.; 2) use a collaborative non-judgmental approach to explore the consequences of letting barriers drive behavior (e.g., "Take a moment to consider the effect on your longevity if you let your preference for sweets determine your behavior."); 3) prompt participants to identify reasons for change, thereby eliciting "change talk"; OR 4) engage participants in a brief self-assessment of motivation for dietary adherence (i.e., "On a scale of 1-10, how important to you is it to stick to your dietary goals today"). Each module is sufficiently impactful because each represents a separate strategy within the MI model for promoting change.[77] This intervention option is expected to facilitate dietary adherence by increasing the salience of participant beliefs about the importance of their dietary goals.
- **Self-Regulation (Strategy).** The final category in the IMS model, *Strategy*, posits that participants must have the capacity and the ability to adhere.[60] The capacity to adhere, specifically to self-regulate dietary intake, depends on the ability maintain awareness of adherence.[80,81] This is consistent with a self-regulation approach used by Dr. Wing (Co-I) in prior BOT studies.[82-84] Dr. Wing's approach encourages self-regulation via prompts

to intensify self-monitoring, which is known to improve dietary adherence.[85-88] We have developed 4 independent modules that prompt self-monitoring and self-awareness efforts: 1) advise participants to record everything that they eat *before they eat it*, with attention to eating in the subsequent few hours; 2) use the "traffic light" model to enhance awareness of dietary intake.[89] This module provides the traffic light categories of foods (i.e., green=healthiest choices, yellow=sometimes choices, and red=rare choices), and asks participants to check-off foods that they intend to eat vs. stay away from in the next few hours; 3) advise participants to track portion sizes carefully and provide a portion size guide that is available to them until the following EMA survey; OR 4) provide a tutorial on noticing hunger/satiety cues and slowing down rate of eating,[90] with an experiential exercise for use during their next eating episode. This intervention option is expected to facilitate the necessary self-regulation strategies required for dietary adherence via improved self-monitoring of diet and hunger/satiety in the hours preceding a possible dietary lapse.

- **Generic Risk Alert (Active Comparator).** The generic risk alert intervention option will be used as an active comparator to the theory-driven intervention options. The generic risk alert controls for the potential impact of receiving a simple push notification, such as heightened awareness of behavior. Participants will be notified that the JITAI algorithm has determined heightened lapse risk in the following 2-3 hours (i.e., "We have detected that your risk of lapsing from your weight loss diet is higher than usual and may require attention.").
- **No intervention (Inactive Comparator).** A no intervention option will be used as an inactive comparator to the theory-driven intervention options and the generic risk alert. Randomizing to no intervention controls for the potential impact of being notified of heightened lapse risk, which could activate any preexisting coping mechanisms. Randomization to this condition involves NO notification that lapse risk is elevated.

C.6 Micro-randomized Trial. The purpose of the 6-month MRT is to optimize a JITAI for dietary lapses by evaluating the effects of 4 theory-driven interventions on the proximal outcome of dietary lapse as compared to active and inactive comparators. The 6-month study period is acceptable and feasible because participants are willing to engage with the JITAI, and they will be compensated for their time. Participants (N=159) will receive 3 months of online BOT+JITAI followed by 3 months of JITAI-only. The MRT includes sequential randomization to intervention options each time the JITAI identifies heightened lapse risk. Participants will complete an orientation session, either in-person at the research center or via the online video chat forum Zoom, followed by baseline, 3-month, and 6-month assessments. The primary outcome is dietary lapse (assessed via EMA). The secondary outcome is objectively-measured eating characteristics (via wrist-watch device at assessments). We will also assess contextual moderators (i.e., location, time of day, active BOT/follow-up, trigger type) for our exploratory aim. JITAI engagement, satisfaction, and weight will be used for descriptive purposes.

C.6.a Participants. We will recruit men and women with overweight or obesity (body mass index 25-50 kg/m^2), aged 18-70. Eligible participants will have been diagnosed with one or more CVD risk factors (prediabetes, type 2 diabetes, hypercholesterolemia, or hypertension). Exclusion criteria are: health problems that preclude weight loss or physical activity, currently pregnant or breastfeeding, currently or recently (< 6 months) enrolled in a commercial weight loss program, weight loss of ≥ 5% of their initial body weight in the last 6 months, currently taking weight loss medication, surgical procedure for weight loss, or history of a clinically diagnosed eating disorder excluding Binge Eating Disorder. We expect that 81% of participants will own a smartphone that can be used for this study.[91] If a participant does not own a smartphone, he or she will be lent one for the study duration. See section 2.2 Eligibility Criteria of the PHS Human Subjects and Clinical Trials Information.

C.6.b Timeline for Treatment. From 2012-2019, we recruited >500 participants/year for online BOT. Thus, we have demonstrated an ability to meet large recruitment targets. Participants will be recruited on a rolling basis (~6-7 participants/month) until the target N=159 is reached. Drs. Goldstein and Thomas have recruited at this rate in other similar recent trials (F32 HL143954, R01 DK095779). The 4-year grant provides sufficient time for data analysis & manuscript preparation with buffer for delays.

C.6.c Recruitment. Participants will be recruited via advertisements in local media (e.g. newspapers, radio) and targeted online advertising (e.g., Google AdWords); flyers and advertisements posted in waiting rooms and exam rooms in primary care offices used in Drs. Goldstein (PI), Thomas, and Wing's (Co-Is) previous studies; informational materials made available as part of the health and wellness program for employees in the Lifespan heath system and hospital network (an approach used in a previous trials); and direct mailings. . Potential participants will also be identified through the Lifespan Healthcare System electronic records. Individuals who may be eligible based on preliminary criteria (age, Body Mass Index, cardiovascular disease diagnosis) will be identified through electronic medical record/chart review and contacted via electronic mailing address and/or home mailing address. Minority participation will be increased via ads in newspapers with high circulation in minority communities. Recruitment flyers will also be sent to agencies serving minority groups. We will use online advertisements on local websites that are popular with men and minority groups. We consistently find that these approaches maximize minority and male recruitment.

C.6.d Screening and Orientation. Interested individuals who respond to advertisements will be given a brief description of the study and will be screened by phone or by online screener using Lifespan's secure REDCap website to determine initial eligibility. For potential participants who are identified through the Lifespan Healthcare System electronic medical record review, Blind Carbon Copy email will be used to ensure patient confidentiality is maintained in the context of 'batch emails'. A two-person verification system will be used where one staff member will prepare the email using the BCC option. Prior to sending, a second staff member will review and confirm that the BCC option is being used appropriately. Individuals who complete the online screener, will be contacted via phone or email to provide any necessary clarifications to their screening questions and proceed to the next step of enrollment. Those who are eligible will be invited to an orientation, either in-person at the research center or via the online video chat forum Zoom, where the study will be described and informed consent obtained. Individuals who decide to complete the orientation via Zoom will be sent a consent form to their home address before the call. Only after the consent form is signed and returned will any further study procedures be completed. After consent is obtained, participants will complete baseline questionnaires, either by paper surveys or using Lifespan's secure REDCap website, and they will complete food diaries and EMA for 1 week before their baseline assessment (which will last approximately 1 hour). If a participant elects to use a paper questionnaire, and does not wish to be present at the research center, the questionnaire will be sent to the participant's home address. Participants must complete >70% of EMA surveys and 7 days of dietary self-monitoring to move forward with the remainder of study procedures. Height, weight, demographic information and weight history will be collected at the baseline appointment, either by a study staff, cellular scale, or self-report. Objective data collection will be the priority, so if a participant elects to attend their assessment via Zoom, cellular scales may be mailed to the participant's home address. Participants will be asked to wear the Actigraph device to measure eating behavior (see **Secondary Outcome Measure** section for more details) for two weeks following the baseline appointment. The participant will be given the Actigraph device in-person after the baseline assessment, or by mail to their home address if they choose to attend the assessment via Zoom (the device will be mailed back to the study team or dropped off in-person). During the baseline appointment, participants will be provided with a calorie and physical activity goal, overview of the program, and tutorial for using the smartphone app and online program. Participants will be asked to complete similar assessments at 3 months and 6 months.

C.6.e Micro-randomization. The PiLR Health system server will micro-randomize the delivery of interventions at each decision point (i.e., when a participant is determined to be at risk for lapse after completing an EMA survey). The randomization is independent of prior randomizations and the participants' responses to previously delivered interventions for lapse.[23] Based on our prior research developing this JITAI,[19] the algorithm predicts heightened states of lapse risk approximately once per day. The once/day estimate is representative of an *average* across participants and we have demonstrated there is substantial individual variability to these data; heightened states of lapse risk can range from 2.75/week to 12/week and fluctuate over time.[19] As such, while the estimated average is once per day, the prediction algorithm within the

proposed JITAI ensures that intervention is provided *in exact moments of individual need* – which is not static within or between individuals – thus reducing participant burden and improving potency of intervention. Our methods are therefore a considerable improvement to providing general daily reminders. Based on these data, intervention options will be randomized an average of 180 times for each participant. Given our primary aim of comparing the immediate, proximal effect of intervention (as compared to no intervention), interventions will be randomized based on the following probabilities: 0.4 no intervention (inactive control), 0.12 to generic risk alerts (active control), 0.12 to Enhanced Education, 0.12 to Self-efficacy, 0.12 to Autonomous Motivation, and 0.12 to Self-regulation. As such, a given participant will receive no intervention at approximately 72 randomization points over the study and 107 (~21-22 each) randomization points will be divided equally among the remaining 5 intervention options.

C.6.f Assessments. Participants will complete assessments with a research assistant (who does not need to be blinded due to sequential randomization) at baseline, 3, and 6 months, to complete the measures described below. All three assessments may all be completed either in-person at the research center, or via the video chat forum Zoom. During the baseline assessment, participants will receive training in how to use the JITAI and RxWL systems. Each participant can earn up to $300, paid in either in cash, check, or gift cards during the MRT. Participants can earn up to $14 ($1 per day) for wearing the ActiGraph >10 hrs per day over two weeks and will receive $16 for completing the study assessment (for a total of $30 per study assessment). Participants will be able to earn $1 per day for responding to >70% of the EMA surveys within the JITAI (up to $180). Lastly, participants can earn a bonus $5 per month for consistent overall adherence to EMA surveys (averaging >80% completed surveys for the month).

C.6.g Primary Outcome Measure – Dietary Lapses. Dietary lapses will be assessed via EMA embedded within the JITAI (see section **C.4.a Decision Points**). Because EMA is better at capturing naturalistic eating and lapse behavior than lab-based tasks,[7,92] it is considered to be the gold-standard measurement for dietary lapse and has been used in our previous trials.[3,9,93] Participants will be asked at each EMA survey to report if they have experienced a lapse since the last survey. Lapse is defined as any "eating or drinking likely to cause weight gain, and/or put weight loss/maintenance at risk". Participants who report lapses will be asked to record the time of day that the lapse occurred. Participants will be asked "how would you describe the lapse?" and can select all that apply of the following options ("I ate a larger portion of a meal or snack than I intended", "I ate when I hadn't intended to eat", "I ate a type of food that I intended to avoid", "I ate too quickly"). Participants will be trained on reporting dietary lapses at the baseline visit, and re-training will occur at 3- and 6-mos visits.

C.6.h Secondary Outcome Measure – Objectively-measured Eating Characteristics. Wrist-based accelerometers will measure frequency of eating, duration of eating episodes, rate of eating, and estimated caloric intake. The goal of including objectively-measured eating is not to distinguish lapse episodes from non-lapse eating (the focus of the PI's F32 award), rather to examine the effects of the intervention options on eating behaviors that we would not otherwise capture via self-report (e.g., longer duration of eating,[94] slower eating,[95] more regular eating pattern[96]). Participants will wear the ActiGraph GT9X Link (ActiGraph, LLC, Pensacola, FL, USA) on their dominant wrist for 2 weeks at each assessment point (baseline, 3- and 6-mos). The ActiGraph uses a 9-axis accelerometer to detect the wrist-roll motion of food being brought to the mouth. Dr. Hoover (Co-I) has developed eating detection and characterization algorithms that use these data to estimate the number of bites taken during a meal with 86% sensitivity.[14] The algorithms also infer the timing and duration of eating with approximately 89% accuracy,[97,98] which (in combination with a bite estimate) can be used to calculate rate of eating.[97] Dr. Hoover also uses multiple regression to estimate kcals/bite based on age and gender, which can then be used to estimate of energy intake with low error (71.21 ± 562.14 kcals) when compared to objective intake.[99]

C.6.i Other Measures - JITAI Tailoring Variables and Contextual Moderators Used in Exploratory Analyses. The following tailoring variables will be measured via EMA (see section **C.4 JITAI for Dietary Lapses** for protocol and previous validation studies): hunger, cravings, missed meals/snacks, presence of

tempting food, urges to eat, socializing (with and without food), watching television, mood, negative interpersonal interactions, seeing advertisements for food, hours of sleep, fatigue, confidence, planned eating, boredom, cognitive load (i.e., amount of tasks with cognitive difficulty), and alcohol consumption.[40] The following contextual moderators will be used to further refine the finalized intervention delivery algorithm within the optimized JITAI: location (self-reported via EMA), type of lapse trigger (self-reported via EMA, see tailoring variables above), and whether participant is in active BOT or no-treatment follow-up. Time of day will be automatically collected by PiLR Health and used as a tailoring variable and contextual moderator.

C.6.j Other Measures – Engagement and Satisfaction. Engagement with the JITAI will be assessed via PiLR Health and EMA. PiLR will automatically timestamp: EMA surveys completed, interventions delivered, interventions accessed, time spent viewing interventions, and degree of engagement (e.g., responses to content). After an intervention is delivered, the next EMA survey will assess engagement (i.e., "To what degree did you implement the advice given at the prior intervention notification?") and satisfaction (i.e., "To what degree did you find the advice given at the prior intervention notification helpful?") with the intervention content.

C.6.k Other Measures - Participant Characteristics. Demographics, health and weight history will be assessed at baseline. Weight will be measured to the nearest 0.1 kg using a digital scale at each assessment; height will be measured to the nearest millimeter with a stadiometer at baseline, using standard procedures. Measurements will be made in light indoor clothing without shoes. If a participant elects to not be present at the research center, height and weight may be self-reported or the participants will be mailed a cellular scale that will transmit their weight both in a remote and secure manner. Height and weight are measured solely for descriptive purposes and to be used in reporting.

C.6.l Other Measures – Moderators and Mediators of Intervention Efficacy. The following measures will be administered at baseline, 3-month, and 6-month assessments due to the potential influence of these constructs on intervention efficacy: the short form of the Behavior Rating Inventory of Executive Function-Adults questionnaire (a 34-item inventory that assesses executive function), the weight and shape concern questionnaire (a 1 item questionnaire that assesses the degree to which concern about weight and shape influences self-perceptions), technology familiarity and attitudes (an 22-item questionnaire to assess how participants feel towards technology), the Three-Factor Eating Questionnaire (an 18-item questionnaire to assess dysregulated eating behaviors), and the short-form of the Weight and Eating Self-efficacy scale (WEL-SF; a 20-item scale that assesses levels of confidence in making behavior changes related to weight loss).

C.6.m Maintaining Engagement and Compliance. Ensuring long-term engagement and compliance is a priority. First, interventions are delivered immediately and present-focused,[100] thus ensuring utilization in the context of everyday life.[101] Second, interventions are an adjunct to strategies provided in RxWL, thus maintaining an optimal level of challenge to generate interest yet avoid frustration by being easy to navigate.[102] Third, the MRT necessitates that the intervention content will be varied, which enhances engagement and prevents fatigue.[64] Participants will be paid for completion of EMA with bonuses for high overall engagement. This procedure ensures adequate data to assess our proposed aims. Participants who have <50% EMA completed during weekly data checks (see Statistical Design and Power), will receive an e-mail notice from the PI. Those who are consistently below the threshold in a given month will receive a phone call from the PI.

C.7 Optimizing the JITAI – Application of the MRT Results. The final stage of the project period will involve conducting the proposed analytical plan to optimize and finalize the JITAI for dietary lapse. The results of the study will be used to adjust the machine learning algorithms within the JITAI to prepare for a traditional RCT. For example, intervention delivery will no longer be randomized, and the intervention empirically determined to have the greatest effect under the current risk conditions will be administered.

C.8 Scientific Rigor and Reproducibility. This proposal represents a robust and unbiased experiment that clearly matches the research aims, with strong promise to advance the science of dietary adherence. We have

described our steps to ensure scientific rigor such as an a priori power analysis, plan for addressing missing data, broad inclusion criteria to maximize diversity, and sequential randomization procedures.

C.9 Biological Variables (Including Sex). The proposed project accounts for biological variables in the provision of intervention (via JITAI), research design, and analysis & reporting plan. The JITAI algorithm that informs intervention incorporates static biological variables such as sex, age, and baseline body mass index. The analytical plan includes sex, age, and body mass index as covariates to estimate their impact on dietary lapse and eating characteristics. Results of these analyses will be communicated in the final project reports.

STATISTICAL DESIGN AND POWER

Sample Size Considerations

We calculated the sample size requirements for the project based on the analyses proposed in Aim 1 (primary analysis) and Aim 2 (secondary analyses). The sample size was calculated according to the procedures for powering micro-randomized trials described in Liao and colleagues,[22] which have been implemented in an online sample size calculator available at https://pengliao.shinyapps.io/mrt-calculator/. Sample sizes calculated in this way enable robust treatment effect estimation using the centered and weighted least square method.[104] This method estimates treatment effect parameters in the model, and it enables inclusion of covariates to reduce noise without incurring bias in the treatment effect model. Like GEE and multi-level models, the centered and weighted least square method accommodates nested nature of the data (decision points nested within participants), and the associated within-person correlation in the outcome.

We calculated power based on the 180-day study duration, and the finding from our preliminary work that individuals were found to be at risk of lapse on average once per day.The once/day estimate is representative of an *average* across participants and we have demonstrated there is substantial individual variability to these data; heightened states of lapse risk can range from 2.75/week to 12/week and fluctuate over time.[19] As such, while the estimated average is once per day, the prediction algorithm within the proposed JITAI ensures that intervention is provided *in exact moments of individual need* – which is not static within or between individuals – thus reducing participant burden and improving potency of intervention. Our methods are therefore a substantial improvement to providing general daily reminders.

With the *average* once per day lapse frequency, we estimate that participants will average 180 decision points over the course of the trial during which he/she can be randomly assigned to intervention options within the just-in-time adaptive intervention (JITAI). We assume a constant 100% availability for intervention randomization when a participant is determined by the JITAI to be in a heightened state of lapse risk because he or she will have just completed an ecological momentary assessment (EMA) survey (indicating that they are near the smartphone and able to engage).

Aim 1. Aim 1 will examine the effect, averaging over time, of providing a JITAI intervention option (generic risk alert or one of 4 theoretically driven interventions) vs. the JITAI 'no intervention' option on dietary lapses. Based on our preliminary data, we are assuming a standardized effect size of .153 for the contrast of providing a JITAI intervention option vs. the JITAI 'no intervention' option. This effect size is equivalent to reducing lapses by an average of 2 lapses per week, with standard error of 3.27, which corresponds to a clinically meaningful effect. Our prior work showed that using our JITAI was associated with reducing lapse by an average of 2 lapses per week, which corresponded to an *additional 2% weight loss* in a 10-week mobile behavioral obesity treatment. Extrapolating this estimate to a 6-month behavioral obesity treatment indicates that reducing 2 lapses per week would enable an *additional 5.2% weight loss* (which is a clinically significant benchmark for weight loss in and of itself,[103] and especially important in the context of a reduced-contact online behavioral obesity treatment program without lapse intervention that produces a modest average of 5% weight loss). As such, we powered the MRT to detect the minimum effect of reducing 2 lapses/week, although we expect the standardized effect between no intervention and any intervention option could be much stronger.

With the projected N=159 (powered by Aim 2, which involves comparison between specific intervention options as described below), we estimate that we will have at least 90% power to detect the specified effect for this aim with type 1 error rate of .05 and a constant probability of providing an intervention option of 0.6.

Aim 2. Aim 2 will examine the differences between the effectiveness of theory-driven JITAI intervention options and generic risk alerts, on immediate, proximal outcome of dietary lapse. Based on our preliminary data, for this contrast we are assuming a standardized effect size of .1. This effect size is equivalent to reducing lapses by an average of 1 lapse per week, with standard error of 3.27, which corresponds to the minimum clinically significant effect of an intervention option as compared to another intervention. For example, if a theory-driven intervention option prevented roughly 26 more lapses than a generic risk alert, that condition would be helping the participant achieve an *additional 2.6% weight loss* in a 6-month online behavioral obesity treatment. We have identified this effect as the minimum clinically important difference, as only 50% of participants in our online behavioral treatment achieve >5% weight loss; therefore, a single intervention option conferring an additional 2.6% of weight loss on average would substantially boost the proportion of participants achieving meaningful weight losses to ~60-70%. We believe our study is adequately powered because a lesser effect would not be clinically significant. Importantly, we are powering on the minimum clinically significant effect, and expect that the observed standardized effect between intervention options could be much higher.

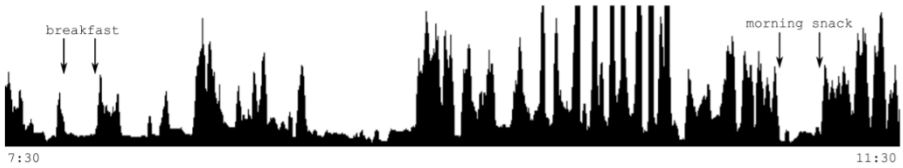
To calculate the required sample size for the contrast between intervention options based on a single theory-driven intervention and generic risk alerts, we use the reduced number of decision points for those two alternatives. Given that both generic risk alerts and each of the theory-driven intervention options are provided with a constant .12 probability, the total number of decision points that can be used to detect the contrast between one type of theory-driven intervention and generic risk alert is 180 * .24, or 43 decision points. Assuming a constant availability of 100% (as above), and that intervention options among these 43 decision points would be provided with a constant .5 probability, the required sample size to detect this contrast at 80% power and type 1 error rate of .05 is 106. Inflating this number by 50% to account for the binary nature of the proximal outcome, we arrive at the required sample size for Aim 2 of **159 participants**. Given that this project is a JITAI optimization trial and that analyses in Aim 2 are secondary, we will not formally control for multiple comparisons, but we will make claims about any findings from this Aim with appropriate caution.

Statistical Analysis

Data Management. Dr. Goldstein (PI) will oversee data management procedures to ensure safe transmission and storage of data, as well as maintain good data quality. Data from the JITAI (EMA, engagement in intervention options) will be stored on an encrypted hospital server. As described in the Research Strategy, a secondary outcome of the proposed micro-randomized trial is objectively-measured eating characteristics via wrist-worn accelerometer (ActiGraph). ActiGraph data will also be stored on an encrypted hospital server. The PiLR Health platform includes tools for real-time reports and data visualization, including protocol adherence. The EMA automatically validates self-report surveys as they are entered to reduce errors. During the initial month of data collection, the PI will review the data weekly to ensure their adequacy and to address any problems. These data checks include procedures for ensuring that micro-randomization (as described in the Research Strategy) is being appropriately executed by PiLR Health. For the remainder of the study Dr. Goldstein (PI) will perform the same review monthly, providing the investigative team with a summary. Data from PiLR Health will be backed up and stored on a monthly basis throughout the project. At the conclusion of data collection, data collected by PiLR Health (i.e., EMA and JITAI engagement) will be cleaned and checked prior to completing the below-described statistical analysis plan. ActiGraph data must be processed and reduced to infer eating characteristics for the secondary outcome assessment.

Processing ActiGraph Data to Infer Eating Characteristics. A secondary outcome of the proposed micro-randomized trial is objectively-measured eating characteristics via ActiGraph. We will use Dr. Hoover's previously validated machine learning algorithms to identify meaningful features of real-world eating behavior (i.e., timing, frequency, duration, rate of eating, and estimated caloric intake) from the ActiGraph data output.[97] A smoothing equation using Gaussian-weighted distribution will be applied to the raw data to reduce the effects of noise. Wrist motion energy will be characterized by the total amount of motion from smoothed data. Peaks in wrist activity (which are critical for identifying eating behavior) will be identified automatically using a custom peak detector developed by Dr. Hoover. Peaks will be used to assist in classifying the start and stop times of eating throughout the day (see figure to the right). Classification of eating will be determined using a naïve Bayes net classifier using four previously validated sensor features (i.e., manipulation, linear acceleration, amount of wrist-roll motion, and regularity of wrist-roll motion). Once eating episodes are classified, we will be able to calculate rate, duration, and frequency of eating. Estimated caloric intake will be evaluated using Dr. Hoover's bite detection algorithm based on the velocity of wrist-roll motion and demographics such as sex and body mass index.[98]

Using peaks in wrist activity to detect eating episodes



Preliminary analyses. Statistical analysis will follow good practices for the evaluation of randomized controlled trials as embodied in the CONSORT statement.[105] Missing data will be imputed using a multiple imputation approach and outcome models averaged across imputations to adhere to the intent-to-treat principle. We will compare the sensitivity of the findings to alternative methods for handling missing data (see **Missing Data** section below). Preliminary analyses will include descriptive statistics and exploratory graphing for all variables of interest measured at all assessment points. We will carry out initial exploratory data analysis to identify outliers such as measurement and recording errors, logical inconsistencies in data and values extreme in the marginal distributions of the variables in questions. Key baseline variables (e.g., baseline BMI, age, sex) will be considered for use as covariates in the analyses described below.

Aim 1. Consistent with Aim 1, we will *"evaluate the effects of any intervention (i.e., theory-driven or generic risk alert) versus no intervention on the occurrence of lapse, in each moment when lapse risk is predicted to be high".* To examine the effect of any intervention (4 theory-driven interventions and generic risk alert conditions) versus no intervention on the occurrence of lapse (via EMA), we will model the probability of lapse occurrence over time using generalized multilevel models.[106-108] This analysis approach is selected to allow for increased power, ability to account for hierarchical data structure (repeated measures nested under participants), and inclusion of all participants regardless of missing data at particular time points.[109] Whether or not intervention is provided at a decision point will be used to predict individual participant's lapse occurrence probability at the following decision point. The estimated coefficient for the indicator represents the overall (average, across all time points) effect of delivering any intervention versus providing no intervention on lapse occurrence probability. Restricted maximum likelihood will be used to estimate model parameters and to test the significance of random effects. In addition, we will add an interaction between the indicator and the index of the day on which the corresponding decision point occurs (i.e., day in the study) to the generalized multilevel model described above. This approach has been recommended in the literature[41] and takes into consideration that the intervention effect is likely to be not evenly distributed over time. The interaction term allows us to examine the linear time trend of the intervention effect. Additionally, we will conduct similar analyses to test the intervention effect on objectively-measured eating characteristics using multilevel models.

Aim 2. Consistent with Aim 2, we will *"compare the effects of theory-driven interventions and generic risk alert on the occurrence of lapse".* To better understand the individual interventions, we will conduct generalized multilevel models to examine differences in intervention effects separately for the five interventions (i.e., four theory-driven interventions and the generic risk alert). Five indicator variables will be used separately to represent whether each of the five interventions is provided at a decision point. This approach allows us to compare the average effects of the 4 theory-driven intervention options vs. generic risk alerts on lapse

occurrence probability.[41] The comparison among the five interventions will be indirectly informed by their estimated effect sizes. Restricted maximum likelihood will be used to estimate model parameters and to test the significance of random effects. Additionally, interactions between the five indicators and day in the study will be added to the models to test the linear time trends in intervention effects. Multilevel models will be conducted in a similar fashion to compare the effect of each of the five intervention conditions to no intervention on eating characteristics.

Aim 3. Aim 3 proposes to "*use the data from the micro-randomized trial to finalize an optimized algorithm for intervention delivery that will drive the JITAI in a future RCT examining the effects on overall weight change in an obesity treatment program."* Aim 3 will involve application of statistical analysis only – no new participant data will be collected. Findings from Aims 1 and 2 will be used to inform the most effective intervention for preventing lapse occurrence. Findings from our exploratory aim (below) will inform which interventions should be delivered dependent on a particular context. For example, if enhanced education is found to be effective only in the afternoon, our optimized algorithm generated from this study will be able to select what intervention to deliver at a decision point given the time of day. The new intervention delivery algorithm generated by Aim 3 will be programmed in R and will operate in tandem with the current lapse prediction algorithm. The complexity of the algorithm is to be determined and dependent upon analyses of the micro-randomized trial; if indicated by the MRT results, we plan to utilize models that are minimally computationally intensive and easy to interpret (e.g., regressions, decision trees). The resulting algorithm will be dynamic and personalized by taking into account baseline variables (e.g., sex, age, race/ethnicity, baseline BMI), specific trigger types as well as contexts (e.g., location, time of day). As such, the finalized JITAI will have optimized decision rules for intervention delivery, so that intervention options are provided at times and in contexts that maximize their effectiveness and minimize user burden.

Exploratory Aim. Consistent with our exploratory aim, to "*examine contextual moderators (e.g., time of day, location) of intervention effects"*, potential moderators (i.e., time of day, location, active treatment/follow-up, trigger type) will be added to the models described in Aims 1 and 2. Moderators will be allowed to interact with the intervention indicators, to determine whether these variables moderate the effect of intervention on primary and secondary outcomes. The moderator will be considered significant if the interaction term is significant. Statistically significant interactions will be interpreted by plotting simple regression lines for each level of categorical variables or for high and low values of continuous variables. This portion of the analysis will help us determine whether the interventions are more effective for certain contexts than others.

Missing Data

Analyses will be on the intent-to-treat sample (every instance of micro-randomization and subsequent intervention delivery will be included in the final analysis) under various assumptions about the missing data mechanism. Sensitivity to these assumptions will be tested. Specifically, we will gather follow-up information and reasons for dropout regardless of protocol completion and censor at the point of loss. We will compare the robustness of our findings using three statistical approaches for handling missing data. First, we will use a multiple imputation approach to impute missing outcomes. Next, we will use inverse probability weighting with propensity scores. This is a two-step method: 1) using logistic regression, the probability of missingness is modeled as a function of baseline covariates and baseline values of the outcome and 2) the inverse of the propensity scores (predicted probabilities of dropout from the first step) serve as weights in our regression model of the outcomes. Provided the data are missing at random (MAR) or that the probability of missingness can be fully explained by observable data, this approach produces asymptotically unbiased estimates. To allow for the possibility that the MAR assumption may not hold, we will also use a third approach, pattern mixture models, in which the distribution of the outcome is assumed to follow a mixture of two distributions: one for those who complete follow up and another for those who do not.

E. PARTICIPANT CONFIDENTIALITY AND DATA STORAGE

In general, we will follow all guidelines outlined by our Institutional Review Board for protecting participant confidentiality in research studies. Participant data confidentiality will be protected through a multi-tiered approach including data collection, data transmission, data handling, and data distribution processes to ensure anonymity both during and after the study. Participant information collected by the research staff will contain only a non-identifiable study ID. A separate form linking study ID and participant identifiers (name, address, contact names and addresses) will be maintained in a locked file stored in an encrypted form.

Additional safeguards are in place to protect participant data collected via sensor devices and electronic forms on smartphones. These data are stored temporarily on the smartphone, but are regularly transmitted to encrypted secure storage on PiLR HEALTH servers. Thus, in the event that a subject's smartphone is lost or stolen, it is very unlikely that a participant's confidential data would be compromised. Data transmitted via smartphones is also heavily encrypted by mobile phone carriers to prevent interception (e.g., from the smartphone to PiLR HEALTH servers). As an additional safeguard, no personally identifiable information will be stored or transmitted via the smartphone. All participant smartphone data will be coded using a unique identifying number. As noted above, any electronic data collected by study staff will be stored in an encrypted form (with a randomly generated 26-character key).

In accordance with NIH Policy on Data Management and Sharing (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-23-053.html), a completely de-identified dataset from enrolled, consented participants will be uploaded to a generalist public data repository (such as Open Science Framework, maintained by the Center for Open Science, or Dataverse, maintained by Harvard) and/or NIH data repository as mandated by the funder (National Institute of Heart Lung and Blood Institute). Data will be stripped of identifiers (participants will be identified using anonymized study identification number, no free text data will be included) and of all dates (i.e., EMA surveys and objective eating characteristics will be numbered and labeled by day in the study [e.g., Day 1, Day 2]dates of observations will be removed, no raw sensor data will be included). The dataset, in the form of a CSV or Excel file, will contain: participant identification number, participant responses to EMA surveys about eating and behavioral, psychological, and environmental factors associated with eating (see "Daily Smartphone Survey Questions" in All Questionnaires attachment), which interventions participants were micro-randomized to and metadata associated with randomization (e.g., risk level), and aggregate objectively-measured eating characteristics inferred from the ActiGraph Link data (i.e., bites, eating rate, duration of each detected eating episode), basic demographic information (including anthropometric information), and summary scores on questionnaires (Technology Acceptance Scales, Three-Factor Eating Questionnaire, Weight Efficacy Lifestyle questionnaire, Weight and Shape Concern question, General Technology Attitudes, Behavior Rating Inventory of Executive Function- Adult). In accordance with procedures that have already been outlined and approved by the funder (see Data Sharing attachment in "NIH Grant Application" in Package 1), the dataset in the repository will be password protected. Researchers can only access the password upon contacting the PI and signing an agreement that: 1) they list all researchers who will have access; 2) they will only use the data for research purposes; 3) they describe their analytic plan and research questions to the research team; 4) they will commit to securing the data using appropriate technology; 5) they will destroy their copy of the data after analyses are complete; 6) they will not share the data with others who are not listed as having access; 6) they will not attempt to identify any of the individual participants.

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