Adaptive Intervention Designs in Pediatric Psychology: The Promise of Sequential Multiple Assignment Randomized Trials of Pediatric Interventions

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This article summarizes the utility of multiphase optimization strategy (MOST) and sequential multiple assignment randomized trial (SMART) processes in the development of empirically derived adaptive interventions (AIs). Recent empirical evidence suggests that SMART designs conducted within the context of a MOST framework can be used for building and optimizing AIs and may lead to better clinical care. SMART designs help optimize AIs by determining the best sequencing of decision rules. However, despite their growing relevance, MOSTs and SMARTs are relatively undeveloped in the development of pediatric interventions. MOST and SMART designs can be used for developing efficient and cost-effective AIs. Intervention research within the field of pediatric psychology may benefit from incorporating these designs.

Keywords: adaptive interventions, multiphase optimization strategy, sequential multiple assignment randomized trial, research design and methods

Pediatric psychology has a challenge: Evidence-based interventions are not effective for all patients within even the most well-planned randomized controlled trials (RCTs). Therefore, we can expect that some number of patients who present to clinics where pediatric psychologists offer services will not be well suited to the current array of evidence-based interventions. Likewise, the provision of some services may not be suitable for specific clinical settings or the available reimbursement practices. Take, for example, the evidence-based interventions available for treatment adherence and adherence to health-promoting behaviors (Cushing, Brannon, Suorsa, & Wilson, 2014; Pai & McGrady, 2014), which in the best cases have standardized effect sizes ($d = .07–.29$). Commonly, these effect sizes are interpreted as small but significant in the context of pediatric psychology research. However, converting these values to clinically meaningful units (i.e., number needed to treat) reveals that a psychologist would need to treat between 11 and 50 patients to see improvements in one patient superior to those seen in a control condition (Furukawa & Leucht, 2011; Magnisson, 2014).

Currently, practicing pediatric psychologists improve these statistics by drawing from their clinical expertise to tailor evidence-based interventions to meet the needs of a given patient over the course of treatment (Roberts, Blossom,
Because most scientific studies do not follow the same iterative case conceptualization that is necessary to optimize clinical care, however, clinicians lack evidence-based decision rules for tailoring care when a patient does not respond immediately to treatment. Thus, clinicians are left with little empirical guidance from the scientific literature on how to make these necessary adaptations. This is a significant problem for the field because health-care models that emphasize high-quality care delivered at low cost will not bear the expense of inefficient interventions that enroll populations unlikely to benefit from their application (Rozensky & Janicke, 2012).

Adaptive interventions (AIs) represent a promising solution for bridging the gap between science and practice. AIs combine the strengths of standardization from pediatric psychology research with the flexibility and adaptation from the clinical suite. Unlike traditional evidence-based interventions, AIs more closely mirror clinical practice in that treatment is individualized based on patients’ characteristics or clinical presentation and then adapted over time in response to their continuing progress (Bierman, Nix, Maples, & Murphy, 2006)—that is, AIs provide clinicians with a validated way of using measures of treatment response, benefit, harm, and/or acceptability collected during treatment to make subsequent treatment decisions and therefore give the promise of a more ecologically valid intervention. In AIs, sequential clinical decision making is formalized by the use of evidence-based decision rules that determine whether, when, and how to adapt the intensity and/or type of treatment to produce the greatest treatment effect using the fewest resources (e.g., clinician time) for a given patient. AIs that are designed to change over time as a function of patient response represent a promising approach to creating efficient interventions (i.e., interventions containing only the components necessary to produce a clinically meaningful effect). Such efforts are critical for the continued growth of pediatric psychology as the U.S. health-care system shifts toward alternative payment models incentivizing high-quality and low-cost care.

Components of AIs

To begin developing an empirically derived AI that addresses whether, when, and how to change the intensity and/or type of treatment included in an intervention, it is necessary to formalize a system that guides the adaptations that will unfold as the intervention progresses. This system is made up of four components: tailoring variables, decision rules, treatment options, and decision points (Almirall et al., 2014). Tailoring variables are the stable (e.g., biological sex) or dynamic (e.g., medication adherence) characteristics of the patient or environment that can trigger adaptations in the AI. Decision rules operationalize changes in treatment type or intensity (treatment options) by linking patients’ values on tailoring variables at a given time (decision point) with the most effective treatment option. Such efforts are critical for the continued growth of pediatric psychology as the U.S. health-care system shifts toward alternative payment models incentivizing high-quality and low-cost care.

There are excellent and comprehensive reports of approaches to developing AIs in the published literature (e.g., Almirall, Nahum-Shani, Sherwood, & Murphy, 2014; Collins, Murphy, & Bierman, 2004; Collins, Murphy, & Strecher, 2005; Collins, Murphy, & Strecher, 2007). However, these reports have focused closely on the technical details of the approach rather than emphasizing the value of a clinical research partnership in the development of an AI. This article intends to fill this gap by (a) reviewing the components, scientific aims, and data analytic strategies of multiphase optimization strategy (MOST) and sequential multiple assignment randomized trial (SMART) methodologies; (b) highlighting the critical role of a strong clinical research partnership in MOST and SMART methodologies; and (c) detailing examples of how MOST and SMART trials could inform clinical practice in pediatric psychology. We hope that this review will provide clinicians and researchers with the background knowledge necessary to synthesize clinical expertise and practices with available research methodologies to develop and evaluate interventions that address the barriers of providing evidence-based care in real-world settings.
MOST

A MOST is a comprehensive framework that is ideal for optimizing and evaluating AIs. The MOST framework uses three phases (i.e., preparation, optimization, and evaluation) to guide psychologists in developing, optimizing, and evaluating their behavioral interventions (Collins et al., 2005). Similar to traditional intervention development, a MOST begins with a preparation phase to identify treatment components to include in the intervention and concludes with a standard RCT comparing the intervention to a suitable control in the evaluation phase. However, the MOST framework is unique in its use of an additional phase of research (i.e., optimization phase) to optimize the intervention prior to evaluating it in an RCT. In the optimization phase, psychologists select and test optimization criteria (e.g., cost-effectiveness, specified level of effectiveness) using a randomized experimental design. Although the optimization criteria are based on the purpose of the AI and therefore may differ between AIs, the testing of the optimization criteria of any AI is accomplished using a SMART design.

Preparation

The preparation phase of a MOST mirrors traditional intervention development in that expert clinical opinion and empirical literature guide the selection of tailoring variables, decision rules, treatment options, and decision points.

Clinical expertise in preparation. Successful translation of behavioral interventions into real-world settings depends, in part, on the intervention’s compatibility and integration with current delivery systems (Carroll & Rounsaville, 2007). Thus, expertise in the real-world clinical management of the condition is critical for success. Ideally, the identified clinical expert will have experience with providing evidence-based interventions to the population of interest, be familiar with the barriers to intervention implementation (e.g., reimbursement, attendance at in-person sessions), and conceptualize the population and treatment in a manner that is consistent with that proposed by the research team.

During the preparation phase, clinical experts’ contributions to the selection of the tailoring variables, treatment components, and decision rules are critical for ensuring that the AI is evaluating treatment components consistent with real-world clinical care (Collins et al., 2004). For example, although review of the empirical literature is a promising approach for identifying tailoring variables, failure to consult clinicians on tailoring variable selection may result in a measure that is too burdensome (e.g., lengthy self-report measure) or costly (e.g., electronic medication adherence monitor) to routinely administer, score, and use as a treatment guide in real-world clinical settings. Similarly, clinical insight about patient and family behaviors indicative of poor treatment response would further inform the choice of tailoring variables, particularly at treatment onset. Furthermore, clinical experts can provide insight into the availability of staff with the necessary prior experience (i.e., experience with the target patient population or treatment) and the skills, certification, or educational requirements to deliver the identified treatment components and assess tailoring variables, an issue directly related to the future sustainability of the intervention (Gitlin & Czaja, 2015).

Optimization

Following preparation, randomized experimentation is used to gather data on the effectiveness of tailoring variables, decision points, and each treatment component and its potential influence on other components (optimization). For example, the optimization phase may include efforts to determine the minimal amount of resources required to obtain a desired treatment response (e.g., clinician time and burden, comparing multiple methods of treatment delivery, number of sessions). In the context of a MOST, this is termed an optimization criterion and would be established a priori to the start of the optimization phase.

Clinical expertise in optimization. Consulting clinicians and administrators to select an optimization criterion consistent with current health-care practices (e.g., number of sessions reimbursed by Medicare, Medicaid, or an insurance company) may facilitate long-term intervention dissemination. For example, if a payer will typically reimburse eight sessions before requiring additional authorization, then achieving remittance of a patient’s symptoms by the eighth session would be an appropriate optimization criterion. This approach is consistent
with research conducted within the effectiveness context (Glasgow, Lichtenstein, & Marcus, 2003), which favors treatments that are brief and cost-effective and minimize the burden on clinicians and patients.

**Optimization Using SMARTs**

The leading methodology for optimizing AIs is an application of the factorial experimental design known as a SMART (Collins et al., 2007). The use of a SMART design represents an important advancement in the pediatric research methodology, as it allows researchers to optimize their AI by systematically examining treatment components and their sequencing to best meet the specified optimization criterion (Almirall, Compton, Gunlicks-Stoessel, Duan, & Murphy, 2012; Collins et al., 2007). SMART designs differ from the standard treatment package approach in that they allow researchers to examine how the performance of individual components and their sequencing may affect outcomes, thereby aiding in the development of treatments that are more effective, efficient, and sustainable.

In a SMART, patients progress through multiple stages designed to evaluate one of the dynamic elements of the AI. Patients are randomized, at least once, to one of several treatment options at each stage of a SMART. Each randomization occurs in response to a decision point that aims to evaluate a specific question concerning an element of the AI. Decision points may correspond to the number of treatment sessions, milestones in the disease process, or changes in a patient’s physical or mental health status. For instance, randomization at the first stage of a SMART allows researchers to evaluate the most appropriate initial treatment component based on the specified optimization criterion. Patients’ response to treatment in the first stage (i.e., assessed by tailoring variables) is used to rerandomize patients at the second stage of treatment. For example, patients who demonstrated nonresponse in the first stage could be rerandomized to one of two enhanced treatments in the second stage, whereas responders could continue to receive the initial treatment or discontinue treatment. Randomization to a second-stage treatment provides information about how to best address treatment nonresponse at the first stage.

**Clinical expertise in SMART design.** To highlight the value of a partnership between psychologists in research and clinical careers, consider the previous assertions that evidence-based treatments are being adapted by clinicians to increase their effectiveness. If this is the case, then clinicians are in the ideal position to offer clinical judgments about which patient characteristics should be incorporated as tailoring variables of an AI. For example, in a team focused on improving medication adherence, the psychologist with more expertise in the empirical literature will have knowledge that can guide the development of an empirically supported manualized protocol. Complementarily, the clinical expert will have experience with adapting the available research literature to the needs of individual patients. Both of these inputs can inform the development of AI treatment components that rely on the empirical literature. The clinical experience of the team will then be ideal for identifying appropriate tailoring variables (e.g., percentage of prescribed doses taken) that will determine the decision rules (e.g., if no response after initial treatment, rerandomize to more intensive treatment) to alter treatment at later stages (Collins et al., 2004).

**Scientific Aims of SMARTs**

Data resulting from SMART designs can be analyzed to obtain information regarding AIs, such as main effects, interactive effects, and optimization (Almirall et al., 2014). Main effect aims identify which treatment option is most effective, on average, at each stage of treatment. For instance, a main effect aim may address What is the most effective initial treatment option? or What treatment option should everyone receive at the outset? This question corresponds to the main effect of the first stage of the intervention. Applied to the capability domain of the theoretical domains framework (TDF; for an overview of the TDF in the context of pediatric adherence interventions, see McGrady, Ryan, Brown, & Cushing, 2015) for adherence promotion intervention development, a relevant question may be Should patients receive a knowledge-based treatment or a knowledge- and skills-based treatment first? To answer this question using a SMART (such as the example presented in Figure 1), patients would be ran-
randomized to a knowledge-based treatment or a knowledge- and skills-based treatment.

SMARTs also allow for the examination of the main effects of second-stage treatment, providing data to explore questions such as What is the most effective treatment option for first-stage nonresponders? or When my first line of treatment fails, what changes to the protocol will I make? To reiterate, this is a question that arises frequently in clinical care. In the hypothetical SMART (see Figure 1), the decision rule is:

If nonadherent, rerandomize to treatment augmented with behavioral regulation (knowledge-based treatment + behavioral regulation or knowledge- and skills-based treatment + behavioral regulation) or a higher dose of the first-stage treatment (higher dose knowledge-based treatment or higher dose knowledge- and skills-based treatment); if adherent, continue with initial treatment (knowledge-based treatment or knowledge- and skills-based treatment).

In the example SMART, data from this step could be used to examine whether nonresponse to knowledge-based treatment or knowledge- and skills-based treatment improves with the addition of behavior regulation training or a higher dose of the initial treatment. Likewise, if the team is interested in determining how to intervene if the treatment effect decays over time, the decision point could be changed to decline in treatment response by some predetermined period (e.g., less than 80% adherence at 16 weeks). In the example SMART, this corresponds to nonresponders of the knowledge-based treatment or the knowledge- and skills-based treatment at the first stage, who would then receive the same treatment at the second stage.

SMART designs can also be used to assess the interactive effects between treatment components in the first and second stages of treatment (Almirall et al., 2014); this is accomplished by systematically varying or “crossing” first-stage treatments with second-stage treatments. One approach to evaluating the interaction is to compare two embedded AIs. For example, the comparison of AI 2 and AI 4 in Table 1 addresses whether patients are more adherent if provided with a knowledge-based treatment, augmented with behavior regulation training for nonresponders (i.e., AI 2), versus a knowledge- and skills-based treatment.
Data Analytic Approach

SMARTs are a type of factorial experimental design (Collins, Nahum-Shani, & Almirall, 2014). Therefore, consistent with other factorial experiments, the aims of a SMART are generally addressed using a simple two-group comparison. For illustrative purposes, suppose that the outcome in the example SMART is medication adherence during the last week of the study. To address the main effect aim—Is it more effective to begin the AI with knowledge-based treatment or knowledge- and skills-based treatment?—a one-way analysis of variance (ANOVA) can be conducted to compare the mean medication adherence across AIs A, B, and C, with the mean across AIs D, E, and F (see Figure 1). This comparison represents the main effect of the first stage. Mean differences represent a significant effect of one treatment (knowledge-based treatment vs. knowledge- and skills-based treatment) over the other. Therefore, the treatment that produces the highest mean would be chosen as the optimal first-stage treatment option.

The main effect of second-stage treatment options addresses the question Among those who do not respond to knowledge-based treatment and knowledge- and skills-based treatment, is there a difference between increasing the treatment dose versus augmenting the initial treatment? by conducting a one-way ANOVA comparing the mean across AIs B and E with the mean across AIs C and F (see Figure 1). The treatment with the higher mean is taken to be the most effective second-stage treatment option for patients who do not respond to the first-stage treatment (i.e., knowledge-based treatment or knowledge- and skills-based treatment). Notably, pooling the means of AIs B and E and comparing the resulting average to the pooled means of AIs C and F captures the effect of the second-stage treatment for nonresponders, controlling for effects of first-stage treatment options (Nahum-Shani et al., 2012b). Similar analyses can be conducted to compare two embedded AIs (e.g., all combinations of first- and second-stage treatments) with the use of response weights (for an extended discussion, see Nahum-Shani et al., 2012a). Notably, questions addressed by SMARTs rely primarily on examining the means of randomized...
Current State of the Literature in Pediatric Psychology

We conducted a systematic review of the literature to assess the current use of MOSTs and SMARTs in the development of pediatric psychological interventions. In March 2016, we searched the PubMed and PsycINFO databases for relevant peer-reviewed articles. Search terms included *sequential multiple assignment randomized trial*, *multiphase optimization strategy*, and *adaptive intervention*. Each of these search terms was combined with secondary terms—*child, adolescent, youth, or pediatric*—totaling 24 searches. Additional articles were identified through the Pennsylvania State Methodology Center’s listing of AIs and SMARTs. Exclusion criteria were then applied to the 28 relevant articles. Articles were excluded for the following reasons:

- The article was not originally published in English (n = 2).
- The study used did not include a pediatric sample (n = 7).
- The study described a secondary analysis of a previously described SMART or MOST (n = 1).
- The study described design procedures (n = 1) or advanced statistical modeling techniques (n = 3) of a SMART.
- The study provided an overview of AIs (n = 3).
- The study was limited to the preparation phase of a MOST (n = 1).
- The study described an AI not developed or evaluated in the context of a MOST or a SMART (n = 4).
- The study called for or made mention of AIs, MOSTs, or SMARTs for use in behavioral interventions (n = 3).
- The study did not conduct or describe the use of an AI, MOST, or SMART (n = 1).

Two studies met the inclusion criteria. Study details are reviewed herein for didactic purposes. In the first study, a SMART was implemented for optimizing a weight loss AI developed for African American adolescents with obesity (Naar-King et al., 2016). In the second study, the purpose of the SMART was to optimize an AI aimed at improving verbal communication among minimally verbal children with autism (Kasari et al., 2014). Both studies used a two-stage SMART to test four components of an AI. In both cases, failure to improve on the dependent variable resulted in rerandomization into augmented treatment (i.e., higher dose of initial treatment or new modality). In the obesity SMART, the tailoring variable was change in percentage of overweight (i.e., ≥3%) and the decision rule was to rerandomize to augmented treatment (i.e., contingency management or continued skills training) if the participant had not met the weight loss target. In the study conducted by Kasari et al. (2014), the tailoring variable was percentage of change on communication variables (i.e., ≥25% change on 7 out of 14 variables) and the decision rule was to rerandomize to augmented treatment (i.e., speech-generating device or high-dose first-stage treatment) if the communication goal was not met. The decision point in both SMARTs occurred after 12 weeks of the initial treatment.

Findings from both studies have potentially important clinical implications for the use of AIs in real-world clinical practice. More specifically, both studies generated evidence of efficient intervention development with decision rules that can be used in future empirical and clinical work. For instance, Naar-King et al. (2016) found that weight loss was similar across all embedded AIs—that is, comparisons among the different combinations of the first-stage (i.e., home based vs. office based) and second-stage (i.e., contingency management vs. skills training) treatments were not statistically different in terms of outcome, which suggests that treatment decisions could be based on cost of delivery or patient preferences. However, it is notable that patients randomized to the home-based (vs. office-based) treatment in the first stage, followed by rerandomization of nonresponders to contingency management at the second stage, demonstrated higher retention rates. Thus, a clinician providing a weight loss intervention to minority populations who are at increased risk for drop-out (Jelalian et al., 2008; Zeller et al., 2004) may consider a home-based intervention that implements contingency management at the
first sign of nonresponse. Kasari et al. (2014) found that the use of a speech-generating device in the first stage of the intervention for children with autism resulted in nearly double the rate of communicative utterance per minute at the conclusion of the intervention. Further, among nonresponders in the first stage of treatment, those receiving high-dose treatment using the speech-generating device during the second stage of the intervention demonstrated significant improvements. This finding provides clear guidance to clinicians that if a patient does not respond to the treatment initially, he or she should receive a higher dose of the speech-generating device. Such clarity in decision rules may prove to be invaluable for both clinicians and administrators as they try to optimize care. Moreover, clinical research teams can take the knowledge from this SMART and carry it forward to the next study, where nonresponders might be randomized to receive the higher dose treatment versus an alternative that is even better at realizing the optimization criterion (e.g., comparing the high-dose treatment to a shorter and less expensive alternative treatment approach). Taken together, findings of both SMARTs highlight the utility of the design for informing the development of decision rules for whether, when, and how to tailor the intensity and/or type of treatment components in pediatric interventions.

Steps for Independent Clinicians

Finally, although SMART and MOST designs are likely not appropriate for single-case designs, other small-N methodologies have been proposed for clinicians who are beginning the work of developing an AI as a pilot in their own clinical settings. One suggestion would be for a clinician to experimentally test the adaptations he or she makes to manualized treatments. For instance, when a provider notices that a patient does not respond to an evidence-based treatment, he or she often makes a change to try to increase the efficacy of the treatment for the patient. It may be possible to conduct a case study, a small-N study, or an aggregated N-of-1 RCT (Cushing, Walters, & Hoffman, 2014; Rapoff & Stark, 2008) as an initial step toward identifying the adaptations that are effective for a subset of patients. Once the clinician has a sense for what adaptations appear to work at this level, he or she can progress to explicitly testing the adaptations as decision rules in a SMART. Notably, because the estimated sample size of a SMART will differ based on its complexity (i.e., randomization schemes and number of stages), clinicians are encouraged to consider sample-size formulas (Feng & Wahed, 2009; Li & Murphy, 2011; Ogbagaber, Karp, & Wahed, 2016) or the online calculator (http://methodologymedia.psu.edu/logranktest/samplesize; Li & Murphy, 2011) developed for SMARTs.

Major Benefits to Clinicians

If the field were to adopt SMART designs for intervention validation, it would address many criticisms commonly raised by the practice community, such as intervention cost and a “cookbook” approach. With regard to cost, we noted previously that reimbursement can be an a priori optimization criterion of the intervention—that is, intervention designers can explicitly state that their program is required to produce an outcome within a specific number of sessions or for a specific cost at the outset. Similarly, SMART trials could move the field away from a cookbook approach to intervention, as they allow intervention designers to rapidly test modularized approaches to treatment. As a result, the clinician will have empirical guidance on how to address the heterogeneity that exists in his or her clinical population.

Conclusion

When working with pediatric populations, clinicians are often faced with difficult decisions about how to adapt treatment when patients demonstrate nonresponse. AIs have the potential to address this heterogeneity in treatment response by providing clinicians with decision rules for whether, when, and how to tailor the intensity and/or type of treatment components. SMART designs conducted within the context of a MOST provide one method for addressing this gap and creating interventions that can be modified to meet the needs of a wide range of patients. Implementation of these designs has the potential to result in the types of high-quality, low-resource interventions increasingly emphasized in the changing U.S.
health-care system (Roensky & Janicke, 2012) and warrants attention in the future.

Despite SMART designs having numerous advantages, evidence suggests that these designs have not been widely adopted by pediatric psychologists. One potential explanation for this is that the novelty of a SMART raises questions among researchers and clinicians about their ability to develop and implement a successful SMART design. In this article, we have provided an overview of the essential elements of an AI and how a SMART design, conducted within the context of a MOST, could be used to examine each of these elements to develop and optimize an AI. Additional resources and examples of SMARTs conducted in the field can be accessed through the Pennsylvania State Methodology Center (https://methodology.psu.edu/ra/adap-inter).

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