On Adaptive Interventions and SMART

Inbal (Billie) Nahum-Shani
Outline

– Adaptive Intervention (AIs)
  ▪ What they are
  ▪ Components
  ▪ Motivation

– Sequential Multiple Assignment Randomized Trial (SMART)
  ▪ How it can be used to inform the development of AIs
  ▪ Key features
  ▪ Sample size considerations
  ▪ SMARTs vs. other designs
  ▪ Examples of SMARTs
Outline

– Adaptive Intervention (AIs)
  ▪ What they are
  ▪ Components
  ▪ Motivation

– Sequential Multiple Assignment Randomized Trial (SMART)
  ▪ How it can be used to inform the development of AIs
  ▪ Key features
  ▪ Sample size considerations
  ▪ SMARTs vs. other designs
  ▪ Examples of SMARTs
Definition of AI

- An intervention design
- …in which intervention options are individualized to accommodate the specific and changing needs of individuals.
- A sequence of individualized treatments.
- Mimics how we make decisions in real-life
- … but aim to guide decision making in clinical, educational, health policy etc.
Definition of AI

- Go by many different names:
  - Adaptive health interventions,
  - Adaptive treatment strategies,
  - *Dynamic treatment regimes (DTRs)*,
  - 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)
Adaptive Drug Court Program

- Low risk: As-needed court hearings + standard counseling
- High risk: Bi-weekly court hearings + standard counseling

Non-compliant

Non-responsive

As-needed court hearing + ICM

Bi-weekly court hearing + ICM

Jeopardy contract: “zero tolerance”

Nahum-Shani, I.
Adaptive Drug Court Program

Low risk

High risk

As-needed court hearings + standard counseling

Bi-weekly court hearings + standard counseling

Non-responsive

Non-compliant

Non-compliant

As-needed court hearing + ICM

Bi-weekly court hearing + ICM

Jeopardy contract: “zero tolerance”

Nahum-Shani, I.
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}
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\}

1. Decision Point:
A time in which treatment options should be considered based on patient information
Adaptive Drug Court Program

As-needed court hearings + standard counseling

Bi-weekly court hearings + standard counseling

Low risk

High risk

Non-responsive

Non-compliant

As-needed court hearing + ICM

Bi-weekly court hearing + ICM

Jeopardy contract: “zero tolerance”
First Stage Decision Rule

At point of entry into the program

\textbf{If} risk = low

\textit{Then}, stage 1 intervention = \{As-needed + SC\}

\textbf{Else if} risk = high

\textit{Then}, stage 1 intervention = \{Bi-weekly + SC\}

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

Program graduation (14 consecutive weekly negative drug urine specimens)

Proximal $\rightarrow$ Short-term goal of decision rules:

Compliance and response in the course of intervention (mediator)
Adaptive Drug Court Program

Low risk
- As-needed court hearings + standard counseling
- Non-compliant
  - Non-responsive
  - As-needed court hearing + ICM
  - Non-compliant
  - Non-compliant
- Jeopardy contract: “zero tolerance”

High risk
- Bi-weekly court hearings + standard counseling
- Non-compliant
  - Non-responsive
  - Bi-weekly court hearing + ICM
  - Non-compliant
  - Non-compliant
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 → 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)

Proximal outcomes
• Based on your theory of change
• Related to prevention, treatment, academic-success
• At various levels: patient, family, clinic
AI: 5 Elements

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

- Monitoring
- Individualizing
- Delivering

Triggered

Adaptation process

Guided

Nahum-Shani, I.
Motivation for Adaptive Interventions

1. High **heterogeneity** in need/response to any one intervention
2. Improvement is **non-linear**
3. Intervention **burden**
4. Intervention **cost**
Summary

- 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.

AI is a sequence of (individualized) treatments

AI is a sequence of decision rules that recommend what to offer, for whom, and when.
• Adaptive Intervention is:
  – a sequence of individualized intervention options
  – that uses dynamic information to decide what type of intervention to offer
  – its objective to guide clinical/academic practice or public health policy.

Summary

AI is a sequence of (individualized) treatments

AI is a sequence of decision rules that recommend what to offer, for whom, and when.
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?
- What tactic should we use for non-responders to treatment A?
- What tactic should we use for responders to treatment A
- How to re-engage patients who are non-adherent or drop-out?
- Location of treatment?
- Mode of delivery?
- How to define non-response?
My Reading List *(Not Complete)*


Other questions about Adaptive Intervention? …
Outline

– Adaptive Intervention (AIs)
  ▪ What they are
  ▪ Components
  ▪ Motivation

– Sequential Multiple Assignment Randomized Trials (SMART)
  ▪ How it can be used to inform the development of AIs
  ▪ Key features
  ▪ Sample size considerations
  ▪ Examples of SMARTs
  ▪ SMARTs vs. other designs
What is a SMART?

- A Multi-Stage Randomized trial
  (Dawson & Lavori, 2004; Lavori & Dawson, 2001; Murphy, 2004)
- Each stage corresponds to a scientific question(s) concerning the selection and adaptation of intervention options.
- Randomization occurs at each decision point of scientific interest
- 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*
AIM-ASD SMART (N=192; R01-HD073975; PI: Kasari)

First-stage intervention

Embedded Tailoring Variable

Second-stage intervention

Experimental Conditions

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

Week 16
SMART Design Principles

• **When to consider a SMART?**
  – When you would like to address questions concerning the construction of an adaptive intervention
  – *Multiple* questions are of interest, regarding multiple decision points
AIM-ASD SMART (N=192; R01-HD073975; PI: Kasari)

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

Treatment Outset | Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement | Week 16
SMART Design Principles

- **Should re-randomization be restricted?**
  - If you have ethical, scientific, or practical reason to do so.
    - Ethical: certain treatment options are not appropriate for a subset of the participants
    - Scientific: based on empirical evidence the best treatment for a specific subset of participants is already established
    - Practical: e.g., save the more intense/costly (step-up) options to those who need it most.
AIM-ASD SMART (N=192)

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 | JASP+EMT | e
| DTT+JASP+EMT | DTT+JASP+EMT | f

Treatment Outset | Week 6: Therapist-rated Clinical Global Impressions Scale of Improvement | Week 16
SMART Design Principles

• **How to select Aims?**
  − Select a primary aim that is important to the development of an adaptive intervention; sample size is based on this aim
  − Collect additional data that could be used to further inform the development of adaptive interventions in secondary aims
Primary Aim: Example 1

*Compare initial intervention options*

**H1:** Starting an AI with JASP+EMT will improve social communication more than starting with DTT.
H1: Comparison of Stage 1 Options
Primary Aim: Example 2

*Compare second stage options for slow-responders*

**H2:** Blending JASP+EMT and DTT for slower responders will improve social communication more than continue.
H2: Stage 2 Options for Slow Responders

First-stage intervention

- DTT
- JASP + EMT

Embedded Tailoring Variable

- Responders
  - DTT
  - JASP + EMT
- Slower responders
  - DTT
  - JASP + EMT

Second-stage intervention

- Relapse Prevention
- Low-level monitoring
- DTT
- DTT + JASP + EMT
- JASP + EMT
- JASP + EMT + DTT

Experimental Conditions

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

Treatment Outset

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

Week 16
Campore embedded adaptive interventions

....first let’s review what we mean by “embedded adaptive intervention”
Embedded Adaptive Intervention 1

First-stage intervention

Embedded Tailoring Variable

Second-stage intervention

Experimental Conditions

DTT

DTT+Parent Training

DTT

DTT+JASP+EMT

JASP+EMT+Parent Tng

JASP+EMT

JASP+EMT+DTT

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

Week 16

Treatment Outset

Responders

Slower Responders

Responders

Slower Responders

b
c
d
e
f
g
h
Start with DTT
Then, at week 6

*If* response status = responder
Then, stage 2 intervention = {add Parent Training}

*Else if* response status = slow responder
Then, stage 2 intervention = {Blend with JASP+EMT}
Embedded Adaptive Intervention 2

First-stage intervention

Embedded Tailoring Variable

Second-stage intervention

Experimental Conditions

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

Week 16
Embedded Adaptive Intervention 3

First-stage intervention

- DTT
- JASP + EMT

Embedded Tailoring Variable

- Responders
- Slower Responders

Second-stage intervention

- DTT + Parent Training
- DTT
- DTT + JASP + EMT
- JASP + EMT + Parent Tng
- JASP + EMT
- JASP + EMT + DTT

Experimental Conditions

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

Treatment Outset

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

Week 16
Embedded Adaptive Intervention 4

First-stage intervention

Embedded Tailoring Variable

Second-stage intervention

Experimental Conditions

DTT

Responder

Slower Responders

JASP + EMT

Responder

Slower Responders

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

Week 16

DTT + Parent Training

DTT

DTT + JASP + EMT

JASP + EMT + Parent Tng

JASP + EMT

JASP + EMT + DTT

a

b

c

d

e

f

g

h
Embedded Adaptive Intervention 4

Start with DTT
Then, at week 6
Stage 2 intervention = {Continue}
...and so on...

...Embedded Adaptive Interventions 5, 6, 7, and 8 are similar but begin with JASP+EMT...
Primary Aim: Example 3

Compare embedded adaptive interventions

**H3:** The AI that begins with JASP+EMT and (a) adds parent training for responders and (b) blends for slower responders…

…will improve social communication more than the similar AI which begins with DTT.
**H3: Comparison of 2 AIs**

- **First-stage intervention**
  - DTT
  - JASP + EMT

- **Embedded Tailoring Variable**
  - Responders
  - Slower Responders

- **Second-stage intervention**
  - DTT + Parent Training
    - DTT
  - DTT + JASP + EMT
  - JASP + EMT + Parent Tng
    - JASP + EMT
  - JASP + EMT + DTT

- **Experimental Conditions**
  - Week 16
1: Compare initial intervention options:
   \textbf{H1}: JASP+EMT is better than DTT
2: Compare subsequent options among slow responders:
   \textbf{H2}: Blending is better than Continue
3: Compare embedded AIs:
   \textbf{H3}: AI #1 is better than AI #5
Sample Size

**H1:** Initial intervention options:
JASP+EMT is better than DTT.

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

**H2:** Subsequent options among slow responders:
Blending is better than Continue.

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

\( N = \text{sample size for the entire trial} \)

<table>
<thead>
<tr>
<th>( \Delta \mu/\sigma = .3 )</th>
<th>( \Delta \mu/\sigma = .5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N = 350 )</td>
<td>( N = 350/\text{SR rate} )</td>
</tr>
<tr>
<td>( N = 126 )</td>
<td>( N = 126/\text{SR rate} )</td>
</tr>
</tbody>
</table>

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

* Assumptions: equal variances, normality, equal # in each group, no dropout.
** AIM-ASD’s was of this type, w/ ES = 0.5, pwr = 90% and acctng for 10% dropout.
Sample Size Examples

**H3:** AI #1 results in better social communication compared to AI #5

- Sample size formula depends on who gets re-randomized
- If both R and SR get 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>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>80%</td>
<td>0.3</td>
<td>698</td>
<td>Both R and SR are re-randomized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5</td>
<td>252</td>
<td></td>
</tr>
</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. (under review)
Secondary Aim: Example

Identify ways to more deeply-tailor the AI.

− Example:

**H4:** Among early responders, those whose parents demonstrate greater buy-in for the initial treatment will benefit more from parent training than from continue.
More Deeply Tailored?

Start with DTT

*Then, at week 6*

*If* response status = responder

*Then, stage 2 = {add Parent Training}*

*Else if* response status = slow responder

*Then, stage 2  = {Blend with JASP+EMT}*

Clinical Global Impressions
Scale of Improvement
Parent Buy-in as a Tailoring Variable?

First-stage intervention

- DTT
- JASP + EMT

Embedded Tailoring Variable

Responders

- DTT + Parent Training
- JASP + EMT + Parent Tng

Slower responders

- DTT
- DTT + JASP + EMT
- JASP + EMT
- DTT + JASP + EMT

Second-stage intervention

Experimental Conditions

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

Treatment Outset

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

Week 16
Example of a More Deeply Tailored AI

Start with DTT

Then, at week 6

If response status = responder
  Then,
    If parent buy-in={high}
      Then, stage 2 = {add Parent Training}
    Else, if parent buy-in={low}
      Then stage 2 ={add parent training or continue}
  Else if response status = slow responder
    Then, stage 2 = {Blend with JASP+EMT}
Methods for Analyzing Data

• Compare first and second-stage intervention options

• Compare AIs with end of study outcome (e.g., Nahum-Shani et al., 2012a)

• Multiple comparisons with the best embedded AI (e.g., Ertefaie et al., 2015)

• Compare AIs with repeated measures outcomes (e.g., Lu et al., 2015)

• Identify ways to more deeply tailor embedded AIs (e.g., Nahum-Shani et al., 2012b; Schulte et al., 2014)
SMARTs vs. Other designs

- RCT
- Non-Responders studies
- Factorial Designs
- Crossover
- Adaptive Trials
- Randomized Discontinuation Design
SMART vs. Randomized Control trial (RCT)

- A randomized control trial (RCT) evaluating an AI compared to a suitable control.
  - The primary aim is to confirm it’s effectiveness compared to an alternative
SMART vs. Non-Responders Trial

- Randomizing non-responders to a given intervention to subsequent intervention options
  - Evidence is sufficient to select a first-line treatment; but there are scientific questions regarding subsequent options for non-responders
  - Also known as the ‘single-stage-at-a-time approach”
  - There are various considerations when building an adaptive intervention based on a series of separate responder or non-responder trials.
1. Delayed effects
2. Drop-out
3. Selection effects
4. Prescriptive effects
SMARTs vs Factorial Experiments

- A SMART is a special form of a factorial; factors are employed sequentially.
- Randomization to subsequent factors in a SMART are often restricted based on early response status.
- In SMART, effects have sequential interpretation.
SMARTs vs Crossover Trials

- A repeated measurements design-- patients cross over from one treatment to another during the course of the trial.

- Typically aim to evaluate stand-alone treatments, not to address questions concerning AIs

- Attempts to wash out the carryover effects while SMARTs are often motivated by such (delayed)
SMARTs vs Adaptive Trials/Designs

• A clinical trial design that allows adaptations or modifications to aspects of the trial while the study is still ongoing (Chang, 2007)

• e.g.,
  – Stop the trial early either for success, futility or harm
  – Drop arms or doses or adjust doses
  – Modify randomization rate to increase probability of allocation to the most appropriate arm

• SMARTs are generally not adaptive designs
  – Design parameters are set a-priori and do not change.
  – But the two concepts can be combined (Cheung et al., 2015; Lee et al., 2015)
SMARTs vs Randomized Discontinuation Trial (RDT)

• A SMART follows all patients who enroll, whereas RDT does not continue to follow participants who are not randomized.
• The focus of RDT is on whether we should continue or discontinue treatment for responders to stage 1.
Other Interesting SMARTs

• ExTENd
  ▪ N=302; NIAAAOSL014851; PI: Oslin

• ENGAGE
  ▪ N=500; P60DA05186; PI: McKay

• SMARTer
  ▪ N=400; R01DK108678; PIs: Spring & Nahum-Shani
ExTENd

First-stage intervention

NTX + Lenient Definition of non-response
NTX + Stringent Definition of non-response

Intermediate outcome

Week 8 Responders
Non-responders
Week 8 Responders
Non-Responders

Second-stage intervention

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

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
**ENGAGE**

**MI-IOP** → motivational interviewing that focuses on helping the patient to engage in the IOP

**MI-PC** → motivational interviewing that includes a choice of four possible treatment options
SMARTer

First-stage intervention | Intermediate outcome | Second-stage intervention | Experimental Conditions
---|---|---|---
App | Response | Continue | Subgroups
App + Coaching | Non-Response | Add TXT | A
| Response | Add TXT & Coaching | B
| Non-Response | Continue | C
| Response | Add TXT | D
| Non-Response | Add TXT & MR | E

Treatment Outset | Assess | Week 12 | Month 12
---|---|---|---
At weeks, 2, 4, and 8

**Abbreviations:**

- App → Mobile Application
- MR → Meal Replacement
- TXT → Text Messages
…and Many Other SMARTs in the field…

- Drug abuse
- ADHD
- Alcoholism
- Obesity
- OCD
- Autism
- Schizophrenia
- Depression
- Insomnia
- Bipolar
- Conduct problems
- Smoking cessation
- Suicide prevention

https://methodology.psu.edu/ra/adap-inter/projects
SMART and MOST

The Multiphase Optimization Strategy (MOST)

- **Preparation**
  - Derive/revise conceptual model
  - Identify set of candidate components
  - Identify optimization criterion

- **Optimization**
  - Optimization trial(s)
    - Factorial experiment
    - Fractional factorial experiment
    - SMART
    - Micro-randomized trial
    - System identification
    - Other
    - Continual improvement process
    - Based on results, identify intervention that meets optimization criterion

- **Evaluation**
  - Confirm effectiveness of optimized intervention via RCT

Continual optimization principle

Resource management principle
The End

Inbal (Billie) Nahum-Shani
Email: inbal@umich.edu

Thank you…

Danny Almirall
Susan Murphy
John Dziak
Jim McKay
Kevin Lynch
Linda Collins
Bonnie Spring
Kelley Kidwell

R01 DA039901 (Nahum-Shani & Almirall)
R01 AA022113 (Bacharach)
U54-EB-020404 (Kumar)
R01 AA023187 (Murphy)
P50 DA039838 (Collins)
R01 DK108678 (Spring & Nahum-Shani)
R01 HD73975 (Kasari)
R01-MH103244 (King)