Adaptive Interventions

Module 1

*Getting SMART*: Experimental Design and Analysis Methods for Developing Adaptive Interventions
Outline

- What are Adaptive Interventions?
- Why use Adaptive Interventions?
- Adaptive Intervention Design Goals
- Summary & Discussion
AIs are individualized sequences of treatments

AIs operationalize clinical practice, and in fact it mimics how we make decisions in real-life.
Definition of AI

- Go by many different names:
  - Adaptive health interventions,
  - Adaptive treatment strategies,
  - Dynamic treatment regimes,
  - Treatment algorithms,
  - Stepped care models,
  - Treatment protocols,
  - Individualized interventions
  - ...
Example

- Adaptive drug court program for drug abusing offenders
  - The goal: Minimize recidivism and drug use
  - Operationalized by graduating from the drug court program
  - Marlowe et al., (2008; 2009; 2012)
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 = (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.
At the termination hearing, the individual is terminated from the program and sentenced on the original charge/s unless he/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.
First Stage Decision Rule

At point of entry into the program:

If risk = low
   Then, stage 1 intervention = {As-needed + SC}

Else if risk = high
   Then, stage 1 intervention = {Bi-weekly + SC}

3. Intervention options:
   Type/Dose

4. Decision rule

5. Outcomes:
   Distal → Long-term goal of intervention:
   Program graduation (14 consecutive weekly negative drug urine specimens)
   Proximal → Short-term goal of decision rules:
   Compliance and response in the course of intervention (mediator)

2. Tailoring Variable:
   Patient information used to make treatment decisions

1. Decision Point:
   A time in which treatment options should be considered based on patient information (Yoshino et al., 2009)
AI: 5 Elements

1. Decision Points
2. Tailoring Variable
3. Decision rule
4. Intervention Options
5. Proximal + Distal Outcomes

- Triggered
- Monitoring
- Individualizing
- Delivering

Adaptation process

Guided
AI: 5 Elements

1. Decision Points
2. Tailoring Variable
3. Decision rule
4. Intervention Options
5. Proximal + Distal Outcomes

Not all individualization is adaptive...
Various Types of Individualization

Individualization can take various forms

Singular vs. Sequential

Static vs. Dynamic
Various Types of Individualization

Singular/Sequential

**Singular:** for each participant, treatment is individualized at most once.

**Sequential:** for some (or all) of the participants, treatment may be individualized multiple times.
Various Types of Individualization

**Static/Dynamic**

**Static**: individualization based on information that is unlikely to change over time as a result of treatment.

**Dynamic**: individualization based on information that can change over time as a result of treatment.

Static examples: baseline symptoms, personality traits, gender, age...
### Various Types of Individualization:

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<thead>
<tr>
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<th>Dynamic</th>
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<td><strong>At program entry</strong>&lt;br&gt;Stage 1 = As-needed + SC&lt;br&gt;<strong>Then, at week 4</strong>&lt;br&gt;If program response = no&lt;br&gt;Then, stage 2 = {more SC}&lt;br&gt;Else if program response = yes&lt;br&gt;Then, stage 2 = {continue}</td>
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Adaptive = Dynamic individualization
AIs provide a paradigm by which to improve clinical, policy, and public health practice which by its nature is often adaptive.

Individualization/personalization/tailoring is achieved by use of a decision rules at each decision point. Each decision rule takes accumulated, ongoing information about the unit (e.g., individual) including past response, adherence, burden, etc., and outputs a recommended, individualized treatment tailored to the circumstances of that unit.

Summary

- Adaptive Intervention is:
  - a sequence of individualized treatments
  - that uses dynamic information to decide what type/dose/modality of treatment to offer
  - its objective to guide clinical practice or public health policy.
A scientist first develops an AI. Later, they are used by clinicians to guide their thinking in actual clinical practice.
Summary

The role of the researcher?

Develop good decision rules to guide clinical practice and health policy

Answer open scientific questions concerning the development of good decision rules
Other Examples of Adaptive Interventions

- McKay (2005; 2009): AIs for alcohol and drug-use disorders
- Booner et al., (2004): Adaptive behavioral contingencies to enhance adherence to methadone treatment in opioid-dependent patients
- Rush et al. (2003) medication algorithms for treating depression, schizophrenia, and bipolar disorders


Adapt the intensity of family-based interventions to the needs and motivation of the family.
Aim: reduce substance use and antisocial behavior among students ages 11–17.

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Adapt the types of engagement strategy to the engagement status of the patient in treatment
How to extend behavioral and pharmacotherapy interventions for alcohol and drug-use disorders

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Population: opioid-dependent patients ($n = 127$) newly admitted to an ambulatory treatment program that provides methadone.

Two types of adaptation:
During the program, they adapted the type of behavioral contingencies to promote counseling attendance and drug negative urine specimens (e.g., latter medication time if you missed a session, discharge from the program if you missed too many sessions).
They also provided a rescue intervention if the participant was classified as a non-responder (defined as a 50% or higher rate of missed counseling sessions or a 50% or higher rate of drug-positive urine specimens (or both) over the first 90 days of randomized care).


Population: patients with major depression, schizophrenia, bipolar disorders
Type of adaptation: mediation algorithms to guide clinical care. Clinicians could deviate from the algorithms.
Here, decision rules are well specified.
Outline

- What are Adaptive Interventions?
- Why use Adaptive Interventions?
- Adaptive Intervention Design Goals
- Summary & Discussion
Why Adaptive Interventions?

1) High **heterogeneity** in need for or response to any one treatment
   
   – What works for one person may not work for another,
   
   – Thus, need to
     
     • Detect early signs of treatment failure
     • and modify the treatment
     • to prevent ultimate treatment failure
Why Adaptive Interventions?

2) Chronic or **waxing and waning** course of disorders
   - Improvement is not linear
   - Need to identify:
     - Intervals during which more intense treatment is required
     - Intervals in which less treatment is sufficient
     - Adapt treatment intensity accordingly

![Rehab Kittens](image)
Why Adaptive Interventions?

3) When treatment is **burdensome**
   - Side effects
   - Patient required to invest Time/Effort
   - Burden leads to non-adherence
   - Non-adherence reduces positive intervention effect

   - Need to:
     - Identify signs of burden
     - Modify intensity based on signs of burden

Burden=exceeds personal resources.
Why Adaptive Interventions?

4) Many treatments are **costly**
   - Certain treatments can be very expensive
   - Resources are often limited
   - Difficulties in scalability
   - Need to:
     - Try less expensive treatment first
     - Offer more costly treatments to people who need it
5) Motivations for adapting mHealth

- **Boredom**
  - Need to change delivery modalities

- **Cognitive overload**
  - Sequence and adapt content to people’s attention capacity

- **Habituation**: repetition → lower arousal
  - Stop intervention from time to time, introduce new content, change presentation.
Outline

• What are Adaptive Interventions?
• Why use Adaptive Interventions?
• Adaptive Intervention Design Goals
• Summary & Discussion
Overview of Design Goals

- Concrete example to guide our discussion
- General design goals: strength and replicability
- Design goals for
  - Distal outcome
  - Proximal outcomes
  - Intervention options
  - Decision points
  - Tailoring variables
  - Decision rules
**Design Goals: Concrete example**

- Help me build a tech-based AI for at-risk drinkers:
  
  **Why at-risk drinking?**
  - Exceeding gender-specific weekly/daily limits at least once in past 3 months
  - Associated with serious adverse consequences

  **Why tech-based (mobile + web)?**
  - Effective approach in reducing at-risk drinking
  - Require substantially lower delivery costs.

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**CLARIFICATION NOTE:** Here we are discussing the design of the adaptive intervention (hence “treatment design”). We are not discussing the design of a trial to inform the development of an AI—that’s the next module on “trial design”.

Weekly limits: Men, > 14; Women, > 7 drinks per week
Daily limits: Men, ≥ 5; Women, ≥ 4 drinks per day
Select intervention options that will affect my proximal outcome.

Use behavioral/social/biological theory, clinical experience, expert opinion, consultation with clinical staff, review of extant literature.

<table>
<thead>
<tr>
<th>Design Goals: Strength</th>
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<tbody>
<tr>
<td>Maximize the <em>strength</em> of the AI <em>(not the trial)</em></td>
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<tr>
<td>- This can be achieved by:</td>
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<tr>
<td>- Define your proximal and distal outcomes,</td>
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<tr>
<td>- Select effective intervention options</td>
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<tr>
<td>▪ That will affect your proximal outcome</td>
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<tr>
<td>- Well chosen tailoring variables,</td>
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<tr>
<td>▪ Theory, clinical experience, expert opinion, consult your clinical staff</td>
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<tr>
<td>- Well measured tailoring variables,</td>
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<tr>
<td>- Well formulated decision rules,</td>
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<td>- Well implemented decision rules.</td>
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Fidelity of implementation -- intervention is delivered in the way it was designed to be delivered.

Non standard scenario: for example when you use self report to measure a tailoring variable (e.g., response/non-response) and the person does not provide the self-report; what would you do, how would you classify this person?
Recall: 5 Elements of AI

1. Decision Points  ← Trigger
2. Tailoring Variable  ← •Monitoring
3. Decision rule  ← •Individualizing
4. Intervention Options  ← •Delivering
5. Proximal + Distal Outcomes  ← Guide
I select this outcome because it is clinically meaningful;
I actually want at-risk drinkers to transition from at–risk to non-at-risk drinking patterns; but I selected a more reasonable proximal outcome given that I want to focus on brief interventions.
Selecting a proximal outcome is important because it will guide the type of intervention you will offer, and/or the tailoring variable that you will select.

If my proximal outcome is stress reduction, my intervention options might be designed to reduce stress (e.g., stress-management intervention), and/or I will adapt the intervention based on the participant’s level of stress.

Response-based pathways: short-term information that is (for obvious reasons) part of the distal outcome:
these are proximal measures that are part of the distal outcome, they form the distal outcome.

Performance-based: these are mechanisms (behaviors, experiences and feelings) that predict the distal outcome.

Engagement-based: these are indicators of engagement and adherence that predict the distal outcome.

Often there are various ways to achieve the distal outcome; the distal outcome can be a combination of all pathways.
Remember, practically, monthly reduction in at-risk drinking will help me achieve my distal outcome.

So, practically, it makes sense to identify participants who do not show sufficient reduction on a monthly basis, and intensify the intervention;

whereas those who show enough reduction can just continue with the initial intervention.
AI Design Goals: Intervention Options

- Select intervention options in light of proximal outcomes

**Stress reduction (Performance-based)**

Stress Management Program including:
- 1 in-person session
- Mobile-based intervention

**Monthly reduction in at-risk drinking days (Response-based)**

1) Intensify with in-person sessions (for participants who do not show sufficient monthly reduction).
2) Continue (for those who show sufficient monthly reduction)

What is the justification for selecting different intervention options for different subgroups?
AI Design Goals: Tailoring Variables

You are in fact asking me to:
* Clearly define the tailoring variable; and
* Justify it.

- How to select a tailoring variable?
  - Select variables that are useful for making intervention decisions.

Useful how???
AI Design Goals: Tailoring Variables

Type 1: The Obvious
Useful in identifying a sub-group for whom specific options should not be considered for obvious practical/ethical/clinical reasons.

Type 2: The Predictor
Useful in identifying a sub-group who need an intervention.

Type 3: The Moderator
Useful in identifying a sub-group of people who would benefit more from one type of intervention option over another.
Another example: Practically, I will not consider an intervention that requires family support to a participant with poor family functioning.

Family functioning is a tailoring variable.
AI Design Goals: Tailoring Variables

Type 2: The Predictor

Useful in identifying a sub-group of people who need an intervention (not clear what type) and a sub-group who do not need an intervention.

Example:

- Empirical evidence suggests that
  - People who remain at risk at week 4 (i.e., non-responders) are likely to fail in long-term (remain at-risk drinkers at week 12)
  - Hence, non-responders require an intervention
In the next slide you will see why I call this the moderator: because it is guided by empirical evidence concerning how this variable moderates intervention effects.
I used this moderated regression to determine whether and how response status can be used to tailor the tactic (i.e., to decide what tactic to offer and for who)

Moderation is used because via moderation I can determine whether the effect of the tactic varies depending on response status (my candidate tailoring variable)

Results: Tactic interacts with the response status in the following way.
Now you know why we call this type of tailoring variable the Moderator: because it is guided by empirical evidence concerning whether and how this variable moderates the intervention effect.

But its not a simple moderation that we are looking for in empirical evidence, it’s a special type of moderation that is informative for decision making.
This slide demonstrates that not all moderators are tailoring variables.
AI Design Goals: Tailoring Variables

Tailoring variables can be

• Baseline variables: gender, age, symptom severity

• Your proximal outcomes
  • Performance-based mechanisms
    Example: Stress, social norms for drinking
  • Engagement/adherence-based mechanisms
    – Example: Weekly engagement in a web-based intervention
  • Short term representations of the distal outcome
    – Example: Monthly at-risk drinking days
Assume that I want to use this instrument to define response and non-responders so that non-responders will receive augment and responders will receive continue. I need to make sure is instrument is reliable and valid.
AI Design Goals: Tailoring Variables

Reliability:
- Test produces stable/consistent results with repeated trials.

Unreliability:
- What if there is no black box?
  - Participants with the same level of drinking mark an answer depending on whatever they think a standard drink is
  - Captures random variability (noise) in the testing method rather than actual differences in at-risk drinking (signal).
  - Unsystematic assignment of people to subsequent interventions.
Assume that because of the way I framed the question, people consistently report that they had fewer at-risk drinking days than they actually did.

Validity is judged by external criteria.
AI Design Goals: Decision Points

- How to select decision points?
  - Based on the *dynamics* of the tailoring variable.
  - **Dynamics:**
    - Frequency at which tailoring variable is likely to change over time
    - In a meaningful manner→ changes are indicative of need for an intervention

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<td>Weekly</td>
<td>Every week</td>
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<td>X weeks after baseline</td>
<td>At week X</td>
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<tr>
<td>Monthly</td>
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<tr>
<td>X months after baseline</td>
<td>At month X</td>
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AI Design Goals: Decision Rules

• Specify a decision rule for each decision point?
  – How to construct good decision rules?
    ▪ Articulate a theoretical model that describes
      o The expected outcome associated with each intervention option, for
        every value of the tailoring variable.
    ▪ Model can be based on:
      o Clinical experience
      o Experimental and observational studies
      o Discussions with research team / clinical staff,
        “What intervention option would be best for people with
        this value on the tailoring variable?”
AI Design Goals: Decision Rules

- How to construct good decision rules?
  - Good decision rules are objective, are operationalized.
  - Strive for comprehensive rules, yet clear and specific
  - Cover situations that can occur in real-life and practice
    o Including when tailoring variable is missing or unavailable.

Accidents at home most commonly occur in the kitchen.

- 5% of iPhone owners have put an iPhone in the washing machine
- 9% of iPhone owners have dropped an iPhone in the toilet
- 6% of iPhone owners have left an iPhone on top of the car and driven off

69% of iPhone accidents are caused by the owner.

SQUARETRADE
AI Design Goals: Decision Rules

- How to operationalize decision rules?

**Bad:** Individuals who drinking too much are non-responders and receive augment.

**Better:** Individuals who experience 2+ heavy drinking days (HDDs) in the past month are declared non-responders and receive in-person in addition to initial treatment.

**Awesome:** Individuals who experience 2+ HDDs in the past month are declared non-responders and receive in-person in addition to initial treatment; Whereas those with HDDs<2 in the past month continue with initial treatment.
Outline

- What are Adaptive Interventions?
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Questions?

More information:


Examples of Critical Decisions

- About treatment *timing*:
  - How long should we use the first treatment
    - before transitioning to a maintenance/relapse prevention treatment? And which treatment should this be?
    - before declaring non-response and moving to another treatment? And which treatment should this be?
Examples of Critical Decisions

- About treatment *engagement*:
  - How do we re-engage patients who are non-adherent?
Examples of Critical Decisions

• About *intervention delivery*
  
  – Who should make health-related goals (patient vs. provider)?
  – The location of the treatment (home, clinic, school)?
  – Mode of delivery (internet vs. in-person)
Examples of Critical Decisions

• About *intervention tactics*

  – For people who do **not respond** well to treatment A
    ▪ Should we enhance the intensity of A or add B
    ▪ Should we enhance the intensity of A or switch to B
    ▪ Should we continue with A or step-up to C

  – For people who **respond** well to treatment A
    ▪ Should we continue or step-down
    ▪ Should we stop immediately or gradually
    ▪ Do we need a booster or not