Module 2:
Sequential, Multiple Assignment, Randomized Trials

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Outline

- What are SMARTs?
- Why SMART Experimental Designs?
- SMART Design Principles and Analysis
- Summary & Discussion

What is a SMART?

- A multi-stage randomized trial
- Each stage corresponds to a critical decision point.
- A randomization takes place at each critical decision point.

The goal of a SMART is
to inform the construction of an Adaptive Intervention.

Motivating Question

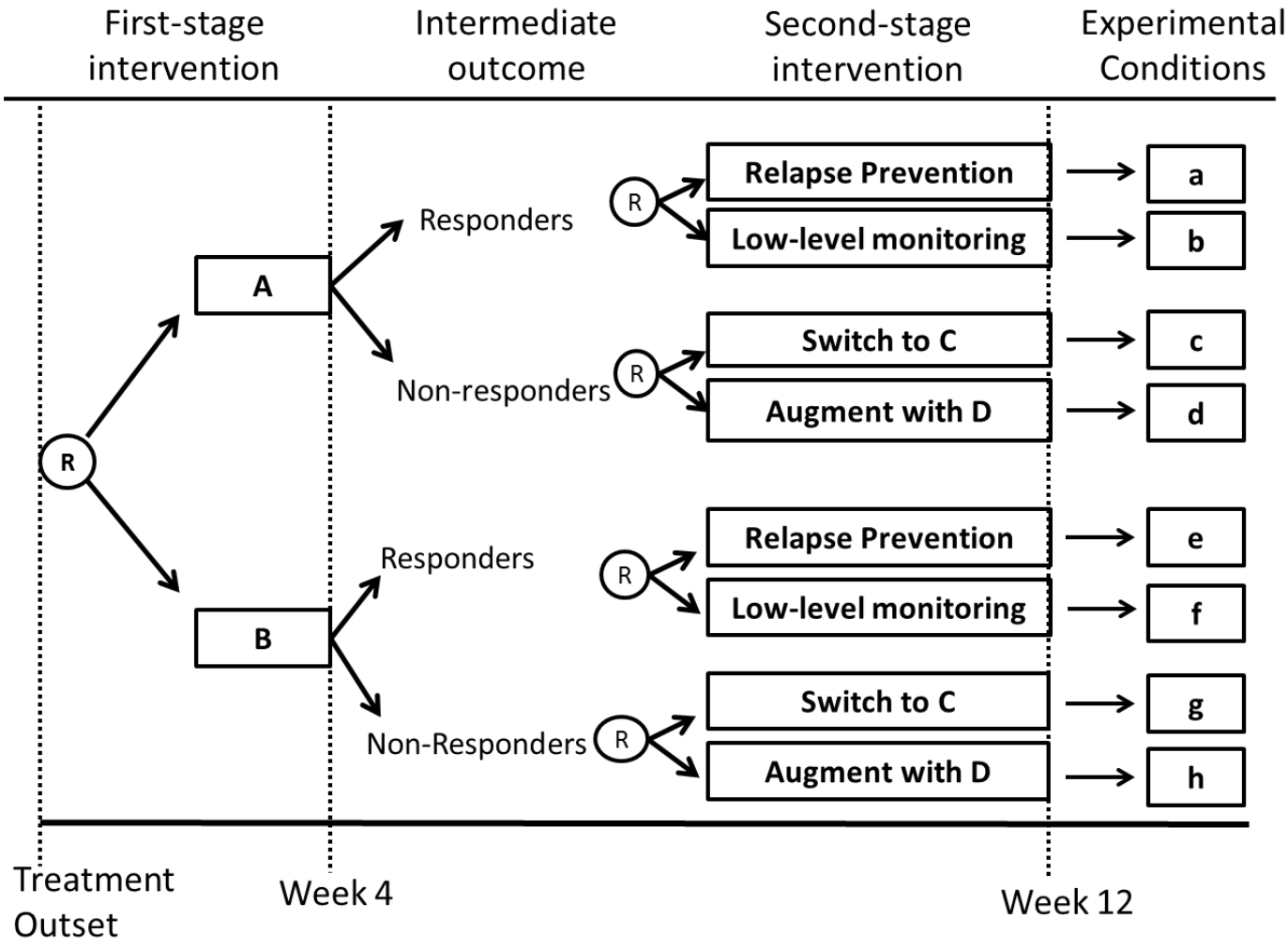
- Hypothetical Goal: AI for treating Minecraft addiction
- Insufficient empirical evidence/theories to determine:

  (a) What is the best way to **initiate treatment** (A vs. B)?

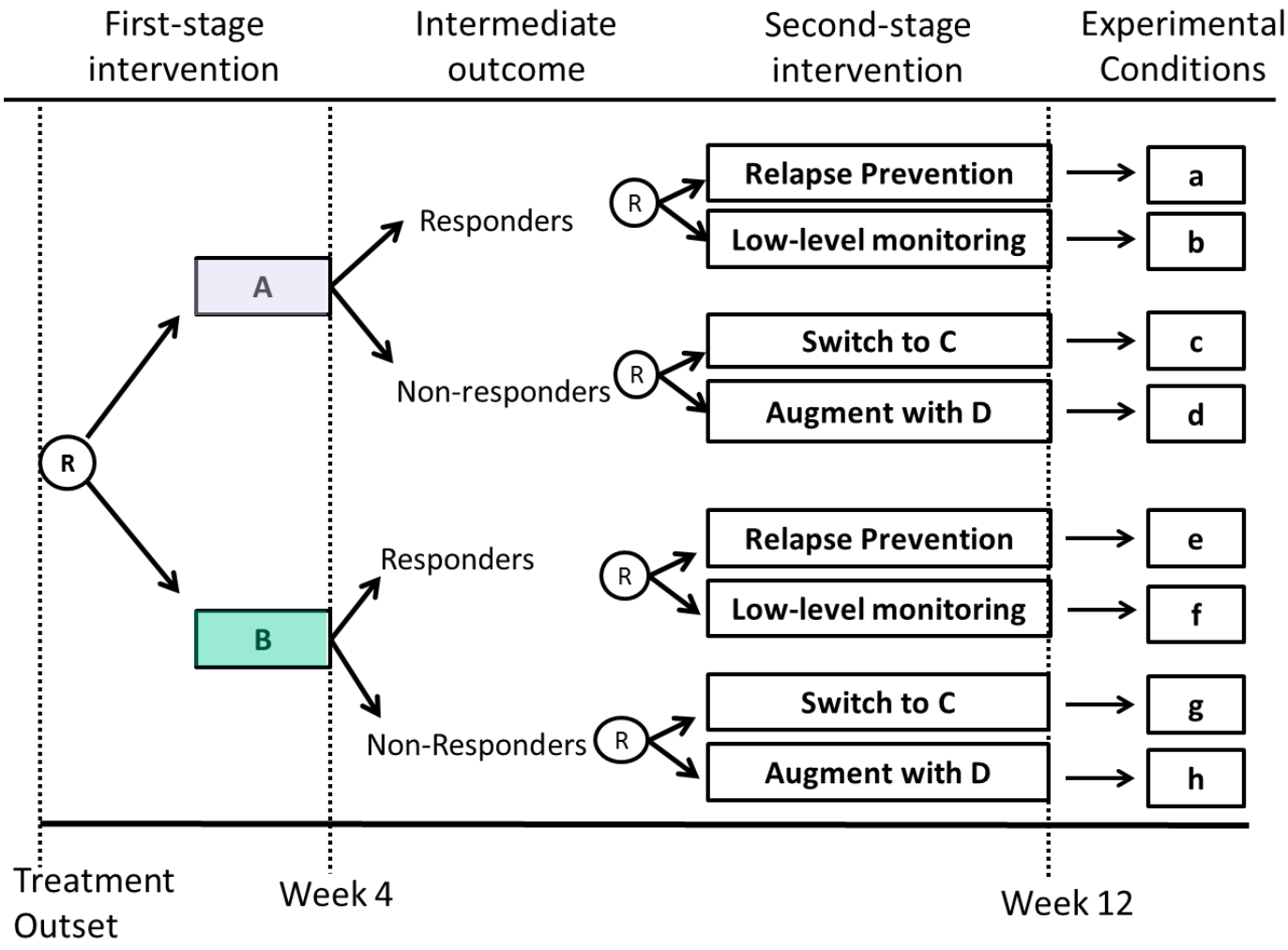
  (b) What is the best approach to modify treatment for **early non-responders** (switch vs. augment)?

  (c) What approach will help maintain Minecraft abstinence among **early responders** (relapse prevention vs. monitoring)?

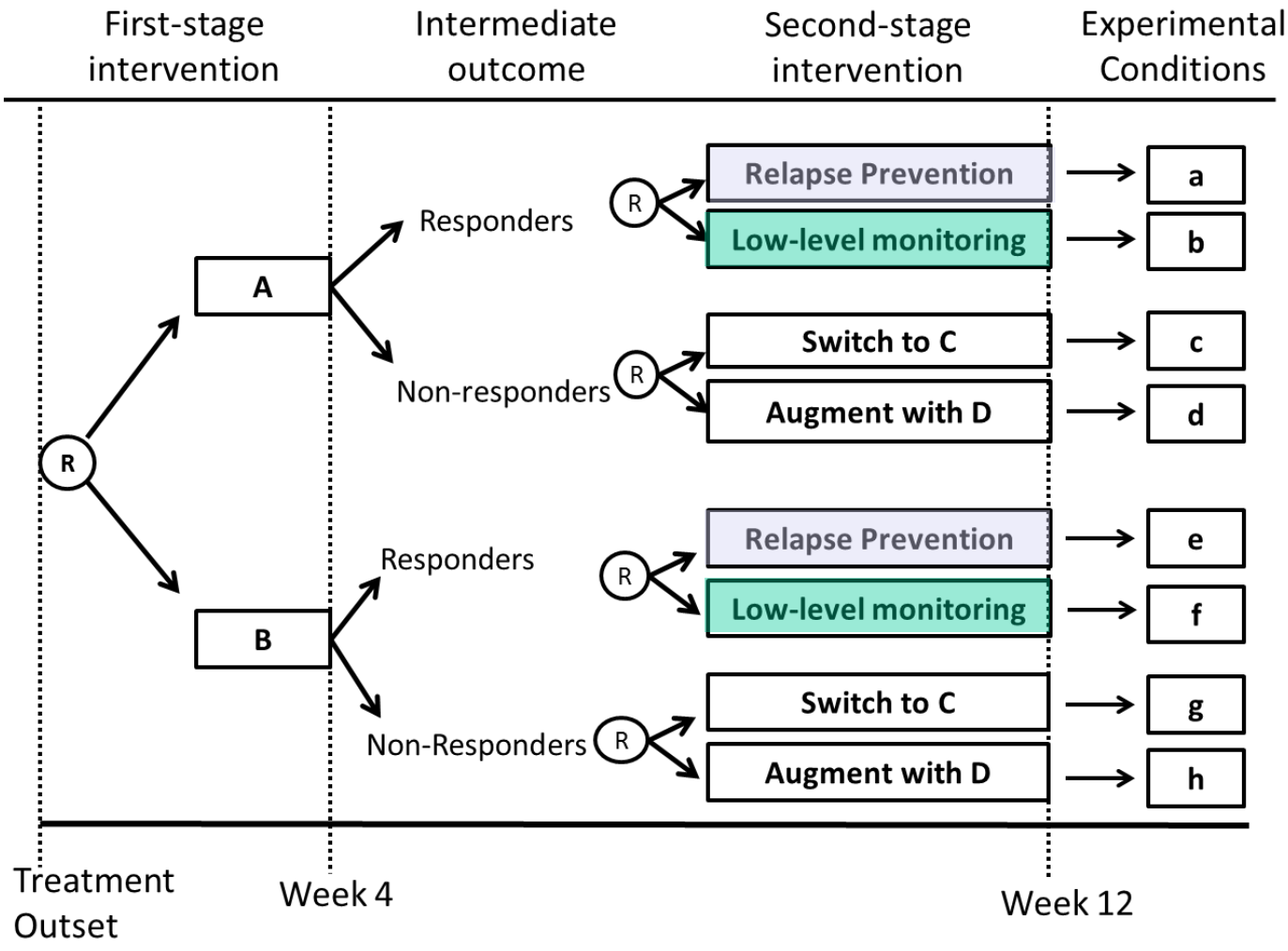
Hypothetical SMART



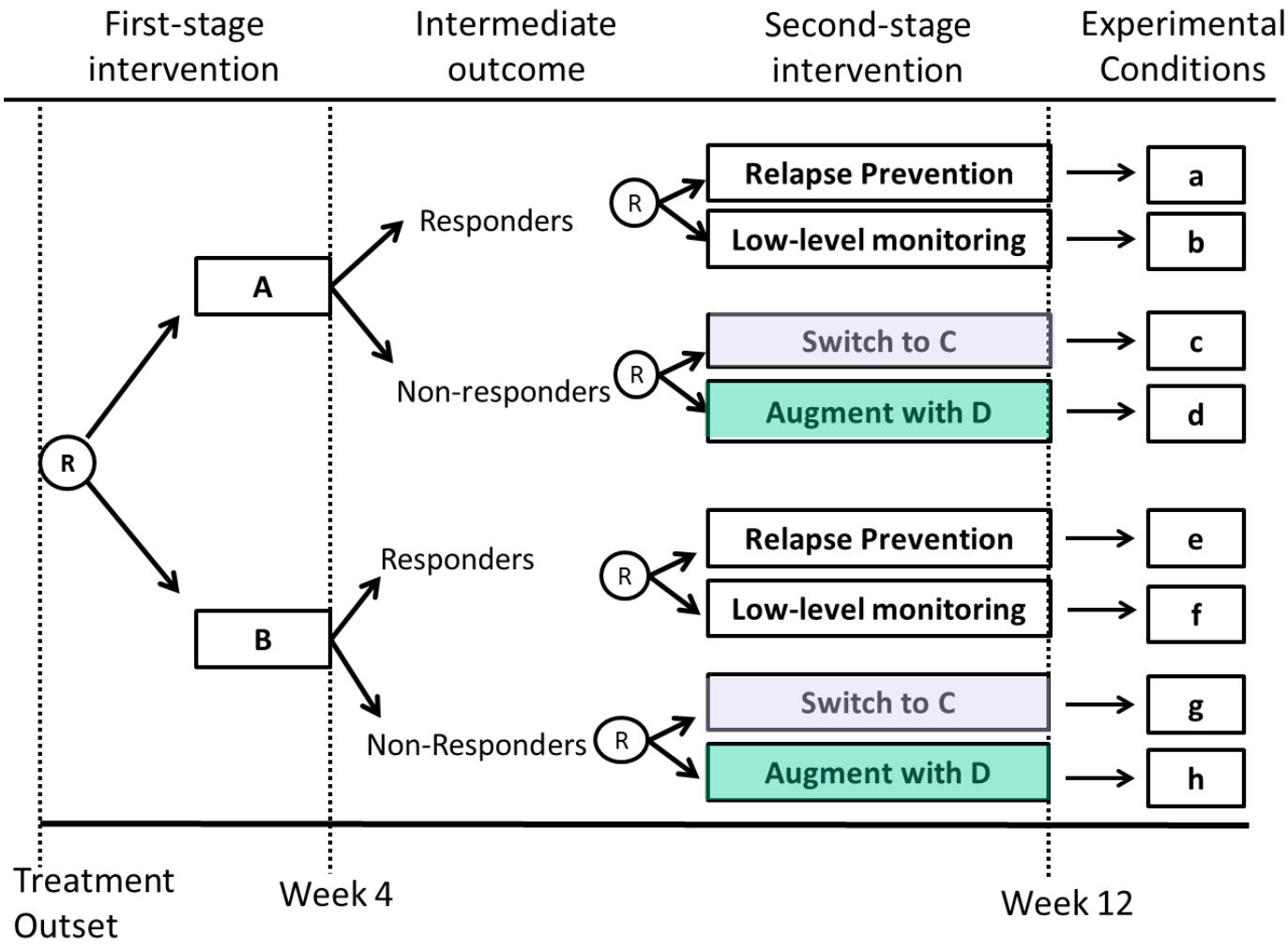
Two Stage 1 Interventions



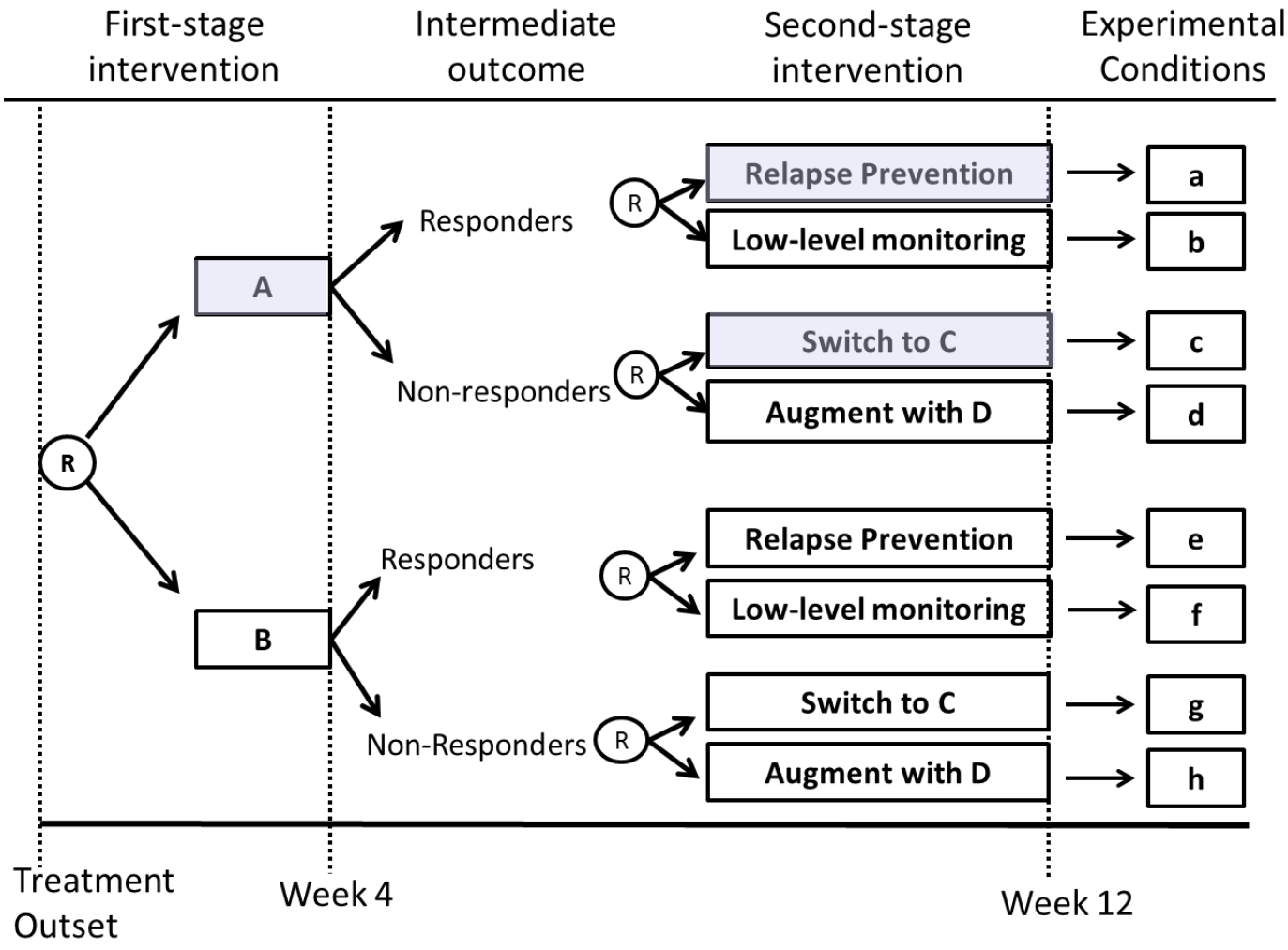
Two Stage 2 Interventions for Responders



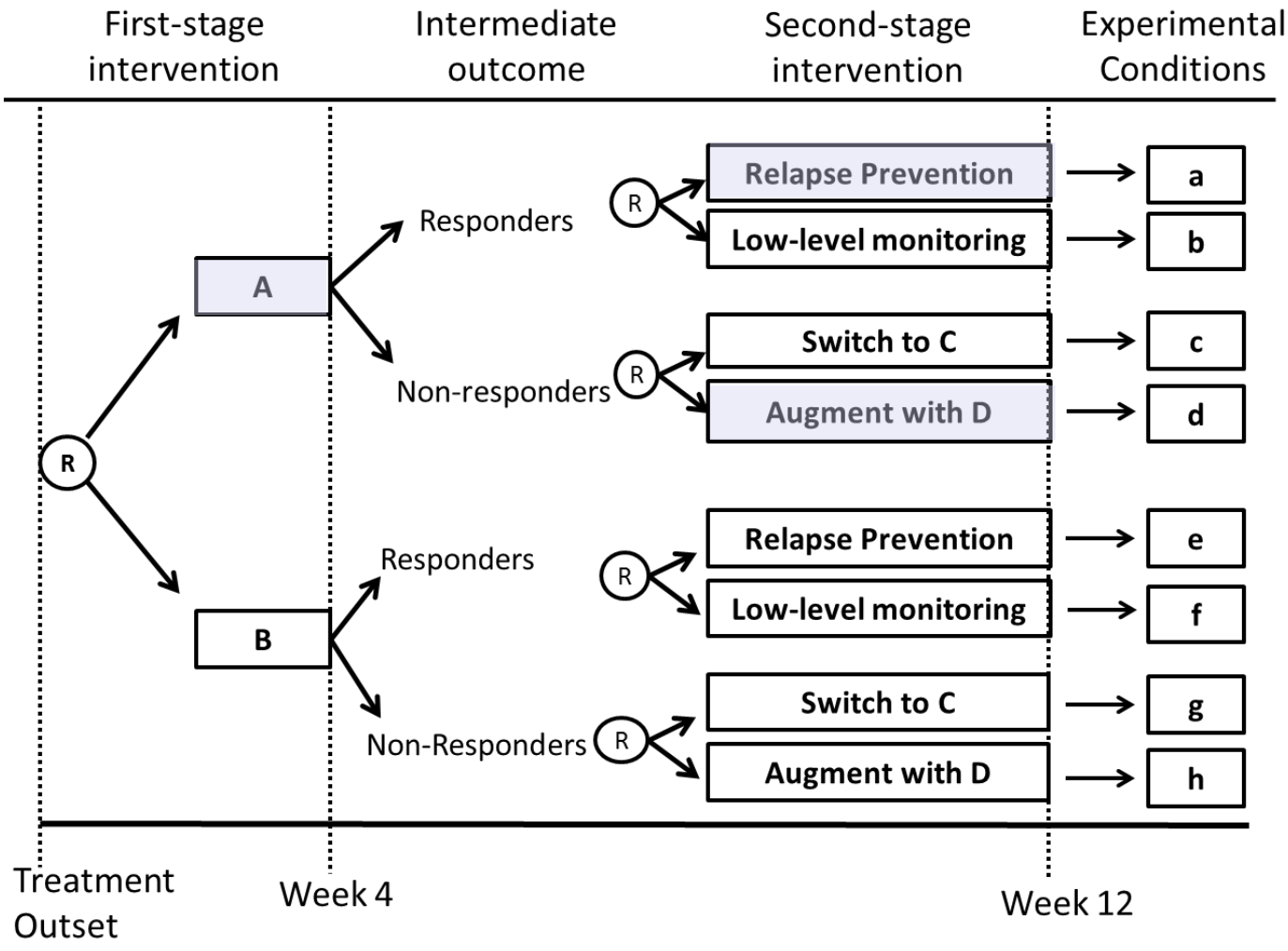
Two Stage 2 Interventions for Non-Responders



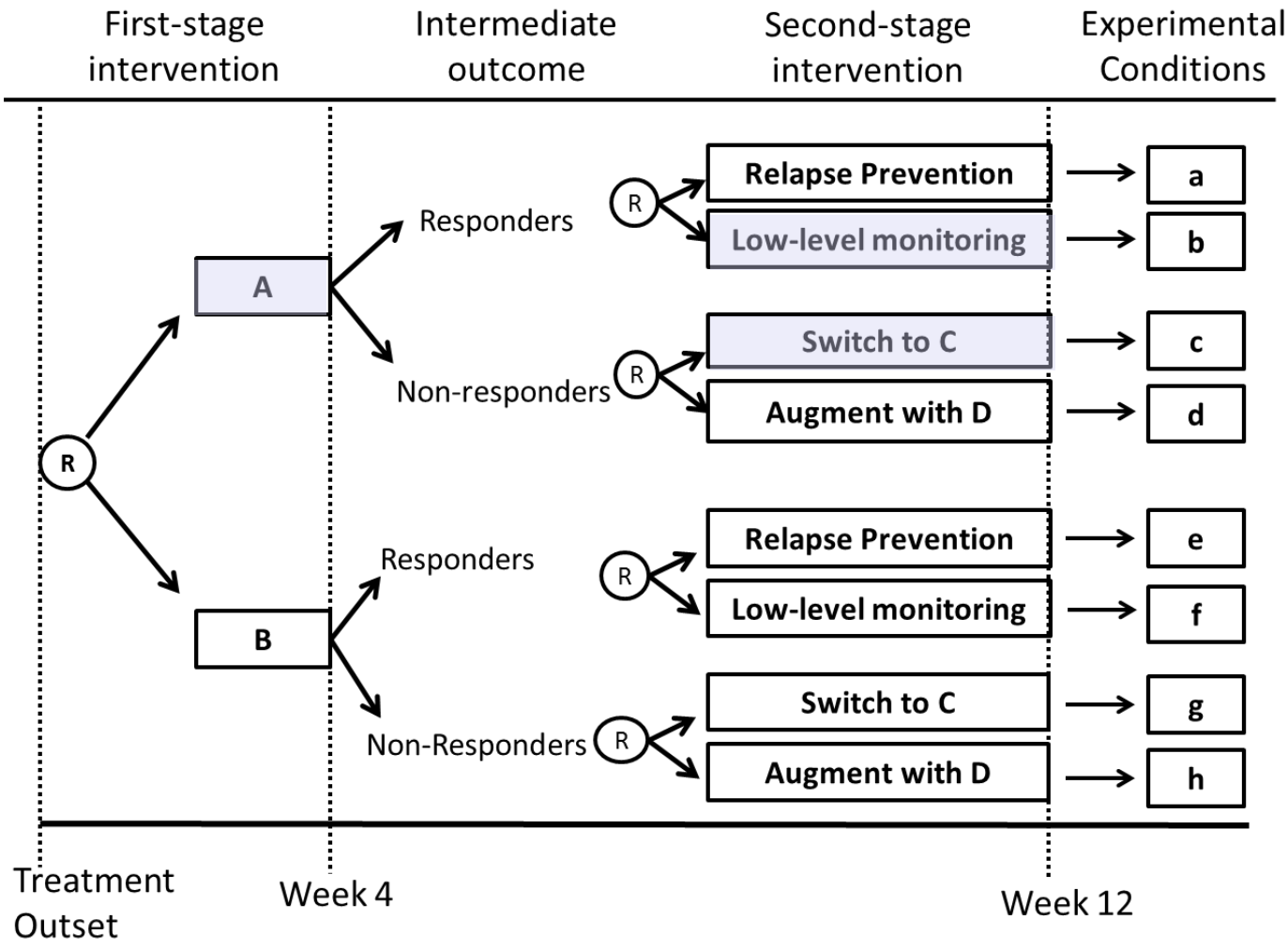
8 Embedded Adaptive Interventions: AI#1



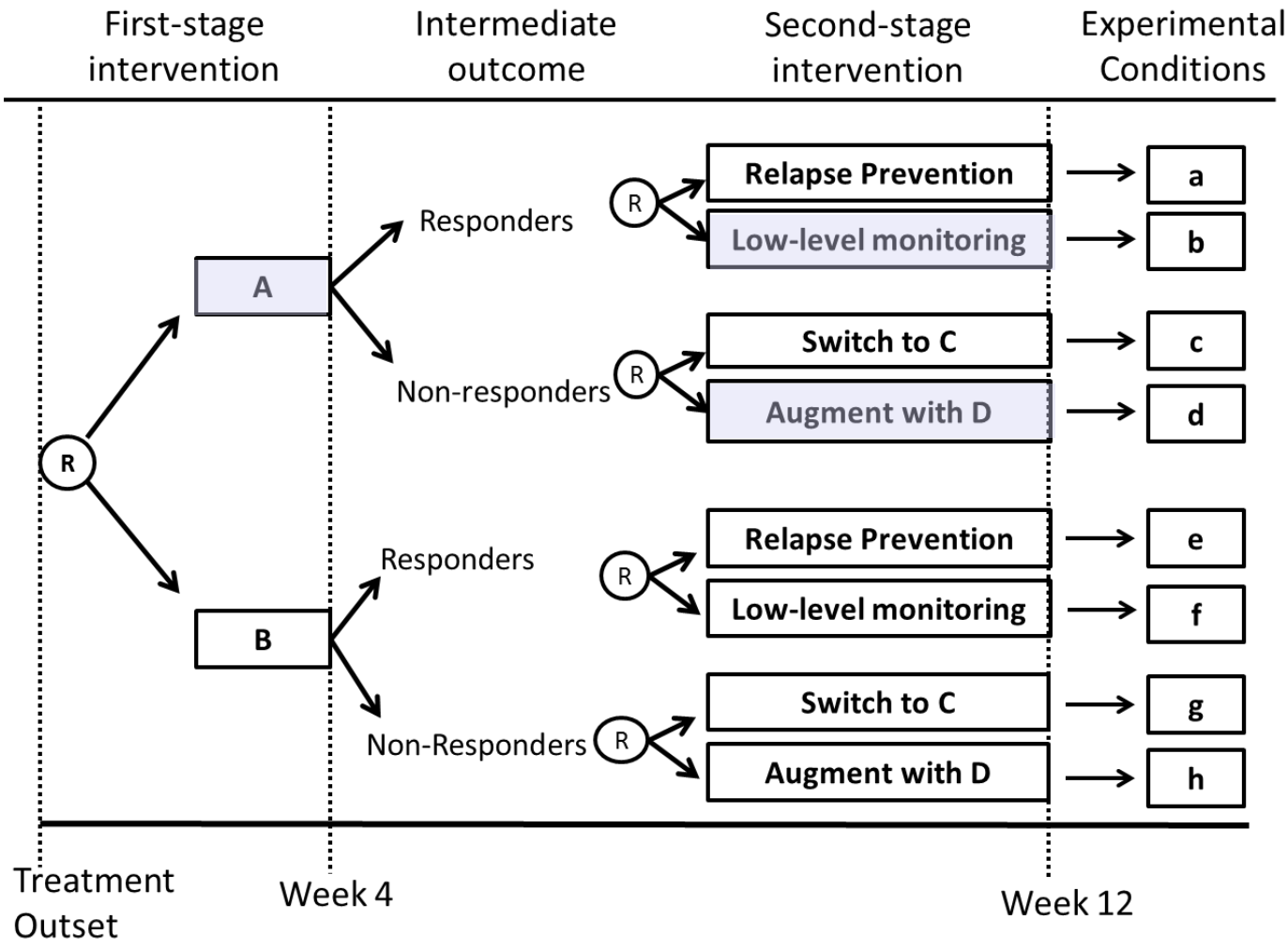
8 Embedded Adaptive Interventions: AI#2



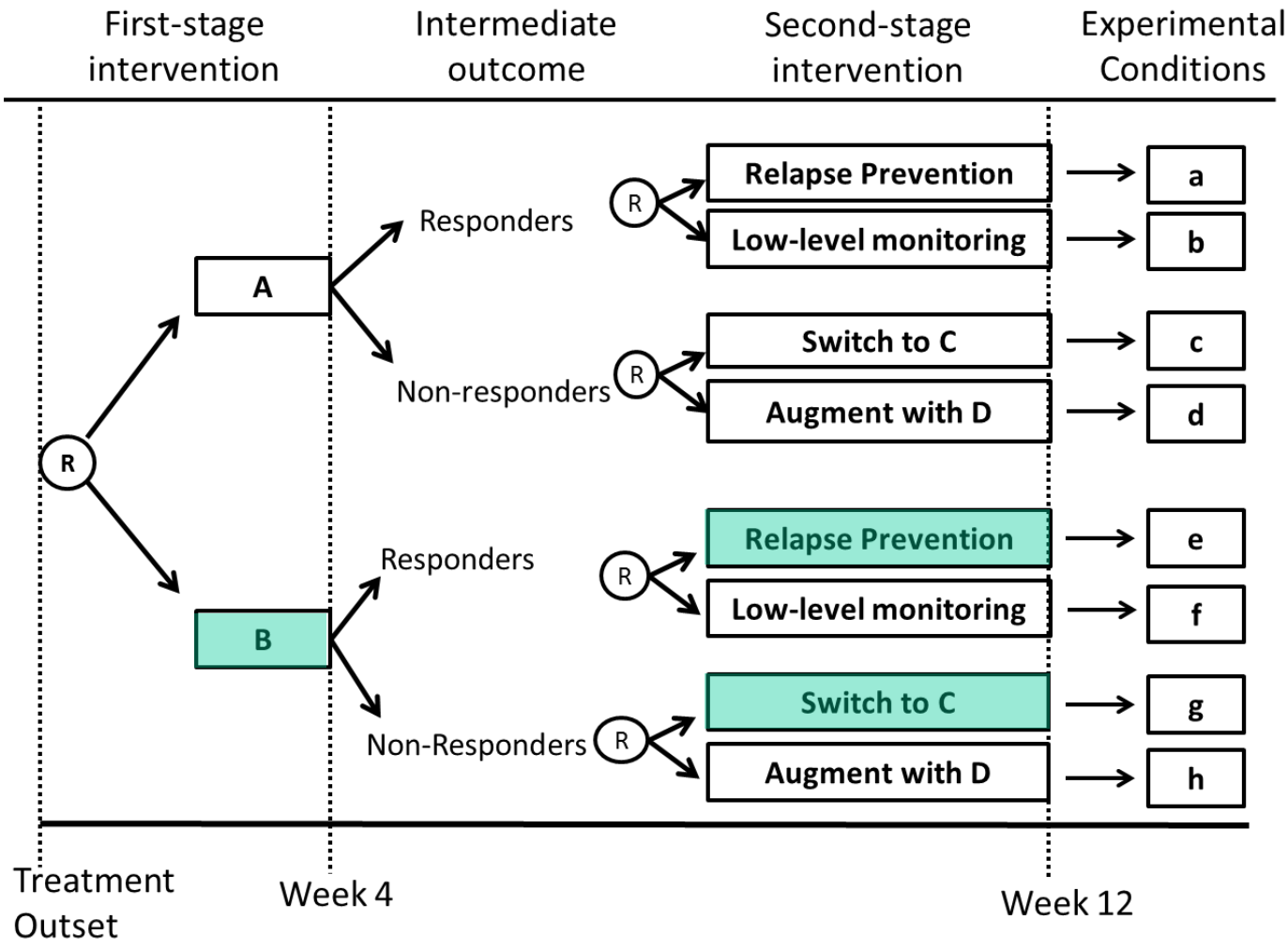
8 Embedded Adaptive Interventions: AI#3



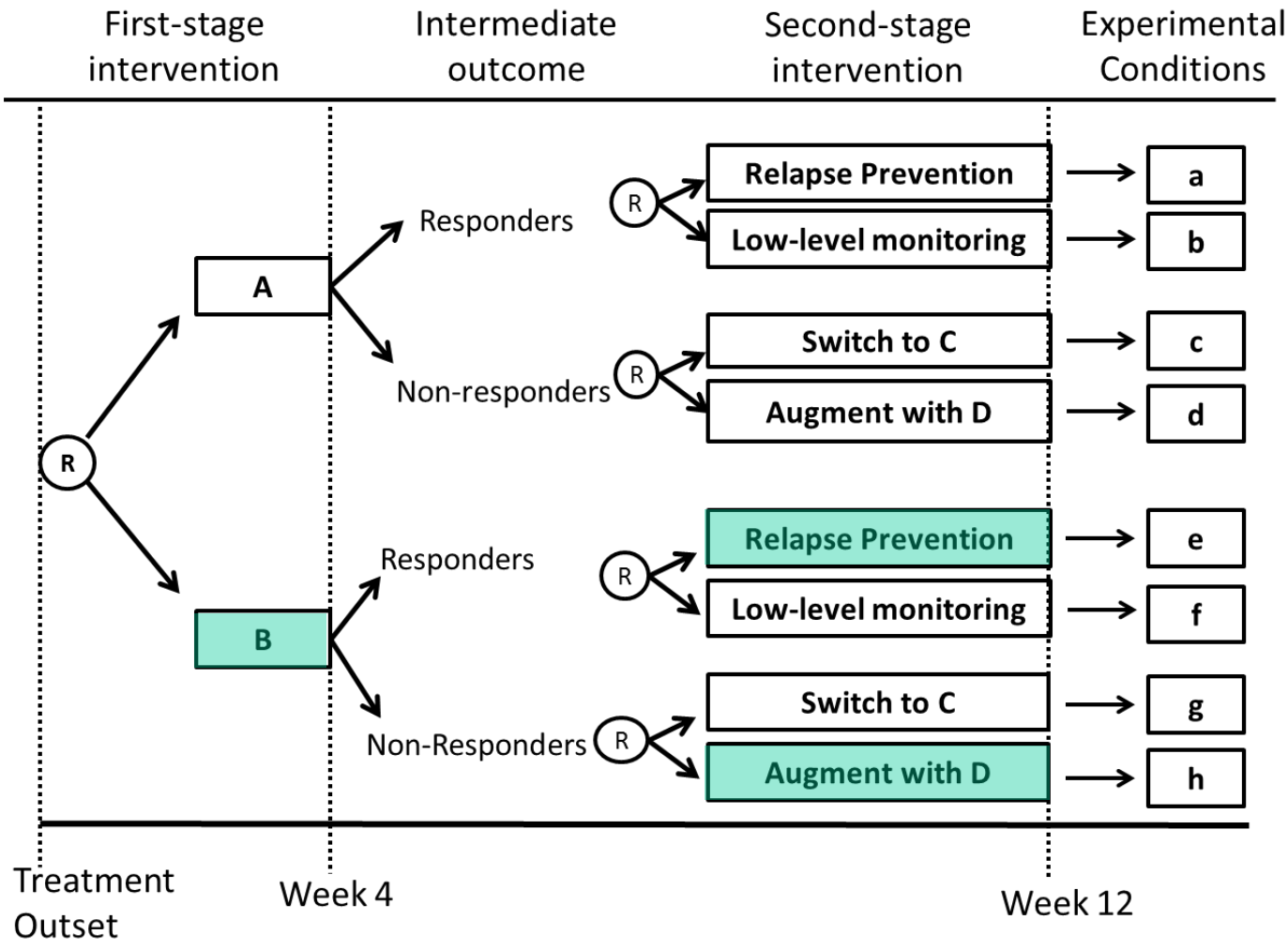
8 Embedded Adaptive Interventions: AI#4



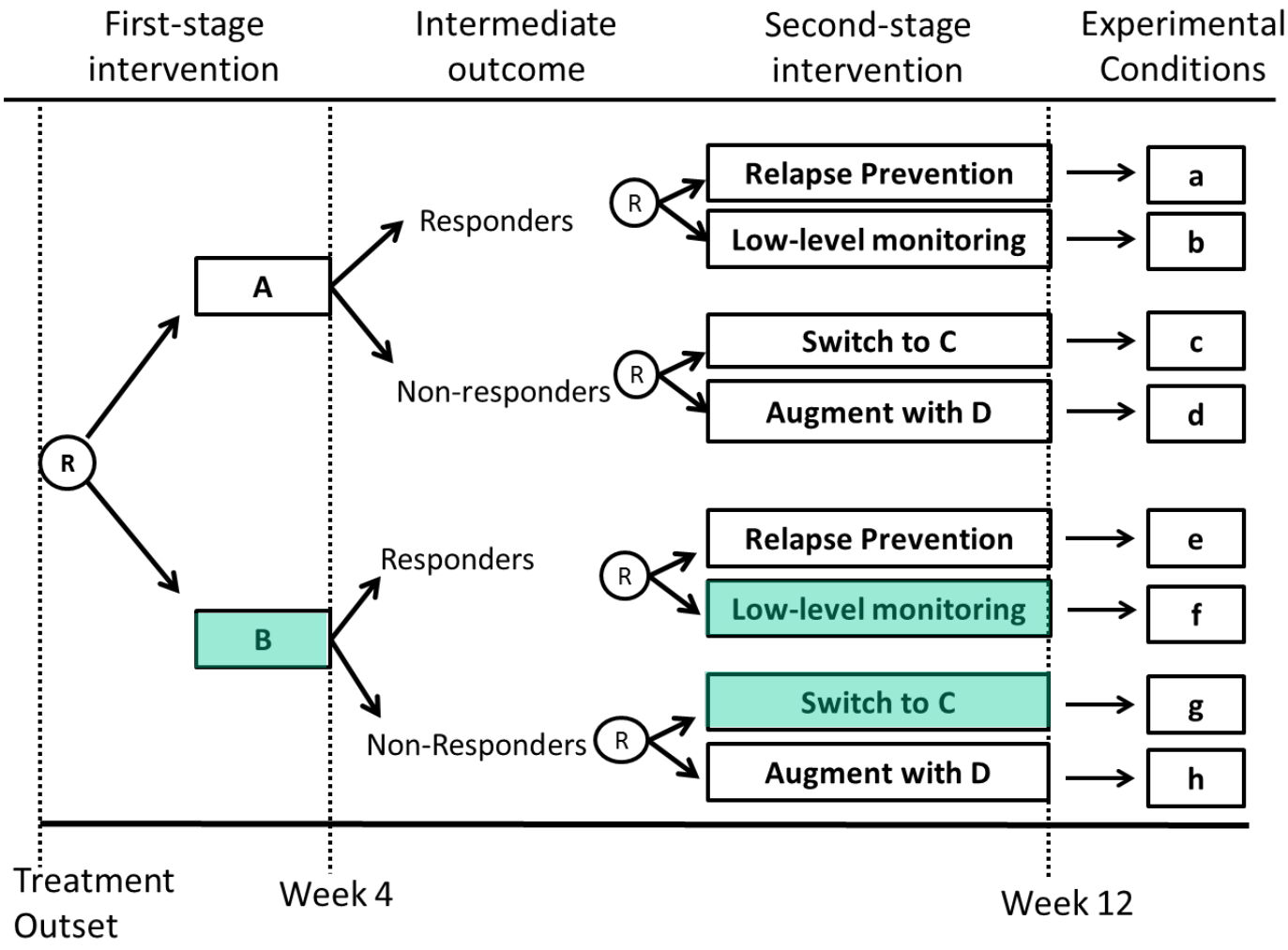
8 Embedded Adaptive Interventions: AI#5



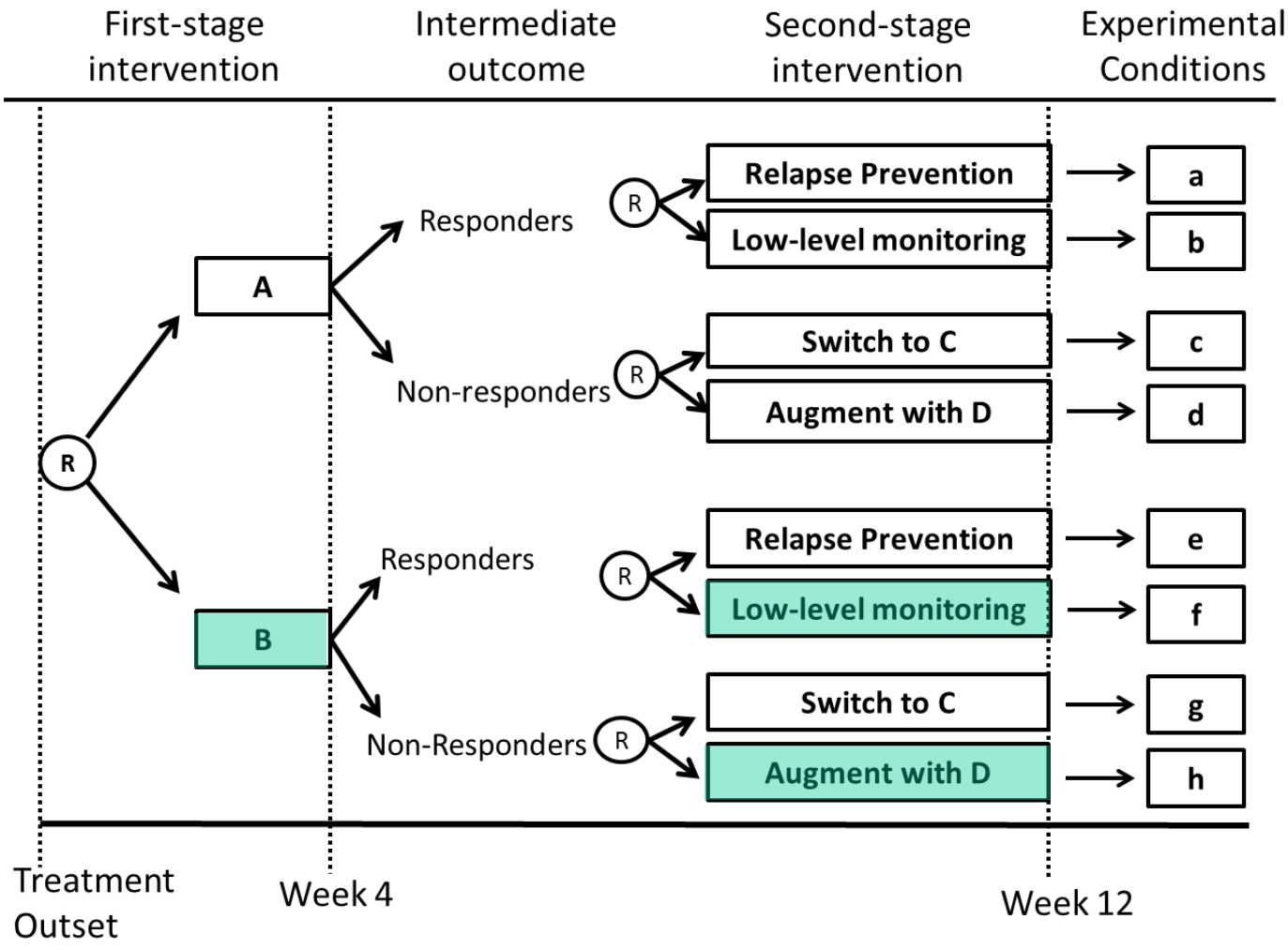
8 Embedded Adaptive Interventions: AI#6



8 Embedded Adaptive Interventions: AI#7

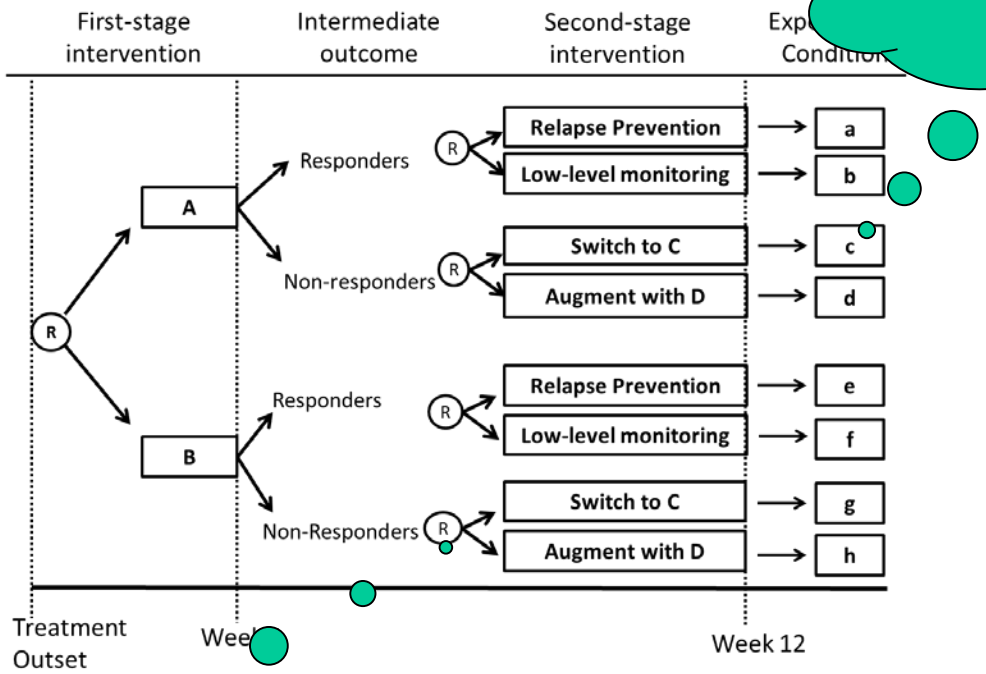


8 Embedded Adaptive Interventions: AI#8



Hypothetical SMART

I'm worried about…
…sample size



This looks too
…complicated

Outline

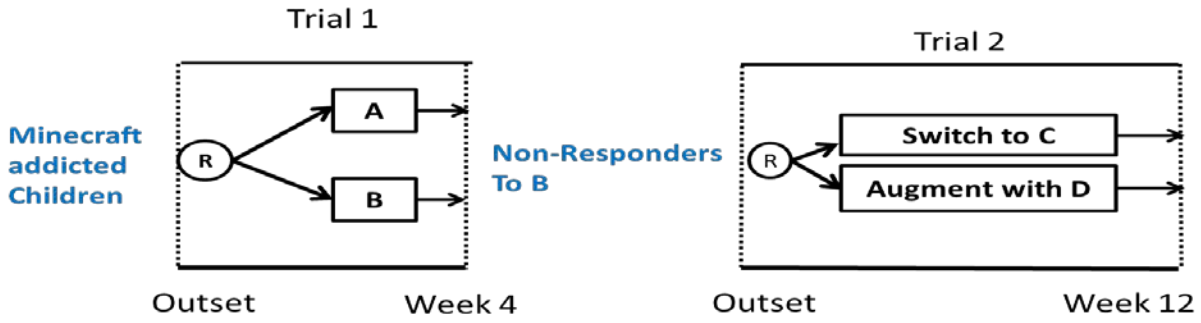
- What are SMARTs?
- Why SMART Experimental Designs?
- SMART Design Principles and Analysis
- Summary & Discussion

Alternative to SMART Design

- An alternative to SMART designs is to use data from multiple, separate trials to construct an Adaptive Intervention.

- This is called the single-stage at a time approach

Alternative to SMART Design



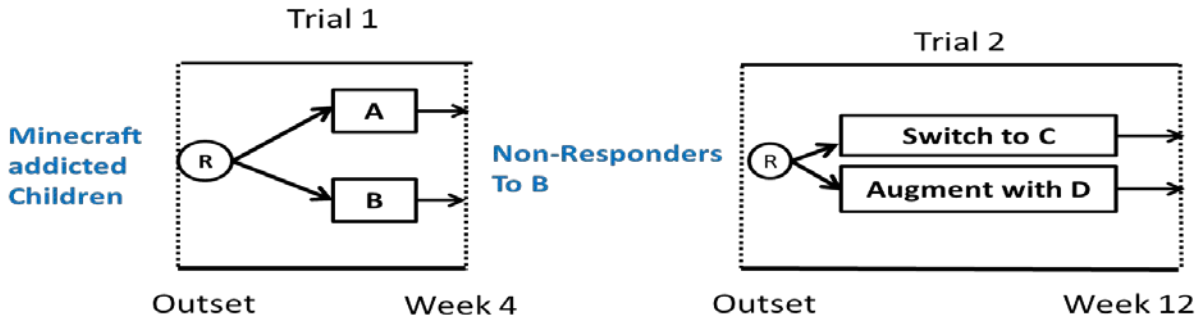
Trial 1:

- Randomized trial of initial intervention options
- Choose the best stage 1 option.

Trial 2:

- Randomized trial of secondary intervention options
- Choose the best stage 2 option.

Single Stage vs. SMART



There are a number of disadvantages to the single-trial at a time approach.

Disadvantage #1: Delayed Therapeutic Effects

Delayed effect:

- Short term effectiveness of initial treatment does not capture its long-term effectiveness when followed by subsequent treatment
  - i.e., when considered part of a sequence of treatments

- Might happen when there are:
  a) Positive Synergies
  b) Negative Synergies

Disadvantage #1: Delayed Therapeutic Effects

Positive synergies:

The intervention option that does not seem best initially (in short-term) is the best in the long term, when considered part of a sequence.

- "A" may not have the best outcomes in 4 weeks
- but "A" may have enhanced long term effectiveness when followed by a second-stage intervention (e.g., Augment)

In other words:

- "A" may lay the foundation for the long-term effectiveness of "Augment"
- "Augment" builds on the gains of "A".

Disadvantage #1: Delayed Therapeutic Effects

Negative synergies:

Intervention option that appears best initially (in short-term) is not best in the long term, when considered as part of a sequence.

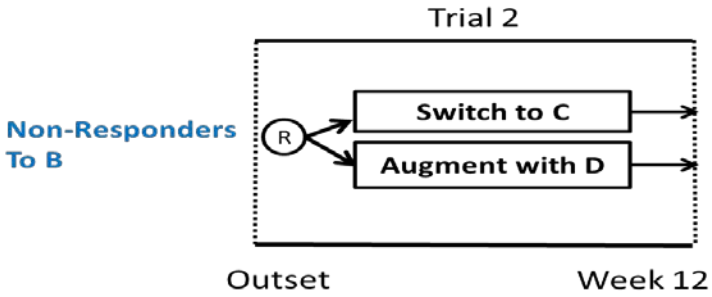
- "A" may produce a higher proportion of responders
- But, the burden imposed by "A" may be sufficiently high so that non-responders are less likely to adhere to subsequent treatments.

Disadvantage #2: Adherence/Drop-out

Participants may be more likely to adhere/remain in SMART

- In the alternate trial of the initial treatments subjects are assigned a fixed treatment.
  - Those who are not improving have no other option besides non-adherence or drop-out.
- SMART, by design, provides alternates for non-improving subjects,
  - This enhances motivation to adhere and remain in the study.

Disadvantage #3: Selection Effect



A study that enrolls non-responders might not sample individuals that represent the population of non-responders

- Only non-responders who are highly motivated will select to participate in this study
- Because of this selection bias I might not realize that I need to provide more support to encourage demoralized non-responders to start treatment again.

Disadvantage #4: Prescriptive Effects

Single stage studies provide limited options to explore ways to more deeply tailor the AI.

- Treatment A may not produce as high a proportion of responders as treatment B.
- But treatment A may elicit symptoms (e.g., non-adherence) that allow you to better match the subsequent treatment to the patient and thus achieve improved response to the sequence of treatments as compared to initial treatment B.

Summary

SMARTs enable us to:

- Capture delayed intervention effects resulting from positive or negative synergy.
- Account for the effects of subsequent treatments when comparing and evaluating initial treatments.
- Improve adherence and reduce attrition among participants who are not responding to the initial intervention.
- Include a sample of non-responders that have broader representation of the population of non-responders.
- Capture data that will enable us to more deeply tailor future adaptive interventions for optimal outcomes.

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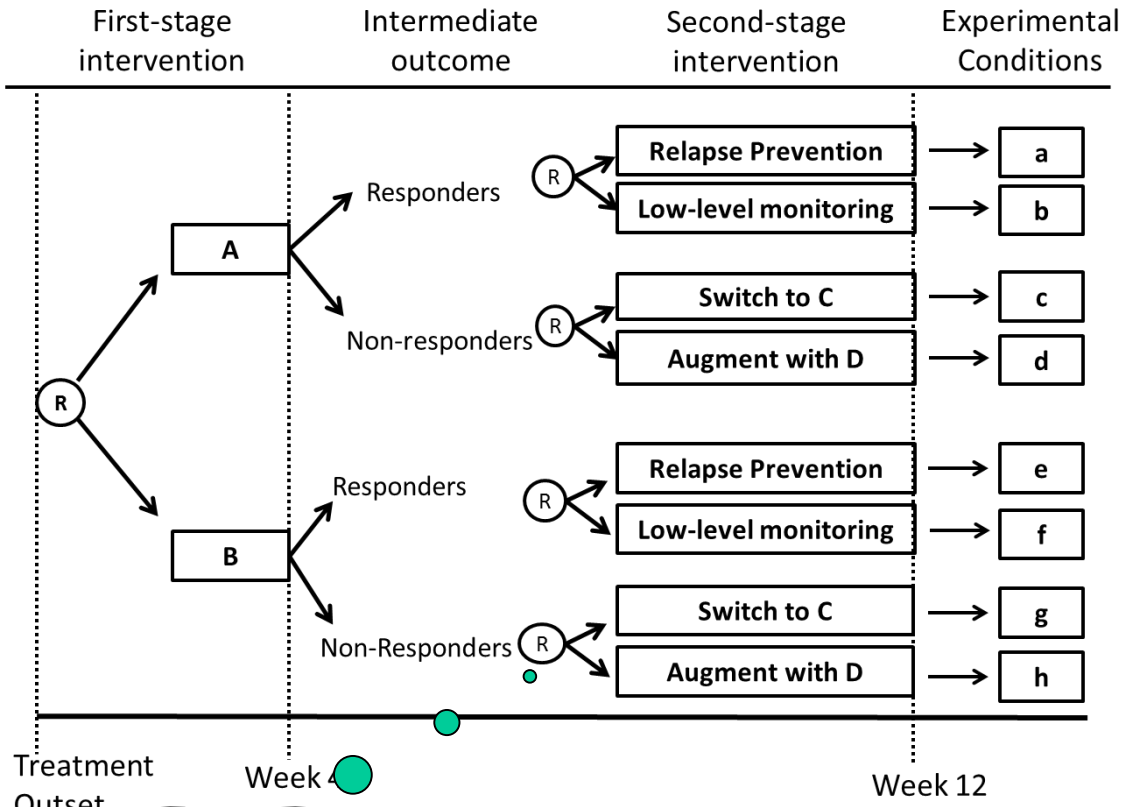
Hypothetical SMART



This looks too …**complicated**

SMART Design Principles

Keep it Simple:

- Focus on a few scientific questions that you seek to address concerning AIs
- Use well-justified tailoring variable to restrict the randomization based on ethical, scientific and practical considerations.
- Use a low dimension summary (responder status) instead of all intermediate outcomes (adherence, etc.) to restrict class of next treatments.

SMART Design Principles

Plan to collect intermediate outcomes needed to ascertain response status.

- But also consider collecting other information that might be useful in ascertaining for whom each treatment works best
- Information that might enter later into the AI
- Namely, candidate tailoring variables

SMART Design Principles

Choose primary hypotheses:

- that are both scientifically important and aid in developing the AI
- Power trial to address these hypotheses

SMART Design Principles

Choose secondary hypotheses:

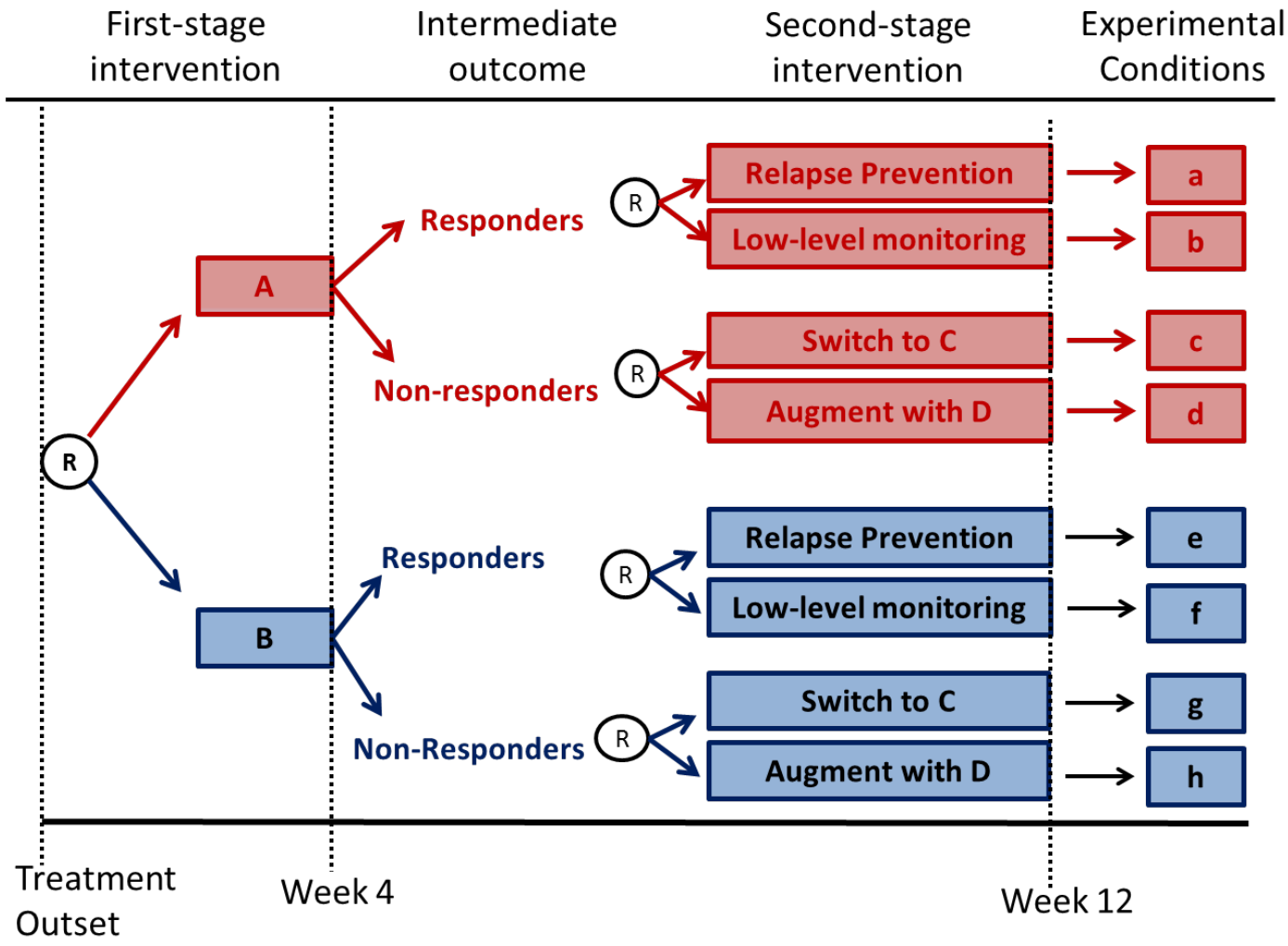
- that further develop the AI and use the randomization to eliminate confounding*
- Trial is not necessarily powered to address these hypotheses.

* Confounding: alternative explanations other than treatment effect for the observed difference

Example of Primary Aims

1. *Comparison of initial options*
    - When sample size is highly constrained.
    - **H1:** The initial intervention option A results in lower symptoms than the initial intervention option B.
        - Controlling for second-stage intervention options

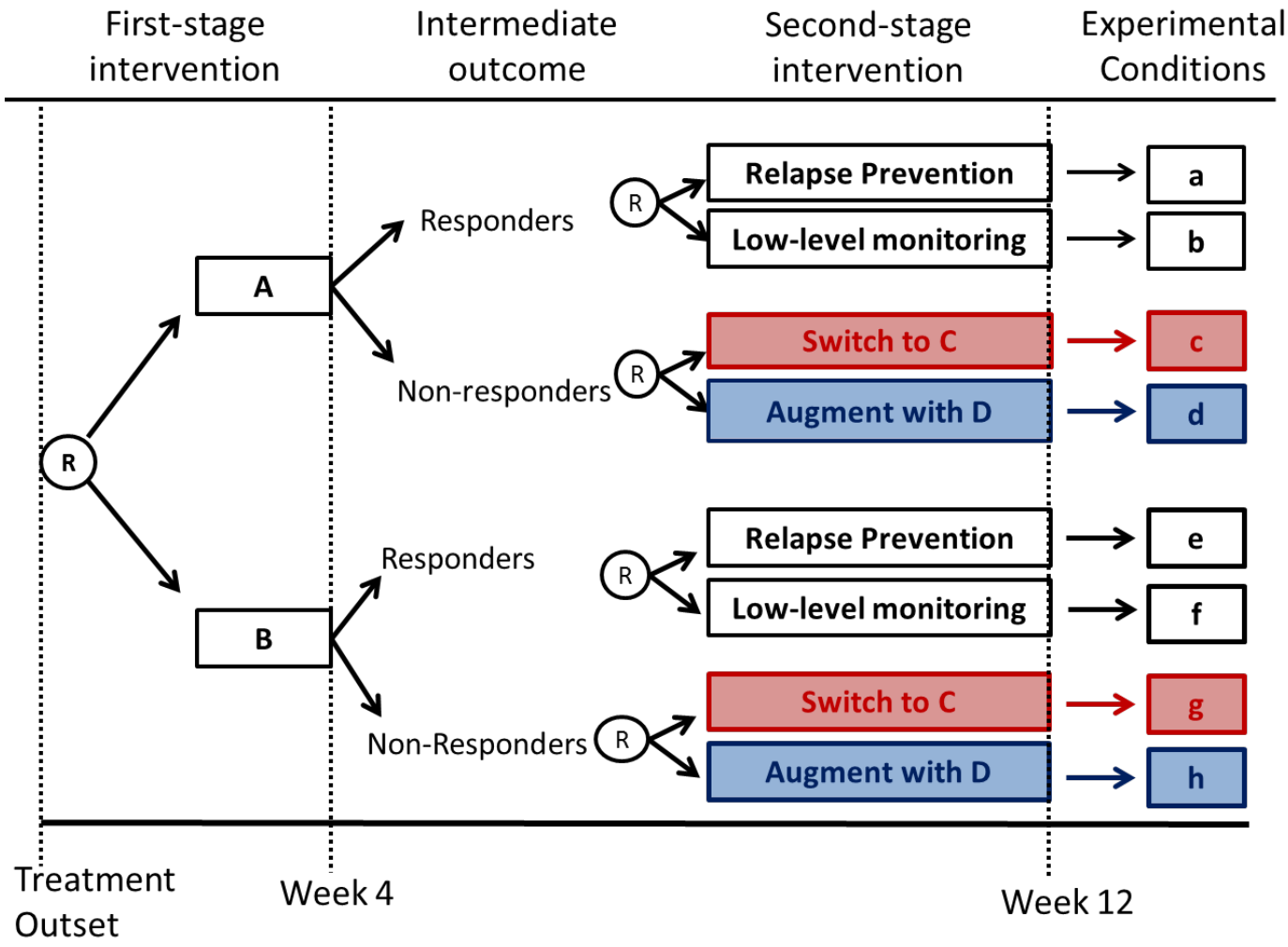
H1: Comparison of First-Stage Options



Example of Primary Aims

2. *Comparison of second stage options for non-responders*
   - When sample size is less constrained.
   - **H2:** Among non-responders a switch to C results in lower symptoms than augmenting with D
     - Controlling for first-stage intervention options

H2: Comparison of Second-Stage Options

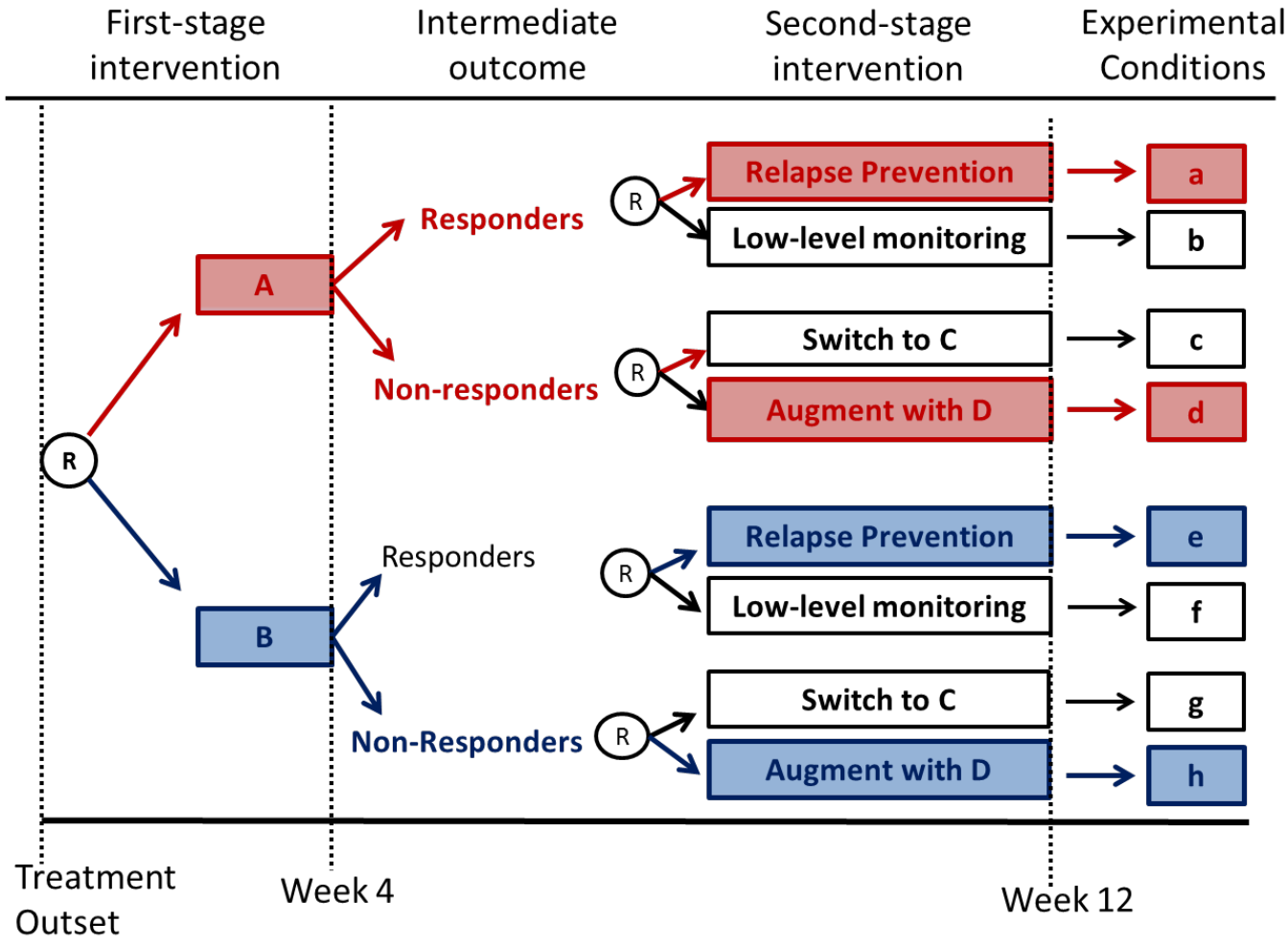


Example of Primary Aims

3. *Comparison of embedded AIs*

   - When sample size is less constrained.
   - **H3:** AI #1 results in improved symptoms compared to AI #2

H3: Comparison of Embedded AIs



SMART Design Principles

Primary Aim that is less useful in developing an AI:

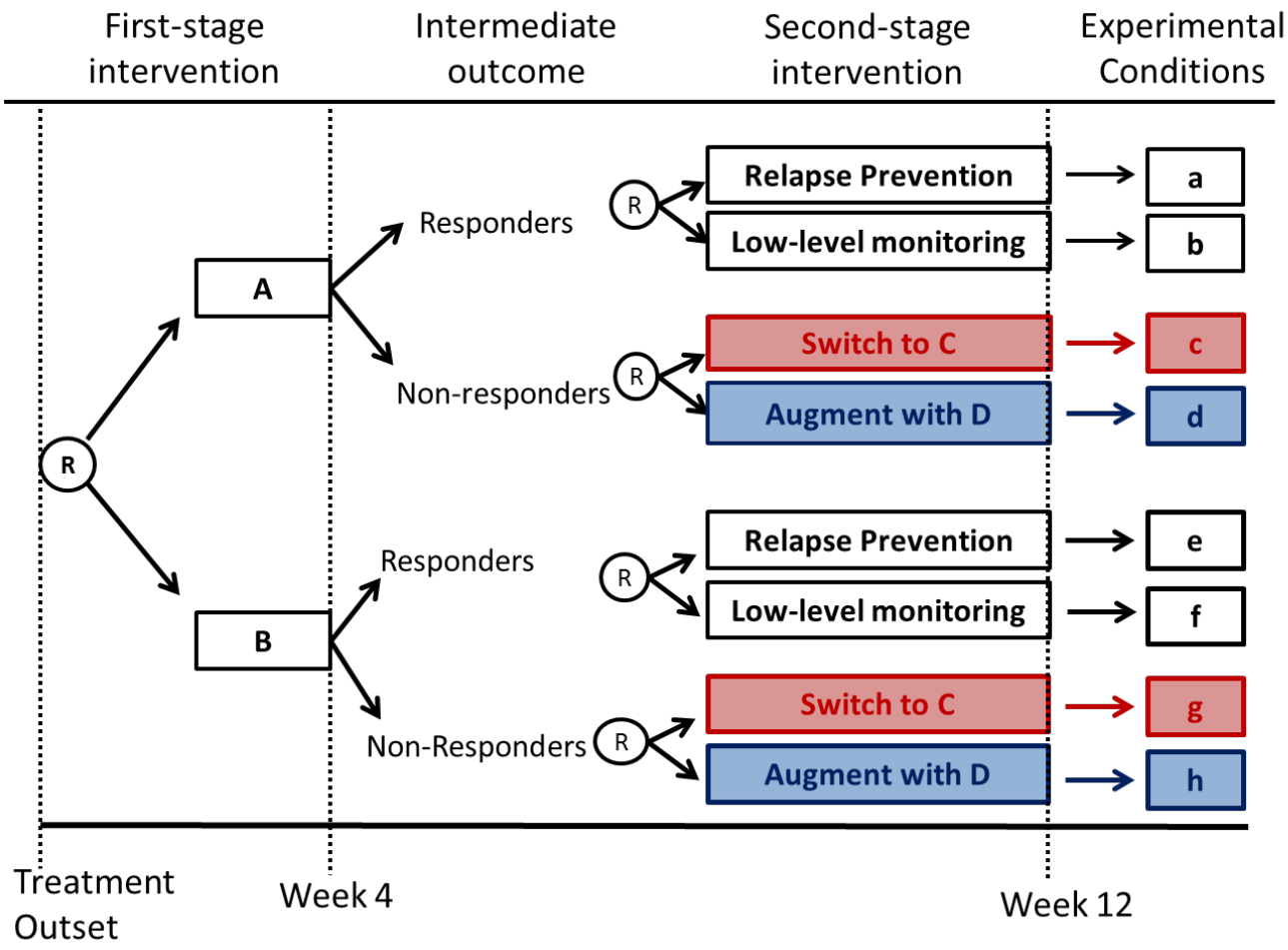
- Compare initial treatments (A vs. B) in terms of intermediate outcomes (proportion of early responders).
- Why less useful?
  - Focus short-term effects=Reading the first half of a book
  - Not considering the implications of second-stage options
- This makes sense only if all second-stage options are equally effective among A and B.

SMART Design Principles

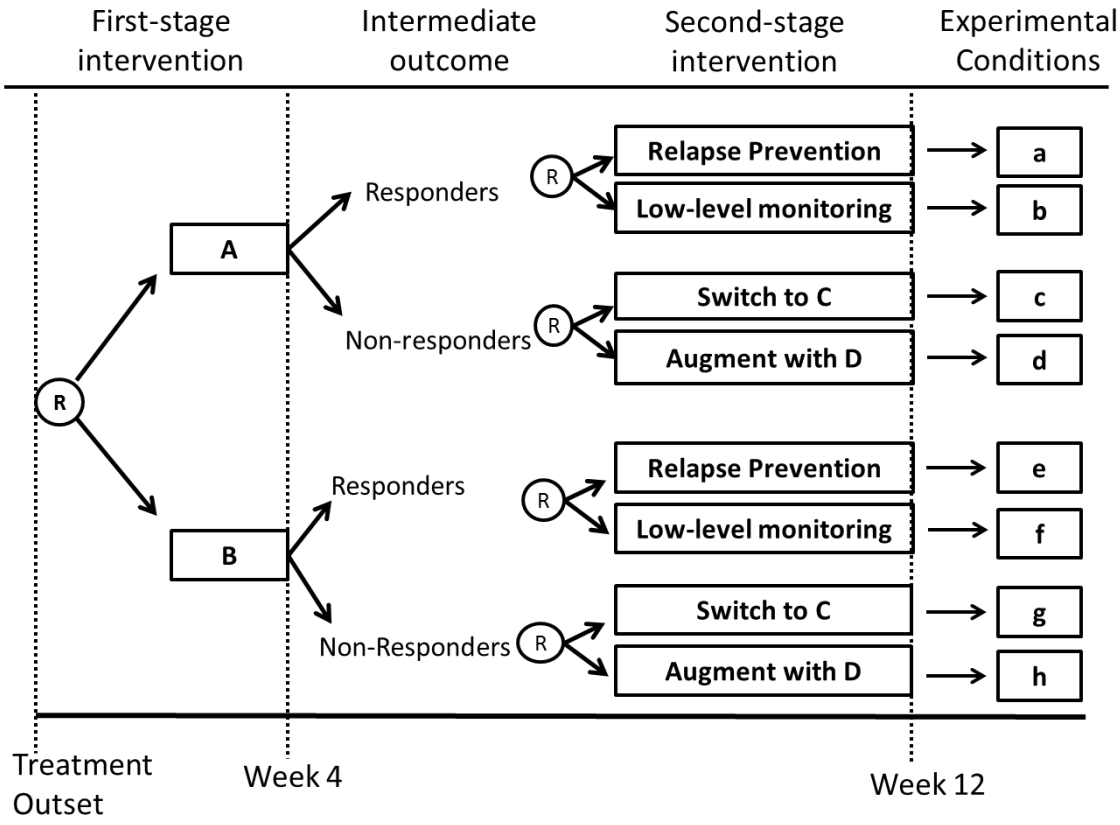
Choose secondary hypotheses that further develop the Adaptive Intervention.

- Example:
  H4: *non-adhering* non-responders will exhibit lower symptoms if their initial treatment is augmented with D as compared to switching to C.

H4: Adherence as a Moderator of Second-Stage Options



Hypothetical SMART



Sample Size

H1: The initial intervention option A results in better outcomes compared to initial intervention option B.

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

H2: Among non-responders a switch to C results in lower symptoms than augmenting with D

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

Sample Size

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

	H1	**H2**
$\Delta\mu/\sigma$ =.3	N = 402	N = 402/ NR rate
$\Delta\mu/\sigma$ =.5	N = 146	N = 146/ NR rate

α = .05 (two sided), power =1 – β =.85

Sample Size

H3: AI #1 has better outcomes compared to AI #2

Type I error rate	Power	Standardized Difference	N	Randomization
0.05/2	80%	0.3	697	Both R and NR are re-randomized
		0.4	392	
		0.5	251	
		0.3 (NR=0.3)	453	Only NR are re-randomized
		0.4 (NR=0.3)	255	
		0.5 (NR=0.3)	163	

In Oetting, A.I., Levy, J.A., Weiss, R.D. Murphy, S.A. (2011), Statistical Methodology for a SMART Design in the Development of Adaptive Treatment Strategies (book chapter)

Outline

- What are SMARTs?
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Summary

Solution: Keep it simple

Solution: Plan sample size for primary aims

Practicum: Working Lunch

Goal: Develop an experimental design to address the scientific questions identified in Practicum 1.

30 minutes: break, lunch

30 minutes: small group work to expand on shared idea

30 minutes: large group discussion/brainstorm