

Micro-randomized Trials for Just-In-Time Adaptive Intervention Development

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Title: Micro-randomized Trials for Just-In-Time Adaptive Intervention Development

Summary: Micro-randomized trials are trials in which individuals are randomized 100's or 1000's of times over the course of the study. The goal of these trials is to assess the impact of momentary interventions, e.g. interventions that are intended to impact behavior over small time intervals. We discuss the design and analysis of these types of trials with a focus on their use in developing JITAs in mobile health.

Outline

- Adaptive Interventions and Just-in-Time Adaptive Interventions
- HeartSteps
- Micro-Randomized Trial
- Sample Size Considerations

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Adaptive Interventions

- Intervention design that takes advantage of response heterogeneity by individualizing intervention options to the specific and changing needs of individuals
- Example: Adaptive drug court program for drug abusing offenders

Marlowe et al., 2008; 2009; 2012

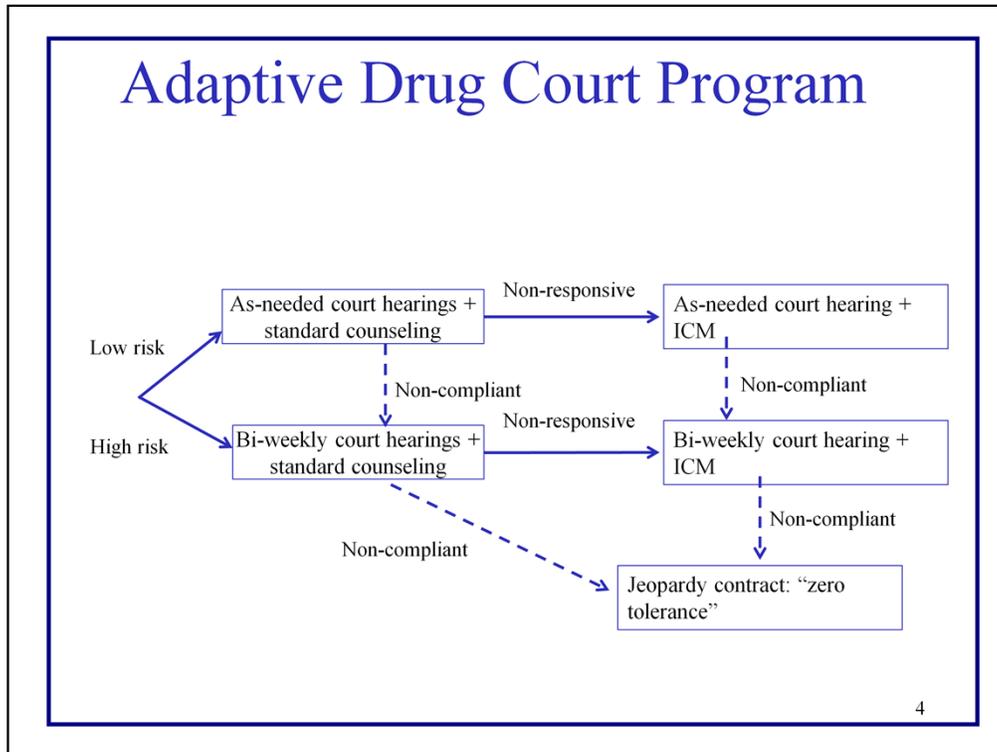
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The idea is that the same treatment is not good for everyone, and each person may need different things at different time points.

Adaptive Interventions in Drug Court: A Pilot Experiment. *Criminal Justice Review* 2008; 33; 343 Douglas B. Marlowe, David S. Festinger, Patricia L. Arabia, Karen L. Dugosh, Kathleen M. Benasutti, Jason R. Croft and James R. McKay

Adaptive interventions may optimize outcomes in drug courts: a pilot study. Marlowe DB, Festinger DS, Arabia PL, Dugosh KL, Benasutti KM, Croft JR. *Curr Psychiatry Rep.* 2009 Oct;11(5):370-6.

Adaptive Programming Improves Outcomes in Drug Court : An Experimental Trial *Criminal Justice and Behavior* 2012 39: 514 Douglas B. Marlowe, David S. Festinger, Karen L. Dugosh, Kathleen M. Benasutti, Gloria Fox and Jason R. Croft



Douglas B. Marlowe: developed and implemented an adaptive intervention for drug offenders

Following their initial court hearing, risk was assessed.

High risk: ASPD (Antisocial Personality Disorder, based on Diagnostic Interview: APD-DI) or history of formal drug abuse treatment otherwise low risk.

These are assessed monthly:

Noncompliance: is (1) falls below threshold for attendance in counseling sessions or (2) fails to provide 2 or more scheduled urine specimens

Nonresponsive = (1) is attending sessions and completing program requirements, and (2) is not committing new infractions, but (3) provides 2 or more drug-positive urine specimens.

If non compliance, contact with the judge is increased.

ICM– intensive clinical case management: Participants are required to meet twice weekly with an intensive clinical case manager who provides individual substance abuse counseling with an emphasis on motivational enhancement, relapse prevention, and cognitive restructuring (“criminal thinking”) techniques.

Jeopardy contract: involves “zero tolerance” for further violations of the rules of the program. Any

further violation leads to a termination hearing, also known as a show-cause hearing. At the termination hearing, the individual is terminated from the program and sentenced on the original charge or charges unless he or she can provide a good reason to be given another chance. The decision of whether or not to grant another chance is within the discretion of the judge

To graduate offender must attend 12 counseling sessions; provide 14 consecutive weekly negative drug urine specimens; remain arrest-free; obey program rules and procedures; pay 200 dollar court fee.

Adaptive Intervention: 5 Elements

The adaptation is guided by consideration of

(1) Distal Outcome and Proximal Response

The adaptation process is composed of

(2) Tailoring Variables,

(3) Decision Rules and

(4) Intervention Options

The adaptation is triggered at

(5) Decision Points

Monitoring, individualizing, delivering

JITAI: Just-in-Time Adaptive Interventions

- A JITAI is an adaptive intervention
- That is
 - delivered when needed
 - & where-ever needed



(Kaplan & Stone, 2013; Spruijt-Metz & Nilsen, 2014)

The same elements that we used to describe an adaptive intervention can be used to describe JITAIs, only that now all these elements are in-the-moment.

Dynamic Models of Behavior for Just-in-Time Adaptive Interventions

Donna Spruijt-Metz, University of Southern California Wendy Nilsen, National Institutes of Health

PERVASIVE computing, 1536-1268/14/2014 IEEE

Kaplan, R. M., & Stone, A. A. (2013). Bringing the Laboratory and Clinic to the Community: Mobile Technologies for Health Promotion and Disease Prevention. *Annual review of psychology, 64*, 471-498.

Riley, W. T., Rivera, D. E., Atienza, A. A., Nilsen, W., Allison, S. M., & Mermelstein, R. (2011). *Health behavior models in the age of mobile interventions: are our theories up to the task?* : Springer.

Different terms have been used in various fields to describe a JITAI, including dynamic tailoring, intelligent real-time therapy, and dynamically and individually tailored EMI

Example

Intervention to reduce heavy drinking and smoking by young adults

- Participants prompted 3/day by mobile device for assessments
 - Smoking urge, self-regulation demands, drinking behaviors
- Urge-surfing interventions delivered by the mobile device *only* if participant reports an urge to smoke.



(Witkiewitz et al., 2014)

Development and evaluation of a mobile intervention for heavy drinking and smoking among college students.

Witkiewitz, Katie; Desai, Sruti A.; Bowen, Sarah; Leigh, Barbara C.; Kirouac, Megan; Larimer, Mary E.

Psychology of Addictive Behaviors, Vol 28(3), Sep 2014, 639-650

Example

Reducing Sedentary Behavior by Office Workers

- Software on the computer measures uninterrupted computer time via mouse and keyboard activity
- Smartphone delivers message to encourage a walking activity *only* if 30 min. of uninterrupted computer activity occurs



(Dantzig et al., 2013)

Quote from paper: whenever 30 min of nearly uninterrupted computer activity was recorded, a short text message (SMS) containing a hyperlink was sent to the participant's smart phone. When participants clicked on this hyperlink, they were shown a message persuading them to be more active. Although all messages contained the same general advice, this advice was phrased in various ways, using four different persuasive strategies. The four strategies are a subset of the six social influence strategies defined by Cialdini [22].

Dantzig, S., Geleijnse, G., & Halteren, A. T. (2013). Toward a persuasive mobile application to reduce sedentary behavior. *Personal and ubiquitous computing*, 17(6), 1237-1246.

Commonalities?

- Both adaptive interventions and JITAIs are time-varying and adaptive
- However in JITAIs technology plays a critical role
 - Information can be obtained when/where needed
 - Interventions can be delivered when/where needed

The same elements that compose an adaptive intervention, also compose a JITAI. However, in a JITAI these elements are in-the-moment – they can occur at any moment.

Just-in-Time Adaptive Intervention 5 Elements

The adaptation is guided by consideration of

(1) Proximal Response and Distal Outcome



In-the-Moment Impact

The adaptation process is composed of

(2) Tailoring Variables,

(3) Decision Rules and

(4) Intervention Options

The adaptation is triggered at

(5) Decision Points



Real-Time

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Distal Outcomes

The goal is to improve a longer-term, distal, outcome

- Substance use cessation; maintain increased activity level; maintain adherence to meds

To improve the distal outcome, the intervention options are formulated to target proximal responses

In MD2K smoking study the distal outcome might be smoking rate.

Proximal Responses

Mediators that may be critical to achieving the long-term goal

- 1) Short term targeted behavior
 - Substance use over x hours
 - Physical activity over x minutes
 - Adherence over next hour
- 2) Short term risk
 - Momentary craving, stress
- 3) Engagement in intervention/Intervention burden

Likely multiple proximal responses

In MD2k study the proximal response might be stress over next x minutes.

Intervention options

- Intervention options:
 - Behavioral strategies, cognitive strategies, self-monitoring, social linkages, motivational,...
 - Whether to provide an intervention or whether to prompt self-monitoring
 - How to provide an intervention option
 - “Provide nothing” option
- Theoretically/scientifically driven (Klein et al., 2011)



In MD2K study the intervention option might be a recommendation to access one of the four stress-regulation apps (headspace; mood-surfing; thought distancing; and cognitive restructuring) residing on the smartphone vs. no recommendation.

Intervention options in JITAs include types of support, sources of support (e.g., automated sources, social sources); and modes of support delivery.

Recommendations

Reach out recommendation
(contact a friend)

Behavioral strategies
(exercise; stay in locations)

that are supportive of change)

Cognitive strategies (relaxation;
reframing)

Motivational messages (reasons
for behavior change; barriers for
change);

Setting goals; modifying goals

Feedback (often with
visualization: fish; flower; garden)

Distractions (game, music, etc.)

Michel Klein et al. have a nice review of all the health behavior change theories used to inform EMIs

Klein, M., Mogles, N., & van Wissen, A. (2011). Why won't you do what's good for you? Using intelligent support for behavior change. In *Human Behavior Understanding* (pp. 104-115). Springer Berlin Heidelberg.

Kennedy et al., (2012) conceptualize the EMIs as active assistance.

Kennedy, C. M., Powell, J., Payne, T. H., Ainsworth, J., Boyd, A., & Buchan, I. (2012). Active assistance technology for health-related behavior change: an interdisciplinary review. *Journal of Medical Internet Research*, 14(3).

Tailoring variables

Tailoring variables are moderators that inform which intervention option is best when, where and for whom.

- Often past proximal responses: stress, activity
- Risk & protective factors: busyness of calendar, momentary mood or craving, location, social context
- Adherence & burden

In MD2K smoking study tailoring variables might be current level of stress (low, moderate, high) and location (home, work), time of day (before work, during work, after work)

indicate risk or vulnerability. --internal risk factors , external risk factors: behaviors, social context, geographical location,

When user ignores assessment requests or ignores intervention

Decision Points

Typical decision points in JITAIs:

- Intervals in time (every x seconds, every x minutes, every x hours)
- When user requests help (presses “help” button”)

Frequency is guided by the dynamics of the tailoring variables and “in-the-moment nature” of the intervention effect.

In the MD2K smoking study, decision points might be every 2 min or even more frequent depending on how variable we think stress may be.

Recall that a decision point is the time in which we need to make critical decisions about the intervention options based on patient information.

decision points can result in the “do nothing intervention option,” hence a decision point every 3 minutes does not imply an intervention every 3 minutes.

Decision Rules

Link patient information to intervention options at decision points

- A decision rule is implemented at each decision point
- A JITAI often includes many different decision rules
- Development of decision rules is guided by an integration of empirical evidence, theory and clinical experience.

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The decision rules are constructed with the aim to impact a proximal/short term response.

We can use the data from the micro-randomized study along with behavioral science to construct decision rules.

Summary of JITAI elements

1. Outcomes

- Distal (scientific/clinical goal) & Proximal Response (guided by mediational theories pinpointing the necessary processes needed to achieve the distal outcome)

2. Intervention options

- Guided by the proximal responses

3. Tailoring variables

- Guided by theory concerning moderation.

4. Decision points

- Guided by the dynamics of tailoring variable and in-the-moment nature of the effect of the intervention option.

5. Decision rules

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- Sample Size Considerations

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HeartSteps

- Goal: Develop a Just-in-Time Adaptive Intervention for Encouraging and Maintaining Physical Activity



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Collaborators:

MD collaborator is Lisa Jackson

Pedja Klasnja

Ambuj Tewari

Eric Heckler

HeartSteps

Distal Outcome:

Activity over the 42 day study.

Proximal Response:

Proximal activity (step count) over next hour.

HeartSteps

Intervention Options:

Whether to provide an intervention: yes/no

- 1) Provide Momentary Lock Screen Activity Recommendation?
- 2) Provide Daily Activity Planning?

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Two types of activity recommendations: reduce sedentary behavior or physical activity
Two types of daily activity planning: structured vs unstructured.

HeartSteps

Decision times:

- 1) Momentary: Approximately every 2-2.5 hours
- 2) Daily: Each evening at user specified time.

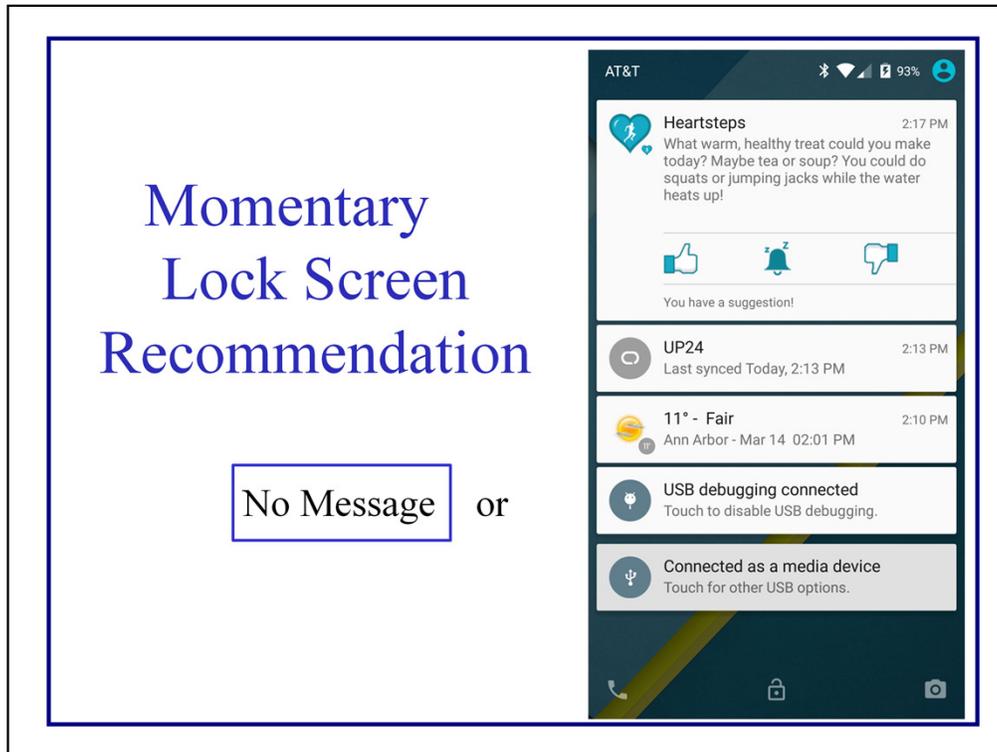
Potential Tailoring Variables:

activity recognition (walking, driving, standing/sitting), weather, location, busyness of calendar, adherence, step count, availability for momentary intervention, self-report: usefulness, burden

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The momentary times were selected because these times are the times at which most people are able to be active

Pre-morning commute, mid-day, mid-afternoon, evening commute, after dinner.



The location of the thumbs up button biases against the person hitting like.

The snooze button turns off the momentary lock screen recommendations for 4 or 8 hours.

Occurs up to 5 times per day

the suggestion, "Need a coffee or tea break? Instead of using the office coffeemaker, why not walk to a nearby cafe and order a to-go cup?," has the following tags:

Location : work

Activity Type : sedentary, active

Time Slot : morning, lunch, afternoon, evening

Weather : outdoor

Day Type : weekday

Outline

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Micro-Randomized Trial

Randomize between appropriate intervention options at decision times → Each person may be randomized 100's or 1000's of times.

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$42 \times 5 = 210$ times in pilot planned study 2160 decision times.

In MD2K smoking cessation study, with 1 minute intervals between decision times and wearing autosense 10 hours per day for 14 days, we have $60 \times 10 \times 14$ decision points at which a person may be randomized.

Micro-Randomized Trial Elements

1. Record outcomes
 - Distal (scientific/clinical goal) & Proximal Response
2. Record potential tailoring variables
3. Randomize among Intervention Options at decision points
4. At End of Trial use Resulting Data to assess moderation, construct decision rules

Why Micro-Randomization?

- Randomization (+ representative sample) is a gold standard in providing data to assess the causal effect of an intervention option.
- Sequential randomizations will enhance replicability and effectiveness of data-based decision rules.

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HeartSteps (42 day study)

- Focus on whether to provide a Momentary Lock Screen Recommendation at the decision times.
- 210 decision times for the lock-screen activity recommendations.

	Randomization Probability	
Lock-screen activity Recommendation?	Yes	$\frac{2}{5}$
	No	$\frac{3}{5}$

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So on average 2 times per day

Micro-Randomized Trial

First Question to Address: Do the intervention options have an effect on the proximal response?

--Test for proximal *main effects* of the intervention

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42*5=210 times in pilot planned study 2160 decision times.

Micro-Randomized Trial

A JITAI involves time varying potentially intensive intervention delivery → potential for accumulating habituation and burden

→

Allow proximal main effects of the intervention components to vary with time

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42*5=210 times in pilot planned study 2160 decision times.

Sample Size for a Micro- Randomized Trial

Determine sample size to detect a *time-varying proximal main effect* of the Lock Screen Recommendation on Activity

Availability & The Main Effect

- Interventions can only be delivered at a decision time if an individual is *available*.
- The proximal main effect of treatment at a decision time is the difference in proximal response between *available* individuals assigned a lock-screen message and *available* individuals who are not assigned a lock-screen message.

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The momentary intervention can be turned off for 1-8 hours by the participant. The intervention is also off if the participant is currently active (e.g. walking) or if the participant may be driving a car

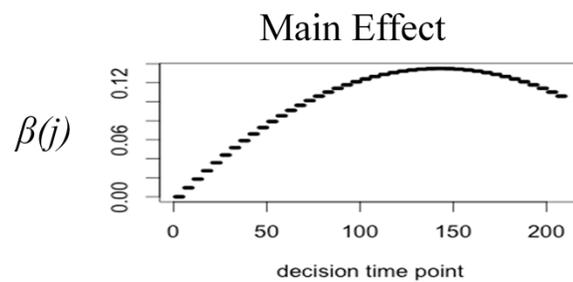
In the MD2K smoking study we might tentatively define availability as:

A person is available if he/she (1) is wearing autosense (our understanding is that autosense will be worn up to 16 hours a day, participants will not wear it when they sleep or when in the shower); if the person is not wearing Autosense, no data will be collected and recommendations will not be pushed); (2) did not receive a message in the past 120 minutes; and (3) is not driving a car.

Adherence (i.e. compliance) is very different from availability. Suppose a person is available at a decision point. However the phone is in their purse across the room. So they don't hear whether the phone pings/ see the lockscreen light up. This person is non-adherent at this decision point. Primary analyses will be intention-to-treat and thus will average over non-compliance.

Proximal Main Effect

Main effect of lock-screen message on proximal response is likely time-varying
 $\beta(j), j=1, \dots, J$



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Main effects are marginal effects!

Why would the main effect vary with time? Proximal effect varies with time (maybe diminishes due to habituation and/or non-adherence). Population of available individuals varies with time. The individuals who are available near the end of the study may be the least sensitive to the influence of the activity message.

Delayed effects which are akin to higher order interactions would be investigated in secondary analyses

Sample Size Calculation

- We calculate a sample size to test:

$$H_0 : \beta(j) = 0, j = 1, 2, \dots, 210$$

- A simple approach is to consider $\beta(j)$ as a quadratic with intercept, β_0 , linear term, β_1 , and quadratic term β_2

and test $\beta_0 = \beta_1 = \beta_2 = 0$

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Since the model for the proximal effect of A_j on Y_j does not depend on time of day, we are averaging any variation

in proximal effect across the occasions during the day (recall we are sizing the study; a primary analysis might be a little more complex and in secondary data analyses one would likely estimate and test if the proximal effect varies by time of day and/or varies by j ,

since j denotes duration in study).

Sample Size Calculation

Because we assume the proximal main effect is approximately quadratic, assessment of the effect of the lock-screen message uses not only contrasts of *between person responses* but also contrasts of *within person responses*.

-- We can expect that the required sample size (number of subjects) will be small.

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The contrasts become within person contrasts due to the assumption of smoothness over time. If the proximal effect at each time point were to be estimated separately then it would be like a two arm study at each time j .

Sample Size Calculation

- Our test is based on GEE regression.
- To calculate a sample size we need to specify a clinically/scientifically important effect to detect.

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Specify Alternative for Sample Size Calculation

SPECIFY:

- Standardized main effects:
 - proximal effect on first day,
 - average proximal effect over trial duration
- Day of maximal proximal effect.

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HeartSteps (42 day study)

Standardized effects:

- initial proximal effect: 0
- average standardized proximal effect over trial duration ?
- day of maximal proximal effect: 28

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Meaningful increase in stepcount is 1000/day

Usual std is 2000/day

Roughly a standardized treatment effect of $200/666 = .3$

HeartSteps Sample Sizes

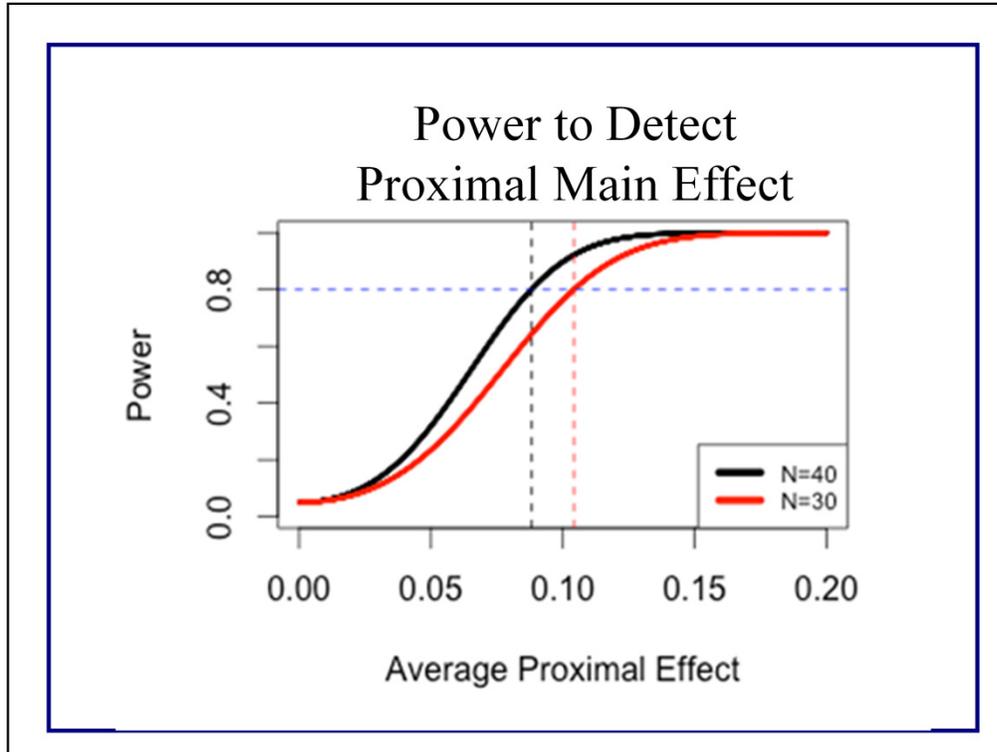
Power=.8, α =.05

Standardized Average Proximal Effect over 42 Days	Sample Size For 70% availability or 50% availability
0.06	81 or 112
0.08	48 or 65
0.10	33 or 43

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Average proximal effect is standardized.

#parameters=6



Average availability is 70%

Simulations indicate:

Method is sensitive to

Guess of average amount of time intervention is on: $1/J \sum_{j=1}^J E[I_j]$.
Choose on the low side to be safe

Guess of average proximal txt effect. Choose on the low side to be safe.

Heteroscedasticity of errors: variance of Y when A=1 is larger than variance of Y when A=0 is problematic

Simulations indicate robustness to

I_{j+1} a function of past A_j 's

Guess at day of maximal proximal effect (we use different function from quadratic when this day is less than $\frac{1}{2}$ of the way through the study—this is not presented here)

Non-symmetry or skewness to residual error distribution .

Positive correlated across time residual errors

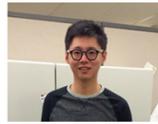
Mixture of people, some of whom have the intervention turned off $x\%$ of time and some who have their intervention turned off $y\%$ of the time where overall $\%$ time turned off is .7 or .5

A Micro-Randomized Trial

- 1) We also micro-randomize other components (e.g. Daily Activity Planning) to obtain a sequential, factorial design.
- 2) Be conservative in planning the trial!
 - 1) Under-estimate the amount of time participants are available for the intervention component.
 - 2) Under-estimate the average proximal effect₄₁

A Micro-Randomized Trial

- 3) Power to detect proximal main effect is robust to interactions and to delayed effects (e.g., burden)
- 4) Secondary data analyses concern time varying effect moderation and data analyses to construct data-driven decision rules for the JITAI



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& Inbal Nahum-Shani



Email if you have questions!

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