Sequential Multiple Assignment Randomized Trials

Huitian Lei and Susan A.Murphy

Introduction

A dynamic treatment regime (DTR) is used to operationalize decision making across multiple stages of treatment. At each stage, a decision rule inputs patients' characteristics and treatment history and outputs a recommended treatment. Sequential Multiple Assignment Randomized Trials (SMART) are used to inform the development of dynamic treatment regimes. A SMART involves multiple treatment stages; each stage is used to address one of the decisions involved in the dynamic treatment regime. Each subject moves through the multiple stages and at each stage the subject is randomly (re)assigned to one of several treatment options. As in standard randomized trials, the randomization allows scientists to make valid causal attributions concerning the relative usefulness of the intervention options without having to make unverifiable assumptions. Three examples of SMART are described below.

Reinforcement Based Treatment for Drug-Addicted Pregnant Women

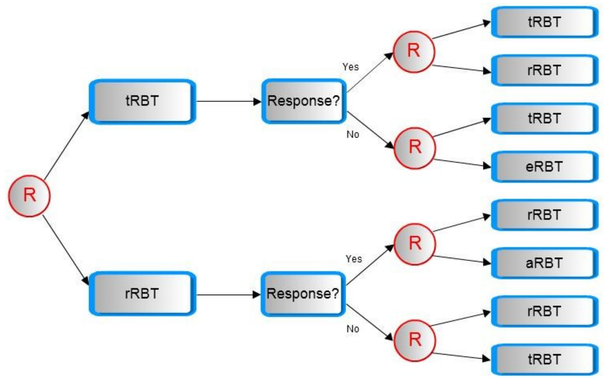

Figure 1: RBT Trial (Jones, PI)

- **Introduction:** Prenatal drug use is often associated with increased risk of pregnancy complications and adverse neonatal outcomes such as pre-eclampsia, stillbirths and premature labor. It is of practical importance to provide drug-addicted pregnant women with efficacious pharmacotherapy-free interventions. Reinforcement Based Treatment (RBT) is an efficacious behavioral treatment to reduce and eliminate drug use.Researchers focus on critical questions regarding the sequences of the levels of intensity of RBT most efficacious for drug-addicted pregnant women and its associated cost-efficacy issues. Four types of RBT examined, with increasing intensity and scope, are abbreviated RBT (aRBT), reduced RBT (rRBT), treatment-as-usual RBT (tRBT) and enhanced RBT (eRBT).
- **Trial Design:** In the first stage, subjects are randomly assigned to tRBT or rRBT. There is a two-week time window for initial responses to interventions to occur. Subjects then enter the second stage being characterized as either early responders or non-responders. If a subject misses unexcused intervention day, provides a positive opioid or cocaine urine specimen, or self-report the use of either drug, she is characterized as an early non-responder. Subjects who do not meet this criterion are identified as early responders. In the second stage, each early non-responder is randomized to one of the two possible subsequent interventions that are at least as intensive in dose and scope as her initial intervention: tRBT or eRBT for tRBT non-responders; rRBT or tRBT for rRBT non-responders. Each early responder is randomized to one of the two subsequent interventions that are at most as intensive in dose and scope as her initial intervention: rRBT or aRBT for rRBT responders; rRBT or tRBT for tRBT responders.
- **Primary Outcomes:** Treatment completion (delivery while in program) and self-reported cocaine and heroin use as verified by urine testing.

For References, Questions and comments please contact ehlei@umich.edu

- **Primary Hypotheses:** Test whether subjects initially receiving tRBT have more positive maternal outcomes than subjects who initially receive less intensive and less costly RBT.
- **Secondary Hypotheses:** Test the interaction between amount of illegal activity (i.e., prostitution) and treatment efficacy of RBT and whether this interaction occurs at both first and second stages of treatment.

Developmental and Augmented Intervention for Facilitating Expressive Language

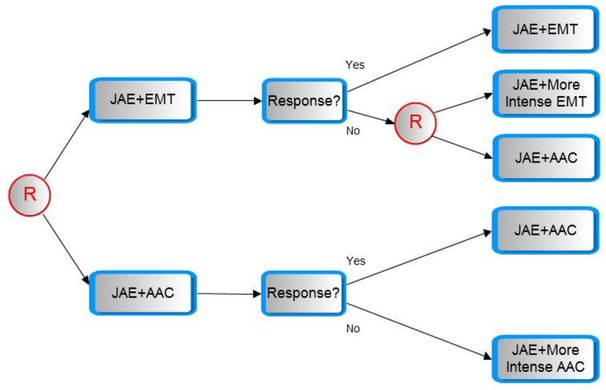

Figure 2: Autism Trial (Kasari, PI)

- **Introduction:** Autistic children who do not respond to traditional interventions to develop spoken language are medically underserved. A novel joint attention/ joint engagement (JAE) intervention is adopted in the study to address the above concerns. To facilitate children's response to JAE using spoken language, two alternative interventions, one focused on spoken communication (EMT) another focused on augmented communication (AAC), are introduced and implemented cooperatively with JAE.
- **Trial Design:** In the first stage, children are randomized to one of the initial interventions (JAE-EMT or JAE-AAC). Children stay with their initial assignment for 3 months and are characterized as responder or non-responder at the end of the 3rd month. A child is defined as a responder if s/he is able to spontaneously produce 20 spoken or augmented words across 5 social communicative areas and generalize 10 words and 3 functions to a different partner. Children who fail to meet this criterion are characterized as non-responder to initial interventions. In the second stage, children who respond to their initial intervention, regardless of the type of intervention, continue with the same intervention. Children who do not respond to initial JAE-AAC intervention receive an increased intensity of the same type of intervention. Children who do not respond to initial JAE-EMT are randomly assigned to either intense JAE-EMT or JAE-AAC.
- **Primary Outcomes:** Number of words used spontaneously during parent-child interaction, number of communicative functions used for each word during parent-child interactions, and generalization of spontaneous words to express multiple communication functions.
- **Primary Hypotheses:** To compare the three adaptive interventions embedded in the trial.
- **Secondary Hypotheses:** Test the interaction between motor functioning (e.g., imitation, praxis) and language outcomes and whether different interventions should be provided depending on children's motor impairment.

Adaptive Pharmacological and Behavioral Treatments for Children with ADHD

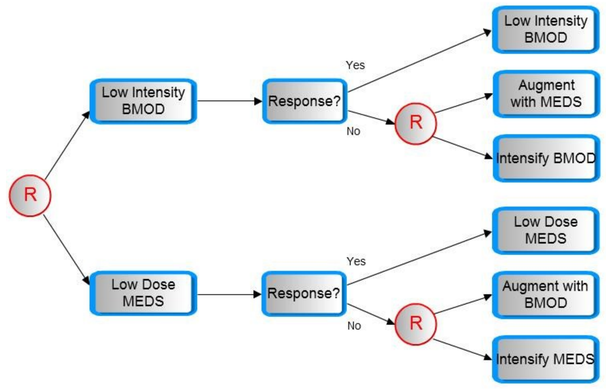

Figure 3: ADHD Trial (Pelham, PI)

- **Introduction:** There has been considerable controversy over the relative effects of pharmacological interventions and behavioral interventions in treating children with Attention-Deficit Hyperactivity Disorder (ADHD). Methylphenidate is used as the primary stimulant medication. Behavioral interventions consist of a school-based intervention, Saturday treatment program and parent training. This study is designed to allow for comparison of different intervention sequences.
- **Trial Design:** In the first stage, children are randomly assigned to receive a low intensity of behavioral modification or a low dose of medication. This stage will continue for 8 weeks, after which the monthly ratings from Impairment Rating Scale (IRS) and Individual List of Target Behaviors (ITB) are evaluated. Children whose average performance on the ITB is less than 75% and who are rated by parents or teachers as impaired (i.e., greater than 3) on the IRS in at least one domain are characterized as non-responders to the initial intervention and proceed to the second stage of randomization. Children who do not meet the criteria of non-response continue with their current assignment. In the second stage, non-responders are randomized to either increased dosage/intensity of the initial intervention or adding a low dose/intensity of the other intervention.
- **Primary Outcomes:** Child and family functioning outcomes.
- **Primary Aims:** To determine the best initial intervention (medication versus behavioral intervention) and the best way to modify intervention for children with inadequate response (escalating dosage of current intervention versus adding a low dose of the other intervention).
- **Secondary Aims:** Testing the interaction between children's previous treatment with stage 2 treatment.

Discussion

SMART allows researchers to investigate the best sequences of treatment and assess interactions with covariates which might be useful in individualizing the treatment sequence.

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