Just-in-Time Adaptive Interventions
&
Micro-Randomized Trials

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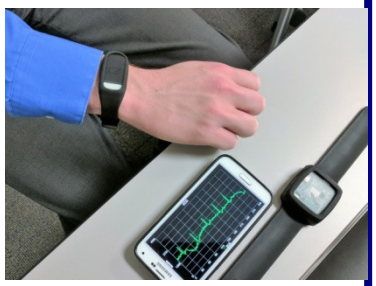
advancing methods, improving health

Sense^2 STOP

- Wearable wrist/chest bands provide multiple physiological sensor streams…; Self-report provides craving, burden,…..
- Stress-management exercises available on smartphone 24/7
- In which contexts should the smartphone remind the user to access the stress-management apps and practice the exercises?



Heartsteps

HeartSteps Activity Coach

- Wearable band senses activity and sleep quality; phone sensors measure busyness of calendar, location, weather; self-report provide burden, utility .....

- In which contexts should the smartphone ping and deliver tailored activity ideas?

Outline

Just-in-Time Adaptive Intervention (JITAIs)

- What are they, Components, Motivation

Micro-Randomized Trials (MRTs)

- Using data to inform the development of JITAIs
- Key features
- Sample size considerations
- MRTs vs. other designs

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Adaptive Intervention: 5 Elements

The adaptation is guided by consideration of

(1) Proximal and Distal Outcomes

The adaptation process is composed of

(2) Tailoring Variables,

(3) Decision Rules and

(4) Intervention Options

The adaptation is triggered at

(5) Decision Points

JITAIs: Just-in-Time Adaptive Interventions

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

(Spruijt-Metz & Nilsen, 2014; Nahum-Shani et al. 2016)

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)

Example

Reducing Sedentary Behavior by Office Workers

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

(Dantzig et al., 2013)

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

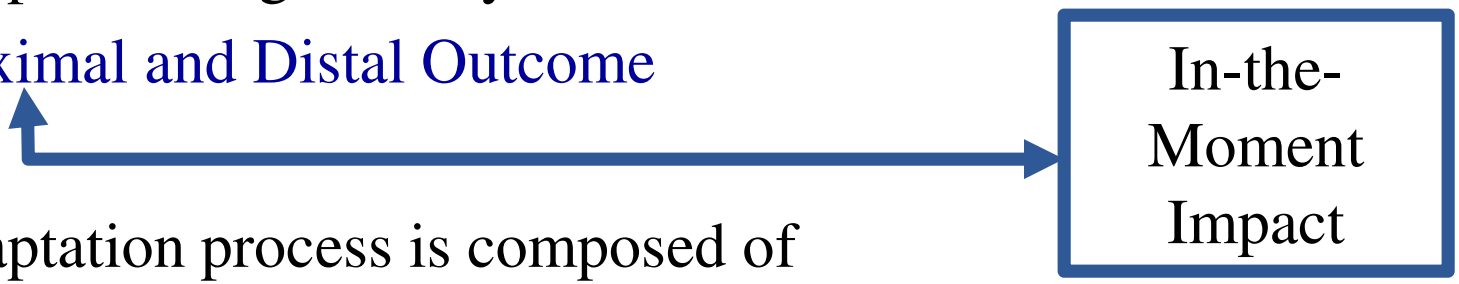
Motivation for JITAIs

1. Individuals may need support when it is difficult or expensive to provide
2. Individuals are not always aware of when they need support
3. Intervention options may have negative effects (burden, habituation)

Just-in-Time Adaptive Intervention
5 Elements

The adaptation is guided by consideration of

(1) Proximal and Distal Outcome



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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 outcomes

Proximal Outcomes

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
   - Current craving, stress
3) Engagement with mobile app/intervention burden

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; West & Michie, 2016)

Tailoring variables

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

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

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.

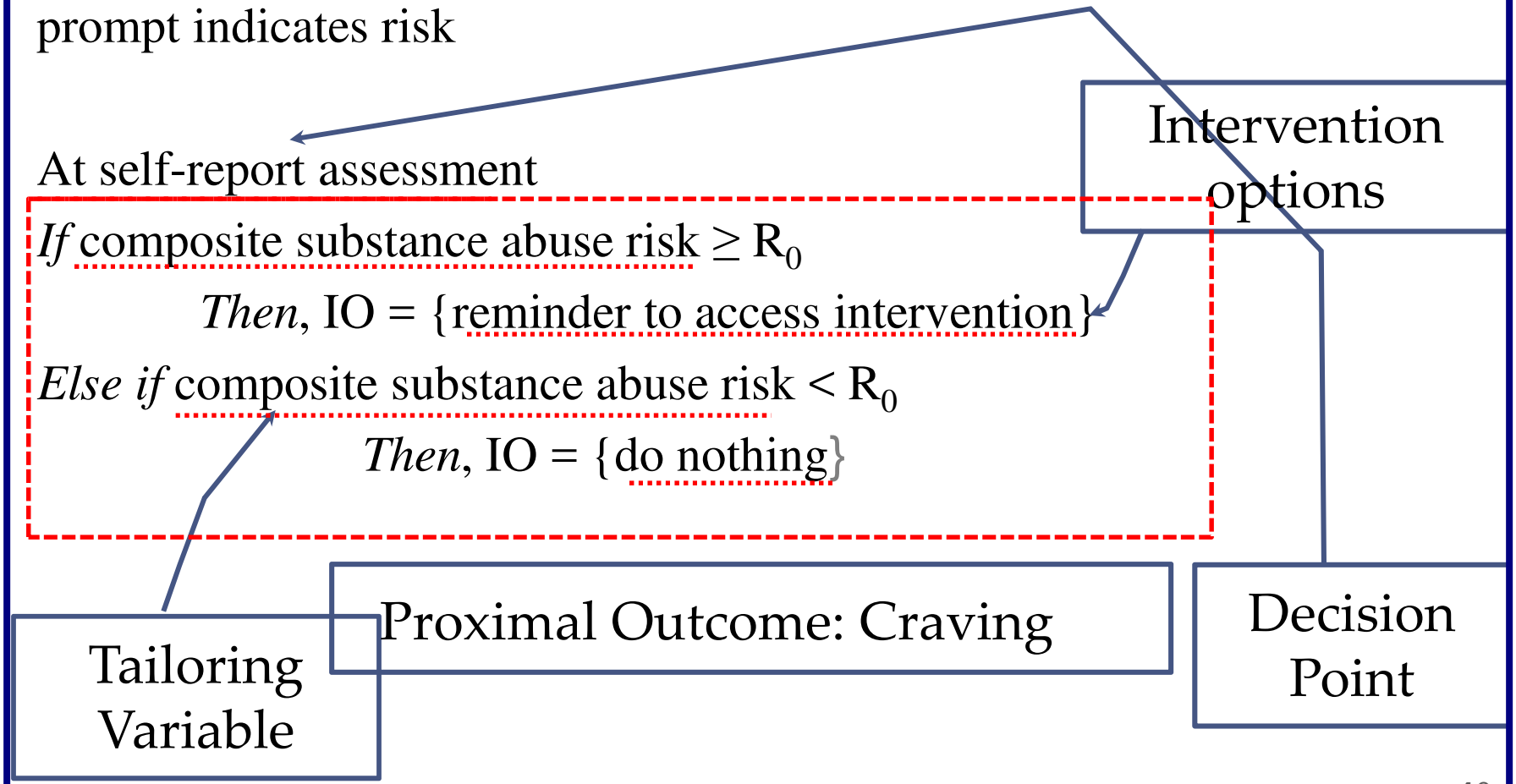
Decision Rules

Link tailoring variables 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.

Decision Rules: Example 1

What to do when composite risk assessment at random prompt indicates risk



Decision Rules: Example 2

At 1 minute intervals

If current accumulated computer activity > P_0

Then, IO= {recommend movement}

Else if current accumulated computer activity ≤ P_0

Then, IO = {do nothing}

Summary of JITAI elements

1. Outcomes
    - Distal (scientific/clinical goal) &
      Proximal Outcome (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 the tailoring variable and in-the-moment nature of the effect of the intervention option.
5. Decision rules

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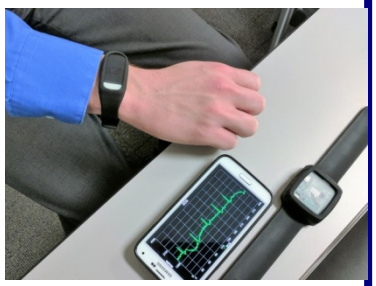


Data from wearable devices that sense and provide treatments

- On each individual: $O_1, A_1, Y_2, \ldots, O_t, A_t, Y_{t+1}, \ldots$

- t: Decision point
- O_t: Observations at t^{th} decision point (high dimensional)
- A_t: Action at t^{th} decision point (intervention option)
- Y_{t+1}: Proximal response (e.g., reward, utility, cost)

Examples

1) Decision Points (Times at which a treatment can be provided.)
    1) Regular intervals in time (e.g. every 10 minutes)
    2) At user demand

HeartSteps: Approximately every 2-2.5 hours

Sense^{2}Stop : Every 1 minute during 10 hour day.

Examples

2) Observations O_t
   1) Passively collected (via sensors)
   2) Actively collected (via self-report)

HeartSteps: classifications of activity, location, step count, busyness of calendar, usefulness ratings, adherence…….

Sense^{2}Stop: classifications of stress, smoking detection, mood, driving,….

Examples

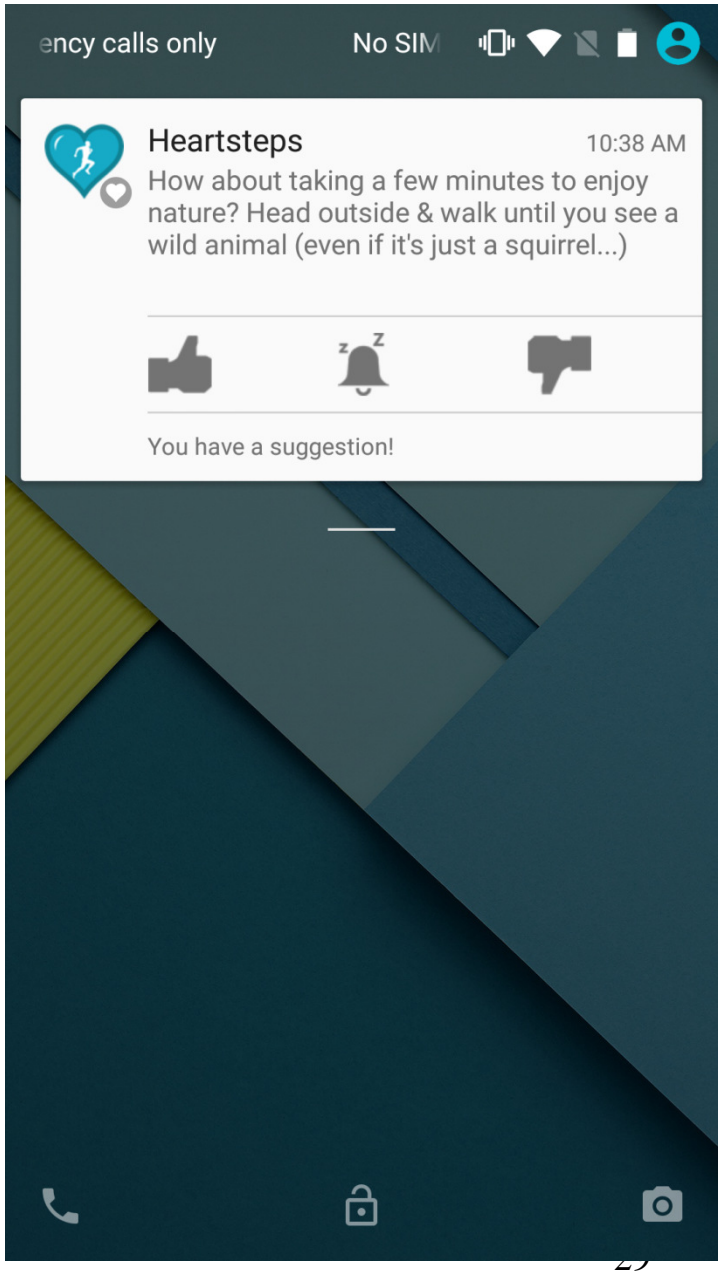
3) Actions A_t
    1) Intervention options that can be provided at a decision time
    2) Whether to provide an intervention

HeartSteps: Tailored activity recommendation notification by phone

Sense^{2}Stop: Reminder to access app so as to practice stress-management exercises

Tailored Activity Recommendation

No Message or



Examples

4) Proximal Outcome (reward) Y_{t+1}

HeartSteps: Activity (step count) over next 30 minutes.

Sense^{2}Stop: Stress over next 120 minutes

Micro-Randomized Trial

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

- These are sequential, "full factorial," designs.
- Design trial to detect main effects.

Why Micro-Randomization?

- Randomization (+ representative sample) is a gold standard in providing data to assess causal effects.

- Sequential randomizations (+ representative sample) will enhance replicability of data analyses (moderation, decision rule development).

Micro-Randomized Trial Elements

1. Record outcomes
   - Distal (scientific/clinical goal) & Proximal Outcome
2. Record context (sensor & self-report data)
3. Randomize among intervention options at decision points
4. Use data after study ends to assess treatment effects, develop warm-start JITAI

Micro-Randomized Trial

How to justify the trial costs?

- Address a question that can be stated clearly across disciplinary boundaries and be able to provide guarantees.
- Design trial so that a variety of further interesting questions can be addressed.

First Question to Address: Do the treatment actions impact the proximal outcome? (aka, is there a *main effect*?)

Micro-Randomized Trial for HeartSteps

- 42 day trial
- Whether to provide a tailored activity recommendation? $A_t \in \{0, 1\}$
- Test for main effects on proximal outcome
- Randomization in HeartSteps

$$P[A_t = 1] = .4 \quad t = 1, \ldots, T = 210$$

Time-varying Main Effects

Time varying potentially intensive/intrusive intervention options $\longrightarrow$ potential for accumulating habituation and burden

$\longrightarrow$

In the test statistic allow the main effect of the intervention options on proximal outcome to vary with time

Availability & the Treatment Effect

- Intervention options can not be delivered at a decision point if an individual is *unavailable*.

- The effect of a treatment option at a decision point is the difference in proximal outcome between *available* individuals assigned an activity recommendation and *available* individuals who are not assigned an activity recommendation.

Availability

- Intervention options can only be delivered at a decision point if an individual is *available*
- Set $I_t=1$ if the individual is available at decision point t, otherwise, $I_t=0$
- Availability is not the same as adherence, nor is it the same as interruptibility, receptivity

Potential Outcomes

- Define

$$\bar{A}_t = \{A_1, A_2, \ldots, A_t\}, \bar{a}_t = \{a_1, a_2, \ldots, a_t\}$$

- Define $Y_{t+1}(\bar{a}_t)$ to be the observed response, Y_{t+1} if $\bar{A}_t = \bar{a}_t$, e.g., $Y_{t+1} = Y_{t+1}(\bar{A}_t)$

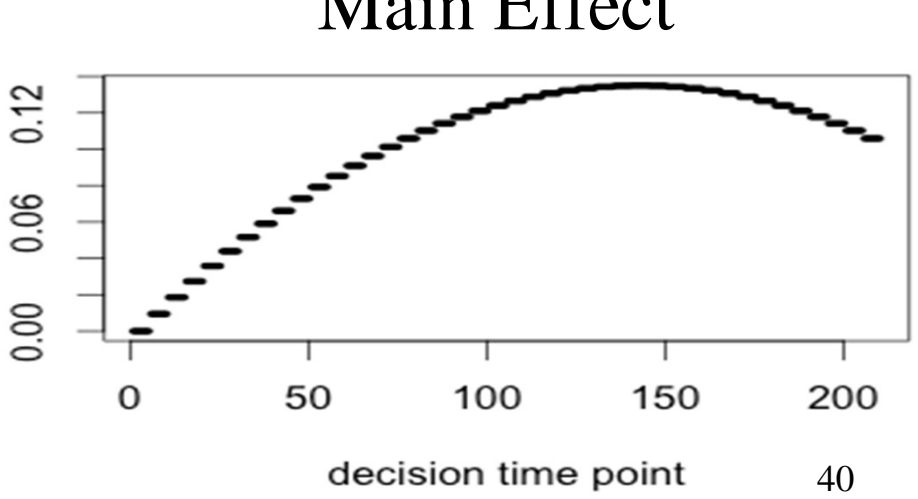
- Define $I_t(\bar{a}_{t-1})$ to be the observed "available for treatment" indicator if $\bar{A}_{t-1} = \bar{a}_{t-1}$

Main Effect

- Define the main effect at time *t* as

$$E\left[Y_{t+1}(\bar{A}_{t-1},1) - Y_{t+1}(\bar{A}_{t-1},0)\middle| I_t(\bar{A}_{t-1}) = 1\right]$$

- What does this main effect mean?



Main Effect

- The randomization implies that

$$E\left[Y_{t+1}(\bar{A}_{t-1},1) - Y_{t+1}(\bar{A}_{t-1},0)\middle| I_t(\bar{A}_{t-1}) = 1\right] =$$
$$E\left[Y_{t+1}|I_t = 1, A_t = 1\right] - E\left[Y_{t+1}|I_t = 1, A_t = 0\right]$$

- Put

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

Design of MRT

Determine the number of participants so that micro-randomized trial can detect a main effect on proximal outcome

The main effect is a time-varying main effect $\beta(t)$, $t=1,\ldots,T$

The main effect is a causal effect.

Sample Size Calculation

- We calculate the number of subjects to test H_0: no effect of the intervention option, i.e., $H_0 : \beta(t) = 0, t = 1, 2, ...T$

- Size to detect a low dimensional, smooth alternate H_1.
  - Example: H_1: $\beta(t)$ quadratic with intercept, β_0, linear term, β_1, and quadratic term β_2 and test $\beta_0 = \beta_1 = \beta_2 = 0$

Sample Size Calculation

Alternative hypothesis is low dimensional

$\longrightarrow$ assessment of the effect of the activity recommendation uses contrasts of *between subject responses* **+** contrasts of *within subject responses*.

--The required number of subjects will be small.

Test Statistic for Sample Size Calculation

Test statistic is based on a least squares projection of $E[Y_{t+1}|I_t = 1, A_t]$ with functions of the form

$$\gamma(t) + \beta(t)(A_t - q_t)$$

where q_t is the randomization probability

q_t =.4 in HeartSteps

- We are not assuming this "model" is correct……..

Test Statistic for Sample Size Calculation

- Test statistic is based on least squares fit of $\gamma(t) + \beta(t)(A_t - q_t)$ to Y_{t+1} when $I_t = 1$

HeartSteps:

$$\beta(t) = \beta_0 + \beta_1 \lfloor \tfrac{t-1}{5} \rfloor + \beta_2 \lfloor \tfrac{t-1}{5} \rfloor^2$$

- You select parameterization of $\gamma(t)$

Alternative for Sample Size Calculation

- One calculates a sample size to detect a given alternative with a given power.

- Alternative:

$$H_1 : \beta_i = d_i \bar{\sigma}, i = 0, 1, 2$$

where d_i is a standardized treatment effect.

Alternative for Sample Size Calculation

- Average conditional variance is

$$\bar{\sigma}^2 = (1/T)\sum_{t=1}^{T} E\left[VAR\left(Y_{t+1}\middle|I_t = 1\right)\right]$$

Specify Alternative for Sample Size Calculation

Scientist indirectly specifies standardized d_i's

- initial main effect: d_0,
- average main effect over trial duration:

$$\frac{1}{T}\sum_{t=1}^{T}\left(d_0 + d_1\lfloor\frac{t-1}{5}\rfloor + d_2\lfloor\frac{t-1}{5}\rfloor^2\right),$$

- and day of maximal main effect: $-\frac{d_1}{2d_2}$

We solve for d_0, d_1, d_2

Test Statistic for Sample Size Calculation

- Put $Y_i = (Y_{i2}, \ldots, Y_{iT+1})^T$ for i^{th} subject

q+3 is the total number of parameters;

X_i is the associated design matrix (T by q+3)

N is sample size

Last 3 columns of X_i contain row entries:

$$I_{it}(A_{it} - q_t), I_{it}(A_{it} - q_t)\lfloor \tfrac{t-1}{5} \rfloor, I_{it}(A_{it} - q_t)\lfloor \tfrac{t-1}{5} \rfloor^2$$

Test Statistic for Sample Size Calculation

- "GEE" test statistic is

$$N\hat{\beta}^T(K\hat{\Sigma}K^T)^{-1}\hat{\beta} = N\hat{\beta}^T(\hat{\Sigma}_\beta)^{-1}\hat{\beta}$$

where $\hat{\Sigma}$ is the usual sandwich estimator of the variance-covariance and K is 3 by $3+q$ matrix picking out columns associated with coefficients β

Sample Size Calculation

- Under simplistic, incorrect (!), working assumptions, Σ_β only depends on polynomials in $\lfloor \frac{t-1}{5} \rfloor$, the marginal distribution of I_t and on the randomization probabilities.

- Σ_β does not depend on the form of $\gamma(t)$

Sample Size Calculation

- Under standard moment assumptions, the asymptotic distribution of the "GEE test statistic" is a Chi-Squared on 3 degrees of freedom with non-centrality parameter:

$$N d^T (\Sigma_\beta)^{-1} d$$

- Instead of a Chi-Squared on 3 degrees we use $\frac{3(N-q-1)}{N-q-3} F_{3,N-q-3}$ with the same non-centrality parameter.

HeartSteps Example

- Standardized d_i's
  - initial effect: d_0=0
  - output average main effect
  - day of maximal main effect: $-\frac{d_1}{2d_2} = 28$
- Projection used to form test statistic:

$$\gamma(t) + \beta(t)(A_{it} - .4), \; t = 1, \ldots, 210$$

where $\gamma(t) = \gamma_0 + \gamma_1 \lfloor \frac{t-1}{5} \rfloor + \gamma_2 \lfloor \frac{t-1}{5} \rfloor^2$

HeartSteps Sample Sizes
Power=.80, False-positive error=.05

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

Same Test Statistic for Analysis

- "GEE" test statistic is

$$N\hat{\beta}^T(K\hat{\Sigma}K^T)^{-1}\hat{\beta}$$

where K is 3 by $3+p$ matrix picking out columns associated with β coefficients

- No working assumptions

Small Sample Adjustment

- $\hat{e}_{it}$ is the i^{th} subject, t^{th} time point residual and $\hat{e}_i = (\hat{e}_{i1}, \ldots, \hat{e}_{iT})^T$

- Adjusted sandwich estimator:

$$\hat{\Sigma} = \hat{\sigma}^2 N \Big(\sum_{i=1}^{N} X_i^T X_i \Big)^{-1} \Big\{ \sum_{i=1}^{N} X_i^T B_i \hat{e}_i \hat{e}_i^T B_i X_i \Big\} \Big(\sum_{i=1}^{N} X_i^T X_i \Big)^{-1}$$

$$B_i = (I - H_{ii})^{-1}$$

Simulation Results
Type 2 Error Rate (2000 data sets)

Average Main Effect (Sample Size)	Power
0.05(115)	0.790
0.06(81)	0.794
0.07(61)	0.800
0.08(48)	0.801
0.09(39)	0.798
0.10(33)	0.803

Planning a Micro-Randomized Trial?

1) Be conservative in planning the trial:

    1) Under-estimate the amount of time participants are available for the intervention.
    2) Under-estimate the average standardized effect

Micro-Randomized Trial

2) Power to detect proximal main effect is robust to interactions and to delayed effects (e.g., burden)

3) Secondary data analyses concern time varying effect moderation and data analyses to construct data-driven decision rules for the JITAI

Micro-Randomized Trials: When are they (not) useful?

- NOT USEFUL: When malleable circumstances are rare: Want to learn the best type of alert to prevent suicide attempt
- USEFUL: When malleable circumstances change rapidly: Stress, urges to smoke, adherence, physical activity, eating
- NOT USEFUL: Proximal response cannot be feasibly assessed.
- USEFUL: Proximal response can be unobtrusively sensed or unobtrusively self-reported.

MRTs
vs
Other designs

- RCT
- N-of-1 Trials (& Crossover Trials)
- Factorial Designs

MRT vs. Randomized Control trial (RCT)

A randomized control trial (RCT) evaluating a JITAI compared to a suitable control.

- Assumes evidence exists to develop a high-quality JITAI including the
  - choice of tailoring variables & decision rules
- The primary aim of an RCT is to confirm the JITAI's effectiveness compared to an alternative
  - Is not well suited to constructing or optimizing a JITAI
- RCT is optimal for evaluation

MRT vs. N-of-1 Trial

N-of-1 Trials are usually multiple cross-over trials in which the order of the treatments are randomized within a person.

- RCT is too expensive or not feasible
  - Test: Is one-time treatment A better than one-time treatment B?
  - Ideally the treatments should have minimal delayed effects so (minimal carryover effects) or N-of-1 design should incorporate a suitable washout period

https://www.effectivehealthcare.ahrq.gov/ehc/products/534/1844/n-1-trials-report-130213.pdf

MRTs vs Factorial Experiments

A factorial design

- is an experimental design involving more than one components (e.g., factors); the levels of the components can be meaningfully crossed.

		Treatment A: NO	Treatment A: YES
Treatment B	NO	Neither A nor B	A only
	YES	B only	Both A and B

A MRT

- is a special form of a factorial; components are employed sequentially in time within a person.
- components can operate at different time scales
- randomization to subsequent components in a MRT may depend on outcomes of prior components

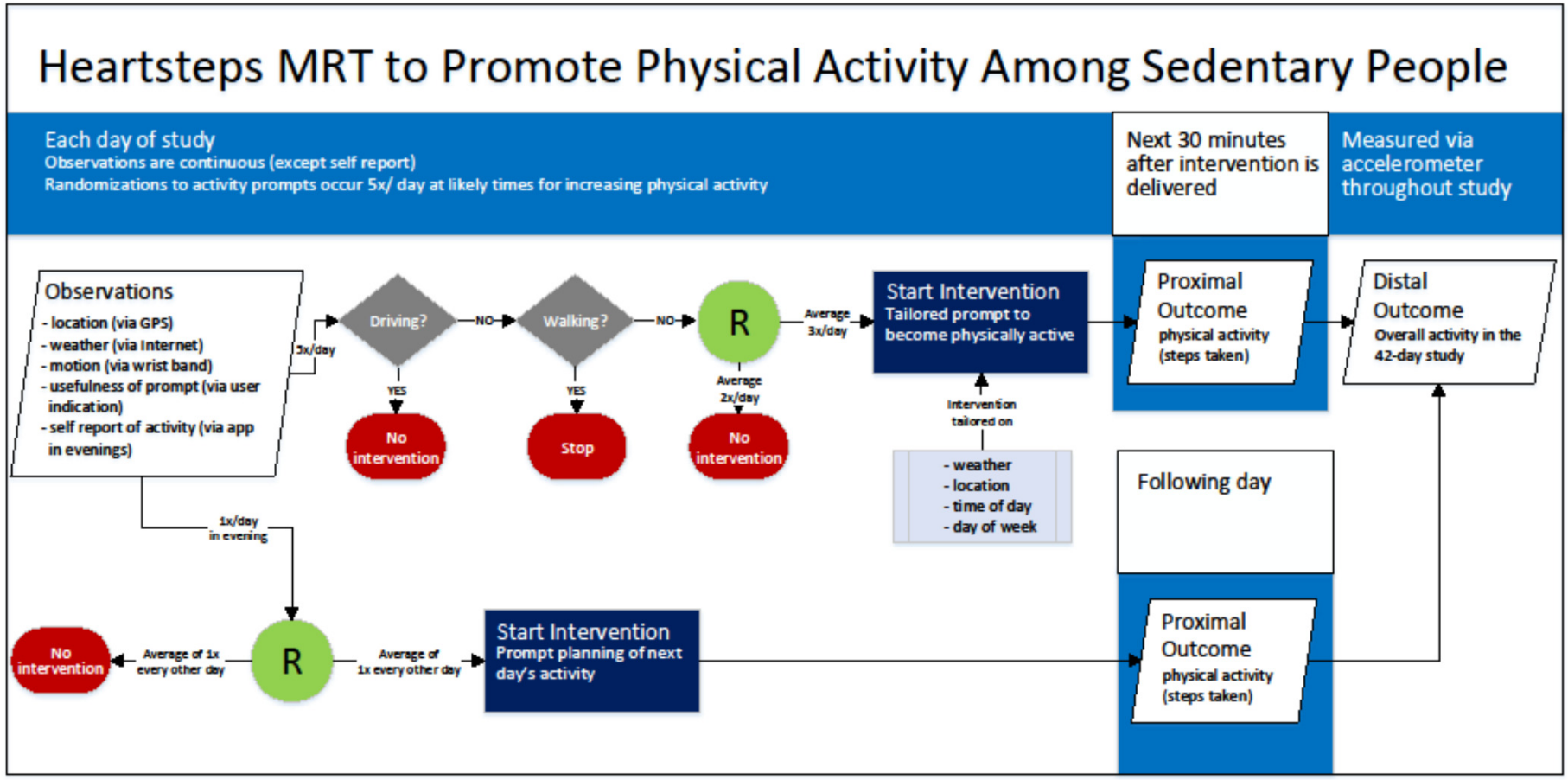
MRTs vs Factorial Experiments

Components can be randomized at different time scales, e.g. in HeartSteps:

Factor 1: Tailored activity recommendation is randomized 5 times per day (yes/no)

Factor 2: Daily activity planning is randomized each evening (yes/no)

MRTs vs Factorial Experiments

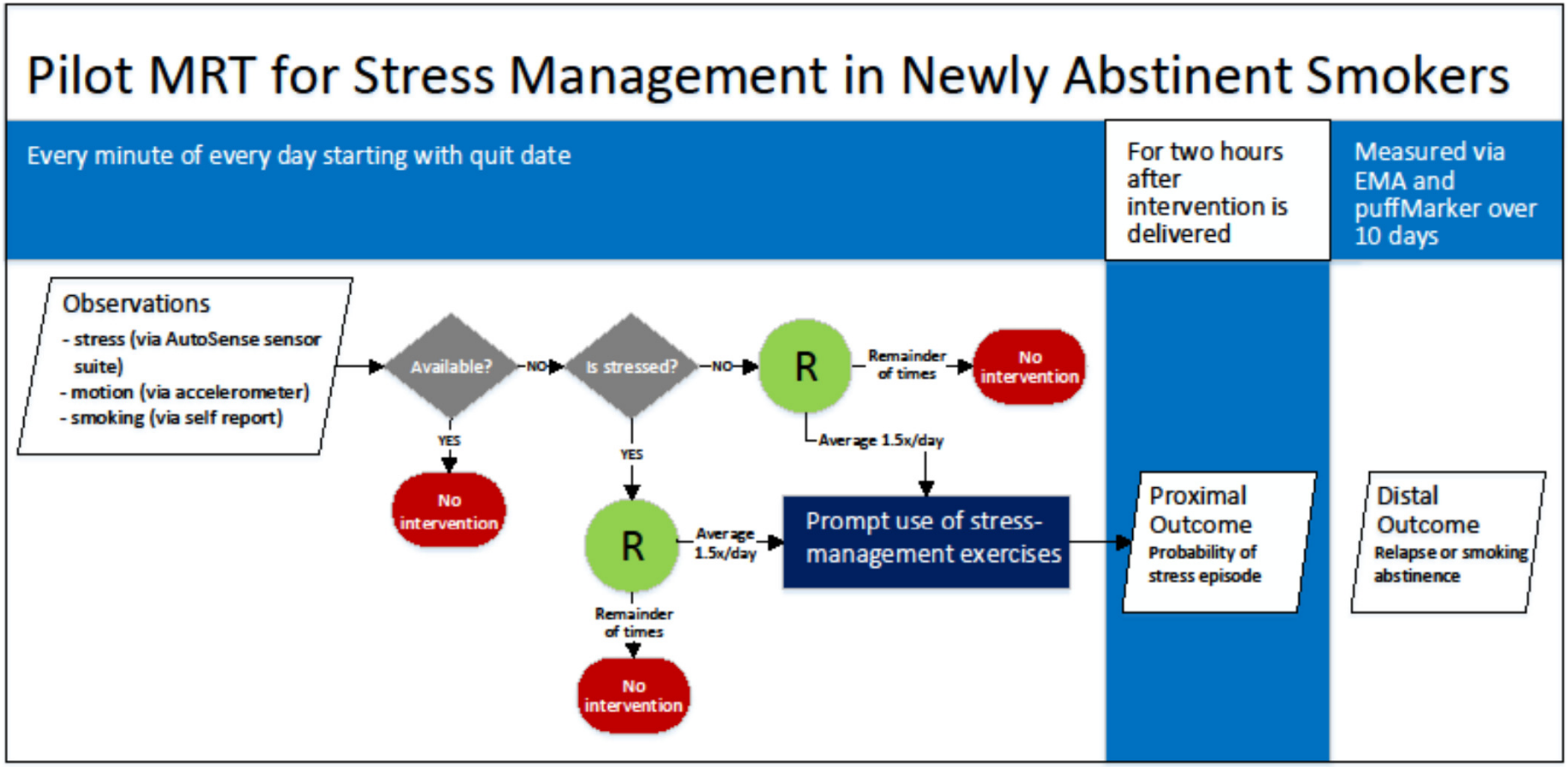


MRTs vs Factorial Experiments

Randomization to subsequent components in a MRT may depend on outcomes of prior components, e.g. in Sense2Stop:

> Randomization probabilities aim to result in an average of 1.5 reminders per day when the person is currently stressed and an average of 1.5 reminders per day when a person is not currently stressed.

MRTs vs Factorial Experiments



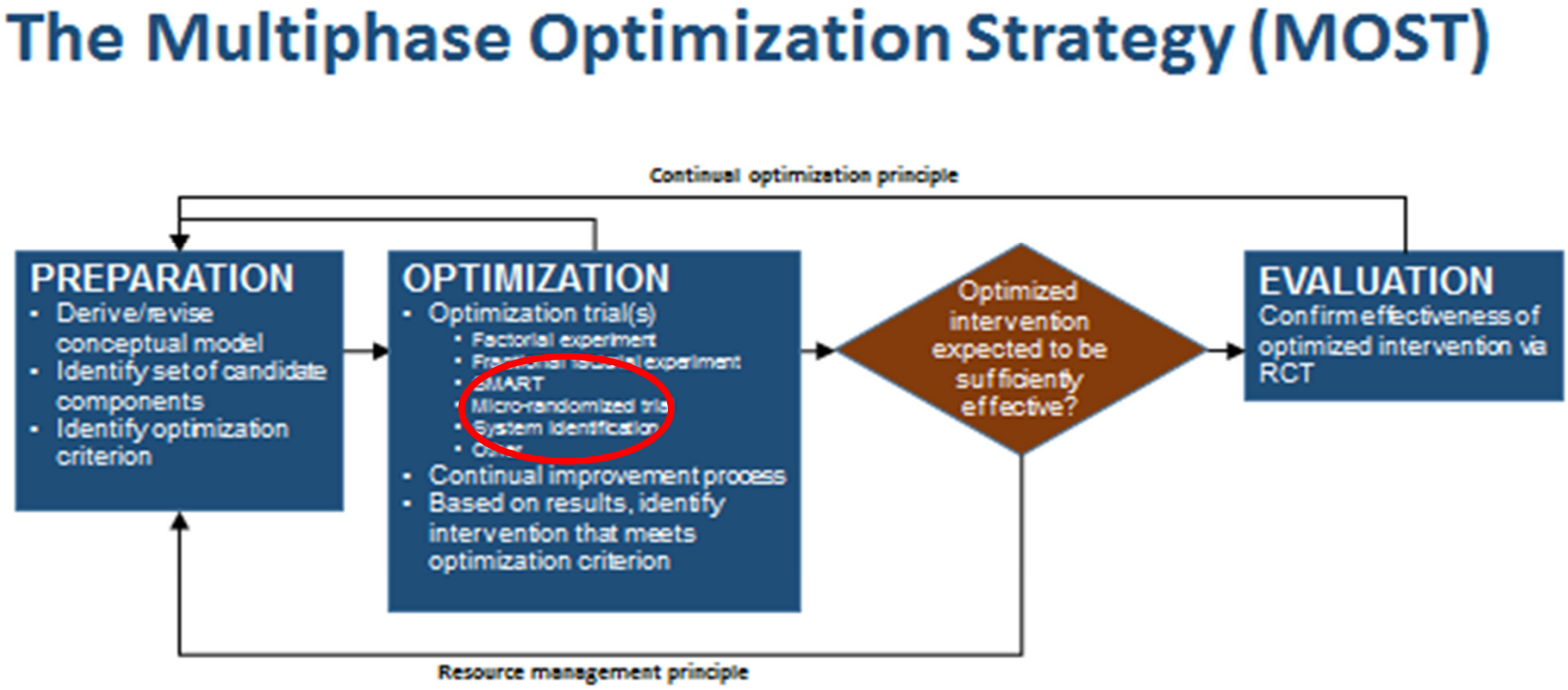
Experimental Design Challenges

Micro-randomized trials are a new type of factorial design

i. Time varying factors→ time varying main effects, time-varying two-way interactions, different delayed effects
ii. Design studies specifically to detect interactions between factors.
iii. Calculator:

https://pengliao.shinyapps.io/mrt-calculator/

MRTs and MOST



Collaborators!