Getting SMART about Dynamic Treatment Regimes: A Conceptual Introduction

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Outline

Dynamic Treatment Regimens What? Why?

Evaluating versus Building an Dynamic Treatment Regimen?

Sequential Multiple Assignment Randomized Trial (SMART) What are SMARTs?

SMART Design Principles

Keep it Simple Choosing Primary and Secondary Hypotheses

Take Home Points

SMART CASE STUDIES

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DYNAMIC TREATMENT REGIMENS

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Dynamic Treatment Regimens

Evaluating versus Building an Dynamic Treatment Regimen? Sequential Multiple Assignment Randomized Trial (SMART) SMART Design Principles Take Home Points SMART CASE STUDIES

What? Why?

Definition: A Dynamic Treatment Regimen is

- a sequence of individually tailored decision rules
- that specify whether, how, or when
- and based on which measures
- to alter the dosage (duration, frequency or amount), type, or delivery
- at critical decision points in the course of care.

Dynamic Treatment Regimens (DTRs) help guide the type of sequential treatment decision making that is typical (and often needed!) of clinical practice.

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Concrete Example of an Dynamic Treatment Regimen ADHD in Children, Ages 6-12



Goal is to minimize the child's symptom profile/trajectory.

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What makes up a Dynamic Treatment Regimen?

- 1. Critical decision points: based on time or other measures
- 2. Tailoring variables: to decide how to adapt treatment
- Decision rules: inputs tailoring variable, outputs one or more recommended treatments



aka: adaptive interventions, adaptive txt strategies, treatment algorithms, medication algorithms, stepped care, txt policies, multi-stage strategies...

Dynamic Treatment Regimens

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What? Why?

Why Dynamic Treatment Regimens? Necessary...

- Nature of chronic disorders/phenomena (substance use, mental health, autism, diabetes, cancer, HIV/AIDS)
 - Waxing and waning course (multiple relapse, recurrence)
 - Life events, comorbidities, non-adherence may arise
- Disorders for which there is no widely effective treatment.
- Disorders for which there are widely effective treatments, but they are costly or burdensome.
- **Bottom line**: High heterogeneity in response to treatment
 - Within person (over time) and between person

All require sequences of treatment decisions!

Ok, so dynamic treatment regimens are great, but... ...there are so many unanswered questions.



Now let's talk research...

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GENERATING HYPOTHESES vs BUILDING vs EVALUATING

DYNAMIC TREATMENT REGIMENS?

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3 Different Research Questions/Aims = 3 Different Research Designs

- Aim 1: When generating hypotheses about an Dynamic Treatment Regimen: e.g., Does augmenting txt (as observed in a previous trial) for non-responders correlate with better outcomes?
- Aim 2: When building an Dynamic Treatment Regimen: e.g, What are the best tailoring variables and/or decision rules?
- Aim 3: When evaluating a particular Dynamic Treatment Regimen: e.g. Does the DTR have a (statistically powered) clinically significant effect compared to suitable control?

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3 Different Research Questions/Aims = 3 Different Research Designs

Ex. Q1: Does augmenting txt for non-responders (as observed in a previous trial) correlate with better outcomes?

Ex. Q2: What are the best tailoring variables or decision rules?

Ex. Q3: Does an already-developed dynamic treatment regimen have a statistically and clinically signif. effect as compared to control intervention?

		Observational	Experimental	
		Studies	Studies	
		e.g., analysis of	e.g.,	e.g.,
Question	Aim	previous RCT	SMART	RCT
1	Hypothesis Gen.	YES	\approx	\sim
2	Building	\approx	YES	\approx
3	Evaluating	\sim	\approx	YES

Dynamic Treatment Regimens Evaluating versus Building an Dynamic Treatment Regimen? Sequential Multiple Assignment Randomized Trial (SMART) SMART Design Principles Take Home Points SMART CASE STUDIES	? What are SMARTs?
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SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIALS (SMARTs)

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What are SMARTs?

What is a Sequential Multiple Assignment Randomized Trial (SMART)?

- Multi-stage trials; same participants throughout
- Each stage corresponds to a critical decision point
- At each stage, subjects randomized to set of treatment options
- The goal of a SMART is to inform the development of dynamic treatment regimens.

I will give you an example SMART, but first...

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What are SMARTs?

Background for an Example SMART

ADHD Treatment in Children Ages 6-12

- Both medication (MED) and behavioral modification (BMOD) have been shown to be efficacious
- However, there is much debate on whether first-line intervention should be pharmacological of behavioral, especially in younger children
- Further, there is a need for a "rescue treatment" if the first treatment does not go well because 20-50% of children do not substantially improve on BMOD or MED
- So important questions for clinical practice include "What treatment do we begin with: BMOD or MED?" "Among non-responders, what second treatment is best?"

Concrete Example of a SMART: Child ADHD

PI: William Pelham, PhD, Florida International University N = 153, 8 month study, Monthly non-response (*ITB* < 75% and *IRS* > 1 domain)



One of Four Dynamic Treatment Regimens Within the SMART



4 Embedded Dynamic Treatment Regimens in this SMART



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Take Home Points SMART CASE STUDIES Keep it Simple Choosing Primary and Secondary Hypotheses

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SMART DESIGN PRINCIPLES

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Keep it Simple Choosing Primary and Secondary Hypotheses

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SMART Design Principles

- KISS Principle: Keep It Simple, Straightforward
- Power for simple important primary hypotheses
- Take Appropriate steps to develop a more deeply-individualized (optimized) Dynamic Treatment Regimen

Dynamic Treatment Regimens Evaluating versus Building an Dynamic Treatment Regimen? Sequential Multiple Assignment Randomized Trial (SMART)

Keep it Simple **Choosing Primary and Secondary Hypotheses**

SMART Design Principles

Take Home Points SMART CASE STUDIES

Keep It Simple, Straightforward

Overarching Principle

At each stage, or critical decision point,...

- Restrict class of treatment options only by ethical, feasibility, or strong scientific considerations
- If you do restrict randomizations, use low dimensional summary to restrict subsequent treatments
 - Use binary responder status
 - Should be easy to use in actual clinical practice
- Collect additional, auxiliary time-varying measures
 - To develop a more deeply-tailored Dynamic Treatment Regimen
 - Think time-varying effect moderators

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Keep it Simple Choosing Primary and Secondary Hypotheses

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SMART Design: Primary Aims

SMART CASE STUDIES

Choose a **simple primary aim/question** that aids development of an dynamic treatment regimen.

Statistical methods used here aim to reduce uncertainty so the investigator can come away with a solid answer.

Sample size for the SMART chosen based on the hypothesis test associated with this aim (e.g., use standard $\alpha = 5\%$).

Primary Aim Example 1

What is the effect of starting with BMOD vs MED on longitudinal outcomes?



Keep it Simple Choosing Primary and Secondary Hypotheses

SMART Design: Secondary Aims

SMART CASE STUDIES

Choose **secondary aims/questions** that further develop the Dynamic Treatment Regimen and take advantage of sequential randomization to eliminate confounding.

Statistical methods used here aim to generate hypotheses, e.g., generate good hypotheses about additional tailoring variables or moderators.

Here, investigators will tolerate hypothesis tests with higher Type-I error, e.g., $\alpha = 10\%$.

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Secondary Aim Example 1

Among non-responders, is it better to INTENSIFY vs AUGMENT? On various occassions, I have seen this be the Primary Aim.



Secondary Aim Example 2

Is there a difference between two of the embedded dynamic treatment regimens? This could also be a Primary Aim.



Sample size calculators exist for this; see Oetting, Levy, Weiss, and Murphy 2011. Zhiguo Li at Duke. Kelley Kidwell at UMich.

Secondary Aim Example 3

Build a more deeply tailored dynamic treatment regimen (go beyond the 4 embedded dynamic treatment regimens). Rarely, would this be a Primary Aim.



TAKE HOME POINTS

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Take Home the Following

- SMARTs are not Adaptive Trial Designs (Confusing!!)
- Dynamic Treatment Regimens individualize treatment up-front and throughout; they are guides for clinical practice
- SMARTs are used to **build** better Dynamic Treatment Regimens
 - Next study: RCT of SMART-optimized DTR vs control
- SMARTs do not have to be complicated; Don't do this! :)
- SMARTs do not necessarily require larger sample sizes

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SMART CASE STUDIES (the most fun part of the conceptual overview!)

Autism SMART (N = 61, a pilot)

PI: Kasari (UCLA). (ages 5-8; planned N = 98 but recruitment difficult, despite multi-site. Wk12 response rates much higher than anticipated.)



Longitudinal Analysis of the Autism SMART

 Y_t = Socially communicative utterances over 36 weeks



Child ADHD SMART

PI: William Pelham, PhD, Florida International University

N = 153, 8 month study, Monthly non-response (*ITB* < 75% and *IRS* > 1 domain)



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Longitudinal Analysis of the ADHD SMART Y_t = Classroom performance over 8 months (school year)



Treatment for Alcohol Dependence

PI: Oslin, University of Pennsylvania



Interventions for Minimally Verbal Children with Autism

PI: Kasari(UCLA), Kaiser(Vanderbilt), Smith(Rochester), Lord(Cornell), Almirall(Mich)



Interventions for Minimally Verbal Children with Autism

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Adaptive Implementation Intervention in Mental Health

PI: Kilbourne; Co-I: Almirall (Aim is to improve the uptake of a psychosocial intervention for mood disorders)



YOU ARE IN FOR A TREAT TODAY AND TOMORROW!

- Thall: DTRs in Oncology
- Moodie: Paving the way for a SMART
- Posters!
- Wang: Feasible DTRs in Oncology
- Laber: Size to estimate a high-quality DTR
- Kidwell: Bringing down the barriers
- Wahed: Sharing of participants across different DTRs
- Zhang: Interpretable DTRs
- Murphy: The future of DTRs in mobile health

Thank you! Questions?







Email me with questions about this presentation:

Daniel Almirall: dalmiral@umich.edu

Find papers on SMART:

- http://www.lsa.stat.umich.edu/~samurphy/ (Susan Murphy)
- http://methcenter.psu.edu (Linda Collins)

More papers and these slides on my website (Daniel Almirall):

http://www-personal.umich.edu/~dalmiral/

EXTRA SLIDES

Almirall, Xu, Nahum-Shani, Collins, Murphy Getting SMART

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Extra Slides

Almirall, Xu, Nahum-Shani, Collins, Murphy Getting SMART

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Hypothesis-generating Observational Studies Post-hoc Analyses Useful for Building Dynamic Treatment Regimens

- Give examples of different observational study questions they can examine using data from a previous 2-arm RCT
- Standard observational study caveats apply:
 - No manipulation usually means lack of heterogeneity in txt options (beyond what is controlled by experimentation in original RCT)
 - Some RCTs use samples that are too homogeneous
 - Confounding by observed baseline and time-varying factors
 - Unobserved, unknown, unmeasured confounding by baseline and time-varying factors

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Hypothesis-generating Observational Studies

Post-hoc Analyses Useful for Building Dynamic Treatment Regimens

- There exists a literature for examining the impact of time-varying treatments in observational studies
 - Marginal Structural Models (Robins, 1999; Bray, Almirall, et al., 2006) to examine the marginal impact of observed time-varying sequences of treatment
 - Structural Nested Mean Models (Robins, 1994; Almirall, et al., 2010, 2011) to examine time-varying moderators of observed time-varying sequences of treatment
 - Marginal Mean Models (Murphy, et al., 2001): to examine the impact of observed dynamic treatment regimens

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Early precursors to SMART

- CATIE (2001) Treatment of Psychosis in Patients with Alzheimer's
- CATIE (2001) Treatment of Psychosis in Patients with Schizophrenia
- STAR*D (2003) Treatment of Depression

Other Alternatives

- Piecing Together Results from Multiple Trials
 - Choose best first-line treatment on the basis of a two-arm RCT; then choose best second-line treatment on the basis of another separate, two-arm RCT
 - Concerns: delayed therapeutic effects, and cohort effects
- Observational (Non-experimental) Comparisons of DTRs
 - Using data from longitudinal randomized trials
 - May yield results that inform a SMART proposal
 - Understand current treatment sequencing practices
 - Typical problems associated with observational studies
- Expert Opinion

Why Not Use Multiple Trials to Construct an DTR Three Concerns about Using Multiple Trials as an Alternative to a SMART

- 1. Concern 1: Delayed Therapeutic Effects
- 2. Concern 2: Diagnostic Effects
- 3. Concern 3: Cohort Effects

All three concerns emanate from the basic idea that constructing an dynamic treatment regimen based on a myopic, local, study-to-study point of view may not be optimal.

Why Not Use Multiple Trials to Construct an DTR Concern 1: Delayed Therapeutic Effects, or Sequential Treatment Interactions

Positive Synergy Btwn First- and Second-line Treatments

Tapering off medication after 12 weeks of use may not appear best initially, but may have enhanced long term effectiveness when followed by a particular augmentation, switch, or maintenance strategy.

Tapering off medication after 12 weeks may set the child up for better success with any one of the second-line treatments.

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Why Not Use Multiple Trials to Construct an DTR Concern 1: Delayed Therapeutic Effects, or Sequential Treatment Interactions

Negative Synergy Btwn First- and Second-line Treatments

Keeping the child on medication an additional 12 weeks may produce a higher proportion of responders at first, but may also result in side effects that reduce the variety of subsequent treatments available if s/he relapses.

The burden associated with continuing medication an additional 12 weeks may be so high that non-responders will not adhere to second-line treatments.

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Why Not Use Multiple Trials to Construct an DTR Concern 2: Diagnostic Effects

Tapering off medication after 12 weeks initial use may not produce a higher proportion of responders at first, but may elicit symptoms that allow you to better match subsequent treatment to the child.

The improved matching (personalizing) on subsequent treatments may result in a better response overall as compared to any sequence of treatments that offered an additional 12 weeks of medication after the initial 12 weeks.

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Why Not Use Multiple Trials to Construct an DTR Concern 3: Cohort Effects

- Children enrolled in the initial and secondary trials may be different.
- Children who remain in the trial(s) may be different.
- Characteristics of adherent children may differ from study to study.
- Children that know they are undergoing dynamic treatment regimens may have different adherence patterns.

Bottom line: The population of children we are making inferences about may simply be different from study-to-study.