Getting SMART about Developing Adaptive Intervention Strategies

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Outline

• Why are adaptive interventions useful?
• What is an adaptive intervention?
• How can SMART designs help us learn about adaptive interventions and improve them?
• What are some things to consider when designing a SMART trial?
• Where do SMARTs fit in the personalization process?
• What are some common misconceptions about adaptive interventions and SMART designs?
Case Studies

• Program for Lung cancer screening and Tobacco cessation (PI: Jospeh, co-I Vock; smoking cessation for adults eligible for low-dose CT scan for lung cancer screening)

• An Adaptive Algorithm-Based Approach to Treatment for Adolescent Depression (PI: Gunlicks-Stoessel, co-I Vock; adolescent depression with IPT & meds)
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Motivation for AIS

- Not everyone responds to the same intervention in the same way (between person heterogeneity)
- Not everyone response to an intervention is consistent over time (within person heterogeneity)
  - Changes in adherence, engagement, burden
  - Accrual of toxicity or delayed side effects
- Many chronic or long-term conditions or diseases — cancer, smoking, substance use disorder, depression, obesity, ADHD, autism, or schizophrenia
- BUT we may have multiple different interventions (or dosages/intensities to try)
How do we treat chronic disease?

- Make an initial treatment decision, monitor for response/adherence, and adjusting treatment based on the individual’s changing course.
How do we treat chronic disease?

- Can we formalize this process to test different strategies improve outcomes?
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Adaptive Intervention Strategy

• Pre-specified sequence of decision rules
• One rule for each possible decision point
• Dictate what type of treatment/intervention, at what dosage/intensity, with what type of delivery (e.g., switch, augment, intensify, stay the same)
• Based on measured patient characteristics (including prior response to treatment)
Adaptive Intervention Strategy

• The intervention/treatment strategy/regime/policy is said to be “adaptive” or “dynamic” or “tailored” because it depends on a person’s evolving characteristic

• Note: Stepped care intervention models are a special case of adaptive interventions
A Rose By Any Other Name

- Adaptive Intervention Strategy (AI or AIS)
- Adaptive Treatment Strategy (ATS)
- Dynamic Treatment Regime (DTR)
- Multistage Treatment Strategy (MTS)
- Treatment Policy (TP)
Example AIS in Smoking Cessation

• Stage 1: Initial Phase TLC (phone counseling + NRT) for 8 weeks
• Stage 2: At end of 8 weeks assess 7 day abstinence
  - IF abstinent (complete responder) continue with TLC (at least monthly phone counseling + NRT) for 48 weeks
  - ELSE combine TLC with pharmacotherapy (MTM)
Tailoring Variables

- The variable and cutoff which determine which intervention a participant should receive are known as tailoring variables and cutpoint
- Smoking cessation AIS: 7 day abstinence
- What can be a tailoring variable?
- Any variable which can be measured can be a tailoring variable
- This does not mean all are equally good ideas
Many Possible Adaptive Interventions

• Are these “good” adaptive interventions?
• How could these adaptive interventions be improved?
Unanswered Questions to Optimize an AIS

• Which treatment or intervention should be offered to individuals initially?
• How frequently should individuals be monitored for response/nonresponse to initial treatment?
• Among individuals who are not responding well to initial treatment, should their initial treatment be intensified, augmented, or switched?
• Among individuals responding to treatment, what maintenance/relapse prevention treatment should be offered?
Optimizing an AIS

• Typically used the following to develop AIS
  - Expert opinion
  - Clinical judgement
  - Piecing together an adaptive intervention using results from separate RCTs

• Can we collect data which would help inform development of an AIS?
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Sequential Multiple Assignment Randomized Trial

- SMART Designs are type of trial design that scientists can use to optimize an AIS
- Can be used to answer any of the previously posed questions
Sequential Multiple Assignment Randomized Trial

• Multi-stage trial design - each stage corresponds to a critical decision
• Participant can be randomly assigned to one of several intervention options at each stage
• Set of available interventions that a single participant may be randomized to at each stage may depend on prior treatment received and/or participant characteristics
• In a SMART, some or all participants are randomized at least twice; i.e., at two or more stages
Case Study #1: PLUTO

- Several behavioral, pharmacological, and combination treatment strategies for smoking cessation
- Treatments yield low rates of long-term abstinence (5-20%), and there is little evidence to help development of an AIS
- Pressing need: USPSTF recommends annual lung cancer screening for those age 55 to 80 years who have a 30 or more pack year history of smoking and who are current smokers or have quit within the last 15 years
Case Study #1: PLUTO

- Smoker identified in lung cancer screening

  - Initial treatment
  - Assess response at 4 weeks
  - Complete responder (no smoking at all) → TLC-Monthly 1
  - Incomplete responder (any smoking) → TLC-Quarterly 2

  - Initial treatment
  - Assess response at 8 weeks
  - Complete responder (no smoking at all) → TLC-Monthly 3
  - Incomplete responder (any smoking) → TLC-Monthly 4

  - TLC-Monthly 5
  - TLC-Quarterly 6
  - TLC-Monthly 7
  - TLC+MTM 8

Baseline → 4W → 8W → Year 1 treatment - 18M outcome
Case Study #1: PLUTO

- Usual care: 8 weeks of telephone counseling + NRT
- Tobacco longitudinal care: continue monthly calls for one year → recycle relapsers and reducers to make additional quit attempts
- TLC algorithm for treatment non-responders
Case Study #1: PLUTO

- TLC is an intensive intervention compared to state quit lines
- Other interventions which are evidence-based which could help those who are struggling
- Key questions:
  1. For those “doing well” can we reduce the frequency of phone counseling
  2. For those “struggling” will offering pharmacotherapy improve outcomes?
Embedded Tailoring Variable/AIS

- Response or nonresponse status at the end of initial-phase TLC is used to tailor the interventions that a subject may be randomized to in the second-phase.
- Because this tailoring variable is part of the study design → “embedded tailoring variable”
- AIS which use this tailoring variable and intervention components in the study are known as “embedded adaptive intervention”
## Embedded AIS in PLUTO

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Case Study #2: Algorithms for Adolescent Depression

- 20% of adolescents experiencing a depressive episode at some point
- Several evidence-based treatments including psychotherapy (interpersonal psychotherapy, cognitive behavioral therapy), antidepressant medication (SSRIs), and their combination.
- Approximately 30-50% of adolescents who receive these treatments do not respond
- Practice parameters recommend systematic and routine assessment and monitoring
- Currently no guidelines to direct therapists regarding how to use those symptom assessments to guide subsequent treatment decisions
Case Study #2: Algorithms for Adolescent Depression

1. **1st Randomization**
   - **ATSs beginning with IPT-A**
     - N = 134

2. **2nd Randomization**
   - **Sufficient Response**
   - **Insufficient Response**

3. **Week 0**
   - **Stage 1 Decision**

4. **Week 4 & 8**
   - **Stage 2 Decision**

5. **Week 16 & 36**
   - **Outcome**

- **Continue IPT-A**, reassess at week 4 & week 8; randomize if insufficient response
  - N = 66 (estimated); Cell 1

- **Add SSRI**
  - N = 34 (estimated); Cell 2

- **Increase dose of IPT-A**
  - N = 35 (estimated); Cell 3

- **Usual Care**
  - N = 66; Cell 4
Specific Aims of PLUTO

- **Primary**: Test whether *incomplete responders* to initial phase of TLC treatment benefit from the addition of MTM
- **Secondary**: Among *complete responders* compare the effect of more intensive (at least monthly) follow-up to less intensive (quarterly) follow-up
- **Exploratory**: Moderators of second-phase treatment (assessment time & # of days smoking in last week)
- **Exploratory**: Compare different embedded adaptive interventions
- **Note**: primary and secondary aim mirror the key questions outlined earlier
Stat Analysis and Power for Primary Aim

• As with factorial designs, common test the main effects of intervention components

• To test primary aim of PLUTO: pool data from all *incomplete responders* randomized to TLC (cells 3 & 7) or TLC+MTM (cells 4 & 8) and compare the outcomes using methods appropriate for the comparison of two groups

• Standard formulas can be used to estimate the sample size of nonresponders needed

• Overall study sample size: Dividing the sample size of nonresponders by the proportion of subjects one anticipates to be nonresponders
Case Study #1: PLUTO

1. Smoker identified in lung cancer screening

   R1

   Initial treatment

   Assess response at 4 weeks

   Complete responder (no smoking at all)

   R2b

   TLC-Monthly

   TLC-Quarterly

   TLC-Monthly

   TLC+MTM

   TLC-Monthly

   TLC+MTM

   TLC-Monthly

   TLC+MTM

2. Incomplete responder (any smoking)

   R2a

   TLC-Monthly

   TLC+MTM

   TLC-Monthly

   TLC+MTM

3. Complete responder (no smoking at all)

   R2b

   TLC-Monthly

   TLC-Quarterly

   TLC-Monthly

   TLC+MTM

4. Incomplete responder (any smoking)

   R2a

   TLC-Monthly

   TLC+MTM

5. TLC-Monthly

6. TLC-Quarterly

7. TLC-Monthly

8. TLC+MTM

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Baseline - 4W - 8W - Year 1 treatment - 18M outcome
Stat Analysis to Compare AIS

- Want to estimate the average response to the AIS “begin with IPT-A and nonresponders receive IPT-A + SSRI”
- Data from participants consistent with that embedded AIS (i.e., participants who follow the treatment paths ending in cells 1 and 2) would be used
- Subjects are compliant with more than one embedded AIS. Therefore, estimators of the anticipated outcome of different embedded AISs may be correlated → robust standard errors
- Responders who are consistent with an embedded AIS are over- or underrepresented relative to what we would expect if everyone in the population were to follow this regimen. Over- or underrepresentation in a sample can be corrected using a weighted analysis
Case Study #2: Algorithms for Adolescent Depression

**1st Randomization**

- ATSSs beginning with IPT-A
  - N = 134

**2nd Randomization**

- Insufficient Response
- Sufficient Response
- 2nd Randomization

**Stage 1 Decision**

**Stage 2 Decision**

**Week 0**

**Week 4 & 8**

**Stage 4 Decision**

**Week 16 & 36**

**Outcome**

- **Continue IPT-A, reassess at week 4 & week 8; randomize if insufficient response**
  - N = 66 (estimated); Cell 1

- **Add SSRI**
  - N = 34 (estimated); Cell 2

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**Usual Care**

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Design Considerations

• Old adage: “Protocolize what you know, randomize what you don’t know”

• Lots to consider as part of SMART
  - Initial phase treatment type, intensity, and duration
  - Tailoring variable, cutpoint, and assessment time
  - Second phase treatment type, intensity, and duration for both “responders” and “nonresponders”

• Cannot randomize them all and usually infeasible to randomize to more than 2-3 levels
Design Considerations: Selecting Treatment Types

• SMARTs are about testing the sequence of interventions not establishing new ones

• Frequently start with a single longitudinal evidence-based intervention and then consider ways to augment/intensify/switch
  - PLUTO: start with TLC and test augmenting with MTM
  - Adolescent depression: start with IPT-A and testing intensifying versus augmenting with SSRI

• Need to consider safety and tolerability (may need pilot)
Design Considerations: Tailoring Variable & Cutpoint

- Often second phase treatment will intensify for those with poor prognosis and focus on maintenance/relapse prevention

- Tailoring variable should
  - Be easily measurable (in the real world)
  - Have good predictive value of the final outcome (e.g., C-index)

- Cutpoint can be chosen to balance sensitivity and specificity
**Design Considerations: Tailoring Variable & Cutpoint**

- **Adolescent Depression**
  - Tailoring variable: Hamilton Rating Scale for Depression (week 4: AUC=.78, p=.01; week 8: AUC=.81, p<.01).
  - At week 4 & 8, a cutoff of 20% and 40% reduction in HRSD from baseline represented the best combined sensitivity (72.7% & 72.7%) and specificity (71.4% & 83.3%).

- **PLUTO**
  - Tailoring variable: 7 day abstinence
  - Cutpoint chosen to identify subgroup where TLC was no better than usual care
Design Considerations: Tailoring Variable & Cutpoint

![Bar chart showing the percentage of participants abstinent at 12M for different groups. The chart compares Longitudinal Care and Usual Care. The groups are Continuous Smokers, Late Quitters, Relapsed Smokers, and Continuous Quitters.](chart.png)
Design Considerations: Assessment Time

- Operating characteristics of tailoring variable depend on when it is measured
- Need to assess nonresponse early enough to avoid discouragement but late enough to catch late relapsers
- Adolescent depression: Assess response to IPT-A twice (4 and 8 weeks). Based on pilot data.
- PLUTO: Randomization to 4 and 8 weeks was based on historical data
Design Considerations: Assessment Time

Sample survival curves from smoking cessation studies
Control Conditions Within a SMART

• Many SMARTs do not include a “control” or “unpersonalized” condition → goal is to test efficacy of several AIS one of which could be carried forward

• SMARTs can be designed to include a suitable control intervention
  - As part of the embedded AIS
  - As part of the initial randomization

• Effect sizes will be smaller comparing two different high quality AISs than comparing AIS to usual care
## Control AIS in PLUTO

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Week 0
Stage 1 Decision

1st Randomization

ATSs beginning with IPT-A
N = 134

Week 4 & 8
Stage 2 Decision

Insufficient Response

2nd Randomization

Sufficient Response

IPT-A ATS 1:  
IPT-A ATS 2:

Continue IPT-A, reassess at week 4 & week 8; randomize if insufficient response
N = 66 (estimated); Cell 1

Add SSRI
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Increase dose of IPT-A
N = 35 (estimated); Cell 3

Week 16 & 36
Outcome

Usual Care
N = 66; Cell 4
Other Common SMART Designs

- SMART with no embedded tailoring variable
Other Common SMART Designs

- SMART in which re-randomization depends on a combination of first-stage treatment and nonresponse to first-stage treatment
Other Experimental Designs

• Factorial Design
• Multi-arm RCT
• Standard RCT or series of two-arm RCTs comparing different adaptive intervention strategies
• Single-stage-at-a-time experimental approach (e.g., nonresponder trial, discontinuation trial, etc.)
Other Experimental Designs: Drawbacks

• Factorial Design – Does not allow embedded tailoring variables
• Multi-arm RCT – Requires larger sample size
• Standard RCT or series of two-arm RCTs comparing different adaptive intervention strategies – Requires MUCH larger sample size
• Single-stage-at-a-time experimental approach (e.g., nonresponder trial, discontinuation trial, etc.) – 1) interventions may have delayed effects or interact with later-stage treatments 2) the types of nonresponding subjects who agree to participate in a trial testing two second-stage treatments may differ from the population of nonresponders
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Personalization Process and Next Steps

- Drug development and approval does not happen as the result of a single randomized experiment → Neither should a personalized intervention algorithm
- Need to think of personalized intervention development in terms of phases analogous to drug development
Phases of Personalization

• Phase I: Pilot SMARTs
  - Willing to have intervention re-randomized?
  - Adhere to the proposed interventions?
  - How do we handle participants who don’t have tailoring variable measured?

• Phase II: SMART study
  - Establish that the personalized interventions have some amount of efficacy
  - Use the data collected to refine personalized algorithms

• Phase II: Confirmatory Trial
More Deeply Tailored Interventions

• Example: “Start with initial phase TLC and assess response status at 4 weeks. If a responder, continue with TLC-Q; else if a nonresponder who has smoked on two or fewer days in the past week continue with TLC-M; else continue with TLC+MTM.”
More Deeply Tailored Interventions

• How do we find more deeply tailored interventions which improve outcomes?
• Short answer: moderators, effect modifiers, interaction which are qualitative in nature
• Long answer: reinforcement learning/machine learning techniques which account for delayed effects - Q-learning, A-learning, C-learning, and outcome weighted learning
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Common Misconceptions of AIS

• Tailoring variables cannot differ based on previous intervention
• An adaptive intervention must recommend a single intervention component at each decision point
• Adaptive interventions seek to replace clinical judgement
• Adaptive interventions are only relevant in treatment settings
• Adaptive interventions are non-standard because they involve randomization
Common Misconceptions of SMART

• SMARTs require prohibitively large sample sizes
• All SMARTs require Multiple-Comparisons Adjustments
• All research on adaptive interventions requires a SMART
• All SMARTs must include an embedded tailoring variable
• All aspects of an embedded adaptive intervention must be randomized
• SMARTs are a form of adaptive research design
• SMARTs never include a control group
• SMARTs require multiple consents
• SMARTs are susceptible to high levels of study drop-out
Next Frontiers for AIS and SMART

• What should the next trial be after a SMART (more deeply tailored AIS or best embedded AIS)?
• How to handle missing data in SMARTs?
• Can we combine some of the phases of personalization?
• How does one recommend a set of possible treatment options which are equivalent?
• How to combine different outcomes and weight patient preference (efficacy vs. toxicity)?
Summary

• Defined Adaptive Interventions and discussed why they are important
• Demonstrated that SMART study designs can be used to develop and improve adaptive intervention as part of a personalization process
• Highlighted 2 SMARTs in the field
Collaborators

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