On Adaptive Interventions and SMART

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Outline

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

– Sequential Multiple Assignment Randomized Trials (SMARTs)
  ▪ What is a SMART?
  ▪ Design principles & analysis

– SMART Case Studies
  ▪ RBT: Treatment for Pregnant Women who are Drug Dependent
  ▪ ExTENd: Treatment of Alcohol Dependence
## Outline

- **Adaptive Intervention (AIs)**
  - What are AIs?
  - Components
  - Motivation

- **Sequential Multiple Assignment Randomized Trials (SMARTs)**
  - What is a SMART?
  - Design principles & analysis

- **SMART Case Studies**
  - RBT: Treatment for Pregnant Women who are Drug Dependent
  - ExTENd: Treatment of Alcohol Dependence
Definition of AI

- An intervention design, not an experimental 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
• Go by many different names:
  – Adaptive health interventions,
  – Adaptive treatment strategies,
  – Dynamic treatment regimens,
  – Treatment algorithms,
  – Stepped care models,
  – Treatment protocols,
  – Individualized interventions
  – ...

Definition of AI
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
  - Non-compliant

- **High risk**
  - Bi-weekly court hearings + standard counseling
  - 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\}

4. Decision rule

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 response} in the course of intervention (mediator)

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

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

1) High **heterogeneity** in need/response to any one intervention
2) Improvement is **non-linear**
3) Intervention **burden**
4) Intervention **cost**
5) Boredom, habituation, cognitive overload
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.

AIs Experienced Differently by Different Stakeholders

AI is a sequence of (individualized) treatments

AI is a sequence of decision rules that recommend what intervention to offer at each critical decision point.
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 (individualized) treatments
- 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?

• Location of treatment (e.g., home or clinic)

• Mode of delivery (e.g., internet or in-person)

• How do we define non-response?
Questions about Adaptive Interventions?
Outline

- Adaptive Intervention (AIs)
  - What are AIs?
  - Components
  - Motivation
- Sequential Multiple Assignment Randomized Trials (SMARTs)
  - What is a SMART?
  - Design principles & analysis
- Case studies
  - RBT: Treatment for Pregnant Women who are Drug Dependent
  - ExTENd: Treatment of Alcohol Dependence
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 point
- 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*
Motivating Questions

• **Hypothetical Aim:** AI for treating Netflix addiction
• Insufficient empirical evidence/theories to determine:
  (a) What is the best way to **initiate treatment** (A vs. B)?
  (b) How to modify treatment for **early non-responders** (switch vs. augment)
  (c) How to maintain Netflix abstinence among **early responders** (relapse prevention vs. monitoring)
Hypothetical SMART

First-stage intervention

Intermediate outcome

Second-stage intervention

Experimental Conditions

Treatment Outset

Week 4

Week 12

Responders

Non-responders

A

B

R

R

R

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
Hypothetical SMART

But I’m worried about…

…sample size

This looks too…

…complicated
Let’s go back to our Hypothetical SMART

<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>R</td>
<td>A</td>
<td>Relapse Prevention</td>
<td>a</td>
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<td>Switch</td>
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<td>Augment</td>
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</tbody>
</table>
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

• Keep it Simple:
  – 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
  – 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
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
---|---|---

- A
- B

- Responders
- Non-responders

- 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
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

First-stage intervention  Intermediate outcome  Second-stage intervention  Experimental Conditions

Treatment Outset  Week 4  Week 12

Responders
A

Non-responders
B

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

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**
  - Treatment Outset
  - Week 4

- **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
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

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

<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>
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</tbody>
</table>

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

*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

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<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 NR are re-randomized</td>
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<tr>
<td></td>
<td></td>
<td>0.5</td>
<td>252</td>
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</tr>
</tbody>
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- *Continuous Outcomes:* Oetting, A.I., et al. (2011)
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
Questions about SMART?
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- Case studies
  - RBT: Treatment for Pregnant Women who are Drug Dependent
  - ExTENd: Treatment of Alcohol Dependence
RBT (PI: Jones): Treatment for Pregnant Women who are Drug Dependence

ExTENd (PI: Oslin): Treatment of Alcohol Dependence
RBT (Jones) $N=300$

No Drugs!
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:**

\[ a\text{RBT} < r\text{RBT} < t\text{RBT} < e\text{RBT} \] (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 rRB; reduce for compliant; continue for non-compliant (least costly/burdensome)
8 Embedded AIs:

2) Start with rRB; reduce for compliant; intensify for non-compliant
**RBT (Jones) \( N=300 \)**

**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 tRB; reduce for compliant; continue for non-compliant.
8 Embedded AIs:

8) Start with tRBT; reduce for compliant; intensify for non-compliant.
RBT (Jones) \( N=300 \)

**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 Dependence

**ExTENd** (PI: Oslin): Treatment of Alcohol Dependence
ExTENd (Oslin) $N=302$

- **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 (Osln) \( N=302 \)

**Population:**

Alcohol Dependent Adults completing an Intensive Outpatient Program (IOP)

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**Diagram Details:**

- **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

**Lenient Definition** ➔ 5+ heavy drinking days in 1 week
**Stringent Definition** ➔ 2+ heavy drinking days in 1 week

**Week 24**

- a
- b
- c
- d
- e
- f
- g
- h
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 to for responders
- Because of various barriers: Physiological/social/psychological

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<td>NTX + Lenient Definition of non-response Week 8 Responders</td>
<td>NTX</td>
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<tr>
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<td>NTX + TDM</td>
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NTX → Naltrexone (opioid antagonist)
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Lenient Definition → 5+ heavy drinking days in 1 week
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ExTENd (Osling) $N=302$

**Treatments:**

- **NTX:** Naltrexone
- **CBI:** cognitive behavioral intervention
- **TDM:** telephone disease monitoring
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 (Osline) \(N=302\)

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

---

**Diagram:****

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

- Week 8 Responders
  - NTX
  - NTX + TDM
- Non-responders
  - NTX + CBI

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

**Legend:**
- NTX → Naltrexone (opioid antagonist)
- TDM → Telephone Disease Management
- CBI → Combined Behavioral Intervention
- **Lenient Definition** → 5+ heavy drinking days in 1 week
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**Week 24**

**Treatment Outset**
8 embedded AIs:

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

8 embedded AIs:

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

**Legend:**
- TDM → Telephone Disease Management
- CBI → Combined Behavioral Intervention
- Lenient Definition → 5+ heavy drinking days
- Stringent Definition → 2+ heavy drinking days
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**
  - **Non-responders** → **Stringent Definition of non-response**
  - **Lenient Definition of non-response** → **Week 8 Responders**

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

- **Second-stage intervention**
  - **NTX** → **a**
  - **NTX+TDM** → **b**
  - **CBI** → **c**
  - **NTX+CBI** → **d**

- **Treatment Outset** → **Week 24**

**Abbreviations:**
- **TDM** → Telephone Disease Management
- **CBI** → Combined Behavioral Intervention
- **Lenient Definition** → 5+ heavy drinking days
- **Stringent Definition** → 2+ heavy drinking days
8 embedded AIs:

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

- **First-stage intervention**: Lenient Definition of non-response
  - Week 8 Responders
  - Non-responders

- **Intermediate outcome**: Stringent Definition of non-response
  - Week 8 Responders
  - Non-Responders

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

**TDM** → Telephone Disease Management
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**Week 24**:
- a
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ExTENd (Osling) $N=302$

8 embedded AIs:

8) Start on NTX; if 2+ HDDs prior to week 8, augment NTX+CBI; else at week 8 offer NTX+TDM

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

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

**Legend:**
- **TDM** → Telephone Disease Management
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ExTENd (Osline) 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).

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
Questions about case studies?
The End

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- Shawna Smith: shawnana@umich.edu
Extra slides
Alternatives to SMARTs in Adaptive Intervention Research

- A **randomized clinical trial** (RCT) evaluating an adaptive intervention versus another adaptive intervention or suitable control
- A “**non-responder RCT**” where non-responders to an initial intervention are randomized to two options
- A “**responder RCT**” where responders to an initial intervention are randomized to two options
- There are various considerations when building an adaptive intervention based on a series of separate responder or non-responder RCTs.
Alternate Approach to Constructing an Adaptive Intervention

• Why not use data from multiple trials to construct the AI?

• The single-stage at a time approach
  – **Trial 1**: Randomized trial of initial intervention options → Choose the best stage 1 option.
  – **Trial 2**: Randomized trial of secondary intervention options → Choose the best stage 2 option.
Alternate Approach

Key Issues:
1. Delayed effects
2. Drop-out
3. Selection effects
4. Prescriptive effects
Reason # 1: Delayed Therapeutic Effects

Delayed effect:

• Short term effectiveness of initial treatment does not capture its long-term effectiveness when followed by subsequent treatment
  – i.e., when considered part of a sequence of treatments
  – Might happen when there are:
    a. Positive synergies
    b. Negative Synergies
Reason # 1a: Delayed Therapeutic Effects

Positive synergies:
• Intervention option that does not seem best initially (in short-term) is the best in the long term, when considered part of a sequence.
  - “A” may not appear best in 4 weeks
  - but may have enhanced long term effectiveness when followed by Augment
  - In other words:
    ▪ A may lay the foundation for the long-term effectiveness of Augment
    ▪ Augment builds on the gains of A.
Reason # 1b: Delayed Therapeutic Effects

Negative synergies:

- Intervention option that appears best initially (in short-term) is not best in the long term, when considered as part of a sequence.
  - “B” may produce a higher proportion of responders
  - But, the burden imposed by B may be sufficiently high so that non-responders are less likely to adhere to subsequent treatments
Subjects more likely to adhere/remain in SMART

- In the alternate trial of the initial treatments subjects are assigned a fixed treatment.
  - Those who are not improving have no other option besides non-adherence or drop-out.
- SMART, by design, provides alternates for non-improving subjects,
  - Enhancing motivation to adhere and remain in the study.
Reason #3: Selection Effect

A Non-Responders study might not represent the population of non-responders

- In the alternate trial 2, I may choose to recruit non-responders to B and randomize to subsequent options.
  - Only non-responders who are highly motivated will select to participate in this study
  - Because of this selection bias I might not realize that I need to provide more support to encourage demoralized non-responders to start treatment again.
Reason #4: Prescriptive Effects

Single stage provides limited options to explore ways to more deeply tailor the AI.

- Treatment A may not produce as high a proportion of responders as treatment B
- but treatment A may elicit symptoms (e.g., non-adherence) that allow you to better match the subsequent treatment to the patient and thus achieve improved response to the sequence of treatments as compared to initial treatment B.
Our scientific questions are about *sequences of treatments*. The approach lets us investigate treatment effects... as part of a sequence... as a standalone treatment.