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Title: **Just-In-Time Adaptive Interventions for Addictive Behaviors (JITAI)**
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A. Précis

Background. Our research group has made extensive use of ecological momentary assessment (EMA) to understand people's daily experiences with opioid craving, use, and lapse. We have also administered clinic-based psychotherapies such as cognitive-behavioral therapy (CBT), in which clients learn to avoid, escape, resolve, or reframe problems (such as stress) that can trigger lapses to drug use. CBT contrasts with ACT (Acceptance and Commitment Therapy), a mindfulness-based approach in which difficult thoughts and feelings are viewed as necessary and potentially valuable components of a full life, to be experienced observantly rather than resolved or reframed. CBT and ACT can and do coexist in a single treatment plan, but we know of no systematic attempt to reconcile their differences. We have also not tried to administer either of them on a mobile device.

Objective. To test a just-in-time adaptive intervention (JITAI)—a treatment given when and where it is needed. Our JITAI will be delivered via smartphone app and will combine elements of two widely used treatments for addiction: CBT and ACT. Our goal is *not* to bring another branded app onto the market, but rather to clarify when and for whom the generic components of such apps are effective or not. This will include determining when CBT is more helpful than ACT and vice versa.

Participant population. Outpatient adults who are in treatment for opioid use disorder (OUD)—up to 185 enrolled (35 for a formative-interview phase, 150 for a trial) for a target of 115 evaluable (30 interviewees, 85 trial participants). Target enrollment will include 40% women and 60% minorities (mostly African-American). In the trial, some participants will receive buprenorphine in our clinic, and others will be receiving buprenorphine or methadone elsewhere; this is a procedural matter, not a component of the experimental design.

Experimental design. After a formative-interview phase, the study will be run as a microrandomized trial that will also include a conventionally randomized between-groups clinical-trial component. In microrandomization, interventions are randomized at the momentary level within person; the effect is measured proximally (e.g., 20 minutes later). This is a powerful way to assess the effects of different interventions administered in the field and to examine "strategy-situation fit," i.e., whether interventions are differentially effective under specific momentary circumstances. We are powering our study mostly to detect (1) any effect of CBT or ACT versus control moments with no intervention given, and (2) preferential advantages of CBT over ACT, and vice versa, as a function of the participant's ability to control (change, escape) a given situation. The between-groups aspect of the design (JITAI group versus EMA-only control group) is needed to demonstrate an effect of our JITAI on traditional, distal measures of outcome, such as reductions in opioid use.

Methods. In the formative-interview phase, we will conduct interviews with people in treatment for OUD who express interest in using a mobile treatment app. We will ask them about day-to-day challenges they currently face in maintaining progress toward their treatment goals, and ask them what might be helpful. Then we will show them item lists, onscreen mockups, and/or functional demos, and we will ask interviewees to comment on the app's likely usefulness, its likely pitfalls, and how we could improve it.

In the clinical trial, participants will be randomized to one of two groups (JITAI vs. EMA-only control). During weeks 1-2, all participants will have baseline assessments of coping styles and personality, and all JITAI participants will be shown a video introducing basic concepts of CBT and ACT. For weeks 3-10 (8 weeks), participants will carry smartphones for EMA with or without JITAI. During week 11, participants will be readministered some of the

assessments from baseline. Participants receiving buprenorphine from us will then be offered a dose taper or encouraged to transfer to continued treatment elsewhere. All participants will come to our clinic thrice weekly for urine testing throughout participation.

Primary outcome measures: (1) Proximal effects of CBT and ACT messages in the JITAI group: decreases over 20-minute intervals in craving and negative mood, with increases in self-efficacy; (2) strategy-situation fit in the JITAI group; (3) group differences in distal effects of treatment (week 11 versus week 2) in terms of self-efficacy and coping flexibility.

Secondary outcome measures: (1) Trait predictors of differential responses to CBT and ACT, in the JITAI group; (2) group differences in frequency of opioid-positive urine over time; (3) time courses of responsiveness to ACT vs. CBT, in the JITAI group; (4) whether the intervention types that benefit participants most when "pushed" by the app are the same ones participants choose when subsequently given the opportunity to "pull" interventions.

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C. Background

1. From mobile assessment to mobile treatment: a microrandomization approach

Anyone who has struggled with addiction, or who has seen the struggle firsthand, knows that recovery and relapse are, to put it technically, dynamic processes (Shiffman, 2005; Van Zundert et al., 2010; Shiyko et al., 2012)—or, to put it in more human terms, processes complicated by frequent and messy changes, often occurring in a matter of moments. Those momentary changes are bound up with events in the physical and social environment. But until recently, life at the momentary level was not amenable to collection of quantitative, statistically aggregable data—or to the systematic application and immediate evaluation of interventions.

That situation improved when one form of addiction, nicotine dependence, began to be studied with ecological momentary assessment (EMA), an electronic method for ambulatory monitoring of behavior and mood (Shiffman et al., 1996). Our research section completed the first large-scale EMA studies in people being treated for addiction to heroin and cocaine, with results that both confirmed and challenged common wisdom (Epstein et al., 2009; Preston et al., 2009; Epstein et al., 2010; Epstein & Preston, 2010; Preston & Epstein, 2011; Epstein & Preston, 2012; Kennedy et al., 2013; Phillips et al., 2013b; Furnari et al., 2015; Preston et al., 2016).

EMA is, as its name suggests, a technique for assessment, not treatment. The self-monitoring required by EMA may produce some behavioral change, a phenomenon called *reactivity*. But reactivity to EMA in addiction is not robust or consistent (McCarthy et al., 2015). Mobile *interventions* need to be implemented purposefully. We have taken small steps toward mobile interventions, such as having participants watch HIV-education videos on smartphones (Phillips et al., 2013a) and issuing daily reminders to complete treatment tasks (Willner-Reid et al., 2016). We now intend to harness the full potential of mobile interventions, using what are called *just-in-time adaptive interventions* (JITAIs). A JITAI is an intervention given only when and where it is needed—e.g., a craving-reduction exercise delivered via smartphone app, either because the user requested it or because an automated system detected a risk of craving (Nahum-Shani et al., 2016).

JITAIs, and mobile interventions in general, do add value to standard treatments for behavioral, psychiatric, and medical problems: a meta-analysis showed an overall effect size of $d = .27$ (95% CL .04 to .50) for "mobile + standard treatment" versus "standard treatment

alone," in terms of the primary outcome measure for each of 25 clinical trials. The effect was especially large when the targeted problem was an addictive disorder such as nicotine or alcohol dependence (d = .50, 95% CL .26 to .73) and when the intervention was implemented as a smartphone app (d = .57, 95% CL .28 to .85) rather than as text messages (d = .31, 95% CL .11 to .53) (Lindhiem et al., 2015).

Nonetheless, in reviewing the literature on JITAIs, we have found that even thoughtfully designed apps may produce very modest results, with high rates of user attrition and only small benefits for the users who do not drop out (e.g., Ploderer et al., 2014). We think there are two main reasons for this, and we intend to address them in this protocol.

First, user engagement tends to be low when users are left on their own to acquire and run the treatment app (e.g., Chittaro & Vianello, 2016). Online-store downloads have not proven an adequate substitute for clinician/patient contact. We think some initial training is needed before an app can begin to assume some of the functions of a clinician, and we will provide that in this protocol—but only to a degree that we think would be practical for community clinics.

Second, there is very little information to guide the design and implementation of a mobile-treatment app for addiction (or any other indication). Existing theories of addiction do not deal in detail with the momentary dynamics of behavior (Riley et al., 2011). Existing treatments for addiction were developed for delivery during scheduled office visits (or inpatient stays) that are spatially and temporally separated from the ambulatory episodes of risk during which they will be needed. Although cognitive-behavioral therapy (CBT) does emphasize that clients should practice recovery-related skills at the appropriate times and places, there are no tested guidelines for matching any specific type of intervention to any specific daily-life situation, nor any established criteria for declaring success. In this protocol, we will address these issues with a clinical trial that incorporates a new kind of design, microrandomization.

Microrandomization, as described by EMA researchers Klasnja and colleagues (2015), is a within-subjects experimental design in which the unit of randomization is the event rather than the person. Each time a mobile intervention is to be delivered (typically several times per day for each person), a random assignment is made among different possible interventions. Outcome is assessed proximally—that is, shortly after the moment of the intervention. The purpose is to collect a kind of measurement that, until now, has never been available: a

measurement of the extent to which a momentary intervention has the immediate effect (for example, an increase in self-efficacy in the context of a stressor) that is theorized to mediate its distal effect (for example, an enduring reduction in relapse risk, as would be assessed in a conventionally designed clinical trial). Microrandomization has precedents in more qualitative "alternating treatments" approaches for single-participant studies (Barlow & Hayes, 1979), but was specifically developed to be compatible with newer forms of inferential statistics, providing strong power to detect very small proximal effects (Liao et al., 2016).

By starting with a microrandomized trial, we can determine which types of momentary intervention are most effective in which contexts. This is the most logical transition from our EMA work (in which we gave no momentary interventions) to trials of more precisely targeted JITAIs.

2. Momentary interventions to be tested in the first arm of this protocol

In selecting the types of intervention to test, we were guided by two considerations. First, there are already hundreds of mobile-health apps purporting to help treat addiction, both in the scientific literature and in the Apple and Google Play stores, with varying degrees of support for their effectiveness. Second, there are, to our knowledge, no published studies using microrandomized designs, and therefore no information on the contextual effectiveness of the techniques incorporated into these apps. Therefore, *our priority is not to develop another branded app, but to reach useful conclusions about the generic treatment approaches shared by most of the existent apps*.

The momentary interventions in addiction-treatment apps are usually based on principles of cognitive-behavioral therapy (CBT), or acceptance and commitment therapy (ACT, pronounced *act*). CBT and ACT can best be distinguished from each other as follows.

In CBT, negative emotional states (including craving, which is a negative state for a person who is trying not to use drugs) are viewed as problems to be solved, and the client learns skills to solve them. The skills might include reframing them more positively, finding ways not to dwell on them, or, when possible, taking action to eliminate their cause (Carroll, 1998).

In ACT, negative emotional states are viewed as a necessary and potentially valuable component of a full life (Hayes et al., 2013). When they occur, the goal is not to solve them, but to experience them in an observant, curious, nonjudgmental way—a practice referred to as *mindfulness*. This is the "acceptance" component of ACT (acceptance of all one's thoughts and

feelings, not the situations that give rise to them) and it has been shown to shorten the duration of negative thoughts and feelings (Ford et al., 2017). The "commitment" component of ACT refers to responding to negative situations in a manner consistent with one's highest long-term values. Long-term values might seem to be an unlikely motivator in people with addiction, who are frequently thought to have shortened time horizons, i.e., a relative insensitivity to rewards or punishments that are not immediate (Petry et al., 1998). But time horizons in addiction are modifiable (Snider et al., 2016; Stein et al., 2016), and our read of the ACT literature leads us to suspect that ACT "present-izes" movement toward distal goals, such that people can derive satisfaction from the sheer fact of acting in accord with those goals regardless of what happens in the long term (Hayes & Smith, 2005). ACT has been helpful in treatment of addiction to stimulants, opioids, cannabis, tobacco, and alcohol (Hoppes, 2006; Brewer et al., 2009; Luoma et al., 2012; Chiesa & Serretti, 2014).[1]

Despite the differences between ACT and CBT, proponents of ACT argue the two are compatible (Hayes et al., 2013). One of the pioneers of CBT-based relapse prevention, Alan Marlatt, proposed a (nonmobile) CBT/mindfulness hybrid treatment called "mindfulness-based relapse prevention," which he classified as a CBT-based approach, though he acknowledged that mindfulness-based skills are actually "*meta*cognitive" (Witkiewtiz et al., 2005).

A microrandomized trial provides an excellent opportunity to see how components of ACT and CBT can best coexist in one treatment plan—that is, in what contexts one might be preferable to the other. Some investigators, comparing patient-reported coping strategies in EMA studies of addiction, have concluded that no strategy is superior to any other: the more strategies used at any one time, the better (O'Connell et al., 2007). Others have found evidence for *strategy-situation fit*, such that, for example, cognitive reappraisal of a stressor produces better results when the situation is uncontrollable than when it is controllable (Haines et al., 2016). Tests for evidence of strategy-situation fit will be part of our outcome analyses.

[1] In smokers, a mobile mindfulness-meditation intervention (different from ACT because ACT exercises do not include formal meditation) reduced cravings and negative mood assessed immediately after each meditation, and reduced smoking over two weeks, compared to a results in "sham meditation" participants who were instructed to be *more* judgmental of their experiences (Ruscio et al., 2016).

3. Two ways to deliver a momentary intervention: push versus pull

Apart from the content of the momentary interventions, we need to consider whether they are to be "pushed" at the user (that is, whether the system initiates them without action from the user) or whether they will be available for "pull" access (access on demand). Each of these has pros and cons. A pure "pull" intervention seems likely to be preferred by users, but would introduce between-person variability in treatment exposure that would be problematic scientifically (adding noise to outcome analyses) and perhaps not ideal clinically (undertreating participants who underestimate their own needs or risks). The ideal app would probably use a hybrid push/pull approach.

For us, however, the choice is dictated by our use of a microrandomized design. The developers of microrandomization (Klasnja et al., 2015) are explicit about this: "Microrandomized trials are not suitable for testing of intervention components that are made available to individuals but which individuals access at will. If a researcher wants to microrandomize a pull intervention component (e.g., graphs for providing feedback on a health behavior), that component first needs to be converted into a push intervention (e.g., a notification to access the graphs)." To keep things as consistent across participants as possible, we will start our clinical trial with a 7-week period of pure "push" interventions, with their content microrandomized. This period will also include a conventional between-groups form of randomization such that one group receives only EMA assessments, with no active mobile intervention. We are including this between-groups variable because microrandomization would allow for assessment only of immediate, context-dependent outcomes, not conventionally assessed overall outcomes. We want to examine both.

Immediately after 7 weeks of pure "push" intervention, the app will allow participants to start "pulling" interventions for another week. We expect this to increase participants' satisfaction with the app, and we will use it to address additional issues, such as whether participants consistently pull the interventions that appeared to work best for them when pushed. Research in smokers suggests that app users do not always choose the craving-reduction techniques that are objectively associated with the largest benefits (Heffner et al., 2015). One question we want to address in this protocol is when the user knows best and when the system knows best.

4. Rationale for a multiple-arm protocol

Our plan for this protocol is to have it encompass the testing of multiple approaches to mobile intervention, of which we are now proposing the first. We intend to add new arms in clear, logical steps (via amendments to be sent for additional scientific review as the IRB deems appropriate). We have two major reasons for designing a protocol that is meant to grow: (1) We are currently developing methods that are clear candidates for incorporation into our JITAIs, such as machine-learning models that use participants' GPS tracks and prior EMA entries to predict stress and drug craving 90 minutes into the future. When those methods are ready for field testing, they will fit precisely into the goal of this protocol—to develop precisely timed and targeted mobile interventions. (2) We are frequently approached by potential collaborators who offer new mobile technologies (such as physiological monitoring for stress detection) and new kinds of mobile-intervention content. Piloting those things will also fit precisely into the goal of this protocol.

Research at the IRP stays at the cutting edge because investigators here can be nimble and flexible in the direction of their projects. With this protocol, we want to ensure that we can embody that virtue. Mobile treatments and their means of delivery evolve far more rapidly than pharmacological ones, and a protocol under which we can keep up with them is both good science and good practice.

D. Study objectives

To develop *just-in-time adaptive interventions* (JITAIs) for addiction.

The specific aims of this research are as follows:

1. To develop procedures for delivery of messages in an app that will be tested in an 8-week assessment/intervention trial.
   - *Assessment.* To develop procedures for EMA of craving, self-efficacy, and drug use that can inform JITAIs.
   - *Intervention.* To develop the messages and algorithms that will form the core of a JITAI.
2. To evaluate our JITAI procedures in a microrandomized trial (with a conventionally randomized between-groups component) assessing proximal and distal effects of messages (CBT- or ACT-based) on self-efficacy and craving.

Hypotheses for *proximal* effects of intervention (time scale of minutes or hours):

1. *Main effect of messaging*. Delivery of either a CBT-based or ACT-based message will increase self-efficacy and decrease cravings and other negative states 20 minutes later, compared with the control message ("thank you for your response").
2. *Strategy-situation fit.* The effects of the messages will be moderated by the circumstances in which they are provided (Haines et al., 2016). For example:

- In situations that are under the participant's control, greater proximal benefits will be associated with active CBT strategies such as avoidance or direct action.
- In situations that are largely out of the participant's control, greater proximal benefits will be associated with acceptance (ACT). Some CBT strategies, such as distraction or cognitive reappraisal of the situation (i.e., interpreting a seemingly negative event as a positive event) might also be useful in those situations, but there is evidence that accepting one's own negative thoughts and emotions (an ACT strategy) confers unique benefits beyond those of reappraisal, shortening the duration of negative mental experiences (Ford et al., 2017).

Hypotheses for *distal* effects of intervention (time scale of weeks):

3. *Main effect of intervention.* The group randomized to JITAI will have better outcomes (e.g. less drug use, higher self-efficacy, a greater increase in flexibility of coping styles) than the EMA-only control group when assessed at week 11.
4. *Differential responses over time.* This "distal" effect is really a summary of proximal effects. We and others have found that drug abstinence is delayed after initiation of CBT, as skills become practiced and integrated into daily life (Carroll et al., 1994; Epstein et al., 2003). We hypothesize, however, that CBT messages will be rated as helpful almost immediately, due to their pragmatic, straightforward nature. ACT messages, which are usually more oblique and koanlike, may have to be seen several times, or lived with for several weeks, before being rated as helpful—but may also stand up better to repetition.
5. *Trait predictors of responsiveness*. Like responsiveness over time, this "distal" effect is really a summary of proximal effects. Although we are not powering the study to assess treatment matching at the person level, we will examine whether trait variables such as personality and preferred coping styles are associated with differential responsiveness to CBT-based versus ACT-based messages.

Push versus pull:

6. We will also assess (but have no directional predictions about) whether the intervention types that seem to benefit participants most when "pushed" by the app are the same ones that participants choose when subsequently given the opportunity to "pull" interventions.

E. Study design and methods

In this section of the protocol, we describe the main experimental aspects of the protocol. We defer description of more routine activities to section G, "Clinical and Laboratory Methods."

1. Overview of arm 1

This arm of the protocol will consist of a formative-interview phase and a subsequent clinical trial, both to be conducted at the NIDA IRP. Participants may enroll in one or both phases. The interview phase will require only 3 to 4.5 hours from each participant. The clinical trial, which will start after we analyze all the interview information, will last up to 11 weeks per participant (plus a 5-week optional buprenorphine taper for participants we treat here).

Information from the interviews will probably lead to adjustments in the procedures for the clinical trial, but we are laying out a general plan here.

2. Arm 1, Phase 1: Formative interviews

We will conduct interviews with up to 35 people who use opioids (with the goal of getting usable data from 30) who express interest in using a mobile treatment app. Some of them are likely to be current or past participants in other Archway studies (some may be receiving office-based buprenorphine treatment from our clinic; others will be in treatment elsewhere), but others may be enrolled by word of mouth.

In the first part of the interview, to be conducted by a team member with counseling experience, we will ask interviewees about day-to-day challenges that arise as they try to adhere to their treatment goals, and what might be useful in moments when they are tempted to lapse. The approach is purposefully open-ended because we do not want our prior assumptions about lapse to preclude our gathering of important information about preventing it. Interviewees will not be encouraged to reexperience stress or craving, and if they do, they will not be sent home until they have had time to relax.

In the second part of the interview, we will show the the interviewee our plans (below) for a treatment app, using item lists, onscreen mockups, and/or functional demos. For all that material, we will ask interviewees to comment on its likely usefulness, its likely pitfalls or possible barriers to using it, and how we could improve it. We will also compile a wish list of app features and a list of things we should avoid.

Interviews will be audiotaped, and the tapes will be transcribed by a HIPAA-compliant service.

We have prior experience conducting this type of qualitative research with our participant population (Heinz et al., 2010).

3. Arm 1, Phase 2: Clinical trial with microrandomization

The following table shows the general timeline, which is explained in the sections that follow. *For analytical purposes, there are only two groups (JITAI vs. EMA control)*. Procedurally, some participants will receive buprenorphine here at Archway (OBOT participants) and others will be treated elsewhere (TE participants). The recruitment of both OBOT and TE participants is not intended to bear directly on the science of the protocol; rather, it helps us enroll participants more quickly (our experience in the 020 protocol is that we enroll

an average of 4 OBOT participants and 4 TE participants every 30 days) and, as an additional advantage, may expand the population to which we can generalize our results (though we have not seen any appreciable demographic differences between OBOT and TE participants).

<table>
<tr><th>week</th><th>JITAI (OBOT)</th><th>EMA control (OBOT)</th><th>JITAI (TE: Treatment Elsewhere)</th><th>EMA control (TE: Treatment Elsewhere)</th></tr>
<tr><td>1</td><td rowspan="2">stabilize on bup;
intro session (EMA + CBT/ACT);
baseline questionnaires</td><td rowspan="2">stabilize on bup;
intro session (EMA);
baseline questionnaires</td><td rowspan="2">intro session (EMA + CBT/ACT);
baseline questionnaires</td><td rowspan="2">intro session (EMA);
baseline questionnaires</td></tr>
<tr><td>2</td></tr>
<tr><td>3</td><td rowspan="7">JITAI – push 4x/day
(first 16 nights will also include “Deep Dive” lessons/exercises on smartphone)</td><td rowspan="8">EMA</td><td rowspan="7">JITAI – push 4x/day
(first 16 nights will also include “Deep Dive” lessons/exercises on smartphone)</td><td rowspan="8">EMA</td></tr>
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<tr><td>7</td></tr>
<tr><td>8</td></tr>
<tr><td>9</td></tr>
<tr><td>10</td><td>JITAI – pull</td><td>JITAI - pull</td></tr>
<tr><td>11</td><td>outcome assessment</td><td>outcome assessment</td><td>outcome assessment</td><td>outcome assessment</td></tr>
<tr><td>12</td><td rowspan="5">bup taper or transfer</td><td rowspan="5">bup taper or transfer</td><td rowspan="5"></td><td rowspan="5"></td></tr>
<tr><td>13</td></tr>
<tr><td>14</td></tr>
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<tr><td>16</td></tr>
</table>

Participants in the formative-interview phase may reenroll for the randomized treatment phase. We want to give them access to the potential benefits of the intervention. When we analyze results, we will test whether the interviewed participants respond differently from newly enrolled participants, as might be expected from their having had input into the app design.

After signing informed consent, each participant will be randomly assigned to one of two groups: JITAI intervention or EMA only.

During the first two weeks of participation, each participant will have an in-person session for training appropriate to his or her study group. All participants will be shown how to use the smartphone to make entries. Participants randomized to the JITAI intervention will be introduced to some basic principles of CBT and ACT. We are forgoing extensive in-person training in the hope of demonstrating that our ambulatory intervention can be effective without that. Mindfulness and ACT, like CBT, can be learned through “unguided self-help” (that is, without in-person training) (Cavanagh et al., 2014). A mere 11 minutes of prerecorded audio instruction on mindfulness, delivered in a clinic, was superior to a relaxation control condition

in helping at-risk drinkers reduce their drinking over the next week (Kamboj et al., 2017). We will provide more support: during the initial in-person session, each participant will watch a video introduction to both CBT and ACT. The video will be approximately 20 minutes long, and will be recorded by a counselor who has experience delivering these kinds of interventions for addiction. We will use just one counselor to discuss both techniques to avoid any confounding by participant preference for one counselor over another.

Before and after the video, one of the investigators at our clinic will talk with the participant to address concerns and discuss any material that the participant found unclear. Investigators will also be available to answer participants' questions about CBT and ACT throughout their time in the study, either during clinic visits, or by phone or online.

The content of the video will be underscored and complemented by a series of lessons/exercises that participants will read at home on their smartphone, one per night, for the first 16 nights of the JITAI intervention. We describe the lessons/exercises (to be referred to as "Deep Dives") further down, after we describe the JITAI intervention.

Baseline questionnaires to be administered during the first two weeks will include:

- The FIT-60 (Flexibility Index Test), a standard measure of traits associated with mindfulness (Batink et al., 2016), such as "I observe my feelings without losing myself in them" and "It is OK if I remember something unpleasant," and (reverse scored) "I believe that some of my thoughts are abnormal or bad and that I shouldn't think like that." We will readminister this at week 11 to test the hypothesis that mindfulness scores will increase more in participants randomized to the JITAI intervention group than in participants randomized to the EMA group.
- The DTCQ (Drug-Taking Confidence Questionnaire) (Sklar & Turner, 1999), an 8-item measure of coping self-efficacy in the context of resisting lapses to drug misuse. We will readminister this at week 11 to test the hypothesis that scores will increase more in participants randomized to the JITAI intervention group than in participants randomized to the EMA group.
- The COPE (Carver et al., 1989), a theory-based, empirically validated 60-item questionnaire assessing both general coping styles and coping behaviors in specific situations. We will use this to test whether preferred coping styles are

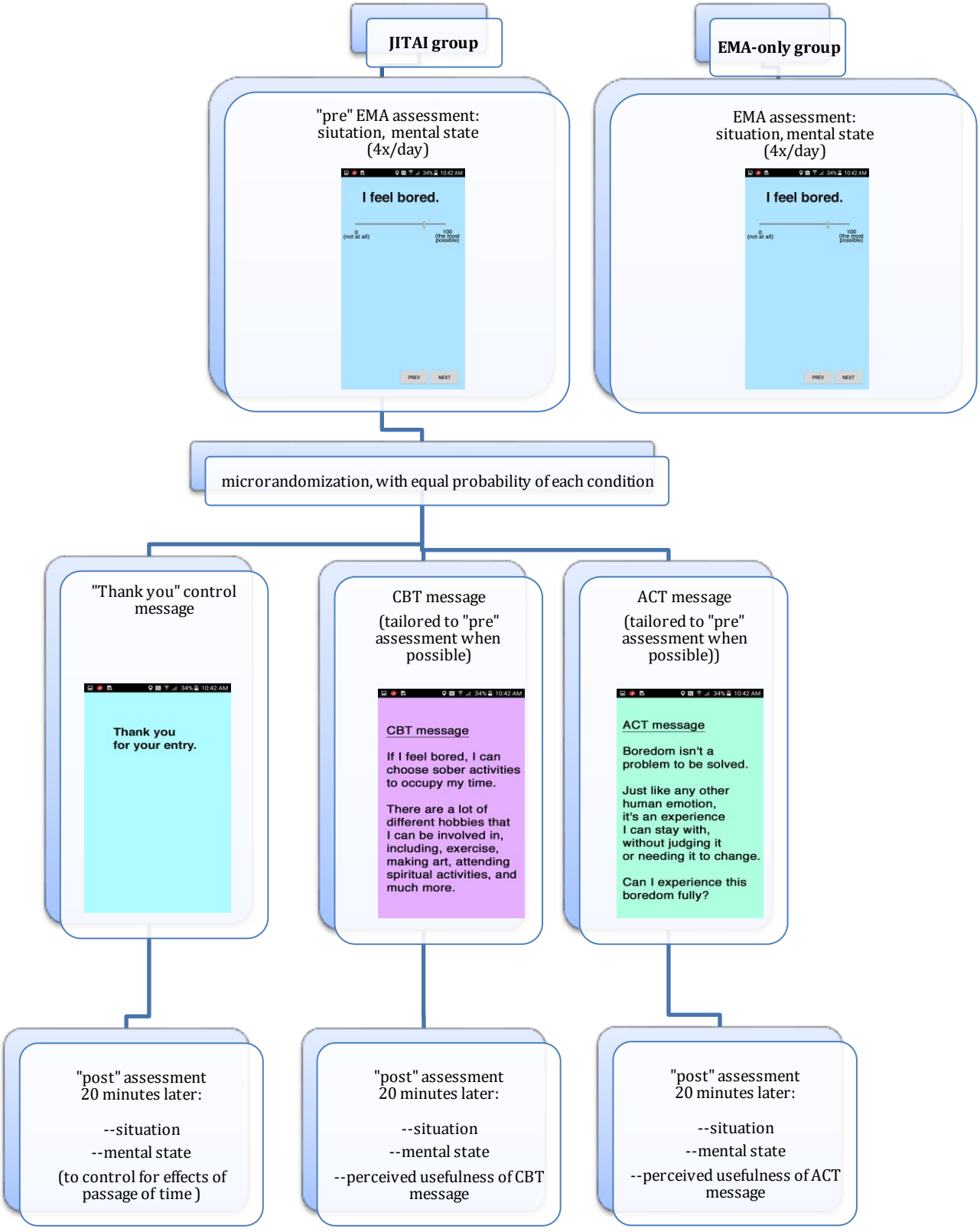
associated with differences in momentary responsiveness to CBT-based vs. ACT-based messages. We will also readminister it at week 11 to test the hypothesis that participants randomized to the JITAI group will begin to adopt a broader range of coping styles than those randomized to the EMA group.

- The Monetary-Choice Questionnaire (MCQ) (Kirby et al., 1999), a 27-item assessment of discounting of future rewards. We will administer this at baseline to test whether people with steep discounting functions are initially resistant to ACT. We will also readminister it at week 11 to test whether participants randomized to the JITAI group will begin to show less discounting.
- The Need for Closure scale (Kruglanski et al., 2013), a 47-item assessment of dislike for ambiguity and uncertainty. We will administer this at baseline to test whether high scorers benefit more from CBT messages than from ACT messages. We will also readminister it at week 11 to test whether participants randomized to the JITAI group (all of whom will be exposed to ACT) will begin to show less need for closure.
- The NEO-PI-3 (McCrae et al., 2005), a standard 240-item personality inventory. Personality traits are not immutable, but to reduce participant burden, we will administer the NEO-PI-3 at baseline only, to test whether any personality traits are associated with differences in momentary responsiveness to CBT-based vs. ACT-based messages.
- The Twelve-Step Participation Questionnaire (TSPQ-21) (Montgomery et al., 1995), a 21-item measure of involvement with self-help groups such as NA. In this protocol, we will neither require nor forbid attendance to twelve-step groups. Twelve-Step principles have more overlap with those of CBT (and perhaps ACT) than is often recognized (McCrady, 1994), but are also different enough to be potentially confusing if offered in combination. We think most participants will use only the parts of Twelve-Step philosophy that resonate with them, in accordance with the Twelve-Step dictum "Take what you like and leave the rest." We will simply assess Twelve-Step involvement at baseline and week 11 so we can check whether it influences and/or is influenced by our JITAI intervention, though we have no firm hypotheses about that.

At the beginning of week 3, we will issue participants a smartphone running our app. All participants will undergo EMA during weeks 3-10. For the JITAI group, those 8 weeks of EMA will be accompanied by momentary interventions: 7 weeks of "push" interventions and 1 week of both "push" and "pull" interventions.

The microrandomized aspect of the protocol—i.e., randomized only at the momentary level, not between groups—will be the content of the interventions in the JITAI group. This will work as follows. Within each day, for each participant, we will designate four one-hour time bands within the participant's typical waking hours, covering morning through late evening. During each of those time bands, the app will push an assessment—actually, a pair of assessments, given 20 minutes apart—with the "pre" assessment followed immediately by either a randomly chosen intervention type or a simple "thank you for your responses."

Thus, the sequence for each push event will follow the **flowchart on the next page**. The flowchart includes mockup screenshots. The "look and feel" of the app will be honed during the formative phase of the protocol, but will be fairly similar to that of the mHealth app developed by the NIDA IRP BIS for our current EMA protocols.


JITAI group
EMA-only group
"pre" EMA assessment:
siutation, mental state
(4x/day)
EMA assessment:
situation, mental state
(4x/day)
I feel bored.
microrandomization, with equal probability of each condition
"Thank you" control message
Thank you for your entry.
CBT message
(tailored to "pre" assessment when possible)
CBT message
If I feel bored, I can choose sober activities to occupy my time.
There are a lot of different hobbies that I can be involved in, including, exercise, making art, attending spiritual activities, and much more.
ACT message
(tailored to "pre" assessment when possible))
ACT message
Boredom isn't a problem to be solved.
Just like any other human emotion, it's an experience I can stay with, without judging it or needing it to change.
Can I experience this boredom fully?
"post" assessment
20 minutes later:
--situation
--mental state
(to control for effects of passage of time)
"post" assessment
20 minutes later:
--situation
--mental state
--perceived usefulness of CBT message
"post" assessment
20 minutes later:
--situation
--mental state
--perceived usefulness of ACT message

For participants in the JITAI group, the content will be as follows:

1. "Pre" Assessment

—"Are you available now?" (If not, allow postponement up to 60 minutes.)

Baseline assessment of mindfulness with 2 items from the CAMS-R (Feldman et al., 2007) as adapted for EMA by Moore and colleagues (2016).
—"I am able to focus on the present moment." (VAS slider 0-100)
—"I am able to accept the thoughts and feelings I have." (VAS slider 0-100)

Baseline assessment of negative mood with items from the PROMIS questionnaire (Bjorner et al., 2014) as adapted for EMA by Moore and colleagues (2016).
—"I feel depressed." (VAS slider 0-100)
—"I feel anxious." (VAS slider 0-100)
—"I feel angry." (VAS slider 0-100)
—"I feel stressed." (VAS slider 0-100)

Baseline assessment of boredom, cue exposure, and drug craving:
—"I feel bored." (VAS slider 0-100)
—"'People, places, or things' are reminding me of drugs." (VAS slider 0-100)
—"I am craving drugs." (VAS slider 0-100; also indicate which drugs)

Baseline assessment of situation category:
—"The best description of my situation right now is…
at home
at work
out doing obligations
out socializing or enjoying myself
other"

Baseline assessment of place:
— The place where I am is pleasant and comfortable (not too hot/cold, noisy, ugly, dangerous, etc.). (VAS slider 0-100)
— "I have privacy right now (or could easily get privacy if I wanted)." (VAS slider 0-100)
— "I could easily be somewhere else right now if I wanted." (VAS slider 0-100)

Baseline assessment of activity:
— "What I'm doing right now is enjoyable for me." (VAS slider 0-100)
— "What I'm doing right now is important to me." (VAS slider 0-100)
— "I could easily get out of what I'm doing right now." (VAS slider 0-100)

Baseline assessment of general self-efficacy:
—"I feel in control of my *responses* to what's happening right now." (VAS slider 0-100)

Baseline assessment of recovery self-efficacy, using an item adapted from Kranzler et al. (2016):
—"I'm confident that I can stick to my treatment goals for the rest of today/tonight." (VAS slider 0-100)

Use of drugs since the previous assessment:
—"I have used an opiate since the previous assessment." (yes/no)
—"I have used cocaine since the previous assessment." (yes/no)
—"I have used other drugs since the previous assessment." (yes/no)

Note: This "pre" assessment will also be given to the EMA-only group four times a day. Everything that follows will be given only to the JITAI group.

2. Microrandomize: CBT, ACT, or a "thank you" control condition:

Some of the responses on the "pre" assessment will be used later, during data analysis, to test hypothesis related to strategy-situation fit (e.g., in terms of situations that are in or out of the participant's control). Some will be used for selection of messages within CBT and ACT conditions, as stated immediately below.

First, the app will randomly choose condition *a*, *b*, or *c*:

(a) "Thank you for your response."

This is a "no intervention" control condition.

(b) CBT message.

When the microrandomly chosen intervention is CBT, the content will be a CBT-based response to the "pre" assessment.

If no problem on the "pre" assessment is rated 50 or above, the app will display a CBT-based message, to be randomly selected from a large bank of such messages. If there is a rating of 50 or above for craving, boredom, anger, or stress, the app will choose a CBT message geared toward the highest-rated problem. Ties will be resolved by random selection of a high-rated problem.

Our initial bank of CBT items (shown in Appendix A) was developed from core sets of items provided by Lorien Abroms, Sc.D., M.A. (who developed and is currently leading an evaluation of the Text2Quit Program for smoking cessation; Abroms et al., 2014; Abroms et al., 2015); and Shawn Costello Whooley, Psy.D. (who was an addictions counselor at our Archway Clinic from 1999-2000 and who is now a practicing clinical psychologist specializing in CBT and ACT). With permission, we may adapt additional content from messages used by Shrier

and colleagues (2014), and from the Check-In app that has been successfully piloted with methadone-maintained outpatients for craving of illicit drugs (Guarino et al., 2016), and from the computer-based CBT4CBT intervention for addiction (Carroll et al., 2014). The final bank of CBT items will consist of those that are rated favorably in our formative interviews.

(c) ACT message.

When the microrandomly chosen intervention is ACT, the content will be an ACT-based response to the "pre" assessment.

If no problem on the "pre" assessment is rated 50 or above, the app will display a general message based on one or more principles of ACT. If any problem on the "pre" interview is rated 50 or above, the app will choose an ACT message geared toward the highest-rated problem. Ties will be resolved by random selection of a high-rated problem.

Our initial bank of ACT items (shown in Appendix A) was developed from a core set of items provided by Shawn Costello Whooley, Psy.D., and from a workbook by Steven Hayes (Hayes & Smith, 2005), who has enthusiastically granted permission. The final bank of ACT items will consist of those that are rated favorably in our formative interviews.

The ACT items and CBT items are intended to be generally distinct from each other, and we will ensure that participants know which is which by consistently color-coding them or using an on-screen banner. We want to minimize potential sources of confusion, one of which would be having to wonder about the context of a message that might have come from either approach.

3. "Post" assessment 20 minutes later

The "post" assessment will consist of the same items that were used in "pre" assessment to assess proximal changes in mindfulness, mood, craving, etc., plus:

If (and only if) a CBT or ACT message was given:
—brief multiple-choice recognition item to document that the message was read and remembered.
—"How useful was the message?" (VAS slider 0-100)

The choice of a 20-minute delay before follow-up is tentative. We want enough time to elapse so that the "pre" situation can play out—e.g., so a drug craving can either pass or become problematic—but not so much time that the "post" assessment is contaminated by new, unrelated events. We may revisit our choice of duration of follow-up after the formative-interview phase.

We are not burdening the EMA-only group with paired "pre" and "post"

assessments because, within the JITAI group, the "thank you" control condition provides the necessary information about effects of the passage of time. The procedures for the JITAI group amount to a complete, self-contained design for assessment of proximal effects. The EMA-only group is included only so we can draw conclusions about overall effects of the intervention at broader time scales.

Evening "Deep Dives" into ACT and CBT. For each of the first 16 evenings, the app will display a more in-depth lesson/exercise for participants in the JITAI group. The display time will have been selected by the participant during the issuing of the smartphone. The participant can "snooze" the "Deep Dive" (reschedule it for later in the evening), but has to read/do it on the scheduled evening. The "Deep Dives" (shown in Appendix B), which should each take approximately 5-15 minutes, will underscore and complement the general teaching on the introductory video. The intention is to provide skill training and philosophical context that will increase the value of the brief daily ACT and CBT messages. "Deep Dives" will alternate nightly between ACT and CBT and will be presented in the same order for all participants. The presentation of lessons in standardized sequence is typical for mobile interventions that include instructional modules. By giving the Deep Dives in the same order for everyone, we can present them more coherently. We think of the 16-night Deep Dive period almost as a psychological analog of a buprenorphine-induction period: at the end of it, every participant will have been titrated up to our targeted "dosage" of concept teaching and skill teaching.

We drew the material for the CBT "Deep Dives" from publicly available sources (such as the NIDA online "toolbox"); we drew the material for the ACT "Deep Dives" from publicly available sources and from a workbook by Steven Hayes (Hayes & Smith, 2005).

We will encourage participants to read/do the "Deep Dives" as scheduled, and we will discharge participants who have not done all 16 within the first 21 nights. That is, we will permit (but not encourage) up to five missed nights, and when a night is missed, the "Deep Dives" will resume with the missed material, adding one night to the total length of presentation.

The "Pull" Period. Participants in the JITAI group who complete the 7-week push period will immediately continue to the 1-week pull period. The pull period will be a superimposition of pull upon of push: push messages and assessments will continue as before, mostly because we want to continue collecting full daily data on every participant. But participants will also be able to initiate (pull) the "Deep Dives" they have already read/done**,** or view messages as

needed. Each time they do so, they will have their choice of: (1) any specific ACT Deep Dive, (2) any specific CBT Deep Dive, (3) an ACT message to be chosen at random by the app, or (4) a CBT message to be chosen at random by the app. Thus, we will be able to assess preferences for both the philosophical approach and the format.

If it is technically feasible, we will give participants access to one additional pull intervention: a "get me out of this" tool, intended to help them extricate themselves from social situations that lead to lapses. When we have interviewed our participants in prior studies to generate personalized craving-induction scripts (Jobes et al., 2015), we have found that one of the more frequent lapse scenarios is a chance encounter with, or phone call from, a friend who casually suggests getting high. We will try to implement a feature that, when surreptitiously pulled by the user, can simulate the arrival of an urgent message (for extrication from in-person encounters) or generate avoidance strategies that the user might not immediately think of (for extrication from phone/online encounters).

EMA data will be transferred wirelessly from participants' phones to servers located at the NIDA BRC under a secure communications system developed by the NIDA Biomedical Informatics Section (BIS). Transfers will be scheduled to occur automatically at least twice a day. Participants will not have to visit the laboratory for these data transfers. If the remote transfers fail, we can manually initiate a wireless transfer when participants make their regularly scheduled laboratory visits. If that fails, we will swap out the participant's phone so BIS can try to recover the data.

During week 11, all participants will be assessed for overall treatment outcome. This will include second administrations of some of the baseline questionnaires (the FIT-60 mindfulness measure, the DTCQ measure of self-efficacy to cope with drug temptations, the MCQ for delay discounting, the TSPQ-21 for Twelve-Step involvement, and the COPE measure of breadth of coping styles). Most other aspects of treatment outcome will be operationalized during data analysis as summary measures from EMA and urine data collected over the course of treatment.

F. Inclusion and exclusion criteria

1. Inclusion criteria

Phase 1: Formative interviews.

The enrollment ceiling is 35 outpatients (to collect evaluable data from 30) who meet these criteria: (1) Age 18-75; (2) physical dependence on opioids (by self-report; can include current agonist maintenance); (3) interest in receiving the types of treatment about which we will be conducting interviews (asked via "fact sheet" on the first day of in-person screening).

Phase 2: Clinical trial with microrandomization.

The enrollment ceiling is 150 outpatients (to collect evaluable data from 85, of whom 50 will be randomized to JITAI, and 35 to EMA control). Treatment may be provided by us in the form of office-based buprenorphine treatment (OBOT) or may be provided elsewhere (Treatment Elsewhere, TE). Participants must meet these criteria:

OBOT participants: (1) Age 18-75; (2) physical dependence on opioids (by positive urine and/or frank opioid withdrawal); (3) interest in receiving the types of treatment we are testing (asked via "fact sheet" on the first day of in-person screening).

Treatment Elsewhere (TE) participants: (1) Age 18-75; (2) receiving methadone or buprenorphine treatment for opioid dependence from a qualified provider in the community; (3) interest in receiving the types of treatment we are testing (asked via "fact sheet" on the first day of in-person screening).

2. Exclusion criteria

Phase 1: Formative interviews. (1) cognitive impairment severe enough to preclude informed consent or valid interview responses (History & Physical and Evaluation to Sign Consent).

Phase 2: Clinical trial with microrandomization.

OBOT and TE participants: (1) History of any DSM-5 psychotic disorder; history of bipolar disorder; current Major Depressive Disorder (MINI structured interview); (2) unresolved symptoms of PTSD that, in the investigators' view, would make it risky for the participant to undertake mindfulness exercises (e.g., observing all one's current negative thoughts and emotions) in an unsupervised setting (MINI structured interview); (3) current dependence on alcohol or sedative-hypnotic, e.g. benzodiazepine (by DSM-5 criteria in MINI structured interview); (4) cognitive impairment severe enough to preclude informed consent or

valid self-report (History & Physical and Evaluation to Sign Consent); (5) Any condition that interferes with urine collection (by self-report, medical records, or physical exam); (6) medical illness (e.g., cirrhosis, nephritic syndrome, thyroid disease, ischemic heart disease, epilepsy, adrenal insufficiency, etc., by self-report, medical records, or physical exam) or medications that, in the view of the investigators, would compromise participation in research.

The exclusion of people with current unresolved PTSD symptoms will apply regardless of whether full criteria for a diagnosis have ever been met. Standard screening on the MINI structured interview will flag those instances, which will be followed up by further questioning from MMG counselors and, as appropriate, consultation between MMG staff and the MAI and/or the Principal Investigator. We will give particular consideration to applicants' stated feelings about whether the JITAI app might be risky for them, but we intend to err on the side of caution.

The exclusion for alcohol or sedative-hypnotic dependence reflects the medical complications of tapering from those substances. We will not automatically exclude applicants who use or have DSM diagnoses involving other substances (such as cannabis). The JITAI intervention, though focused on opioids and cocaine, is likely to be relevant to most drugs of abuse.

G. Clinical and laboratory methods

OBOT participants: We will provide office-based buprenorphine treatment. Participants will visit the clinic at least 3 times a week. If needed, participants can be asked to come in for visits up to 5 times in the first 7 days to help with induction or to establish a pattern of attendance. Participants will receive buprenorphine doses delivered in the clinic, with take-home doses given for the rest of the week. Urine and breath samples will be collected at each study visit under direct observation by trained staff (prior to dosing) during weeks 1-11 and during the optional buprenorphine taper (weeks 12-16). Urine will be tested on site, by dipstick, for drug metabolites; the panel used at Archway currently includes tests for amphetamines, benzodiazepines, buprenorphine, cannabinoids, cocaine, MDMA, methadone, morphine (heroin metabolite), and oxycodone. An aliquot of each urine specimen will be immediately labeled and frozen at -30°C in case additional analyses are needed (e.g., if a result is inconclusive). The drug-test results are used as research data (reflecting one element of treatment response) and to help the Archway counselor assess participants' ongoing treatment needs.

Breath will be tested for alcohol using an Alco-Sensor III (Intoximeter, Inc.; St. Louis, MO). The breath results are used as research data and to help the counselor assess needs; they are also used by the Archway nurses to help determine when a buprenorphine dose should be withheld for safety.

Additionally, participants will self-report recent drug use using a standardized questionnaire on these days.

These procedures will continue through the entirety of the study.

Treatment Elsewhere (TE) participants: Participants will visit the clinic 3 days per week. As these participants are receiving their treatment outside of the NIDA IRP, staff will not be monitoring or dosing methadone or buprenorphine in these participants. Urine testing, breath testing, and self-report will be the same as for OBOT participants, except that an alcohol-positive breath reading cannot affect dosing decisions.

Research vs. Clinical care

We deliver buprenorphine treatment in a manner consistent with standard clinical care. It is necessary to deliver these forms of treatment within our research clinic because the required level of data collection would not be practical outside of treatment delivery or in a community clinic. Urine drug testing is a standard in clinical care; however, the frequency of collection (three times weekly) is greater than in most community treatment programs and is part of the research methodology in this protocol. All other measures are considered part of research.

The weekly counseling session will be delivered by a master's-level counselor at Archway. The focus will be on case management, meaning practical matters such as job searches, housing stability, medical/dental/insurance issues, and GEDs. Participants can also raise emotional issues as needed.

The timeline below is in chronological order (including duration of study, number of visits, and time commitment for participants).

Day 1: Consent and beginning of treatment

Participants will visit the clinic three days a week. Participants will be allowed to reschedule an appointment twice during the study if they miss an appointment or need to come in on an earlier day.

- Participants' buprenorphine will be stabilized during weeks 1 and 2 using flexible dosing under the supervision of the MAI.

Week 1-2: During the first two weeks, participants will undergo training appropriate to their randomized group; for the EMA control group, this will consist only of training on how to do EMA, not video material on CBT or ACT. Participants will also fill out baseline questionnaires, usually on a separate day.

End of Week 2

JITAI/EMA begins. Each participant will be issued a smartphone and reminded how to use it.

Week 11: Discontinuation of JITAI/EMA; outcome assessment.

- JITAI/EMA will end after week 10. Participants will be compensated for return of the smartphone.
- All participants will be readministered some of the baseline questionnaires (as specified above in the questionnaire descriptions) to assess changes in mindfulness, self-efficacy, need for closure, and coping styles.

Weeks 12-16: Optional buprenorphine taper for OBOT participants.

- Participants will be encouraged to and assisted in transferring to a community treatment program for continuation of care. Participants who do not wish to transfer to continued treatment in the community will be tapered from buprenorphine at Archway over 5 weeks with an optional additional 2 weeks if needed to secure transfer or to treat opioid withdrawal symptoms and minimize chances of relapse. At any time during the taper, participants can choose to transfer to another program.
- Transfer of care/continuity of care – Throughout the study, counselors will be engaged with participants about plans for care/treatment/counseling following discharge from the study (i.e., aftercare). Aftercare, of some kind, is always recommended. For those participants who continue to use illicit drugs or who relapse to use, community-based methadone and/or buprenorphine programs are recommended. Participants will be given a list of treatment programs and must initiate the contact. Archway staff will supply the transfer summary and help to coordinate a transfer date. Depending on the participants' input and status, a drug-free counseling center or Narcotics Anonymous (NA) may also be recommended. Throughout their time at Archway, participants have access to lists of alternative and aftercare programs, private MDs as well as applications for financial support, subsidized healthcare, health insurance, job and housing opportunities, etc.
- Due to clinical considerations, taper procedures can occasionally alter the total number

of days in each study phase, and thus in the general timeline of the study. Further, due to the lack of a medication dose ceiling in this protocol and the desire to maximize taper success and participant comfort, the study physician may: (1) hold the medication taper at a given dose, which may add up to 2 weeks to this phase; (2) alter the taper decrement by requesting a specified dose decrease (e.g., decrease buprenorphine by 2mg x 3 days) which will slow the rate of taper and may add up to 2 weeks to this phase; and (3) may prescribe medications for the symptomatic relief of withdrawal signs and symptoms. These medications may include but are not limited to: ibuprofen, acetaminophen, hydroxyzine, dicyclomine, magnesium hydroxide, loperamide, and trimethobenzamide. These clinically indicated steps may add up to 2 weeks to the medication taper, which would result in a maximum total of a 7-week taper. These decisions will be made by the study physician as medically indicated based on withdrawal signs and symptoms and cravings.

Compliance with EMA and JITAI

If an OBOT participant misses 4 appointments, he or she may be discharged with a 21-day taper. Given their shorter length of participation, TE participants can be discharged if they miss 3 visits.

Participants must complete entries for at least 82% of all random prompts. This will be assessed weekly. Participants will receive approximately 28 prompts per week. Missing five entries per week would correspond to a compliance rate of 82.1%. If a participant falls below the 82% completion rate one week, the participant will be reminded of the requirement; if the participant remains below 82% during the next week, the participant will be eligible to be discharged. In the JITAI group, each pair of "pre" and "post" assessments will be counted as part of the same entry; both have to be completed for the entry to be considered completed.

Each participant will have a brief weekly meeting with a study-team member to receive a small payment (discussed in Section S, Compensation) for compliance with EMA requirements, or to be warned that he or she needs to comply with EMA requirements.

Participants in the JITAI group must read/do all 16 "Deep Dive" lessons/exercises within the first 21 nights of the JITAI intervention. Failure to do so will result in discharge.

If the participant is receiving OBOT at Archway, he or she will have a 21-day medication taper and be assisted into transferring to community-based treatment..

Mishaps (lost or damaged smartphones).

Participants who lose or damage their smartphone during the study may be issued another one. ("Damage" is defined as anything that renders the smartphone permanently unusable for study purposes, including a cracked screen.) A second mishap will lead to discharge with a 21-day taper.

At the end of week 10, participants will return the smartphone to us. If this is their first issued smartphone and it is not damaged (as defined above), they may choose to keep it or return it for $300. If this is their second issued smartphone and it is not damaged (as defined above), they may choose to keep it or return it for $100.

Prior to the start of buprenorphine taper, OBOT participants will have the following choices: (a) to remain in the study through the taper phase, or (b) to transfer to another program.

Other procedural issues

Continuation of participants who have been hospitalized or incarcerated during the study: At any given time, it can be expected that several participants will be either hospitalized or incarcerated for short periods. If those participants return to the program immediately after their release, we will re-admit them to Archway after they are medically evaluated to resume. This can result in participants being in treatment for more than 16 weeks.

Because circumstances vary greatly across participants, we have chosen not to adopt a rigid cutoff for the maximum time a patient's participation can be delayed in this way. In the past, our informal cutoff has typically been about two weeks.

During a participant's incarceration, we will follow NIDA IRP procedures regarding research on prisoners: no data will be collected from the participant, and he or she will not be contacted by NIDA IRP staff or Archway staff. However, the participant will be permitted to inform Archway staff that he or she is incarcerated. After the participant is released, he or she will be permitted and encouraged to contact NIDA IRP staff or Archway staff and ask to be continued in the study. We will then decide whether to reactivate the participant, based on scientific and medical criteria.

Collection of data from incarcerated participants will not be an issue, because, like other personal property, the devices will be routinely confiscated by prison authorities upon entry and not returned until the prisoner is released. If the devices are returned to us and they somehow do contain data from time during incarceration, we will delete those data.

On some occasions, initiation of mobile data collection will begin later than scheduled. This typically occurs when the participant cannot meet with the experimenter at the appropriate time to receive the necessary introduction to the experimental condition. In all cases, all data collection will start as close as possible to the protocol schedule.

A 21-day taper will be offered to OBOT participants who choose to withdraw voluntarily from the study. Participants will also be discharged (with a 21-day taper for OBOT participants) if they meet one or more of the following termination criteria: (1) missing 4 (OBOT) or 3 (TE) study visits; (2) on 6 occasions, bringing in a dead smartphone following a missed clinic visit; (3) violating clinic rules; (4) failing to comply with smartphone data collection; or (5) losing or damaging two smartphones. In some cases, where disruptive behavior is a risk to staff or other participants, the OBOT taper may be less than 21 days. Any taper, whether administrative or voluntary, will include take-homes for Saturdays and Sundays.

H. Collection and storage of human specimens or data

Electronic data will be stored on the NIDA IRP's secure, password-protected system of electronic medical records (Clinical Data Warehouse; CDW). Paper records are stored in the Archway clinic under double lock in an area where individuals who are not part of the study staff do not have access (BRC building; room number 01B605). After the study is completed and data have been analyzed, the paper records will be stored at an NIH-approved commercial facility for the storage of sensitive data until approval for their disposal has been given.

Audio from the formative interviews will be sent without identifiers to a HIPAA-compliant professional transcription service. These services typically transcribe medical records. We will not permit the service to keep or share data. We will keep the transcripts indefinitely on secured servers. The audio will be accessible only to investigators and will be deleted when all interview data have been summarized—most likely within a year.

Stored biological specimens will be kept in a secure freezer in the Archway's NIDA freezer room until they are analyzed (BRC building; room 01B405). Specimens may be used for future analyses not described in the current protocol, but only after approval from the IRB. Any unplanned loss or destruction of the samples will be reported by the PI to the IRB.

Participants will be given the option of having their samples destroyed and/or having their data deleted, with the caveat that this might not be possible if the samples or data have already been shared (in an IRB-approved collaboration) with other researchers.

I. Statistical analysis

1. Outcome measures

Formative-interview phase

We are not using standardized questionnaires for the formative interviews, nor *a priori* cutoffs for outcome. Instead, this phase will be an iterative, collaborative process in which interviewees help us determine the extent and nature of changes to the content and interface of the JITAI app. We will replace any content (or interface elements) that multiple interviewees find confusing, unhelpful, or inappropriate. Any changes resulting from the formative interviews will, of course, be reflected in an amendment that the IRB will review.

As we note below, in the section on "gender/ethnic/race categories at risk," focus-group data collected by another team of investigators in Washington, DC, show that low-SES African-American clinic attendees find mindfulness exercises helpful and empowering (Spears et al., 2017). This is an encouraging finding. A major purpose of our formative interviews will be to help ensure that our JITAI intervention is viewed similarly by the diverse groups of people for whom we intend it. If we notice any tendency for responses to differ by race, sex, or socioeconomic status, we may submit an amendment to expand the formative-interview phase.

Microrandomized trial

Proximal outcome measures (JITAI group only)
Decreases in problems in the 20 minutes from "pre" to "post" assessment
Ratings of usefulness at "post" assessment.

Distal outcome measures (JITAI group vs. EMA group)
FIT-60 mindfulness questionnaire (week 2 vs. week 11)
DTCQ for coping self-efficacy (week 2 vs. week 11)
COPE for coping-style flexibility (week 2 vs. week 11)
MCQ for delay discounting (week 2 vs. week 11)
Need for Closure scale (week 2 vs. week 11)
TSPQ-21 for Twelve-Step Involvement (week 2 vs. week 11)
opioid and other drug use (3x/week urine tests throughout study)

2. Analysis of study outcomes

Hypothesis 1, proximal: Main effect of messaging (delivery of either a CBT-based or ACT-based message will increase self-efficacy and decrease cravings and other negative states 20 minutes later, compared with the control message).

We will use multilevel random-intercept models (with data from the JITAI group only) to test the hypothesis of a proximal benefit of messages. The dependent variables, in separate models, will be participants' ratings of self-efficacy, craving, mood, and message helpfulness in EMA "post" assessments, controlling for the ratings in "pre" assessments. The main independent variable will be message type: active (CBT or ACT) versus none ("thank you" control condition). We will use an autoregressive error structure to account for within-person correlations. A significant beneficial effect on any of the outcome measures (self-efficacy, craving, mood, message helpfulness) will be taken as partial support for the hypothesis; significant beneficial effects on all the outcome measures will be taken as full support.

Hypothesis 2, proximal: Strategy-situation fit (the effects of the messages will be moderated by the circumstances in which they are provided).

The main analysis here (again, with data from the JITAI group only) will be a test of whether CBT messages are most effective in controllable situations and ACT messages are most effective in noncontrollable situations. We will categorize a situation as *noncontrollable* when a participant gives a response of less than 50/100 on either of these two "pre" items: (1) "I could easily be somewhere else right now if I wanted," (2) "I could easily get out of what I'm doing right now." Otherwise, we will categorize the situation as *controllable*. In the subset of instances in which an active message was given, multilevel models similar to those for hypothesis 1 will be run with the predictors Intervention Type (either CBT or ACT), controllability (y/n), and their interaction. A significant interaction (in the expected direction) on any of the outcome measures (self-efficacy, craving, mood, message helpfulness) will be taken as partial support for the hypothesis; significant beneficial effects on all the outcome measures will be taken as full support.

Other aspects of strategy-situation fit to be tested will include the setting (e.g., home, work, obligations, recreation), the nature of the problem (e.g., craving, boredom, anger), and cue exposure ("'People, places, or things' are reminding me of drugs"). We will also examine alternative ways of operationalizing the controllability of a situation, because we know of no standardized way of doing so. In particular, we will examine the escapability of a situation in conjunction with its desirability, incorporating items such as "The place where I am is pleasant and comfortable (not too hot/cold, noisy, ugly, dangerous, etc.," "What I'm doing right now is

enjoyable for me," and "What I'm doing right now is important to me." We do not have *a priori* hypotheses for these analyses, and we will state that clearly when we report them.

Hypothesis 3, distal: Main effect of intervention (the group randomized to JITAI will have better outcomes—e.g. less drug use, higher self-efficacy, a greater increase in flexibility of coping styles—than the EMA-only control group when assessed at week 11).

These analyses, unlike the preceding ones, will use data from both the JITAI group and the EMA control group.

For group differences in mindfulness (FIT-60), coping self-efficacy (DTCQ), and coping-style flexibility (COPE), we will use analyses of covariance (ANCOVAs); in each ANCOVA, the dependent variable will be the score on the relevant measure at week 11, the categorical predictor will be group (JITAI vs. EMA) and the covariate will be the score at week 2.

The analyses on those questionnaire responses can be done only for participants who reach week 11. However, we will also test for a group difference in opioid use (thrice-weekly urinalyses) across the duration of the study. This analysis will use a generalized linear mixed model, so missing data (whether from early dropout or missed visits) will result in appropriately adjusted standard errors.

For a more stringent assessment of drug-use outcome, we will also compare the proportion of participants in each group who "succeed" in treatment (by completing week 11 *and* testing opioid-negative that week). Cessation of opioid use is not the main outcome measure for this study; we are more interested in psychological changes that might plausibly lead to good long-term outcomes. Nonetheless, we will assess and report this measure of treatment response.

Hypothesis 4, distal: Differential responses over time (CBT messages will be rated as helpful almost immediately; ACT messages may have to be lived with for several weeks, but may also stand up better to repetition).

In the JITAI participants, we will test this hypothesis with time-varying effect models (TVEMs) (Shiyko et al., 2012). These are extensions of multilevel models that can assess whether the relationship between a predictor and outcome becomes larger or smaller over time. If we see the predicted patterns of change on the "post" item "How useful was the message?,"

we will take that as full support for this hypothesis. If we see it only on other outcome measures (self-efficacy, craving, mood), we will take that as partial support.

Hypothesis 5, distal: Trait predictors of responsiveness (although we are not powering the study to assess treatment matching at the person level, we will examine whether trait variables such as personality and preferred coping styles are associated with differential responsiveness to CBT-based versus ACT-based messages).

This will be tested (with data from the JITAI group only) in multilevel models similar to those for hypothesis 1, with the predictors Intervention Type (either CBT or ACT), Trait, and their interaction. Specific predictions to be tested are: (1) high scorers on the baseline "Need for Closure" scale will benefit more from CBT messages than from ACT messages; (2) participants with steep discounting functions on the Monetary-Choice Questionnaire will be initially resistant to ACT.

The NEO personality inventory and our other trait measures offer many potential predictors, and we do not have *a priori* hypothesis for most of them. In reporting results from any of these analysis, we will specify that they were exploratory, and we will state clearly how many analyses we ran.

Hypothesis/analysis 6 (push versus pull: we will also assess, but have no directional predictions about, whether the intervention types that seem to benefit participants most when "pushed" by the app are the same ones that participants choose when subsequently given the opportunity to "pull" interventions).

For each participant in the JITAI group, we will use multilevel models with person-specific slopes to quantify the relative overall effectiveness of CBT vs. ACT messages during the "push" weeks, in terms of proximal changes craving, self-efficacy, and/or mood. We will then calculate the participant's relative overall preference for CBT vs. ACT content during the "pull" week. These can be straightforwardly shown in a scatterplot with an accompanying bivariate correlation coefficient.

3. Criteria for statistical significance

The criterion for statistical significance will be set at $p \leq 0.05$, two-tailed. For hypothesized effects that do not reach statistical significance, we will calculate Bayes factors (Dienes, 2014), which help determine whether "nonsignificant" findings favor the null or the alternative hypothesis or whether they should be considered inconclusive.

J. Required sample size

For the formative-interview phase, we anticipate that 30 interviewees will be sufficient to give us feedback on our prototype materials and app interface. We may revisit this if we find that responses are highly variable across interviewees. We expect that most people who agree to be interviewed will provide usable information, so we are setting out enrollment ceiling at 35.

For the microrandomized trial, which is longer and more demanding, we expect a higher rate of dropout. We will enroll up to 150 participants to reach a target of 85 (50 JITAI, 35 EMA control) who complete the week-eleven outcome assessment. The calculations that led us to that total are as follows.

For hypothesis 1 (the proximal main effect of messaging in the microrandomized trial), we used a power-and-sample-size calculator <https://pengliao.shinyapps.io/mrt-calculator/> developed specifically for microrandomized studies (Liao et al., 2016). This calculation applies specifically to the JITAI group, not the EMA control group. As Liao et al. (2016) point out, there is very little precedent for determining what a proximal effect size should look like, but small studies with microrandomized designs can often detect seemingly small effects, on the order of d = .15. We decided that the most important consideration was to set our beta level high (.90, rather than the conventional .80), and we started by entering the following assumptions:

> *Days of study*: 56 [eight weeks of "push" intervention].
> *Number of decision time points per day*: 4.
> *Randomization probability*: 0.67 [66.7% of messages would be either CBT or ACT; 33.3% would be the "thank you" control message].
> *Expected availability*: 0.80 at first, decreasing quadratically as participants become less compliant over eight weeks, for an average of 0.60.
> *Proximal treatment effect*: d = 0.15 on average, starting much smaller (0.05) and increasing quadratically over 4 weeks as participants understand the messages better.
> *Desired power*: 0.90.

The other values in the calculator were left at their defaults. With those assumptions, we would require only 25 evaluable participants in the JITAI group to detect what seems like a small main effect of messaging. However, this calculation does not indicate our power for hypothesis 2, strategy-situation fit.

Therefore, we (the investigators and IRP biostatistician Jennifer Schroeder, Ph.D.) contacted Dr. Liao's group for advice on using their calculator for an analysis in which an effect moderator (controllability of the situation by the participant) was not experimentally

randomizable. Using their suggested inputs (which included decreasing the "availability" parameter), and assuming (based on our own prior EMA data) that the split between controllable and uncontrollable situations would be roughly 50-50, we calculated that we would have power of .90 to detect a strategy-situation fit as small as d = .16 with a sample size of 49 evaluable participants in the JITAI group. If the controllable/uncontrollable split were 60-40 in either direction, we could still detect a strategy-situation fit as small as d = .164. If the controllable/uncontrollable split were 70-30 in either direction, we could still detect a strategy-situation fit as small as d = .174.

In the EMA study we cited that showed strategy-situation fit, effect sizes (which we calculated from the regression betas and SDs in a data table) were on the order of d = .21 to d = .39.

Based on all those considerations, we aim to collect a full eight weeks of JITAI data from 50 participants (rounding up from 49) in the JITAI group.

For hypothesis 3, comparing overall treatment effects between the JITAI group and the EMA control group, power is far more straightforward—it can be expressed in terms of a generic comparison between two independent samples. For the sake of both expediency and maximum beneficence, we will use deliberately unequal randomization (Dumville et al., 2006), assigning fewer people to the EMA control group than to the JITAI group.

A meta-analysis we cited earlier suggested effect sizes on the order of .57 for a smartphone intervention versus standard treatment (Lindhiem et al., 2015). For some of the comparisons of interest here, such as expansion of the repertoire of coping strategies, group differences are likely to be even larger, because our control condition will not include any instruction relevant to them. With evaluable data from 50 participants in the JITAI group and 35 in the EMA control group, we will have power of .90 (in two-tailed tests) to detect a group difference of d = .70 or larger in any overall outcome. At the more conventional beta of .80 (in two-tailed tests), we will have power to detect a d of .60 or larger.

K. Plans for enrollment at multiple sites

Not applicable.

L. Human-subjects protection plan

1. Rationale for subject selection based on gender/ethnic/race categories at risk

Participant selection will be equitable, without regard to nationality, sex, race, religion, or creed. The anticipated racial/ethnic and sex distribution will reflect that of the local community and drug-using population.

The use of mindfulness interventions in the US might seem, on its face, like a trend that would appeal primarily to a culturally or economically privileged few. In fact, however, focus-group data from Washington, DC, show that low-SES African-American clinic attendees find mindfulness exercises helpful and empowering (Spears et al., 2017). Lessons learned from those prior focus groups, and from the formative interviews we do, will help shape our interventions.

2. Recruitment plan

Recruiting

Standard recruitment efforts employed by MMG will be used for this nonresidential treatment study (See NIDA/IRP Medical Policy and Procedure Manual). MMG advertises extensively in a variety of newspapers that are read by both sexes and all ethnicities. Special outreach efforts are made toward women and minorities.

Ads will be submitted to the IRB for approval before they are used.

Our experience with OBOT and TE patients in the 020 protocol is that we enroll each type at a rate of about 4 every 30 days. If that rate (8 enrollees every 30 days) is maintained, we should reach our enrollment target of 175 in just under 660 days, with roughly equal numbers of OBOT and TE participants.

Screening methods

Study candidates will be screened under Protocol 415. During screening, Treatment Elsewhere candidates will be asked to sign an authorization for release of information so we can confirm their enrollment in opioid-agonist treatment. Screening measures in 415 will include: medical history; physical examination; Addiction Severity Index (ASI); SCID (or MINI) plus counselor evaluation for DSM-5 disorders; blood specimen for NIDA chemistry 2 panel, CBC with differential, and hepatitis C antibody.

Consent documents and process

Individuals applying for the study and meeting its eligibility criteria will be asked to give informed consent. Consent will be obtained only by the investigators and co-investigators named on this protocol, all of whom have completed NIH's electronic course in human-research ethics, and all of whom are qualified to answer questions about the study. Any study candidate who has questions or concerns about medical aspect of the study will be offered a chance to talk with the study physician before signing consent. After the consent form is read to or by the study candidate, he/she will take a 10-item quiz to ensure that he/she understands the protocol. A score of 80% and correct response on 2 required questions will be considered passing; if the score is lower than that and/or the participant incorrectly answers a required question, the quiz will be re-administered once. If a study candidate does not pass the consent quiz a second time, he or she will not be enrolled in the study. The process will be documented in the CDW by the investigator who obtains consent. The consent form contains all required elements. Participants may sign the consent form on paper or electronically in CDW/HuRIS. Regardless of consent method, participants will be given hardcopies of their signed consent forms.

3. Justification for exclusion of vulnerable populations

Children under 18 will not be included because their treatment needs are likely to differ substantially from those of older users.

We will exclude people who are cognitively impaired to the extent that they cannot give informed consent, cannot benefit from the treatment offered, or cannot give self-reports appropriately. Self-report is a central outcome measure; including participants who cannot do it would invalidate the study. Including people who cannot give informed consent or who could not benefit from the type of treatment offered cannot be justified for this study.

Pregnancy will not be a criterion for exclusion or discharge. We arrived at this decision after intensive discussion of the issue with the NIDA IRB during its initial review of the protocol. Buprenorphine maintenance is beneficial for pregnant women with opioid dependence and for their fetuses (Johnson et al., 2003). EMA monitoring is not considered risky for pregnant women or their fetuses and has not been an exclusion criterion for our prior or current EMA studies. For the JITAI intervention, our reasoning is as follows, based on subparts a-j of 45 CFR 46.204. (a) Studies of JITAIs in at least a thousand women, with or without substance-use disorders (e.g., Heron & Smyth, 2010; Free et al., 2011; Gustafson et al., 2014; Shrier et al., 2014; Muuraiskangas et al., 2015; Tufts et al., 2015), have not suggested any

effects that would increase risk to pregnant women or fetuses. (b) Any risk to fetuses from a woman's use of the JITAI app is not greater than minimal, and the purpose of this protocol is the development of important biomedical knowledge that cannot be obtained by any other means than a microrandomized study in a relevant, representative sample. (c) The protocol minimizes any risk that is associated with the JITAI. (d) Informed consent will be obtained from any pregnant woman who enrolls. (e) Not applicable (benefit is not solely to the fetus). (f) If any information arises on reasonably foreseeable risks to fetuses from a JITAI, participants will be informed. (g) No pregnant children will be enrolled. (h) No inducements will be offered to terminate a pregnancy. (i) No one involved in the research will have any part in decisions about termination of pregnancy. (j) No one involved in the research will have any part in decisions about the viability of a neonate.

Another factor in our decision to include pregnant women is that, had we decided to exclude them, the regulations in 45 CFR 46.204 require that we justify the exclusion. In reviewing recent literature on the bioethics of research in pregnant women, we found a strong trend toward advocacy for a default of inclusion rather than exclusion, for reasons of social justice (Goldkind et al., 2010; Macklin, 2010; Blehar et al., 2013; White, 2015; Hunt et al., 2017). In other words, bioethicists seem to be moving toward a consensus that exclusion of pregnant women from research should carry a heavier burden of proof than inclusion. We do not think we can meet that burden of proof for this protocol.

4. Evaluation of risks/discomforts and benefits ratio

The formative-interview phase of this study is minimal risk; the clinical-trial phase is more than minimal risk.

Potential benefits

Direct Benefits

The formative-interview phase is not expected to provide any direct benefit.

The clinical-trial phase may provide a direct benefit for participation who are randomized to the JITAI group. For OBOT participants (in both the JITAI and EMA groups), the buprenorphine administered during the study will probably decrease illicit opioid use, and the weekly counseling may further reduce opioid and other drug use and reduce HIV-risk behaviors.

Indirect Benefits

This study is likely to yield generalizable knowledge about mobile interventions for addiction.

Risks

Risks associated with interviews in the formative phase

The in-depth part of the interview will include questions about day-to-day challenges. This part of the interview will be conducted only by investigators who have the clinical background required to respond swiftly and sensitively to any unexpected reactions. One of those investigators, for example, has safely overseen more than 80 research sessions in which participants were administered moderate or high doses of the psychedelic drug psilocybin, a situation that calls for highly tuned clinical skills. The other investigator has a doctorate in social work, with extensive practicum experience in recovery centers. Our clinic's master-level counselor will also be standing by.

All of this represents an abundance of caution, because the in-depth part of the interview will not involve probing of any traumatic or difficult material. Interviewees will not be encouraged to reexperience stress or craving, and if they do, they will not be sent home until they have had time to relax. The in-depth part of the interview will be followed by a light lunch and a more app-focused interview.

Risks associated with mobile data collection

Carrying the smartphones may be a burden to participants; we will try to reduce this burden by providing carrying cases. There is a risk of loss of confidentiality associated with carrying information on drug use; this risk will be minimized as the smartphone will only have a coded identification number and will be password-protected. Carrying these devices may increase the likelihood of being robbed; however, as most people now carry such devices, it is not likely that the risk of robbery is substantially increased over the usual risks; we have issued mobile electronics to hundreds of participants in prior studies without having encountered this problem. Again, all information we collect will be protected under an NIH-issued Certificate of Confidentiality.

Risks associated with mobile messages/exercises (JITAI group only)

Mobile messages/exercises carry the same risks and burdens as EMA, such as inconvenience. Like standard office-based counseling, some of the messages/exercises could lead the participant to confront emotionally difficult material. We will minimize this risk by

excluding study candidates with unresolved symptoms of PTSD, avoiding any messages/ exercises that focus on trauma, and giving participants contact information for a counselor.

If a smartphone malfunctions, participants may briefly cease to receive the intervention. We will minimize this risk by fixing or replacing any malfunctioning smartphone at the next clinic visit, so the intervention will resume within 1-3 days. This is shorter than the usual gap between sessions of office-based counseling.

Smartphone apps like the one we are developing do not require oversight by the FDA; the FDA's current policy specifically excludes them from such requirements: https://www.fda.gov/medical-devices/device-software-functions-including-mobile-medical-applications/examples-software-functions-which-fda-will-exercise-enforcement-discretion.

Risks associated with questionnaires and interviews at the IRP

Some of the interviews and questionnaires may be stressful or psychologically difficult for participants because the topics covered are personal, including drug use, mental state, and living conditions. However, participants will be told throughout their time in the study that they are free to skip questions with which they feel uncomfortable. Legal and social risks are possible in that study participants engage in illegal activities. However, with assurances of confidentiality, backed up by a Certificate of Confidentiality from the Department of Health and Human Services, we have encountered few challenges and foresee no problem with this issue. Further, participants interact with Archway staff regularly, which provides the opportunity for regular monitoring of both physical and mental well-being. If a participant is upset by a questionnaire, interview, or by any other procedure or a personal event, he or she will have access to master's-level counselors with whom they can discuss such concerns or feelings.

Risks associated with buprenorphine (OBOT participants only):

The side effects of buprenorphine are similar to those of methadone, including headache, sedation, nausea, vomiting, abdominal pain, and constipation. However, since buprenorphine is a partial mu-opioid agonist, the intensity of these side effects may be less than that produced by full mu-opioid agonists such as methadone (Eissenberg et al., 1996). Appendix C lists the side effects listed in the PDR for buprenorphine tablets. In the proposed study, participants presenting with signs of opioid toxicity or opioid withdrawal will be evaluated by a physician, and appropriate dose adjustments made. Participants will be warned not to take any sedatives, hypnotics, or antidepressants on their own during the study, and will be asked to inform us if

any such drugs are prescribed by an outside physician. There is a slight risk of buprenorphine overdose, but this risk will be minimized by titration of dose and close monitoring for side effects. There is a risk of buprenorphine overdose is when participants are given take-home doses. When take-home doses are given, participants will be instructed to use them only as directed, and not take buprenorphine in combination with other substances (for example, alcohol, benzodiazepines, barbiturates, or other sedatives); this is also mentioned in the consent form. Participants must show Archway staff that they have obtained a lockbox for safe storage of medication; this requirement is consistent with community practice. Lockboxes can be purchased at Wal-Mart and similar stores for approximately $10-12. The lockbox requirement will apply to all participants, because even those who live alone might have houseguests. Spoken and written education regarding safe storage of take-homes will be provided to all participants. Participants will be asked to obtain a lockbox prior to study consent and bring it in at consent. If a participant does not obtain a lockbox in time for his or her first take-home, Archway will lend a lockbox for that weekend.

The buprenorphine dose range used in this study will be within the limits allowed by the FDA guidelines. Within the context of the study, doses for each participant can be adjusted based on feedback from the participant and the clinical judgment of the Archway staff, the medical advisory physician, and the investigators. If a patient shows signs of intoxication, the MAI will adjust the buprenorphine dose accordingly. Buprenorphine will be discontinued if a participant experiences severe side effects. Participants who are withdrawn from buprenorphine will experience opioid withdrawal symptoms, but these symptoms will be minimized by the gradual nature of the taper.

Risks associated with specimen collection:

The risks associated with urine collection are minimal. Participants may experience embarrassment from being observed while giving urine samples; this risk is minimized by having the observation always occur through a one-way mirror, by a staff member of the same sex as the participant.

To minimize the risks described above, participants will be closely monitored by clinic staff during clinic visits. Any unusual behavior or participant complaint will be relayed to the nurses and to the MAI. Before dispensing each buprenorphine dose, nurses will query the participants on their clinical state. The physical layout of Archway Clinic promotes excellent

communication; the study physician's office directly faces the dispensary windows where participants will be reporting every weekday. Should a safety issue arise, the MAI may ask a participant to visit the NIDA IRP clinical research program on a day he or she is not normally scheduled to come in. If there is a suspicion of intoxication, the study physician will talk with the participant to try to determine what drug (i.e., buprenorphine, other opioids, cocaine, alcohol, or sedatives) has caused the intoxication. Participants are regularly queried about outside medications—OTC, herbal, and prescription. Because many medications can cause constipation or increase QTc interval, the study physician will review each new outside medication and decide about its safety based upon the dose and administration frequency. The physician may recommend discontinuation of the outside medication, reduce the dose of buprenorphine, or continue monitoring, depending on what is best for the participant's medical health.

The investigators, NIDA IRP counselors, and medical staff will address psychological or medical issues that may arise during the study. Supervisory sessions and case conferences will be used to review clinical issues. NIDA IRP health personnel will be available 24 hours a day in the event of a medical problem. If immediate medical assessment or intervention is required, the participant will be escorted to an appropriate medical facility. NIDA/IRP medical policies will be followed.

5. Subject monitoring

A. Parameters monitored: Because each patient is to be seen at Archway three days a week, any events can be readily noted: nurses routinely ask patients if they are experiencing any new health problems and record all adverse events. Under our current system, the nurses make weekly entries into NIDA/IRP's Clinical Data Warehouse (CDW, a Microsoft SQL Server database) including patient identifying information, the nature of the problem, date reported, date of onset, expectedness, seriousness, relatedness to the intervention, action taken, and outcome; the MAI can update and clarify this information, but cannot delete it. Periodically, the MAI reviews the adverse-events information, noting any trends and reporting them to the IRB as appropriate. Patients' weight will be measured once per month; other vital signs may be taken to assess changes in participants' clinical condition. As part of usual Archway procedures, we routinely collect data on attendance, urine-test results, opioid-withdrawal symptoms, other subjective and psychological effects, and requests for dose

changes. The physician will review all lab results and make referrals and recommendations as appropriate.

B. Criteria for individual subject withdrawal/termination

Nonmedical criteria for termination . Participants will be discontinued from the study if they: (1) miss 4 study visits (OBOT) or miss 3 visits (TE, no taper as these participants do not receive treatment at Archway); (2) violate clinic rules; 3) fail to comply with EMA data collection; or (4) lose or damage two smartphones. Participants receiving OBOT from us will be offered a 21-day taper and assisted in finding a treatment provider in the community.

Participants receiving OBOT from us will be discontinued from the study possibly without a taper if they miss 3 consecutive scheduled visits.

Participants will be discontinued from the study (possibly with a taper of less than 21 days, which might not be at Archway) if they: (1) are rude and/or disruptive to the staff or to other patients; (2) try to buy or sell drugs on clinic or hospital property; (3) deface or damage clinic property; (4) try to tamper with a urine sample (for instance, by bringing urine from home, or by adding something to the urine).

Medical Criteria for Termination. Participants may be discontinued if they develop a psychiatric or medical comorbidity not related to the study intervention that precludes safe participation in the protocol, as judged by the MAI. Though the side-effect profile of buprenorphine is well known, some participants may have more severe manifestations of typical side effects such as constipation or sedation. Our general policy is that if a side effect (e.g., constipation) becomes too bothersome to the participant, or so severe that in our judgment the risk: benefit ratio is affected, the MAI will likely decrease the buprenorphine dosage until the side effect abates. If side effects cannot be adequately addressed with medication dose decreases, the participant will be given a buprenorphine taper and referred for treatment in the community.

6. Conflicts of interest

NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts of interest to report.

M. Protection of participants' privacy and confidentiality

A. *For medical records and research data:* All participant records generated by NIDA IRP staff will be accessible to authorized NIDA IRP staff only and will be kept in locked files or password-protected electronic files (i.e., NIDA IRP's Clinical Data Warehouse; CDW, a Microsoft SQL Server database). All data forms will be identified by ARC number, not participant name.

B. *EMA data*: The smartphones will require a password to display or upload any of the data participants have entered. EMA data will be transferred wirelessly from participants' phones to servers located at the NIDA BRC under a secure communications system developed by the NIDA Biomedical Informatics Section (BIS). Transfers will be scheduled to occur automatically at least twice a day. All other research data are covered by Section A (above).

C. *For stored samples:* Samples and data will be stored using ARC numbers, not participant names. Data will be kept in password-protected computers. Samples will be kept in locked storage. Only study investigators will have access to the samples and data.

D. *A Certificate of Confidentiality will be obtained.* To the extent legally possible, the NIDA IRP will not release participants' information to outside agencies without participants' explicit consent. However, in the event of a medical emergency, pertinent information will be provided to attending physicians.

N. Study agents/interventions

The mobile interventions are described in section E.

O. Plan for reporting unanticipated problems and adverse events

We will report adverse events in accordance with Federal and NIH requirements.

P. Data and safety monitoring

i. Monitoring Mechanism: The Principal Investigator will be responsible for data and safety monitoring. The Medical Advisory Investigator will examine the adverse-event data for safety concerns and report to the PI. The Lead Associate Investigator or a designee will examine data for integrity and report to the PI. A DSMB is not necessary for this study.

ii. Frequency: Data will be examined once a year at the time of continuing review. In addition, adverse event data will be examined periodically as new events occur.

iii. Criteria for stopping the study: If the rate of dropout (defined as failure to complete the intervention and/or the 11-week outcome assessment) is greater than 50% after the first 10 participants have been enrolled, we will temporarily stop enrollment and explore ways to modify the study. Otherwise, the study will be stopped after we complete data collection from our target number of completers.

iv. Advanced plans for interim/futility analyses: There are no current plans for an interim/futility analysis.

v. Information to be monitored: The information monitored will fall into three groups.

1. *Participant Safety*: While we continually monitor adverse events for serious situations, yearly we will assess all adverse events to understand the risks that may be associated with the study. As participants can receive buprenorphine, we will monitor the literature for any health concerns associated with that treatment. Should a question arise out of the literature we will conduct an analysis of adverse event data to protect our participants.
2. *Study Demographics*: We will monitor recruiting and enrollment data to assure the consistency of our efforts with enrolling a diverse population representative of Baltimore.

vi. Communication: The MAI and LAI will bring safety and data integrity concerns to the PI. Safety and data integrity concerns will be immediately brought to the attention of the IRB and the Clinical Director via problem reports.

Q. Clinical monitoring plan

As required by NIH HRPP SOP 23: the PI and all AIs are current in our training on participant protection; we have reviewed potential conflicts of interest; and the protocol is open to auditing by the IC, OHSRP, and other authorized bodies.

R. Data/records management

1. Quality assurance

To ensure validity and integrity, most data will be collected directly from participants via smartphone or computer, and we will create and use checklists and standard operating procedure (SOP) manuals for data collection. Quality-assurance monitoring will be conducted by the PI at least yearly.

2. Relationship to other protocols

Screening for this study will be conducted under protocol 415. Participants are not otherwise required to have participated in any other protocol to be eligible for the current protocol. It is expected that data obtained from this protocol may be combined and/or compared with that obtained in other protocols. Additionally, data from other protocols may be combined and/or compared with those obtained in this protocol.

3. Data-sharing description

We share information with researchers outside the NIH in two ways:

Most commonly, we have specific partnerships with researchers outside the NIH. They sign an agreement with the NIH to share data. This agreement indicates the type of data that can be shared and what can be done with those data.

Also, we may put data into one or more scientific databases, where it is stored along with information from other studies, with all the data stripped of identifiers such as name, address, or ARC number. A researcher who wants to study the information must apply to the database and be approved. Researchers with an approved study may be able to see and use the data from this protocol, along with that from many other studies. We do not expect any direct benefits for participants from this use of protocol data, but it may lead to new discoveries that that could benefit public health. The Principal Investigator is open to answering any questions about how these data may be used.

Participants may stop participating in this study at any time. They may subsequently decide to withdraw permission for the use of their individual data and specimens. If they choose, we will destroy their data. However, we may not be able to destroy data once they have been shared with other researchers.

4. Technology transfer

Not applicable.

S. Compensation

a. Participants will be compensated for time and research-related inconveniences. Participants are not compensated for activities directly related to receiving treatment (e.g., the JITAI group's nightly "Deep Dive" readings, or the momentary "pre" assessments needed for message selection in the JITAI group). Thus, total compensation will be the same for JITAI and EMA-only participants.

b. Amount of compensation will be as follows:

Formative-interview Participants

- $90 in cash on completion of the interview, which we expect to take approximately 3 to 4.5 hours.

OBOT Participants

- $40 in cash on completion of questionnaires during week 2.
- $30/week cash if at least 82% of EMA entries are completed that week
- If participants have not lost or broken a smartphone during the study, at the end of the JITAI/EMA phase, they will receive $300 upon return of the phone. If they have lost or broken one and been issued a second, they will receive $100 upon return of that phone.
- $40 in cash on completion of questionnaires during week 11.
- Totals:
  - Questionnaires: $80 (2 * $40)
  - EMA compliance: $240 (8 * $30)
  - Return of smartphone: $300
- Likely Maximum Total: $620

Treatment Elsewhere (TE) participants

- $40 in cash on completion of questionnaires during week 2.
- $30/week cash if at least 82% of EMA entries are completed that week
- If participants have not lost or broken a smartphone during the study, at the end of the JITAI/EMA phase, they will receive $300 upon return of the phone. If they have lost or broken one and been issued a second, they will receive $100 upon return of that phone.
- $40 in cash on completion of questionnaires during week 11.
- Unlike OBOT participants, the TE participants will earn $5 for each visit, and a $10 bonus at the end of the week if they have attended every visit that week. This is necessary because we are not providing treatment to these participants; they need compensation for the time they spend at Archway and their time in transit.
- Totals:
  - Questionnaires: $80 (2 * $40)
  - EMA Compliance: $240 (8 * $30)
  - Return of smartphone: $300
  - Visit Compensation $275 (11*25)

- Likely Maximum Total: $895

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