Precision Medicine: Lecture 10
Microrandomized Trials

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Outline

Introduction

Microrandomized Trial Design

Data-Analytic Issues in Microrandomized Trials

Microrandomized Trials and Theoretical Grounding of JITAI Design

Implementation Considerations for Microrandomized Trials

Conclusion

mHealth

- Mobile health (mHealth) refers to the use of mobile technologies in healthcare
- With the advent of capable, affordable, and user-friendly mobile devices, mHealth is increasingly being employed to deliver interventions to users in their natural environments
- mHealth can be used to connect people with their healthcare providers, or alert them to relevent training, social support, etc
- This can improve access to care in under served populations where regular clinic visits are infeasible
- Potential for delivering real-time, tailored interventions

mHealth

- A common approach is to use the mobile device to enable users to access health interventions wherever and whenever they feel they need help
- For example, a person who is trying to quit smoking might access coping strategies when she is experiencing strong cravings
- While helpful, such "pull" interventions rely on a person to be aware and motivated to request the intervention during these states of vulnerability or opportunity
- In contrast, a "push" approach to mHealth interventions makes use of sensors, self-report, and computer algorithms to decide when an intervention is needed, and what intervention might be most appropriate

Just in time adaptive interventions

- Using sophisticated sensing devices (e.g., GPS) and phone-based ecological momentary assessment (EMA), it is possible to deliver interventions when they will have the largest influence on a person's behavior
- For example, for smokers, a moment of temptation to smoke can be a turning point toward relapse or abstinence
- mHealth interventions work best when they can adaptively respond to an individuals' actions and states and deliver intervention options when and where they are most needed
- mHealth DTRs are called "just in time adaptive interventions (JITAIs)"

Comparison to other frameworks

	RCT	SMART	MRT
Randomization	Once	Small number	Hundreds
Purpose	Confirmatory	Exploratory	Exploratory
Goal	Optimal treatment	Optimal DTR	Optimal JITAI
Time horizon	Single stage	Finite horizon	Infinite horizon

Table 1: Comparison of RCTs, SMARTs, and MRTs.

- MRTs may seem like an extension of SMARTs to a larger number of randomizations, but there are major differences in terms of application and analysis

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Microrandomization

- Microrandomization involves randomly assigning an intervention option at each relevant decision point
- For a typical multicomponent intervention, all components may be randomized concurrently, making microrandomization a form of a sequential factorial design
- Since intervention options are randomly assigned at each decision point, a long study may randomize each person hundreds or thousands of times
- Microrandomized trials are well-suited for optimizing JITAIs for two main reasons
  - Microrandomized trials enable assessment of the intervention's time-varying effects
  - Microrandomized trials are highly efficient because each intervention component is repeatedly randomized for each person

- Microrandomized trials enable assessment of the intervention's time-varying effects
  - Randomization produces compositional balance in unobserved and unknown factors, and thus differences in outcomes between these conditions can be more confidently attributed to the differing treatments
  - Repeated randomization allows researchers to assess how intervention components' causal effects change over the course of the study
- Microrandomized trials are highly efficient
  - Repeated randomization allows effect estimation to take advantage not only of the contrasts in outcomes between people, but also contrasts in outcomes when the same person is randomized to a different intervention option
  - Within-subject comparisons enable microrandomized studies to require far fewer participants than traditional full factorial designs

Distal, Proximal, and Lagged Outcomes

- Microrandomized trials are designed to assess causal effects of each randomized intervention component
- Defining the intervention outcomes is a key aspect of the design of a microrandomized trial
- The ultimate goal in many studies cannot be accurately measured on a daily basis (distal outcomes)
  - Did participant quit smoking?
  - Did participant develop a healthy lifestyle?
- Therefore, we must look at outcomes that can be evaluated more frequently (proximal outcomes)
  - Did participant smoke less today?
  - Was participant more active today?
- Distal outcomes are (presumably) achieved through the accumulation of proximal outcomes

Distal, Proximal, and Lagged Outcomes

- Proximal outcomes are the direct effect of a particular intervention, and are analogous to primary outcomes in RCTs
- A microrandomized trial can investigate not only proximal but also lagged effects
- The participant may ignore an intervention when it is given, but they might remember and engage with the intervention at a later time
- An understanding of such lagged effects is critical to developing low-burden JITAIs by identifying characteristics or contexts for which the frequency of intervention can be scaled back while maintaining target behavior

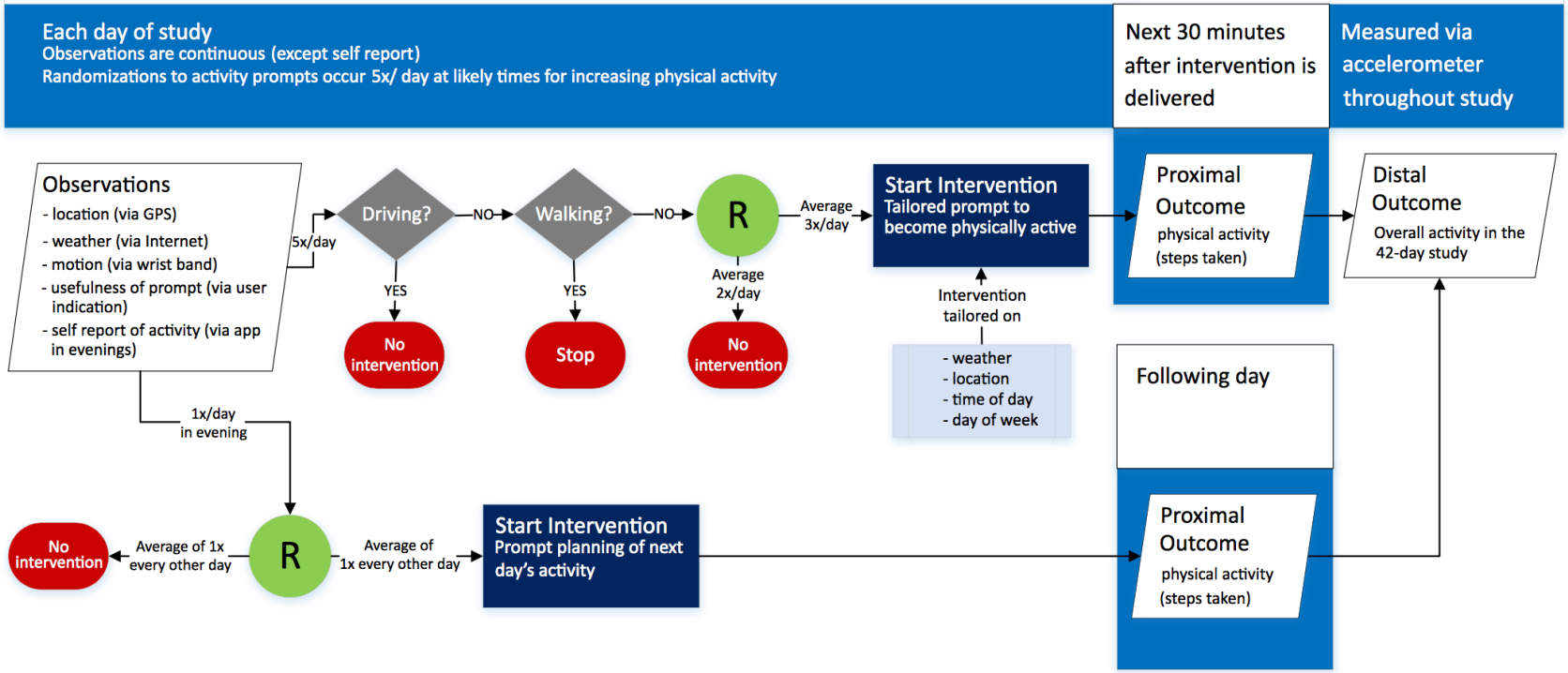
Research Questions for Microrandomized Trials

- A microrandomized trial can help researchers answer the following questions:
  - What are the proximal and lagged effects of an intervention component?
  - How do the proximal and lagged effects of an intervention component change over time?
  - Which factors (time-invariant or time-varying) moderate an intervention component's proximal or lagged effects?
- Answers to such questions will help us assess whether the interventions are working as intended and determine the contexts in which to give interventions to maximize efficacy
- It is such optimizations of JITAIs that microrandomized trials are designed to support

Example: HeartSteps

- HeartSteps consists of a wristband activity tracker that monitors users' steps throughout the day and an Android application intended to encourage walking
- For the purposes of the MRT, the phone application contains two main intervention components:
  (a) Daily activity planning
  (b) contextually relevant suggestions for physical activity
- The daily activity planning involves the formulation of plans that specify when, where, and how a person will engage in a goal-advancing behavior
- The contextually relevant suggestions for physical activity adapt to the user's current situation — time of day, location, weather, etc — which should make them easier to follow

Heartsteps MRT to Promote Physical Activity Among Sedentary People



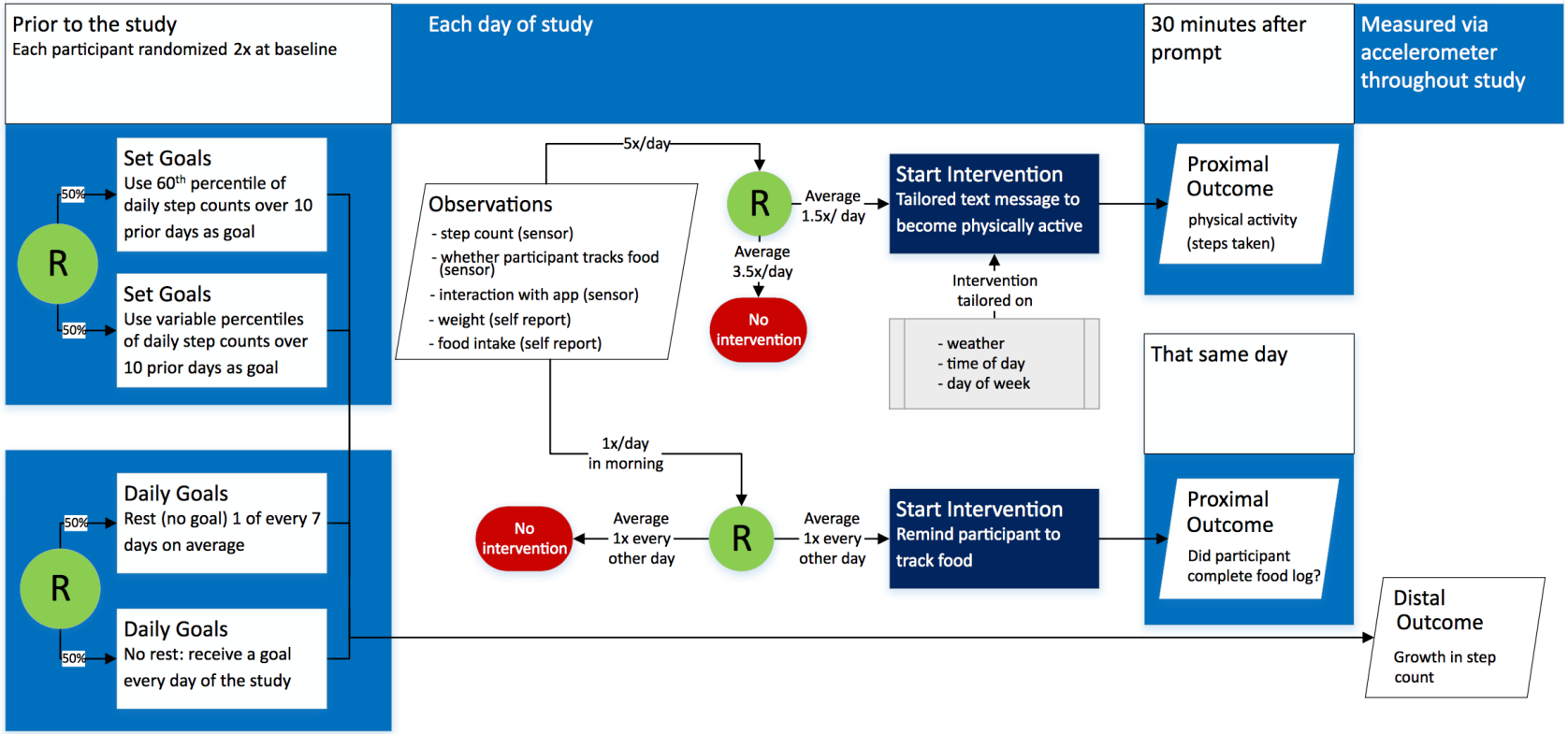
Randomization and Participant Availability

- The core concept behind microrandomized trials involves randomizing the options for a particular intervention component each time that intervention component may be delivered
- Sometimes it may be inappropriate to deliver an intervention
  - For HeartSteps' activity suggestions, we do not want to deliver a suggestion if a participant is already walking or while driving
- In such cases, randomized intervention-component delivery takes place only when the participant is available for the intervention
- During unavailable times, these intervention components would never be delivered, and the data for those decision points would include an "unavailable" indicator

Example: BariFit

- Physical activity remains low after bariatric surgery which can lead to medical complications
- The BariFit trial was desigend to promote weight maintenance among people who received bariatric surgery using two main components
  - Increase physical activity by sending context dependent prompts
  - Improve diet by reminding participants to track food intake
- At the time of development, this project was novel in its use of separate randomizations at the start of the study, on a daily basis, and five times throughout the day

BariFit MRT to Promote Weight Maintenance Among People Who Received Bariatric Surgery



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Analyses for Assessing Proximal Effects

- Microrandomized trials generate intensive longitudinal data
- Many of the modeling approaches used to analyze intensive longitudinal data, such as multilevel models (MLMs) and generalized estimating equations (GEEs) can be used in microrandomized trials to assess overall treatment effects and factors that might moderate those effects
- Primary analyses often focus on detecting minimum clinically significant differences in the proximal main effects
  - That is, whether each randomized intervention component is showing its intended proximal effect

Participant availability

- Effect estimation for intervention components that depend on participant availability require a more nuanced concept of the proximal main effect
- The proximal main effect compares the outcome when treatment is delivered versus not delivered, but only among individuals who are available for treatment
- For some intervention components, the population of available individuals may change over the course of the trial
- For example, in HeartSteps, individuals for whom the intervention is working might already be active at the randomization points

Analyses of Time-Varying Moderation

- Microrandomized-trials are also able to assess how other time-varying factors moderate proximal effects of intervention components over time
- Questions about time-varying moderation are particularly important because the same individual can receive an intervention in many different contexts
- Knowing how the context at decision times moderates the effect of an intervention can help create decision rules that maximize receptiveness to the intervention

Power

- A detailed discussion of sample size calculations for microrandomized trials is beyond the scope of this class
- A consideration unique to microrandomized trials is that the power depends on the proportion of time participants will be available for an intervantion
  - If participants are available 50% of the time, HeartSteps requires 43 subjects
  - If available 70% of the time, it reduces to 33 subjects
- Preliminary power calculations show that microrandomized trials are highly efficient
- The high efficiency of microrandomized trials is due to their ability to take advantage of both between-subject and within-subject contrasts in the proximal outcome.

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JITAI Design

- Behavioral theories are used to design JITAI's, but there are issues
- We do not know how to translate abstract theoretical constructs into technological behavior-change intervention components
- Behavioral theories are often not granular enough to guide the design of decision rules for the delivery of intervention components
- For example, how soon should a physical-activity goal be decreased if a participant starts to repeatedly miss the current goal?
- Microrandomized trials can help advance the design of behavior-change technologies by comparing different implementations of a behavior-change technique

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Deciding Which Components to Randomize

- A key consideration in the design of a microrandomized trial is the decision regarding which intervention components and options to randomize
- This choice should be governed by a combination of scientific, design, and usability considerations
- In general, one would randomize intervention components for which:
  - There is insufficient scientific evidence for their effect on the proximal outcome
  - We do not sufficiently understand the dynamics of their operation over time
- Randomization could also be among different types of interventions that can be delivered at the same decision points

Defining Proximal Outcomes

- For some components, proximal outcomes can be relatively clear and easily measurable
  - For a goal-setting component of a walking intervention, the attainment of the daily step goal is an obvious proximal outcome.
- For other components, no such unambiguous proximal outcomes present themselves
- A proximal outcome which is not a shorter-time-scale version of the distal outcome requires a theory of mediation (i.e., that individuals smoke to reduce stress), which must be tested or theoretically justified
- The data collected in a microrandomized trial allows for testing of such mediational relationships

Defining Proximal Outcomes: Example

- What is the right proximal outcome for the HeartSteps contextual activity suggestions?
  - Is it whether or not the specific activity contained in the message was followed as suggested?
  - Is it the absolute step count for a period after the suggestion was delivered? If so, over what period?
  - Is it the change in the step count for a period following the suggestion over the step count for an equally long period prior to the suggestion?
- The only way to accurately tell whether the person followed the suggestion would be to ask
- Asking would act as an intervention in its own right, confounding the effects of the suggestions themselves
- Thus, step count was the preferred proximal outcome

Pull vs Push Interventions

- Although they are a powerful way of optimizing JITAIs, microrandomized trials have several limitations
- Microrandomized trials are only applicable for testing of push interventions — reminders or prompts that are delivered to individuals based on a set of decision rules.
  - If a researcher wants to microrandomize a pull intervention component that component first needs to be converted into a push intervention
  - For example: graphs for providing feedback on a health behavior can be converted to notifications to access the graphs
- Push interventions can be burdensome, so microrandomization will be typically limited to a subset of components of an mHealth intervention

Limitations

- The analyses of microrandomized trial data focus on proximal outcomes
  - Microrandomized trials are most appropriate for testing of intervention components for which proximal outcomes are well defined, and can be measured in a low-burden way
- As a within-subject design, microrandomized trials are not suitable for testing of interventions for very rare events
  - For example: Interventions for prevention of manic episodes in bipolar disorder, which would be experienced by few people during a study and seldom experienced repeatedly by any one person over the course of the trial
  - Interventions for such rare events should be optimized through traditional cross-sectional designs

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Conclusions

- Disease management often requires precise timing of interventions
- Mobile technologies can collect data and deliver tailored interventions
- Effectiveness of mHealth interventions may depend on patient state
- JITAIs formalize the idea of precise timing of interventions
- Estimating JITAIs requires new ways of thinking about clinical trials
- MRTs estimate JITAIs by randomizing patients many times