Adaptive Interventions and SMART Designs

Daniel Almirall, Inbal “Billie” Nahum-Shani, Linda M. Collins, Susan A. Murphy and many colleagues and friends

Optimization of Behavioral and Biobehavioral Interventions

NIH, September 9, 2016
Rough Outline

- Part 1(a): Adaptive Intervention Designs 1:00PM – 1:45PM
- Part 1(b): SMART Study Designs 1:50PM – 2:30PM
- Long Break 2:30PM – 2:45PM
- Part 2: SMART Case Studies 2:45PM – 4:00PM
Adaptive Interventions

Part 1(a)

Optimization of Behavioral and Biobehavioral Interventions

NIH, September 9, 2016
Outline for Part 1(a)

- What are adaptive interventions (AIs)?
- What are the elements of an AI?
- Why do we need AIs?
What are adaptive interventions (AIs)?
What are the elements of an AI?
Why do we need AIs?
Definition of AI

A sequence of **individually tailored decision rules** that...

- Specify *whether, how or when*—and based on *which measures*—to alter the
  - dosage (duration, frequency or amount),
  - type, or
  - delivery of intervention components
- at *critical decision points* in the course of care.
Example 1 of an AI

- ADHD in children ages 6 – 12

- Response status measured monthly by the school teacher
  - Based on two measures: Non-response if: Impairment Rating Scale $\geq 1$ domain & Individualized Targeted Behaviors < 75%

```
Example of an AI

MED

Responder

Non-Responders

Maintain: MED

Augment: MED + BMOD
```
Some Characteristics of an AI

- An **intervention design** (not an experimental design!)
- …in which **intervention options are individualized** to accommodate the specific and changing needs of individuals.
- Leads to a **sequence** of individualized treatments.
- Mimic how we make **decisions in real-life**.
- **Replicability** is important.
Different terms are often used to refer to an “adaptive intervention”

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

Example 2 of an AI

- 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)
Adaptive Drug Court Program

Low risk

High risk

As-needed court hearings + standard counseling

Bi-weekly court hearings + standard counseling

Non-responsive

Non-compliant

As-needed court hearing + ICM

Non-compliant

Bi-weekly court hearing + ICM

Non-compliant

Jeopardy contract: “zero tolerance”
Outline for Part 1(a)

- What are adaptive interventions (AIs)?
- What are the elements of an AI?
- Why do we need AIs?
AI: 5 Elements

1. Decision Points

2. Tailoring Variable

3. Decision rule

4. Intervention Options

5. Proximal + Distal Outcomes

---

Triggered

- Monitoring
- Individualizing
- Delivering

Guided

Adaptation process
Adaptive Drug Court Program

- Low risk
  - As-needed court hearings + standard counseling
  - Non-responsive
  - Non-compliant

- High risk
  - Bi-weekly court hearings + standard counseling
  - Non-responsive
  - Non-compliant

- Non-responsive
  - As-needed court hearing + ICM
  - Non-compliant

- Non-compliant
  - Bi-weekly court hearing + ICM
  - Non-compliant

- Non-compliant
  - Jeopardy contract: “zero tolerance”
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\}

5. Outcomes:
Distal $\rightarrow$ Long-term goal of intervention:
  \textit{Program graduation} (14 consecutive weekly negative drug urine specimens)
Proximal $\rightarrow$ Short-term goal of decision rules:
  \textit{Compliance} and \textit{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
Identify the 5 elements in AI Example 1?

- ADHD in children ages 6 – 12

- Response status measured monthly by the school teacher
  - Based on two measures: Non-response if: Impairment Rating Scale ≥ 1 domain & Individualized Targeted Behaviors < 75%
Example 3 of an AI

- Older, minimally-verbal children with autism, ages 5 – 8

- Response status measured by therapist, based on Clinical Global Impressions-Improvement scale (Slow response if CGI-I > 2)

- By necessity, CGI-I is defined differently depending on whether child is in DTT or JASP initially
Outline for Part 1(a)

- What are adaptive interventions (AIs)?
- What are the elements of an AI?
- Why do we need AIs?
Motivation for AIs

1) High **between person heterogeneity** in need/response to any one intervention
   
   e.g., what works for Danny may not work for Shawna

2) High **within person heterogeneity**, or “non-linear improvement,” or the “waxing and waning” of disorders
   
   e.g., what’s needed for Danny now may not be needed later
   
   e.g., think health behavior maintenance or adherence issues

3) Intervention **burden or cost**
AIs Experienced Differently by Different Stakeholders

- Adaptive Intervention is:
  - a sequence of individualized intervention options
  - that uses dynamic information to decide what type/dose/modality of intervention to offer
  - Its objective to guide clinical/academic practice or public health policy.
Adaptive Intervention is:

- a sequence of individualized intervention options
- that uses dynamic information to decide what type of intervention to offer
- Its objective is to guide clinical/academic practice or public health policy.

AI is experienced differently by different stakeholders:

AI is a sequence of decision rules that recommend what intervention to offer at each critical decision point.
The Role of the Researcher

Develop **good decision rules** to guide clinical/academic practice and policy

Answer **open scientific questions** concerning the development of good decision rules
Examples of Scientific Questions

• How long should we use the first treatment?
  – …before declaring non-response and moving to another treatment?
  – …before transitioning responders to a maintenance/lower-intensity treatment?

• What tactic should we use for non-responders to treatment A?
  – Continue with A; enhance intensity of A; add B; switch to B; step-up to C?

• What tactic should we use for responders to treatment A?
  – Should we continue or step-down?
  – Should we stop immediately or gradually?
  – Do we need a booster or not?

• How do we re-engage patients who are non-adherent or drop-out?
• Where should we deliver the treatment (e.g., home or clinic)?
• How should we deliver treatment (e.g., internet or in-person) ?
• How do we define non-response?
Some Myths or Misconceptions about AIs

- **MoM 1**: Tailoring variables must be defined in exactly the same way regardless of history of treatment
- **MoM 2**: An adaptive interventions must recommend a single intervention component at each decision point
- **MoM 3**: Adaptive interventions seek to replace clinical judgement
- **MoM 4**: Adaptive interventions are only relevant in treatment settings
- **MoM 5**: Adaptive interventions must involve randomization
- **MoM 6**: The tailoring variables in an adaptive intervention are research assessments
Questions about Adaptive Interventions?
Sequential, Multiple Assignment, Randomized Trials

Part 1(b)

Optimization of Behavioral and Biobehavioral Interventions

NIH, September 9, 2016
Outline for Part 1(b)

• What are Sequential Multiple Assignment Randomized Trials (SMARTs)?
• Trial Design Principles and Analysis
• But not everyone needs a SMART
• Discussion & Questions
What is a SMART?

- A Multi-Stage Randomized trial
- Each stage corresponds to a critical decision point
- A randomization takes place at each critical decision
- Some (or all) participants are randomized more than once, often based on earlier covariates

The goal is to inform the construction of effective adaptive interventions
Hypothetical SMART

First-stage intervention

Intermediate outcome

Second-stage intervention

Experimental Conditions

Treatment Outset

Week 4

Week 12

Responders

Non-responders

Responders

Non-Responders

R

A

B

R

R

R

Relapse Prevention

Low-level monitoring

Switch

Augment

Relapse Prevention

Low-level monitoring

Switch

Augment

a

b

c

d

e

f

g

h
A Real-world SMART in Autism!

First-stage intervention | Embedded Tailoring Variable | Second-stage intervention | Experimental Conditions
--- | --- | --- | ---
DTT | Responders | DTT+Parent Training | a
| Slower responders | DTT | b
| Responders | DTT+JASP+EMT | c
| Slower Responders | JASP+EMT+Parent Tng | d
| JASP+EMT | e
| JASP+EMT | f
| DTT+JASP+EMT | g
| | h

Treatment Onset: Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement

Week 16
Hypothetical SMART

But I’m worried about…

…sample size

This looks too

…complicated
Outline for Part 1(b)

- What are Sequential Multiple Assignment Randomized Trials (SMARTs)?
- **Trial Design Principles and Analysis**
- But not everyone needs a SMART
- Discussion & Questions
Let’s go back to our Hypothetical SMART
SMART Design Principles

• The justification for a SMART
  – Is the need/importance of answering multiple questions in the development of a high-quality adaptive intervention
  – The multiple questions are at two or more decision stages for the same person
SMART Design Principles

• **Keep it Simple:**
  
  - *Pick your battles*—focus on just a few scientific questions concerning AIs.
  
  - Restricted randomizations, *if any*, should be based on *ethical, scientific, or practical* considerations.
  
  - If randomizations are restricted, the embedded tailoring variable is realistic (*real-world*) and low-dimensional
Let’s go back to our Hypothetical SMART

First-stage intervention

Intermediate outcome

Second-stage intervention

Experimental Conditions

<table>
<thead>
<tr>
<th>Responders</th>
<th>A</th>
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<tbody>
<tr>
<td>Non-responders</td>
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<table>
<thead>
<tr>
<th>Responders</th>
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</tr>
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<tbody>
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<td></td>
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</tbody>
</table>

- **Week 4**
  - Responders (A):
    - Relapse Prevention
    - Low-level monitoring
    - Switch
    - Augment
  - Non-responders (A):
    - Relapse Prevention
    - Low-level monitoring
    - Switch
    - Augment

- **Week 12**
  - Responders (B):
    - Relapse Prevention
    - Low-level monitoring
    - Switch
    - Augment
  - Non-responders (B):
SMART Design Principles

• **Keep it Simple:**
  
  – *Pick your battles*—focus on just a few scientific questions concerning AIs.
  
  – Restricted randomizations, *if any*, should be based on *ethical, scientific, or practical* considerations.
  
  – If randomizations are restricted, the embedded tailoring variable should be realistic (*real-world*) and low-dimensional
Let’s go back to our Hypothetical SMART
SMART Design Principles

- Plan to collect intermediate outcomes needed to ascertain response status.
  - But also consider collecting other information that might be useful in ascertaining for whom each treatment works best
  - Namely, candidate tailoring variables
Choose a primary aim that:

- Is scientifically important; and
- Aids in developing the AI.

Often, sample size is based on a hypothesis test with adequate statistical power based on this aim.
SMART Design Principles

• Choose secondary aims that:
  – Further develop the AI
    – Using baseline AND time-varying data

Sample size does not have to be determined based on these hypotheses. This is a basic randomized trial design principle not new to SMARTS!
Examples of Primary Aims

1. *Comparison of initial options*

   - **H1**: The initial intervention option A results in lower symptoms than the initial intervention option B.
     
     - Controlling for second-stage intervention options
H1: Comparison of Stage 1 Options

First-stage intervention

Intermediate outcome

Second-stage intervention

Experimental Conditions

Treatment Outset Week 4 Week 12

Responders

Non-responders

Responders

Non-responders

Relapse Prevention
Low-level monitoring
Switch
Augment
Relapse Prevention
Low-level monitoring
Switch
Augment

a
b
c
d
e
f
g
h
Examples of Primary Aims

2. *Comparison of second stage options for non-responders*

- **H2**: Among non-responders, switching treatments results in lower symptoms than augmenting existing treatment
  - Controlling for first-stage intervention options
H2: Comparison of Stage 2 Options

<table>
<thead>
<tr>
<th>First-stage intervention</th>
<th>Intermediate outcome</th>
<th>Second-stage intervention</th>
<th>Experimental Conditions</th>
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<tbody>
<tr>
<td>Treatment Outset</td>
<td>Week 4</td>
<td>Week 12</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Responder</td>
<td>Relapse Prevention</td>
<td>a</td>
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<td></td>
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<td>Low-level monitoring</td>
<td>b</td>
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<tr>
<td>B</td>
<td>Non-Responder</td>
<td>Switch</td>
<td>c</td>
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<td>Augment</td>
<td>h</td>
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</table>
Examples of Primary Aims

3. *Comparison of embedded adaptive interventions*

- **H3**: Adaptive intervention #1 results in improved symptoms compared to adaptive intervention #2
H3: Comparison of 2 AIs

First-stage intervention

Intermediate outcome

Second-stage intervention

Experimental Conditions

1. Relapse Prevention
2. Low-level monitoring
3. Switch
4. Augment

Responders

Non-Responders

Treatment Outset

Week 4

Week 12

Experimental Conditions:

a

b

c

d

e

f

g

h
Sample Size

**H1:** The initial intervention option A results in lower symptoms than the initial intervention option B.

- *Sample size formula is same as for a two group comparison.*

**H2:** Among non-responders, switching results in lower symptoms than augmenting.

- *Sample size formula is same as a two group comparison of non-responders.*
**Sample Size**

\[ N = \text{sample size for the } \text{entire} \text{ trial} \]

<table>
<thead>
<tr>
<th></th>
<th>H1</th>
<th>H2</th>
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<tbody>
<tr>
<td>( \Delta \mu / \sigma = .3 )</td>
<td>( N = 352 )</td>
<td>( N = 352 / \text{NR rate} )</td>
</tr>
<tr>
<td>( \Delta \mu / \sigma = .5 )</td>
<td>( N = 128 )</td>
<td>( N = 128 / \text{NR rate} )</td>
</tr>
</tbody>
</table>

\( \alpha = .05 \) (two sided), power = \( 1 - \beta = .80 \)

*Assumptions: equal variances, normality, equal # in each group, no dropout.*
**Sample Size**

**H3:** AI #1 results in improved symptoms compared to AI #2
- Analysis is non-standard (so sample size calculation is too)
- Sample size formula depends on who gets re-randomized

<table>
<thead>
<tr>
<th>Type I error rate (2-sided)</th>
<th>Power</th>
<th>Standardized Difference</th>
<th>N</th>
<th>Randomization</th>
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</thead>
<tbody>
<tr>
<td>0.05</td>
<td>80%</td>
<td>0.3</td>
<td>698</td>
<td>Both R and NR are re-randomized</td>
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<tr>
<td></td>
<td></td>
<td>0.5</td>
<td>252</td>
<td></td>
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</tbody>
</table>

- **Continuous Outcomes:** Oetting, A.I., et al. (2011)
- **Survival Outcomes:** Feng, W. and Wahed, A., (2009); Li, Z. and Murphy, S.A., (2011)
- **Binary Outcomes:** Kidwell, K.M., et al. (In preparation)
Example of Secondary Aims

- Choose secondary hypotheses
  - That further develop the AI
  - Example:
    
    **H4:** non-adhering non-responders will exhibit lower symptoms if their initial treatment is switched as compared to augment
Example Secondary Aim: Adherence as a moderator tailoring variable

- **First-stage intervention**
  - A
  - B

- **Intermediate outcome**
  - Responders
  - Non-responders

- **Second-stage intervention**
  - Relapse Prevention
  - Low-level monitoring
  - Switch
  - Augment

- **Experimental Conditions**
  - a
  - b
  - c
  - d
  - e
  - f
  - g
  - h

- **Timeline**
  - Treatment Onset
  - Week 4
  - Week 12
Outline for Part 1(b)

- What are Sequential Multiple Assignment Randomized Trials (SMARTs)?
- Trial Design Principles and Analysis
- But not everyone needs a SMART
- Discussion & Questions
Not everyone needs a SMART…

With SMARTs, our scientific questions are about *sequences of treatments*

What if…

...I’m really just concerned about non-responders [responders]?

...I want to *evaluate* outcomes for one or more adaptive interventions?

Study design

Non-responder [responder] study

RCT
Some Myths or Misconceptions about SMARTs

• MoM 1: SMARTs require **prohibitively large sample sizes**.
• MoM 2: All SMARTs require **multiple-comparison adjustments**.
• MoM 3: All **adaptive intervention research** requires a SMART.
• MoM 4: SMARTs must include an **embedded tailoring variable**.
• MoM 5: All aspects of an adaptive intervention must be **randomized**.
• MoM 6: SMARTs are a form of **adaptive research design**.
• MoM 7: SMARTs **never include control groups**.
• MoM 8: SMARTs require **multiple consents**.
• MoM 9: SMARTs are susceptible to **high levels of drop out**.
Outline

• What are Sequential Multiple Assignment Randomized Trials (SMARTs)?
• Trial Design Principles and Analysis
• But not everyone needs a SMART
• Discussion & Questions
Questions about SMART?
SMART Case Studies: A Look Under the Hood of 3 SMARTs

Part 2

Optimization of Behavioral and Biobehavioral Interventions

NIH, September 9, 2016
Case Studies

**RBT** (PI: Jones): Treatment for Pregnant Women who are Drug Dependent

**ExTEND** (PI: Oslin): Treatment of Adult Alcohol Dependence

**ADEPT** (PI: Kilbourne): Depression in Implementation Science
Case Studies

**RBT** (PI: Jones): Treatment for Pregnant Women who are Drug Dependent

**ExTENd** (PI: Oslin): Treatment of Adult Alcohol Dependence

**ADEPT** (PI: Kilbourne): Depression in Implementation Science
RBT (Jones) $N=300$
RBT (Jones) $N=300$

First-stage intervention

- rRBT
- tRBT

Intermediate outcome

- early-compliant
- early-non-compliant

Second-stage intervention

- aRBT
- rRBT
- c

- rRBT
- tRBT
- d

- tRBT
- rRBT
- f

- tRBT
- e

- eRBT
- g

- eRBT
- h

Experimental Conditions

- a
- b
- c
- d
- e
- f
- g
- h

aRBT → abbreviated RBT
rRBT → reduced RBT
tRBT → treatment-as-usual RBT
eRBT → enhanced RBT
RBT (Jones) $N=300$

Population:

Pregnant women using opioid or cocaine.
RBT (Jones) $N=300$

**Rationale:**

Reinforcement based treatment (RBT) is efficacious, however

- RBT is costly and burdensome;
- About 40% do not respond as well as desired.
RBT (Jones) \( N=300 \)

Treatments:

\[ \text{aRBT} < \text{rRBT} < \text{tRBT} < \text{eRBT} \] (increasing order in intensity/scope or RBT)
Critical Questions:

• Can the traditional version of RBT be reduced in intensity and scope?

• Should a woman who does not respond quickly continue on the same version of RBT or be moved to a more-intensive, larger-scope version?

• Can the intensity and scope of RBT be reduced if a woman responds quickly?
Embedded Tailoring variables:

*Early compliance status*, assessed at week 2, by

- Self-reported drug use,
- Results of urine tests
- Attendance on intervention days

Non-compliant if

- Self-reported drug use; or
- Positive opioid/cocaine urine specimen; or
- Missed an intervention day with no excuse.
8 Embedded AIs:

1) Start with rRBT; reduce for compliant; continue for non-compliant (least costly/burdensome)
8 Embedded AIs:

2) Start with rRBT; reduce for compliant; intensify for non-compliant
8 Embedded AIs:

3) Always rRBT (not adaptive)
8 Embedded AIs:

4) Start with rRBT; continue for compliant; intensify for non-compliant
8 Embedded AIs:

5) Always tRBT (non-adaptive)
8 Embedded AIs:

6) Start with tRBT; continue for compliant; intensify for non-compliant. (most costly/burdensome)
8 Embedded AIs:

7) Start with tRBT; reduce for compliant; continue for non-compliant.
8 Embedded AIs:

8) Start with tRBT; reduce for compliant; intensify for non-compliant.
Primary Aim:
Compare always tRBT vs. always rRBT
In terms of program completion (delivery of child while in treatment).

Secondary Aim:
Baseline moderators
e.g., baseline amount of illegal activity (e.g., prostitution).
Case Studies

**RBT** (PI: Jones): Treatment for Pregnant Women who are Drug Dependent

**ExTENd** (PI: Oslin): Treatment of Adult Alcohol Dependence

**ADEPT** (PI: Kilbourne): Depression in Implementation Science
ExTENd (Osling) $N=302$

**Diagram Description:**

- **First-stage intervention:**
  - NTX + Lenient Definition of non-response
  - NTX + Stringent Definition of non-response

- **Intermediate outcome:**
  - Week 8 Responders
  - Non-responders

- **Second-stage intervention:**
  - NTX
  - NTX + TDM
  - CBI
  - NTX + CBI

**Treatment Outset:**
- NTX → Naltrexone (opioid antagonist)
- TDM → Telephone Disease Management
- CBI → Combined Behavioral Intervention

**Week 24:**
- a
- b
- c
- d
- e
- f
- g
- h

**Definitions:**
- Lenient Definition → 5+ heavy drinking days in 1 week
- Stringent Definition → 2+ heavy drinking days in 1 week
ExTENd (Osling) \( N=302 \)

First-stage intervention

<table>
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Intermediate outcome

<table>
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Second-stage intervention

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<td>CBI</td>
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Treatment Outset

- **NTX** → Naltrexone (opioid antagonist)
- **TDM** → Telephone Disease Management
- **CBI** → Combined Behavioral Intervention

**Lenient Definition** → 5+ heavy drinking days in 1 week

**Stringent Definition** → 2+ heavy drinking days in 1 week

Week 24
ExTENd (Osllin) $N=302$

**Population:**

Alcohol Dependent Adults completing an Intensive Outpatient Program (IOP)

---

**Diagram:***

- **First-stage intervention**: NTX + Lenient Definition of non-response
- **Intermediate outcome**: Non-responders → NTX, NTX + TDM, CBI, NTX + CBI
- **Second-stage intervention**: NTX, NTX + TDM, CBI, NTX + CBI

**Notations and Definitions:**

- NTX → Naltrexone (opioid antagonist)
- TDM → Telephone Disease Management
- CBI → Combined Behavioral Intervention
- **Lenient Definition** → 5+ heavy drinking days in 1 week
- **Stringent Definition** → 2+ heavy drinking days in 1 week

---

**Legend:**

- Week 8 Responders
- Non-responders
- Treatment Outset
- Week 24
ExTENd (Oslin) $N=302$

Rationale:

Naltrexone (NTX, an opiate antagonist) is efficacious but

• Around 1/3 of patients relapse while on NTX,
• Hence, need to develop rescue tactics for non-responders
• And long-term maintenance tactics for responders
• Because of various barriers: Physiological/social/psychological
ExTENd (Osln) \(N=302\)

Treatments:

- NTX: Naltrexone
- CBI: cognitive behavioral intervention
- TDM: telephone disease monitoring

![Diagram of treatment flow and outcomes](image_url)
Critical questions:

• What type of rescue tactic would be useful among non-responders to NTX?

• What type of maintenance tactic would be useful among responders to NTX?

• What extent of drinking behavior best reflects non-response to NTX?
ExTENd (Oslin) \( N=302 \)

Embedded tailoring variable:

- **Response/non-response status**, measured based on:
  
  Weekly self report of heavy drinking days (HDDs).
  
  >5 drinks/day males;  
  >4 drinks/day females

- Non-response if during first 8 weeks of NTX:
  
  Lenient: 5+ HDDs  
  Stringent: 2+ HDDs
ExTENd (Osling) N=302

8 embedded AIs:

1) Start on NTX; if 5+ HDDs prior to week 8, switch to CBI; else at week 8 continue NTX
ExTENd (Osling) \( N=302 \)

8 embedded AIs:

2) Start on NTX; if 5+ HDDs prior to week 8, augment NTX+CBI; else at week 8 continue NTX
ExTENd (Oslin) \(N=302\)

8 embedded AIs:

3) Start on NTX; if 5+ HDDs prior to week 8, switch to CBI; else at week 8 offer NTX+TDM
ExTENd (Osling) \( N=302 \)

8 embedded AIs:

4) Start on NTX; if 5+ HDDs prior to week 8, augment NTX+CBI; else at week 8 offer NTX+TDM

First-stage
intervention

Intermediate
outcome

Second-stage
intervention

Lenient
Definition of
non-response

Week 8
Responders

NTX

NTX+TDM

a

NTX+TDM

b

CBI

c

NTX+CBI

d

Stringent
Definition of
non-response

Week 8
Responders

Non-responders

Lenient Definition \( \rightarrow \) 5+ heavy drinking days
Stringent Definition \( \rightarrow \) 2+ heavy drinking days

TDM \( \rightarrow \) Telephone Disease Management
CBI \( \rightarrow \) Combined Behavioral Intervention

Week 24

Non-Responders

NTX

e

NTX+TDM

f

CBI

g

NTX+CBI

h
ExTENd (Osling) \( N=302 \)

**8 embedded AIs:**

5) Start on NTX; if 2+ HDDs prior to week 8, switch to CBI; else at week 8 continue NTX

![Diagram](image)
ExTENd (Oslin) $N=302$

8 embedded AIs:

6) Start on NTX; if 2+ HDDs prior to week 8, augment NTX+CBI; else at week 8 continue NTX
ExTENd (Osling) \( N = 302 \)

8 embedded AIs:

7) Start on NTX; if 2+ HDDs prior to week 8, switch to CBI; else at week 8 offer NTX+TDM
**ExTENNd (Osln) N=302**

8 embedded AIs:

8) Start on NTX; if 2+ HDDs prior to week 8, augment NTX+CBI; else at week 8 offer NTX+TDM
ExTENd (Oslin) \( N=302 \)

**Primary Aim:**

Among non-responders, compare NTX+CBI vs. CBI, in terms of percent days abstinent during the study.

**Secondary Aim:**

- Effect of TDM for responders;
- Compare two criteria for non-response;
- Moderators (e.g., distress, severity of dependence, adherence in first stage).

\[ \text{NTX} \rightarrow \text{Naltrexone (opioid antagonist)} \]
\[ \text{TDM} \rightarrow \text{Telephone Disease Management} \]
\[ \text{CBI} \rightarrow \text{Combined Behavioral Intervention} \]

**Lenient Definition** → 5+ heavy drinking days in 1 week

**Stringent Definition** → 2+ heavy drinking days in 1 week
Case Studies

**RBT** (PI: Jones): Treatment for Pregnant Women who are Drug Dependent

**ExTENd** (PI: Oslin): Treatment of Adult Alcohol Dependence

**ADEPT** (PI: Kilbourne): Depression in Implementation Science
ADEPT (Kilbourne) \( K > 60, \ N > 300 \)

First-stage intervention | Second-stage intervention | Third-stage intervention | Experimental Conditions
--- | --- | --- | ---
Non-responding sites after 6 months of REP enter the study

**REP** → replicating effectiveness programs toolkit $
**EF** → external facilitator: off-site, research team, tech assistance $$
**IF** → internal facilitator: on-site provider, direct line to leadership, time is protected, address unobserv org barriers, develop sustainability plan $$$
ADEPT (Kilbourne) \( K > 60, \ N > 300 \)

First-stage intervention

Second-stage intervention

Third-stage intervention

Experimental Conditions

Non-responding sites after 6 months of REP enter the study

\( \text{REP} \rightarrow \text{replicating effectiveness programs toolkit} \$

\( \text{EF} \rightarrow \text{external facilitator: off-site, research team, tech assistance} \$

\( \text{IF} \rightarrow \text{internal facilitator: on-site provider, direct line to leadership, time is protected, address unobserved org barriers, develop sustainability plan} \$

\( \text{Responder} \)

\( \text{Non-responder} \)

\( \text{Discontinue REP+EF} \rightarrow \text{A} \)

\( \text{Continue REP+EF} \rightarrow \text{B} \)

\( \text{Add IF (REP+EF+IF)} \rightarrow \text{C} \)

\( \text{Discontinue REP+EF+IF} \rightarrow \text{D} \)

\( \text{Continue REP+EF+IF} \rightarrow \text{E} \)
ADEPT (Kilbourne) $K > 60, \, N > 300$

**Population:**

Sites that do not respond to 6 months of initial REP implementation intervention

Patients in those sites who have mood disorders
ADEPT (Kilbourne) \(K > 60, \ N > 300\)

Embedded Tailoring

Variable:

Site is a non-responder at month 12 if:

<50% of enrolled patients have received <3 sessions
ADEPT (Kilbourne) $K > 60, N > 300$

3 embedded AIs for sites initially not-responding to REP:

1) Start on REP+EF; if non-responder at month 12, then continue REP+EF; otherwise, discontinue REP+EF

\[\text{REP} \rightarrow \text{replicating effectiveness programs toolkit $\$$} \]
\[\text{EF} \rightarrow \text{external facilitator: off-site, research team, tech assistance $$} \]
\[\text{IF} \rightarrow \text{internal facilitator: on-site provider, direct line to leadership, time is protected, address unobserv org barriers, develop sustainability plan $$} \]
ADEPT (Kilbourne) $K > 60, N > 300$

3 embedded AIs for sites initially not-responding to REP:

2) Start on REP+EF; if non-responder at month 12, then continue REP+EF+IF; otherwise, discontinue REP+EF

$\text{REP} \rightarrow \text{replicating effectiveness programs toolkit }$

$\text{EF} \rightarrow \text{external facilitator: off-site, research team, tech assistance }$

$\text{IF} \rightarrow \text{internal facilitator: on-site provider, direct line to leadership, time is protected, address unobserv org barriers, develop sustainability plan }$
ADEPT (Kilbourne) \( K > 60, \ N > 300 \)

3 embedded AIs for sites initially not-responding to REP:

3) Start on REP+EF+IF; if non-responder at month 12, then continue REP+EF+IF; otherwise, discontinue REP+EF+IF

\( \text{REP} \rightarrow \text{replicating effectiveness programs toolkit} \$

\( \text{EF} \rightarrow \text{external facilitator: off-site, research team, tech assistance} \$

\( \text{IF} \rightarrow \text{internal facilitator: on-site provider, direct line to leadership, time is protected, address unobserv org barriers, develop sustainability plan} \$

---

**Diagram:**

First-stage intervention

- REP+EF

Second-stage intervention

- Non-responder
  - REP+EF
  - Add IF (REP+EF+IF)

Third-stage intervention

- Responder
  - Discontinue REP+EF
  - Continue REP+EF

- Non-responder
  - Discontinue REP+EF+IF
  - Continue REP+EF+IF
ADEPT (Kilbourne) \( K>60, \ N>300 \)

**Primary Aim:**
Among sites initially not responding to 6 months of REP, what is the effect of REP+EF versus REP+EF+IF on change in individual mental health quality of life?

**Secondary Aim:**
- Among sites not responding after 12 months to REP followed by REP+EF, what is the effect of REP+EF+IF versus staying the course on REP+EF
- Compare the three embedded adaptive implementation interventions on mental health quality of life
- Cost-benefit analyses
More Case Studies (book in progress…)

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<th>Full-scale SMARTs</th>
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<th>Intervention Domain</th>
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<td>Adaptive Approach to Naltrexone Treatment for Alcoholism (Oslin)</td>
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<td>Personalized Weight Loss Programming (Sherwood)</td>
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<td>Minimally Verbal Children With Autism in the Community (Kasari)</td>
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<td>Weight Loss for African American Adolescents (Naar-King)</td>
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<td>Improving Symptom Management in Cancer (Sikorskii)</td>
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<td>Mothers First ADHD Study (Chronis-Tuscano/Stein)</td>
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<td>Suicide Prevention Among College Students (Pistorella)</td>
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<tr>
<td>Social and Academic Engagement in Children with Autism (Kasari)</td>
<td>✓</td>
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<td>✓</td>
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</tbody>
</table>

| Sample Size | 2 302 | 2 500 | 2 192 | 3 500 | 3 1000 | 2 180 | 3 331 | 3 80† | 2 300 | 2 300 | 2 400 |

† 60 community-based mental health clinics are randomized initially. It is expected there will be approximately 20 patients per clinic.
‡ 32 classrooms (across 2 schools) are randomized initially. It is expected there will be 1 or 2 children with autism per classroom.
Questions about SMART Case Studies?