STUDY DESIGNS

IN BIOMEDICAL RESEARCH

Personalized Medicine:

ADAPTIVE DESIGN: SMART TRIALS

ADAPTIVE CLINICAL TRIALS

An adaptive clinical trial is a clinical trial that evaluates a treatment (or treatments) by *observing participant outcomes (accumulating data)* on a *prescribed schedule,* and *modifying parameters* of the trial protocol in accord with those observations.

The trial protocol is set *before* the trial begins and pre-specifies the adaptation schedule and processes.

The general goal of an adaptive clinical trial is **to learn quickly from accumulating data and to apply what is being learnt** as quickly as possible – in the same trial.

Key Word: “rolling”

An adaptive clinical trial is adaptive *by design*; adaptation is a *prospective* feature.

It is not a post hoc remedy for poor planning in the conduct and analysis of a trial. It is not a way to salvage a study that is not going as planned.

There are different forms of adaptation – including changing sample size, but the more visible one in recent years is modifying/changing intervention during trial.

Reasons for considering adaptive interventions:

1. Patients may vary in their response to treatment.
2. The effectiveness of intervention may change over time.
3. The presence of, or evolving, comorbidities.
4. Relapse.
5. Side effects (intensity of the treatment is reduced).
6. Difficulties in maintaining adherence to interventions.

Four key elements

1. **Sequence of decisions regarding patient care**
   - ✓ **Most interventions require *decisions* such as, "If the patient is unresponsive to the initial treatment, what treatment should we provide next?" or "Once the patient has stabilized, what treatment is needed to prevent relapse?“**
2. **The set of treatment options at each decision point**
   - ✓ **For example, if a patient is unresponsive to a drug, should the dosage be increased, should the drug be discontinued, or should counseling be increased? These are *treatment options*.**

3. **Tailoring variables**

- ✓ **These are the factors used *to trigger a change in the treatment.* These can be things like early signs of nonresponse, manifestation of side effects, or environmental or social characteristics. The idea is to identify the variables that best indicate when the appropriate treatment has to be changed.**

4. **A sequence of decision rules**

- ✓ **This links the first three components. There should be one decision rule per decision. The tailoring variables provide information about which of the treatment options is most appropriate for the patient at the time of the decision.**

Adaptation could take different forms and could be implemented in any phase of clinical trials; one of a new but popular one is the SMART trial.

SMART is S.M.A.R.T.

- S – Sequential
- M – Multiple
- A – Assignment
- R – Randomized
- T – Trial

For many individuals, substance abuse – for example - possesses characteristics of chronic disorders in that individuals experience repeated cycles of cessation and relapse. Viewing drug dependence as an "chronic", relapsing disorder is increasingly accepted and effective treatment strategies are desirable for managing the variable course disorder.

There are circumstances for substance abuse and other chronic diseases where:

(1) There are more than one treatments which might work but none stands out nor dominating,

(2) Some subjects might be successfully treated once but other subjects might need more than one regiment; successful ones might relapse.

Therefore, strategies are needed to individualize treatment via decision rules that recommend when and how treatment should be changed. Recommendations are based on patient characteristics and outcomes collected during treatment such as patient response or progress and adherence.

The development of adaptive treatment strategies requires consideration of the ordering of treatments, the timing of changes in treatment, and the use of measures of response, burden, and adherence collected during treatment to make further treatment decisions. The sequential multiple assignment randomized trial (SMART) is a newer such adaptive treatment strategy. It retains the most basic element of conventional experiment design: the randomization. Subjects are often randomized multiple times.

In addition to substance abuse, a number of SMART trials have also been conducted to deal with Depression (Lavori et al. 2001, Rush et al. 2003) , Alzheimer (Schneider 2001), Cancer (melanoma, Freda et al. 2009), and Autism (Kasari et al. 2014).

As a detailed illustration, we start with a trial for Smoking Cessation conducted locally (U of M).

Clinical trials have demonstrated the efficacy of behavioral, pharmacological, and combination treatment strategies for smoking cessation; but researchers have focused on evaluating "one-time" treatment strategies delivered in isolation. Results? These treatments yield low rates of long-term abstinence – in the range of 5%-20% depending on the population of smokers and the type and intensity of treatment.

Treatments of mental health problems have very similar poor long-term results (therefore, there have been several SMART to evaluate and form mental health treatment programs).

That leaves practitioners with frustration of scant guidance on how to manage smoking cessation treatment over time, especially on how to "tailor" therapy based on patients' response to initial treatment which maybe different from patient to patient. An "adaptive intervention" is desirable; and SMART was considered. The goal is to prove that chronic care is more effective than episodic care.

Setting:

Investigators recruited subjects from two Lung Cancer Screening Programs, one at the University of Minnesota and one at the Minneapolis VA Medical Center. These are older (aged 55-79) current daily smokers with a smoking history of 30 pack-years or greater who were willing to choose a quit day within the next 12 months. Some exclusion criteria applied; for example, psychotic disorders or depression.

The pack-year is a unit for measuring the amount a person has smoked over a long period of time. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For example, 1 pack-year is equal to smoking 20 cigarettes (or 1 pack) per day for 1 year, or 40 cigarettes per day for half a year, and so on. One pack-year is the equivalent of 365.24 packs of cigarettes or 7,305 cigarettes.

OVERALL DESIGN PLAN:

1) Subjects will be randomized the first time into 2 subgroups receiving different “first-line treatments”; actually, it’s the same treatment (very standard counseling plus nicotine replacement therapy – only different lengths.
2) At the end of first-line treatment, depending on the outcome, each will be randomized the second time receiving subsequent “second-line treatments”

First Randomization:

All participants will receive a first-line treatment starting with the quit date. First randomization will occur at baseline ("R1", into group A or B) when participant selects a quit date; however, the participant and the counselor will be blinded to treatment assignment until 4 weeks later.

First-line treatment for Group A will last 4 weeks; at this time, depending on the result of the first-line treatment, subjects will receive second randomization. First-line treatment for Group B will last 8 weeks; after that, subjects will receive their second randomization, also depending on the result of the first-line treatment.

First-line Treatments:

This is the conventional one-time treatment for all participants. It consists of 4 or 8 weeks of counseling with nicotine replacement therapy (NRT); key element is the length. NRT maybe monotherapy (patch, gum, lozenge) or combination therapy (patch + gum, patch + lozenge). Subjects receive periodic calls; call contents include problem-solving, skills training, and social supports. Results are classified as complete responders (success) or incomplete responders (failure; any smoking after quit date).

Subsequent or second-line Treatments:

After the first-line treatment, subsequent treatments include Tobacco Longitudinal Care (TLC) and Medication Therapy Management (MTM), an rather intensive pharmacological treatment. The total intervention program will be 12 months regardless of randomized treatment group and regardless of transitional outcomes.

Tobacco Longitudinal Care (TLC) is a well-established care model for tobacco treatment. It is a 12-month program – regardless of outcomes; there are 2 versions for which calls are made every 3 months (**TLC-Quarterly**) or every month (**TLC-Monthly**)

Medication Therapy Management (MTM) is an intensive pharmacological treatment. Its services expands the toolbox available in TLC to include in-person consultation with a pharmacist, the prescription drugs Bupropion or Varenicline, or combination medications (NRT + Bupropion).

Second Randomization:

1) Complete responders from first-line treatment, regardless of which group they were in, will be randomized to receive either TLC-monthly or TLC-quarterly.

2) Incomplete responders from first-line treatment, regardless of which group they were in, will be randomized to receive either TLC-quarterly or MTM (Medication Therapy Management)

Primary Outcome:

The primary (binary) outcome for all analyses will be whether or not smokers achieve 6-month prolonged abstinence measured at 18 months after the baseline assessment. All analyses will be governed by the "Intent-to-Treat" principle.

Primary Specific Aim:

Among incomplete responders, long-term abstinence rates will be higher in smokers randomized to TLC + MTM compared to TLC (that is TLC + TLC).

There are also some secondary Specific Aims; for example:

(1) The length of the first-line treatment: 4 weeks versus 8 weeks

(2) The frequency of calls: TLC-monthly versus TLC-quarterly

The analysis for each aim could be simple, say, a Chi-square test, But, except for the primary Specific Aim, tests for other aims should subject to multiple decision adjustment

RATIONALE FOR STUDY DESIGN

Further pharmacological treatment, in this study represented by MTM, requires pharmacy personnel with specialized clinical skills and training, face-to-face contact, and additional patient burden and expense. **The Primary Aim will answer the important question of whether the additional benefit provided by a more complex clinical treatment model** is sufficient to offer it on the large scale afforded by attendance at lung cancer screening programs.

Summary:

(Conventional) Clinical Trials evaluate (one-time) treatments whereas SMART's evaluate "treatment programs" which, in many cases, would be more useful for real life practices. The two key words are "sequential" and "multiple" – and randomization.

Summary:

In this particular case of a study to form a smoking cassation program, results of this SMART would help to form guidance covering: (1) optimal length of the first-line treatment, and (2) optimal choice of a subsequent treatment depending on the outcome of the first-line treatment appropriate for each subject.

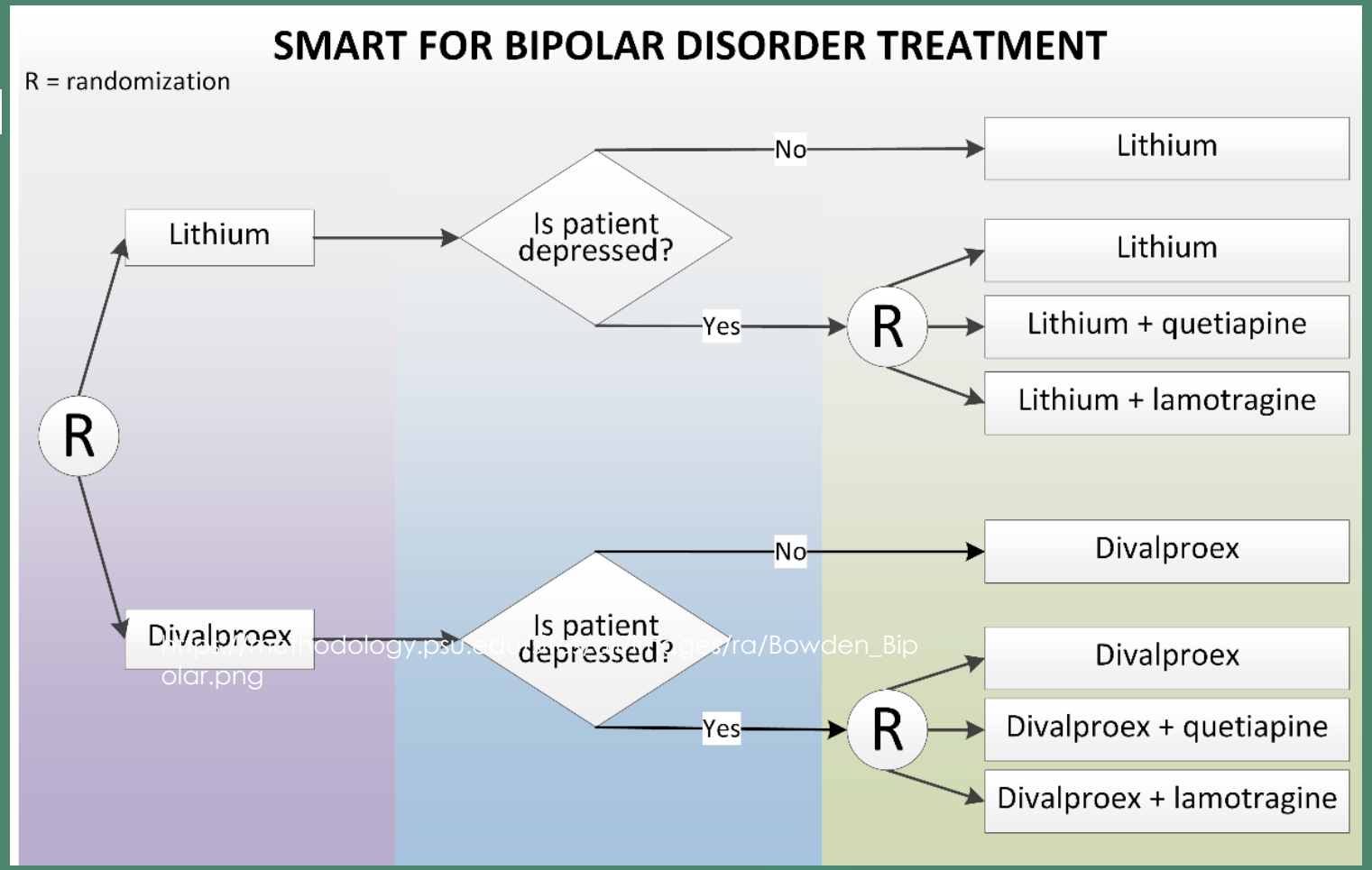
Major Goal of SMART

The main goal of SMART Design is to answer scientific questions holistically and rigorously (i.e. randomized):

(1) SMART trials typically consist of two phases; treatment assigned on phase II depends on the result of Phase I by separate randomizations.
(2) SMART trials focus on the order and the timing in which treatments are administered to individuals in the trial.

The Sequential Multiple Assignment Randomized Trail (SMART)

Example #2 (Bipolar Disorder): The Sequential Multiple Assignment Randomized Trial (SMART) provides high-quality data that can be used to construct adaptive interventions.



The SMART Design: A Summary

- In a SMART there is a separate stage for each of the critical decisions involved in the adaptive intervention.
- At each stage, all participants are randomly assigned to treatment options. By randomizing participants multiple times, scientists can assess *the effectiveness of each stage.* So, *several adaptive interventions are embedded* within each SMART design for testing.

Example #3: ADHD; SMART study in which rerandomization to the second-stage intervention options depends on an intermediate outcome

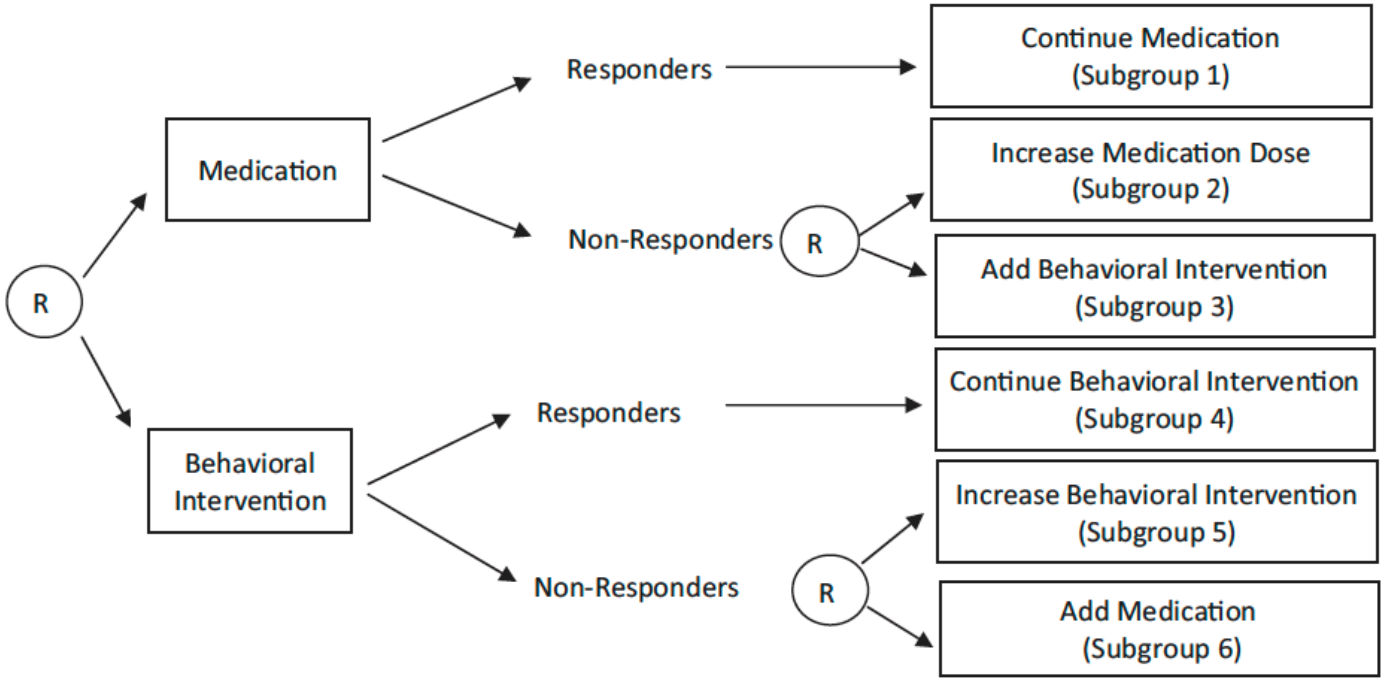


Figure 1. Sequential multiple assignment randomized trial for attention-deficit/hyperactivity disorder (ADHD) study.

Nahum-Shani, I., Qian, M., Almirall, D., Pelham, W. E., Gnagy, B., Fabiano, G. A., . . . Murphy, S. A. (2012). Experimental design and primary data analysis methods for comparing adaptive interventions. *Psychological Methods, 17*(4), 457-477. http://dx.doi.org/10.1037/a0029372

In examples 2 and 3, unlike example 1, the second randomization applied only to non-responders of the first-line treatment which is very common because responders do not need to change treatment.

Example #4: MELANOMA

This study shows a different design feature in the second randomization.
There are two treatment phases, each lasts 6-8 weeks. In the first randomization, subjects were randomized to two different first-line treatments; those failed first-line treatment were randomized either to the other treatment (switch) or the combined therapy.

Randomized PHASE I

- First-line Interventions: Escitalopram or MPH
- Participants are classified as either a “remitter” or a “non-remitter” after Phase I treatment
  - Remitter – Experience a remission of neurobehavioral symptoms
  - Non-remitter – Do not experience a remission of neurobehavioral symptoms
- Participants undergo treatment for 6- 8 weeks

Randomized PHASE II

Participants also undergo treatment for 6- 8 weeks:

(1) Remitter patients from phase I receive the same treatment in Phase II, not randomized (similar to Examples 2 and 3)

(2) Non-remitter patients who received Escitalopram during Phase I, will be randomly allocated to either MPH (switch) or MPH + Escitalopram (combination); Non-remitter patients who received MPH during Phase I, will be randomly allocated to either Escitalopram (switch) or MPH + Escitalopram (combination)

AIMS AND STATISTICAL ANALYSES

- Comparing First-Stage Intervention Groups
- Comparing Second-Stage Intervention Options
- Identifying the best “Treatment Program”

Primary and secondary specific aims are set by investigators. No new/fancy methods are needed; still conventional ones: t-test, Chi-square test, ANOVA, and Regression. Sample size is determined based on a chosen primary aim.

EXAMPLE #5:

Communication Intervention for Minimally Verbal Children With Autism: an Application of SMART

Kasari, Connie, et al. “Communication Interventions for Minimally Verbal Children With Autism: A Sequential Multiple Assignment Randomized Trial.” *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 53, no. 6, 2014, pp. 635–646.

Background

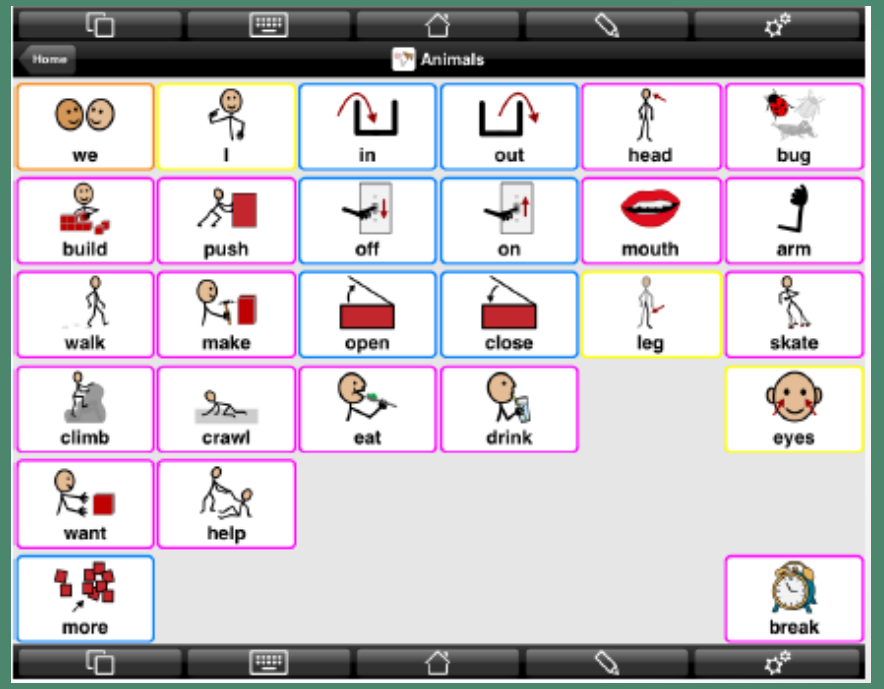
- **Communication impairment** is a core deficit in children diagnosed with autism spectrum disorders (ASD)
- Approximately 25% to 30% of children with ASD remain minimally verbal even after years of intervention
- Given low motivation for social communication, early intervention may be insufficient to initiate the social process of communication
- The problem (incidence and prevalence) is growing and new approaches are needed that address critical deficits for this very heterogeneous population of children

Three Current Interventions

- Joint Attention, Symbolic Play and Emotion Regulation (JASP)
  - focused on the development of prelinguistic gestures and play skills within the play-based interactions

- Enhanced Milieu Teaching (EMT)
  - used responsive interaction and systematic modeling and prompting to promote spontaneous, functional spoken language

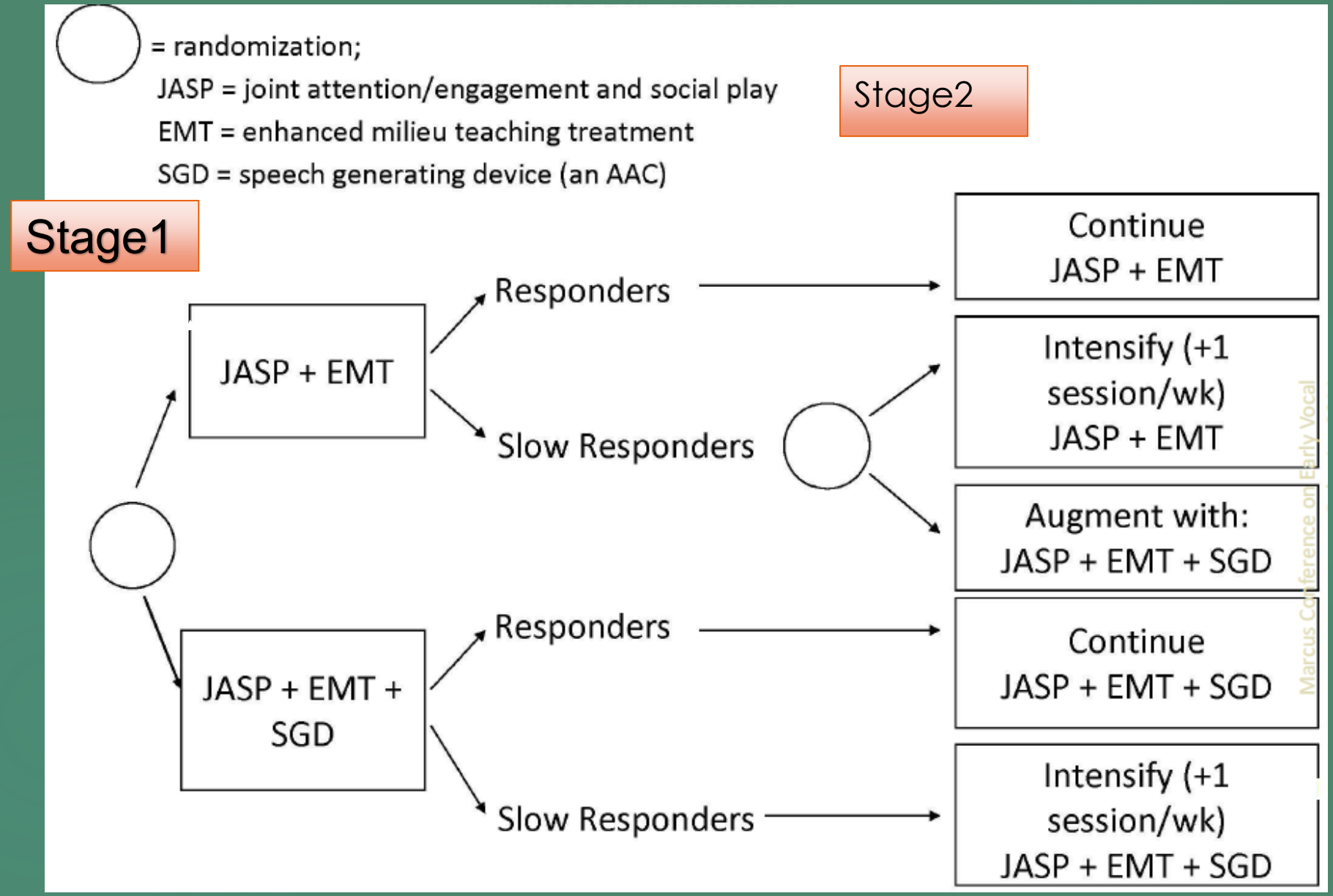
- Speech Generating Device (SGD)
  - display symbols that produce voice output
    communication when selected



Objective of the Study

- To construct and systematically test an adaptive intervention that used JASP+EMT and varied the addition of an SGD with minimally verbal school-aged children
- Primary aim of SMART: main effect of stage 1 treatment (JASP+EMT+SGD) versus (JASP+EMT)
- Secondary aim of SMART: comparison of embedded adaptive interventions

- A longitudinal (repeated outcome measures at baseline and weeks 12, 24 and 36), 3-site SMART design
- Study participants are 61 minimally verbal children diagnosed with autism
  - 51 males; 10 females
  - 48% white, 23% African American, 19% Asian American, 5% Hispanic, 5% other



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Comparisons

- **Primary:**

  JASP + EMT (spoken) vs JASP + EMT + SGD at

  12, 24, 36 weeks

- **Secondary:**

  JASP + EMT followed by Intensified JASP + EMT

  JASP + EMT followed by JASP + EMT + SGD

  JASP + EMT + SGD followed by Intensified JASP + EMT + SGD

New design feature:
Repeated measurements

More Comprehensive Statistical Analysis

- Outcome variables:

  - Total Social Communicative utterances (TSCU)

  - Total Number of Different Words (TNDW)

  - Total Comments (TCOM)

- The planned sample size was based on the primary aim using the primary outcome TSCU

- Included covariates:

  Age, gender, ethnicity, ADOS score and site

- Longitudinal regression models were used to examine mean differences in the primary outcome and secondary outcomes between the 2 stages (JASP+EMT+SGD) versus JASP+EMT) at weeks 0, 12, 24, and 36.

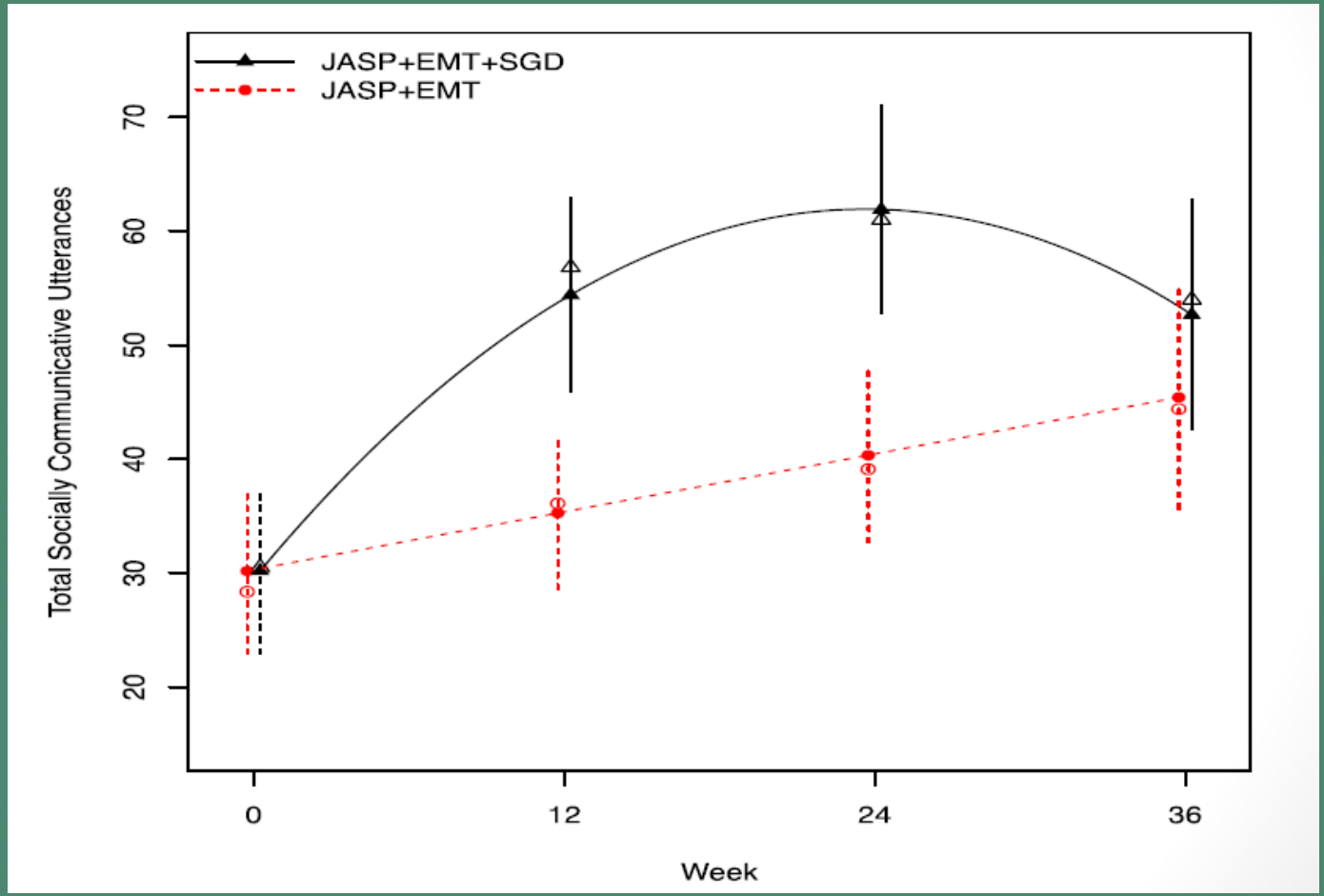
Result:

	Baseline			12 weeks			Treatment Responders
	TSCU	TNDW	TCOM	TSCU	TNDW	TCOM	
JASP+ EMT	28.4	16.8	7.0	35.3	24.3	8.1	62.2%
JASP + EMT + SGD	30.5	17.6	5.1	54.4	33.1	14.1	77.7%
(difference)				19.1	8.8	6.0	15%
Effect Size				.57	.34	.51	
P value	NS	NS	NS	.00	.00	.00	0.20 NS

Social communicative utterances (TSCU), Number of different word roots(TNDW) and number of comments (TCOM)were derived from a naturalistic language sample with a blinded clinician

Good outcome!

Results



Long-term? Gap is narrowing!

Conclusions

- Interventions with the SGD was superior in producing more spontaneous communicative utterances than interventions with the blended intervention and spoken language only.
- 1 of the first studies that show increases in spontaneous communication with different types of words and functions beyond requesting.
- However, long-term effects are not very clear.

Summary: Advantages of SMART

- Increased validity of analyses aimed at discovering when the effect of one intervention is enhanced by subsequent or prior interventions
- Increased validity of analyses aimed at discovering useful tailoring variables
- Increased ability to reduce the impact of cohort effects.
- Provide high-quality data for the construction of adaptive interventions

SMART trials help advance research in many areas in the behavioral and social sciences; popularity is on the rise. Applications in cancer research start show up in recent years.

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