An Introduction to Adaptive Interventions and SMART Designs in Education

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Abstract

Education practice often requires teachers and other school personnel to adapt interventions over time in order to address between-student heterogeneity in response to intervention (e.g., what works for one student may not work for the other) or within-student heterogeneity (e.g., what works now may not work in the future for the same student). An adaptive intervention allows education practitioners to do this in a prespecified, systematic, and replicable way through a sequence of decision rules that guides whether, how, and when to modify interventions. In an adaptive intervention, the practitioner modifies the dosage or type of intervention, or the mode of delivery to meet the unique and changing needs of students as they progress over time. The sequential, multiple assignment, randomized trial (SMART) is one type of multistage, experimental design that can help education researchers build high-quality adaptive interventions. Despite the critical role adaptive interventions can play in various domains of education, research about adaptive interventions and about the use of SMART designs to develop effective adaptive interventions in education is in its infancy. This paper defines an adaptive intervention and reviews the components of this design, discusses the key features of the SMART, and introduces common research questions for which SMARTs may be appropriate.

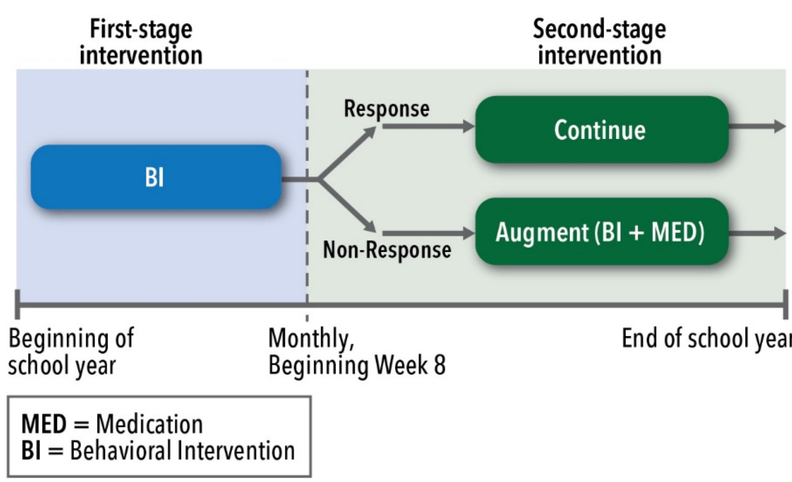
Introduction

Educational practice often requires adapting and readapting an intervention provided to a student in order to address the student's changing needs. Here, adaptation refers to modifying the dosage (duration, frequency, or amount), type, or delivery modality of interventions based on ongoing information about the student's progress and response. This approach is often necessary when the type of intervention that works for one student may not work for the other (between-student heterogeneity), or when the type of intervention that works now for one student may not work in the future for the same student, or vice versa (within-student heterogeneity).

An adaptive intervention is a prespecified, replicable sequence of decision rules that guides whether, how, when, and which measures to use to make critical decisions about interventions in education settings. Adaptive interventions capitalize on differences in how students respond to intervention by providing appropriate modifications for those who need them (e.g., those who are not showing the anticipated improvement) and when they need them (e.g., as soon as it becomes clear that the intervention is not working adequately).

As an example, consider a student-level adaptive intervention designed to improve the school performance of children with attention-deficit/hyperactivity disorder (ADHD) (Figure 1). This is a simplified example taken from a study, *Adaptive Treatments for Children with ADHD,* described in more detail below (Grant # R324B060045 https://ies.ed.gov/funding/grantsearch/details.asp?ID=396; PI: Pelham; Pelham et al., 2016), which was funded by the U.S. Department of Education Institute of Education Sciences (IES). This example includes two types of interventions for ADHD: medication and behavioral intervention. At the beginning of the school year, all children receive a low-intensity behavioral intervention consisting of behavioral parent training and a brief teacher consultation to establish a Daily Report Card. Children who do not respond adequately to the behavioral intervention (as measured by rating scales completed by the child's teacher at specified intervals) receive medication in addition to the behavioral intervention. Children who respond adequately continue with the behavioral intervention. This intervention is "adaptive" because information about the child's response to the intervention is used to individualize subsequent intervention, namely, to determine whether and how to make modifications.

Figure 1. Example adaptive intervention in Childhood ADHD



Educators and researchers have studied or implemented adaptive interventions in various settings, including to prevent absenteeism (e.g., Impact Evaluation of Parent Messaging Strategies on Student Attendance), prevent conduct problems among high-risk children (Bierman, 2002), prevent substance use in children (Dishion & Kavanagh, 2000; Dishion et al., 2002), improve reading (Connor et al., 2013; Connor et al., 2011), treat childhood ADHD (Pelham et al., 2016), and address the needs of children with autism spectrum disorder (ASD; Almirall et al., 2016).

Researchers often have many questions that prevent them from building a high-quality adaptive intervention. Typically, these questions relate to the effectiveness of specific components that make up an adaptive intervention—that is, questions concerning ***building*** an adaptive intervention. They must determine which intervention options are most beneficial for particular students, the best way to monitor students for the purpose of adapting the intervention, and the best way to individualize the intervention to address the unique and changing needs of individuals. Often these questions cannot be answered using existing theories of change, expert opinion, or the literature.

The sequential, multiple assignment, randomized trial (SMART) is a novel multistage, experimental design that can help education researchers address these types of scientific questions used to build adaptive interventions. Despite the critical role adaptive interventions can play in various domains of education, research using the SMART design (or other designs) to systematically build effective adaptive interventions in education is still in its infancy. Most SMART studies have been implemented in health sciences. The SMART is a relatively new experimental tool, hence most educational researchers are not yet exposed to this design as part of their formal graduate training.

This report is for education scientists interested in developing high-quality adaptive interventions and understanding the usefulness of SMARTs in building them. The report will address how adaptive interventions can contribute to educational practice and how SMARTs can support educational researchers to construct adaptive interventions. We do not intend this report to be highly technical or comprehensive, but rather a guide to help researchers determine whether to consider adaptive interventions and whether the SMART is the appropriate experimental tool for their research interests. We encourage readers who have additional questions beyond what is addressed in this report to review the additional resources referenced in the appendixes.

The report is organized as follows:

- Introduction to the components of adaptive intervention.
- Overview of SMART studies and their role in building empirically based adaptive interventions.

- Typical primary and secondary research questions motivating SMART studies, including an overview of how investigators can use data from a SMART to address research questions.
- Guidelines investigators can use to determine if a SMART design is appropriate.
- Appendixes with (1) a glossary of key terms (Appendix A), (2) a compilation of common misconceptions about adaptive interventions (Appendix B) and SMART designs (Appendix C), and (3) links to some websites with additional resources such as sample size calculators or SMART data analysis software (Appendix D).

Throughout, we use the IES-funded Childhood ADHD SMART study referenced above to illustrate ideas. ADHD can negatively impact a child's ability to attend and perform at school (Kent et al., 2011). According to one study using nationally representative data (Xu et al., 2018), the estimated prevalence of diagnosed ADHD among U.S. school-aged youth (ages 4-17) in 2016 was 10.2 percent. Further, students with ADHD incur a significant monetary cost to the U.S. education system (Robb et al., 2011), and ADHD is one of the most well-represented disorders within special education settings (Fabiano & Pyle, 2019). Evidence-based treatments for ADHD include medication with psychostimulants (Conners, 2002; Greenhill et al., 2002) and behavioral interventions (Evans, Owens, & Bunford, 2014; Fabiano et al., 2009). However, questions remain about the best way to sequence and individualize these treatment options to improve student classroom behavior and academic outcomes (Pelham et al., 2016). The Childhood ADHD SMART study was conducted to address this knowledge gap. Appendix E includes two additional examples of SMART studies in education settings to illustrate possible variations in SMART designs.

Adaptive Interventions

What Is an Adaptive Intervention?

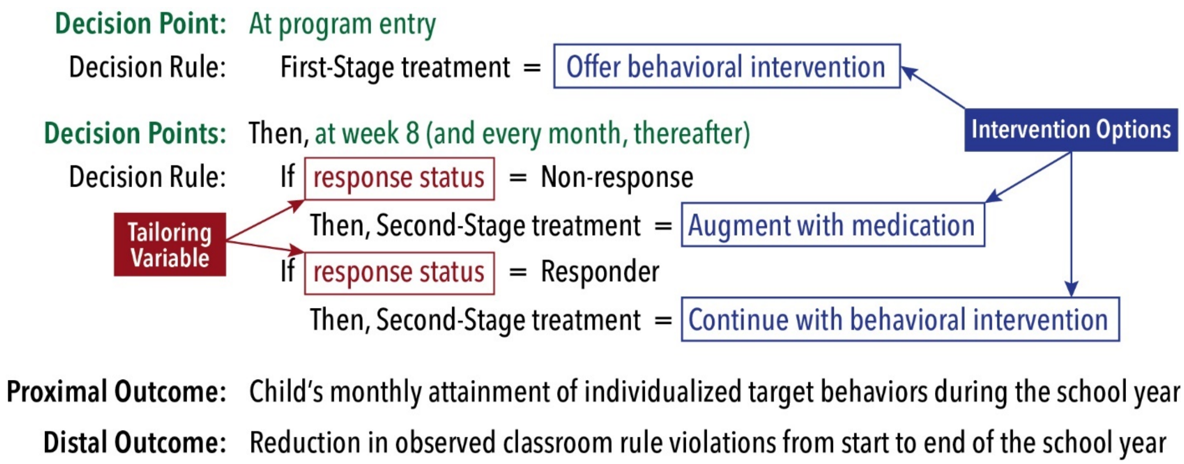
In an adaptive intervention, the practitioner (or some other entity) modifies the dosage (duration, frequency, or amount), type, or delivery mode of an intervention in order to meet the unique and changing needs of individuals (or organizations). Adaptive interventions can guide the efforts of teachers, therapists, school professionals, health service providers, or other education practitioners to deliver individualized interventions. An adaptive intervention is prespecified and clearly defined via explicit decision rules that use observations from students at program entry and as they progress through the intervention to guide whether, when, or how to modify the intervention. The prespecified nature of adaptive interventions increases replicability in authentic education settings and in research that aims to further optimize or evaluate their effectiveness.

What Are the Components of an Adaptive Intervention?

Consider again the example adaptive intervention (Figure 1) for improving the school performance of children with ADHD. At the beginning of the school year, all children receive the behavioral intervention; then, at week 8 (and each month thereafter), the intervention is individualized (i.e., different intervention options are offered to different subgroups of individuals) based on the child's response status.

Schematics such as the one shown in Figure 1 are a common and useful way of describing an adaptive intervention. A second way to describe an adaptive intervention is via the use of "if-then" statements. Figure 2 uses if-then statements to describe the same adaptive intervention depicted in Figure 1. This approach makes it clearer that adaptive interventions are composed of a sequence of decision rules.

Figure 2. Adaptive intervention components



Every adaptive intervention contains the following six key components, each described below.

Decision Points: Points in time in which the practitioner is faced with making an intervention decision. In the example adaptive intervention, decision points occur at program entry, at week 8, and each month thereafter.

Tailoring Variable(s): Information about the individual that practitioners use to decide whether and how to modify the intervention. In the example, the tailoring variable is the child's response status, a binary measure that distinguishes each child as a responder or nonresponder. Note that this tailoring variable is a summary of two teacher-rated measures: the Impairment Rating Scale (IRS; Fabiano et al., 2006) and the Individualized List of Target Behaviors (ITB; Pelham et al., 1992).

Intervention Options: Different types of treatments, tactics, dosages (duration, frequency, or amount), or modalities used to deliver intervention. An intervention stage refers to the time after a decision point during which the individual experiences the assigned intervention option. In the example, there is one first-stage intervention option (behavioral intervention) and two second-stage intervention options (augment with medication or continue with the initial intervention). The second-stage intervention options are tailored to the participant's response to the first stage.

Decision Rules: Prespecified intervention procedures that link the tailoring variable(s) to specific intervention options. For each decision point, the decision rules prespecify the appropriate intervention option under various conditions. In the ADHD intervention, the first decision rule offers behavioral intervention to all children who enter the program. Subsequent decision rules (monthly starting at week 8) offer an augmented intervention consisting of behavioral intervention and medication for children identified as nonresponders or continued behavioral intervention for children identified as responders.

Distal Outcome: The ultimate, long-term goal of the intervention. The distal outcome in the example adaptive intervention is reduction in observed classroom rule violations from the start to the end of the school year.

Proximal Outcomes: Short-term goals or mechanisms of change the intervention is intended to impact to achieve the distal outcome. The proximal outcomes in the example adaptive intervention include the child's monthly attainment of individualized target behaviors (for example, work completion, complying with teacher directions, behavior toward peers) in the course of the school year.

What Is the Rationale for Adaptive Interventions in Education?

Ideally, an adaptive intervention offers the best intervention to each student and provides only as much intervention as necessary at any given time. This approach can help practitioners, schools, and policymakers more effectively allocate scarce resources to those students who need it most. Adaptive interventions can be useful in settings where:

(1) Not all students benefit from the same intervention (that is, students are likely to have different responses);

(2) The intervention that works now for one student may not work in the future for the same student or vice versa (such as when a student initially responds to an intervention but later stops progressing); and

(3) Effective interventions cannot be made available to all students in the target population or for the entire duration of intervention (perhaps due to limited time, money, or other resources).

Several organizing frameworks highlight the importance of modifying interventions to address the changing needs of students (Sugai & Horner, 2009). For example, a multitiered system of supports (MTSS; Sugai et al., 2019) is a general education service delivery model aiming to achieve academic and behavioral outcomes for all students. MTSS uses increasingly intensive tiers of instruction and intervention combined with an objective assessment system to deliver individualized support that address students' academic and behavior needs (Pullen et al., 2018). MTSS is considered an overarching framework, or an "umbrella" to a range of tiered systems of support, such as response to intervention (RTI) and Schoolwide Positive Behavior Support (SWPBS; Sugai & Horner, 2009). RTI, which traditionally focuses on student academics (Goodman-Scott & Grothaus, 2017), begins with high-quality instruction for all students in the general student population. Practitioners closely monitor student progress to make good instructional and intervention decisions, and those students who show signs of academic difficulties receive more intense services in order to address their difficulties and improve academic outcomes (Berkeley et al., 2009; Fuchs & Fuchs, 2007; Sugai & Horner, 2009). SWPBS, which traditionally focuses on student behavior (Pullen et al., 2018), attempts to build the social culture necessary for schools to be effective learning environments. This approach includes (1) primary tier interventions—typically, screening and universal interventions; (2) secondary tier interventions, which typically include more structured intervention practices, more frequent behavior feedback, and more active supervision; and (3) tertiary interventions, which typically include more intensive support. A protocol specifies how evaluations of student responsiveness to a particular tier should determine in practice whether and when a student should transition from one tier to another (Sugai & Horner, 2009).

While the example frameworks described above highlight the value of adaptive interventions in the context of multitier interventions, this approach could also benefit other domains. For example, in the area of professional development, adaptive interventions can provide a clear protocol for offering additional training and resources based on teachers' changing needs for support. Similarly, in the area of interactive learning environments (such as computerized systems that engage users in learning processes [Renkl & Atkinson, 2007]), adaptive interventions can help preplan when and how the system or the teacher should offer additional support (automated, human, or both). (See Nahum-Shani et al., 2013, for examples of how adaptive interventions can be used to specify when and how the system should provide or withhold a hint when learners press the support button during a problem-solving task.)

The frameworks described above implicitly emphasize the need to "step up" the intervention with more intense (and often costlier) options for those who need it (see "stepped care" models in substance use; Brooner & Kidorf, 2002; Sobell & Sobell, 2000). Adaptive interventions, however, can also be used to preplan whether and how to "step down" an intervention, offering less intense or less costly intervention options to those who are doing well. Adaptive interventions can also combine stepped up and stepped down strategies.

How Can Adaptive Interventions be Expanded Beyond the Student-Level?

The adaptive intervention for the childhood ADHD example operates and produces outcomes at the student level. However, adaptive interventions also can be designed to impact student level outcomes by using intervention components at other levels, such as the teacher, classroom, school clinic, or school.

For example, the Adaptive School-Based Implementation of Cognitive Behavioral Therapy (CBT) Study (Kilbourne et al., 2018; see details in Appendix E) includes four adaptive interventions aiming to improve student-level outcomes by improving the quality and total number of CBT sessions delivered by mental health school professionals. One school-level intervention option employed is an ongoing, CBT-skills-coaching intervention for all mental health professionals within the school. Another intervention option, known as Facilitation, addresses school-level barriers that prevent school professionals from adopting or implementing evidence-based practices, such as communication barriers or conflict with school leadership. Further, the investigators assessed the tailoring variable (response status) at the school level, classifying schools as either nonresponsive or responsive based on the quality of CBT delivery within the school. In this example, all intervention components are employed at the school level, but the ultimate goal is to improve outcomes at the level of the students.

Adaptive interventions can also include components employed at multiple levels simultaneously. These adaptive interventions are called multilevel adaptive interventions. For example, the adaptive interventions considered in the IES-funded pilot study, *Getting SMART About Social and Academic Engagement of Elementary Aged Students With ASD* (Grant # R324U150001 https://ies.ed.gov/funding/grantsearch/details.asp?ID=1758), includes intervention components delivered at multiple levels, including the school, the classroom, and the student (see Figure 1 of Almirall et al., 2018b). These adaptive interventions aim to improve social and academic outcomes for schoolchildren with ASD. One of the adaptive interventions considered in this study begins with a school-level intervention known as Remaking Recess (Kretzmann, Shih, & Kasari, 2015), which is intended to promote social engagement during unstructured school times on the playground. This is followed (at week 4) by a classroom-level intervention known as Classroom Supports (National Research Council, 2001), which provides the teacher with skills to improve the behavioral regulation and classroom management of children, and then (at week 12) by an intervention that targets the individual child via either the parent or the child's peers. The tailoring variable is at the student level, whereby at week 20, children are identified either as responders or slow responders based on playground observations taken by a paraprofessional. Early responders continue with the assigned child-level intervention; slower responders are offered an integrated intervention that targets the child via parents and peers.

In sum, there is no requirement that intervention options in an adaptive intervention be employed only at the student level, even when the goal is to improve student-level outcomes. Depending on the theory of change guiding intervention development and practical considerations, an adaptive intervention can employ components at multiple levels beyond the student. In the autism example above, intervention is provided at the level of the school, the level of the classroom, and then at the level of the child. Appendix B speaks to additional misconceptions investigators often have regarding adaptive interventions.

How Can Intervention Components be Selected and Integrated to Form an Effective Adaptive Intervention?

To construct an adaptive intervention, an investigator must select and integrate the six components of an adaptive intervention (decision points, tailoring variables, intervention options, decision rules, distal outcome, and proximal outcomes). Ideally, the investigator will rely on empirical evidence, existing theories, practical considerations, clinical considerations, or some combination of these to guide this process.

As is typical for any type of intervention research, the investigator will begin by identifying a target population (for example, school children with ADHD), selecting a primary distal outcome, then articulating a clinically or academically meaningful goal for the target population based on this distal outcome (for example, reduction in observed classroom rule violations by the end of the school year).

Then, the investigator will identify proximal outcomes by articulating a theory of change. This model specifies mechanisms of change—processes or events—that can lead to (or prevent) the distal outcome. These mechanisms (the proximal outcomes) should be malleable; that is, they should be subject to change via an intervention. In the childhood ADHD example, the investigators selected the proximal outcomes (child's attainment of individualized target behaviors) based on evidence suggesting that they would reduce observed classroom rule violations by the end of the school year and that these mechanisms of change could potentially be modified via an intervention.

Guided by the selected proximal outcome(s), the investigator will identify intervention options that are likely to impact the selected proximal outcomes in the desired direction. In the childhood ADHD example, behavioral intervention and medication were selected based on evidence suggesting that they likely improve the child's attainment of individualized target behaviors.

The theory of change should also guide the selection of tailoring variables. These variables contain information that is useful in identifying subgroups of participants who will likely benefit from different intervention options. Often, the mechanisms of change selected as proximal outcomes are also selected as tailoring variables because this information can be used to identify early those participants who do not experience sufficient improvement and require intervention modification. In the childhood ADHD example, investigators selected response status as a tailoring variable based on evidence indicating that responders and nonresponders require different subsequent intervention options: responders will do well if they continue with the initial intervention whereas nonresponders require intervention modification. The child's attainment of individualized target behaviors is both the proximal outcome and one of the measures used to assess the tailoring variable (early response status). This is based on evidence suggesting that children who do not experience improvement in attaining an individualized target behavior early in the course of the intervention are less likely to show progress toward the proximal or distal outcomes without a change in treatment.

A theory of change requires a determination of *when* meaningful change is expected to occur. This consideration guides the selection of decision points in an adaptive intervention. For example, in the childhood ADHD example it was expected that at minimum two months were needed following the start of intervention before expecting meaningful change in the child's attainment of individualized target behaviors. Additionally, meaningful change was expected to occur at monthly time intervals thereafter.

Finally, the investigator uses this theory of change to integrate the components of an adaptive intervention such that they work together to improve the proximal and distal outcomes. To clarify what it means and why it is important to select and integrate the components of an adaptive intervention so that they work well together, consider possible positive or negative synergies between the components comprising an adaptive intervention. In this context, positive synergies represent scenarios in which a component that seems suboptimal as a standalone component leads to the most beneficial outcomes as part of an adaptive intervention (i.e., as part of a sequence of individualized interventions). Negative synergies represent scenarios in which a component that seems beneficial as a standalone component leads to suboptimal outcomes when used as part of an adaptive intervention. Below we provide hypothetical examples of positive and negative synergies between first and second-stage intervention options and their implications on the effectiveness of the adaptive intervention.

Positive Synergies: Consider the decision to employ behavioral intervention as the first stage intervention option in the adaptive intervention for childhood ADHD (Figures 1 and 2). Ideally, this decision is based on evidence suggesting that the behavioral intervention is an effective approach to initiate an adaptive intervention that then adds medication for nonresponding children, while continuing the behavioral intervention for responding children. For example, suppose that existing evidence indicates that, although the behavioral intervention leads to less short-term improvement in behavioral outcomes compared to medication (e.g., up to 4 months; Swanson et al., 1993; Craig et al., 2015; Pelham et al., 1993), the behavioral intervention builds psychosocial skills that likely improve the effectiveness of the second-stage options for nonresponders (add medication) and responders (continue with the behavioral intervention) (Pelham et al., 2016). This implies that as a standalone component the behavioral intervention may not be as effective as medication in the short term. However, the behavioral intervention may be highly effective as part of an adaptive intervention since the second-stage options likely capitalize on the psychosocial gains achieved by offering the behavioral intervention initially. This is an example of positive synergy between the initial intervention option and the subsequent options. In this case, selecting to begin with the behavioral intervention is expected to lead to a more effective sequence of intervention options compared to starting with medication.

Negative Synergies: Consider the decision to add medication to the behavioral intervention as the second-stage intervention option for nonresponders in the adaptive intervention for childhood ADHD (Figures 1 and 2). Ideally, this decision is based on evidence suggesting that adding medication is an effective approach to treating nonresponding children *who initially received a behavioral intervention*. Suppose, instead, that the investigator decides to add medication based on existing evidence suggesting that medication is effective as a standalone intervention (rather than as part of a sequence of individualized interventions that starts with a behavioral intervention). This may seem like a logical choice given the extent of research on medication for ADHD. This approach may lead to the development of a suboptimal adaptive intervention if the effectiveness of medication differs depending on whether it is provided as a standalone intervention or following another intervention. For example, it is possible that although medication is an effective standalone approach to treating childhood ADHD, it is actually less effective when offered to nonresponders who first received a behavioral intervention. If this were true, then this is an example of negative synergy between the initial intervention option (behavioral intervention) and the subsequent option (adding medication for nonresponders). In this case, selecting to add medication as a second-stage option for children nonresponsive to a behavioral intervention would ultimately undermine the effectiveness of the adaptive intervention.

Summary: Positive or negative synergies between the first-stage and second-stage intervention options could be sufficiently strong so as to lead to delayed effects of first-stage interventions. In this setting delayed effects occur, for example, when (1) a first-stage intervention is not effective in the short term but is effective in the longer term when followed by second-stage interventions as part of an adaptive intervention, or (2) when there is a reversal in the direction of the short-term effectiveness of a first-stage intervention vs. its effectiveness when followed by a second-stage intervention as part of an adaptive intervention (Nahum-Shani et al., 2019). These scenarios highlight the importance of selecting intervention components based on empirical evidence demonstrating their efficacy as part of a sequence of decision rules comprising an adaptive intervention, rather than as standalone components. However, often such evidence does not exist (Collins, 2018; Collins & Kugler, 2018), and there are unanswered scientific questions regarding the selection and integration of components in an adaptive intervention. In the next section, we discuss how SMART studies can be used to address these questions.

Sequential Multiple Assignment Randomized Trials (SMART)

What Is a SMART?

The SMART (Lavori & Dawson, 2014; Murphy, 2005) is an experimental design that education researchers can use to efficiently answer multiple scientific questions concerning the selection and integration of the components that make up an adaptive intervention. A SMART involves multiple stages of randomizations, meaning that some or all individuals (or organizations) participating in a SMART are randomized more than once; this is the SMART's defining feature.

Examples of SMARTs outside of education. Researchers have used SMARTs to develop adaptive interventions for depression (Gunlicks-Stoessel et al., 2016), weight loss (Naar-King et al., 2016), cancer (Kidwell, 2014), smoking cessation (Fu et al., 2017), substance abuse (McKay et al., 2015), schizophrenia (Shortreed & Moodie, 2012), and juvenile delinquency prevention (August, Piehler, & Bloomquist, 2016).

Examples of SMARTs in education. To our knowledge, the few completed SMART studies in the area of education mainly have addressed ASD (Kasari et al., 2014; Almirall et al., 2016; Almirall et al., 2018a) and ADHD (Pelham et al., 2016). Other SMARTs currently in the field include the following IES-funded studies:

- Impact Evaluation of Parent Messaging Strategies on Student Attendance *(Contract # ED-IES-16-C-0017 https://ies.ed.gov/ncee/projects/evaluation/other_messaging.asp)*
- *Cohesive Integration of Behavior Support Within a Process of Data-Based Intervention Intensification (Grant # R324N180018 https://ies.ed.gov/funding/grantsearch/details.asp?ID=2212)*
- *Adaptive Response to Intervention (RTI) for Students With ADHD (Grant # R305A170523 https://ies.ed.gov/funding/grantsearch/details.asp?ID=2073)*

The latter two studies—the *Cohesive Integration of Behavior Support Within a Process of Data-Based Intervention Intensification* study and the *Adaptive Response to Intervention (RTI) for Students with ADHD*—represent examples that promise to inform adaptive interventions within the context of the MTSS framework.

Ongoing SMARTs also include a study to improve the adoption of Cognitive Behavioral Therapy in school settings (Kilbourne et al., 2018) and a study to improve social communication outcomes in children with autism who are minimally verbal (*Adaptive Intervention for Minimally Verbal Children With ASD*; PI: Kasari), reviewed briefly in Appendix E.

What Types of Scientific Questions Can Be Answered With a SMART?

SMARTs are typically motivated by scientific questions concerning (1) the comparison of intervention options at specific decision points of an adaptive intervention, (2) the comparison of multiple adaptive interventions, and (3) the identification of additional tailoring variables in an adaptive intervention. Below, we provide examples of scientific questions consistent with each of these three motivations.

Suppose in the context of the childhood ADHD example, the investigators did not have sufficient empirical evidence to determine the answers to the following four questions:

> Question 1: Which intervention option is the best to offer initially as part of an adaptive intervention: behavioral intervention or medication?
>
> Question 2: What subsequent intervention option is the best for children who show signs of early nonresponse to the intervention: is it better to augment the original intervention option with another type of intervention (Augment) or enhance the intensity of the initial intervention (Intensify)?
>
> Question 3: What sequence of decision rules (that is, which adaptive intervention) is best: the sequence described in Figures 1 and 2 or an alternative sequence that recommends medication initially and then augmenting with a behavioral intervention for nonresponders and continuing medication for responders?

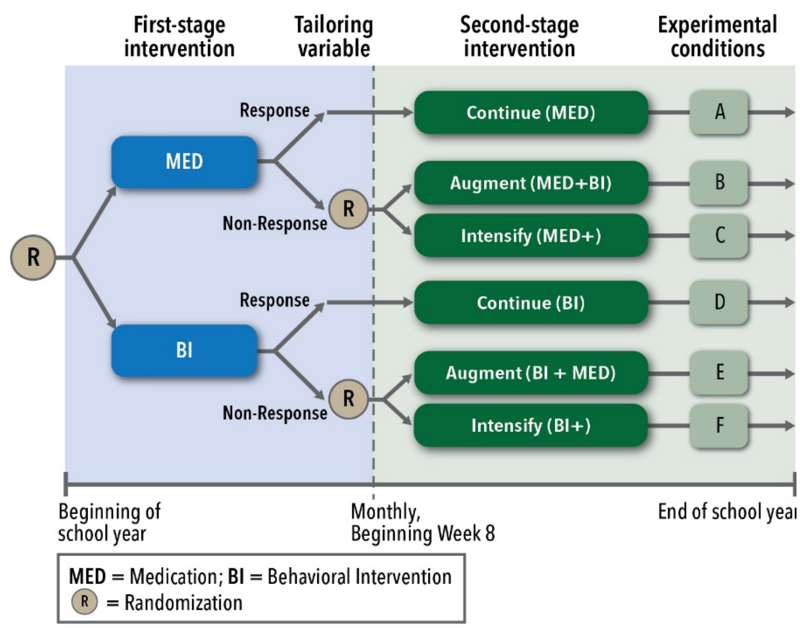
Question 4: Should the adaptive intervention include additional tailoring variables beyond the child's early response status? Specifically, can information regarding the child's adherence to the initial intervention be used to identify a subgroup of nonresponding children who would benefit more from the Augment option than the Intensify option?

Questions 1 and 2 both concern the comparison of intervention options at specific decision points of an adaptive intervention, question 3 concerns the comparison of multiple adaptive interventions, and question 4 concerns the identification of additional tailoring variables beyond those already included in an adaptive intervention.

How Can SMART Data Be Used to Address Common Scientific Questions Concerning the Development of an Adaptive Intervention?

Figure 3 depicts the ADHD SMART study, discussed earlier in this paper, to systematically answer scientific questions concerning the construction of an adaptive intervention for children aged 5 to 12 with ADHD (PI: Pelham). At the beginning of the school year, investigators randomly assigned 152 children to either low-dose medication (MED) or low-intensity behavioral intervention (BI) (First stage). At week 8, and monthly thereafter, children were assessed for responsiveness. Children showing inadequate response (nonresponders) were rerandomized with equal probability to either increase the intensity/dose of the initial intervention (Intensify: MED+ or BI+) or add the other intervention (Augment: MED+BI or BI+MED) (Second stage). Children showing adequate response (responders) continued with the initial intervention and were monitored monthly. The primary outcome was classroom rule violations based on objective observations of classroom behavior at the end of the school year. This experimental design resulted in six experimental conditions, labeled A through F in Figure 3, and four embedded adaptive interventions (described in more detail below).

Figure 3. Childhood ADHD SMART study



Note that such a design ensures that randomized subgroups are compositionally similar given past characteristics (known or unknown) up to the point of randomization. For example, the group of children randomized to MED (conditions A+B+C) are compositionally similar to the group of children randomized to BI (D+E+F) in terms of all known or unknown characteristics prior to the beginning of the school year (baseline characteristics). Similarly, for example, the group of BI nonresponders randomized to Augment (condition E) is compositionally similar to the group of BI nonresponders randomized to Intensify (condition F) in terms of all known or unknown characteristics up to the point of nonresponse. However, such a design does not assume that the children within each of the conditions A through F are homogeneous; for example, nonresponding children within condition F may differ based on the time at which they transitioned from first stage BI to second-stage BI+.

Data from this childhood ADHD SMART can answer the four scientific questions outlined earlier.

1. Which intervention option is the best to offer initially?

This question concerns the comparison of two initial intervention options. Specifically, the investigator would like to determine whether starting with a behavioral intervention is better than starting with medication in terms of classroom behavior (primary outcome) at the end of the school year. The investigator can make this determination by comparing the mean outcome for the participants who received medication initially (conditions A + B + C) to the mean outcome for those who received the behavioral intervention (conditions D + E + F; see Figure 3).

This design amounts to a two-group comparison between half of the sample who started with medication and the other half who started with a behavioral intervention. This comparison represents the “main effect” of the first-stage intervention options, averaging over the second-stage intervention options for responders and nonresponders. The investigator can use standard data analysis methods for this comparison. Specifically, he or she can use standard regression approaches for comparing initial intervention options in terms of an end-of-study outcome (Nahum-Shani et al., 2012a). The investigator can also use standard longitudinal data analysis methods (for example, linear mixed models [Verbeke & Molenberghs, 2009], also known as mixed-effect, random effects, hierarchical linear, or growth curve models) for comparing initial intervention options in terms of outcome trajectories.

2. What subsequent intervention option is the best for nonresponders?

This question concerns the comparison of the second-stage intervention options among nonresponders. Specifically, the investigator would like to determine whether nonresponders would benefit more from the Intensify option vs. the Augment option based on changes in classroom behavior (primary outcome) at the end of the school year. The investigator can make this determination by comparing the mean outcomes for the nonresponders who were assigned to the Augment tactic (conditions B + E) and those who were assigned to the Intensify tactic (conditions C + F; see Figure 3). This design amounts to a two-group comparison between half of the nonresponders who received the augmented intervention and the other half of nonresponders who received the intensified intervention. This comparison represents the “main effect” of the second-stage intervention options among nonresponders, averaging over first-stage intervention options. Similar to the comparison of initial intervention options, researchers can use standard data analysis approaches to compare second-stage intervention options among nonresponders. However, the analysis will only include nonresponders to the initial intervention.

3. What sequence of decision rules (i.e., which adaptive intervention) is better compared to another?

This question concerns the comparison of two embedded adaptive interventions. The sequential randomizations in the childhood ADHD SMART give rise to four "embedded" adaptive interventions (Table 1).

Table 1: Four Adaptive Interventions Embedded in the ADHD SMART

Adaptive Intervention	First Stage	Response Status	Second Stage	Cells Fig. 2
(1) "MED-BI"	MED	Responder	Continue	A+B
		Nonresponder	Augment	
(2) "MED-MED"	MED	Responder	Continue	A+C
		Nonresponder	Intensify	
(3) "BI-MED"	BI	Responder	Continue	D+E
		Nonresponder	Augment	
(4) "BI-BI"	BI	Responder	Continue	D+F
		Nonresponder	Intensify	

One of the four embedded adaptive interventions—labeled "BI-MED" (#3 in Table 1) and represented by cells D+E—is illustrated in Figure 3 above. All four embedded adaptive interventions in the childhood ADHD SMART use the child's response status as a tailoring variable.

Here, the investigator would like to determine whether students have better long-term behavioral outcomes if they start with behavior intervention and add medication later for nonresponding children (BI-MED adaptive intervention) or start with medication and add in the behavioral intervention for nonresponding children (MED-BI adaptive intervention).

The investigator can make this determination by comparing the outcome among the participants who are consistent with the BI-MED adaptive intervention (meaning responders to the behavioral intervention and nonresponders who were assigned to augment with medication; conditions D+E in Figure 3) with the outcome among the participants who are consistent with the MED-BI adaptive intervention (responders to medication and nonresponders who were assigned to augment with behavioral intervention; conditions A+B in Figure 3).

Unlike the standard regression analyses associated with the main effect aims, the regression analysis for comparing embedded adaptive interventions in a prototypical SMART such as the childhood ADHD study requires a small adjustment involving weights that are a function of the known randomization probabilities. Nahum-Shani and colleagues (2012a) discuss the intuition for this adjustment. They provide details regarding the method and example code for comparing adaptive interventions in terms of an end-of-study outcome. Nahum-Shani and colleagues (2019) describe use of repeated outcome measurements to compare embedded adaptive interventions.

4. Should the adaptive interventions include additional tailoring variables?

This question concerns whether baseline and time-varying information collected in the course of the SMART can be useful in identifying additional tailoring variables beyond the child's response status. While the childhood ADHD SMART uses response status as the only tailoring variable, other data collected during the SMART study can yield useful information to further tailor the adaptive intervention in the future.

For example, the investigator may wish to examine whether the second-stage intervention option for nonresponders should be tailored to the child's level of adherence to the initial intervention. Evidence could indicate that among nonresponders, those who were nonadherent to the initial intervention benefit more from augmenting the initial intervention, whereas no differences exist (between the two subsequent tactics) among adherent nonresponders. This finding can inform an adaptive intervention that not only tailors the second-stage intervention options based on the child's response status, but also based on his or her adherence to the first stage intervention—offering an augmentation to nonresponders who did not adhere to the initial intervention, either augmentation or intensification to adherent nonresponders, and continuing the initial intervention for responders. As an alternative example, the investigator may wish to examine whether the second-stage intervention option for nonresponders should be tailored based on the time at which the child showed signs of inadequate response.

Similarly, the investigator may wish to examine whether the first-stage intervention option should be tailored to baseline information, such as gender, age, treatment history, or the severity of a child's initial symptoms. For example, assume the results indicate that children who were prescribed medication in the past benefit more from the behavioral intervention initially compared to medication, whereas those who were not prescribed medication in the past benefit more from medication initially compared to the behavioral intervention. This finding can inform an adaptive intervention that not only tailors the second-stage intervention options to the child's response status, but also tailors the first-stage options based on whether the child was prescribed medication in the past.

Data analyses to address this type of question are similar to standard moderator analyses (Kraemer et al., 2006). In standard moderator analyses of data from standard randomized trials, investigators often fit regression models with an interaction term between the (randomized) intervention assignment indicator and a baseline covariate. Analyses associated with the development of more deeply tailored adaptive interventions using data arising from a SMART are similar but (1) the covariates included in the interactions can be both baseline or time-varying, and (2) intervention assignment is time-varying (e.g., stage 1 intervention options and stage 2 intervention options among nonresponders). Q-learning regression is one approach that is easy to understand and useful for addressing this type of question (Nahum-Shani et al., 2012b). Q-learning is a generalization of moderated regression analysis to multiple stages of intervention with a specific focus on exploring candidate time-varying tailoring variables. Accessible tutorials to this approach can be found in Nahum-Shani et al. (2012b) and Nahum-

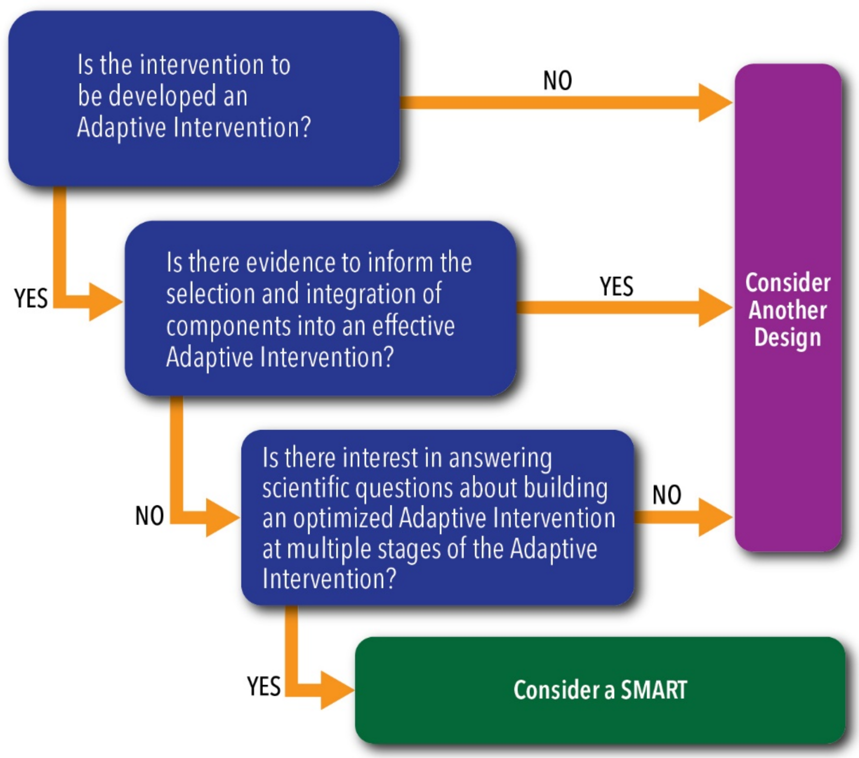
Shani et al. (2017). The methodological literature concerning methods to address this type of scientific question is now extensive and growing rapidly. While it is outside the scope of this article to provide a comprehensive review, here we list a few variants or extensions of Q-learning which serve as a starting point (and in Appendix D we provide links to related software): interactive Q-learning (Laber, Linn, & Stefanski, 2014); classification based methods (Zhang et al., 2012; Zhang, et al., 2013); dynamic weighted ordinary least squares (Wallace & Moodie, 2015); and decision lists (Zhang et al., 2015; Zhang et al., 2018).

When to Consider a SMART Design

The starting point for considering a SMART is whether the investigator is interested in *building an effective adaptive intervention* (Collins, 2018; Collins & Kugler, 2018). If, instead, the goal is to *evaluate an adaptive intervention* that already exists, a SMART is not necessary. For example, if the ultimate goal is to confirm that an existing adaptive intervention is superior to a standard of care intervention, then a standard confirmatory randomized controlled trial (RCT) comparing the adaptive intervention to a suitable control may be the most appropriate design. SMART designs do not represent an alternative to confirmatory RCT designs.

The SMART is a useful experimental tool for investigating how to select and integrate adaptive intervention components. However, it is not the only type of randomized trial design for building an effective adaptive intervention (Almirall et al., 2018b). Other trial designs can be useful depending on the scientific questions motivating the study. This section proposes three questions investigators can ask themselves to help determine whether to consider a SMART (see Figure 4).

Figure 4. Guidelines for determining whether a SMART should be considered

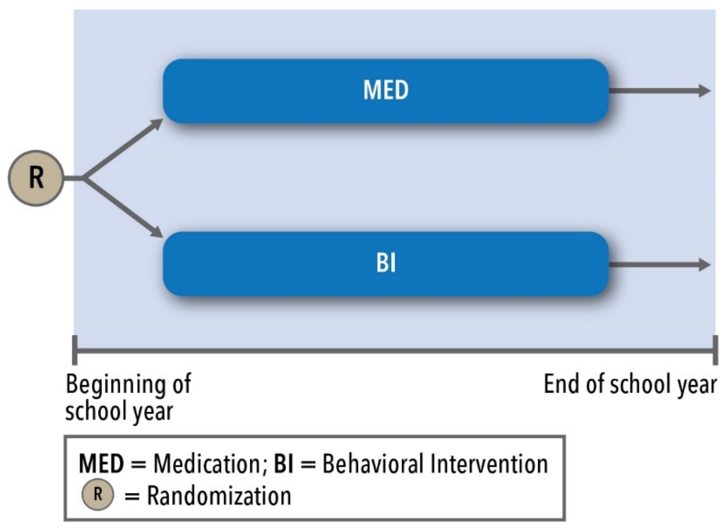


1. Is the Intervention to Be Developed an Adaptive Intervention?

If yes, consider a SMART. Investigators may consider a SMART if the intervention they seek to build is an adaptive intervention. Recall that an intervention is adaptive if (1) it includes individualization, namely the use of information about the targeted unit (for example, the student, the classroom, the school) to select intervention options, and (2) the information used for individualization is dynamic, meaning that the information used to decide which intervention option to offer can change over time, including possibly as a result of prior intervention. As an example, recall that in the childhood ADHD study described above, the investigators were motivated to develop an intervention that uses dynamic information about the child's response status to decide whether to continue the initial intervention (if the child is responding) or modify the initial intervention (if the child is not responding adequately). Because the goal was to develop an adaptive intervention for childhood ADHD, the investigator considered a SMART.

If no, you may not need a SMART. Investigators may consider an alternative design if the intervention they seek to build does not include individualization (meaning the plan is to offer the same intervention to all targeted units) or the intervention includes individualization solely based on static information (i.e., information that is unlikely to change as a result of the intervention such as age, gender, and stable personality traits). Consider a hypothetical scenario where an investigator wishes to develop a nonadaptive intervention for childhood ADHD. In this scenario, the investigator is interested in determining whether this intervention should include either medication or behavioral intervention and in understanding for whom medication (vs. behavioral intervention) would be beneficial based on gender, age, and symptom severity. In this case, the investigator may consider a standard two-arm randomized trial (see Figure 5), assigning children with ADHD to either medication or behavioral intervention, with age, gender, and symptom severity measured at baseline to enable investigation of these variables as moderators of the effect of medication (vs. behavioral intervention). Since the goal in this hypothetical scenario is to develop an intervention that offers the same intervention to all children (i.e., a nonadaptive intervention), a SMART is not needed.

Figure 5. Randomized trial comparing two interventions

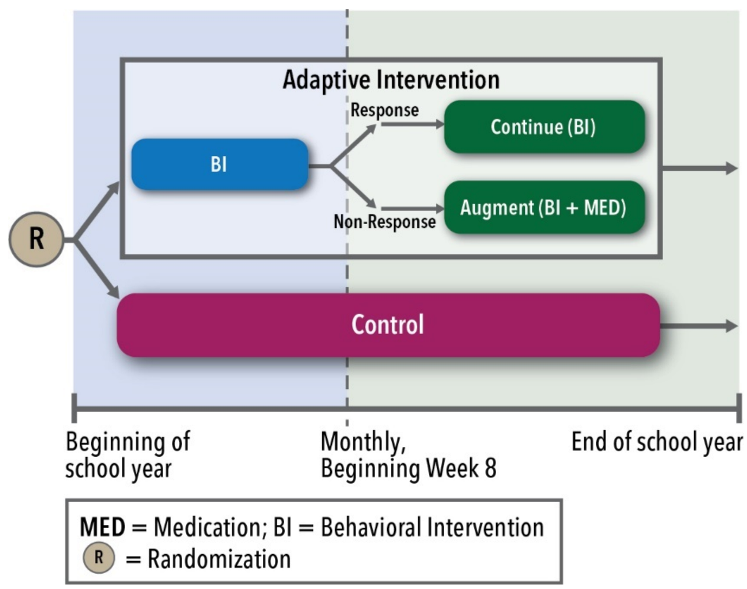


2. Is There Evidence to Inform the Selection and Integration of Components Into an Effective Adaptive Intervention?

If yes, you may not need a SMART. Investigators may consider an alternative design (like a standard RCT) if they are confident that they can select or construct an effective adaptive intervention based on existing expertise or empirical evidence. Suppose the adaptive intervention for childhood ADHD in Figures 1 and 2 was built based on a combination of clinical expertise, results from separate prior studies suggesting the efficacy of the behavioral intervention and its integration with medication (though not necessarily as a stage 2 intervention option for nonresponders to the behavioral intervention), and sufficient evidence supporting the feasibility of the adaptive intervention. Suppose, further, that the investigator is now interested in evaluating this adaptive intervention *to confirm its effectiveness* without further questions concerning how best to select and integrate its components. In this case, the investigator may consider a standard two-arm RCT assigning children with ADHD either to the adaptive intervention or to a suitable control condition (a business-as-usual intervention, for example) to confirm the effectiveness of the adaptive intervention (see Figure 6). Since in this hypothetical example investigators can build on existing evidence to select and integrate intervention components into an effective adaptive intervention package, a SMART is not needed. In such a setting, investigators should consider an RCT to confirm the efficacy of the adaptive intervention package compared to control.

If no, consider a SMART. Investigators may consider a SMART if existing evidence (empirical, theoretical, or practical) is insufficient to guide the selection and integration of components into an effective adaptive intervention. The childhood ADHD SMART study was motivated by insufficient evidence to inform the selection and integration of intervention components. It was unclear which intervention option would be best to offer initially (behavioral intervention or medication) and what subsequent intervention option would be best for children who do not respond to the intervention (add another type of intervention or enhance the intensity of the initial intervention). Since there were unanswered scientific questions concerning the construction of an effective adaptive intervention, a SMART was considered.

Figure 6: Confirmatory randomized control trial comparing an adaptive intervention to a suitable control

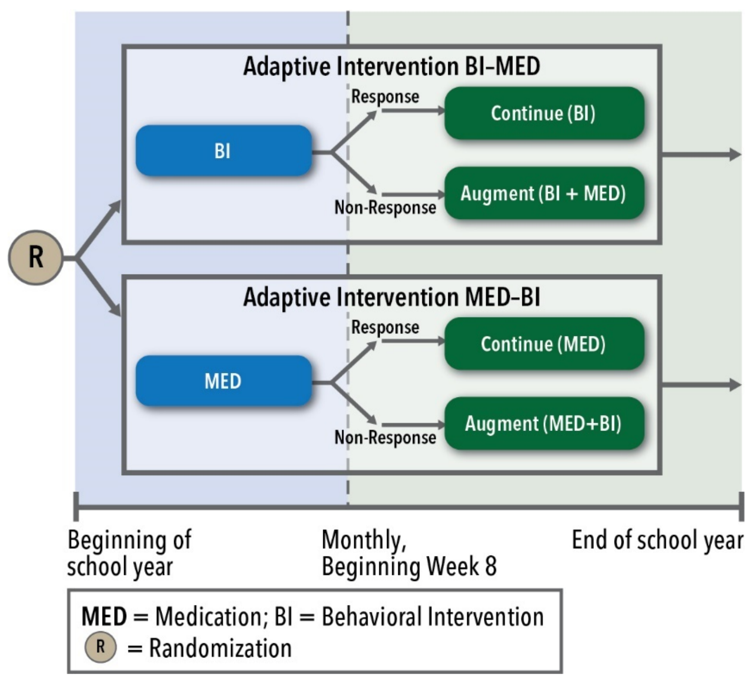


3. Is There Interest in Answering Scientific Questions About Multiple Stages of the Adaptive Intervention?

If yes, consider a SMART. Investigators may consider a SMART if there are scientific questions about multiple stages in the adaptive intervention. As noted earlier, an intervention stage refers to a period of time following a decision point in which the individual experiences the assigned intervention option. Recall that the goal of the childhood ADHD study was to develop a two-stage adaptive intervention: the first stage starts at the beginning of the school year and ends either when the child is clarified as a nonresponder or at the end of the school year (for responsive children), and the second stage starts when the participant is identified as a nonresponder and ends at the end of the school year. This study was motivated by scientific questions relating to both the first stage (which intervention option is better to offer initially: behavioral intervention or medication) and the second stage intervention options (what subsequent intervention option is best for nonresponding children: add another type of intervention or enhance the intensity of the initial intervention). The investigators considered a SMART since they were interested in answering scientific questions about the selection of intervention options at multiple stages in an adaptive intervention.

If no, you may not need a SMART. Investigators may consider alternative designs if the questions motivating the study concern only one stage in an adaptive intervention. Almirall and colleagues (2018) discuss how investigators can use singly randomized trials (SRTs) where units are randomized only once in the course of the trial, to inform the development of empirically based adaptive interventions when the scientific questions motivating the trial concern only one intervention stage or the comparison of two adaptive interventions.

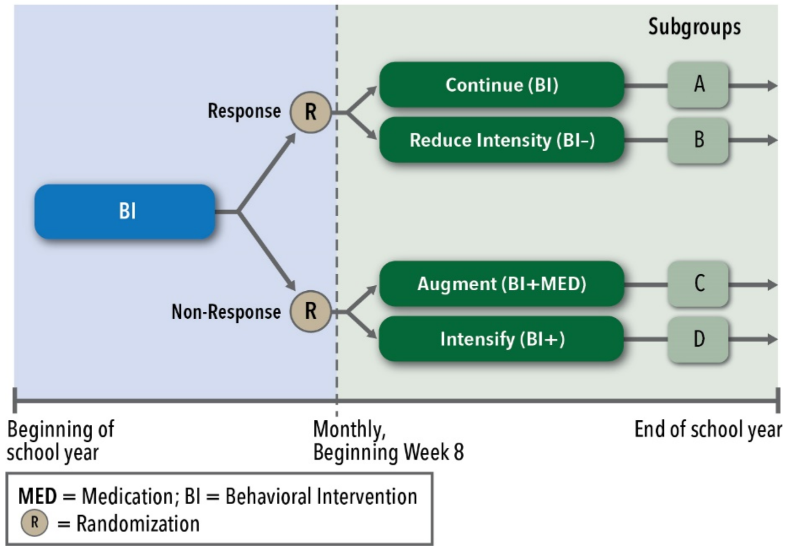
Figure 7: Randomized trial comparing two adaptive interventions



Consider a scenario where an investigator is researching the following scientific question: Is the adaptive intervention that starts with a behavioral intervention and then adds medication for nonresponding children and continues the behavioral intervention for responding children (BI-MED) better than another adaptive intervention that is identical in all respects except that it begins with medication instead of the behavioral intervention (MED-BI)? Such a question contrasts two adaptive interventions. In this case, the investigator may consider a two-arm randomized trial that assigns children with ADHD to either the BI-MED adaptive intervention or the MED-BI adaptive intervention (see Figure 7). The trial in Figure 7 is not a SMART because participants are randomized only once; it is a singly randomized trial.

Consider a second scenario where an investigator can build on existing evidence to select behavioral intervention as the first-stage for childhood ADHD, but there is insufficient evidence to determine (1) whether augmenting with medication is better than intensifying the behavioral intervention for nonresponders, and (2) whether, among responders to the behavioral intervention, it is better to continue with the behavioral intervention or reduce its intensity. In this case, the investigator may again consider a singly randomized trial where all children with ADHD initially receive a behavioral intervention and nonresponders are randomized to two subsequent "rescue" options and responders are randomized to two subsequent "maintenance" options (see Figure 8). Again, the trial shown in Figure 8 is not a SMART because no participants are randomized more than once; it is a singly randomized trial.

Figure 8. Singly randomized trial comparing second-stage options among responders and nonresponders



Although the example trial designs in Figures 7 and 8 are not SMARTs, both are useful for informing scientific questions concerning how to build an effective adaptive intervention. Specifically, these hypothetical trials are designed to answer scientific questions that concern one stage in an adaptive intervention. Hence, participants are randomized only once in the course of the trial.

Summary: While all SMARTs require that an investigator be interested in answering scientific questions related to an adaptive intervention, not all research related to an adaptive intervention requires a SMART. Research relating to the ***evaluation*** of an adaptive intervention may require a standard RCT, and research relating to ***only one of the stages*** in an adaptive intervention may require a singly randomized trial. In both cases, the adaptive intervention is the focus of research, but since the scientific questions do not concern the selection and integration of components ***at multiple stages*** of the adaptive intervention, a SMART should not be considered. As with any study, investigators should choose the randomized trial design based primarily on the scientific questions motivating the investigation, as opposed to choosing questions that fit a particular randomized trial design. Appendix C speaks to additional misconceptions investigators often have regarding SMART designs.

Future Directions

Because educational practice is most often conducted at multiple levels (for example, children nested within classrooms that are nested within schools), a critically important direction for future research relates to *Multi-level Adaptive Interventions*—that is, adaptive interventions that guide sequential, intervention decision-making across multiple levels. Such multi-level adaptive interventions include those in which intervention is first tailored at the level of the classroom and subsequently tailored at the level of the children within the classroom (depending on how each child responds to the classroom-level intervention). Multi-level adaptive interventions also include those in which new clusters are generated as part of an earlier intervention stage (e.g., a child is first offered a group therapy or online support network), and subsequent intervention is tailored at the level of the cluster (e.g., depending on how each group responds to therapy); here, the clusters are not preexisting, such as with classrooms or schools (Nahum-Shani et al., 2017; Nahum-Shani & Dziak, 2018).

Directions for future research include understanding and addressing challenges that might arise in the conduct of multi-level adaptive interventions, as well as in the design of studies to optimize them. Pilot studies are one approach to investigating feasibility and acceptability concerns prior to mounting a full-scale trial to optimize or evaluate a multilevel adaptive intervention (e.g., see Schoenfelder et al., 2019; Chronis-Tuscano et al., 2016; August et al., 2016; Gunlicks-Stoessel et al., 2016; and Almirall et al., 2012). These pilot studies may prove useful for understanding the challenges or limitations that may arise when employing multilevel adaptive interventions in authentic school settings. Future research should focus on making singly- or sequentially-randomized trials useful for optimizing various types of multilevel adaptive interventions, whether they involve preexisting clusters (Almirall et al., 2018a; Almirall et al., 2018b) or clusters that are generated as part of the intervention (Nahum-Shani et al., 2017; Nahum-Shani & Dziak, 2018).

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Appendixes

Appendix A. Glossary of Key Terms

This glossary defines key terms selected based on their appearance in the report and in the literature related to adaptive interventions and SMART designs.

Adaptive Intervention

An intervention design using tailoring variables to guide whether, when, or how to modify the intervention over time. When an adaptive intervention is delivered to an individual, the individual progresses through multiple intervention stages. Each stage begins with a decision point, and—at each decision point—tailoring variables are used by a decision rule to select the appropriate intervention option for the individual. An adaptive intervention includes decision points, intervention stages, tailoring variables, intervention options, and decision rules. Adaptive interventions typically do not involve randomization.

Decision Rules

Guidelines describing how information about the individual should be linked to intervention options. The decision rules pre-specify, for each decision point, what intervention option should be offered under various conditions.

Distal Outcome

The prespecified, long-term goal of the intervention.

Dynamic Treatment Regimen

This is another term for "adaptive intervention." This term is more commonly used in the statistical, epidemiological or clinical trials literature. Other terms that have been used in place of "adaptive intervention" include "adaptive treatment strategy," "treatment policy," "treatment protocol," and "treatment algorithm."

Embedded Adaptive Intervention

A prespecified adaptive intervention that is part of the SMART (i.e., embedded in the SMART), by design. Most SMARTs include a number of embedded adaptive interventions. These adaptive interventions are formalized ahead of the trial. A common research question motivating a SMART concerns the comparison of embedded adaptive interventions.

Embedded Tailoring Variable

A tailoring variable that is used as part of the design of a SMART to restrict the provision of subsequent stage intervention options.

Enhanced Nonresponder Trial

Like a nonresponder trial (see below), a design in which first-stage intervention is provided, and nonresponders are randomized to two or more intervention arms. However, unlike typical nonresponder trials, in an enhanced nonresponder trial, participants are consented to be part of the study prior to first-stage treatment, and both responders and nonresponders are followed for outcome assessments. An enhanced nonresponder trial may generate knowledge that is useful for the development of an adaptive intervention, but it is not a SMART because participants experience at most a single randomization. See Almirall et al. (2018b) for additional discussion.

Intervention Decision Point

The point in time during which an intervention decision is made.

Intervention Options

Alternatives for the type/dose of intervention that may be offered at any given intervention decision point.

Intervention Stage

A period of time following a decision point in which the individual experiences the assigned intervention option.

Non-responder Trial

One in which a first-stage intervention is provided, and nonresponders are randomized to two or more intervention arms. Typically, in a nonresponder trial, researchers do not measure outcomes for responders; only the randomized nonresponders are followed for outcome assessments. Further, typically in a nonresponder trial, participants are consented at or following the point of nonresponse. A nonresponder trial may generate knowledge that is useful for the development of an adaptive intervention, but it is not a SMART because participants experience at most a single randomization.

Prototypical SMART

A SMART where all individuals in the target population are randomized to two first-stage intervention options and then nonresponders to first-stage intervention are rerandomized to two second-stage intervention options. This is currently the most common type of SMART. Not all SMARTs will employ a prototypical SMART design; the type of SMART designed will depend on the scientific questions the investigator seeks to answer.

Proximal Outcomes

The prespecified, short-term goals the intervention is intended to impact in order to achieve the distal outcome. The proximal outcomes guide the selection of the decision points, tailoring variables, intervention options, and decision rules.

Sequential Multiple Assignment Randomized Trial (SMART)

An experimental design involving multiple stages of randomization, meaning that some or all individuals (or organizations) participating in a SMART are randomized more than once. In a SMART, the sequential randomizations can be generated upfront (e.g., prior to the beginning of first-stage treatment), rather than sequentially, but revelated in real-time. However, due to anticipatory effects, generating the randomized lists ahead of time (and attempting to keep them locked) could inadvertently influence outcomes prior to subsequent stages should research staff, intervention staff, and/or participants have knowledge of subsequent stage treatment assignments. Hence, a recommended practice is to conduct the randomization *and* reveal the assigned options in "real time," namely at their designated decision points (see Nahum-Shani et al., 2019).

Tailoring Variable

Baseline or time-varying information from the individual that is useful in deciding the type/dose of intervention at each decision point.

Unrestricted SMART

The prototypical SMART is an example of a restricted SMART in that the second-stage intervention is restricted to nonresponders only. In an unrestricted SMART, all individuals are randomized repeatedly in a way that does not depend on prior information.

Appendix B. Common Misconceptions About Adaptive Intervention Designs

Misconception #1: The same tailoring variable must be used for all individuals in an adaptive intervention.

- There is no requirement that the same tailoring variable be used for all individuals in an adaptive intervention.
- A tailoring variable (or a set of tailoring variables)—including how/when the measures that make up the tailoring variable are collected (e.g., monitoring schedule)—could differ by individual, including based on previous information about the individual.
  - Example of how the tailoring variable may differ by previous intervention: To determine how to intervene next, a child with autism who begins with an intervention that focuses on Discrete Trials Training (Smith et al., 2001) might be monitored based on the number of unique words used; whereas, a child who begins with a more naturalistic, play-based intervention such as might be monitored based on social engagement.
  - Example of tailoring frequency: individuals at higher risk for substance use relapse might be monitored more frequently for environmental risk than individuals with lower risk.

Misconception #2: An adaptive intervention must recommend a single intervention component at each level of a tailoring variable.

- There is no requirement that an adaptive intervention recommends only a single intervention component at each level of a tailoring variable.
- At any one or more decision points, an adaptive intervention could recommend a *set* of interventions (components) instead of a *single* intervention (component).
  - For example, for certain individuals at certain decision points, there may be no evidence that a single intervention (component) is better than another. In this case, the adaptive intervention may recommend a set of interventions (components).

Misconception #3: Adaptive interventions seek to replace clinical judgement.

- The goal of adaptive interventions is not to replace clinical or educational practice.
- The goal of adaptive interventions is to guide practice.
- Clinical judgement may play a role in the assessment or collection of tailoring variables.
- In cases where an adaptive intervention recommends a set of interventions (components), clinical judgement could be used to make the decision about which intervention to assign/recommend.
  - For example, consider the results of a hypothetical study which suggest that there is no evidence of a difference between increased behavioral intervention dose (+BMOD) or adding medication (+MED) among children with ADHD identified as nonresponders to initial behavioral modification. Based on these results (until additional information becomes available), an adaptive intervention might

recommend the set of both +BMOD or +MED for nonresponders, and leave the final decision up to the child, parent, therapist, or schoolteacher.

Misconception #4: Adaptive interventions are relevant only in clinical treatment practice.

- Clinical treatment practice is not the only domain that could benefit from adaptive interventions.
- Adaptive interventions are relevant in any domain where sequential (or dynamic) intervention decision-making is necessary. These include the following:
  - preventive interventions, such as those designed to reduce risky behavior;
  - education interventions, such as those targeting academic achievement or absenteeism;
  - health promotion interventions designed to encourage healthy habits; or
  - implementation interventions aimed at improving the uptake of evidence-based treatments.

Misconception #5: Adaptive interventions involve randomization.

- Adaptive interventions (typically) do not involve randomization(s)
- Adaptive interventions (typically) are prespecified interventions that use clearly articulated decision rules to link a value of a tailoring variable to an intervention (component) or a set of interventions (components).
- Randomization is used in studies that seek to develop or evaluate adaptive interventions, such as standard randomized controlled/clinical trials, enhanced (non)responder trials, or sequential multiple assignment randomized trials (SMARTs).

Appendix C. Common Misconceptions About SMART Research Designs

Misconception #1. Sample size requirements are prohibitively large, and sample size calculations for a SMART design are complicated.

- As with any trial, sample size calculations in a SMART are a function of the hypothesis tests (or estimation procedures) related to the primary aim of the SMART.
- SMART designs do not necessarily require large sample sizes or complicated sample size calculations.
- There are now a number of easy-to-use sample size calculators for data arising from a SMART, including calculators for an end-of-study continuous outcome, an end-of-study binary outcome, a continuous repeated measures outcome, a survival outcome, and for data arising from a cluster-randomized SMART.
- See Appendix D for links to online sample size calculators.

Misconception #2. All SMARTs require multiple-comparison adjustments.

- SMART designs do not necessarily require multiple-comparison adjustments.
- As with any randomized trial, multiple-comparison adjustments are required when addressing the primary research question involves testing multiple outcome measures, or multiple comparisons (e.g., two or more pairwise comparisons). SMARTs are no different in this respect.

Misconception #3. All research on adaptive interventions requires a SMART.

- Not all research on adaptive interventions requires a SMART design.
  - For example, a standard two-arm randomized trial can be used to evaluate an adaptive intervention, by comparing it to a suitable control condition.
- SMARTs are just one type of research design (experimental design) that researchers can use to build (rather than evaluate) adaptive interventions. Other designs are possible. For example, researchers could use an enhanced nonresponder trial, which is not a SMART, (Almirall et al. 2018b) to inform the development of adaptive interventions by examining how best to treat nonresponders to an initial intervention.

Misconception #4. All SMARTs must include an embedded tailoring variable.

- SMARTs do not have to include an embedded tailoring variable.
- An unrestricted SMART design is often used in situations when there is no scientific, practical, or ethical rationale for embedding a tailoring variable as part of the SMART.
  - For example, researchers may use an unrestricted SMART design to (1) randomize all participants to two intervention options at stage 1 and (2) rerandomize all participants to two intervention options at stage 2. In this example, the choice of stage 2 intervention is not dependent on characteristics of the participant, the choice of assigned stage 1 intervention option, or any outcomes to stage 1 intervention.

Misconception #5. All aspects of an adaptive intervention must be randomized in a SMART.

- Not all aspects of an adaptive intervention require randomization in a SMART (or in any study of adaptive interventions).
- As with any randomized trial, a single SMART study might answer only a handful of questions related to the development or evaluation of an adaptive intervention.
  - For example, consider a SMART that examines how best to intervene with children with autism who are slow-responders to a naturalistic intervention without a device (by randomizing these children to two intervention options) but does not randomize children who are slow-responders to the naturalistic intervention with a device (these children all received intensified intervention).

Misconception #6. SMARTs never include a control group.

- A SMART may be designed to include a suitable control group.
  - For example, one of the adaptive interventions embedded in a SMART might represent "business as usual" which would serve as a suitable control.

Misconception #7. SMARTs require multiple consents.

- SMARTs differ from standard trial designs in that a participant may be randomized multiple times. Multiple randomizations, however, do not mean that a separate consent is required at each randomization point.
- As with any randomized trial, we recommend SMARTs employ a single study consent protocol with all participants prior to the initial randomization. We view consent as a study-specific procedure; not a randomization-specific procedure. Of course, the study consent protocol would include informing participants of all possible sequences of intervention components the participant might be assigned to during the course of the study.
  - For example, consider a SMART that (1) randomizes children with ADHD to initial behavioral modification (BMOD) vs initial medication (MED), (2) continues initial intervention for children who are not identified as nonresponders, and (3) rerandomizes nonresponding children to increased intervention vs. combined BMOD+MED. In this study, parents/children consent once, up front (i.e., prior to the first randomization) to being part of the entire study (both stages of intervention) and to the possibility of receiving one of the four embedded adaptive interventions.

Misconception #8. SMARTs are susceptible to high levels of participant attrition.

- SMARTs are no more likely to produce high levels of participant attrition than standard randomized trial designs (Moodie, Karran, & Shortreed, 2016).

Misconception #9. All intervention options randomized in a SMART must be evidence-based.

- SMARTs do not require that all intervention options to which individuals are randomized be evidence based (i.e., shown to be efficacious in prior efficacy research), although in practice this is sometimes the case.

- In many cases, investigators may be interested in examining the effect of intervention options that are critical to building a high-quality adaptive intervention but that would never be studied/evaluated on their own.
  - For example, consider a SMART that randomizes individuals to different options for monitoring the individual for response vs nonresponse (and then also subsequently rerandomized responders or nonresponders). It would be unlikely that previous trials have examined what is the best way to monitor individuals for response vs nonresponse in isolation.

Appendix D. Useful Links

Recommended List of Introductory Readings for Adaptive Interventions and SMART

https://methodology.psu.edu/ra/adap-inter/bib

List of Known SMART Projects (with Schematics) up to 2016

https://methodology.psu.edu/ra/adap-inter/projects

Sample Size Calculator for SMARTs with Binary or Continuous Outcome

https://nseewald1.shinyapps.io/SMARTsize/

Incomplete List of Additional Software to Analyze Data Arising from SMARTs

Software suite, including SAS PROC QLEARN and qlaci for R:
https://methodology.psu.edu/downloads

DTRreg for R:
https://www.jstatsoft.org/article/view/v080i02

qLearn for R:
https://cran.r-project.org/web/packages/qLearn/qLearn.pdf

DynTxRegime for R:
https://cran.r-project.org/web/packages/DynTxRegime/DynTxRegime.pdf

iqLearn for R:
https://cran.r-project.org/web/packages/iqLearn/iqLearn.pdf

Decision Lists for R:
https://cran.r-project.org/web/packages/listdtr/listdtr.pdf

Appendix E. Other Example SMART Studies in Education

In the main body of this report, the Childhood ADHD SMART (Study 1) was used to illustrate ideas. In this Appendix, we describe two additional example SMARTs in education (Studies 2-3) that differ in their design features from the childhood ADHD study, which we refer to here as Study 1. Our goal is not to provide a detailed account of each study. Rather, our goal is to illustrate variety in design possibilities. For each SMART, we provide the study's overarching goal, discuss the intervention options considered, discuss important design considerations, list the specific questions, and describe the study flow. We also summarize how Studies 1, 2, and 3 differ from each other.

Study 2 aims to develop an adaptive intervention for minimally verbal children with autism spectrum disorders (ASD) and Study 3 focuses on developing an adaptive school-based implementation of cognitive behavioral therapy (CBT).

Study 2: Adaptive Interventions for Minimally Verbal Children With ASD

Study 2 differs from the childhood ADHD study (Study 1) in important ways:

- In Study 2, both responders and slower responders are rerandomized at the beginning of stage 2; whereas in Study 1 only nonresponders are rerandomized.
- In Study 2, the stage 2 randomization occurs at a fixed time point—early responders and slow responders were rerandomized at week 6—whereas, in Study 1 the stage 2 randomization could occur at different time points, depending on when the child triggers a nonresponse based on monthly ratings.
- Study 2 includes eight embedded interventions, two of which are not adaptive (always JASP and always DTT). In contrast, all four embedded interventions in Study 1 are adaptive.

Study Goal: An estimated 30-40 percent of school-aged children with ASD remain minimally verbal even after receiving years of interventions. Little is known about minimally verbal children with autism because they are often excluded from research studies. The overarching goal of this NIMH-funded study (PI: Kasari) is to build the most effective 16-week, two-stage, adaptive intervention involving four intervention options (explained below).

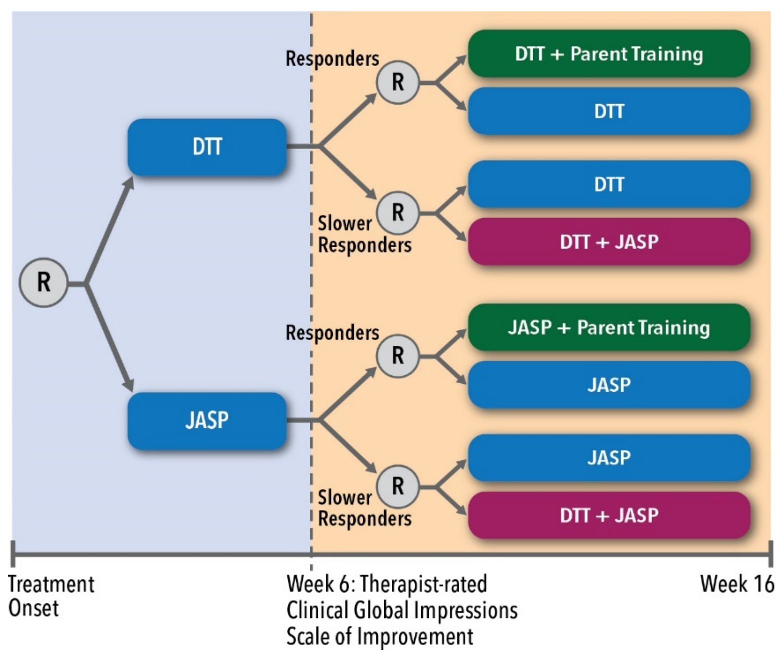
Intervention Options: A number of intervention options are available that could help improve social communication in these children: Discrete trials training (DTT; Smith et al., 2001) is an intervention that is based on the principles of applied behavior analysis. In DTT, communication and related skills (e.g., sounds, gestures, or words) are taught through systematic adult therapist-led direct instruction. Joint attention symbolic play and emotional regulation combined with enhanced milieu training (JASP for short; Kasari et al., 2014) is a developmentally anchored behavioral intervention which assumes that communication skills develop from social interactions. In JASP, specific social engagement strategies, symbolic representations, and early communication forms are modeled and naturally reinforced by adult therapist responses to the child. Another option is blended JASP+DTT that combines aspects of the two interventions in the context of a single therapy session. A final promising intervention option is parent training (PT; Kaiser, Hancock, & Trent, 2007), in which the child's primary therapist coaches the child's parent (or guardian) in skills related to JASP or DTT with the goal of promoting improvement in social communication in the home environment.

Intervention Design Considerations: Both JASP and DTT are evidence based, with core principles of DTT generally considered to be the "standard of care." Except for PT, which takes place in the child's home, all interventions in this study take place before or after hours at the child's elementary school. Due to the cost of delivering PT in the home and its conjectured role as an intervention designed to "generalize" intervention gains beyond the school, PT is considered feasible only as a second-stage intervention for children showing early signs of response (defined below). The blended intervention option JASP+DTT is also costly since its delivery requires a highly skilled therapist trained in principles of both JASP and DTT. Given JASP+DTT's cost and its conjectured role as an intervention designed to accelerate improvements in children who are not responding quickly enough (if at all), JASP+DTT is considered feasible only as a second-stage intervention for children showing slow response (defined below).

Specific Questions: The study was motivated by the following questions: (1) Is it better to begin intervention with JASP vs. DTT (primary question)? (2) For children who show early signs of response to the intervention, is it better to add parent training or continue the initial intervention? (3) For children who show early signs of slow response, is it better to offer combined JASP+DTT or continue with the initial intervention? The primary outcome is a blinded measure of change in spontaneous socially communicative utterances from baseline to week 16.

SMART Design: Figure 9 shows a schematic of Study 2. At baseline, children are randomized (with equal probability) to either JASP or DTT as first-stage intervention. After approximately 6 weeks of stage 1 intervention, early response versus slow response status is measured using the therapist-rated, seven-item Clinical Global Impressions-Improvement scale (CGI-I ≥ 3 to 7 are considered slower responders; Guy, 1976) adapted for use with children with ASD. In stage 2, early responders to each

Figure 9: Adaptive intervention for minimally verbal school children with ASD SMART study



intervention are randomized (with equal probability) to continue their initially assigned intervention versus augmented intervention that involves PT. In stage 2, slower responders to each intervention are randomized (with equal probability) to continue their initially assigned intervention versus an augmented intervention that combines JASP and DTT.

Study 3: Adaptive School-Based Implementation of CBT

Study Goal: Depressive and anxiety disorders affect 20-30 percent of school-age youth. Cognitive behavioral therapy (CBT; Ginsburg et al., 2008) can improve outcomes in these disorders and ultimately lead to improved school performance. Students access mental health services at schools more than anywhere else, but school professionals (SPs; e.g., school counselors, school social workers) are generally not trained to deliver CBT, or they experience other barriers that limit providing effective CBT to students. The overarching goal of this NIMH-funded study (PI: Kilbourne) is to build the most effective 15-month, 3-stage, school-level adaptive implementation intervention involving three distinct implementation strategies (known as Replicating Effective Programs (REP; Kilbourne et al., 2007), Coaching, and Facilitation) to improve the uptake of CBT by SPs at schools.

> Study 3 differs from Studies 1 and 2 in important ways:
>
> - In Studies 1 and 2, the goal was to develop individual-level adaptive interventions to improve individual-level outcomes. In contrast, in Study 3 the goal is to develop a school-level adaptive intervention to improve the outcome of school professionals within schools. As a result, Study 3 is a clustered SMART, i.e., schools are the unit of randomization but the outcome is at the SP-level.
> - In Study 3, the primary aim compares an adaptive intervention versus a nonadaptive intervention: namely, the costliest embedded intervention (offer REP+Coaching in stage 2, continue REP+Coaching in stage 3 to responding schools, and offer REP+Coaching+Facilitation in stage 3 to sub-optimally responding schools) versus the least expensive embedded intervention (offer REP alone at all stages).

Intervention Options: A number of school-level intervention options are available that could help schools implement CBT and therefore improve mental health outcomes of its students in need of mental health services. They vary in terms of intensity, cost, and theoretical foundation: REP combines customized CBT packaging, didactic training, and technical support to improve CBT uptake by the SP. Coaching (Beidas et al., 2012) extends training via live supervision to improve the SP's competence and acceptance. Facilitation (Kilbourne et al., 2015) is used to mentor SPs in strategic thinking to promote self-efficacy in championing the use of CBT and securing administrator support at the school.

Intervention Design Considerations: Schools receive training on identifying schoolchildren with depressive and anxiety disorders who could benefit from CBT as part of the didactic in-person training component within REP. Coaching is considered feasible only after SPs at the school have had ample time to identify students in order to facilitate live supervision of CBT delivery. This consideration provided the rationale for possibly offering coaching at stage 2, which is 2 months following the start of REP. Facilitation is not considered feasible during stage 1 or stage 2 because it is designed to address prolonged barriers (i.e., processes that require ample time to become visible), such as lack of self-efficacy in championing the use of CBT. In addition, facilitation is not considered feasible for schools that already were responding (defined below) by the end of stage 2, thus providing the rationale for possibly offering facilitation at stage 3, following the start of stage 1 REP and the possibility of coaching in stage 2.

Specific Questions: The study includes two adaptive and two nonadaptive implementation interventions. The most intensive study intervention is an adaptive intervention that offers all schools (1) REP in stage 1, (2) REP+coaching in stage 2, (3) continued REP+coaching in stage 3 for schools that do not require additional assistance following stage 2 intervention (defined below), and (4) REP+coaching+facilitation in stage 3 for schools that require additional assistance following stage 2 intervention. The least intensive study intervention is one that offers REP alone for 15 months. The study was motivated by the following questions: (1) What is the effect of the most intensive adaptive implementation intervention versus offering REP alone (primary question)? (2) Does the effect of REP+coaching vs. REP alone in stage 2 differ depending on school-aggregated SP factors pertaining to perceptions of CBT or prior training in CBT? (3) Does the effect of augmenting with facilitation vs. not in stage 3 differ depending on satisfaction with stage 2 implementation support or CBT delivery during stage 2? The primary outcome is the total number of CBT sessions delivery by SPs over the course of 18 months.

SMART Design: Figure 10 shows a schematic of Study 3. A total of 114 high schools (including more than 200 SPs) received REP for 2 months in November to December 2018 (stage 1). After 2 months, schools were randomized with equal probability to continue REP or to augment REP with coaching (stage 2). At the end of 2 additional months, suboptimally responding schools (defined as at least 1 SP at the school delivered CBT to 10 or fewer students) are rerandomized to continue with their previously assigned implementation strategy or to augment with facilitation (stage 3). Stage 3 intervention continues for a total of 11 months. The total duration of intervention for all schools is 15 months. Months 16-18 constitute a 3-month research follow-up period (no intervention).

Figure 10. Adaptive school-based implementation of CBT SMART study