Using Data to Inform Sequential, Individualized Clinical Decision Making

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Outline

• Adaptive Interventions
• SMART experimental designs
• Trial Design Principles and Analysis
• Exploring Individualization using the “Adaptive Interventions for Children with ADHD” study (W. Pelham, PI).
Adaptive Interventions are individually tailored sequences of interventions, with treatment type and dosage changing according to patient outcomes. Operationalize clinical practice.

- McKay (2009) Treatment of Substance Use Disorders
- Marlowe et al. (2008) Drug Court
- Rush et al. (2003) Treatment of Depression
Why Adaptive Interventions?

– High heterogeneity in response to any one treatment
  • What works for one person may not work for another
  • What works now for a person may not work later (and relapse is too common)
– Lack of adherence or excessive burden is common
– Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient
Example of an Adaptive Intervention

• Adaptive Drug Court Program for drug abusing offenders.

• Goal is to minimize recidivism and drug use.

• Marlowe et al. (2008)
Adaptive Drug Court Program

- As-needed court hearings + standard counseling
  - Low risk
  - High risk
- Bi-weekly court hearings + standard counseling
  - Non-responsive
- As-needed court hearings + ICM
  - Non-compliant
- Bi-weekly court hearings + ICM
  - Non-compliant
- Court-determined disposition
The Big Questions

• What is the best sequencing of treatments?

• What is the best timings of alterations in treatments?

• What information do we use to make these decisions? (how do we individualize the sequence of treatments?)
Why SMART Studies?

What is a sequential, multiple assignment, randomized trial (SMART)?

These are multi-stage trials; each stage corresponds to a critical decision and a randomization takes place at each critical decision.

Goal of trial is to inform the construction of adaptive interventions.
Sequential Multiple Assignment Randomization

**Initial Txt** | **Intermediate Outcome** | **Secondary Txt**
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- Early Responder
- Nonresponder

**Tx A**

- Early Responder
- Nonresponder

**Tx B**

- Early Responder
- Nonresponder

**Tx C**

- Relapse Prevention
- Low-level Monitoring
- Switch to Tx C
- Augment with Tx D

**Tx D**

- Relapse Prevention
- Low-level Monitoring
- Augment with Tx D
Examples of “SMART” designs:

- CATIE (2001) Treatment of Psychosis in Schizophrenia
- Pelham (primary analysis) Treatment of ADHD
- Oslin (primary analysis) Treatment of Alcohol Dependence
- Jones (in field) Treatment for Pregnant Women who are Drug Dependent
- Kasari (in field) Treatment of Children with Autism
- McKay (in field) Treatment of Alcohol and Cocaine Dependence
SMART Design Principles

• **KEEP IT SIMPLE**: At each stage (critical decision point), restrict class of treatments only by ethical, feasibility or strong scientific considerations. Use a low dimension summary (responder status) instead of all intermediate outcomes (adherence, etc.) to restrict class of next treatments.

• Collect intermediate outcomes that might be useful in ascertaining for whom each treatment works best (adherence, etc.); information that might be used to individualize treatment.
SMART Design Principles

• Choose primary hypotheses that are both scientifically important and aid in developing the adaptive intervention.
  • Power trial to address these hypotheses.

• Conduct secondary analyses that further develop the adaptive intervention and that use the randomization to eliminate confounding.
EXAMPLE: *(sample size is highly constrained)*: Hypothesize that controlling for the secondary treatments, the initial treatment A results in lower symptoms over the duration of the study than the initial treatment B.
EXAMPLE 1

Initial Txt  Intermediate Outcome  Secondary Txt

Tx A  
- Early Responder  
  - Relapse Prevention
  - Low-level Monitoring
  - Switch to Tx C
  - Augment with Tx D

Tx B  
- Early Responder
  - Relapse Prevention
  - Low-level Monitoring
  - Switch to Tx C
  - Augment with Tx D

Nonresponder  
- Switch to Tx C
- Augment with Tx D
Exploring Greater Individualization using the “Adaptive Interventions for Children with ADHD” study (W. Pelham, PI)

Q-Learning
Example: Pelham ADHD Study

A. Begin low-intensity behavior modification
   8 weeks
   Assess: Adequate response?
   Yes
   Random assignment:
   No
   Random assignment:

B. Begin low dose medication
   8 weeks
   Assess: Adequate response?
   Yes
   Random assignment:
   No
   Random assignment:

A1. Continue, reassess monthly; randomize if deteriorate

A2. Add medication; bemod remains stable but medication dose may vary

A3. Increase intensity of bemod with adaptive modifications based on impairment

B1. Continue, reassess monthly; randomize if deteriorate

B2. Increase dose of medication with monthly changes as needed

B3. Add behavioral treatment; medication dose remains stable but intensity of bemod may increase with adaptive modifications based on impairment
Exploring Greater Individualization via Q-Learning

Q-Learning is an extension of regression to sequential treatments.

• This regression results in a proposal for an optimal adaptive intervention.
• A subsequent trial would evaluate the proposed adaptive intervention.
Adaptive Interventions for Children with ADHD

• Stage 1 data: \((X_1, A_1, R_1)\)
  – \(R_1 = 1\) if responder; =0 if non-responder
  – \(A_1 = 1\) if BMOD, \(A_1 = -1\) if MED
  – \(X_1\) includes baseline school performance, \((Y_0)\) and prior medication \((S_1)\)
    • \(S_1 = 1\) if prior use of medication; =0, if not.

• Stage 1 involves all children
Adaptive Interventions for Children with ADHD

• Stage 2 data: \((X_2, A_2, Y)\)
  – \(Y\) = end of year school performance
  – \(A_2=1\) if Enhance, \(A_2=-1\) if Augment
  – \(X_2\) includes the month of non-response, \((M_2)\) and a measure of adherence in stage 1 \((S_2)\)
    • \(S_2=1\) if adherent in stage 1; =0, if non-adherent

• Stage 2 involves only children who do not respond in Stage 1 \((R_I=0)\).
Q-Learning for SMART Studies

• Conduct the regressions in backwards order! E.g. Stage 2 first, then Stage 1.

• Why?
  – Stage 1 dependent variable must control for Stage 2 treatment.
  – Stage 1 dependent variable is a predictor of $Y$ under optimal treatment in stage 2.
  – Stage 2 analysis is used to construct the predictor of $Y$, $\hat{Y}$
Stage 2 Regression for Non-responding Children

- Dependent Variable: \( Y \) (end of school year performance)
- Treatment: \( A_2 = 1 \) if Enhance, \( A_2 = -1 \) if Augment
- Interactions with Treatment, \( A_2 \): stage 1 treatment \( (A_1) \) and adherence \( (S_2) \)
- Controls: baseline school performance, \( (Y_0) \) and baseline prior medication \( (S_1) \), month of non-response \( (M_2) \)
Stage 2 Regression for Non-responding Children

- A1=BMOD; S2=High Adherence (Difference=1.26, P<.01)
- A1=BMOD; S2=Low Adherence (Difference=1.61, P<.001)
- A1=MED; S2=High Adherence (Difference=1.46, P<.001)
- A1=MED; S2=Low Adherence (Difference=1.41, P<.01)
Stage 1 Regression for All Children

- Dependent Variable: $\hat{Y}$ (predicted end of school year performance under optimal stage 2 treatment)
- Treatment: $A_I = 1$ if BEMOD, $A_I = -1$ if MED
- Interactions with Treatment, $A_I$: prior medication ($S_I$)
- Control: baseline school performance, $(Y_0)$
Stage 1 Regression for All Children

- S1=Acceptability of medication
  Difference = 0.40,
  Adaptive 95% CI: (-1.1314, 0.2724)

- S1= No knowledge re Acceptability of Medication
  Difference = 0.49,
  Adaptive 95% CI: (0.0746, 0.8978)
Adaptive Intervention Proposal

**IF** medication has not been used in the prior year
**THEN** begin with BMOD;
**ELSE** select either BMOD or MED.

**IF** the child is nonresponsive and was non-adherent, **THEN** augment present treatment;
**ELSE IF** the child is nonresponse and was adherent, **THEN** select intensification of current treatment.
Discussion

• Software in R for Q-Learning out and, in SAS, is coming out soon!
  https://methodology.psu.edu/ra/adap-treat-strat/qlearning

• Aside: Non-adherence is an outcome (like side effects) that indicates need to tailor treatment.
This seminar can be found at:
http://www.stat.lsa.umich.edu/~samurphy/seminars/SBM.04.29.11.pdf

This seminar is based on work with many collaborators some of which are: L. Collins, K. Lynch, J. McKay, D. Oslin, T. Ten Have, I. Nahum-Shani & B. Pelham. Email me with questions or if you would like a copy:

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Adaptive Treatments for Children with ADHD

- Stage 2 regression for $Y$:

$$(1, Y_0, S_1, A_1, M_2, S_2)\alpha_2 + A_2(\beta_{21} + A_1\beta_{22} + S_2\beta_{23})$$

- Stage 1 outcome: $R_1 Y + (1 - R_1)\hat{Y}$

$$\hat{Y} = (1, Y_0, S_1, A_1, M_2, S_2)\hat{\alpha}_2 + |\hat{\beta}_{21} + A_1\hat{\beta}_{22} + S_2\hat{\beta}_{23}|$$
Adaptive Treatments for Children with ADHD

- Stage 1 regression for $\hat{Y}$:

$$ (1, Y_0, S_1)\alpha_1 + A_1(\beta_{11} + S_1\beta_{12}) $$

- Interesting stage 1 contrast: should the knowledge that medication is highly acceptable, determine the best initial treatment in the sequence?
Jones’ Study for Drug-Addicted Pregnant Women

- **tRBT**
  - 2 wks Response
  - Random assignment:
    - **rRBT**
    - **tRBT**
  - Nonresponse
  - Random assignment:
    - **tRBT**
    - **eRBT**
- **rRBT**
  - 2 wks Response
  - Random assignment:
    - **aRBT**
    - **rRBT**
  - Nonresponse
  - Random assignment:
    - **tRBT**
    - **rRBT**
Oslin ExTENd

Early Trigger for Nonresponse

Random assignment:

8 wks Response

Nonresponse

Random assignment:

Late Trigger for Nonresponse

Random assignment:

8 wks Response

Nonresponse

Random assignment:

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone