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

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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

Sequential, Individualized Treatment is Often Needed

- Management of many health disorders 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 (unit).

- This type of sequential decision-making is necessary when there is high level of individual heterogeneity in response to treatment.
  - e.g., many chronic disorders, conditions for which there is no widely effective treatment, or conditions for which there are widely effective treatments but they are burdensome, costly, or carry side effects.
  - e.g., mental health, substance use, weight loss

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

Definition of an Adaptive Intervention

- 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.

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aka: dynamic treatment regimen/regime, adaptive treatment strategy, treatment policy, treatment algorithms, medication algorithms, etc.

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.
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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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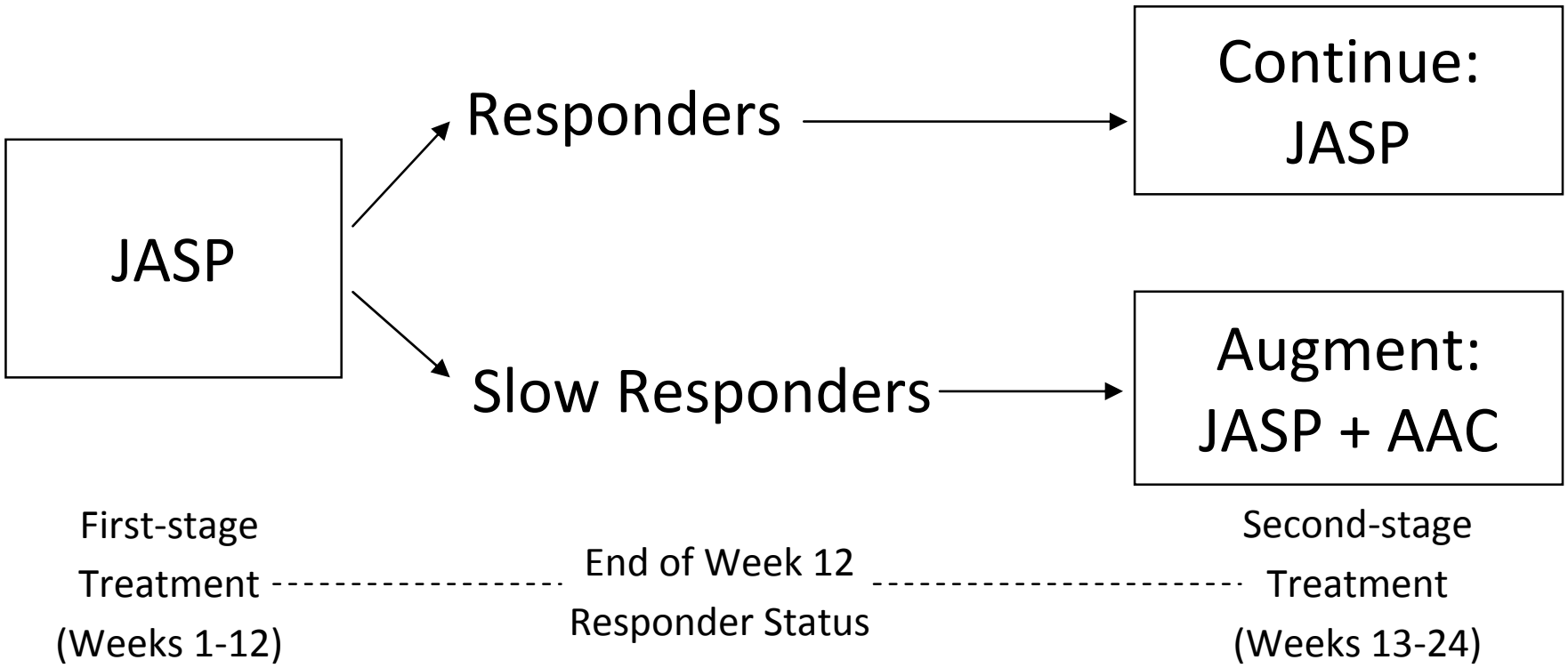

How was response/slow-response defined?

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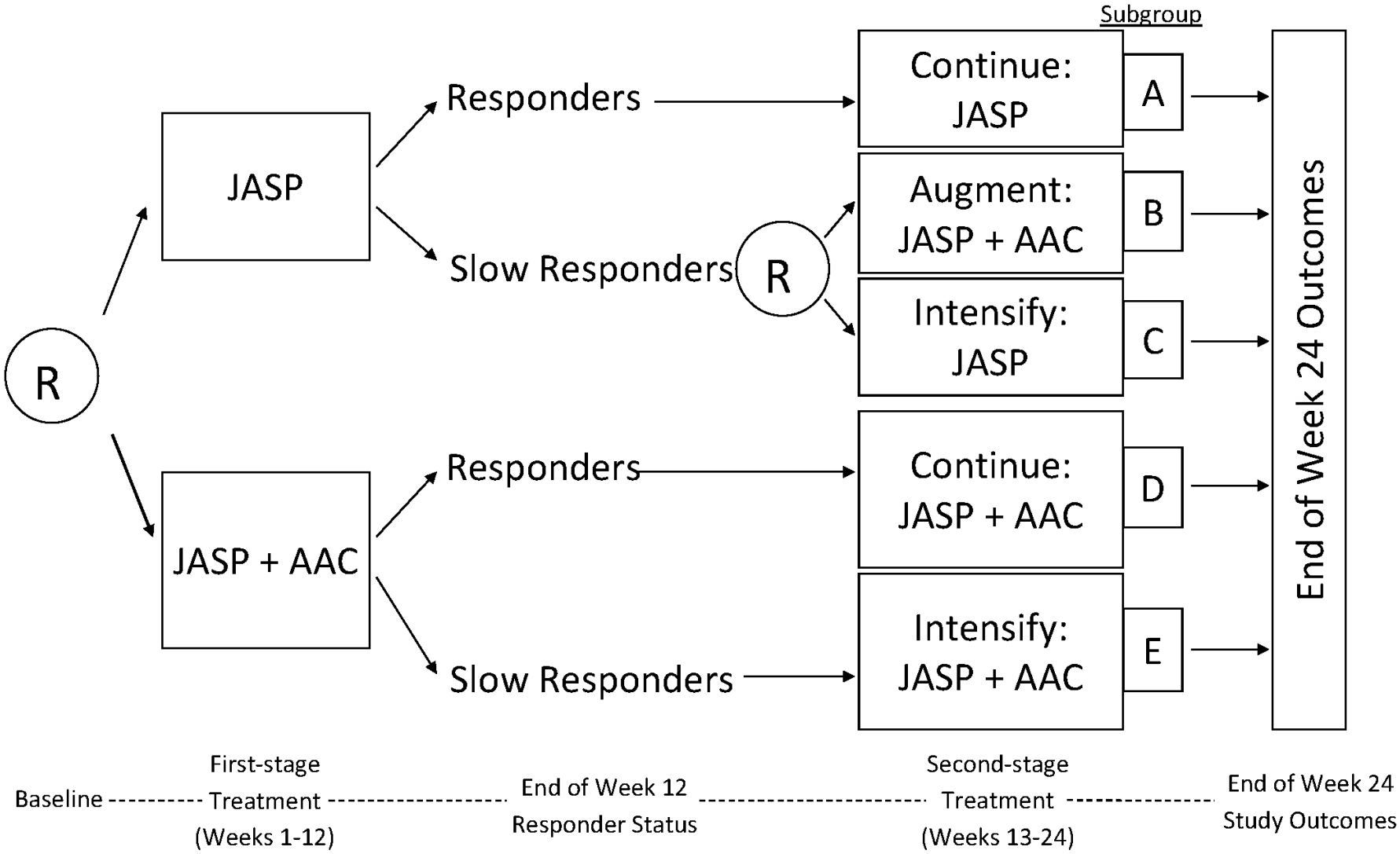
SMARTs were developed explicitly for the purpose of building a high-quality Adaptive Intervention.

On the Design of SMART Case Study 1

Example of a SMART in Autism Research

PI: Kasari (UCLA).

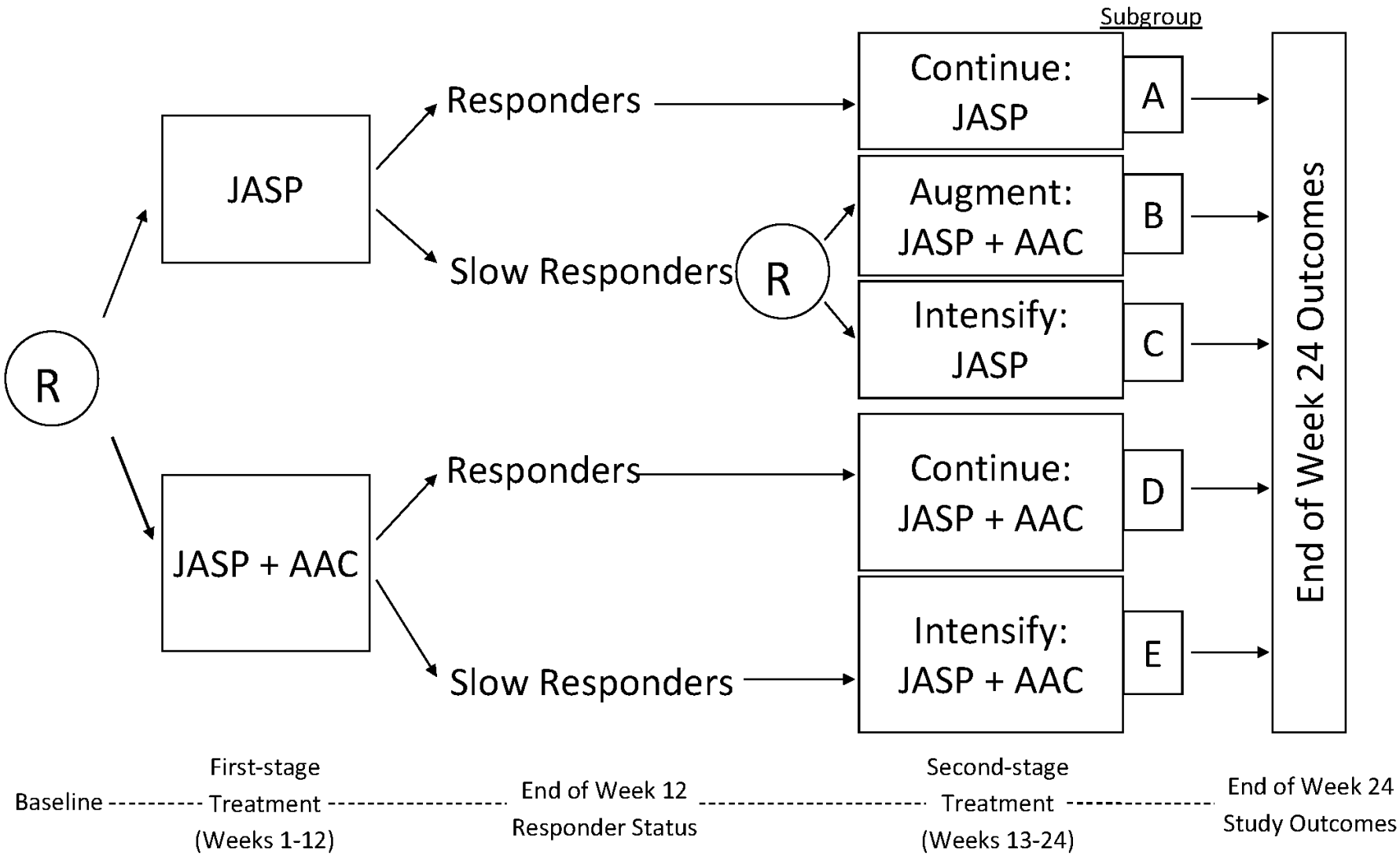


Example of a SMART in Autism Research

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:

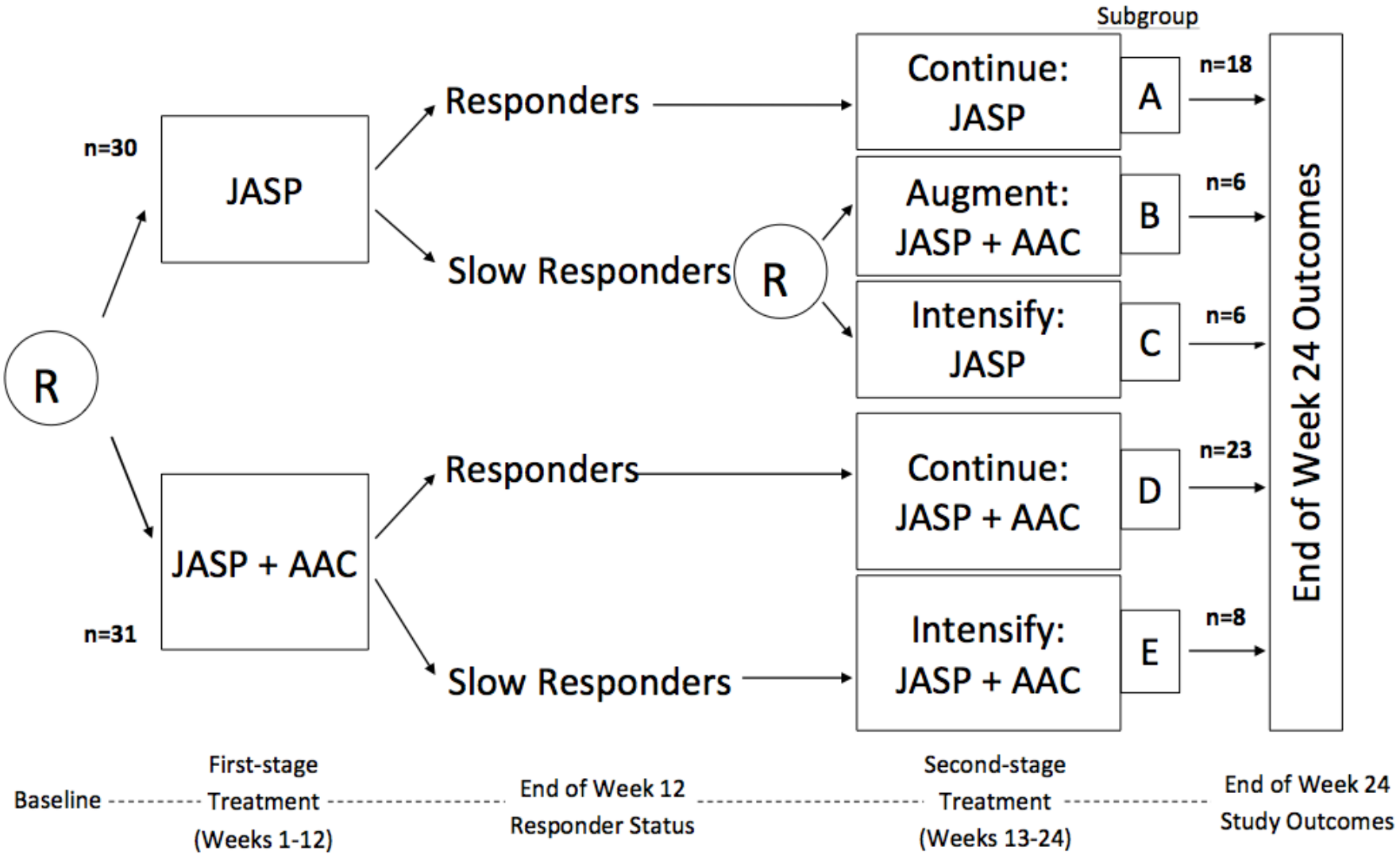
- Primary Aim: What is the best first-stage treatment in terms of spoken communication at week 24: JASP alone vs JASP+AAC?

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

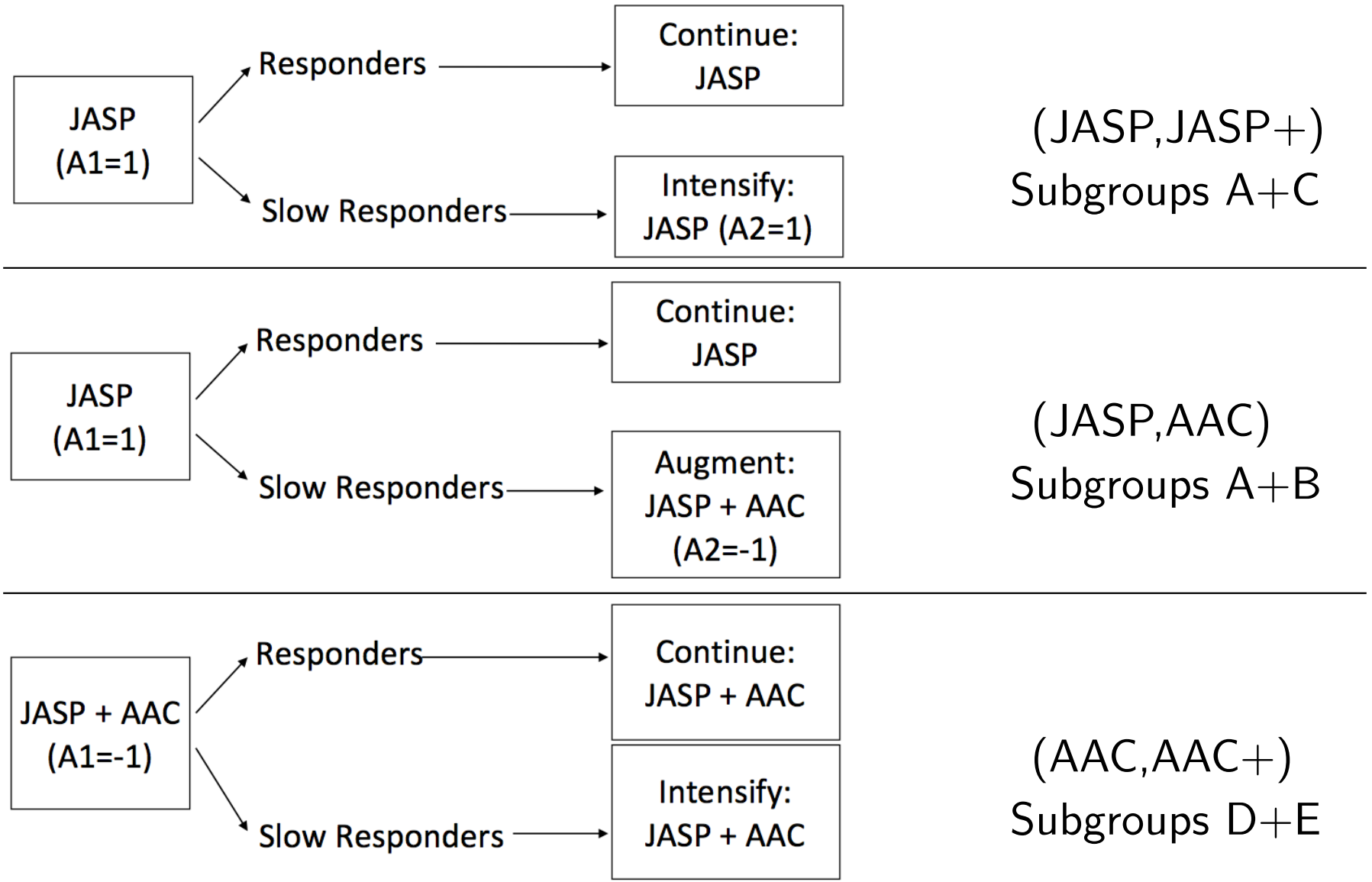
- Secondary Aim: Which is the best of the three adaptive interventions embedded in this SMART? (This is explained shortly.)

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

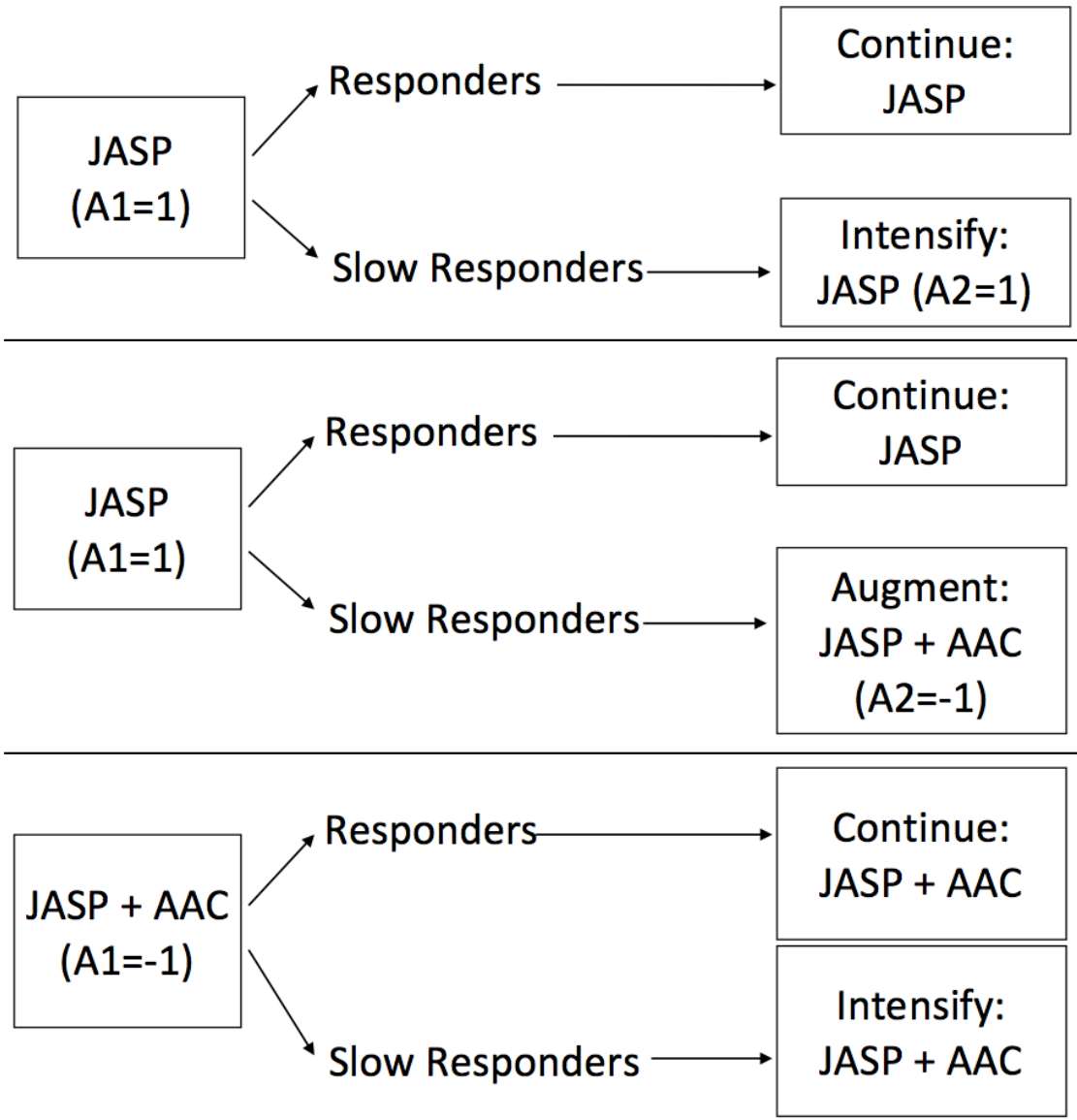
Challenges in the Conduct of this Initial Autism SMART

- 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

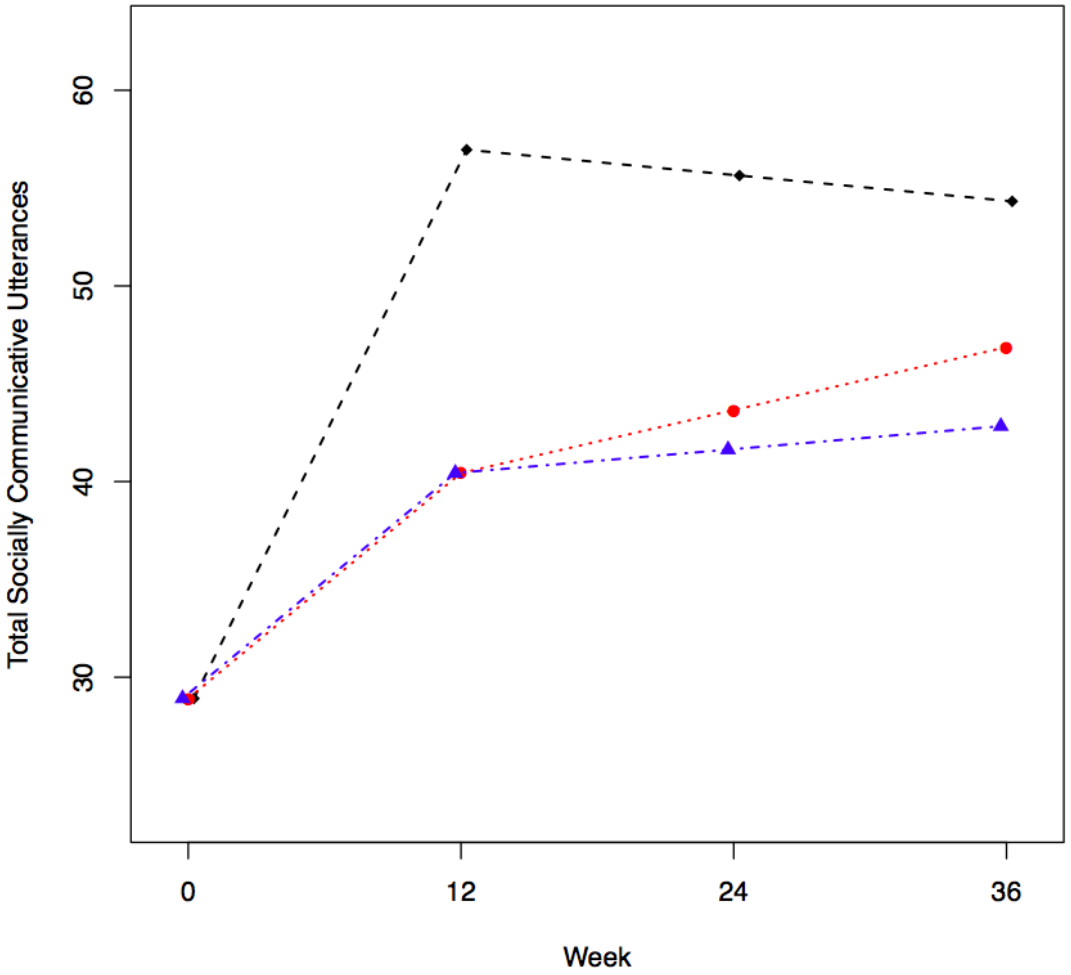


Results from an Analysis of the Autism SMART

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

	WRR Known Wt		
ESTIMAND	EST	SE	PVAL
Intercept	50.00	3.5	< 0.01
age	-0.96	2.8	0.73
male	2.08	14.9	0.89
white	-11.00	8.0	0.17
siteUCLA	8.12	9.2	0.38
siteVandy	10.14	8.8	0.25
scuBase	0.78	0.2	< 0.01
A_1	-10.5	3.9	< 0.01
$I(A_1 = 1)A_2$	-3.2	1.9	0.10
(AAC,AAC+)	60.5	5.8	< 0.01
(JASP,AAC)	42.6	4.9	< 0.01
(JASP,JASP+)	36.3	5.0	< 0.01
(AAC,AAC+) vs (JASP,JASP+)	24.3	7.9	< 0.01
(AAC,AAC+) vs (JASP,AAC)	17.9	8.2	0.03
(JASP,AAC) vs (JASP,JASP+)	6.4	3.8	0.10

Analysis of Longitudinal Outcomes in the Autism SMART



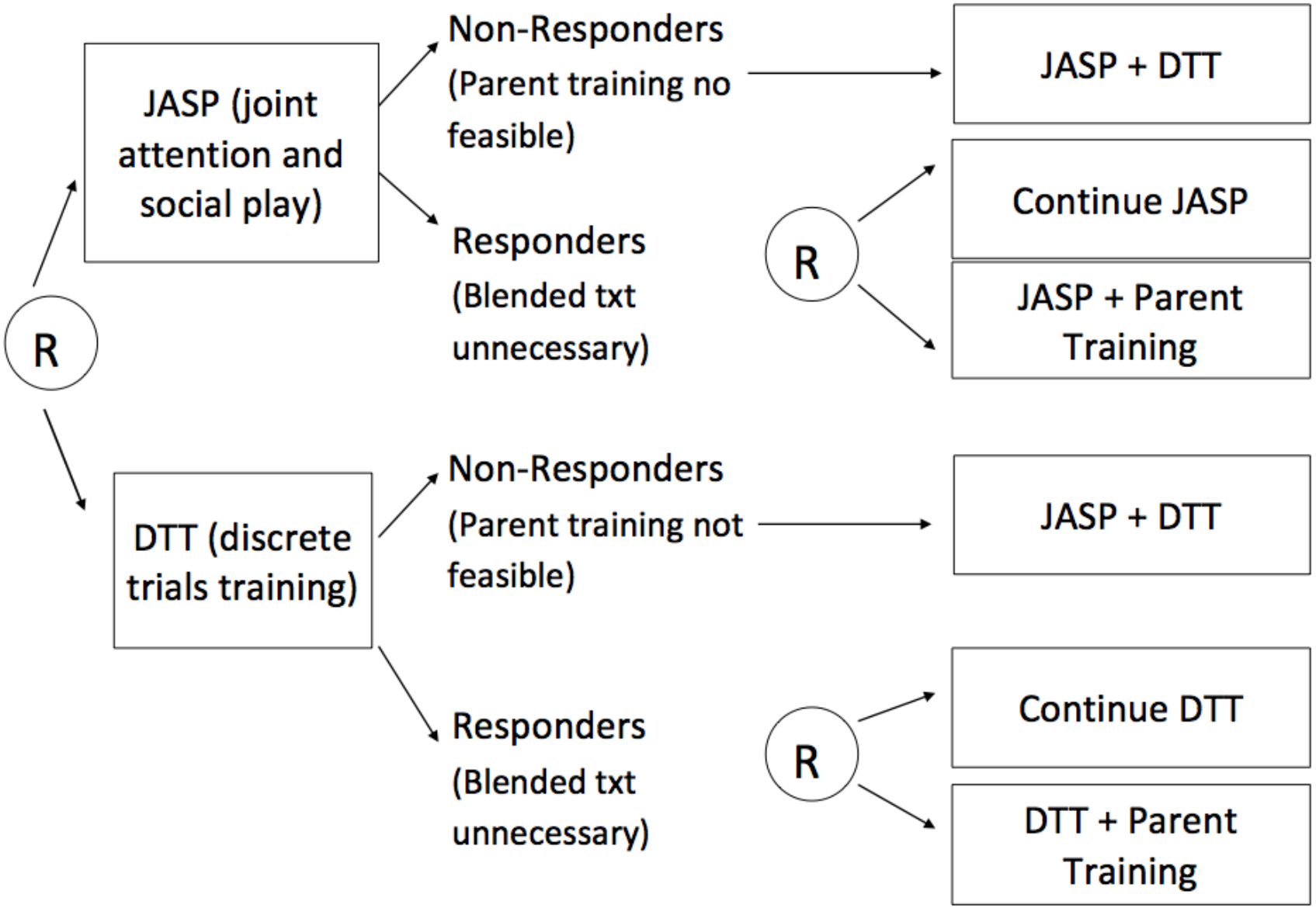
Average level of spoken communication over 36 weeks (i.e., AUC/36) for each AI

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?

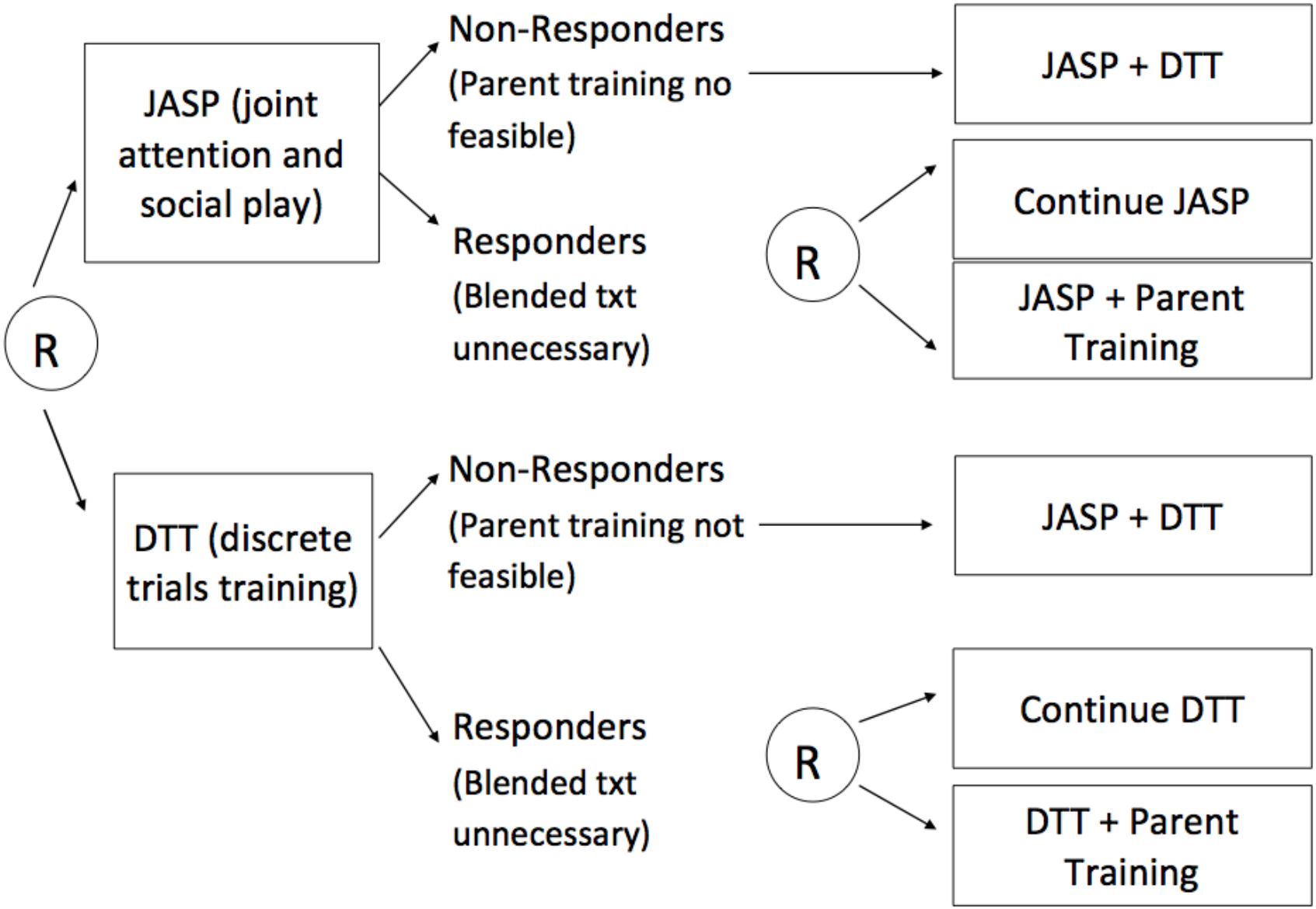
  (Study sized $N = 192$ for this aim; subgroups A+B+C vs D+E+F)

- 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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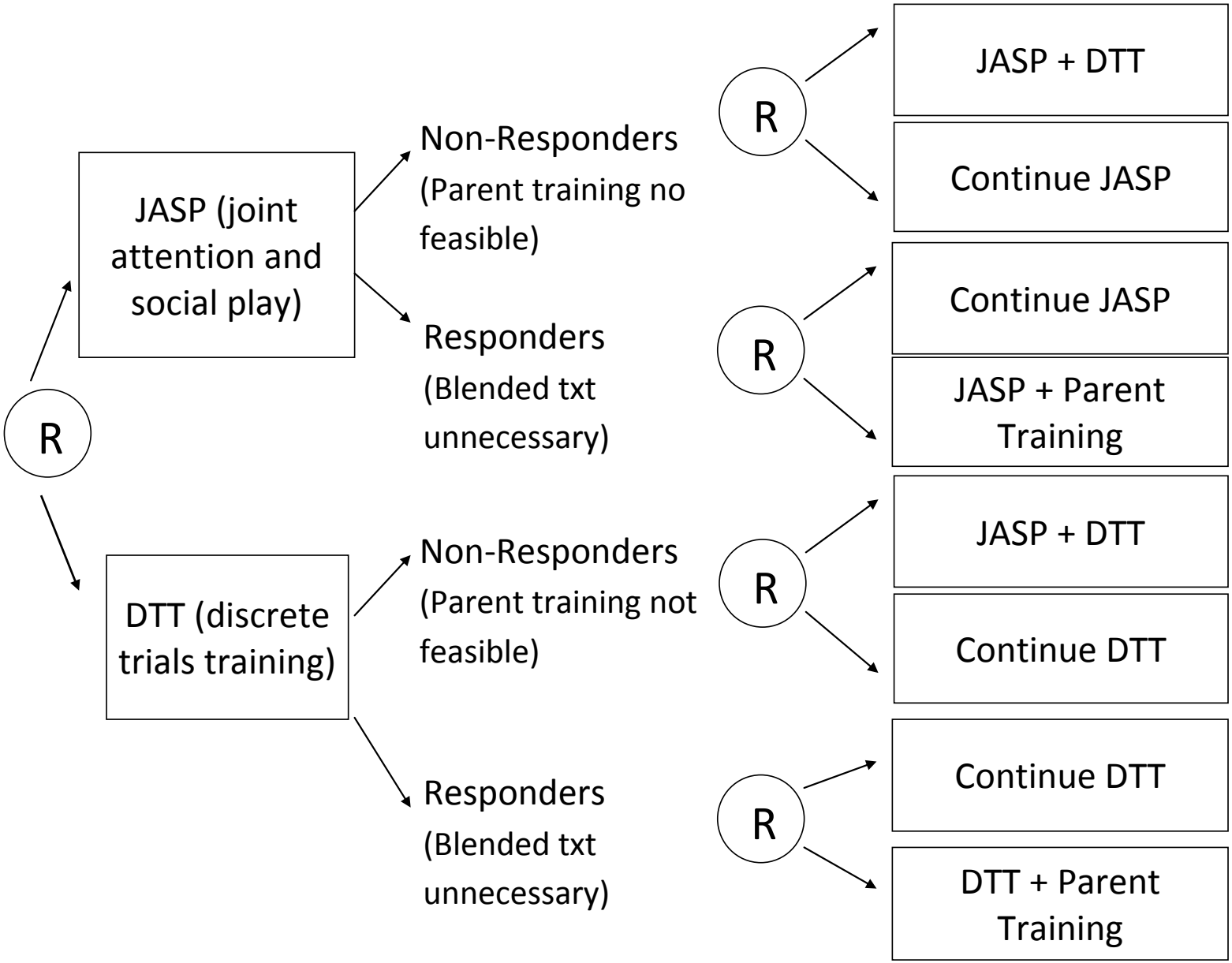
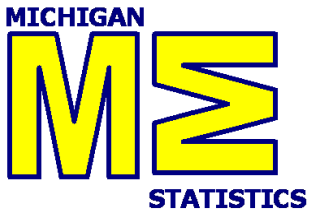


Conclusions and Some Final Remarks

- 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.
- SMART to optimize; then RCT to evaluate
  (SMARTs are one of the tools in the MOST toolbox)
- SMARTs are not "adaptive randomized trial designs" but they do inform "adaptive intervention designs"

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

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