On Adaptive Interventions and SMART

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Outline

- Adaptive Intervention (AIs)
  - What they are
  - Components
  - Motivation
- Sequential Multiple Assignment Randomized Trial (SMART)
  - How it can be used to inform the development of AIs
  - Key features
  - Sample size considerations
  - SMARTs vs. other designs
  - Examples of SMARTs

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Definition of AI

- An intervention design
- …in which intervention options are individualized to accommodate the specific and changing needs of individuals.
- A sequence of individualized treatments.
- Mimics how we make decisions in real-life
- … but aim to guide decision making in clinical, educational, health policy etc.

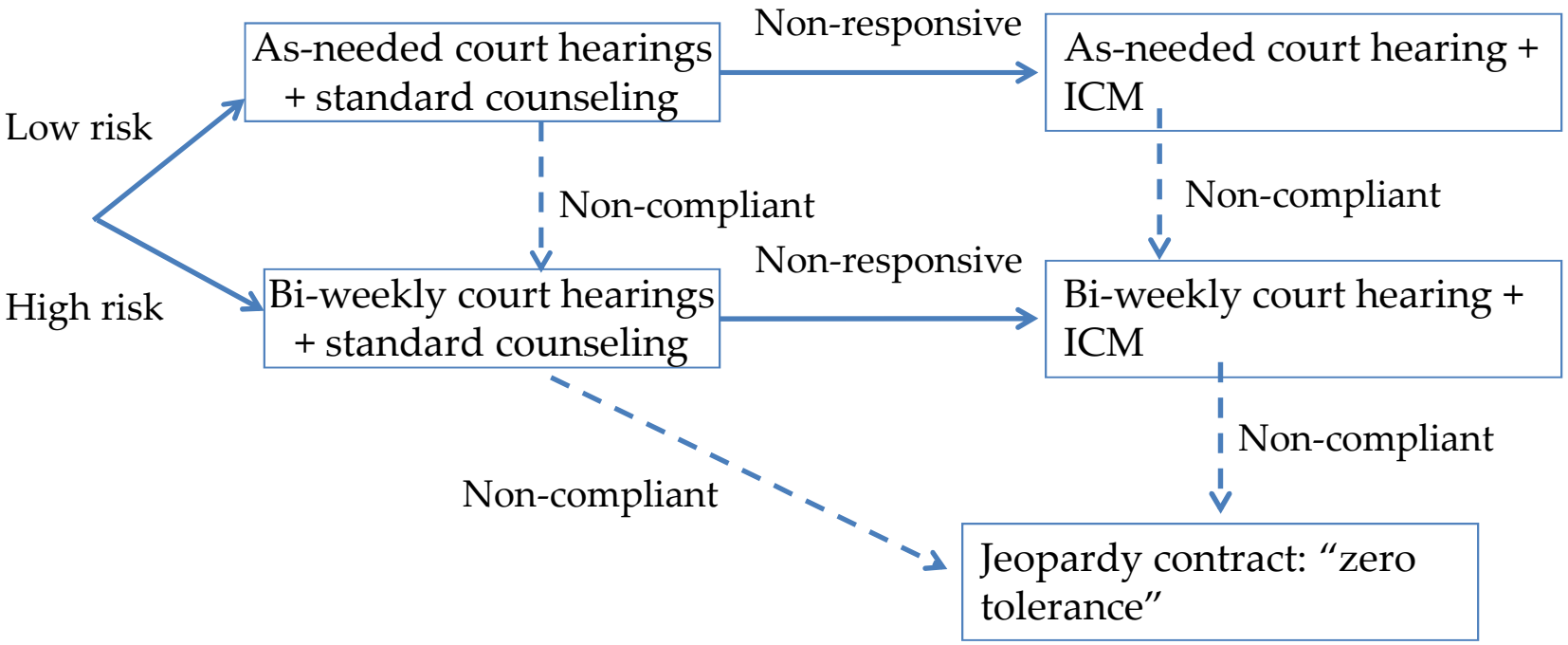
Definition of AI

- Go by many different names:
  - Adaptive health interventions,
  - Adaptive treatment strategies,
  - ***Dynamic treatment regimes (DTRs),***
  - Treatment algorithms,
  - Stepped care models,
  - Treatment protocols,
  - Individualized interventions
  - ...

Example

- Adaptive drug court program for drug abusing offenders
  - The goal: Minimize recidivism and drug use
  - Operationalized by graduating from the drug court program
  - Marlowe et al., (2008; 2009; 2012)

Adaptive Drug Court Program



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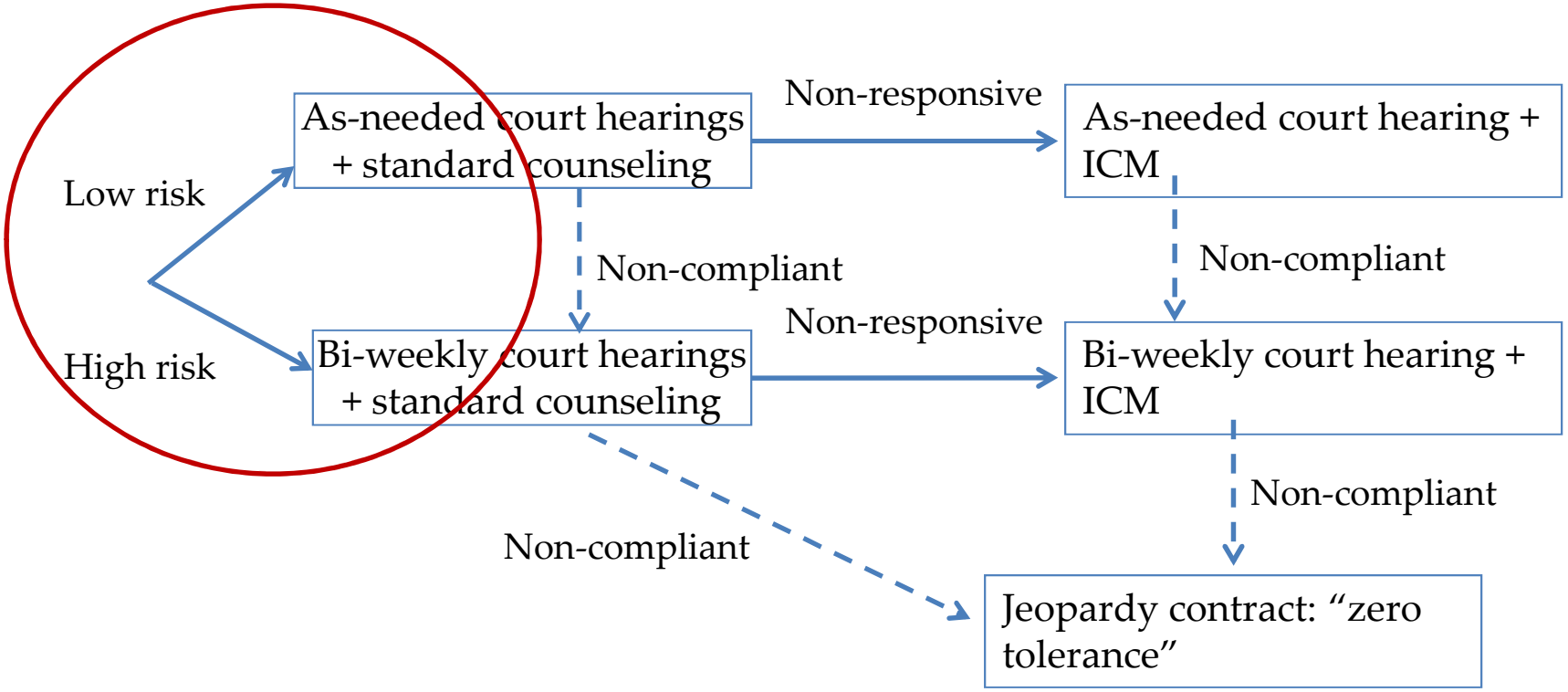

First Stage Decision Rule

At point of entry into the program

If risk = low

Then, stage 1 intervention= {As-needed + SC}

Else if risk=high

Then, stage 1 intervention = {Bi-weekly + SC}

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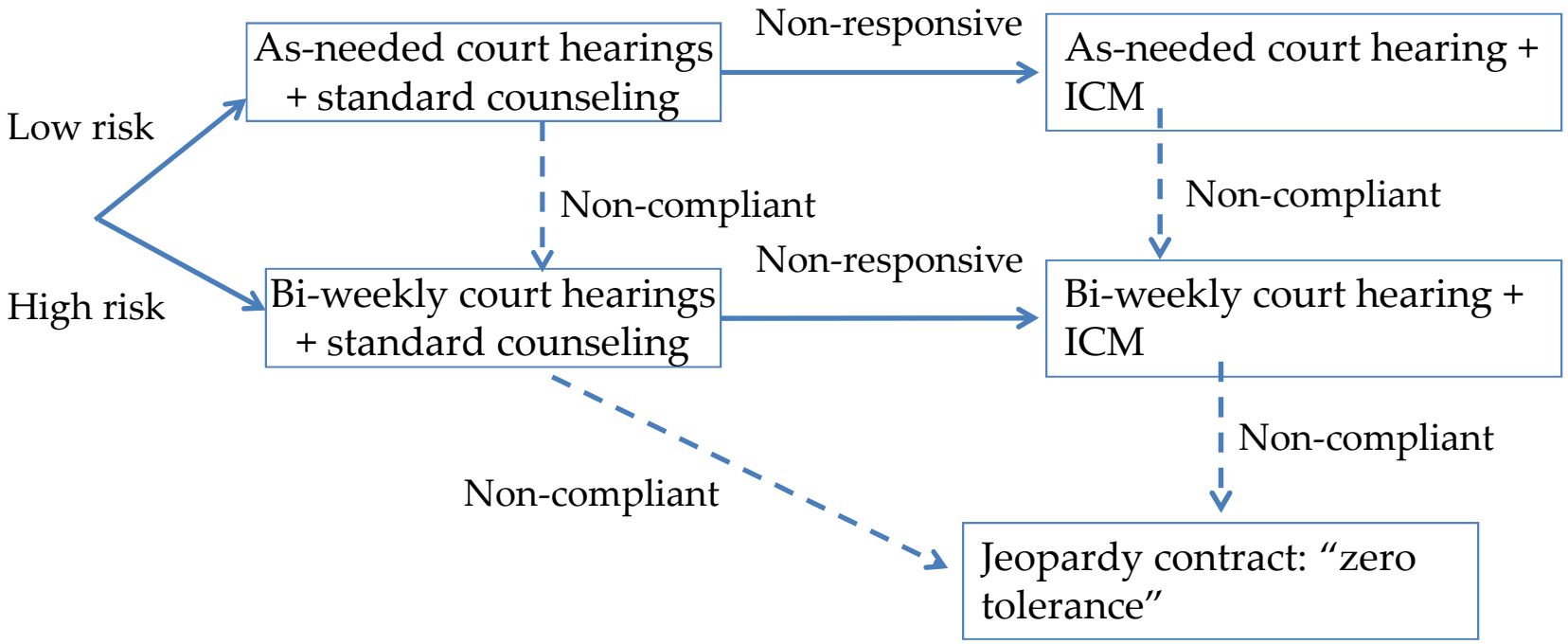
1. Decision Point:
A time in which treatment options should be considered based on patient information

Adaptive Drug Court Program



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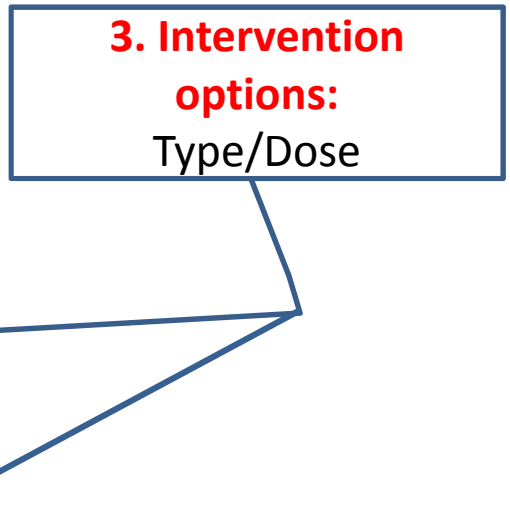
2. Tailoring Variable:
Patient information used to make treatment decisions

First Stage Decision Rule



At point of entry into the program

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First Stage Decision Rule

4. Decision rule

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First Stage Decision Rule

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5. Outcomes:

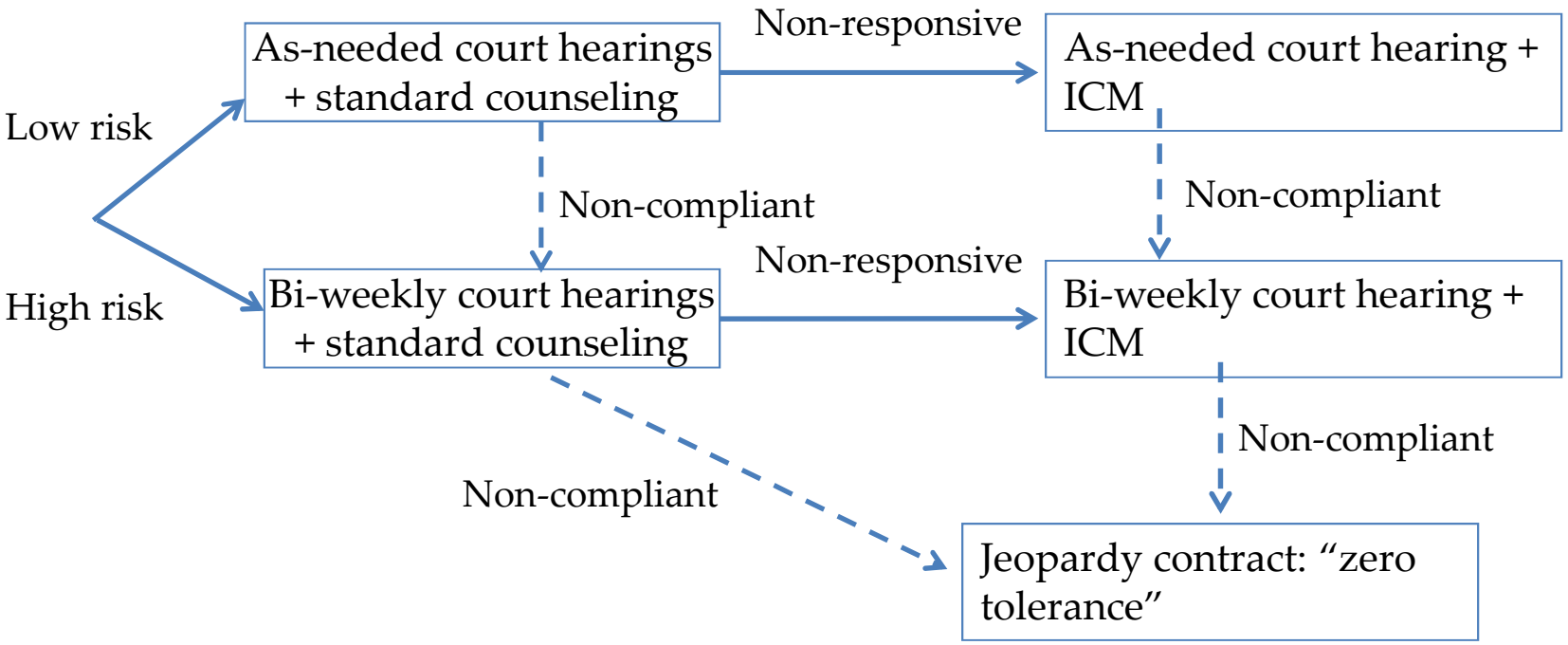
Distal →Long-term goal of intervention:

Program graduation (14 consecutive weekly negative drug urine specimens)

Proximal→ Short-term goal of decision rules:

Compliance and *response* in the course of intervention (mediator)

Adaptive Drug Court Program



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Proximal outcomes

- Based on your theory of change
- Related to prevention, treatment, academic-success
- At various levels: patient, family, clinic

AI: 5 Elements

1. Decision Points ⟵ **Triggered**
2. Tailoring Variable ⟵
3. Decision rule ⟵
4. Intervention Options ⟵

- Monitoring
- Individualizing
- Delivering

} **Adaptation process**

5. Proximal + Distal Outcomes ⟵ **Guided**

Motivation for Adaptive Interventions

1. High **heterogeneity** in need/response to any one intervention
2. Improvement is **non-linear**
3. Intervention **burden**
4. Intervention **cost**

Summary

- Adaptive Intervention is:
  - a sequence of individualized intervention options
  - that uses dynamic information to decide what type/dose/modality of intervention to offer
  - Its objective to guide clinical/academic practice or public health policy.

AI is a sequence of (individualized) treatments

AI is a sequence of decision rules that recommend what to offer, for whom, and when.

Summary

- Adaptive Intervention is:
  - a sequence of individualized intervention options
  - that uses dynamic information to decide what type of intervention to offer
  - Its objective to guide clinical/academic practice or public health policy.

AI is a sequence of (individualized) treatments

AI is a sequence of decision rules that recommend what to offer, for whom, and when.

The Role of the Researcher

Develop good decision rules to guide clinical/academic practice and policy

Answer **open scientific questions** concerning the development of good decision rules

Examples of Scientific Questions

- How long should we use the first treatment?
- What tactic should we use for non-responders to treatment A?
- What tactic should we use for responders to treatment A
- How to re-engage patients who are non-adherent or drop-out?
- Location of treatment?
- Mode of delivery?
- How to define non-response?

My Reading List ***(Not Complete)***

- Collins, L. M., Murphy, S. A., & Bierman, K. L. (2004). A conceptual framework for adaptive preventive interventions. *Prevention science*, *5*(3), 185-196.
- Davidian, M., Tsiatis, A. B., & Laber, E. (2016). Dynamic Treatment Regimes. In George, S.L., Wang, X., Pang, H. (Eds.). *Cancer Clinical Trials: Current and Controversial Issues in Design and Analysis*; Chapman & Hall; 409.
- Lavori, P. W., & Dawson, R. (2004). Dynamic treatment regimes: practical design considerations. *Clinical trials*, *1*(1), 9-20.
- Lei, H., Nahum-Shani, I., Lynch, K., Oslin, D., & Murphy, S. A. (2012). A" SMART" design for building individualized treatment sequences. *Annual review of clinical psychology*, *8*, 21-48.
- McKay, J. R. (2009). *Treating substance use disorders with adaptive continuing care*. American Psychological Association.

Other questions about Adaptive Intervention? …

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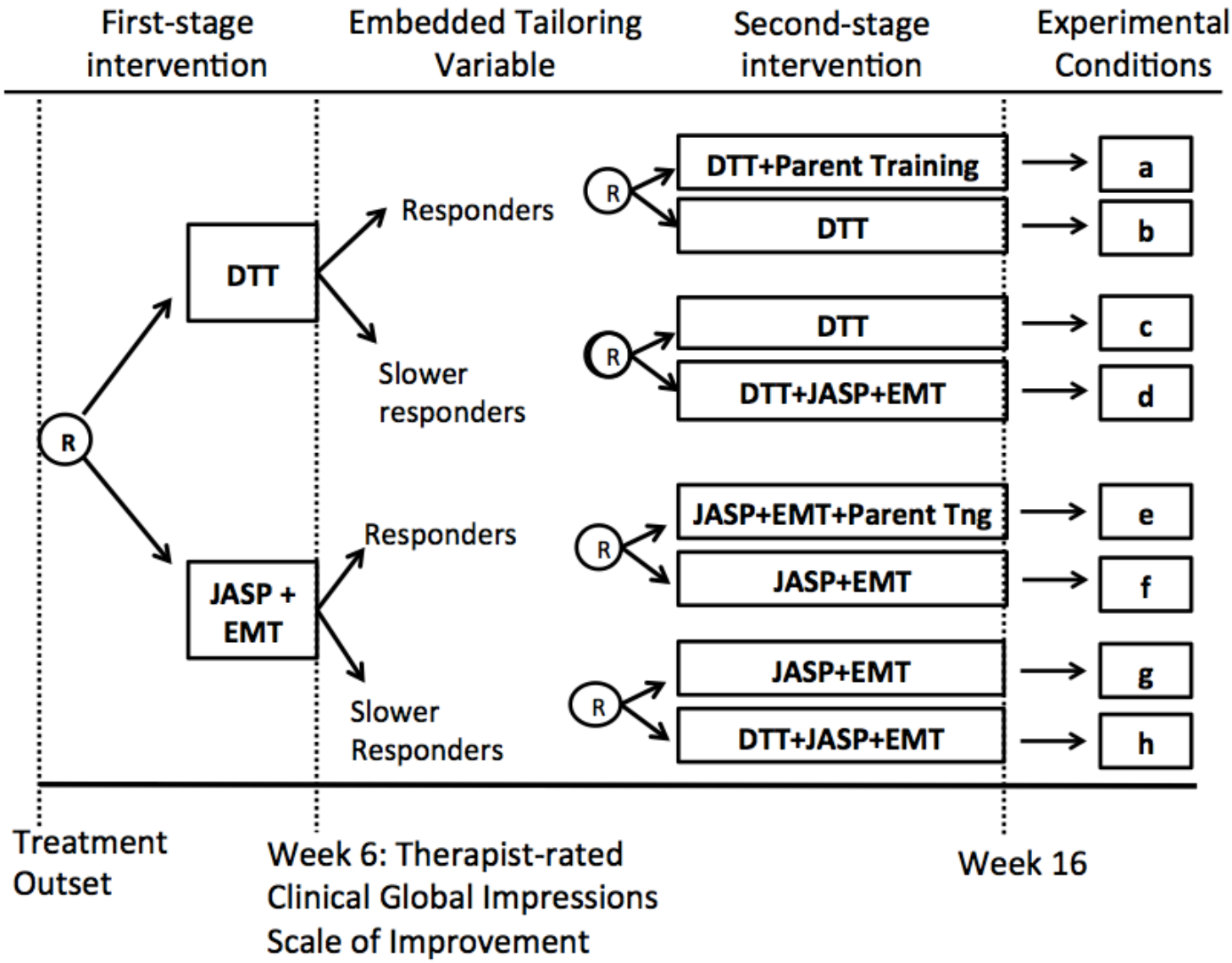
  - Sample size considerations
  - Examples of SMARTs
  - SMARTs vs. other designs

What is a SMART?

- A Multi-Stage Randomized trial
  (Dawson & Lavori, 2004; Lavori & Dawson, 2001; Murphy, 2004)
- Each stage corresponds to a scientific question(s) concerning the selection and adaptation of intervention options.
- Randomization occurs at each decision point of scientific interest
- Some (or all) participants are randomized more than once, often based on earlier covariates

The goal is to inform the construction of effective adaptive interventions

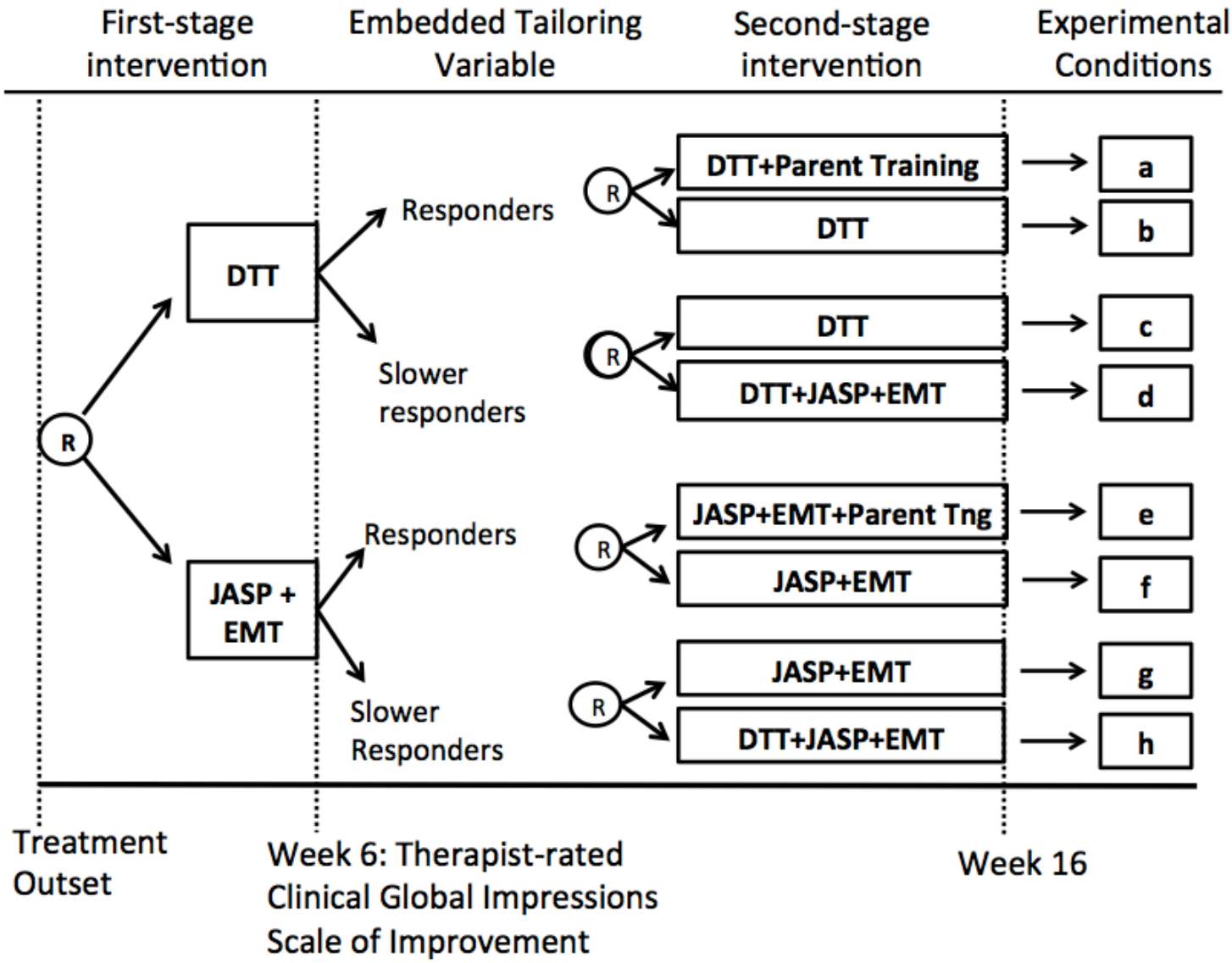
AIM-ASD SMART (N=192; R01-HD073975; PI: Kasari)



SMART Design Principles

- **When to consider a SMART?**
  - When you would like to address questions concerning the construction of an adaptive intervention
  - ***Multiple*** questions are of interest, regarding multiple decision points

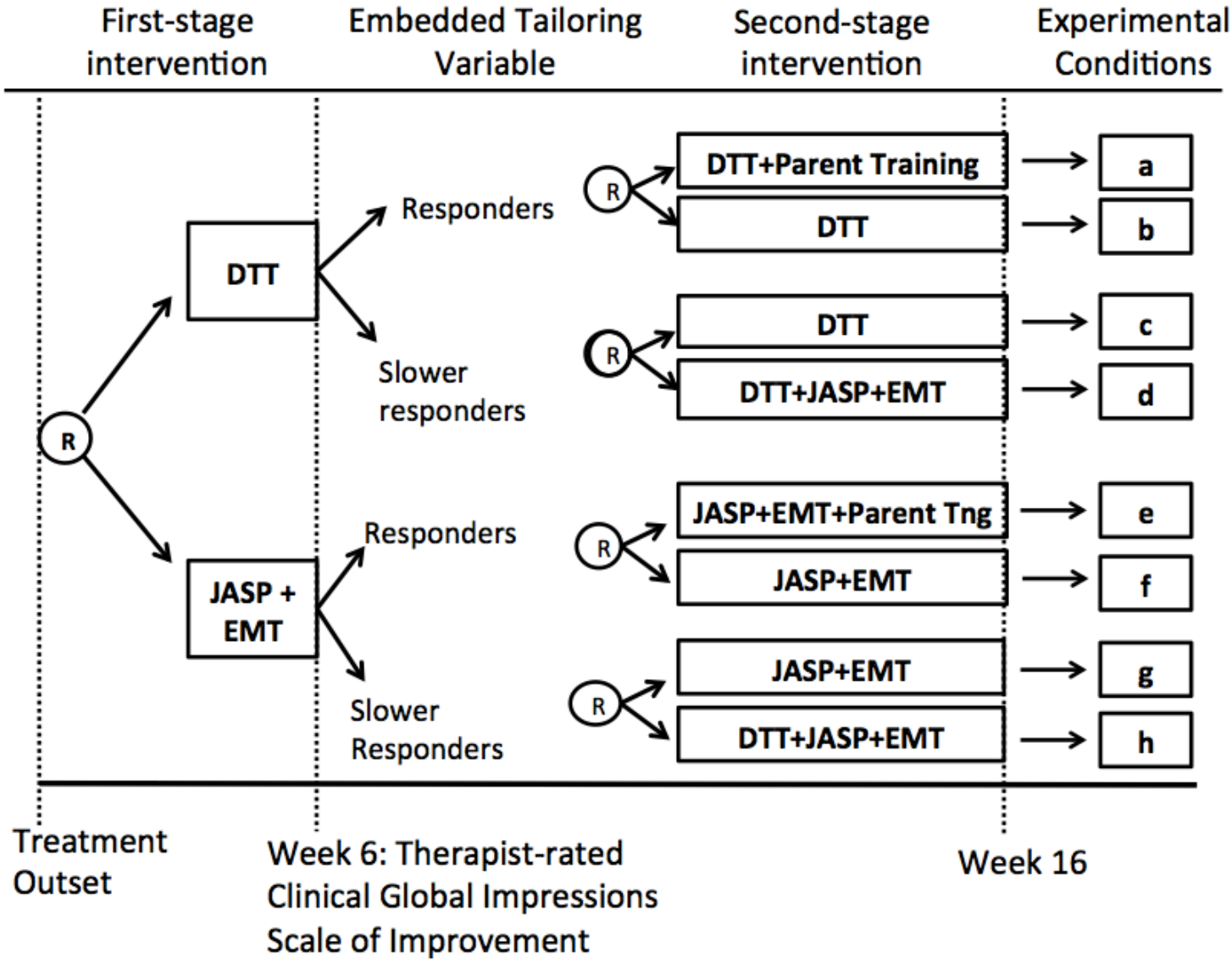
AIM-ASD SMART (N=192; R01-HD073975; PI: Kasari)



SMART Design Principles

- **Should re-randomization be restricted?**
  - If you have ethical, scientific, or practical reason to do so.
    - Ethical: certain treatment options are not appropriate for a subset of the participants
    - Scientific: based on empirical evidence the best treatment for a specific subset of participants is already established
    - Practical: e.g., save the more intense/costly (step-up) options to those who need it most.

AIM-ASD SMART (N=192)



SMART Design Principles

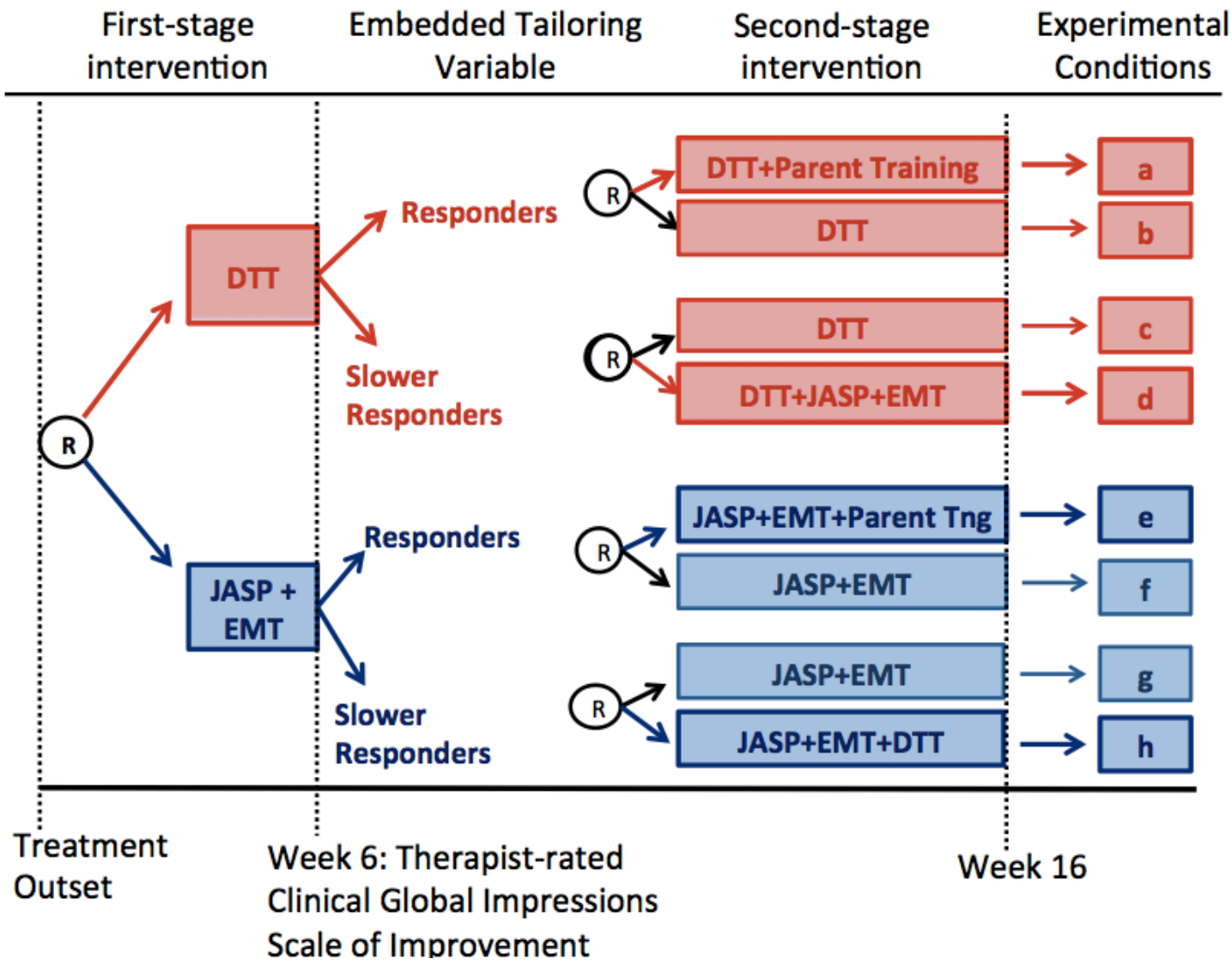
- **How to select Aims?**
  - Select a primary aim that is important to the development of an adaptive intervention; sample size is based on this aim
  - Collect additional data that could be used to further inform the development of adaptive interventions in secondary aims

Primary Aim: Example 1

Compare initial intervention options

H1: Starting an AI with JASP+EMT will improve social communication more than starting with DTT.

H1: Comparison of Stage 1 Options

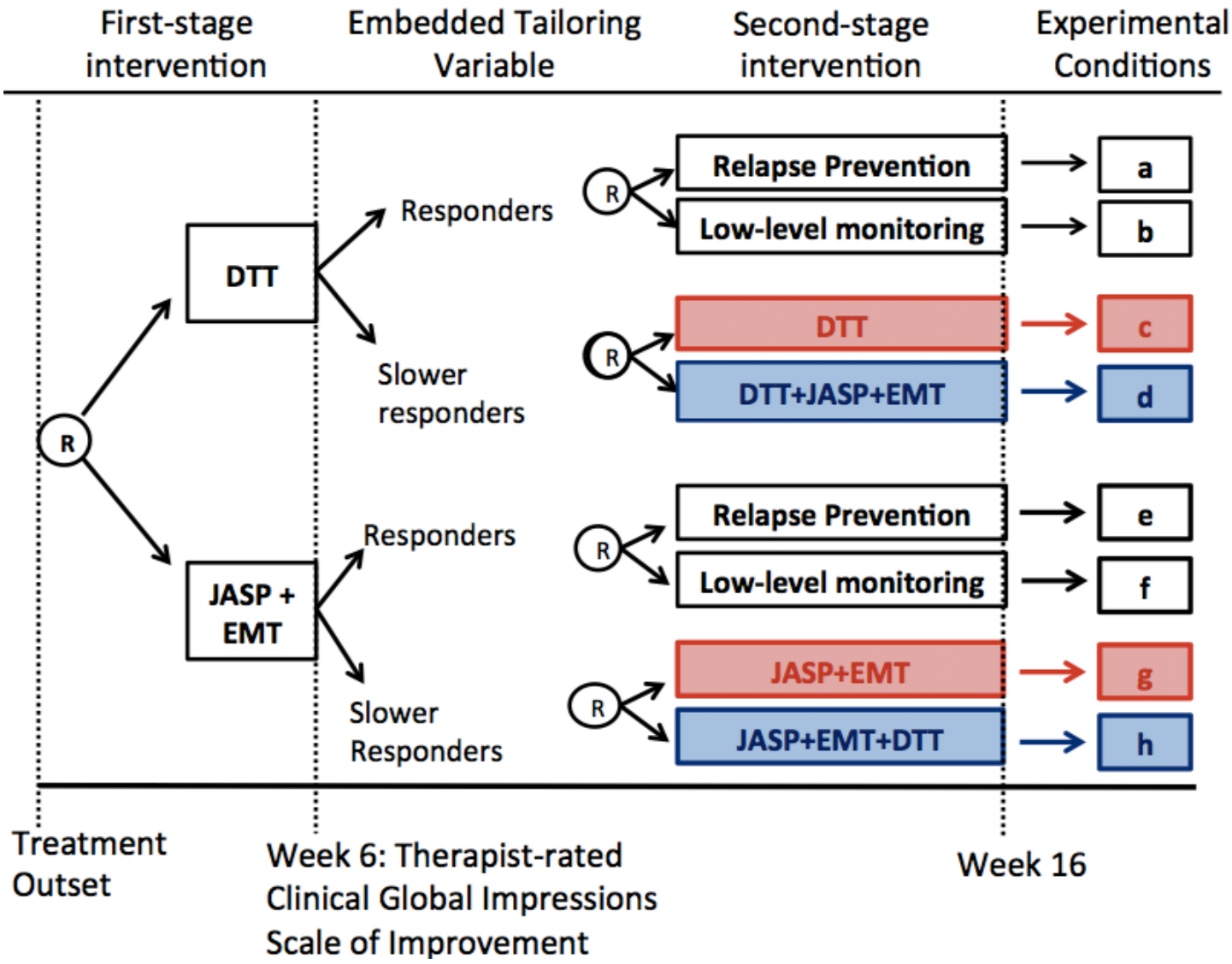


Primary Aim: Example 2

Compare second stage options for slow-responders

H2: Blending JASP+EMT and DTT for slower responders will improve social communication more than continue.

H2: Stage 2 Options for Slow Responders

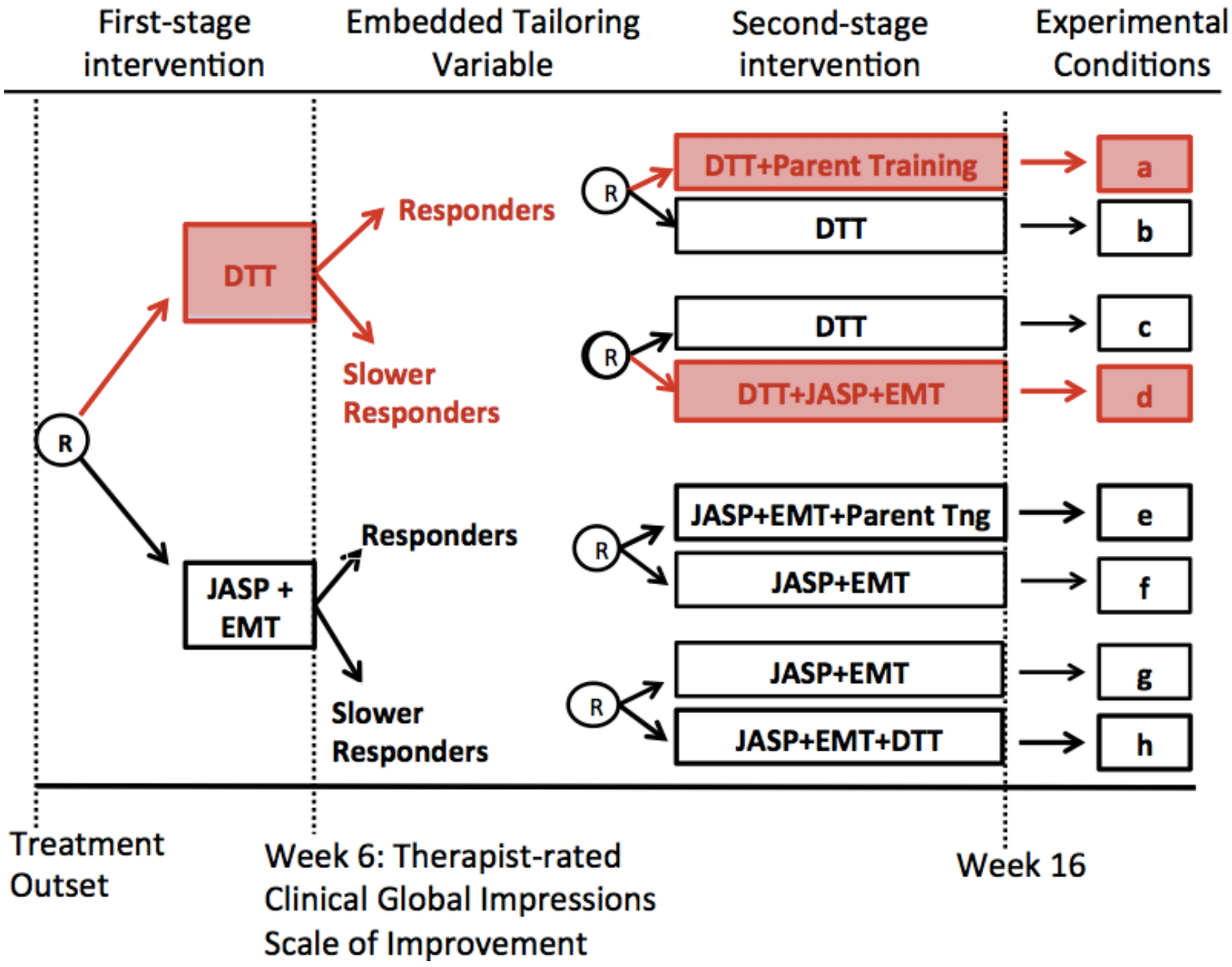


Primary Aim: Example 3

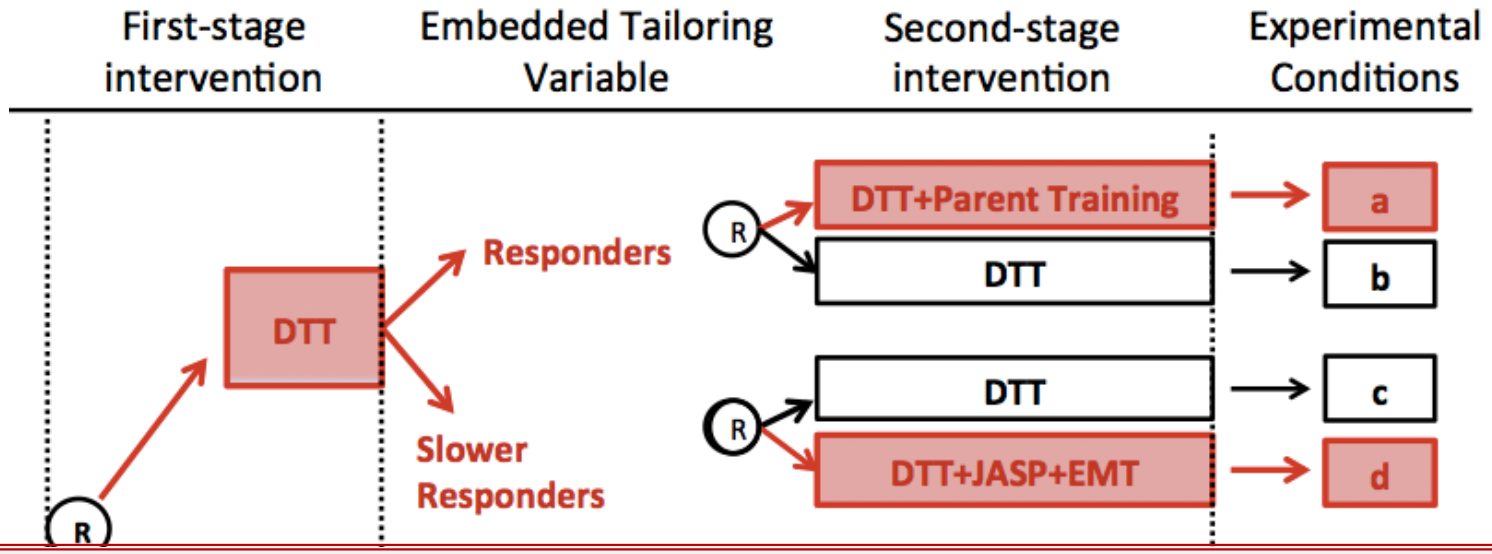
Campore embedded adaptive interventions

….first let's review what we mean by "embedded adaptive intervention"

Embedded Adaptive Intervention 1



Embedded Adaptive Intervention 1



Start with DTT

***Then*, at week 6**

***If* response status = responder**

***Then*, stage 2 intervention= {add Parent Training}**

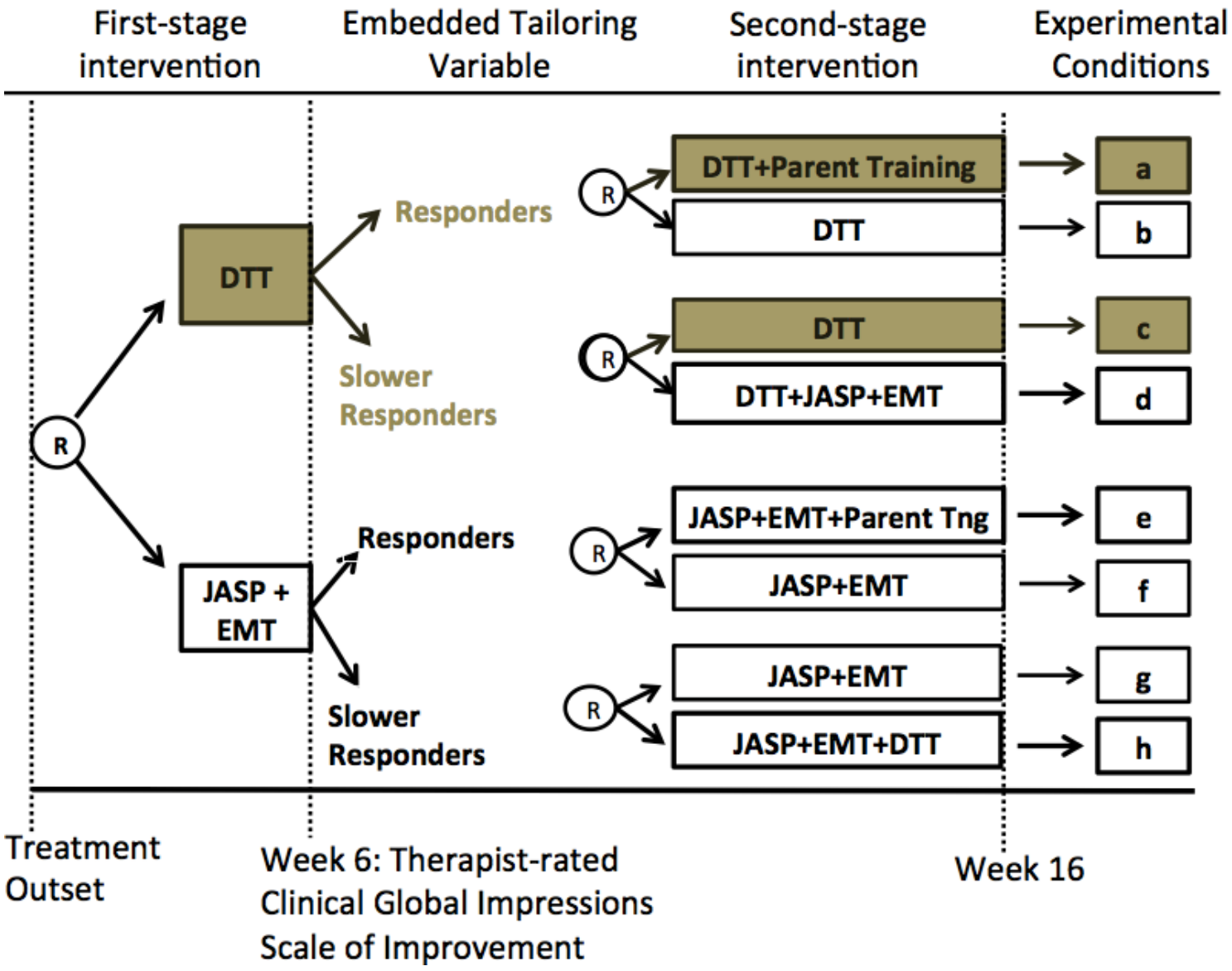
***Else if* response status = slow responder**

***Then*, stage 2 intervention = {Blend with JASP+EMT}**

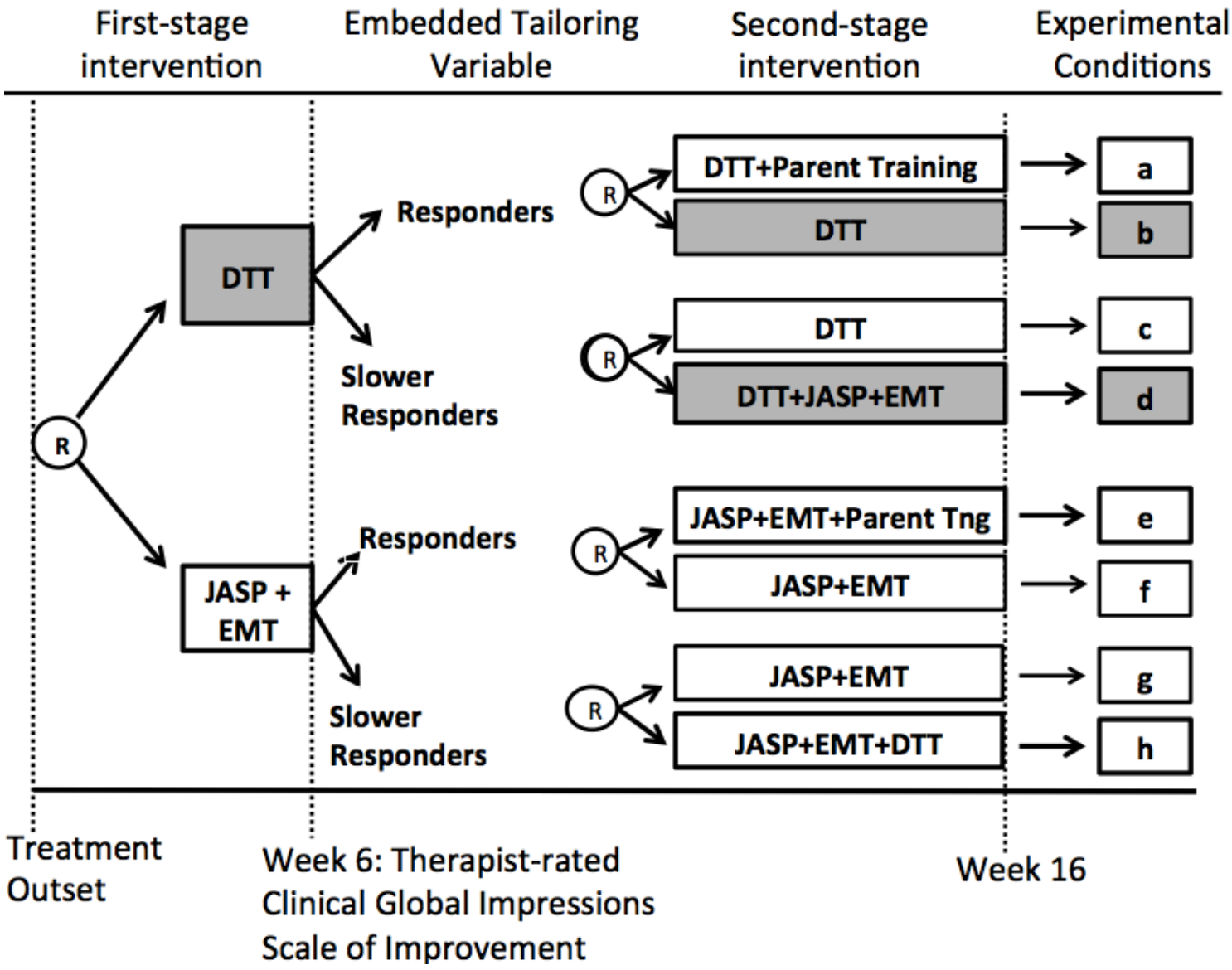
Clinical Global Impressions

Scale of Improvement

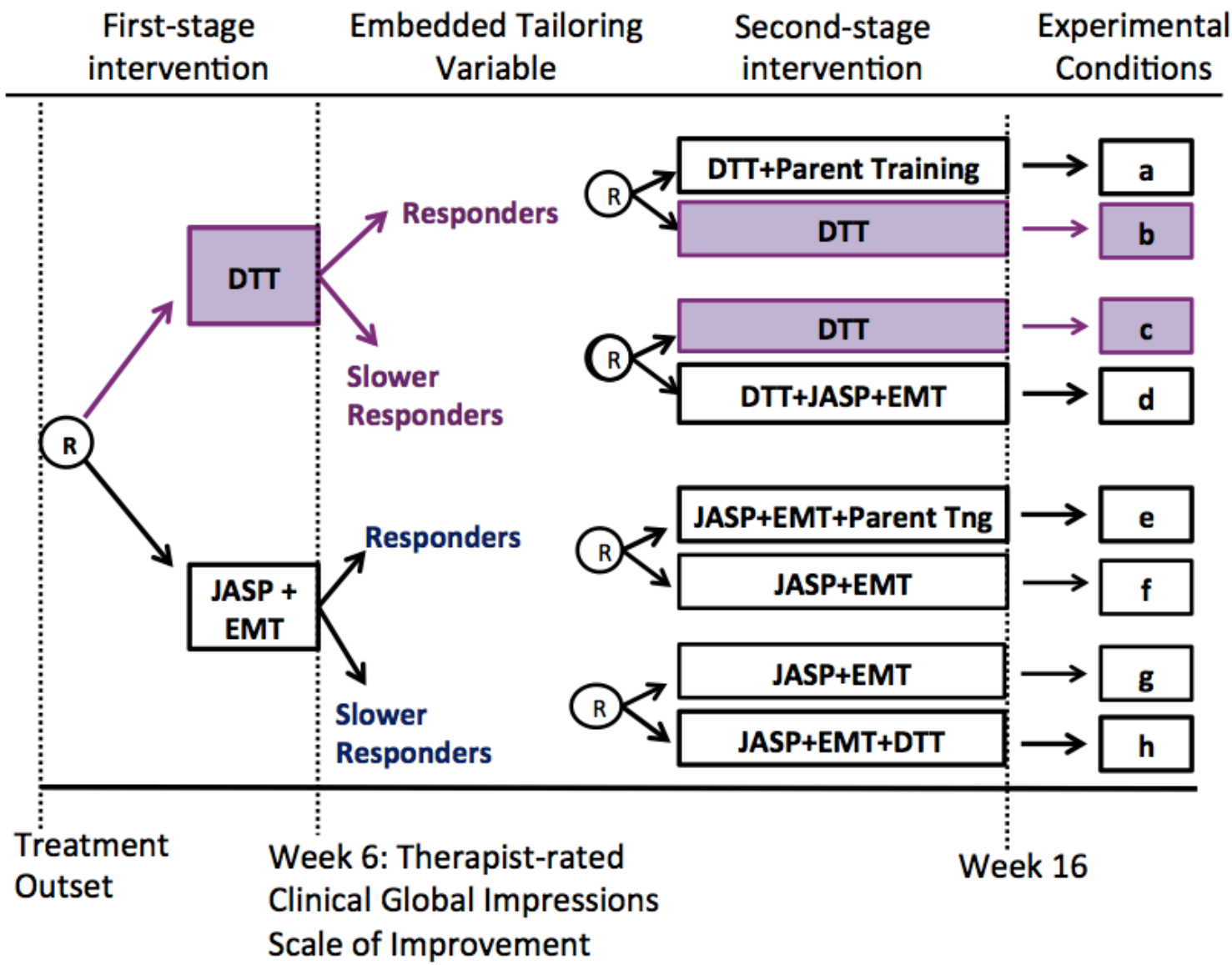
Embedded Adaptive Intervention 2



Embedded Adaptive Intervention 3



Embedded ~~Adaptive~~ Intervention 4



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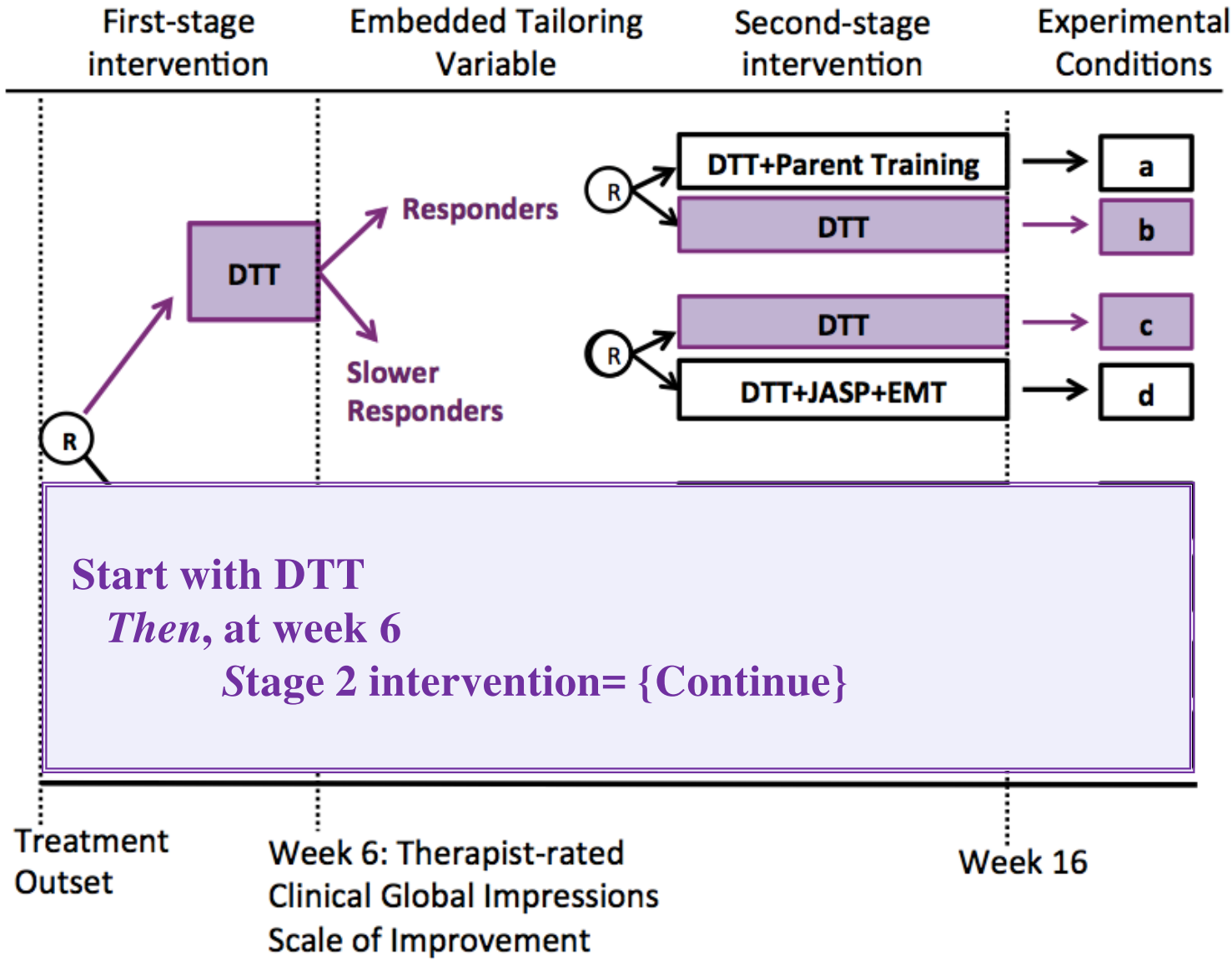


…and so on...

…Embedded Adaptive Interventions 5, 6, 7, and 8 are similar but begin with JASP+EMT…

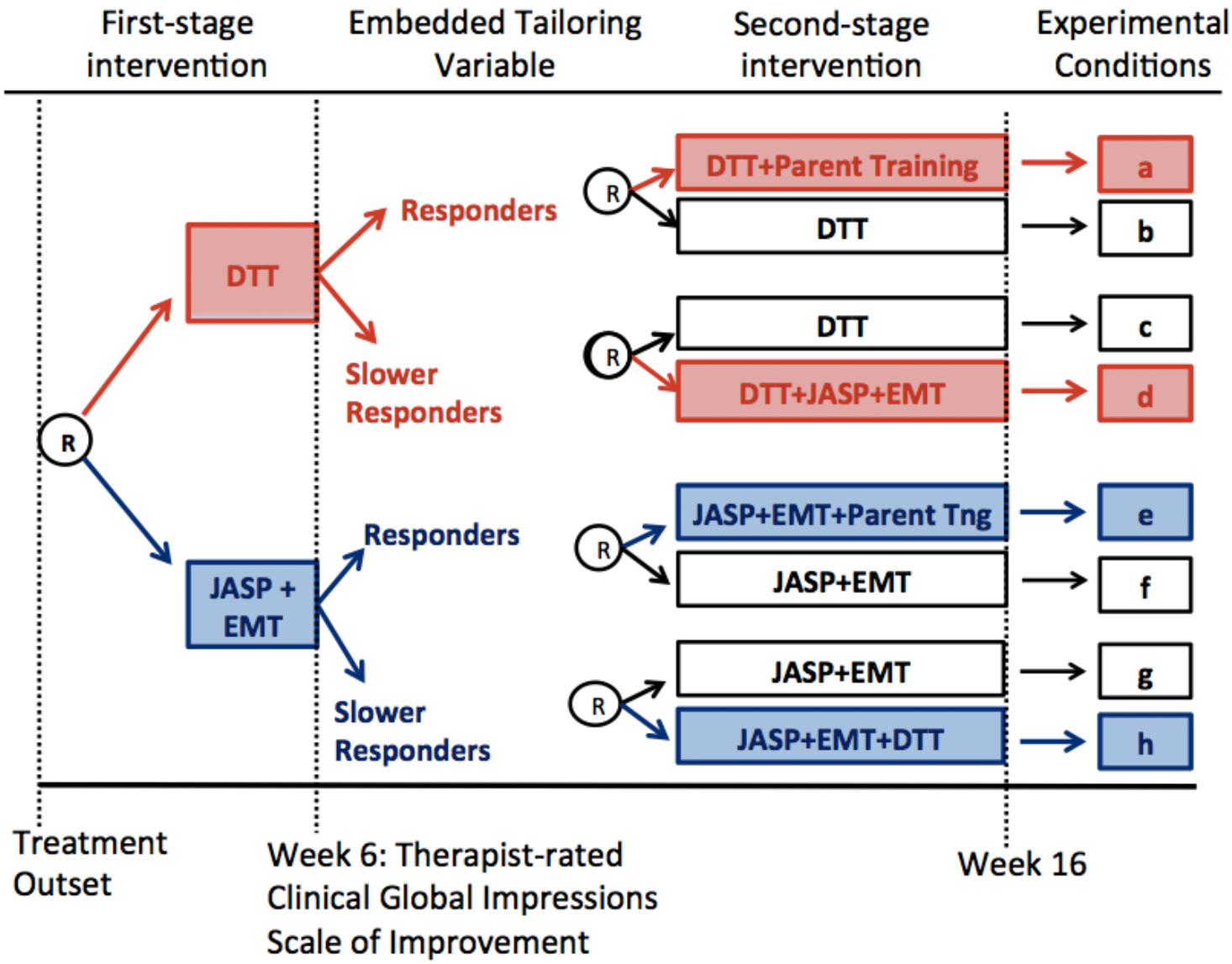
Primary Aim: Example 3

Compare embedded adaptive interventions

H3: The AI that begins with JASP+EMT and (a) adds parent training for responders and (b) blends for slower responders…

…will improve social communication more than the similar AI which begins with DTT.

H3: Comparison of 2 AIs



Primary aim Examples

1: Compare initial intervention options:

H1: JASP+EMT is better than DTT

2: Compare subsequent options among slow responders:

H2: Blending is better than Continue

3: Compare embedded AIs:

H3: AI #1 is better than AI #5

Sample Size

H1: Initial intervention options:

JASP+EMT is better than DTT.

- *Sample size formula is same as for a **two group comparison**.*

H2: Subsequent options among slow responders:

Blending is better than Continue.

- *Sample size formula is same as a **two group comparison of slow responders**.*

Sample Size Examples

N = sample size for the ***entire*** trial

	H1	**H2**
$\Delta\mu/\sigma$ =.3	N = 350	N = 350/ SR rate
$\Delta\mu/\sigma$ =.5	N = 126	N = 126/ SR rate

α = .05 (two sided), power =1 – β =.80

* Assumptions: equal variances, normality, equal # in each group, no dropout.

** AIM-ASD's was of this type, w/ ES = 0.5, pwr = 90% and acctng for 10% dropout.

Sample Size Examples

H3: AI #1 results in better social communication compared to AI #5

- Sample size formula depends on who gets re-randomized
- If both R and SR get re-randomized

Type I error rate (2-sided)	Power	Standardized Difference	N	Randomization
0.05	80%	0.3	698	Both R and SR are re-randomized
		0.5	252	

- *Continuous Outcomes:* Oetting, A.I., et al. (2011)
- *Survival Outcomes:* Feng, W. and Wahed, A., (2009); Li, Z. and Murphy, S.A., (2011)
- *Binary Outcomes:* Kidwell, K.M., et al. (under review)

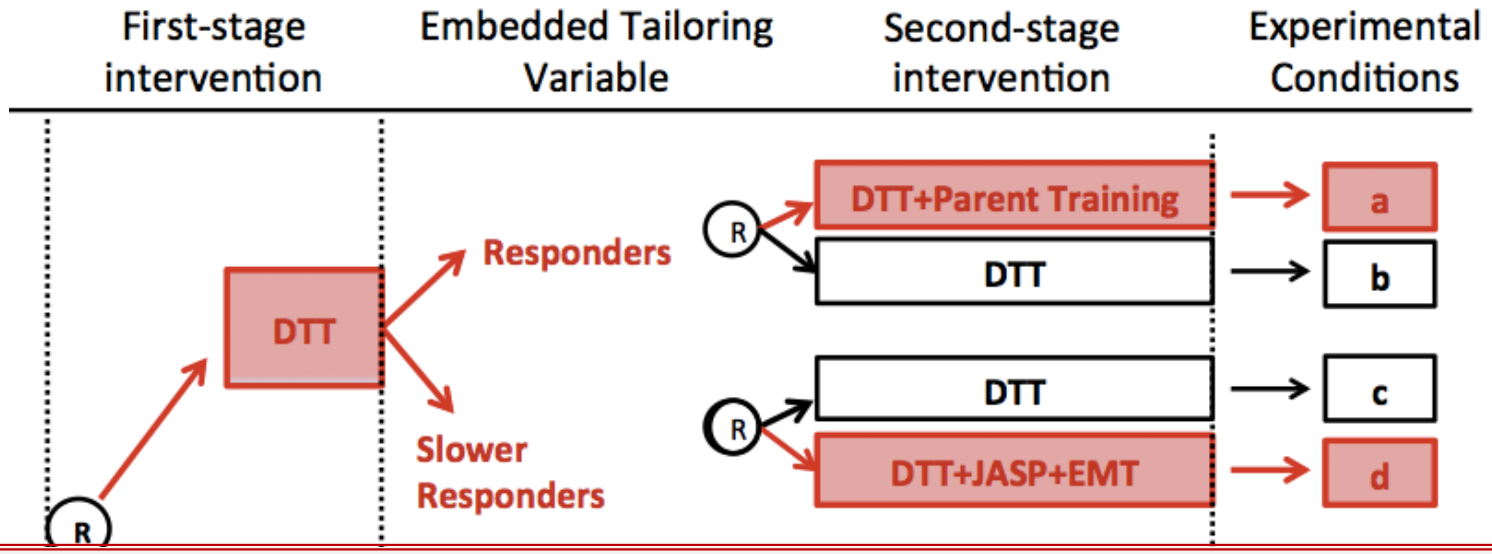
Secondary Aim: Example

Identify ways to more deeply-tailor the AI.

- Example:

H4: Among early responders, those whose parents demonstrate greater buy-in for the initial treatment will benefit more from parent training than from continue.

More Deeply Tailored?



Start with DTT

***Then*, at week 6**

***If* response status = responder**

***Then*, stage 2 = {add Parent Training}**

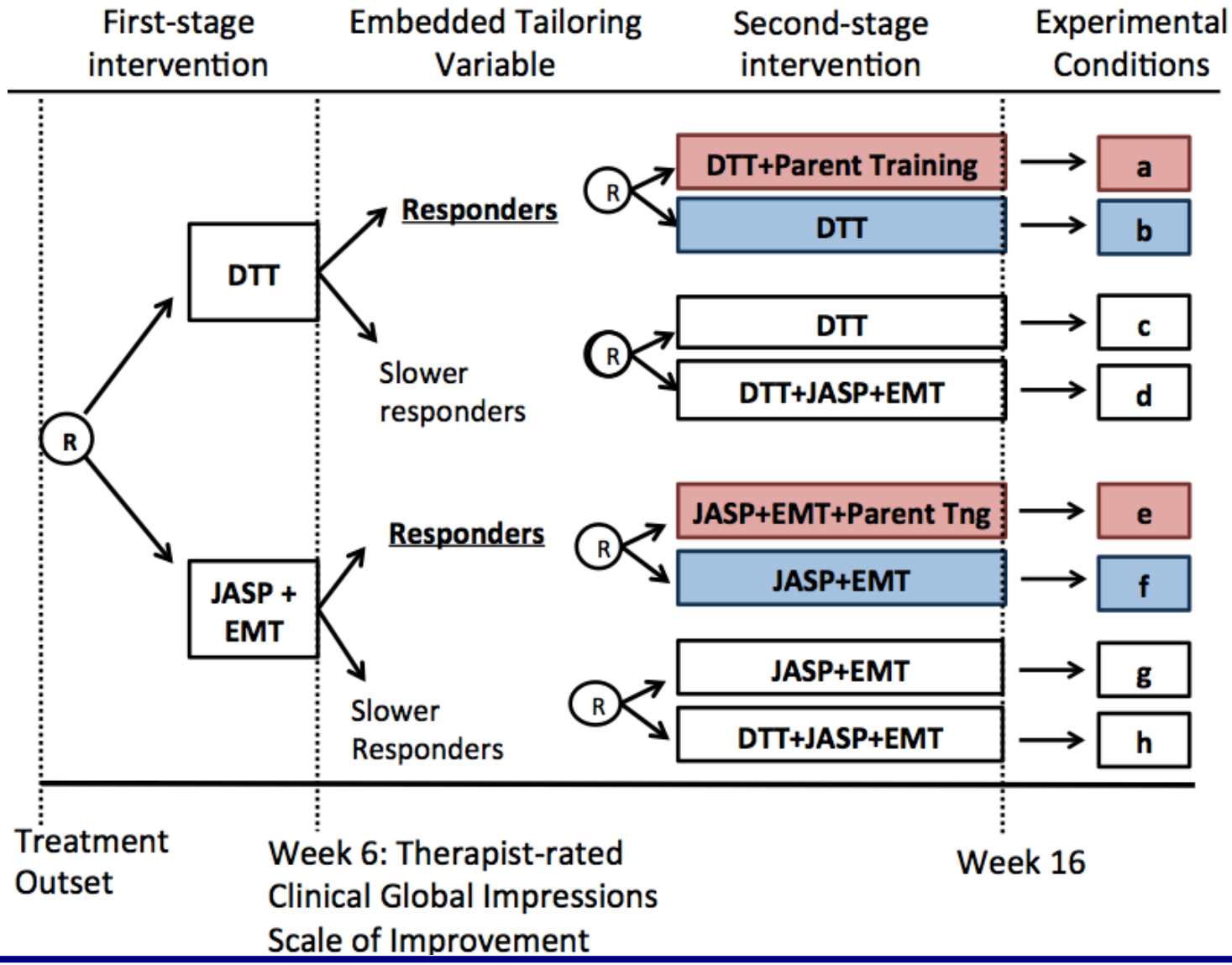
***Else if* response status = slow responder**

***Then*, stage 2 = {Blend with JASP+EMT}**

Clinical Global Impressions

Scale of Improvement

Parent Buy-in as a Tailoring Variable?



Example of a More Deeply Tailored AI

Start with DTT
Then, at week 6
_If_ response status = responder
Then,
_If_ parent buy-in={high}
Then, stage 2 = {add Parent Training}
Else, if parent buy-in={low}
Then stage 2 ={add parent training or continue)
Else if response status = slow responder
Then, stage 2 = {Blend with JASP+EMT}

Methods for Analyzing Data

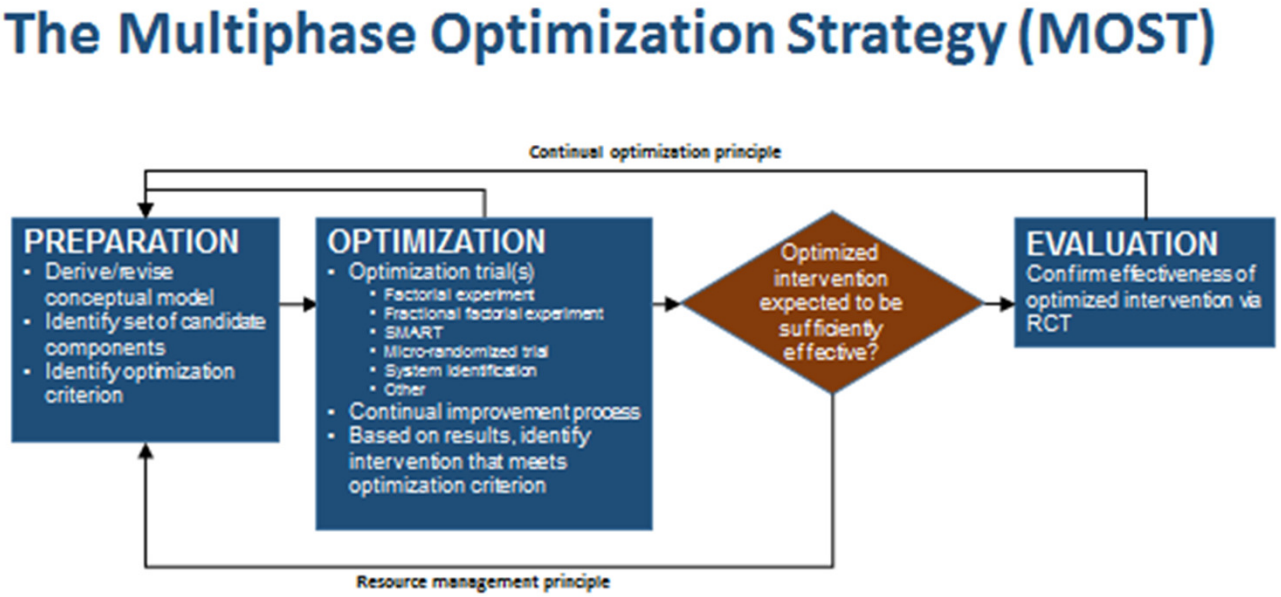
- Compare first and second-stage intervention options
- Compare AIs with end of study outcome (e.g., Nahum-Shani et al., 2012a)
- Multiple comparisons with the best embedded AI (e.g., Ertefaie et al., 2015)
- Compare AIs with repeated measures outcomes (e.g., Lu et al., 2015)
- Identify ways to more deeply tailor embedded AIs (e.g., Nahum-Shani et al., 2012b; Schulte et al., 2014)

SMARTs vs. Other designs

- RCT
- Non-Responders studies
- Factorial Designs
- Crossover
- Adaptive Trials
- Randomized Discontinuation Design

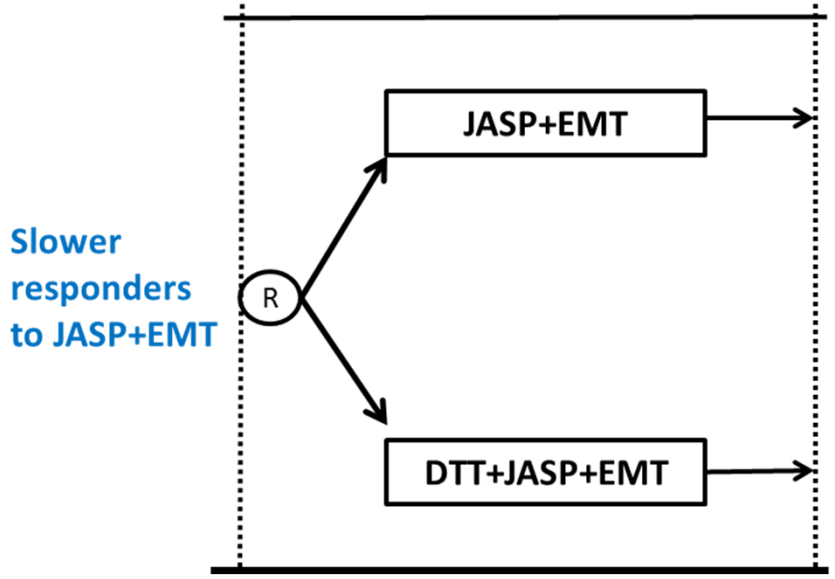
SMART vs. Randomized Control trial (RCT)

- A randomized control trial (RCT) evaluating an AI compared to a suitable control.
  - The primary aim is to confirm it's effectiveness compared to an alternative



SMART vs. Non-Responders Trial

- Randomizing non-responders to a given intervention to subsequent intervention options
  - Evidence is sufficient to select a first-line treatment; but there are scientific questions regarding subsequent options for non-responders
  - Also known as the 'single-stage-at-a-time approach"
  - There are various considerations when building an adaptive intervention based on a series of separate responder or non-responder trials.



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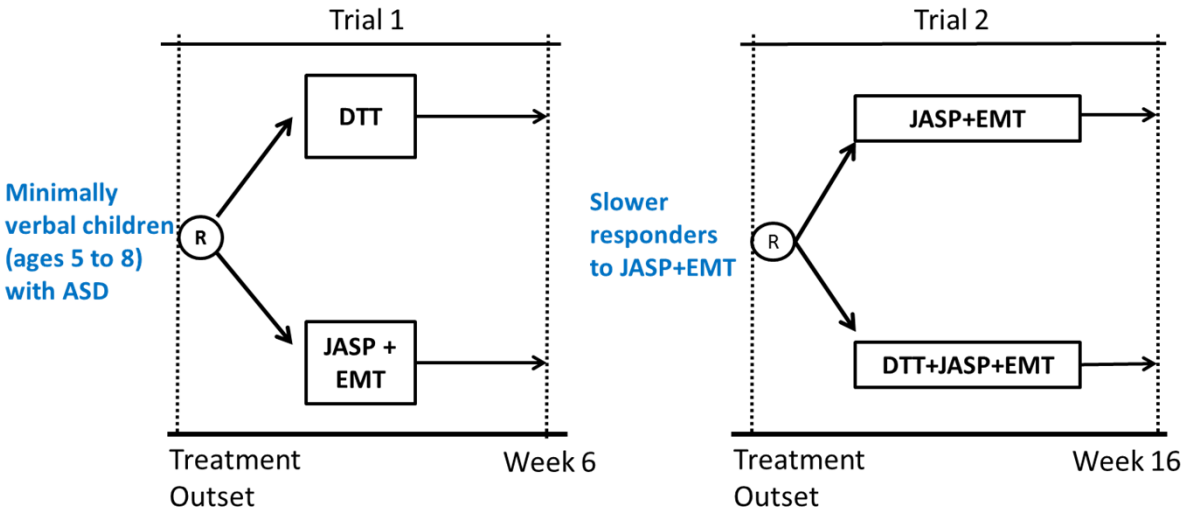
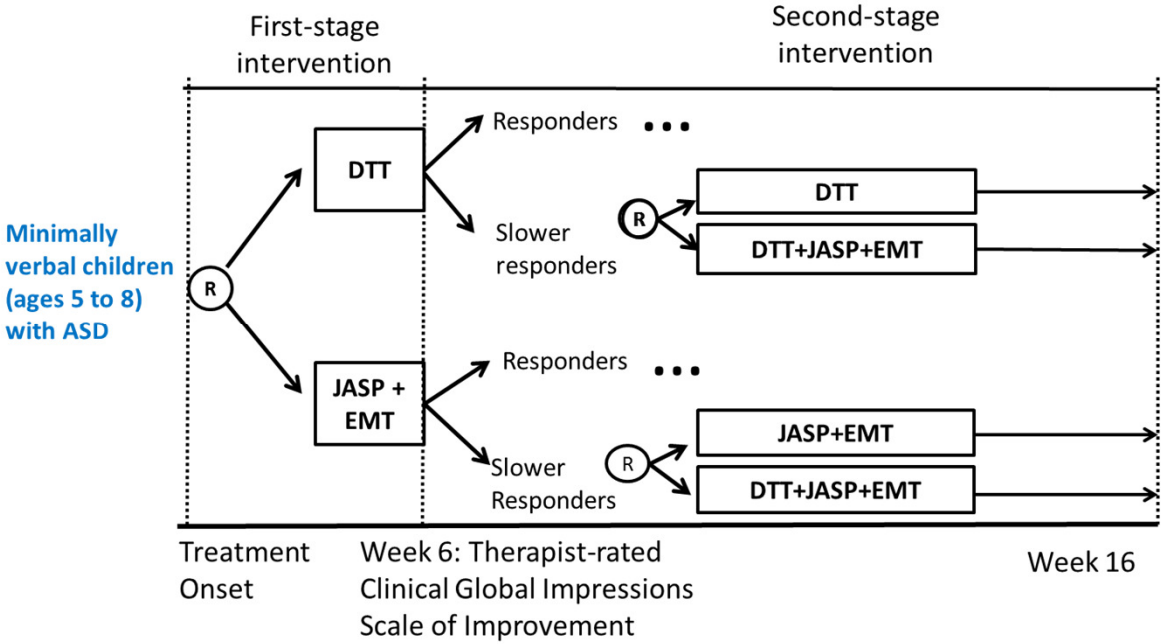


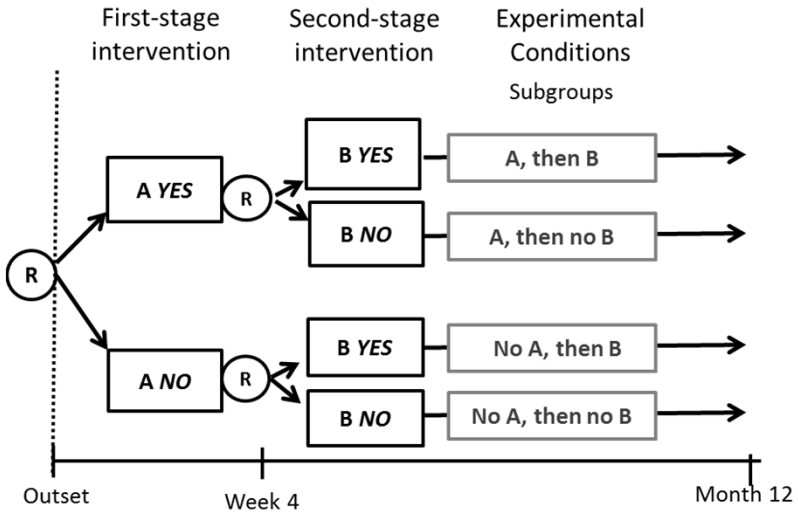


1. Delayed effects
2. Drop-out
3. Selection effects
4. Prescriptive effects

SMARTs vs Factorial Experiments

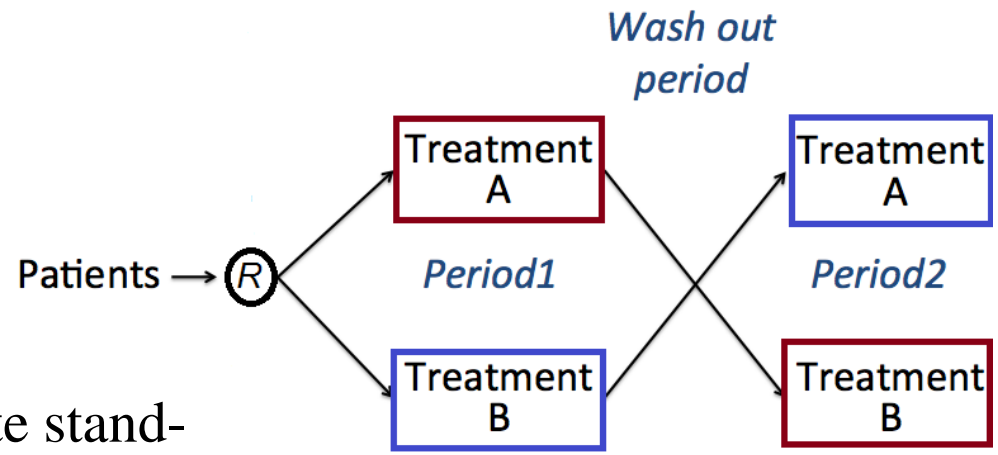
- A SMART is a special form of a factorial; factors are employed sequentially.
- Randomization to subsequent factors in a SMART are often restricted based on early response status
- In SMART, effects have sequential interpretation.

		Treatment A: NO	Treatment A: YES
Treatment B	NO	Neither A nor B	A only
	YES	B only	Both A and B



SMARTs vs Crossover Trials

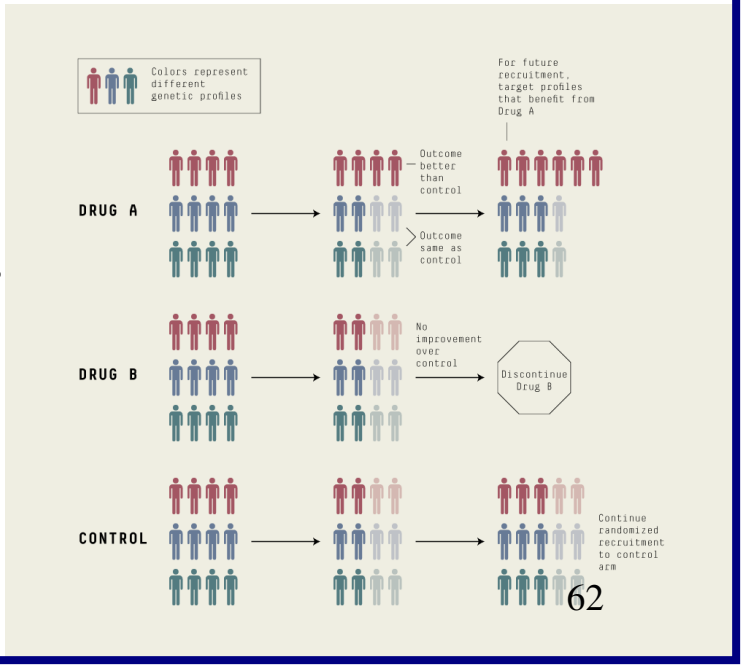
- A repeated measurements design-- patients cross over from one treatment to another during the course of the trial.



- Typically aim to evaluate stand-alone treatments, not to address questions concerning AIs
- Attempts to wash out the carryover effects while SMARTs are often motivated by such (delayed)

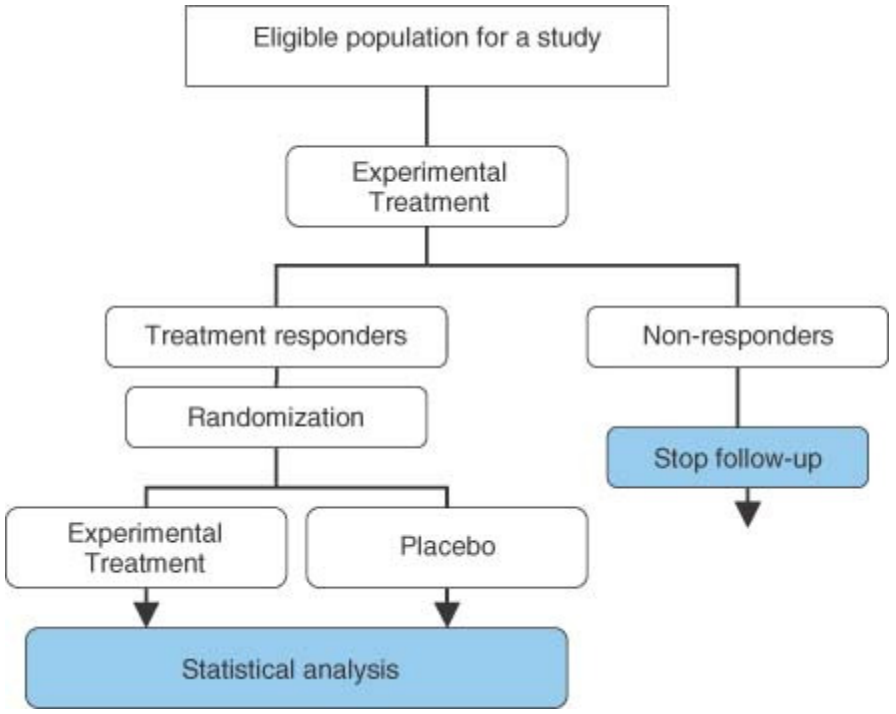
SMARTs vs Adaptive Trials/Designs

- A clinical trial design that allows adaptations or modifications to aspects of the trial while the study is still ongoing (Chang, 2007)
- e.g.,
  - Stop the trial early either for success, futility or harm
  - Drop arms or doses or adjust doses
  - Modify randomization rate to increase probability of allocation to the most appropriate arm
- SMARTs are generally not adaptive designs
  - Design parameters are set a-priori and do not change.
  - But the two concepts can be combined (Cheung et al., 2015; Lee et al., 2015)



SMARTs vs Randomized Discontinuation Trial (RDT)

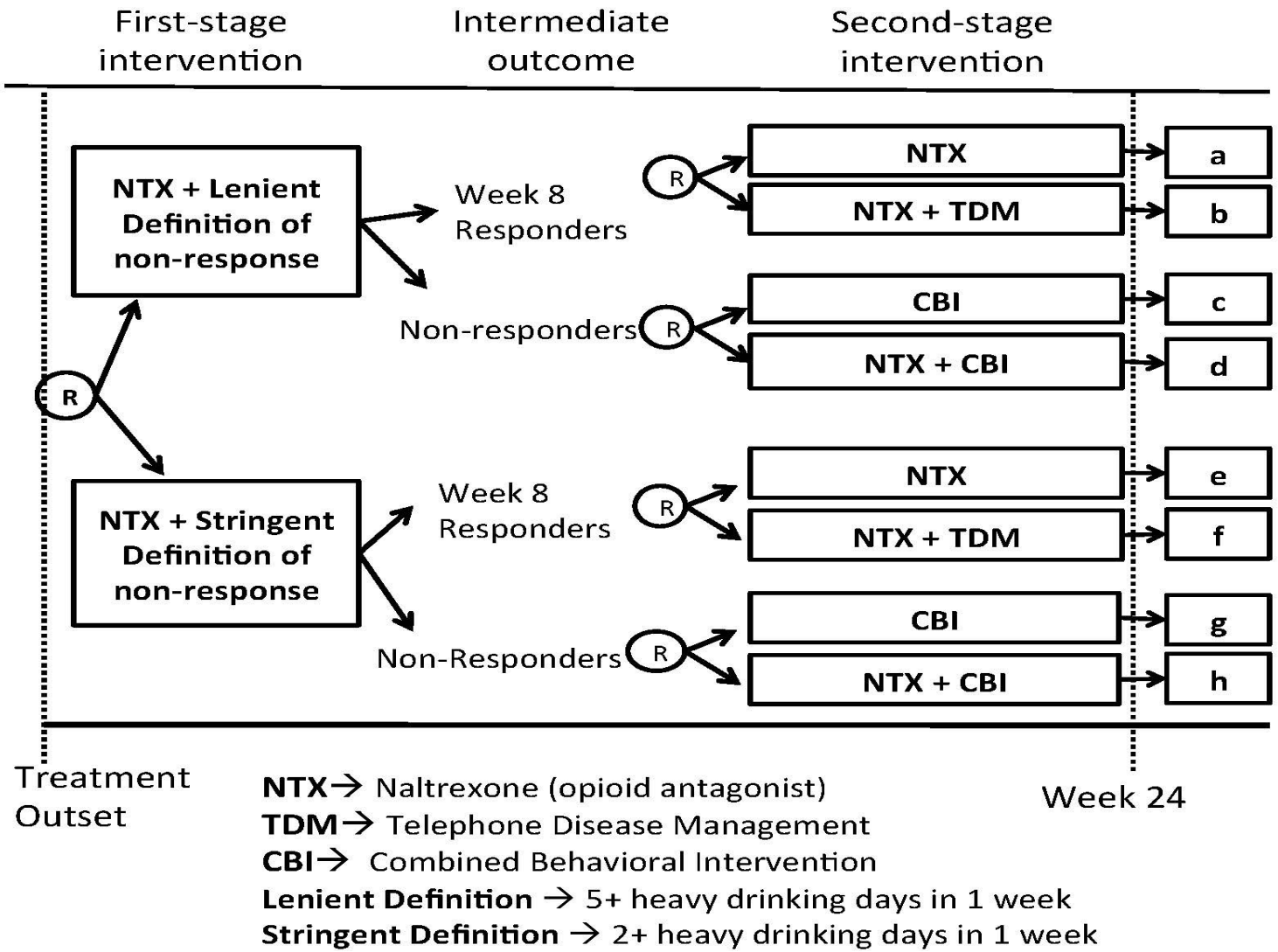
- A SMART follows all patients who enroll, whereas RDT does not continue to follow participants who are not randomized
- The focus of RDT is on whether we should continue or discontinue treatment for responders to stage 1.



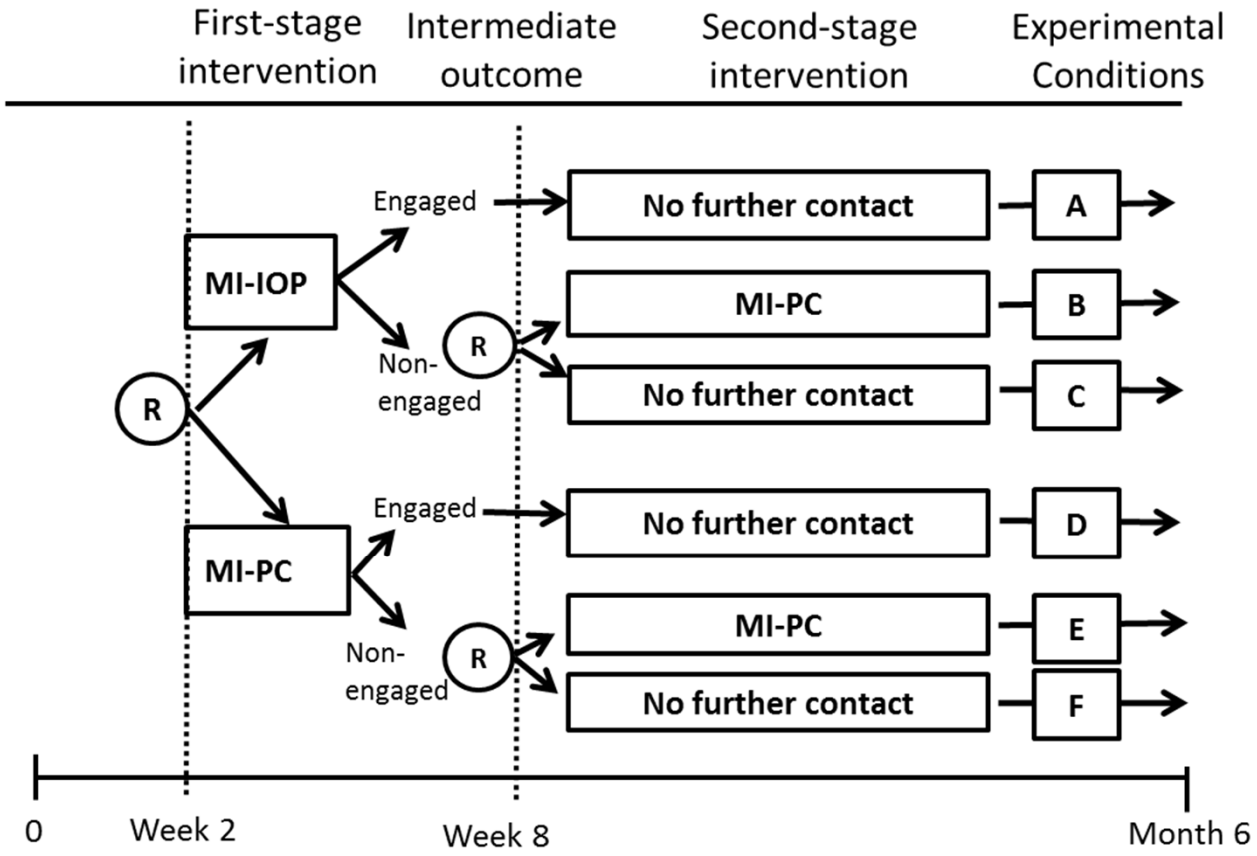
Other Interesting SMARTs

- ExTENd
  - N=302; NIAAAOSL014851; PI: Oslin
- ENGAGE
  - N=500; P60DA05186; PI: McKay
- SMARTer
  - N=400; R01DK108678; PIs: Spring & Nahum-Shani

ExTENd


First-stage intervention
Intermediate outcome
Second-stage intervention
NTX + Lenient Definition of non-response
Week 8 Responders
Non-responders
NTX + Stringent Definition of non-response
Week 8 Responders
Non-Responders
R
NTX
NTX + TDM
CBI
NTX + CBI
a
b
c
d
e
f
g
h
Treatment Outset
Week 24
NTX→ Naltrexone (opioid antagonist)
TDM→ Telephone Disease Management
CBI→ Combined Behavioral Intervention
Lenient Definition → 5+ heavy drinking days in 1 week
Stringent Definition → 2+ heavy drinking days in 1 week

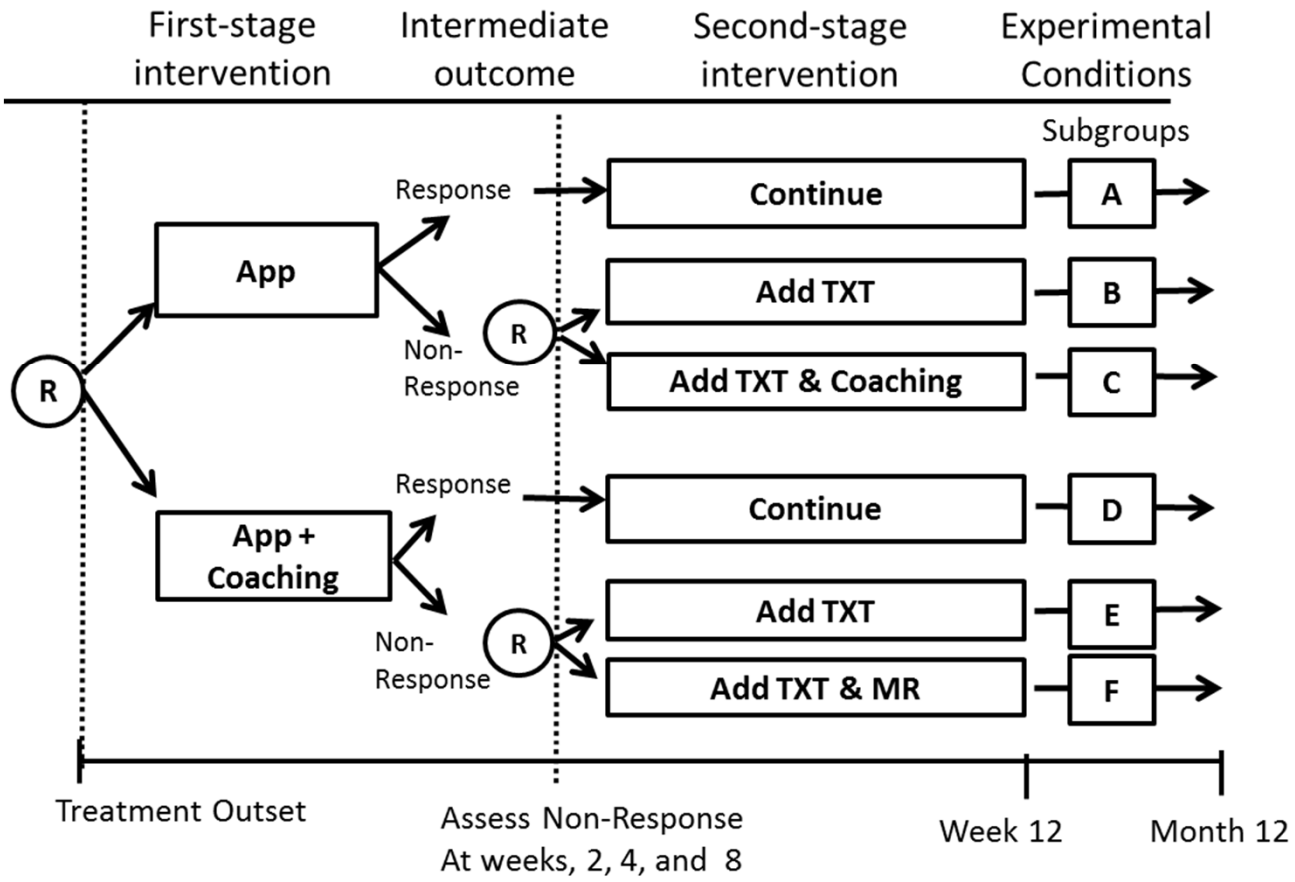
ENGAGE



MI-IOP→ motivational interviewing that focuses on helping the patient to engage in the IOP

MI-PC→ motivational interviewing that includes a choice of four possible treatment options

SMARTer



App→ Mobile Application
MR→ Meal Replacement
TXT→ Text Messages

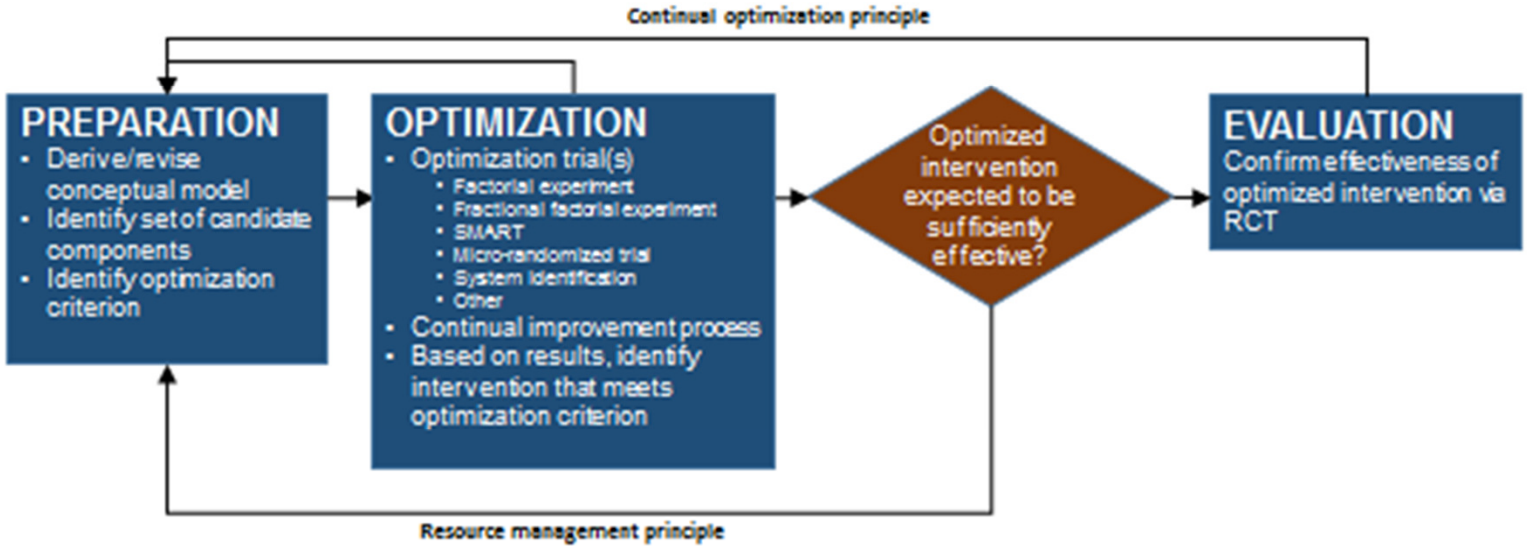
…and Many Other SMARTs in the field…

- Drug abuse
- ADHD
- Alcoholism
- Obesity
- OCD
- Autism
- Schizophrenia
- Depression
- Insomnia
- Bipolar
- Conduct problems
- Smoking cessation
- Suicide prevention

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

SMART and MOST

The Multiphase Optimization Strategy (MOST)



The End

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Thank you…

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Susan Murphy
John Dziak
Jim McKay
Kevin Lynch
Linda Collins
Bonnie Spring
Kelley Kidwell

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