Sequential Multiple Assignment Randomized Trials

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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.

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

- **Introduction**: Prenatal drug use is often associated with increased risk of pregnancy complications and adverse neonatal outcomes such as pre-ecclampsia, 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 unexplained intervention day, provides a positive opioid or cocaine urine specimen, or self-reports the use of another 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 tRBT for tRBT non-responders, rRBT or tRBT for RBT non-responders. Each early responder is randomized to one of the two subsequent interventions that are at least as intensive in dose and scope as her initial intervention: tRBT or tRBT for RBT responders, rRBT or tRBT for RBT responders.

- **Primary Outcomes**: Treatment completion (delivery while in program) and self-reported cocaine and heroin use as verified by urine testing.

- **Primary 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.

- **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.

- **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. We acknowledge NIMH R01-MH-080035, NIDA grant P50-DA-010075 for support.

Adaptive Pharmacological and Behavioral Treatments for Children with ADHD

- **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 who achieve average performance at IRS and ITB 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 for 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 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).