Getting SMART about Combating Autism with Adaptive Interventions: Novel Treatment and Research Methods

1. Introduction to Sequential Multiple Assignment Randomized Trials and Adaptive Interventions: Two Case-studies in Autism
Daniel Almirall, University of Michigan

2. A SMART Approach to Increasing Communication Outcomes
Ann Kaiser, Vanderbilt University

3. Modularized Evidence-based Clinical Decision-Making: A Rescue Protocol for Non-responders
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4. Adaptive Interventions for Peer-related Social Skills: Identifying Patterns Indicating Need for Treatment Change
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Discussion Roger Bakeman, Georgia State University

Sequential Individualized Treatment Often Needed in ASD

- Intervention in autism often entails a sequential, individualized approach whereby treatment is adapted and re-adapted over time in response to the specific needs and evolving status of the individual.
- This type of sequential decision-making is necessary when there is high level of individual heterogeneity in response to treatment.
  - e.g., what works for one child may not work for another
  - e.g., what works now may not work later
- Adaptive interventions help guide this type of individualized, sequential, decision making

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Developing Adaptive Interventions for Children with Autism who are Minimally Verbal: Two SMART Case Studies

Daniel Almirall, Connie Kasari*, Xi Lu,
Ann Kaiser,** Inbal N-Shani, Susan A. Murphy

Univ. of Michigan, *Univ. of California Los Angeles, **Vanderbilt Univ.

International Meeting for Autism Research
Atlanta, GA

Outline

- Adaptive Interventions and SMART Studies in Autism
- SMART Case Study 1 (this trial is completed)
  - The Study Design
  - Some Challenges in the Conduct of the SMART
  - Analysis and Results
- SMART Case Study 2 (this trial is in the field)
  - The Study Design
  - A Story on Why the Design Was Changed
- Summary and conclusions

Adaptive Interventions and SMART, briefly

Definition of an Adaptive Intervention

- Adaptive Interventions (AI) provide one way to operationalize the strategies (e.g., continue, augment, switch, step-down) leading to individualized sequences of treatment.

- A sequence of decision rules that specify whether, how, when (timing), and based on which measures, to alter the dosage (duration, frequency or amount), type, or delivery of treatment(s) at decision stages in the course of care.

Example of an Adaptive Intervention in Autism (Some Background First...)

- $\geq$50% of children with autism who received traditional interventions beginning at age 2 remained non-verbal at age 9 years of age.
- Failure to develop spoken language by age 5 increases likelihood of poor long-term prognosis of adaptive functioning

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- One promising, non-traditional behavioral intervention for improving spoken language is Joint Attention and Symbolic Play with Enhanced Milieu Training (JASPER-EMT or "JASP" for short).

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- One promising, non-traditional behavioral intervention for improving spoken language is Joint Attention and Symbolic Play with Enhanced Milieu Training (JASPER-EMT or "JASP" for short).
- Another promising approach is the use of Augmentative or Alternative Communication (AAC) devices. However, AAC's are costly, burdensome and not all children may need it. There is essentially no (rigorous) research in this area—despite all the rave!

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- One promising, non-traditional behavioral intervention for improving spoken language is Joint Attention and Symbolic Play with Enhanced Milieu Training (JASPER-EMT or "JASP" for short).
- Another promising approach is the use of Augmentative or Alternative Communication (AAC) devices. However, AAC's are costly, burdensome and not all children may need it. There is essentially no (rigorous) research in this area—despite all the rave!

The above provides motivation for considering the development of an adaptive intervention involving AAC's in context of JASP among older, minimally-verbal children with autism.

Example of an Adaptive Intervention in Autism

For minimally verbal children with autism spectrum disorder

- Stage One JASP for 12 weeks;
- Stage Two At the end of week 12, determine early sign of response:
  - IF slow responder: Augment JASP with AAC for 12 weeks;
  - ELSE IF responder: Maintain JASP for 12 weeks.

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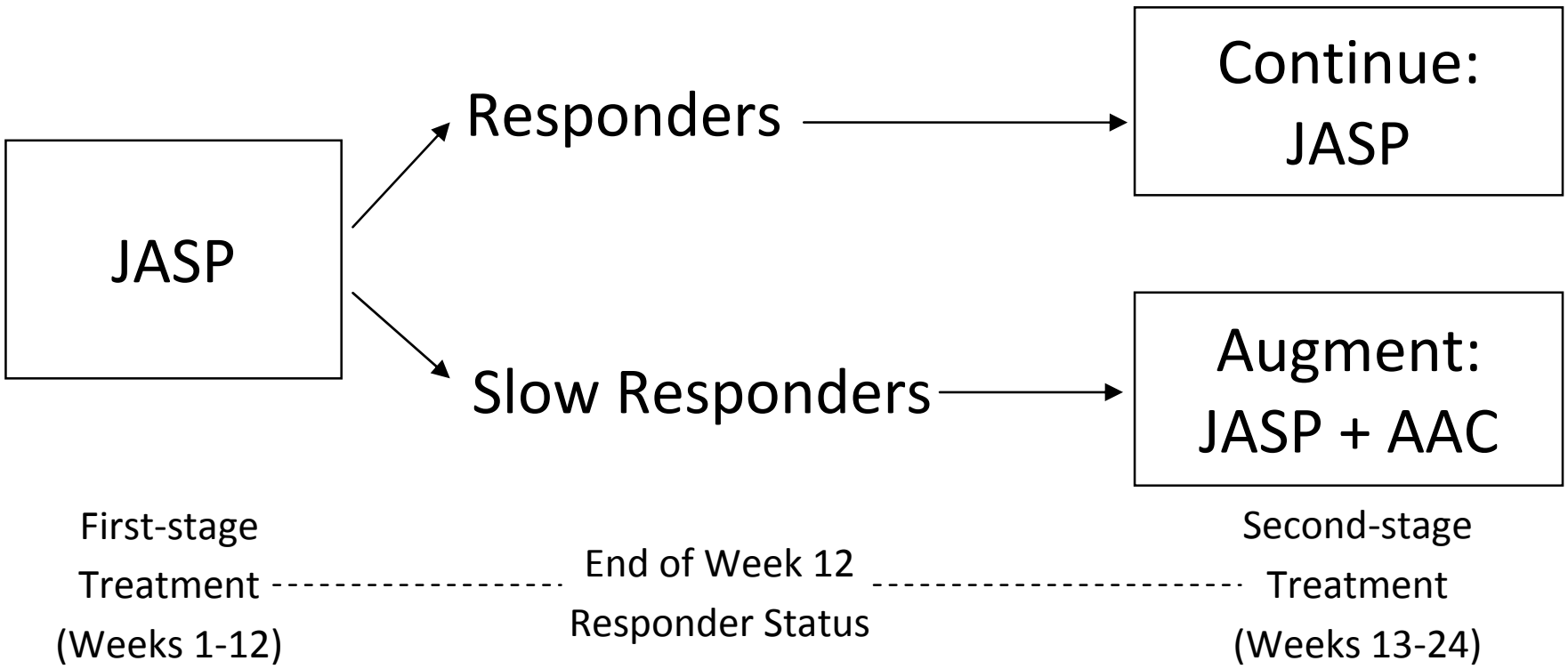

How was response/slow-response defined?

- Percent change from baseline to week 12 was calculated for 7 variables:
- 7 variables: socially communicative utterances (SCU), percent SCU, mean length utterance, total word roots, words per minute, total comments, unique word combinations

- Responder: if $\geq$25% change on $\geq$7 measures;
- Slow Responder: otherwise (includes kids with no improvement)

Many Unanswered Questions when Building an Adaptive Intervention.

- Often, a wide variety of critical questions must be answered when developing a high-quality adaptive intervention. Examples:
  - Is it better to provide AAC from the start?
  - How long to wait before declaring a child a slow responder to JASP?
  - Who benefits from initial AAC versus who benefits from delayed AAC?
  - For slow responders, what is the effect of providing the AAC vs intensifying JASP (not providing AAC)?
- Insufficient empirical evidence or theory to address such questions.
- In the past, relied on expert opinion & piecing together an AI with separate RCTs.

Sequential Multiple Assignment Randomized Trials (SMARTs) can be used to address such questions empirically, using experimental design principles.

What is a Sequential Multiple Assignment Randomized Trial (SMART)?

- A type of multi-stage randomized trial design.
- At each stage, subjects randomized to a set of feasible/ethical treatment options.
- Treatment options latter stages may be restricted by early response status (response to earlier treatments).

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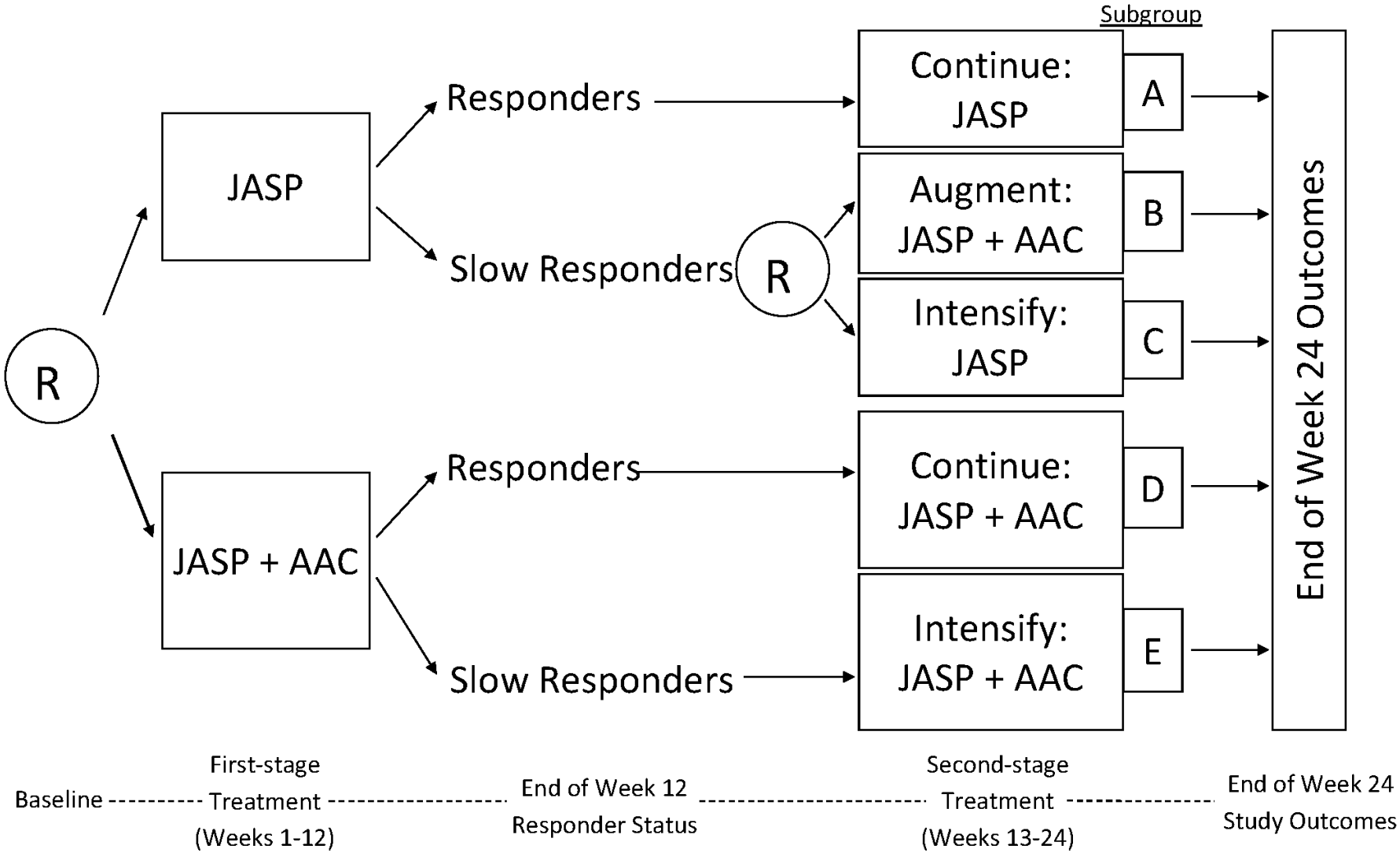
SMARTs were developed explicitly for the purpose of building a high-quality Adaptive Intervention.

On the Design of SMART Case Study 1

Example of a SMART in Autism Research

PI: Kasari (UCLA).

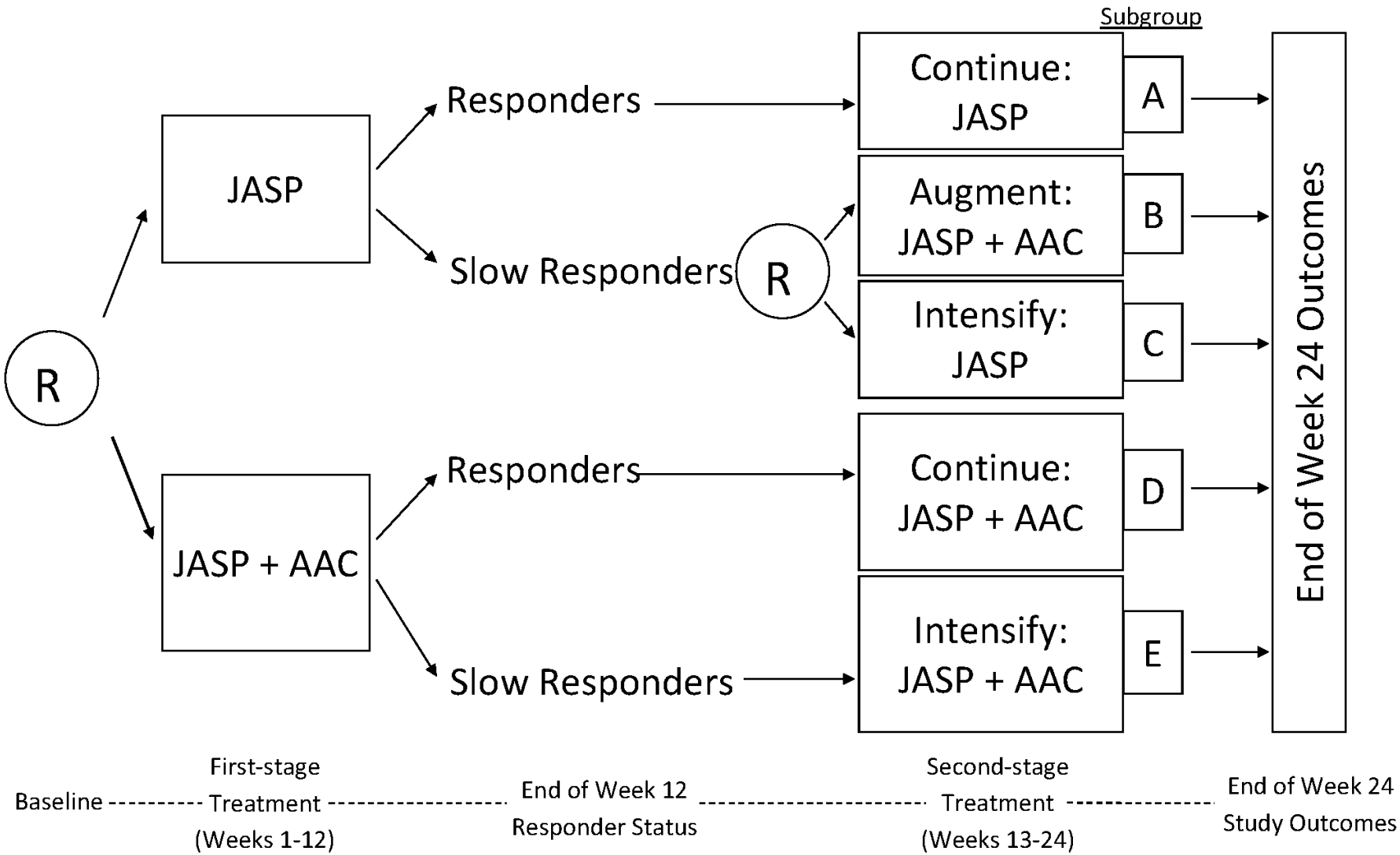


Example of a SMART in Autism Research

The population of interest:

- Children with autism spectrum disorder
- Age: 5-8
- Minimally verbal: $<$20 spontaneous words in a 20-min. language test
- History of treatment: $\geq$2 years of prior intervention
- Functioning: $\geq$2 year-old on non-verbal intelligence tests

Example of a SMART in Autism Research



SMARTs permit scientists to answer many interesting questions useful for building a high-quality adaptive intervention.

The specific aims of this example SMART were:

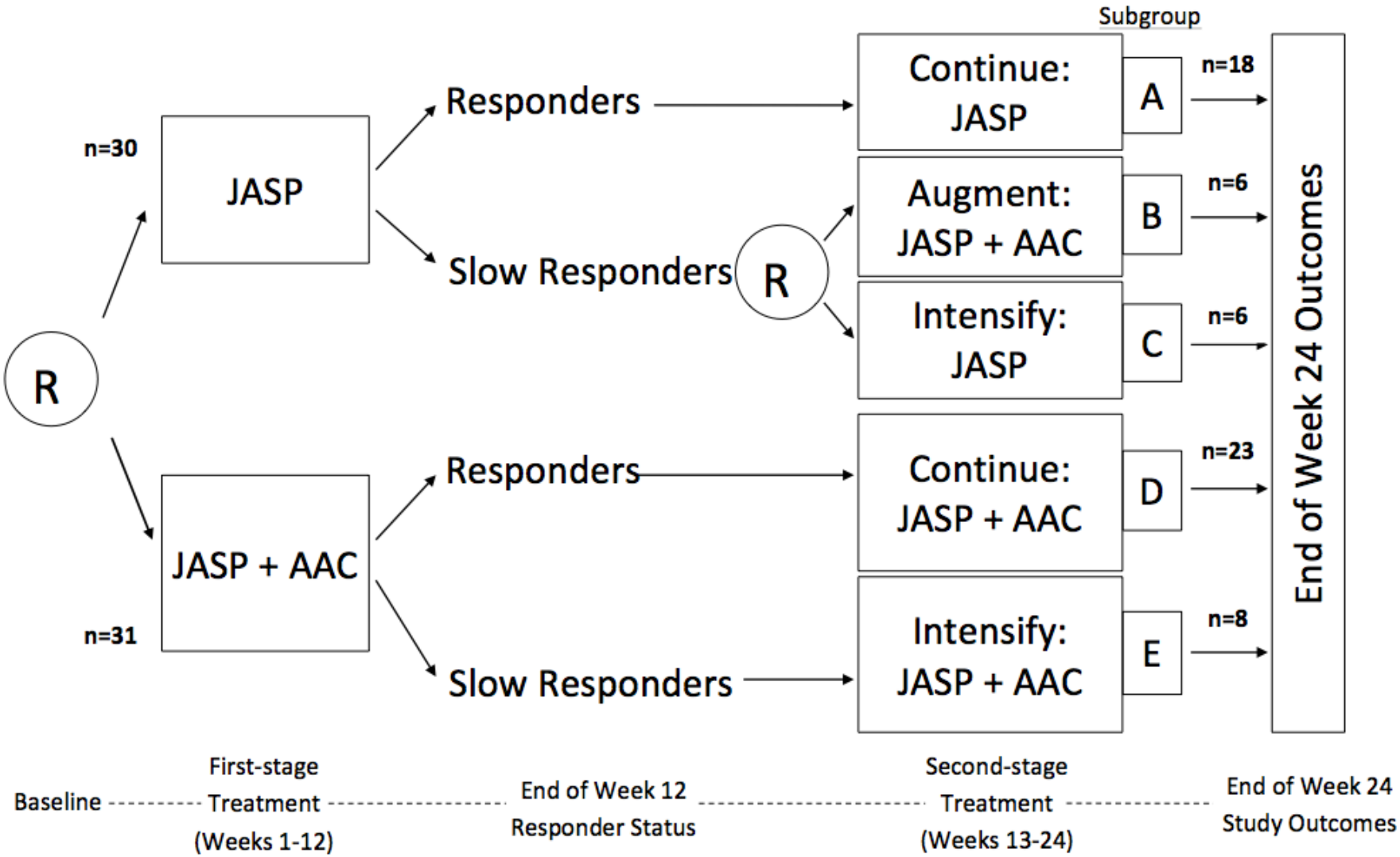
- Primary Aim: What is the best first-stage treatment in terms of spoken communication at week 24: JASP alone vs JASP+AAC?

  (Study sized $N = 98$ for this aim; subgroups A+B+C vs D+E)

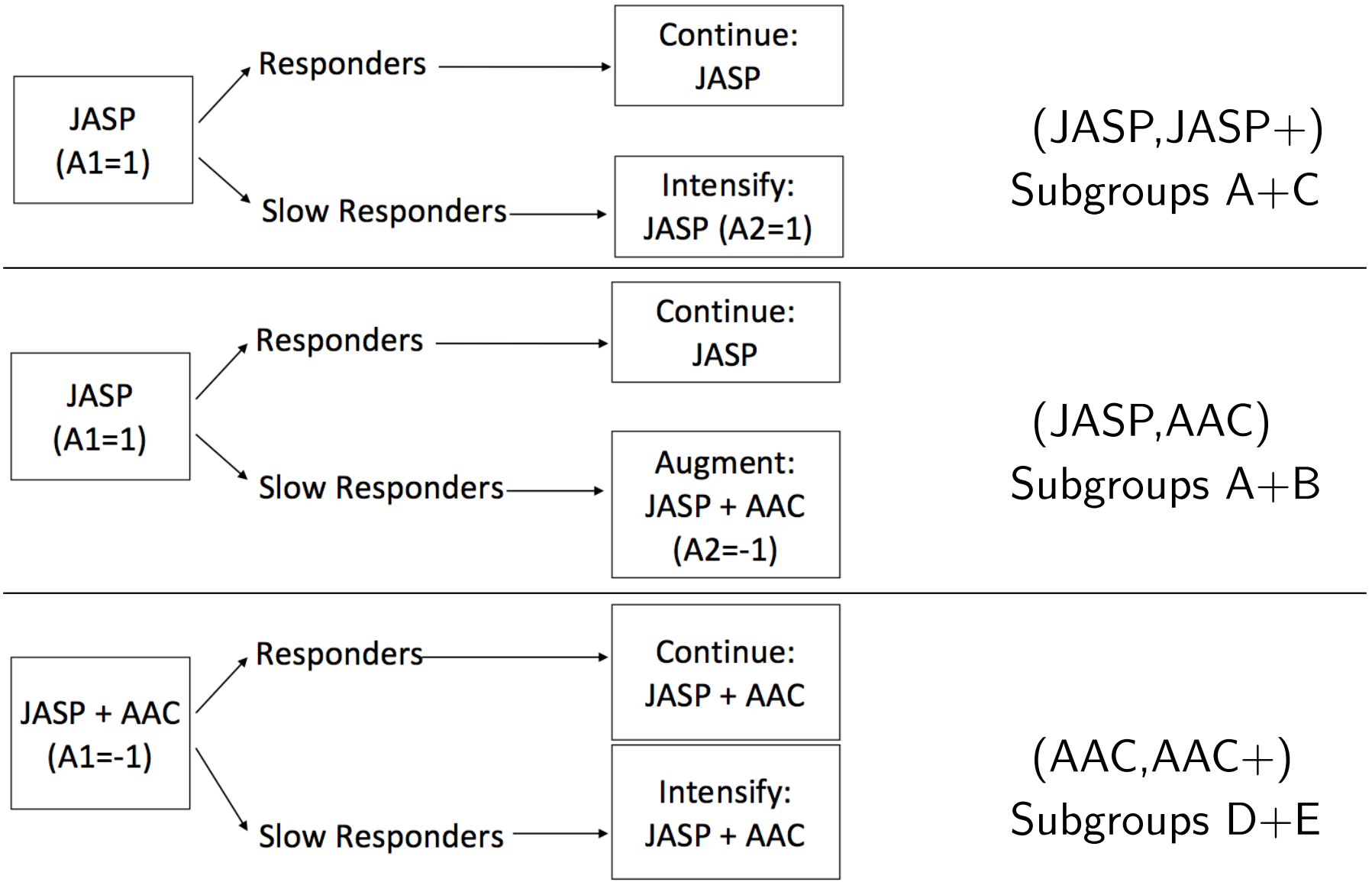
- Secondary Aim: Which is the best of the three adaptive interventions embedded in this SMART? (This is explained shortly.)

Example of a SMART in Autism Research ($N = 61$)

PI: Kasari (UCLA).



Recall: The 3 AIs Embedded in the Example Autism SMART



On the Conduct of SMART Case Study 1

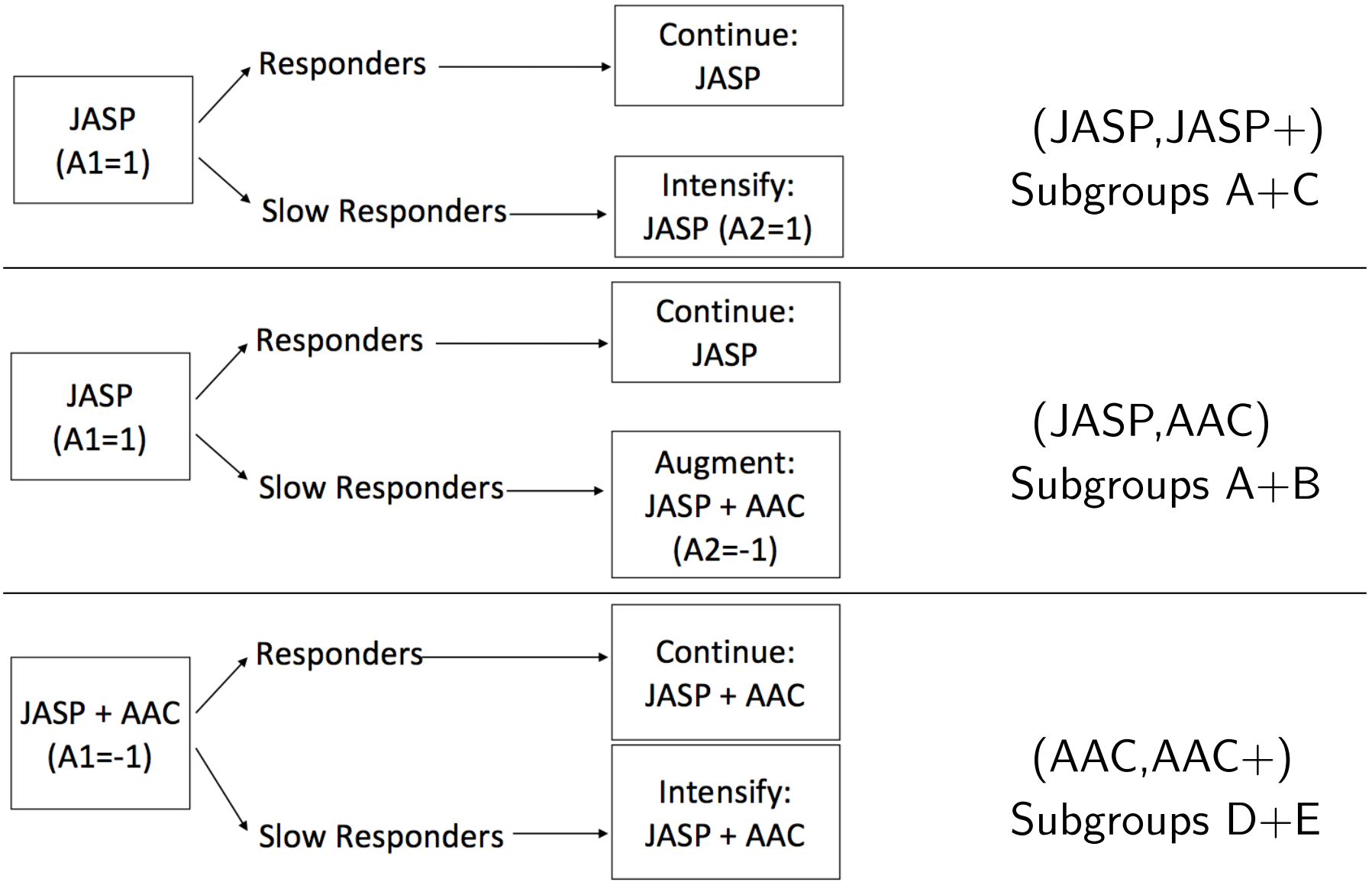
Challenges in the Conduct of this Initial Autism SMART

- Slow responder rate, while based on prior data, was lower than anticipated during the design of the trial.
- Responder/Slow-responder measure could be improved to make more useful in actual practice.
- There was some disconnect with the definition of slow-response status and the therapist's clinical judgment.

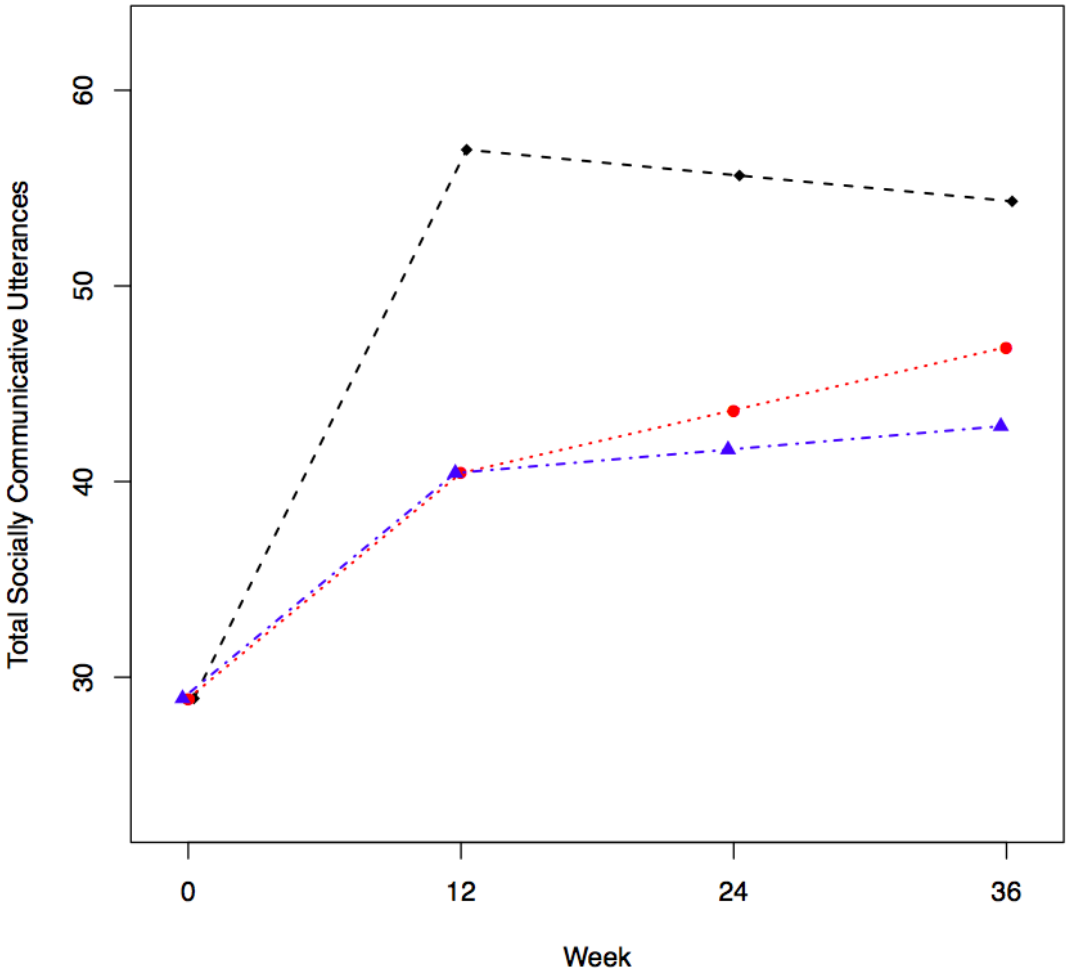
On the Analysis of SMART Case Study 1

We will focus on an analysis of the Secondary Aim:
Which is the best of the three adaptive interventions embedded in this SMART?

Recall: The 3 AIs Embedded in the Example Autism SMART



Analysis of Longitudinal Outcomes in the Autism SMART



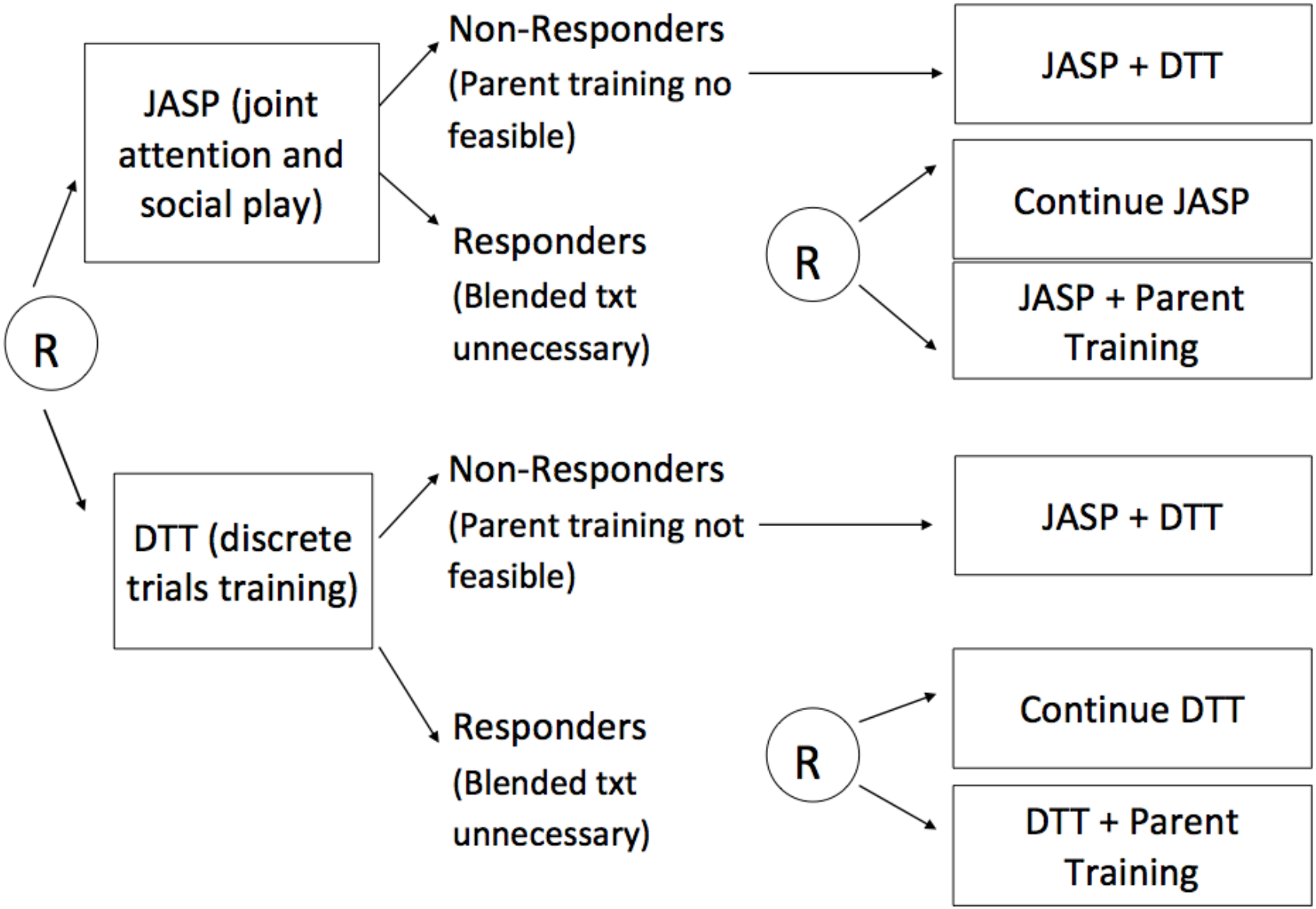
Average level of spoken communication over 36 weeks (i.e., AUC/36) for each AI

AI	Estimate	95% CI
(AAC,AAC+)	51.4	[45.6, 57.3]
(JASP,AAC)	40.7	[34.5, 46.8]
(JASP,JASP+)	39.3	[32.6, 46.0]

On the Design of SMART Case Study 2 (really quick story)

Interventions for Minimally Verbal Children with Autism

PIs: Kasari(UCLA), Almirall(Mich), Kaiser(Vanderbilt), Smith(Rochester), Lord(Cornell)



Primary and Secondary Aims

The specific aims of this example SMART are:

- Primary Aim: What is the best first-stage treatment in terms of spoken communication at week 24: JASP vs DTT?

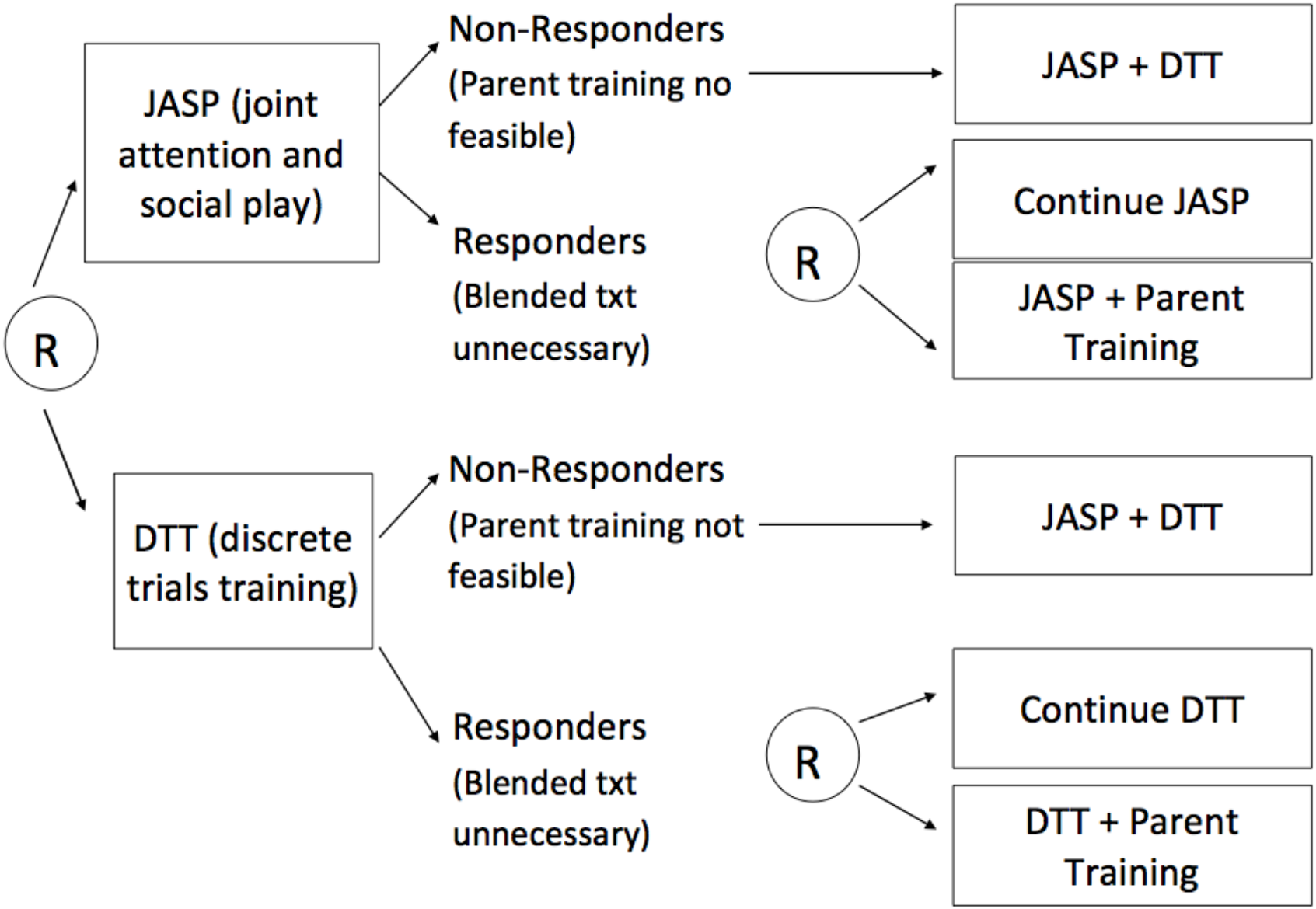
  (Study sized $N = 192$ for this aim; subgroups A+B+C vs D+E+F)

- Secondary Aim 1: Determine whether adding a parent training provides additional benefit among participants who demonstrate a positive early response to either JASP or DTT.

- Secondary Aim 2: Compare and contrast four pre-specified adaptive interventions.

What the original study did not aim to examine?

But in post-funding conversations, there was great interest in the effect of JASP+DTT!



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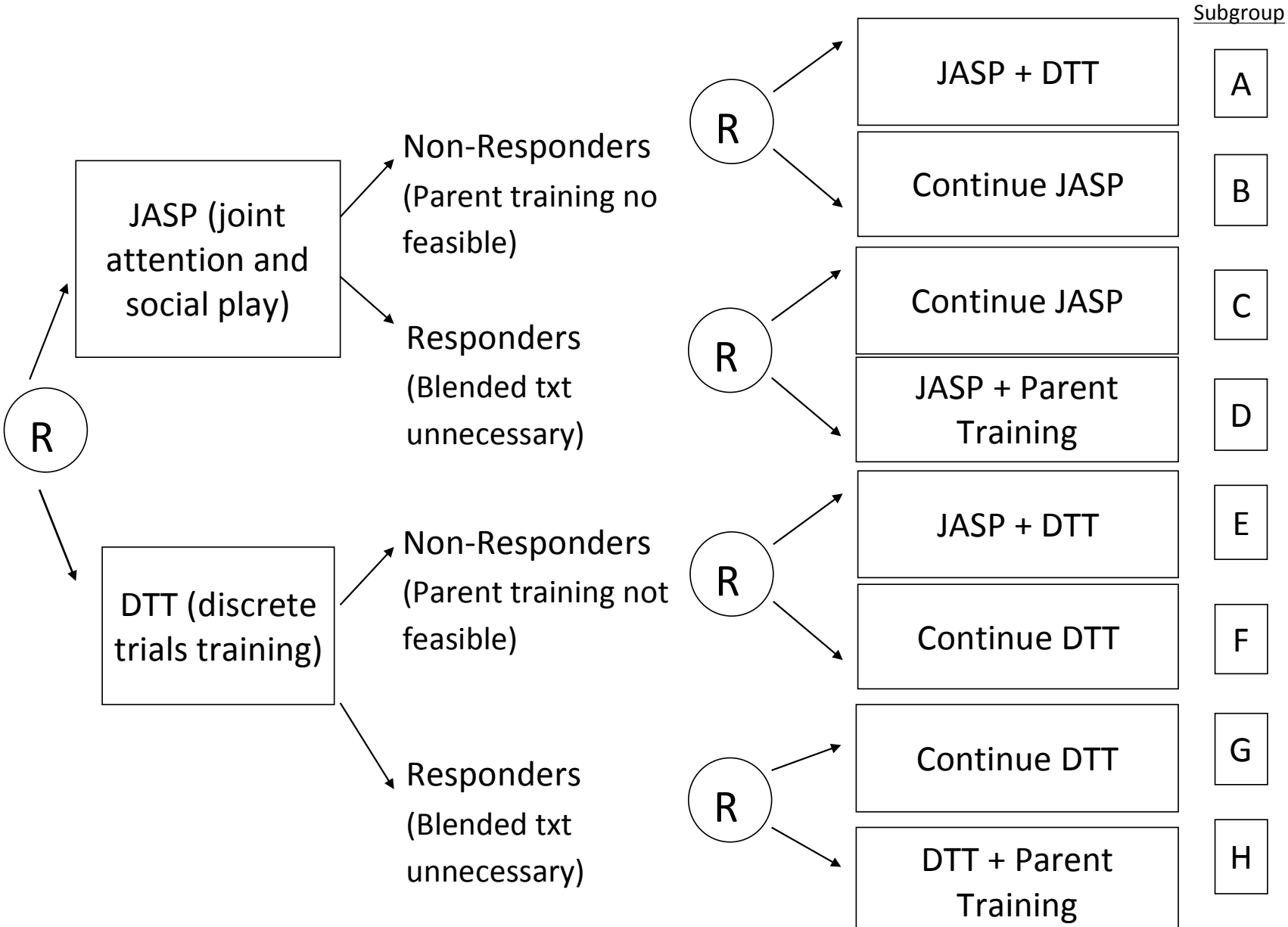


Primary and Secondary Aims

The specific aims of this example SMART are:

- Primary Aim: What is the best first-stage treatment in terms of spoken communication at week 24: JASP vs DTT?

  (Sized $N = 192$ for this aim; compares A+B+C+D vs E+F+G+H)

- Secondary Aim 1: Determine whether adding a parent training provides additional benefit among participants who demonstrate a positive early response to either JASP or DTT (D+H vs C+G).

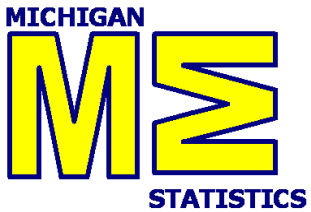
- Secondary Aim 2: Determine whether adding JASP+DTT provides additional benefit among participants who demonstrate a slow early response to either JASP or DTT (A+E vs B+F).

- Secondary Aim 3: Compare eight pre-specified adaptive interventions. Note, we can now compare always JASP vs always DTT!

Conclusions and Some Final Remarks

- Adaptive interventions are useful guides for clinical practice.
- SMARTs are useful for answering interesting questions that can be used to build high-quality adaptive interventions, including to compare (or select the best among) a set of adaptive interventions.
- SMARTs are factorial designs
- SMART to optimize; then RCT to evaluate

Thank you!



More About SMART:

- http://methodology.psu.edu/ra/adap-inter

More papers and these slides on my website (Daniel Almirall):

- http://www-personal.umich.edu/~dalmiral/

Email me with questions about this presentation:

- Daniel Almirall: dalmiral@umich.edu

Thanks to NIDA, NIMH and NICHD for Funding:

- P50DA10075, R03MH09795401, RC4MH092722, R01HD073975

Extra, Back-pocket Slides; Slightly More Technical

A Simple Regression Model for Comparing the Embedded AIs

$Y(a_1, a_2)$ denotes SCU at Wk 24 under AI (a_1, a_2). X's are mean-centered baseline (pre-txt) covariates. Consider the following marginal model:

$$E[Y(a_1, a_2)|X] = \beta_0 + \eta^T X + \beta_1 a_1 + \beta_2 I(a_1 = 1) a_2$$

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$E[Y(1, 1)] = \beta_0 + \beta_1 + \beta_2 =$ (JASP,JASP+)

$E[Y(1, -1)] = \beta_0 + \beta_1 - \beta_2 =$ (JASP,AAC)

$E[Y(-1, .)] = \beta_0 - \beta_1 =$ (AAC,AAC+)

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$-2\beta_1 + \beta_2 =$ (AAC,AAC+) vs (JASP,JASP+)

$-2\beta_1 - \beta_2 =$ (AAC,AAC+) vs (JASP,AAC)

$-2\beta_2 =$ (JASP,AAC) vs (JASP,JASP+)

How Do We Estimate this Marginal Model?

$$E[Y(a_1, a_2)|X] = \beta_0 + \eta^T X + \beta_1 a_1 + \beta_2 I(a_1 = 1) a_2$$

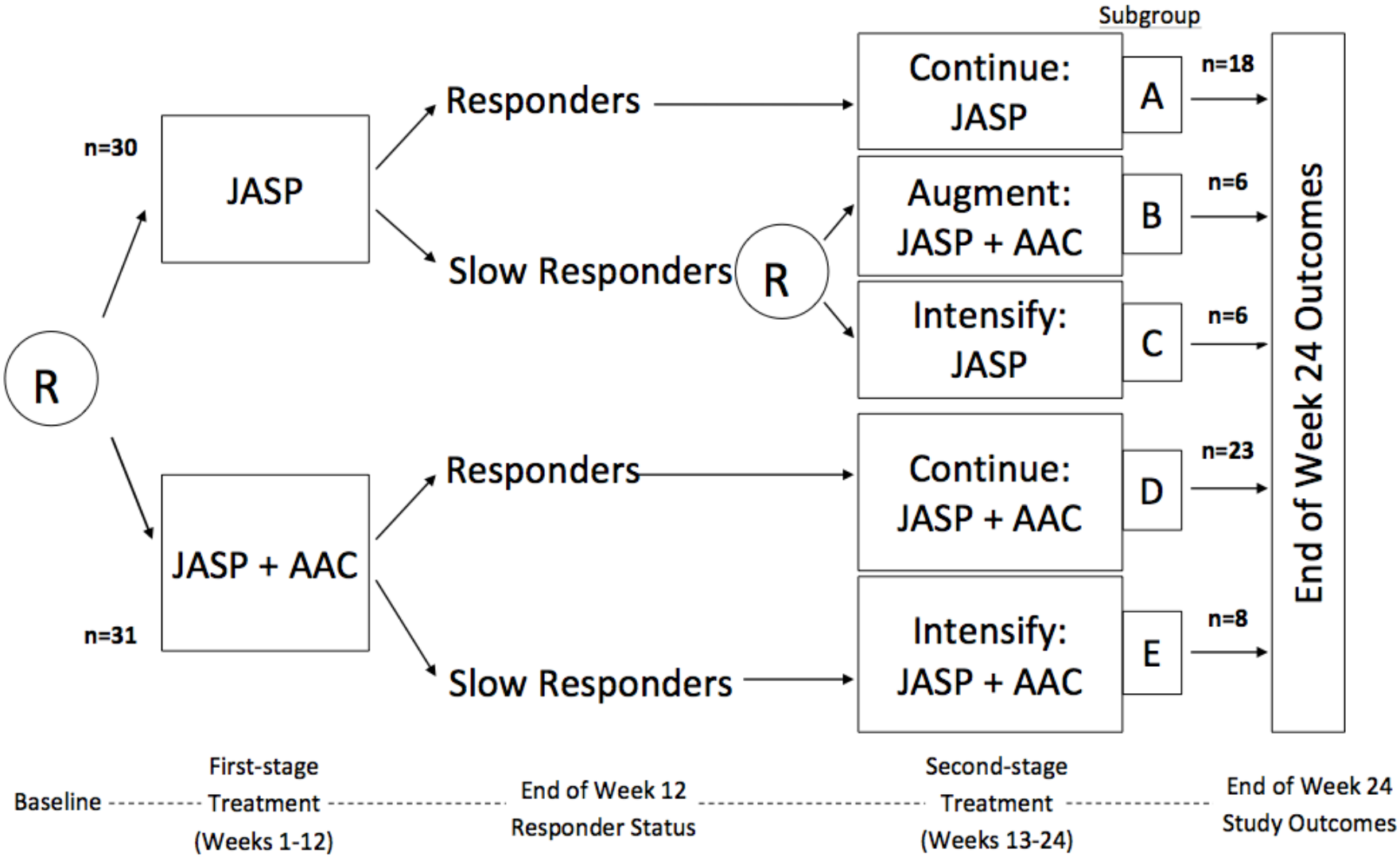
The observed data is $\{X_i, A_{1i}, R_i, A_{2i}, Y_i\}$, $i = 1, \ldots, N$.

Regressing Y on $[1, X, A_1, I(A_1 = 1)A_2]$ often won't work. Why?

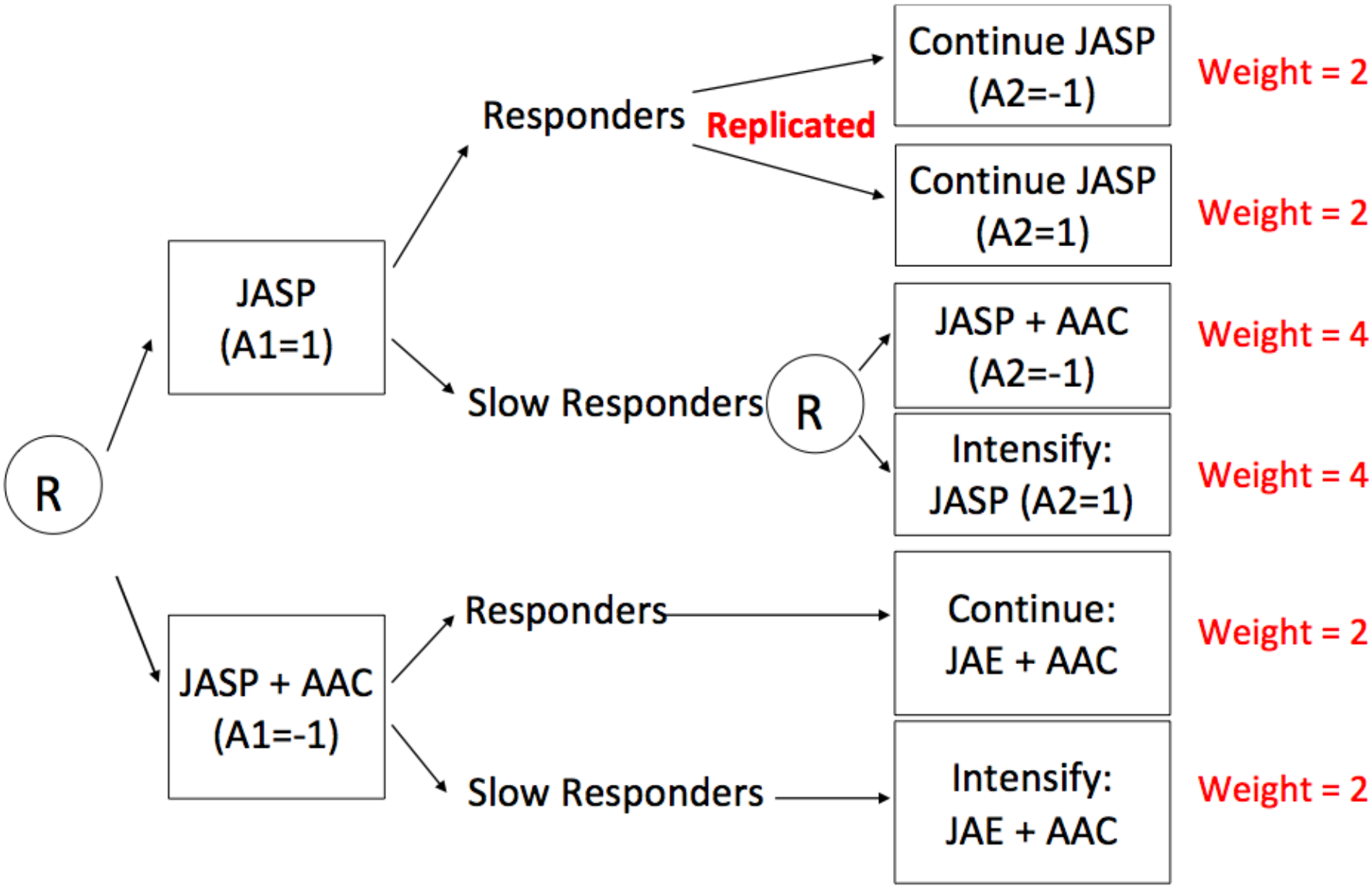
- By design, there is an imbalance in the types individuals following AI#1 vs AI#3 (for example)? This imbalance is due to a post-randomization variable R. Adding R to this regression does not fix this and may make it worse!
- How do we account for the fact that responders to JASP are consistent with two of the embedded AIs?

We use something called weighted-and-replicated regression. It is easy!

Before Weighting-and-Replicating



After Weighting-and-Replicating



Weighted-and-Replicated Regression Estimator (WRR)

Statistical foundation found in work by Orellana, Rotnitzky and Robins:

- Robins JM, Orellana L, Rotnitzky A. Estimation and extrapolation in optimal treatment and testing strategies. Statistics in Medicine. 2008 Jul; 27:4678-4721.
- Orellana L, Rotnitzky A, Robins JM. Dynamic Regime Marginal Structural Mean Models for Estimation of Optimal Dynamic Treatment Regimes, Part I: Main Content. Int J Biostat. 2010; 6(2): Article No. 8.
- (...ditto...), Part II: Proofs of Results. Int J Biostat. 2010;6(2): Article No. 9. 4678-4721.

Very nicely explained and implemented with SMART data in:

- Nahum-Shani I, Qian M, Almirall D, et al. Experimental design and primary data analysis methods for comparing adaptive interventions. Psychol Methods. 2012 Dec; 17(4): 457-77.

Weighted-and-Replicated Regression Estimator (WRR)

- Weighting (IPTW): By design, each individual/unit has a different probability of following the sequence of treatment s/he was offered (weights account for this)
  - e.g., $W = 2I\{A_1 = 1, R = 1\} + 2I\{A_1 = -1\} + 4I\{A_1 = 1, R = 0\}$.
- Replication: Some individuals may be consistent with multiple embedded regimes (replication takes advantage of this and permits pooling covariate information)
  - e.g., Replicate (double) the responders to JASP: assign $A_2 = 1$ to half and $A_2 = -1$ to the other half
  - e.g., The new data set is of size $M = N + \sum I\{A_1 = 1, R = 1\}$
- Implementation is as easy as running a weighted least squares:

$$(\hat{\eta}, \hat{\beta}) = \arg\min_{\eta,\beta} \frac{1}{M} \sum_{i=1}^{M} W_i (Y_i - \mu(X_i, A_{1i}, A_{2i}; \eta, \beta))^2.$$

- SE's: Use ASEs to account for weighting/replicating (or bootstrap).

An Interesting Connection Between Estimators

Recall Robins' G-Computation Estimator (not to be confused with the G-Estimator which is an entirely different thing!:)

$$\widehat{E[Y(1,1)]} = \widehat{E}[Y|\text{A}]\widehat{Pr}[\text{R}=1|\text{JASP}] + \widehat{E}[Y|\text{C}](1-\widehat{Pr}[\text{R}=1|\text{JASP}])$$

$$\widehat{E[Y(1,-1)]} = \widehat{E}[Y|\text{A}]\widehat{Pr}[\text{R}=1|\text{JASP}] + \widehat{E}[Y|\text{B}](1-\widehat{Pr}[\text{R}=1|\text{JASP}])$$

$$\widehat{E[Y(-1,.)]} = \widehat{E}[Y|\text{D}]\widehat{Pr}[\text{R}=1|\text{AAC}] + \widehat{E}[Y|\text{E}](1-\widehat{Pr}[\text{R}=1|\text{AAC}])$$

This estimator is algebraically identical to fitting the WRR Estimator with no covariates and sample-proportion estimated weights (rather than the known true weights).

Comparing these two provides a way to compare the added-value of adjusting for covariates in terms of statistical efficiency gains.

Results from an Analysis of the Autism SMART

Recall: $N = 61$, and the primary outcome is SCU at Week 24 (SD=34.6).

	WRR with Covts and Known Wt			WRR with no Covts and with SAMPLE PROP $\widehat{\text{Wt}}$ (G-Comp)		
ESTIMAND	EST	SE	PVAL	EST	SE	PVAL
(AAC,AAC+)	60.5	5.8	< 0.01	61.0	6.0	< 0.01
(JASP,AAC)	42.6	4.9	< 0.01	38.2	6.9	< 0.01
(JASP,JASP+)	36.3	5.0	< 0.01	40.0	8.0	< 0.01
(AAC,AAC+) vs (JASP,JASP+)	24.3	7.9	< 0.01	21.0	10.2	0.04
(AAC,AAC+) vs (JASP,AAC)	17.9	8.2	0.03	22.8	9.4	0.02
(JASP,AAC) vs (JASP,JASP+)	6.4	3.8	0.10	-1.8	7.7	0.82

What's the lesson? The regression approach is more useful. (And, it is a good idea to adjust for baseline covariates!) Of course, this is well-known.

But the story gets even more interesting...

Improving the Efficiency of the WRR by Estimating the Known Weights with Covariates

By design, we know the true weights. That is,

- Since $Pr(A_1) = 1/2$ and $Pr(A_2 = 1 \mid A_1 = 1, R = 0) = 1/2$,
- then $W = 4I\{A_1 = 1, R = 0\} + 2I\{$ everyone else $\}$.

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However, from work by Robins and colleagues (1995; also, Hirano et al (2003)), there are gains in statistical efficiency if using an WRR with weights that are estimated using auxiliary baseline (L_1) and time-varying (L_2) covariate information. Here's how to do it with the autism SMART:

- The observed data is now $\{L_{1i}, X_i, A_{1i}, R_i, L_{2i}, A_{2i}, Y_i\}$
- Use logistic regression to get $\widehat{p_1} = \widehat{Pr}(A_1 \mid L_1, X)$
- Use logistic regression to get $\widehat{p_2} = \widehat{Pr}(A_2 \mid L_1, X, A_1 = 1, R = 0, L_2)$.
- Use $W = I\{A_1 = 1, R = 0\}/(\widehat{p_1}\widehat{p_2}) + I\{$ everyone else $\}/\widehat{p_1}$.

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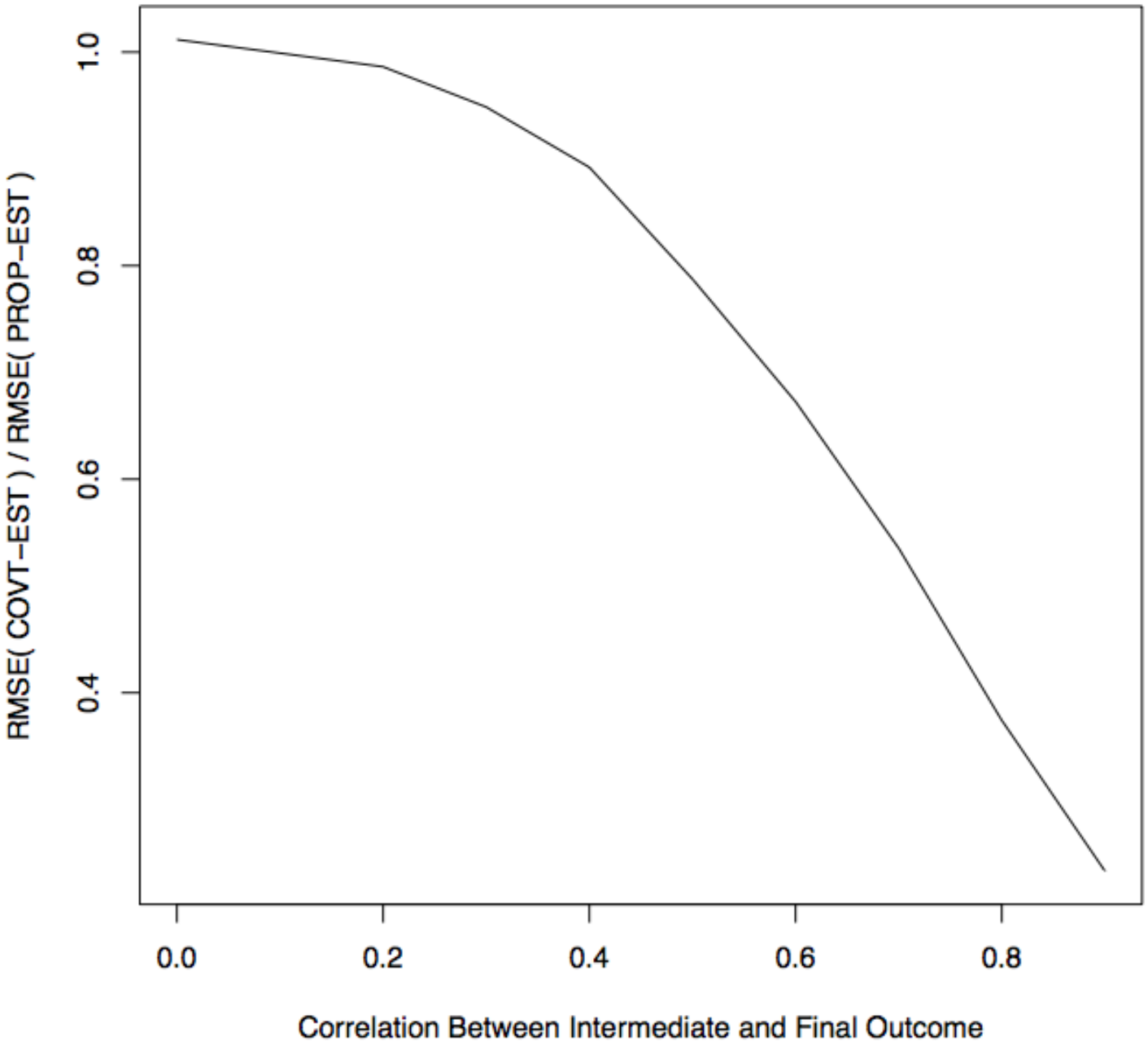
- Use logistic regression to get $\widehat{p_2} = \widehat{Pr}(A_2 \mid L_1, X, A_1 = 1, R = 0, L_2)$.
- Use $W = I\{A_1 = 1, R = 0\}/(\widehat{p_1}\widehat{p_2}) + I\{$ everyone else $\}/\widehat{p_1}$.

The key is to choose L_t's that are highly correlated with Y!

Sim: Relative RMSE for (AAC,AAC+) vs (JASP,JASP+)



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ESTIMAND	EST	SE	PVAL	EST	SE	PVAL
(AAC,AAC+)	60.5	5.8	< 0.01	60.2	5.6	< 0.01
(JASP,AAC)	42.6	4.9	< 0.01	43.1	4.5	< 0.01
(JASP,JASP+)	36.3	5.0	< 0.01	35.4	4.4	< 0.01
(AAC,AAC+) vs (JASP,JASP+)	24.3	7.9	< 0.01	24.9	7.4	< 0.01
(AAC,AAC+) vs (JASP,AAC)	17.9	8.2	0.03	17.1	7.9	0.03
(JASP,AAC) vs (JASP,JASP+)	6.4	3.8	0.10	7.7	3.0	0.01

The WRR implementation with covariates and covariate-estimated weights permits us to obtain scientific information from a SMART with less uncertainty.

Rule-of-thumb concerning which auxiliary variables to use in the WRR for comparing embedded of AIs in a SMART.

Key is to include in L_t variables which are (highly) correlated with Y, even if not of scientific interest. A potentially useful rule-of-thumb (not dogma):

- Include in L_1, all variables that were used to stratify the initial randomization.
- Include in L_2, all variables that were used to stratify the second randomization.
- Let the science dictate which X's to include in the final regression model.
  - e.g., Investigator may be interested in whether baseline levels of spoken communication moderate the effect of JASP vs JASP+AAC.
  - Of course: It is possible for $X = L_1$, but not possible for X to include any post-A_1 measures.

Challenges to Address in Longitudinal Setting

- Modeling Considerations: The intermixing of repeated measures and sequential randomizations requires new modeling considerations to account for the fact that embedded AIs will share paths/trajectories at different time points (this is non-trivial)
- Implications for Interpreting Longitudinal Models: (1) Comparison of slopes is no longer appropriate in many circumstances; (2) Need for new, clinically relevant, easy-to-understand summary measures of the mean trajectories over time
- Statistical: Develop an estimator that takes advantage of the within person correlation in the outcome over time

An Example Marginal Model for Longitudinal Outcomes

Y_t : # Socially Communicative Utterances at week t. $t = 0, 12, 24, 36$

The comparison of embedded AIs with longitudinal data arising from a SMART will require longitudinal models that permit deflections in trajectories and respect the fact that some embedded AIs will share paths/trajectories up to the point of randomization.

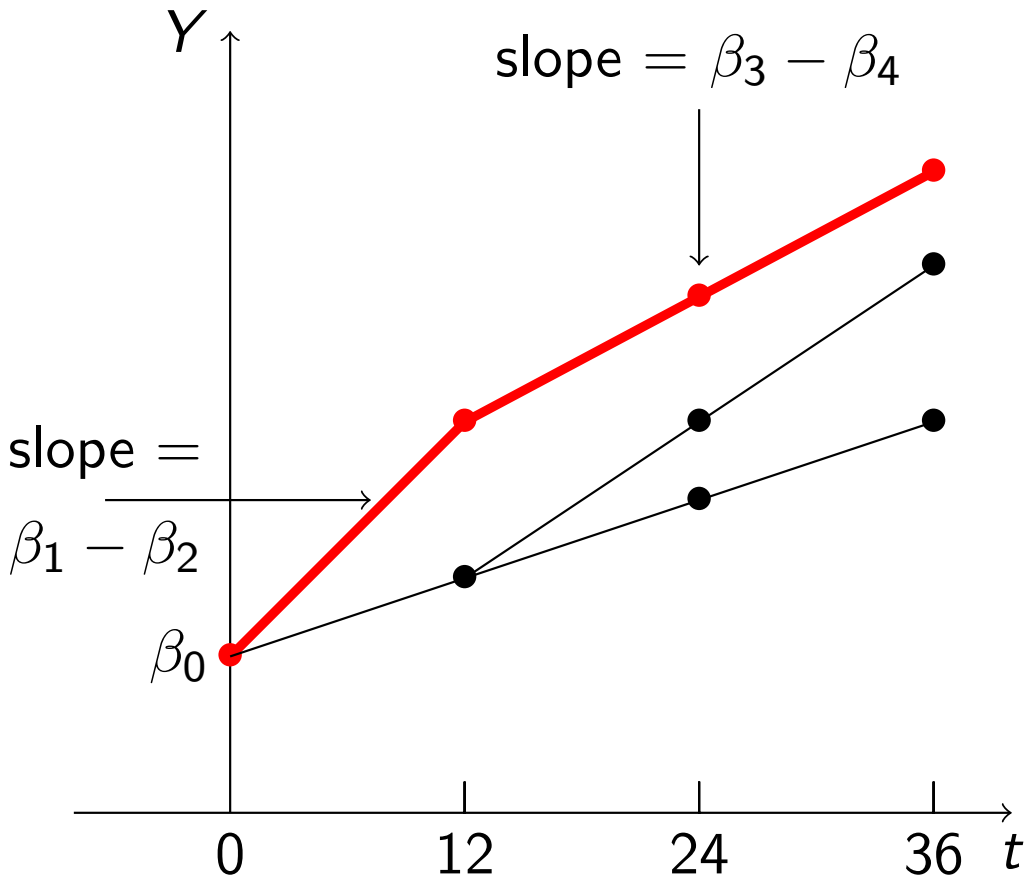
An example is the following piece-wise linear model:

$$E[Y_t(a_1, a_2)|X] = \beta_0 + \eta^T X + 1_{t\leq 12}\{\beta_1 t + \beta_2 t a_1\}$$
$$+ 1_{t>12}\{12\beta_1 + 12\beta_2 a_1 + \beta_3(t-12) + \beta_4(t-12)a_1 + \beta_5(t-12)a_1 a_2\}$$

where X's are mean-centered baseline covariates.

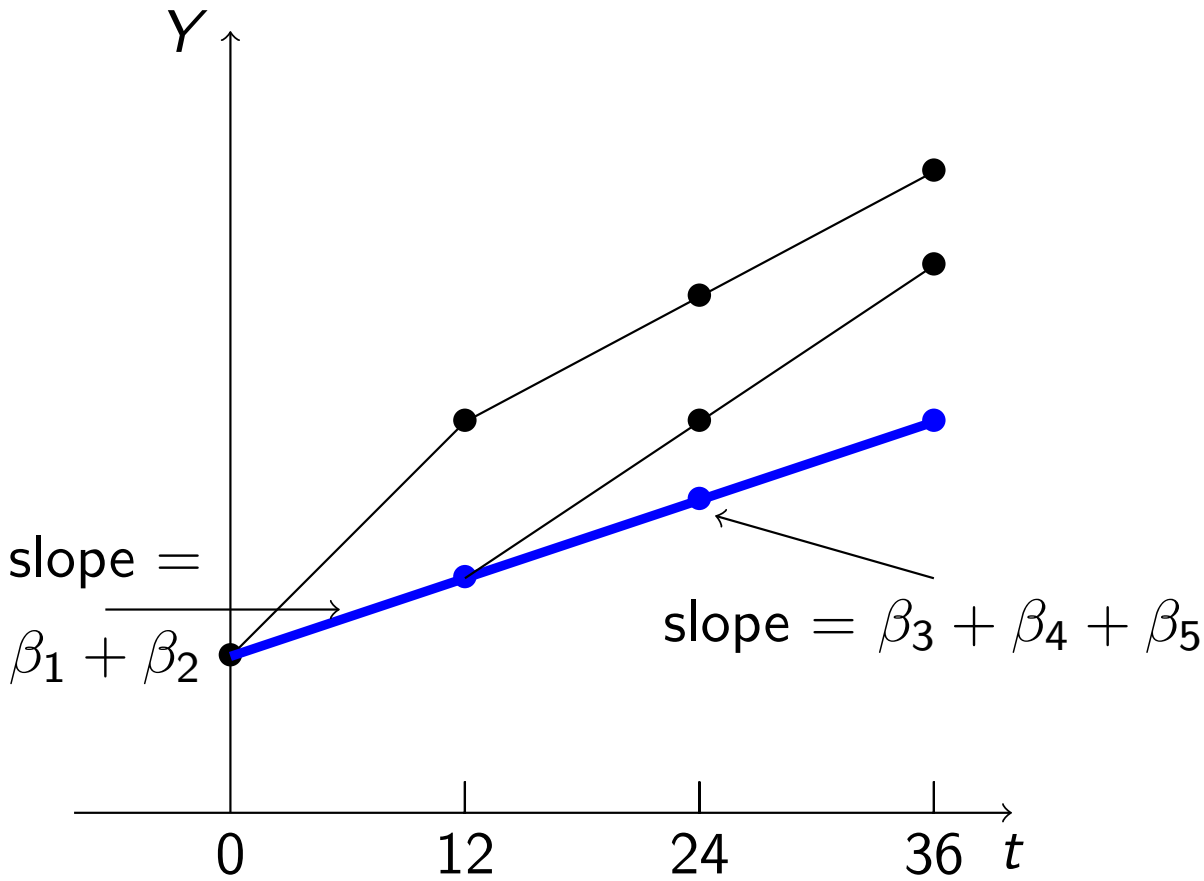
Modeling Considerations

Regime (-1,0): (AAC, AAC+)



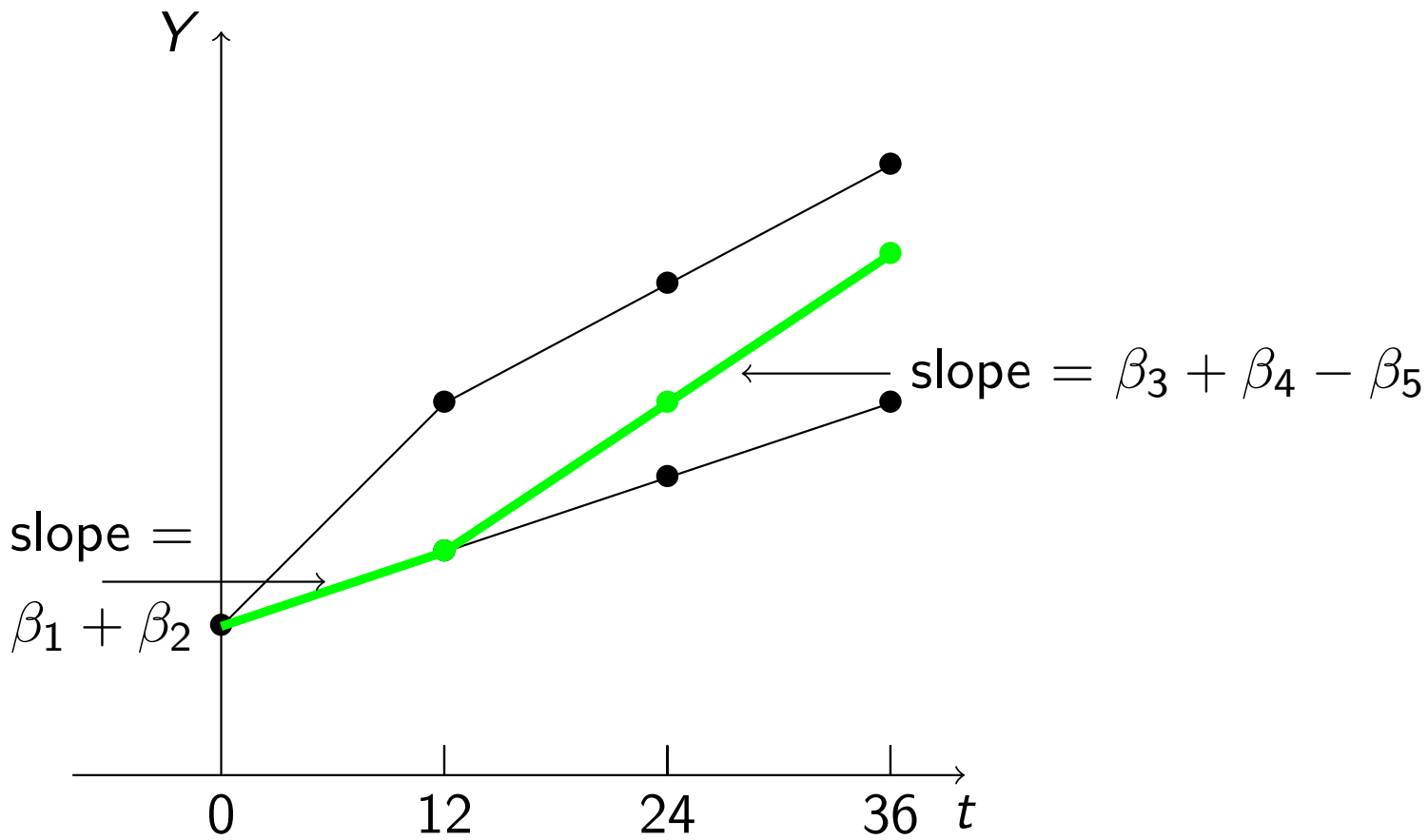
Modeling Considerations

Regime (1,1): (JASP, JASP+)



Modeling Considerations

Regime (1,-1): (JASP, AAC)



Implications of New Modeling Considerations for Summarizing each AI

- Potential Solution: Summarize each AI by the area under the curve (during an interval chosen by the investigator)
- Clinical advantage: AUC is easy to understand clinically; it is the average of the primary outcome over a specific interval of time
- Statistical inference is easy: AUC is linear function of parameters (β's) in marginal model

Statistical: WRR Estimator for Longitudinal Outcomes

We use the following estimating equation to estimate marginal model for longitudinal outcomes:

$$0 = \frac{1}{M}\sum_{i=1}^{M} D_i(X_i, \bar{A}_i) V_i^{-1} W_i(Y_i - \boldsymbol{\mu}_i(X_i, \bar{A}_i; \beta, \eta)),$$

where

- Y_i: a vector of longitudinal outcomes, i.e. $(Y_{i,0}, Y_{i,12}, Y_{i,24}, Y_{i,36})^T$; $\boldsymbol{\mu}_i$ a vector of corresponding conditional means;
- D_i: the design matrix, i.e. $\left(\frac{\partial \boldsymbol{\mu}_i(X_i,\bar{A}_i;\beta,\eta)}{\partial \beta^T}, \frac{\partial \boldsymbol{\mu}_i(X_i,\bar{A}_i;\beta,\eta)}{\partial \eta^T}\right)^T$;
- W_i: a diagonal matrix containing inverse probability of following the offered treatment sequence at each time point;
- V_i: working covariance matrix for Y_i.

SMART Approach to Increasing Communication Outcomes in ASD

Connie Kasari, Ann Kaiser, Kelly Goods, Jennifer Nietfeld, Pamela Mathy, Rebecca Landa,

Susan Murphy, Daniel Almirall

University of California, Los Angeles

Vanderbilt University

Kennedy Krieger Institute

University of Michigan

Characterizing Cognition in Nonverbal Individuals with Autism(CCINIA 2008-2011),funded by Autism Speaks

Core Deficit: Social Communication in Children with ASD

- Social Communication is core deficit in ASD
- Communication interventions have been successful in improving outcomes for some but not all children with ASD
- Critical area for research and for innovative designs that advance our understanding of how to best sequence interventions.

Minimally Verbal Children with Autism

- Between 25-30% of children with autism remain minimally verbal by school age (Kasari et al, 2013; Anderson 2009)
- Most of these children are not "nonverbal"
  - Very low rates of verbalization
  - Limited diversity
  - Single words, rote phrases
- Relatively unstudied population
- Few intervention studies
  - No randomized trials with school age children
  - Pickett et al (2009) review of 167 case studies
    - Positive results for relatively younger (5- 7 yrs) and higher IQ (>50)
    - Primarily ABA discrete trial type interventions
    - 70% of individuals increase in words; 30% increase in phrases or sentences

Specific Aims of the Study

- Goal: To construct an adaptive intervention that utilized a naturalistic behavioral communication intervention (JASPER + EMT) with the added variation of an SGD with minimally verbal school aged children with ASD

- **Aim 1: To examine the effect of the adaptive intervention beginning with JASP+EMT+SGD versus the adaptive interventions beginning with JASP+EMT verbal only**

- **Aim 2: To compare the outcomes of three adaptive interventions**

Criteria for Minimally Verbal Participants

- Less than 20 spontaneous words
- Ages 5-8 years
- Minimum of 24 months cognition (Leiter) and receptive language (PPVT)
- Diagnosis of autism or ASD
- 2 years previous treatment
- No fluent use of AAC

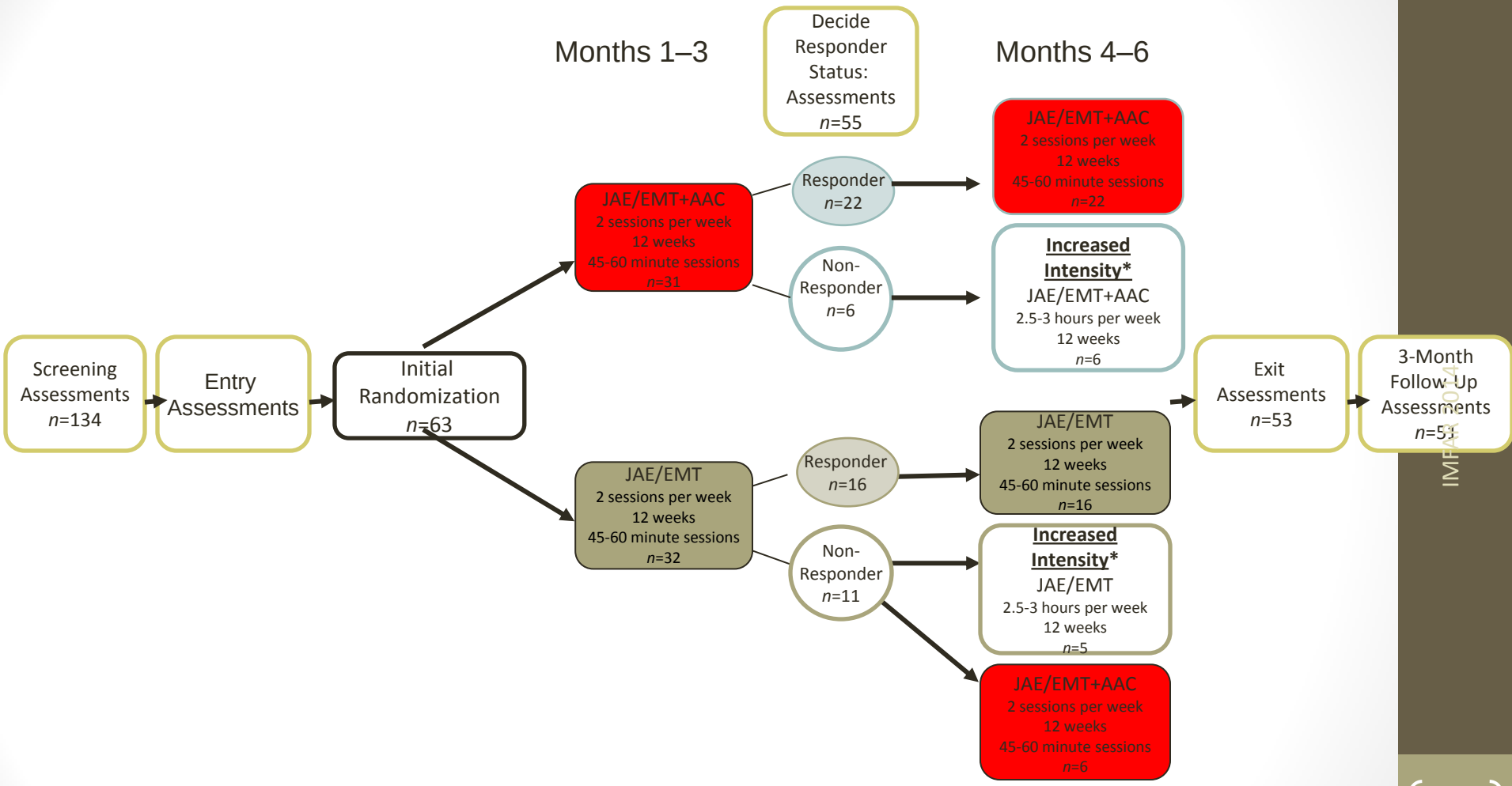
Study Participants

- **61 minimally verbal children diagnosed with autism**
  - **60 met ADOS criteria for autism**
  - **Mn ADOS score 19.55 (SD 4.27)**

  - **51 males; 10 females**
  - **48% white, 23% African American, 19% Asian American, 5% Hispanic, 5% other**
  - **Mn age 6.31 years (SD 1.16)**

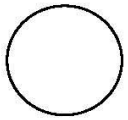
  - **Mn unique words: 16.62 (SD 14.65)**
  - **Mn PPVT-4 : 2.72 years (SD .68)**
  - **Mn Nonverbal Cognitive (Leiter): 68.18 (SD 18.68); range 36 - 130**

Sequential multiple assignment randomized trial (SMART) Design



IMFAR 2014

SMART DESIGN

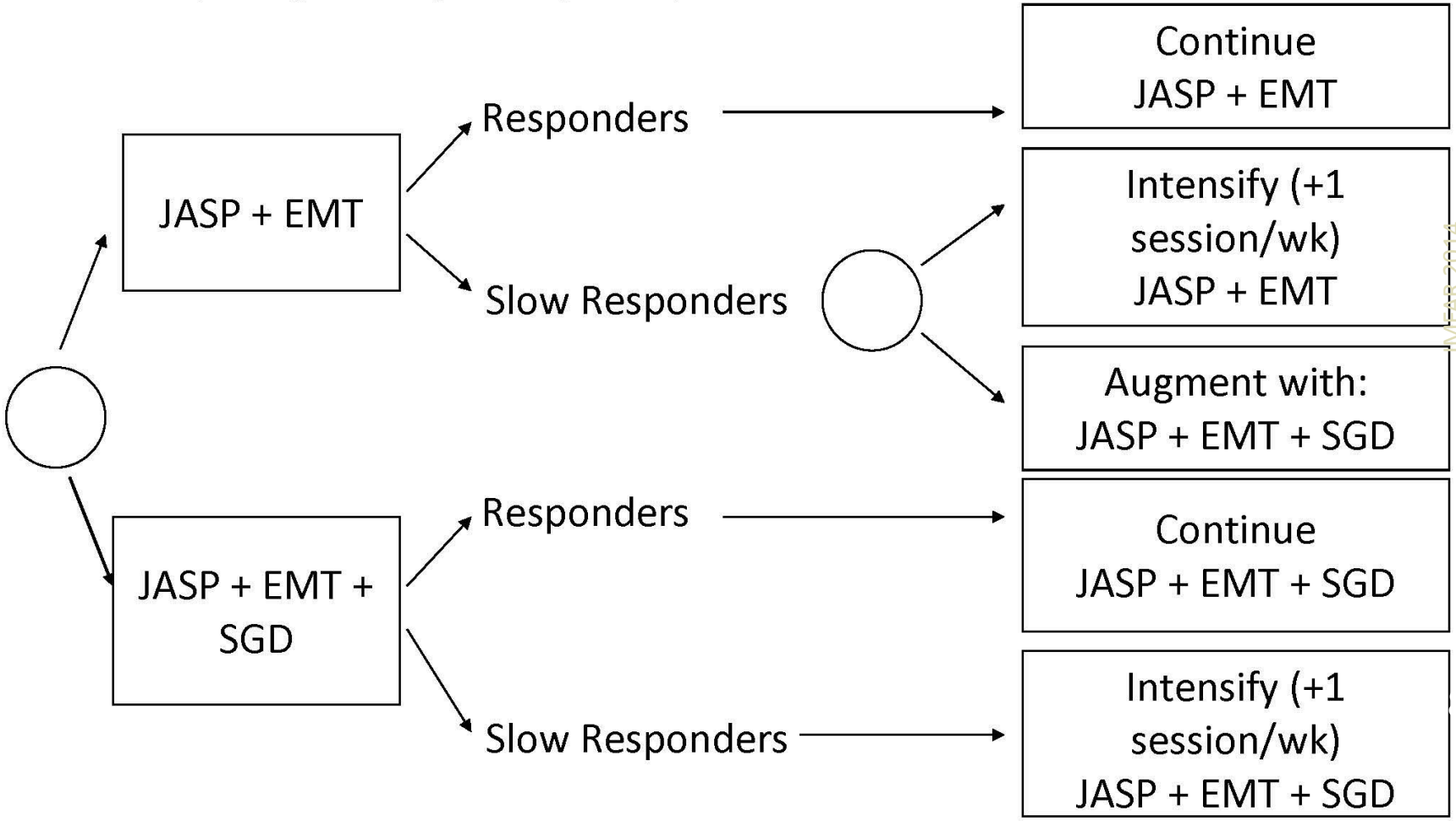


= randomization;

JASP = joint attention/engagement and social play

EMT = enhanced milieu teaching treatment

SGD = speech generating device (an AAC)



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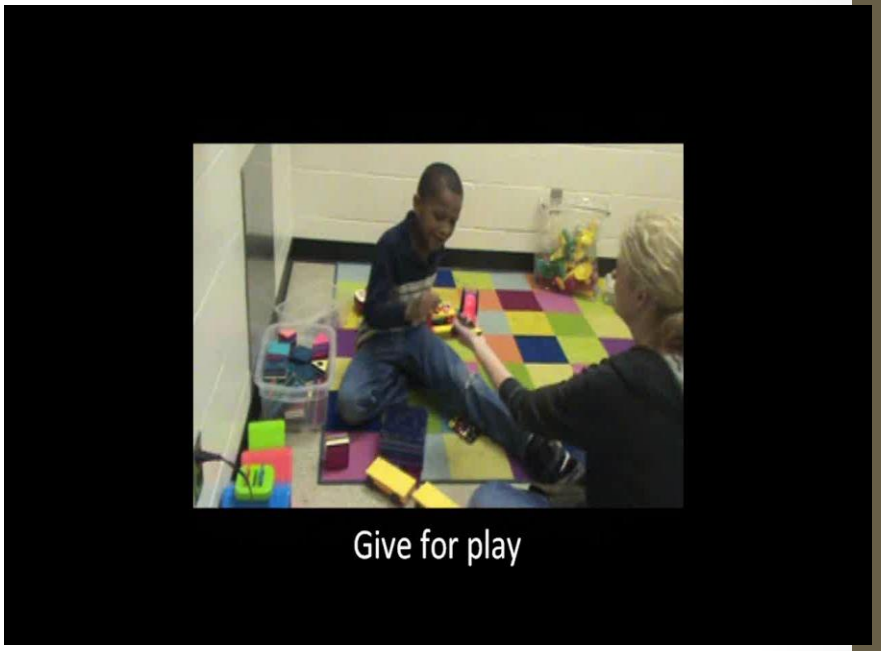
Intervention

- **Blended JASP+ EMT**
  - Joint Attention, Symbolic Play and Emotion Regulation (JASP; Kasari et al 2006)
  - Enhanced Milieu Teaching (EMT; Kaiser, et al 2000)
  - Naturalistic, interactive, play based
  - Model and prompt joint attention, symbolic play, and verbal and nonverbal communication contingent on child's interests and responses
  - Goals: increase engagement, social initiations, symbolic play and social communication, especially commenting
- **JASP+ EMT Spoken Language Only**
- **JASP +EMT + SGD**



SGD in JASP-EMT

- SGD available to the child
- Programmed pages for toys sets
- Used communicatively with the child
  - 50% of adult utterance
  - 70% of adult expansions
- Child could respond to prompts with either SGD or spoken language
- Embedded in JASPER-EMT interactions; focus on social use

Intervention Implementation

- Phase 1
  - 24 40-minute sessions in clinic play room
  - Parents watched most sessions
  - 4-6 toys sets preferred by child
  - Primary comparison JASP +EMT (spoken) vs. JASP + EMT + SGD

- Phase 2
  - 24 40-minute sessions in clinic play room
  - Parents trained in sessions (Teach, model, coach, review)
    - Parents taught JASP +EMT
    - Parents taught use of SGD
  - 4-6 toys sets preferred by child
  - Treatment variations:
    - JASP +EMT (spoken)
    - JASP + EMT + SGD
    - Intensified JASP + EMT
    - JASP + EMT + SGD
    - Intensified JASP + EMT + SGD

Non-responders were reassigned to one of these

Early Responder

≥25% improvement on 7 or more of the following variables

Session Data (Mn Sessions 1/ 2 vs Mn Sessions 23/ 24)

- Total Social Communicative Utterances
- Percentage Communicative Utterances
- Number Different Word Root
- MLUw
- # Comments
- Words per Minute
- Unique Word Combinations

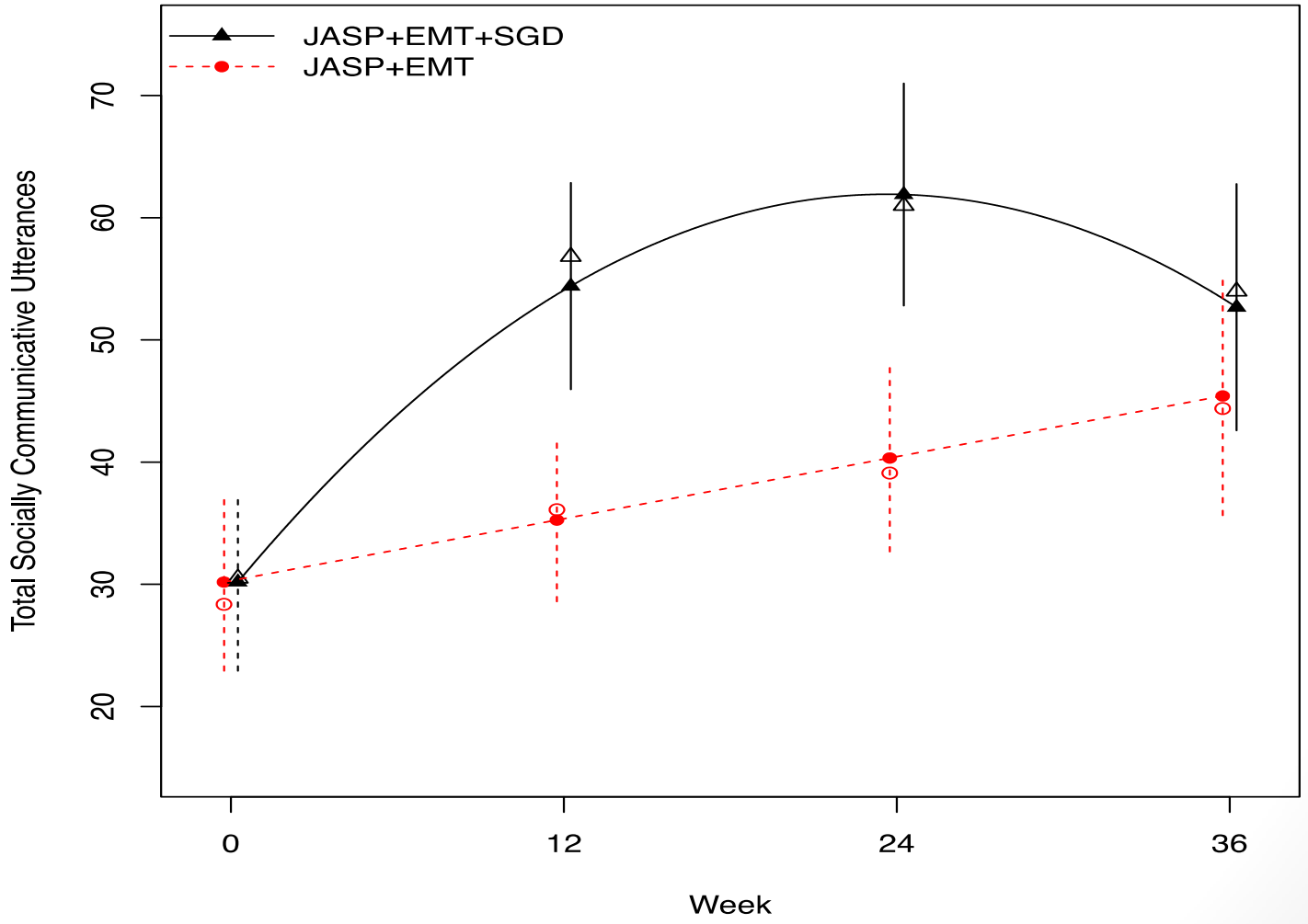
Language Sample (Screening vs 12 weeks)

- Total Social Communicative Utterances
- Percentage Communicative Utterances
- Number Different Word Roots
- MLUw
- # Comments
- Words per Minute
- Unique Word Combinations

Results

- **Aim 1: To examine the effect of the adaptive intervention beginning with JASP+EMT+SGD versus the adaptive interventions beginning with JASP+EMT verbal only**
- **Spontaneous Communicative Utterances (spoken or AAC)**
- Midpoint (12 weeks of intervention)
  - JAE/EMT + AAC > JAE/EMT
    - More social communicative utterances (SCU)(*d*= .76, p <0.01)
    - Percentage of communicative utterances *d*= .59, p = 0.02)
- End of Treatment (24 weeks of intervention)
  - JAE/EMT + AAC > JAE/EMT
    - More social communicative utterances (*d*= .60, p =0.02)
    - Percentage of communicative utterances (d= .75, p> 0.01)

Primary aim results for the primary outcome (TSCU).

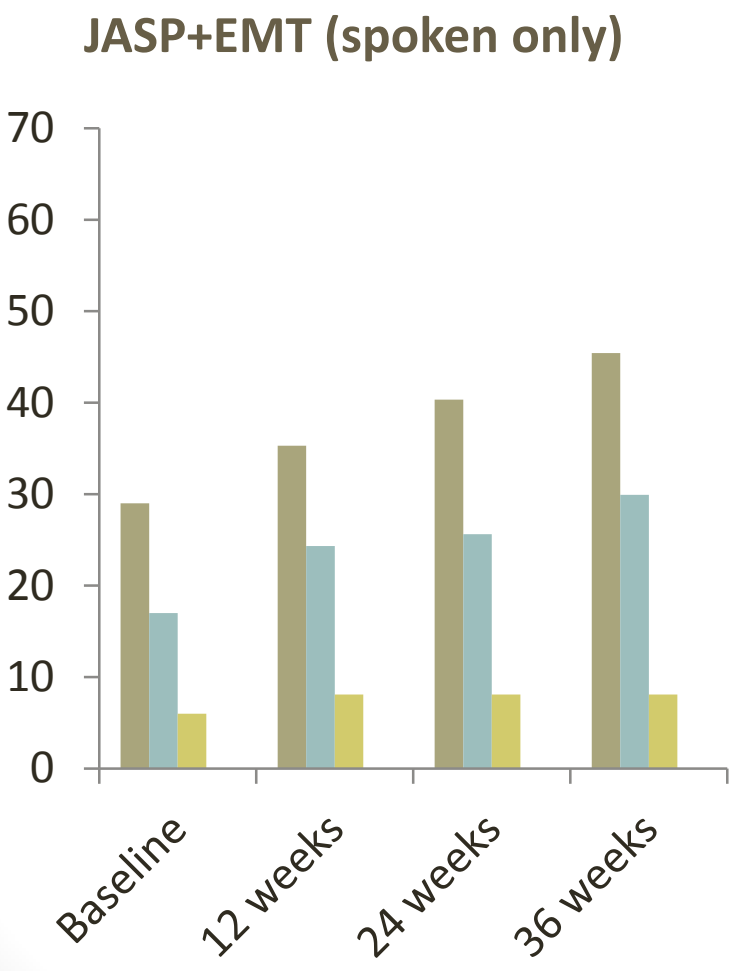


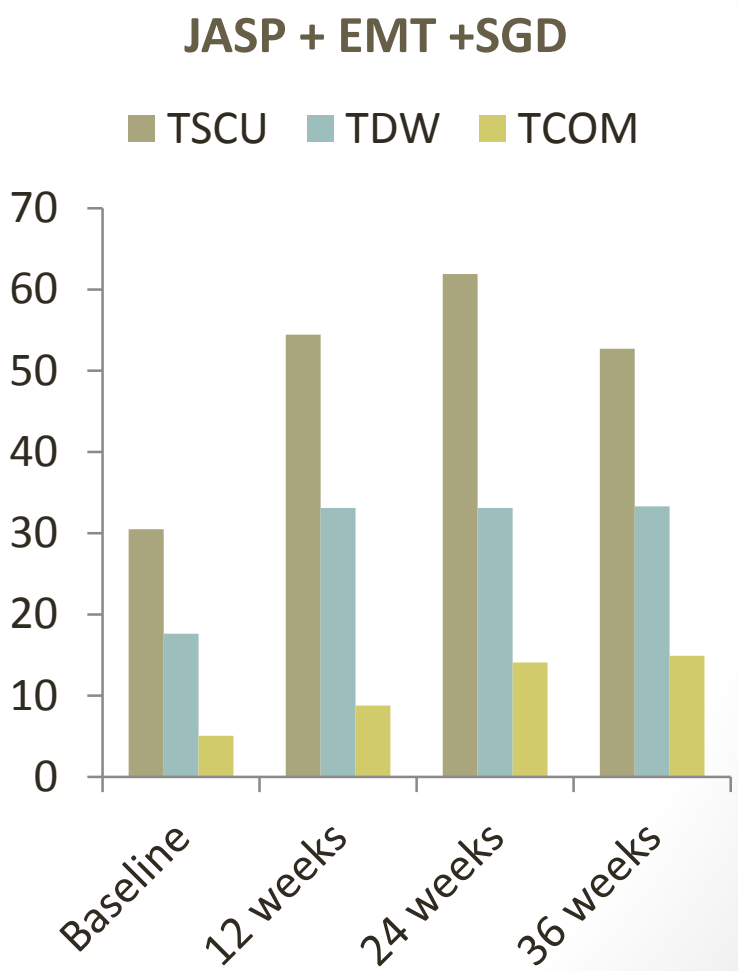
Open plotting characters denote observed means; closed denote model-estimated means. Error bars denote 95% confidence intervals for the model-estimated means.

Results

- **AIM 1**
- **Secondary outcome measures**
- Greater percentage of participants in the JASP + EMT+ SGD group (77%) were early treatment responders than in the JASP +SGD group (62%)
- Participants in the JASP + EMT +SGD group had :
  - greater Number of Different Word Roots (NDW),
  - more comments (COM) than participants in JASP+ EMT group

Outcomes 12, 24 & 36 weeks





Results

- **Aim 2: To compare the outcomes of three adaptive interventions**
- Adaptive interventions beginning with JASP+EMT+SGD and intensified JASP+EMT+SGD had the greatest impact on SCU at 24 and 36 weeks (MN 58.5; 52.5) ($p<.05$)
- Adaptive interventions which augmented JASP+EMT with SGD led to greater SCU (MN 42.7) than the adaptive intervention which intensified JASP+EMT (MN 39.6) (NS)

Summary

- Using blended JASP-EMT, minimally verbal children can make significant progress in social communication after age 5
- Children gain more in SCU, NDW and comments when they begin JASP-EMT treatment with an AAC device
- Children who were slow responders, gained more in SCU when adapted interventions included SGD
- AAC device can be effective when used within the context of a naturalistic intervention teaching foundations of communication with others
- Results persist over time, but differences between groups are attenuated at followup; suggesting both approaches may have long term benefits

Future Research

- Promising results, need replication
- Small N for adapted treatments; comparisons should be interpreted with caution
- Ongoing NIH-ACE study extends current study to larger sample and compares to DTT
- Research is needed to determine the potential for developing spoken language in minimally verbal children
  - Relate to benchmarks for communication development
  - Extend adaptation to include additional active ingredients of effective treatment
  - Use of SMART design to continue studying adaptions

Acknowledgements

- Funding Agency : Autism Speaks # 5556
- Families and Children who participated
- UCLA, Vanderbilt and Kennedy Krieger Research Teams

- For more information
  - Ann.Kaiser@Vanderbilt.edu
  - Kasari@gseis.ucla.edu

RESCUE PROTOCOL FOR NON-RESPONDERS: EVIDENCE BASED CLINICAL DECISION- MAKING

Connie Kasari, Ph.D.
Bruce Chorpita, PhD
University of California, Los Angeles

The issue

- Researchers, clinicians and parents recognize that for interventions, one size does not fit all

- Given this situation, WHEN and HOW do we make decisions about WHAT to change in an intervention?

- Clinical decision making in practice…..
  - Sometimes even when child is not making progress we stick to the protocol (when we should change something)
  - Traditionally researchers are concerned with whether the protocol is implemented with fidelity
  - In practice we want to know, 'What progress is the child is making?'

To reiterate…..

- We are concerned with helping children who are ‘minimally verbal’ and school aged to ‘talk’ more
  - Spontaneous communication (via spoken language and/or AAC)
  - For functions other than just responding or requesting
- These are children who have already been exposed to early interventions (some of them with large doses of top notch treatments)
- But they remain minimally verbal far longer than majority of children (most talk by age 5-6 years)
- We need to uncover what aspects of treatments work for these children---what WE need to do to help them!

We learned from previous SMART trial

- We assigned all children to the same JASP-EMT intervention with or without the support of SGD
- Learned that children's outcomes were better with SGD (outcomes = # socially communicative utterances)
- If children made slow progress we re-randomized them to augmentation (addition of the SGD or increased sessions
- Clinicians HOWEVER believed that some children making slow progress might have benefitted from other strategies or modules of intervention
  - For example, more discrete trials for skills (e.g. DTT), or anxiety reduction strategies
  - Thus we needed to think about other manualized and evidence-based interventions to bring in for children making slow progress
- This information influenced the next SMART

CONSIDERATIONS FOR NEXT STUDY

AIM-ASD SMART

- We chose 2 initial treatments, both evidence-based to improve language outcomes--- DTT (discrete trial training) or to JASP-EMT
  - DTT because some children would benefit from well implemented DTT given previous history with ABA
  - JASP-EMT because it was efficacious in last SMART trial

- All children were given access to communication system
  - Picture Exchange Systems (PECS) since DTT typically involves PECS
  - SGD for JASP-EMT (now commonly iPad with Proloquo2go software)

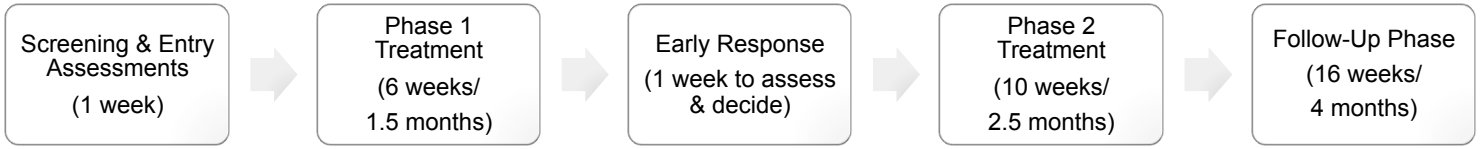
AIM-ASD SMART

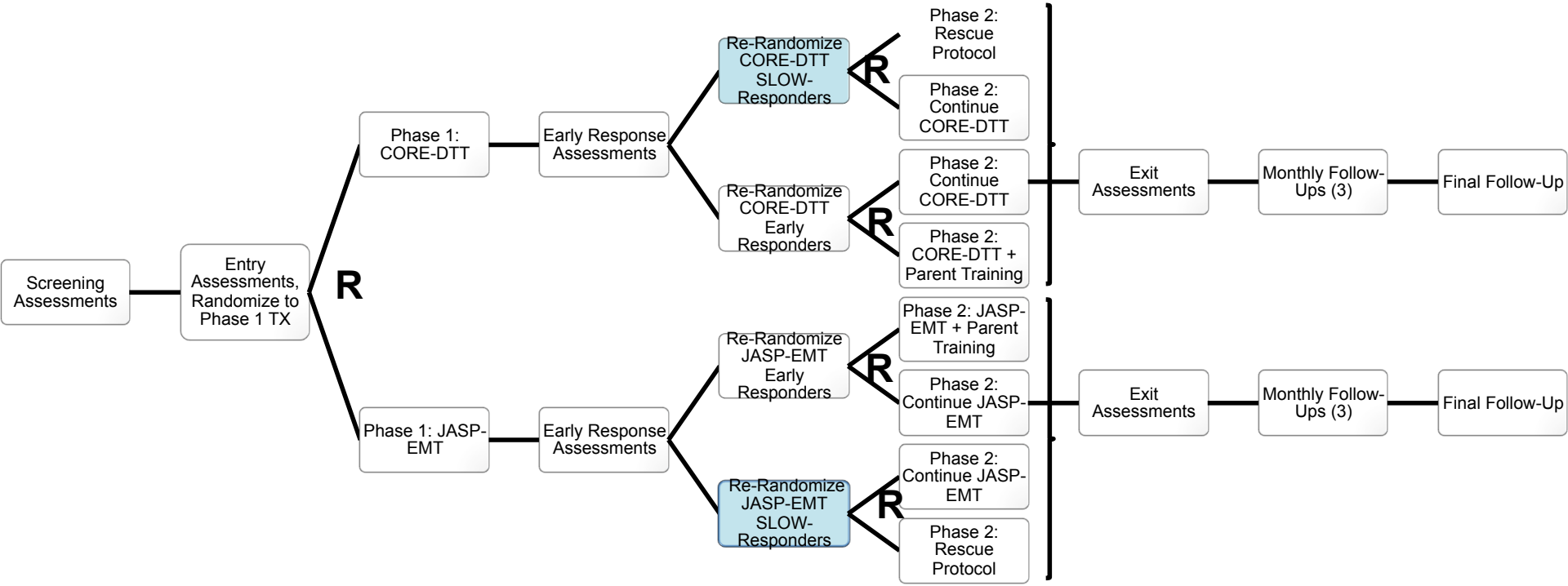
- From our previous experience we knew we could expect quick progress (after about 24 – 30 sessions) for about half of all children—they respond well to the intervention they are assigned

- But this also means that about half will be slow responders to the interventions
  - These children may just need more time
  - OR that the intervention they are receiving needs augmentation

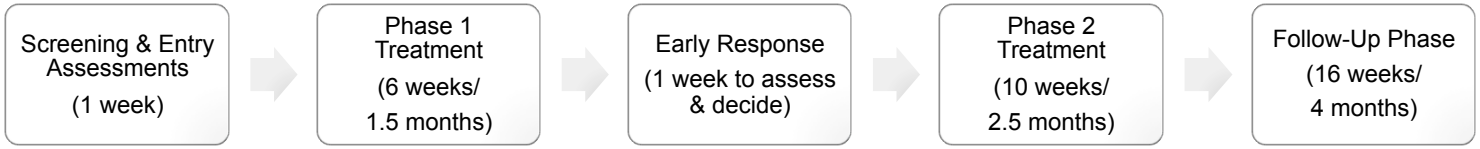
- To augment slow responders this study, we created a 'rescue protocol' involving aspects of all three manualized treatments

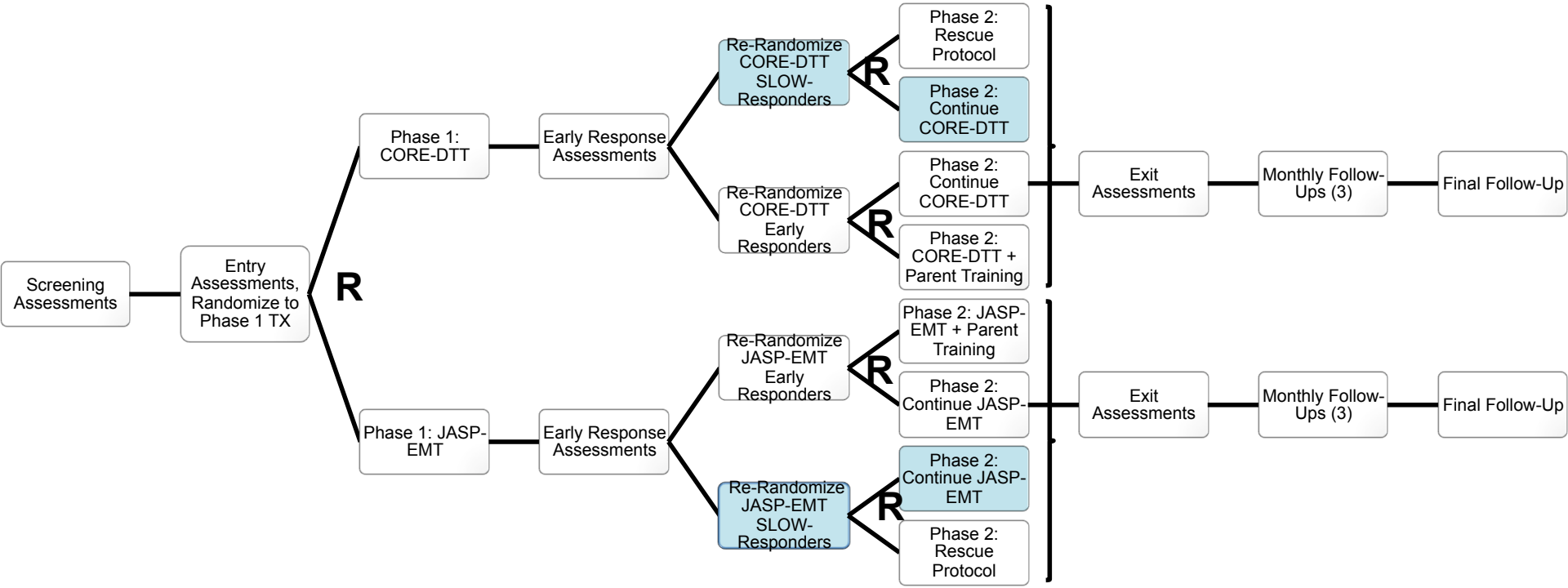
AIM-ASD Design Overview



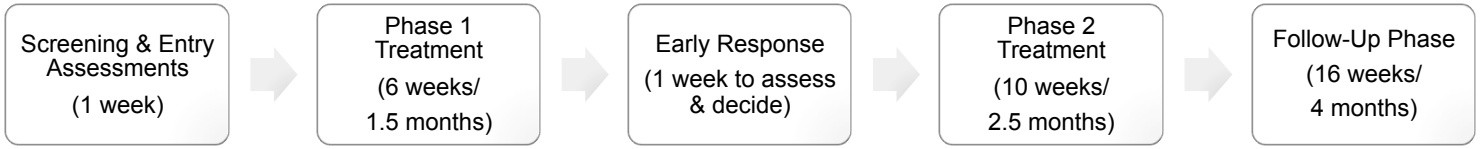


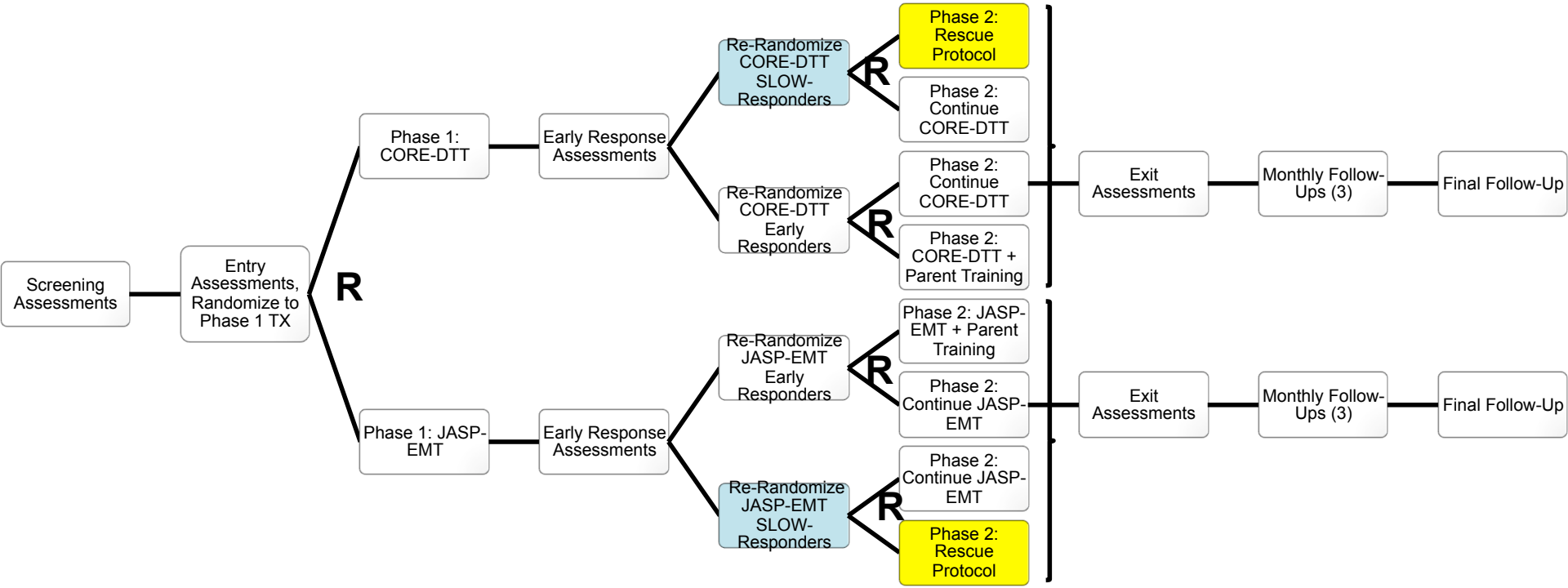
AIM-ASD Design Overview





AIM-ASD Design Overview





Rescue protocol

- For children randomized to receive a 'rescue protocol' if they are making SLOW progress at the 6 week responder stage

- RESCUE involves the *combination of all treatments (DTT and JASP-EMT) as appropriate* to move child to positive trajectory

- Rescue protocols involve highly individualized plans that are culled from existing manualized (and evidence-based) protocols

RESCUE PROTOCOL

Given highly individualized nature of the protocol, how do we systematize and document change?

Some precedent……

- Dashboards for mapping treatment plan and progress in other areas of childhood disorders (Chorpita et al, 2008)

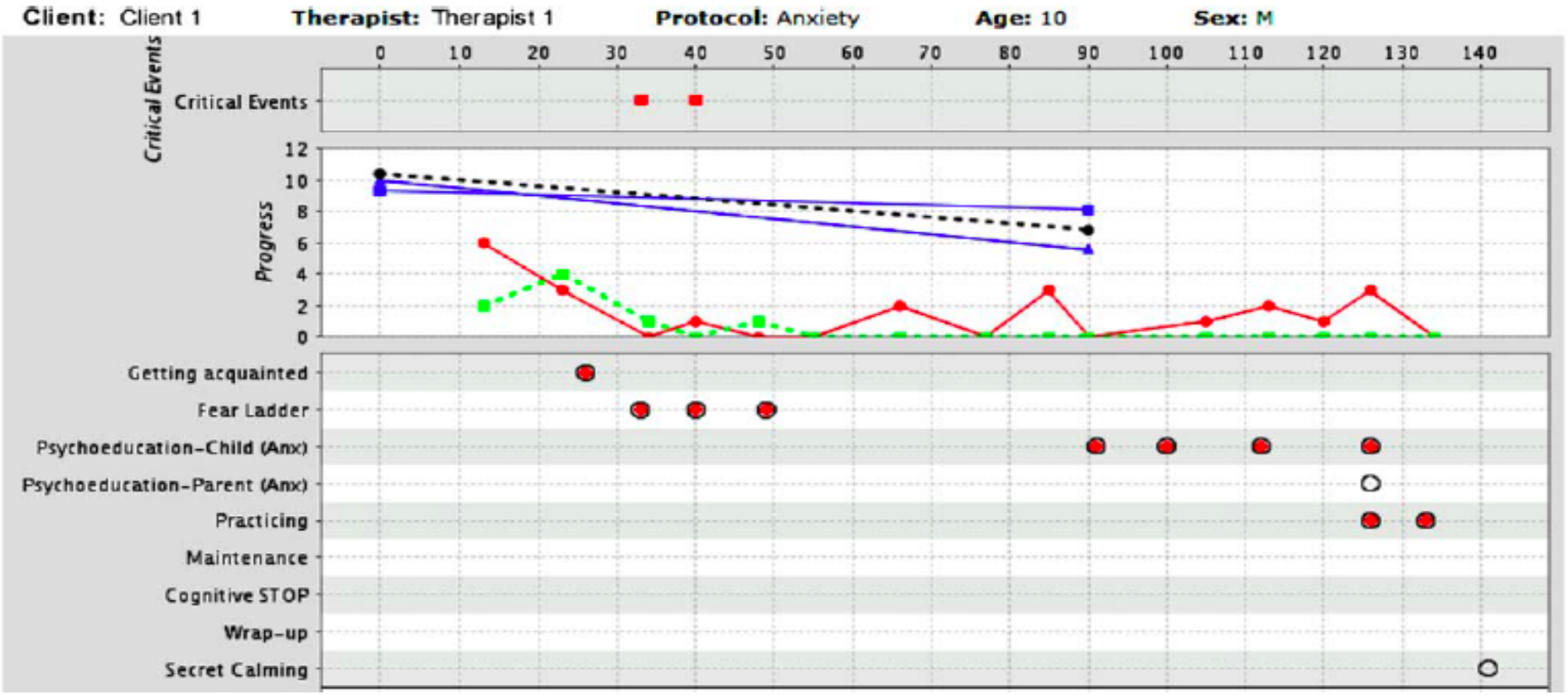
- Involves clinical decision making……
  - Balance of evidence based planning and informed adaption
  - Use of evidence based modules (the idea of distillation and matching) (Chorpita & Daleiden, 2013)
  - Distilling the strategies and components of effective treatment and matching to the characteristics of the child

Adm Policy Ment Health (2008) 35:114–123
DOI 10.1007/s10488-007-0151-x

ORIGINAL PAPER

Driving with Roadmaps and Dashboards: Using Information Resources to Structure the Decision Models in Service Organizations

Bruce F. Chorpita · Adam Bernstein ·
Eric L. Daleiden · The Research Network on Youth Mental Health



In similar fashion…..

- We have developed data sheets to map treatment planning for an individual child using components of each treatment (DTT and JASP-EMT) and delivery details

- Information about our planning is documented, as well as the evidence of our attempts (data collected)

- Information from each week feeds into planning for the next with the primary goal of making child progress on outcome measure of concern (spontaneous communication)

Child ID: 20031 **Interventionist:** CDM
Date: 5.12.10 **Week:** 2
# of Sessions Completed: 4 **# of Sessions Missed:** 0

AAC

Type of AAC used:
- [x] iPad
- [ ] Sign
- [ ] PECS
- [ ] None
- [ ] Picture Symbols

100% JASP-EMT.

Type of Symbol Used:
- [ ] Real Picture of Object
- [ ] Mayer-Johnson symbols
- [ ] Real Photo of Related but Different Object
- [x] Proloquo2Go symbols

4 trials

JASP-EMT

Instructions: Please respond to the following questions using the rating scale below.
Rating Scale: 0 = frequently 1 = sometimes 2 = rarely/never

Routines
How often is the child engaged in play routines?
0 1 2
What level of structure/support is needed for the child to engage in play routines?
- [ ] None
- [ ] Heavy modeling
- [ ] Environmental arrangement
- [ ] Extra person present
- [x] Visual cues
- [ ] Table top

Comments: _____

Joint Engagement
How often was the child unengaged?
0 1 2
How often was the child object/person engaged?
0 1 2
How often is the child in a supported engaged state?
0 1 2
How often was adult support needed to maintain joint engagement?
0 1 2
Comments: _____

Joint Attention
Joint attention gesture target:
- [x] Point
- [ ] Show
- [ ] Give

How often does the child initiate joint attention gestures (i.e., point, show give)?
0 1 2
How often does the child imitate therapist's modeled joint attention gestures?
0 1 2
Comments: _____

Language
Child language target level:
- [x] 0-1 words
- [ ] 2-3 words
- [ ] 4+ words

How often does the child initiate spontaneous language?
0 1 2
How often does the child comment?
0 1 2
How often does the child request?
0 1 2
How often does the child need support to initiate? (i.e., EA, time delay, milieu episode)?
0 1 2
Comments: _____
How often does the child use a diversity of words (i.e., new words, repetitions)?
0 1 2
Comments: _____

Child ID: 2021 **Interventionist:** _____

Date: _____ **Week:** 1

# of Sessions Completed: _____ **# of Sessions Missed:** _____

Play

Child's play level:

☐ Simple play ☒ Combination ☐ Presymbolic ☐ Symbolic

Does the child initiate functional play acts within routines?

0 1 2

Does the child imitate therapist's modeled play acts?

0 1 2

Toys used: Engstarter, cookie monster, marble house, farm, puzzle/pig

Comments: _____

PRIMING TRIALS

NONE

Priming Target	Mon	Tues	Wed	Thur	Fri	Avg # of trials daily	Avg level of prompt required	Sufficient Progress? Yes or No	If No, Problem Solving Date
# of trials: Prompt: Accuracy:									
# of trials: Prompt: Accuracy:									
# of trials: Prompt: Accuracy:									
# of trials: Prompt: Accuracy:									
# of trials: Prompt: Accuracy:									

Generalization of Primed Skills to Play

Comments:

_____

_____

_____

_____

_____

_____

Rescue Log

Rescue Daily Session Log- Draft

Interventionist

# of Sessions Completed: (1~10)

# of Sessions Missed: (0~5)

% of Session JASP-EMT:

% of Session DTT:

Type of AAC used: (iPad, PECS, picture symbols, sign, none)- dropdown menu

Type of symbol used: (real photo of object, real photo of related but different object, Mayer-Johnson symbols, Proloquo2Go symbols)

Number of symbols in array per page:

Rescue log for routines

Routines

How often is the child engaged in play routines? ☐ (0~2)

What level of structure/support is needed for the child to engage in play routines?

- ☐ None
- ☐ Environmental arrangement
- ☐ Visual cues
- ☐ Heavy modeling
- ☐ Extra person present
- ☐ Table top

Comments

Rescue Log for Joint Attention

Joint attention gesture target:

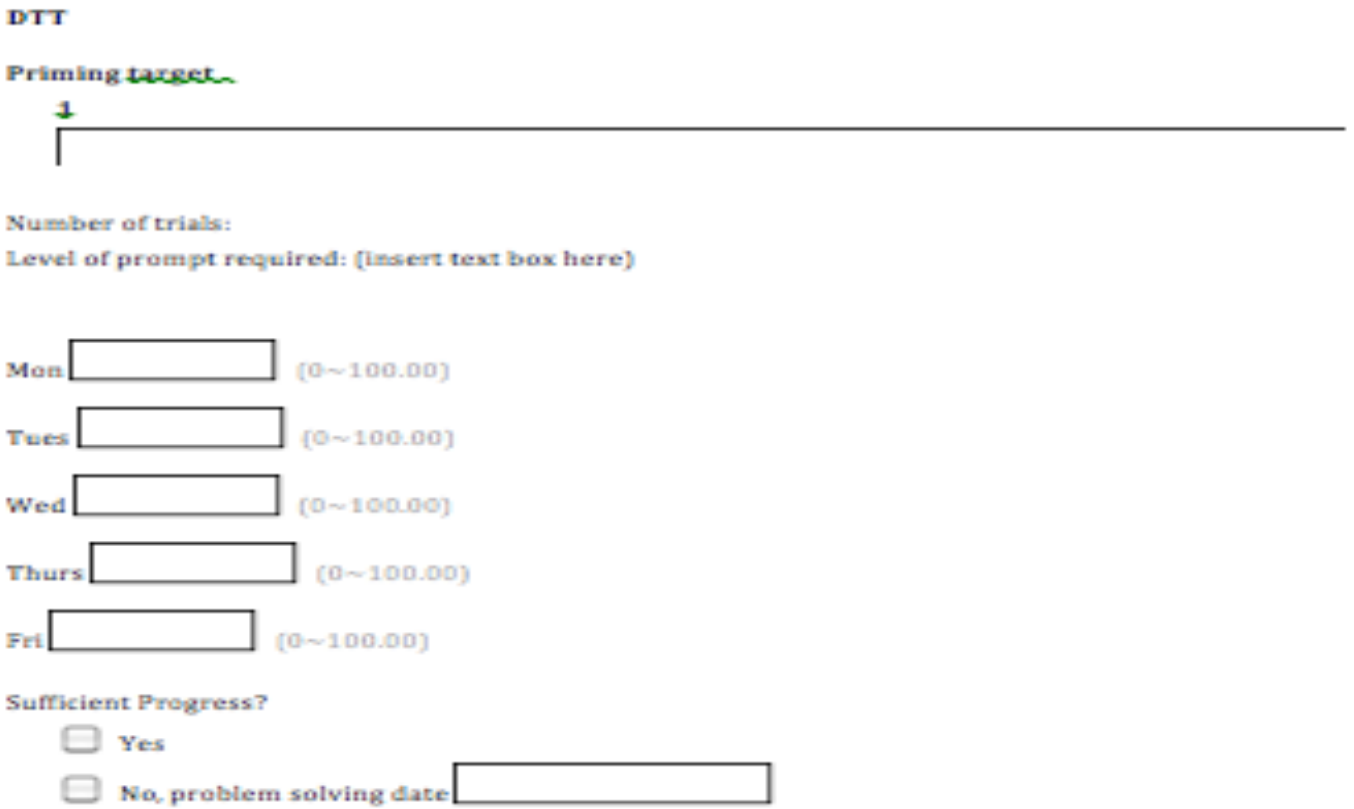
- ☐ Point
- ☐ Show
- ☐ Give

How often does the child initiate joint attention gestures (i.e., point, show give)? ☐ (0~2)

How often does the child imitate therapist's modeled joint attention gestures? ☐ (0~2)

Comments

Rescue Log for DTT priming



Rescue Log for Language

Child language target level:

- ☐ 0-1 words
- ☐ 2-3 words
- ☐ 4+ words

How often does the child initiate spontaneous language? ☐ (0~2)

How often does the child comment? ☐ (0~2)

How often does the child request? ☐ (0~2)

How often does the child need support to initiate? (i.e., EA, time delay, milieu episode)? ☐ (0~2)

Comments

Video Example

Conclusions

- The goal for us is to make use of the clinical dashboard system already developed

- What we hope to learn from this trial is what it takes to put all children (who are minimally verbal) on a positive developmental trajectory

- Understanding the ways in which treatments can be adapted is critical in further delineating evidence based practices, and the future of effective treatments for ASD

Adaptive Intervention for Minimally Verbal Children with ASD (AIM-ASD) (funding NICHD and NICDC)

Connie Kasari, PhD
UCLA

Ann Kaiser, PhD
Vanderbilt University

Catherine Lord, PhD
Weill Cornell Medical

Tristram Smith, PhD
University of Rochester

Statistical Core

Daniel Almirall, PhD Susan Murphy, PhD
University of Michigan

Data Coordinating Center

Catherine Sugar, PhD
UCLA

DEVELOPING AN ADAPTIVE TREATMENT STRATEGY FOR PEER-RELATED SOCIAL SKILLS FOR CHILDREN WITH AUTISM SPECTRUM DISORDERS

Wendy Shih, Stephanie Patterson Shire, and Connie Kasari

Outline

- Background
  - Social challenges for children with ASD in schools.
  - Need for adaptive treatment
- Purpose of our study
- Current study design
- Methods
  - Measure
  - Classification and Regression Tree (CART)
- Results
- Summary
- Conclusion

Background

Autism spectrum disorder (ASD) influences children's development in the domains of communication, social skills, and behavioral flexibility.

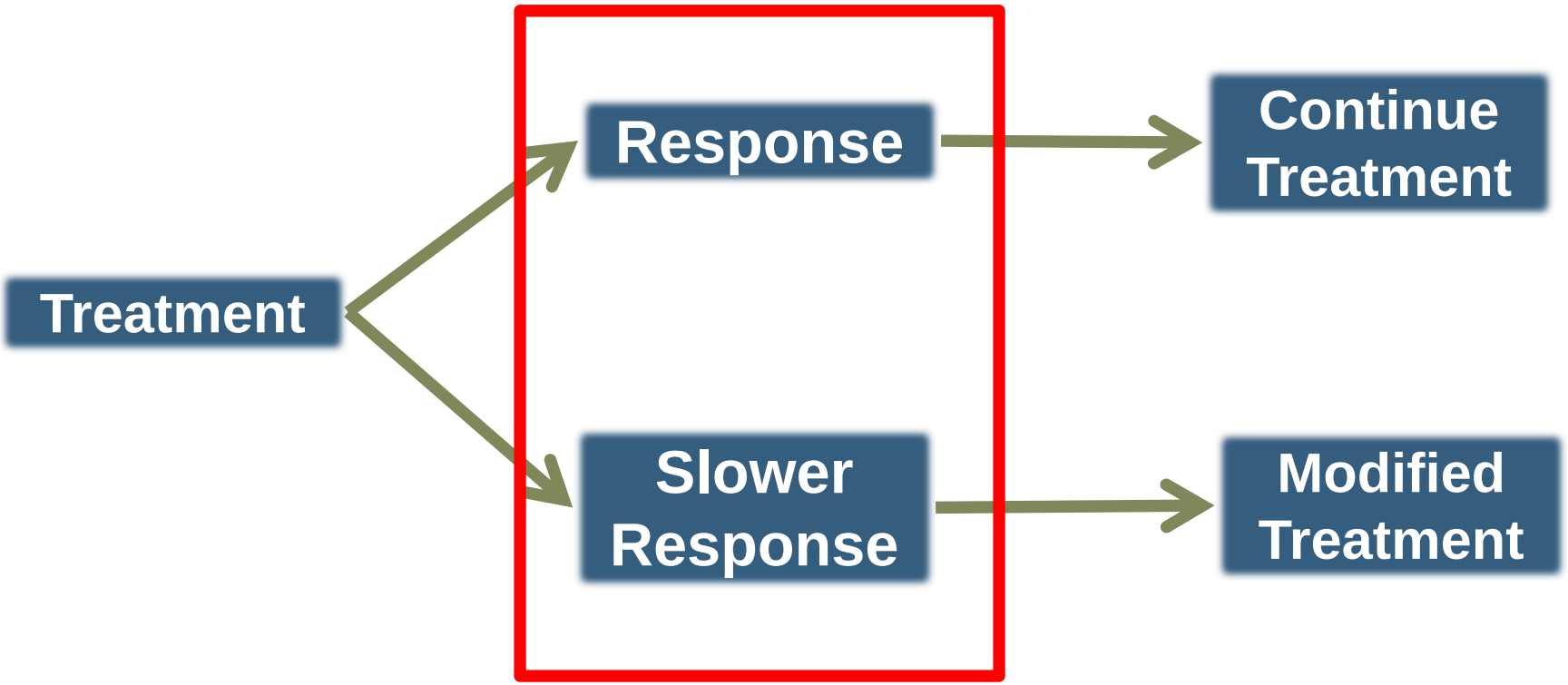
Background

Background

- Interventions have been developed to address the social challenges experienced by many children with ASD, but with mixed success

- One-size-fits-all approach to social skills intervention may not maximize the potential of this wide range of children with ASD

Adapting interventions based on children's response to intervention is a necessary next step that is currently limited in the autism research literature.



Most interventionists rely on their own expert clinical judgment, the consensus judgment of those around them, and behavioral theory to determine when treatment should be altered.

Purpose of Study

- Our study focuses specifically on the following question: “For children with autism who are receiving a social skills intervention, ***is it possible*** to identify early who are the children in need of an intervention modification based on playground observations of peer engagement?”

- In order to begin developing high quality adaptive interventions in autism, an important open question is ***how*** to identify early on (i.e., during treatment) the children who need a modification in their treatment.

Current Study Design

- Randomized controlled trial comparing two different social skills interventions conducted in elementary schools
  - ENGAGE (*n*=82) and SKILLS (*n*=68).
- Excluded
  - Exhibited procedural deviation
  - Had engagement similar to typically developing peers at entry (*n*=21, 14%)

Current Study

Variable: Mean (SD)	All Children (N=92)	SKILLS (*n*=40)	ENGAGE (*n*=52)	p-value
Male: *n* (%)	75 (81.50%)	21 (80.00%)	43 (82.70%)	0.953
Age	8.14 (1.39)	8.1 (1.46)	8.17 (1.34)	0.804
Race: *n* (%)				0.83
African American	10 (10.87%)	4 (10.00%)	6 (11.54%)	
Caucasian	39 (42.39%)	18 (45.00%)	21 (40.38%)	
Hispanic	16 (17.39%)	5 (12.50%)	11 (21.15%)	
Asian	16 (17.39%)	8 (20.00)	8 (15.38%)	
Other	4 (4.35%)	2 (5.00%)	2 (3.85%)	
Missing	7 (7.61%)	3 (7.50%)	4 (7.69%)	
ADOS Diagnosis: Autism *n* (%)	75 (81.52%)	30 (75.00%)	45 (86.54%)	0.253
ADOS Subscales				
Communication	4.26 (2.05)	4.00 (2.09)	4.46 (2.01)	0.286
Reciprocity	9.38 (3.00)	8.90 (3.06)	9.75 (2.92)	0.179
Social Communication	13.52 (4.86)	12.62 (5.10)	14.21 (4.60)	0.121
Imagination	0.92 (0.77)	0.95 (0.88)	0.90 (0.69)	0.778
Stereotypical	3.00 (2.28)	3.02 (2.36)	2.98 (2.24)	0.927
IQ (Stanford Binet 5)	89.58 (15.32)	90.62 (16.03)	88.81 (14.88)	0.580
POPE Engagement at Entry (%)	29.10 (22.40)	32.40 (22.95)	30.97 (22.65)	0.491

Methods: Measure

Playground Observation of Peer Engagement (POPE)

- The **POPE** is a time-interval behavior coding system.
- Observers watch for 40 seconds and code for 20 seconds.
- Outcome: POPE Engagement at end of study.
- Predictors: POPE Engagement at entry, midpoint, changes from entry to midpoint.

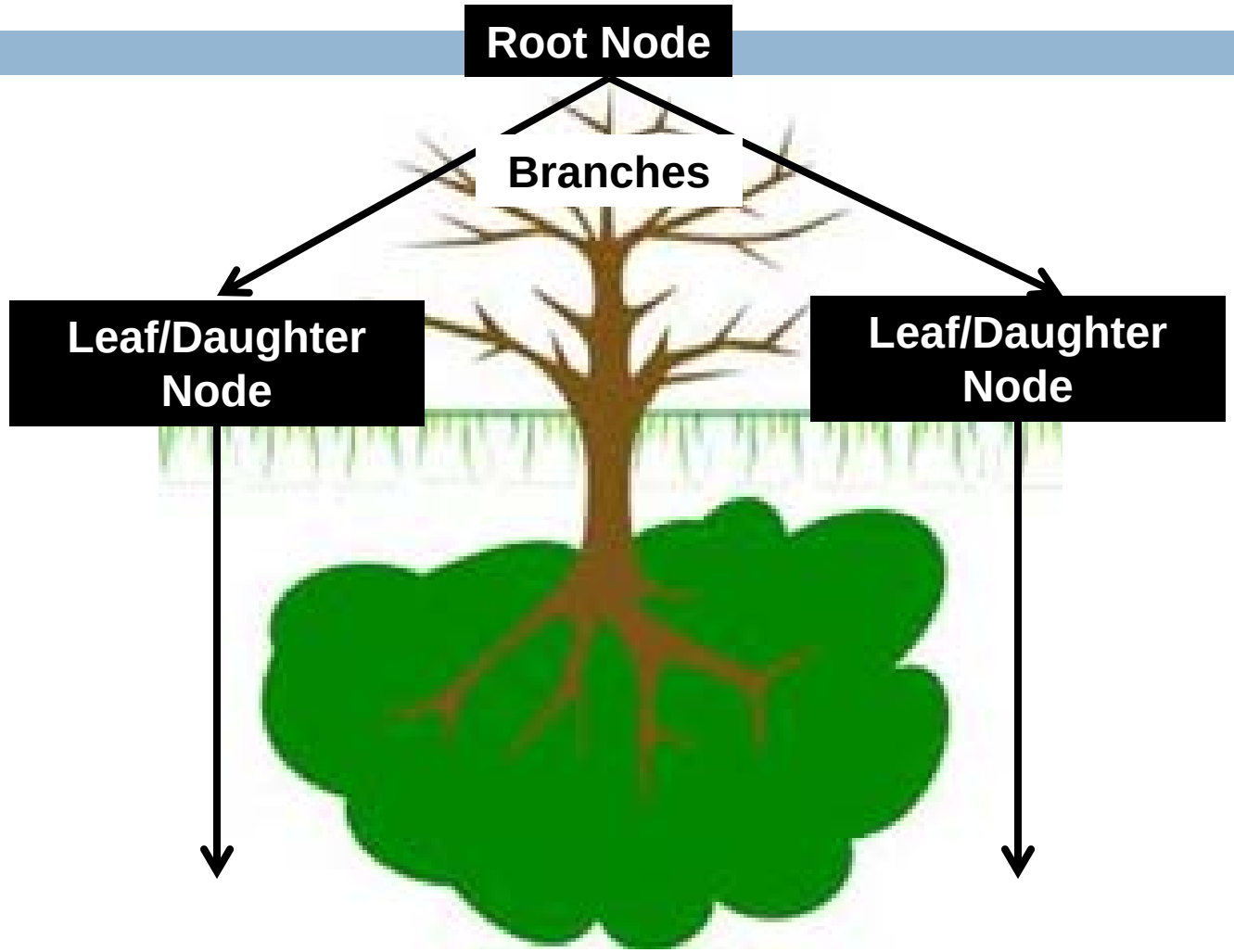
Kasari, C., Rotheram-Fuller, & Locke, J. (2005). Playground Observation of Peer Engagement (POPE) Measure. Unpublished manuscript: Los Angeles, CA: University of California Los Angeles.

Methods: Engagement States

Solitary	Onlooking	Parallel
Parallel Aware	**Joint Engagement**	**Games with Rules**

Kretzmann, M., & Kasari, C. (2012). The Remaking Recess Treatment Manual. Unpublished manuscript: Los Angeles, CA: University of California Los Angeles.

Methods: Classification and Regression Tree (CART)



Terminal subgroups: Set of Possible Outcomes

Breiman, L., Friedman, J., Stone, C. J., & Olshen, R. A. (1984). *Classification and regression trees*. CRC press.

Method: CART Overview

1. Splitting rule: search through all possible splits to choose the best splitter that minimizes impurity

- Purity
  - **Regression Trees** (continuous measure): use sum of squared errors.
  - Classification Trees (categorical measure): choice of *entropy*, *Gini measure*, "*twoing*" splitting rule.

2. Stopping rule:

- There is only one observation in each of the child subgroups
- All observations within each subgroup have the identical distribution of predictor variables, making splitting impossible

3. Assignment of each terminal subgroup to a class/value.

- **Average of the outcome variable in the terminal subgroup**
- Normally simply assign class based on the majority class in then subgroup

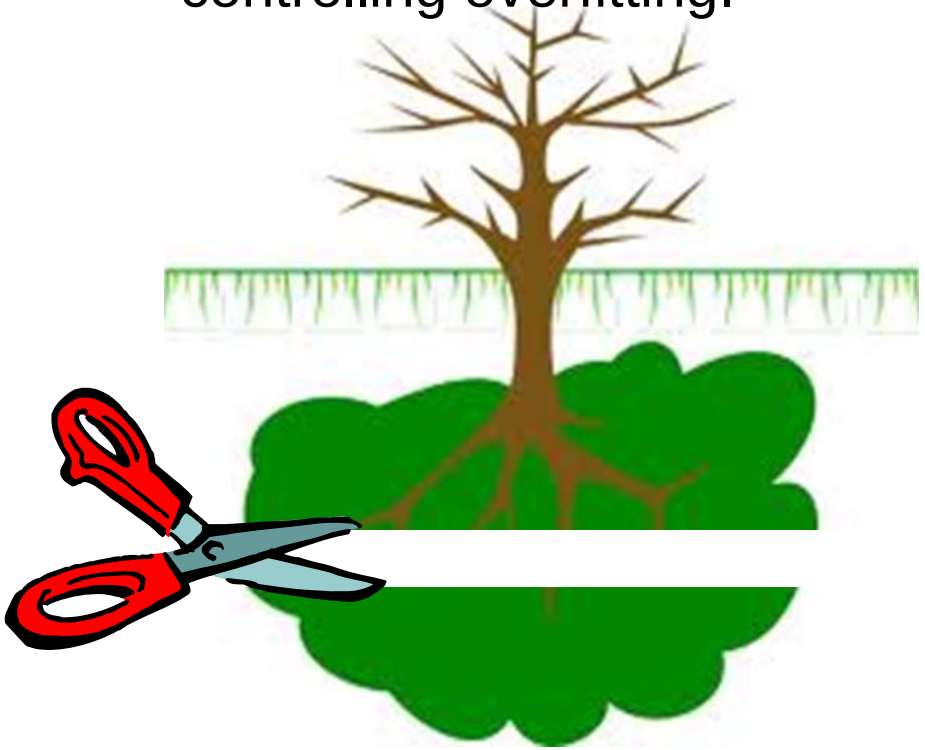
Methods: Strengths and Limitations of CART

Strengths

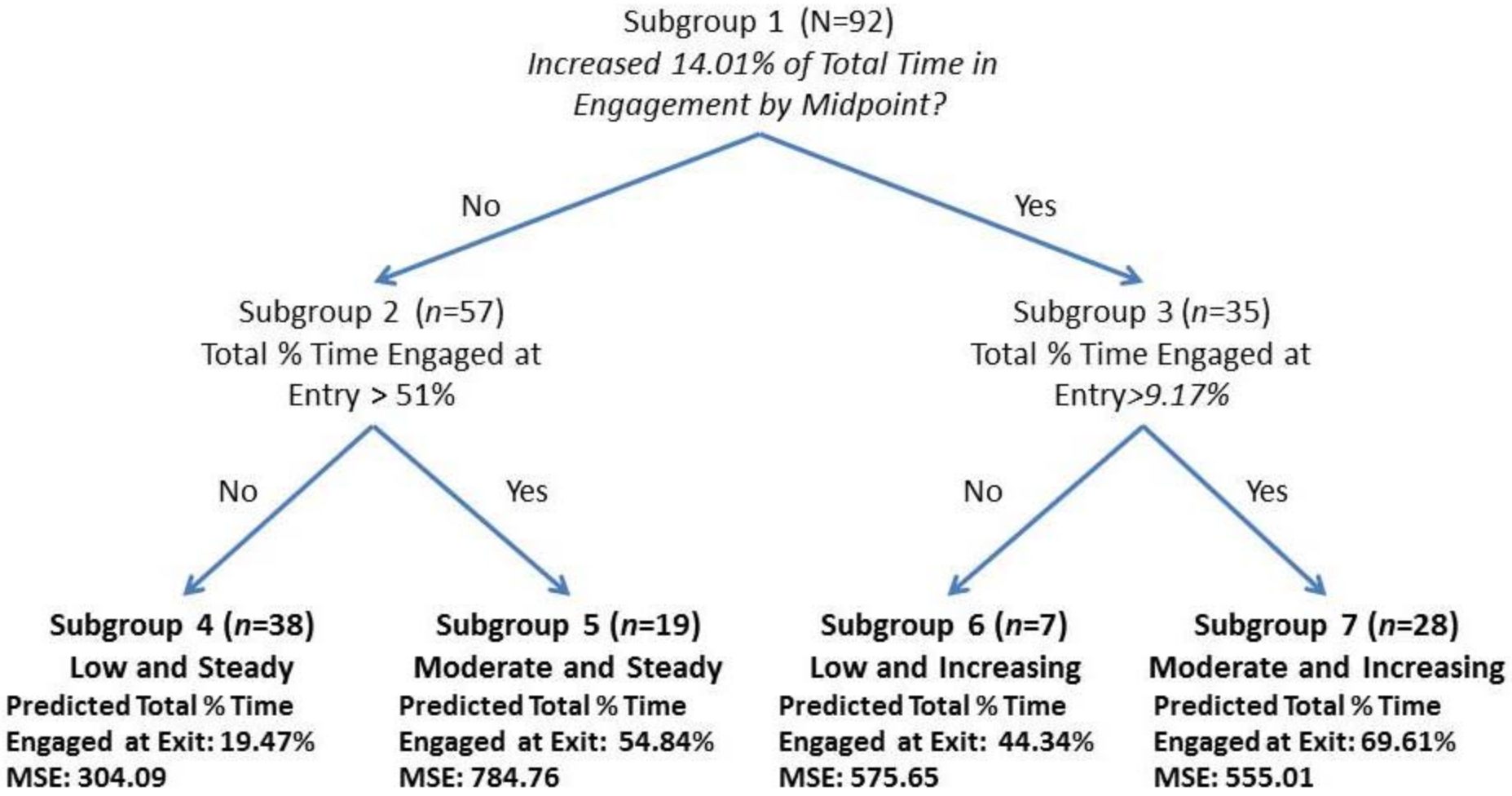
- Extremely fast at classifying unknown records
- Easy to interpret for small-sized trees; visually appealing
- Accuracy is comparable to other classification techniques for many simple data sets

Limitation

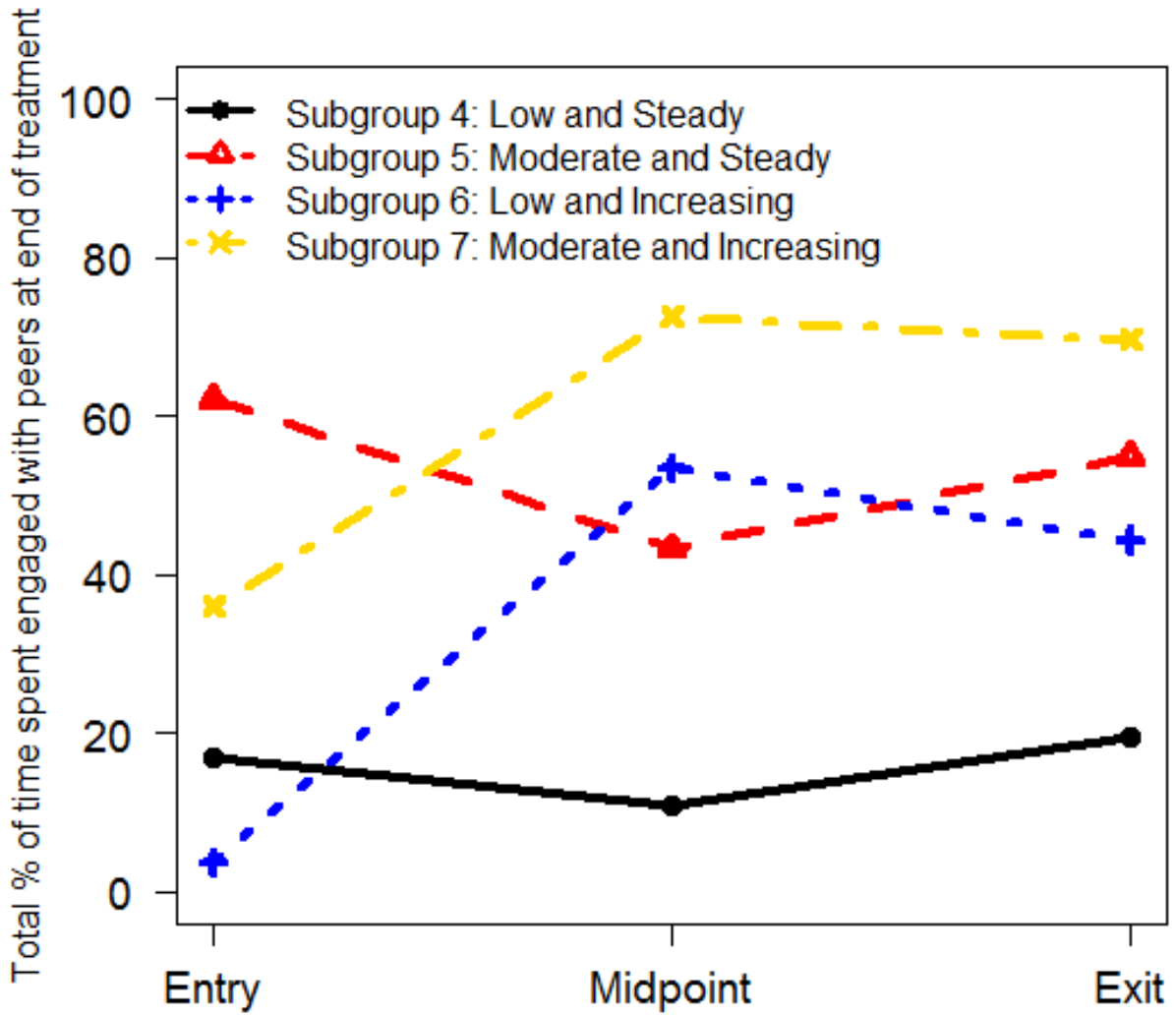
- Over-fitting
- Pruning is a strategy for controlling overfitting.



Results: POPE Engagement CART Tree



Results: Trajectories of Engagement by Identified Subgroups



Results

- The CART approach identified four meaningful subgroups based on the 92 children's total percentage of time engaged measured at entry and changes from entry to midpoint.

- Two subgroups of children who made little progress by midpoint were identified and this may suggest that they need additional supports to have positive peer engagement outcomes.

Result

Variable: Mean (SD)	Subgroup 4 Low and Steady	Subgroup 5 Moderate and Steady	Subgroup 6 Low and Increasing	Subgroup 7 Moderate and Increasing	p-value
Male: *n* (%)	30 (78.9%)	16 (84.2%)	7 (100%)	22 (78.6%)	0.571
Chronological Age	8 (1.47)	8 (1.45)	7.43 (0.98)	8.61 (1.23)	0.132
IQ (Stanford Binet 5)	85.32 (15.57)	94.16 (14.02)	91.86 (19.73)	91.54 (14.03)	0.160
Race: *n* (%)					0.070
African American	6 (15.79%)	2 (28.57%)	1 (5.26%)	1 (3.57%)	
Caucasian	18 (47.37%)	2 (28.57%)	6 (31.58%)	13 (46.43%)	
Hispanic	3 (7.89%)	2 (28.57%)	3 (15.79%)	8 (28.57%)	
Asian	9 (23.68%)	0 (0%)	5 (26.32%)	2 (7.14%)	
Other	0 (0%)	1 (14.29%)	2 (10.53%)	1 (3.57%)	
Missing	2 (5.26%)	0 (0%)	2 (10.53%)	3 (10.71%)	
ADOS					
Communication	4.92 (2.25)	4.26 (1.79)	4.43 (2.51)	3.32 (1.47)	0.017
Reciprocity	10.45 (3.01)	8.89 (2.47)	9.14 (4.18)	8.32 (2.64)	0.029
Social Communication	15.08 (5.33)	13.16 (4.02)	13.57 (6.45)	11.64 (3.67)	0.039
Imagination	1.03 (0.88)	0.95 (0.62)	0.71 (0.76)	0.82 (0.72)	0.646
Stereotypical	3.95 (2.68)	2 (2.05)	2.57 (0.98)	2.5 (1.53)	0.006
POPE Engagement %					
Entry	16.79 (14.98)	62.1 (8.42)	3.62 (3.71)	35.93 (13.68)	p<0.001
Midpoint	10.75 (14.18)	43.26 (24.61)	53.53 (21.81)	72.48 (19.06)	p<0.001
Exit	19.47 (17.67)	54.84 (28.78)	44.34 (25.92)	69.61 (23.99)	p<0.001

Summary

- The 1st split serves as a proxy for determining a potential cutoff for establishing treatment responder status → Increased by 14.01% in total time spent engaged change from entry to exit?

- These 2nd and 3rd splits can help define the resulting responder group or slow-responder group into more detailed subgroups. → Total % Time Engaged at Entry > 51%?

  Total % Time Engaged at Entry>*9.17%*

These subgroups may be clinically relevant due to the different rates of response and different amounts of change in intervals spent engaged with peers from study entry to midpoint.

Conclusion

- Substantial heterogeneity in children's response to treatment with multiple clinically salient subgroups embedded within the larger group
- Augmentation to the current intervention is needed
- CART can be useful in defining metrics that could be used to build an adaptive treatment sequences for children
- Future studies to further investigate these benchmarks may be useful in making treatment decisions

Acknowledgement

- Connie Kasari
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- Michelle Dean
- Mark Kretzmann
- And everyone in the Kasari Lab

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Thank You