SMART Case Studies

Module 3

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

Inbal (Billie) Nahum-Shani, Daniel Almirall
Outline

• Treatment of Children with Autism (PI: Kasari)
• ADHD SMART (PI: Pelham): Treatment of ADHD
• RBT (PI: Jones): Treatment for Pregnant Women who are Drug Dependence
• ExTENd (PI: Oslin): Treatment of Alcohol Dependence
• REP Implementation Science (PI: Kilbourne)

• Summary Comparison of the five SMARTs
SMART Case Studies

- Treatment of Children with Autism (PI: Kasari)
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Autism Study (Kasari)

First-stage intervention

JASP+EMT

JASP+EMT + SGD

Intermediate outcome

Early Response

Slow Response

Second-stage intervention

Week 12

JASP+EMT

Intensified JASP+EMT

JASP+EMT+SGD

JASP+EMT+SGD

Intensified JASP+EMT+SGD

Month 6

Subgroups

A

B

C

D

E

Treatment Outset

JASP → Joint Attention and joint Engagement
EMT → Enhanced Milieu Teaching
SGD → Speech Generating Device (e.g., an iPad or DynaVox)
Autism Study (Kasari)

• Population:
  – Non-verbal children with ASD who have not made progress by age 5 even though they have received traditional intensive behavioral language interventions
Autism Study (Kasari)

• Rationale:
  – These children experience poor outcomes yet represent 25-30% of children with ASD.
  – Planning for a “rescue” if the first treatment does not go well is crucial.
  – Speech generating devices (eg, iPads) are costly and no rigorous research, despite all the rave!
  – Can SGDs improve outcomes in the context of promising behavioral language interventions?
Autism Study (Kasari)

- **Treatments:**
  - JASP+EMT: naturalistic behavioral intervention
  - SGD: Speech generating device

- **Critical questions:**
  - In the context of JASP+EMT, do we provide SGDs to all children with ASD from the start?
  - Among non-responders to JASP+EMT alone, should we intensify JASP+EMT or augment with SGD?
Autism Study (Kasari)

First-stage intervention

Intermediate outcome

Second-stage intervention

Subgroups

JASP→ Joint Attention and joint Engagement
EMT→ Enhanced Milieu Teaching
SGD→ Speech Generating Device (e.g., an iPad or DynaVox)
Autism Study (Kasari)

- Seven Embedded Tailoring Variables:
  - (a) total social communicative utterances,
  - (b) percentage communicative utterances,
  - (c) number different word roots,
  - (d) mean length of utterance in words,
  - (e) number of utterances where the function is to comment,
  - (f) words per minute, and
  - (g) unique word combinations

- Measured two ways at the end of week 12: therapist measured & blinded evaluator
Autism Study (Kasari)

• How were the 14 measures (7 embedded tailoring variables measured 2 ways) used?

• Child is an early responder at week 12 if:
  – The child had 25% or more improvement on 7 or more of the 14 measures.
Autism Study (Kasari)

First-stage intervention

JASP+EMT

JASP+EMT +SGD

Intermediate outcome

Early Response

Slow Response

Second-stage intervention

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Intensified JASP+EMT

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B

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Treatment Outset

Week 12

Month 6

JASP → Joint Attention and joint Engagement
EMT → Enhanced Milieu Teaching
SGD → Speech Generating Device (e.g., an iPad or DynaVox)
3 Embedded Adaptive Interventions

1) Start with JASP+EMT; if non-responder JASP+EMT+SGD, else JASP+EMT

2) Start with JASP+EMT; if non-responder (JASP+EMT)$^+$, else JASP+EMT

3) Start with JASP+EMT+SGD; if non-responder (JASP+EMT+SGD)$^+$, else JASP+EMT+SGD
Autism Study (Kasari)

First-stage intervention

Intermediate outcome

Second-stage intervention

Treatment Outset

Week 12

Month 6

JASP → Joint Attention and joint Engagement
EMT → Enhanced Milieu Teaching
SGD → Speech Generating Device (e.g., an iPad or DynaVox)
Autism Study (Kasari)

• Primary Aim
  – To compare change in total communicative utterances (primary outcome) over 6 months for starting with JASP+EMT+SGD vs JASP+EMT

• Secondary Aim
  – Investigate moderation by baseline variables, investigate if other variables might be used to tailor treatment.
Autism Study (Kasari)

First-stage intervention

JASP+EMT

JASP+EMT + SGD

Treatment Outset

Intermediate outcome

Early Response

Slow Response

Week 12

JASP+EMT

Intensified JASP+EMT

JASP+EMT+SGD

Intensified JASP+EMT+SGD

Month 6

JASP+EMT

Intensified JASP+EMT

JASP+EMT+SGD

Intensified JASP+EMT+SGD

Subgroups

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SMART Case Studies

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ADHD (Pelham)

First-stage intervention: MED

Intermediate outcome:
- Response: Continue
- Non-Response: Augment

Second-stage intervention:
- Continue: Subgroups A
- Augment: Subgroups B
- Intensify: Subgroups C

Experimental Conditions:
- Subgroups D
- Subgroups E
- Subgroups F

Timeline:
- Beginning of school year
- Week 8
- End of school year
ADHD (Pelham)

Population & Rationale:

– Children with ADHD, ages 6-12
– Much debate on whether the first-line intervention should be pharmacological or behavioral, especially among younger children.
– Planning for a “rescue” if the first treatment does not go well is crucial because 20-50% do not substantially improve on first treatment.
ADHD (Pelham)

• Treatments:
  – MED, BMOD, MED+BMOD, intensified MED, intensified BMOD

• Critical Decisions/Questions:
  – Which treatment to provide first: BMOD vs MED?
  – Which treatment to provide non-responders: intensify initial treatment vs augment with the other?
ADHD (Pelham)

- Embedded Tailoring Variables
  - (a) Teacher reported Impairment Scale (IRS),
  - (b) Teacher reported individualized list of target behaviors (ITB)

- How and when is (non) response assessed?
  - At 8 weeks and every 4 weeks thereafter
  - The criterion for non-response is average performance of <75% on the ITB and a rating of impairment in at least one domain on the IRS.
ADHD (Pelham)

- **First-stage intervention**: MED, BMOD
- **Intermediate outcome**:
  - Response: Continue, Augment, Intensify
  - Non-Response: Continue, Augment, Intensify

- **Second-stage intervention**:
  - Subgroups: A, B, C, D, E, F

- **Experimental Conditions**:
  - Subgroups:
    - A: Continue
    - B: Augment
    - C: Intensify
    - D: Continue
    - E: Augment
    - F: Intensify

- **Timeline**:
  - Beginning of school year
  - Week 8
  - End of school year
4 Embedded Adaptive Interventions

1) Start with BMOD; if non-responder intensify BMOD, else continue BMOD

2) Start with BMOD; if non-responder BMOD +MED, else continue BMOD

3) Start with low-dose MED; if non-responder Intensify MED, else continue low-dose Med

4) Start with low-dose MED; if non-responder BMOD+MED, else continue low-dose Med.
ADHD (Pelham)

• Primary Aim
  – To compare the change in teacher ratings of child behavior across 8 months between: Starting with MED vs starting with BMOD

• Secondary Analyses
  – Investigate moderation of the effect of initial treatment/secondary treatment/adaptive treatment strategies by baseline variables; investigate if other variables might be used to tailor treatment.
SMART Case Studies

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RBT (Jones)

First-stage intervention

Intermediate outcome

Second-stage intervention

Experimental Conditions

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>Week 2</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>rRBT</td>
<td></td>
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<tr>
<td>tRBT</td>
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</tbody>
</table>

Early-compliant

Early-non-compliant

aRBT $\rightarrow$ abbreviated RBT

rRBT $\rightarrow$ reduced RBT
tRBT $\rightarrow$ treatment-as-usual RBT
eRBT $\rightarrow$ enhanced RBT
Population & Rationale:

• Pregnant women using opioid or cocaine
• Reinforcement based treatment (RBT) is an efficacious intervention, however
  – RBT is costly to administer and time-consuming (high burden) on the part of the participant,
  – About 40% of participants do not respond as well as desired
Critical Questions:

– (a) whether the traditional version of RBT can be reduced in intensity and scope;
– (b) whether a woman who does not respond quickly should continue on the same version or be moved to a more-intensive, larger-scope version of RBT; and
– (c) whether the intensity and scope of RBT can be reduced if a woman responds quickly.
RBT (Jones)

- **Treatments:**
  - aRBT < rRBT < tRBT < eRBT (increasing order in intensity/scope or RBT)

- **Embedded Tailoring Variables:**
  - a) self-reported drug use,
  - b) results of urine tests, and
  - c) attendance on intervention days
• How and when is non-compliance assessed at week 2?

• The criterion for non-compliance is
  – missing an intervention day with no excuse, or
  – a positive opioid or cocaine urine specimen, or
  – self-report use of either drug.

• It is a combination of non-compliance and non-response
RBT (Jones)

First-stage intervention: rRBT or tRBT

Intermediate outcome:
- Early-compliant: aRBT or rRBT
- Early-non-compliant: rRBT or tRBT

Second-stage intervention:
- aRBT
- rRBT
- tRBT
- eRBT

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

Treatment Outset: R

Week 2: R

Notes:
- aRBT → abbreviated RBT
- tRBT → treatment-as-usual RBT
- rRBT → reduced RBT
- eRBT → enhanced RBT
8 Embedded Interventions (6 are Adaptive)

1) Always tRBT (not adaptive)

2) Start with tRBT; if non-responder tRBT, if responder rRBT

3) Start with tRBT; if non-responder eRBT, if responder tRBT

4) Start with tRBT; if non-responder eRBT, if responder rRBT
8 Embedded Interventions (6 are Adaptive)

5) Always rRBT (not adaptive)

6) Start with rRBT; if non-responder tRBT, if responder rRBT

7) Start with rRBT; if non-responder rRBT, if responder aRBT

8) Start with rRBT; if non-responder tRBT, if responder aRBT
Primary Aim
– To compare program completion (delivery of child while in treatment) of the always tRBT arm versus the always rRBT arm (two non-adaptive interventions!)

Secondary Aim
– Investigate moderation by baseline variables, investigate if other variables might be used to tailor treatment.
RBT (Jones)

- **First-stage intervention**
  - rRBT
  - tRBT

- **Intermediate outcome**
  - early-compliant
  - early-non-compliant

- **Second-stage intervention**
  - aRBT
  - rRBT
  - tRBT

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

**Abbreviations**
- aRBT → abbreviated RBT
- tRBT → treatment-as-usual RBT
- rRBT → reduced RBT
- eRBT → enhanced RBT
SMART Case Studies

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ExTENNd (Oslin)

First-stage intervention

- NTX + Lenient Definition of non-response
  - Week 8 Responders
  - Non-responders

Second-stage intervention

- NTX
- NTX + TDM
- CBI
- NTX + CBI

Week 24

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
ExTENd (Oslin)

Population & Rationale:

- Alcohol Dependent Adults who completed an Intensive Outpatient Program
- Naltrexone (NTX, an opiate antagonist) is efficacious but clinical use is limited.
  - Around 1/3 of patients relapse while on NTX.
  - Would like to inform longer term management based on NTX
  - Non-adherence is common
ExTENd (Osling)

• Treatments:
  – NTX: Naltrexone (in person, includes MM)
  – CBI: cognitive behavioral intervention
  – TDM: telephone disease monitoring (MM via phone)

• Embedded Tailoring Variable:
  – Weekly self report of heavy drinking days.
Critical Questions:

– (a) What extent of drinking behavior best reflects non-response to NTX?
– (b) What type of treatment would be useful among participants who do not respond adequately to NTX?
– (c) What type of treatment would be useful among participants who respond adequately to NTX?
ExTENd (Osli)

How and when is (non) response assessed?

• Initially, each week, for 8 weeks
  – Early trigger criterion for non-response: 2 or more heavy drinking days since beginning NTX
  – Late trigger criterion for non-response: 5 or more heavy drinking days since beginning NTX

• If, after 8 weeks, the non-response criterion is not met then the participant is a responder.
ExTENd (Osln)

First-stage intervention

NTX + Lenient Definition of non-response
- Week 8 Responders
  - NTX
  - NTX + TDM

NTX + Stringent Definition of non-response
- Week 8 Responders
  - CBI
  - NTX + CBI

Intermediate outcome

Non-responders
- NTX
- NTX + TDM
- CBI
- NTX + CBI

NTX
- NTX + TDM
- CBI
- NTX + CBI

Second-stage intervention

Non-responders
- NTX
- NTX + TDM
- CBI
- NTX + CBI

Treatment Outset

NTX → Naltrexone (opioid antagonist)
TDM → Telephone Disease Management
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Week 24
8 Embedded Adaptive Interventions

1) Start with NTX; if 2 HDD occurs prior to 8 weeks, augment to CBI+NTX, else at 8 weeks continue on NTX

2) Start with NTX; if 2 HDD occurs prior to 8 weeks, switch to CBI, else at 8 weeks continue on NTX

3) Start with NTX; if 2 HDD occurs prior to 8 weeks, augment to CBI+NTX, else at 8 weeks continue on NTX+TDM
ExTENNd (Oslin)

8 Embedded Adaptive Interventions

4) Start with NTX; if 2 HDD occurs prior to 8 weeks, switch to CBI, else at 8 weeks continue on NTX+TDM

5) …if 5 HDD then CBI+NTX; else NTX…

6) …if 5 HDD then CBI; else NTX…

7) …if 5 HDD then CBI+NTX; else NTX+TDM…

8) …if 5 HDD then CBI; else NTX+TDM…
ExTENd (Osling)

• Primary Aim
  – Focus is on non-responders to NTX
  – Compare percent days abstinent on CBI+NTX versus to CBI alone.

• Secondary Aim
  – Test effectiveness of TDM for responders
  – Test two criteria for non-response; assess moderation (psychosocial distress, severity of alcohol dependence, adherence in first stage)
ExTENd (Osln)

First-stage intervention  | Intermediate outcome  | Second-stage intervention
---|---|---

**NTX** + Lenient Definition of non-response  
- Week 8 Responders  
- Non-responders

**NTX** + Stringent Definition of non-response  
- Week 8 Responders  
- Non-Responders

<table>
<thead>
<tr>
<th>Treatment Outset</th>
<th>Naltrexone (opioid antagonist)</th>
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<tbody>
<tr>
<td><strong>NTX</strong> → <strong>NTX</strong> + TDM</td>
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<tr>
<td><strong>NTX</strong> → <strong>NTX</strong> + CBI</td>
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<table>
<thead>
<tr>
<th>Second-stage intervention</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
</table>
| **CBI**  
**NTX**  
**NTX** + CBI  
**NTX** + CBI |

**Week 24**

**TDM** → Telephone Disease Management

**CBI** → Combined Behavioral Intervention

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

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REP Adaptive Implementation

At the outset:
- REP → Replicating Effective Programs (core components)
- EF → External Facilitator (external to the site)
- IF → Internal Facilitator (internal at the site)

First-phase intervention:
- REP

Second-phase intervention:
- REP+EF
- REP+EF+IF

Third-phase intervention:
- Discontinue
- Continue REP+EF
- Augment: REP+EF+IF
- Discontinue
- Continue: REP+EF+IF

Subgroups:
- A
- B
- C
- D
- E

Months 18 (Outcomes through Month 24)

Responding sites continued on REP through Month 18 (remain in study)
Implementation science is a very different kind of research endeavor.

• Evidence based treatments rarely leave the academic shelf and get transmitted to community-based practices

• e.g., Life Goals Collaborative Care (LGCC)
  – Evidence-based mental health treatment for patients with mood disorders (e.g., major depressive disorder, bipolar)

• In implementation science goal is to develop implementation interventions (at the site-level) to ensure adoption of EBTs in the community.
REP Adaptive Implementation

Population & Rationale:

• Research-to-practice gap in psychosocial EBTs such as Life Goals (LG). Organizational barriers!

• Implementation interventions exist to improve adoption of EBTs; however, approximately 75% sites do not adopting EBTs by month 6

• Goal is to develop an adaptive implementation intervention to improve adoption of LG at 80 small, low-resourced, community-based sites/practices across CO, AR, MI
REP Adaptive Implementation

Treatments (at site-level):
- REP: Replicating Effective Programs
- REP+EF: Add external facilitation
- REP+EF+IF: Add internal facilitator

• Embedded Tailoring Variable:
  - Number of patients at the site receiving Life Goals
  - Among those enrolled, the percent of group sessions received
    • Recall LG involves four 2-hour weekly group sessions
Critical questions:

• Among sites not-responsive to REP at month 6, do we augment with REP+EF vs REP+EF+IF?
• Among sites not-responsive to REP+EF at month 12, do we augment with REP+EF+IF or continue?
How and when is non-response defined? A site/practice is non-responsive if

– <10 of the identified patients at the site receiving LG within 6 months, and
– Enrolled patients received <75% of group sessions
  • Recall LG involves four 2-hour weekly group sessions

• May appears to be a low bar; however, based on prior data 75% sites do not meet this criteria!
  – And those that do not meet at month 6, are highly likely not to meet it even 6 additional months later
REP Adaptive Implementation

At the outset

REP → Replicating Effective Programs (core components)
EF → External Facilitator (external to the site)
IF → Internal Facilitator (internal at the site)
REP Adaptive Implementation

3 embedded adaptive implementation interven.

All begin with REP; if respond, continue REP for 12mo; else if non-responsive at 6mo…

1. REP+EF for 6mo; if response at 12mo, discontinue; else, continue REP+EF

2. REP+EF for 6mo; if response at 12mo, discontinue; else, continue REP+EF+IF

3. REP+EF+IF for 6mo; if response at 12mo, discontinue; else, continue REP+EF+IF
REP Adaptive Implementation

• Aims focus on non-responders to 6mo REP

• Primary Aim
  – Compare MH-QOL (primary), functioning, psychiatric sx, #LG encounters (secondary) between sites REP+EF vs REP+EF+IF.

• Secondary Aim
  – Compare REP+EF vs REP+EF+IF among sites still not responding at 12mo
  – Cost-effectiveness comparison of 3 embedded adaptive interventions
Quickly Compare the Five SMART Case Studies

We will compare along these 4 dimensions:

1) Which units are multiply randomized?
2) When does the re-randomization occur?
3) Types of the critical questions
4) Primary aims (=> study sizing)
Comparison of SMART Studies

Which units are multiply randomized?

• A subset of non-responders:
  - ASD (only slow-responding children to JASP+EMT)
  - REP (only non-responding sites to REP+EF)

• All non-responders:
  - ADHD
  - Drug Abusing Pregnant Women
  - Alcohol Dependence

• All responders:
  - Drug Abusing Pregnant Women
  - Alcohol Dependence
Comparison of SMART Studies

When is the second randomization?

• At one fixed point in time only
  - ASD (month 3)
  - REP (month 12)
  - Drug Abusing Pregnant Women (week 2)
  - Alcohol Dependence (responders at week 8)

• At any one of several fixed times
  - ADHD (at month 2 and then monthly)
  - Alcohol Dependence (non-responders at week 2 and weekly until week 8)
Comparison of SMART Studies

What kinds of critical questions?

• Which treatment first and which second?
  - ASD
  - ADHD
  - Drug Abusing Pregnant Women

• How soon to give up on initial treatment and which treatment to provide next?
  - Alcohol Dependence

• Which treatment second and which third?
  - REP
Comparison of SMART Studies

What are the primary research questions?

• Main effect of stage/phase 1 treatment
  - ASD
  - ADHD
  - REP

• Main effect of stage/phase 2 treatment
  - Alcohol Dependence (among non-responders)

• Comparison of two embedded interventions
  - Drug Abusing Pregnant Women
Module 3 Practicum

- Major goal is to draft an initial SMART (90min)

- Review and revise the list of critical scientific questions you made at the end of Module 1
- Continue sketching a SMART design in your field
- Sketch (2-3 sentences) rationale for your SMART

- Individual work (10min)
  Group work (35min)
  Group discussion (45min): 2-3 groups volunteer