Adaptive Interventions and SMART Design: What, Why and How?

OPRE: What Works, Under What Circumstances, and How? Methods for Unpacking the ”Black Box” of Programs and Policies

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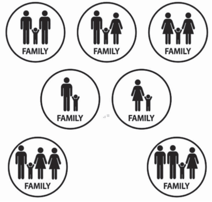


http://www.vanderbilt.edu/magazines/peabody-reflector/2009/06/to-build-a-better-community/

ADAPTIVE INTERVENTIONS: WHAT?

An adaptive intervention (AI)

- is a sequence of individually tailored treatments that specify whether, how and/or when to alter the intensity, type, dose, or delivery of treatment at critical decision points in the course of care
- operationalizes sequential decision making
- a.k.a. adaptive treatment strategies, dynamic treatment regimes, stepped care, treatment policies

Adaptive Interventions: What?

An example of an AI that occurs in the school context and over the entire school year in the treatment of children with ADHD

- AI: First, offer low-dose medication; then add behavioral intervention for non-responders and continue low-dose medication for responders.
- Decision Rule:
  - First-stage intervention={Medication}
  - Evaluate at week 8 and monthly, IF {non-response},
  - THEN second-stage intervention={add behavioral intervention}
  - ELSE continue first-stage intervention.

Adaptive Interventions: What?

Ingredients

- **Critical Decisions**: intervention options
- **Tailoring Variables**: decide how to adapt treatment.
  - In ADHD, response was evaluated at week 8 and then every 4 weeks based on ratings from the Impairment Rating Scale (IRS) and individualized list of target behaviors (ITB). Non-response defined by <75% on ITB and rated as impaired on at least one domain from IRS.
- **Decision Rules**: inputs baseline, treatment and tailoring variable information up to the point of the critical decision and outputs subsequent treatment options.

Adaptive Interventions: Why?

- Due to the waxing and waning course of many chronic disorders, an intervention that demonstrates short-term success for an individual may not lead to long-term success (**within-person heterogeneity**)
- Not all individuals respond or adhere to interventions to the same degree, have the same side-effect profile, respond within the same time-frame, to any given intervention or treatment package (**between-person heterogeneity**)
- One size does not fit all or even one all of the time

Adaptive Interventions: How?

- There are often **many questions that need to be answered to develop a good AI**
  - What is the best first-line therapy for children with ADHD?
  - What is the best measure of response to see if the intervention is successful?
  - Can children who do not respond on the initial treatment be rescued with further treatment? If so, is it best to switch treatment, add treatment, or intensify dose of current treatment?
- **Black Box Approach**: in the past, AIs were developed based solely on expert opinion, clinical/public policy expertise, piecing together an AI based on literature and evaluated using an RCT

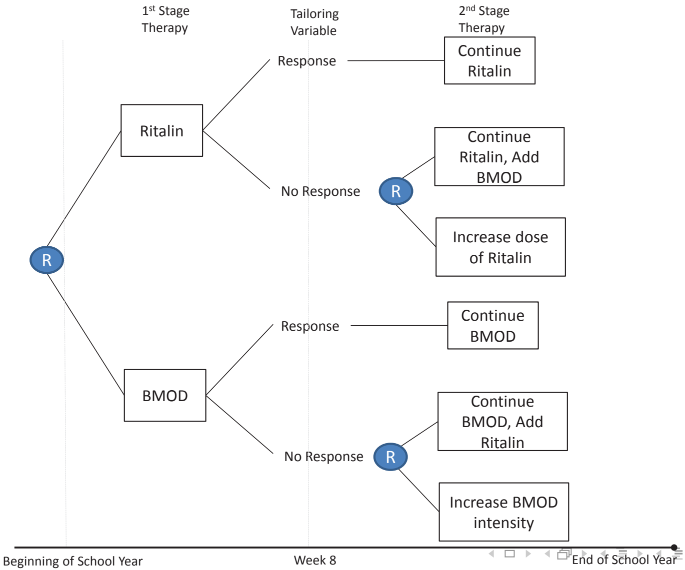
SMART: What?

- Build AIs by using a Sequential Multiple Assignment Randomized Trial (**SMART**) to provide evidence-based tailored interventions (unpack the black box)
- All or some of the participants are randomized to a set of treatment options at each critical decision point (stage) based on tailoring variable
- Same participants are followed throughout entire trial

SMARTs: What & Why

- Inform the **development of AIs** while more closely mimicking treatment process
- Develop a proposal for an AI, which could then be tested in a 2-arm randomized trial against an appropriate alternative
- Evaluate the **timing, sequencing and tailored selection of treatments** through randomization
- Collect information on other variables (besides tailoring variable of interest) and use observed data to estimate more **personalized decision rules**

ADHD SMART Example: Design (PI: W. Pelham)



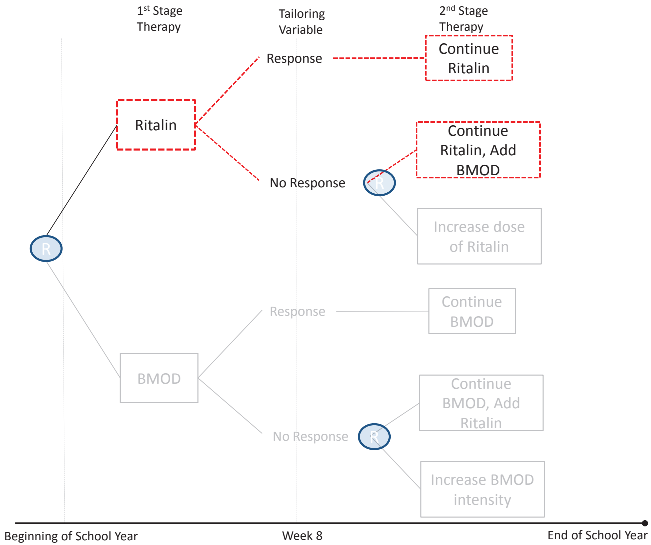
ADHD SMART Example: Primary Objectives

- Test the **main effect** of beginning with medication versus beginning with BMOD on the rate of non-response and ending dosages
- Test the **main effect** among non-responders of augmenting or intensifying treatment?
- Power trial on one of these objectives (similar to powering usual RCT)

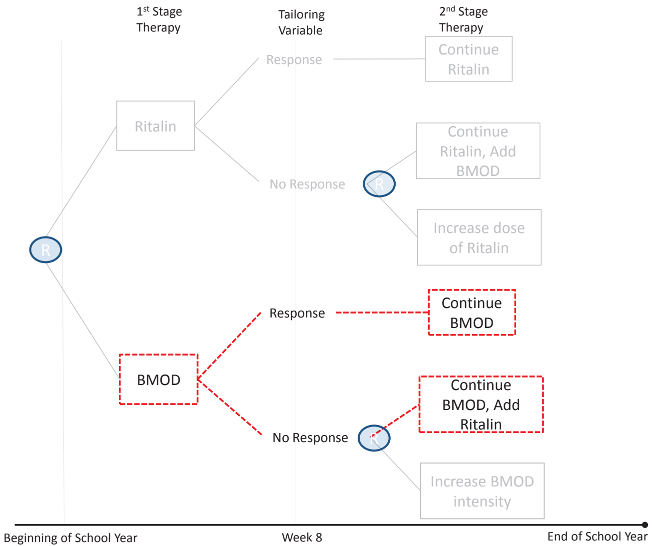
ADHD SMART Example: Secondary Objectives

- **Embedded AIs**: Compare child behavior at end of 9 months between two AIs of scientific importance (start with med and add behavior therapy for non-responders vs. start with behavior therapy and add medication for non-responders)
- Use methods to compare AIs (for example, recycled and weighted estimating approach, see Nahum-Shani et al. 2012 p.457-477)

ADHD SMART Example: Embedded AI



ADHD SMART Example: Embedded AI



ADHD SMART Example: Secondary Objectives

- **Further Tailoring**: Assess how **baseline variables** (severity of impairment, comorbid child psychopathology, prior med history) impact choice of first-stage intervention and how **time-varying variables** (IRS and ITB ratings, adherence) impact choice of augmenting or intensifying second-stage treatment for non-responders
- Use methods to personalize AIs (Q-learning, for example see Nahum-Shani et al. 2012 p. 478-494)

SMART: How?

Motivate a SMART by science and let the natural treatment process guide the design,
do not try to apply a SMART only due to its novelty and possibilities

SMART: How?

- **Treatment options**: must be used or could be used in practice- ask a clinician or community organizer how he/she would treat a person over time to develop the possible embedded AIs
- **Tailoring Variable**: denotes early signs of non-response; use low dimensional summary to restrict second-stage treatments; must be agreed upon by experts in the field and clinically feasible
- Ability to collect research evaluations **on schedule** necessary for critical decisions
- Organized treatment and research team with **systematic data collection**

SMART: How?

- SMART design may differ depending on ethical, feasible or strong scientific concerns
- Keep the SMART design **simple** and the AIs **realistic**
- **Power on primary objective** (See `http://methodology.psu.edu/downloads` for sample size calculators)
- Collect additional, **auxiliary time-varying measures** to use in secondary analysis to more deeply tailor AI (time-varying effect moderators)
- Start with a **pilot study** to see if feasible and obtain focus group input

Conclusion

- AIs personalize treatment over time and guide practice
- SMARTs build effective AIs
- AIs take advantage of and SMARTs learn about within and between person heterogeneity

CONCLUSION

Questions?

Please follow up
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Thank you to Danny Almirall & Inbal Nahum-Shani at University of Michigan for all their input and materials.

Additional Selected Reading

- Lei, H. et al. A 'SMART' Design for Building Individualized Treatment Sequences. Annu. Rev. Clin. Psychol. 2012 8:21-48
- Nahum-Shani et al. Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions. Psych. Methods. 2012 17(4): 457-477
- Almirall et al. Designing a Pilot Sequential Multiple Assignment Randomized Trial for Developing an Adaptive Treatment Strategy. Statistics in Medicine. 2012 31(17):1887-902.
- Moodie et al. Demystifying optimal dynamic treatment regimes. Biometrics. 2007 63: 447-455.
- Lavori, P.W., Dawson, R. Dynamic Treatment Regimes: Practical Design Considerations. Clinical Trials. 2004. 1(1):9-20.
- Chakraborty, B. Dynamic Treatment Regimes for Managing Chronic Health Conditions: A Statistical Perspective. Am. J. Public Health. 2011 101(1):40-45.
- Zhao, Y. et al. New Statistical Learning Methods for Estimating Optimal Dynamic Treatment Regimes. JASA. 2014 DOI:10.1080/01621459.2014.937488
- Nahum-Shani et al. Q-learning: A Data Analysis Method for Constructing Adaptive Interventions. Psych. Methods. 2012 17(4): 478-494

- Search for terms: ”dynamic treatment regime”, ”adaptive treatment strategy”, ”adaptive intervention”, ”sequential multiple assignment randomized trial”
- Selected authors to browse: S. Murphy, D. Almirall, I. Nahum-Shani, B. Chakraborty, M. Kosorok,E. Laber, P.W. Lavori, R. Dawson, J. Robins, M. Hernan, E. Moodie, Z. Li, A. Wahed, W. Feng, X. Tang, O. Bembom, M. Van der Laan, M. Davidian, B. Tsiatis