



Presented by
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Sequential Multiple Assignment Randomized Trials

SMARTs

Module 2

 55 min



Outline

Example Adaptive Intervention

Define Sequential Multiple Assignment
Randomized Trial (SMART)

What do you need to know about SMART
data analytic methods

What do you need to know about SMART
sample size planning

Q&As about SMART



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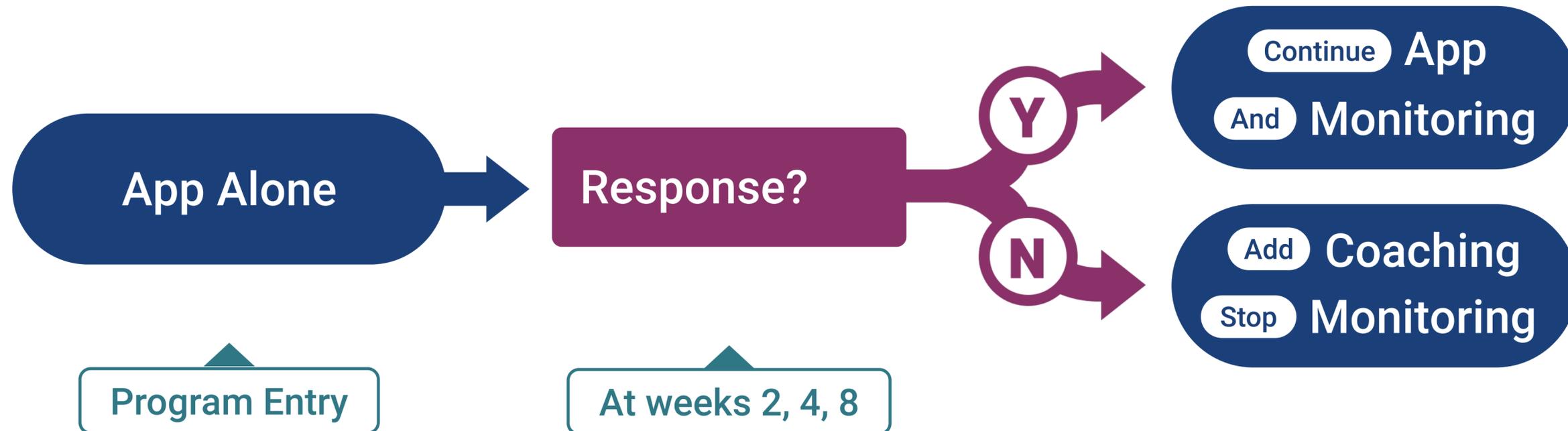
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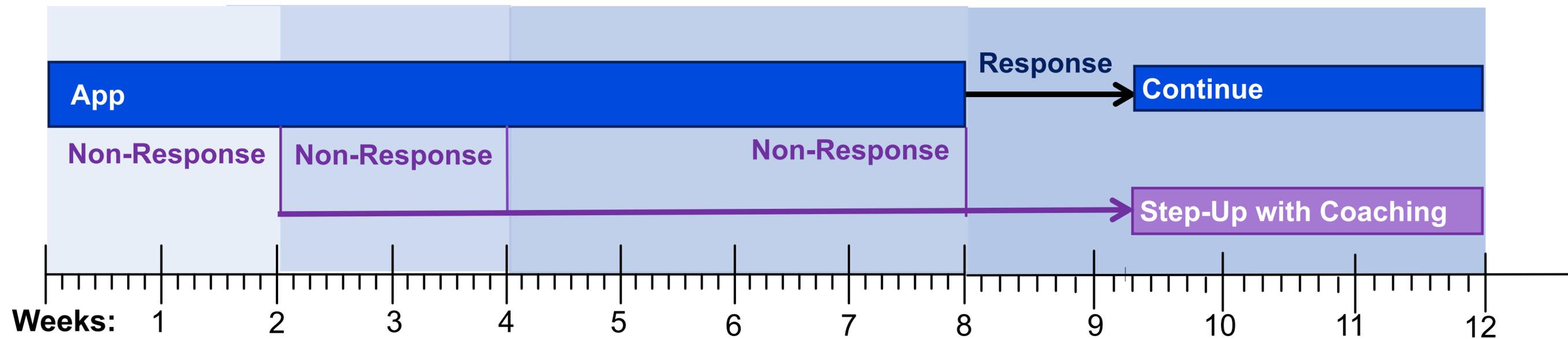
Q&As about SMART



Weight loss in overweight & obese adults

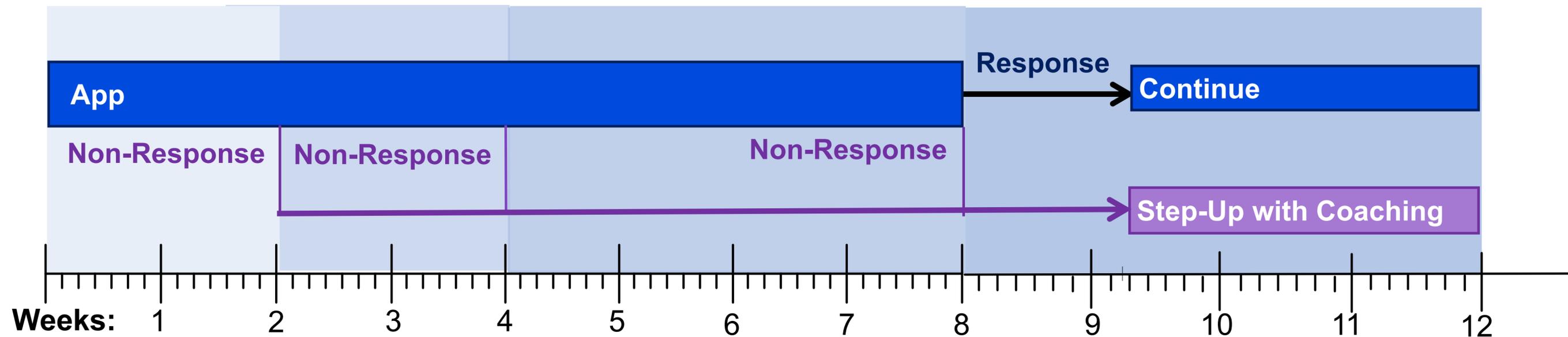


Weight loss in overweight & obese adults



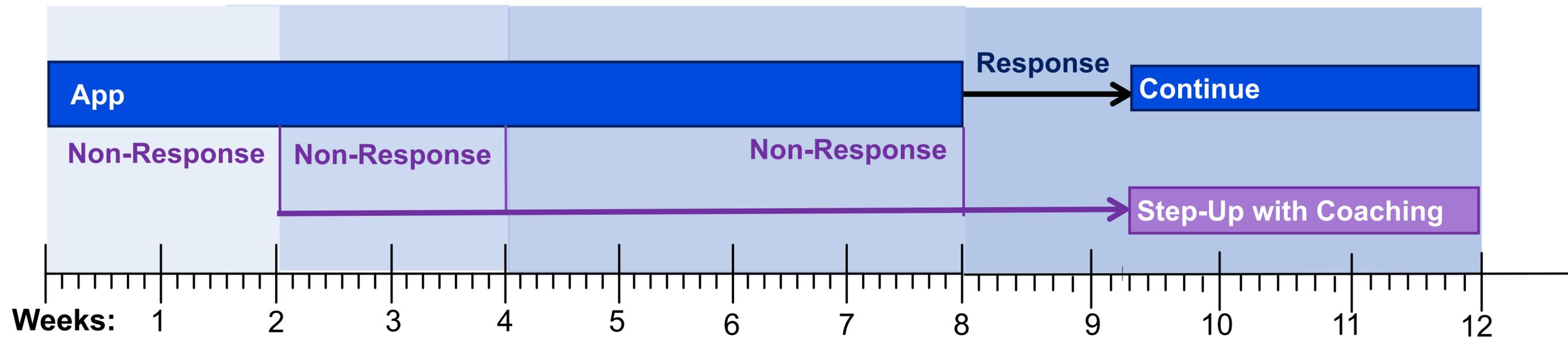
Weight loss in overweight & obese adults

Often, investigators don't have sufficient evidence or clinical expertise to guide how best to assemble the components of an adaptive intervention using existing intervention options



Weight loss in overweight & obese adults

Other times, investigators have questions about whether and how to include new intervention options in an adaptive intervention such as this.



Typical Optimization Questions

- What treatment should be offered initially?
- How long should we offer the first treatment?
- What tactic should we use for non-responders to the intervention?
- What tactic should we use for responders to the intervention?

Typical Optimization Questions (continued)

- How to re-engage participants who are non-adherent?
- What is the best way to define non-response?
- Is it more effective and cost-effective to use the more burdensome intervention first, and then step-down for individuals doing well? Or should we stick with a stepped-up intervention model?

In a grant proposal, these questions are expressed as primary or secondary aims!

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Example Adaptive Intervention

**Define Sequential Multiple Assignment
Randomized Trial (SMART)**

What do you need to know about SMART
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Q&As about SMART



Definition of a Sequential Assignment Randomized Trial (SMART)

- An experimental design, not an intervention design
- A type of multistage randomized trial
- Each stage corresponds to a scientific question or questions concerning the selection and adaptation of intervention options
- A randomization takes place at each decision point of scientific interest
- Some or all participants are randomized more than once

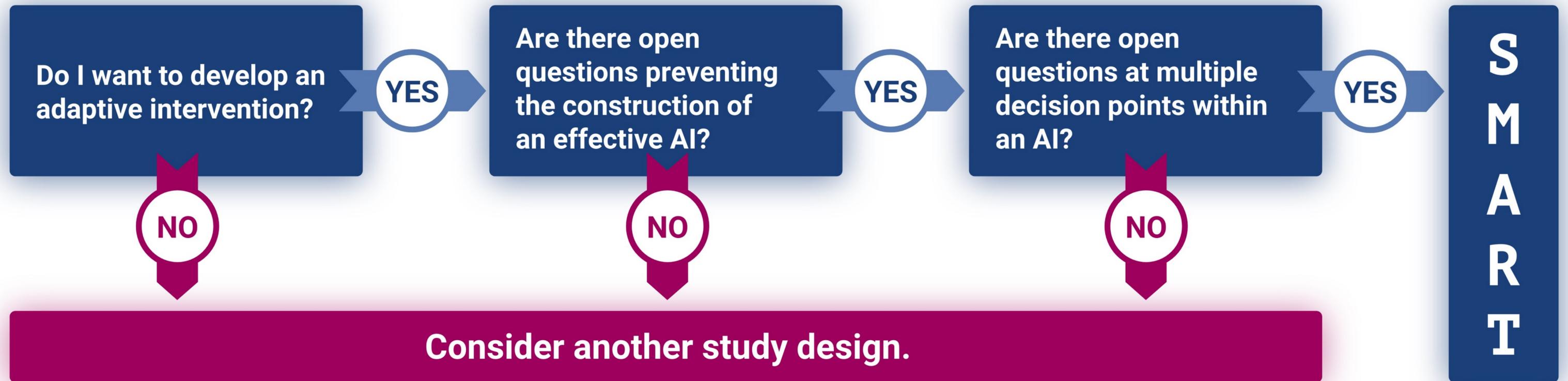
What is the Ultimate Goal of a SMART?

**To inform the construction
of a high-quality adaptive intervention.**

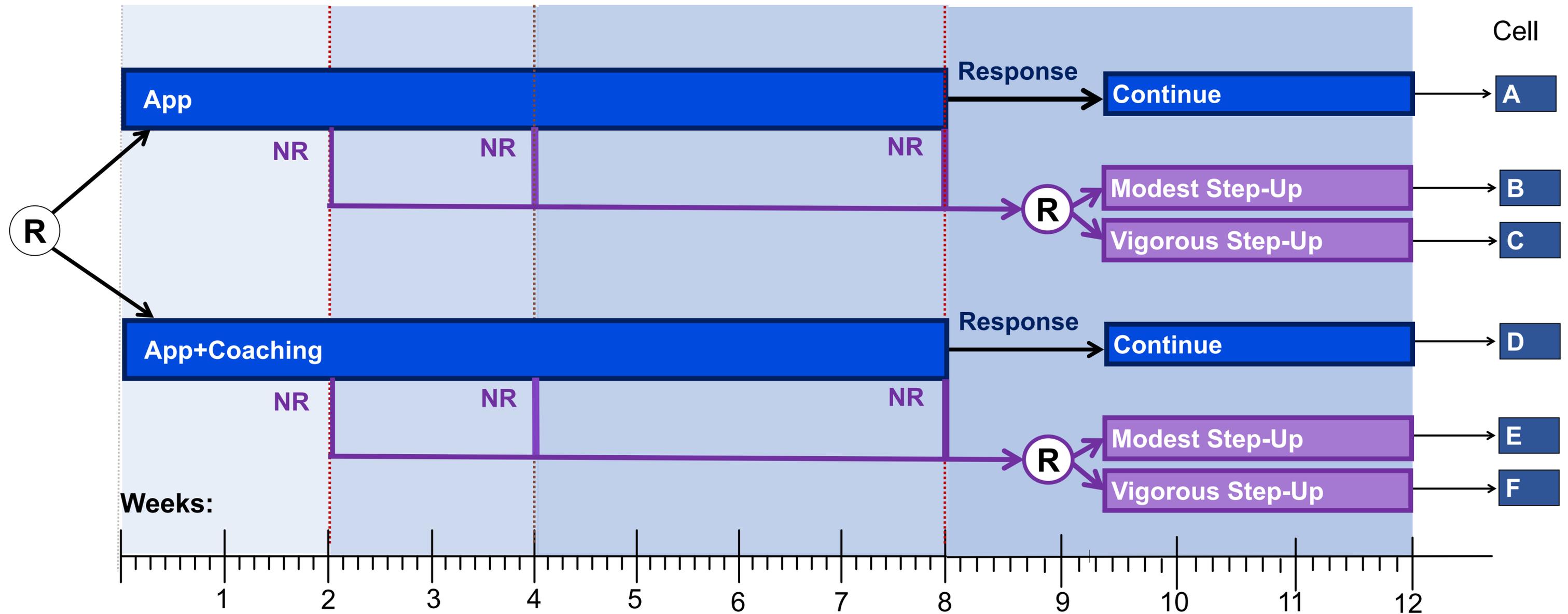
How does the SMART do this?

By answering a set of questions that will lead to an optimized adaptive intervention.

Not all research about adaptive interventions requires a SMART



Weight loss in overweight & obese adults



The 3 most common primary aims in a SMART:

Aim Type 1. Main effect of initial intervention options

Aim Type 2. Main effect of subsequent intervention options

Aim Type 3. Compare embedded adaptive interventions



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Aim Type 1. Main effect of initial intervention options

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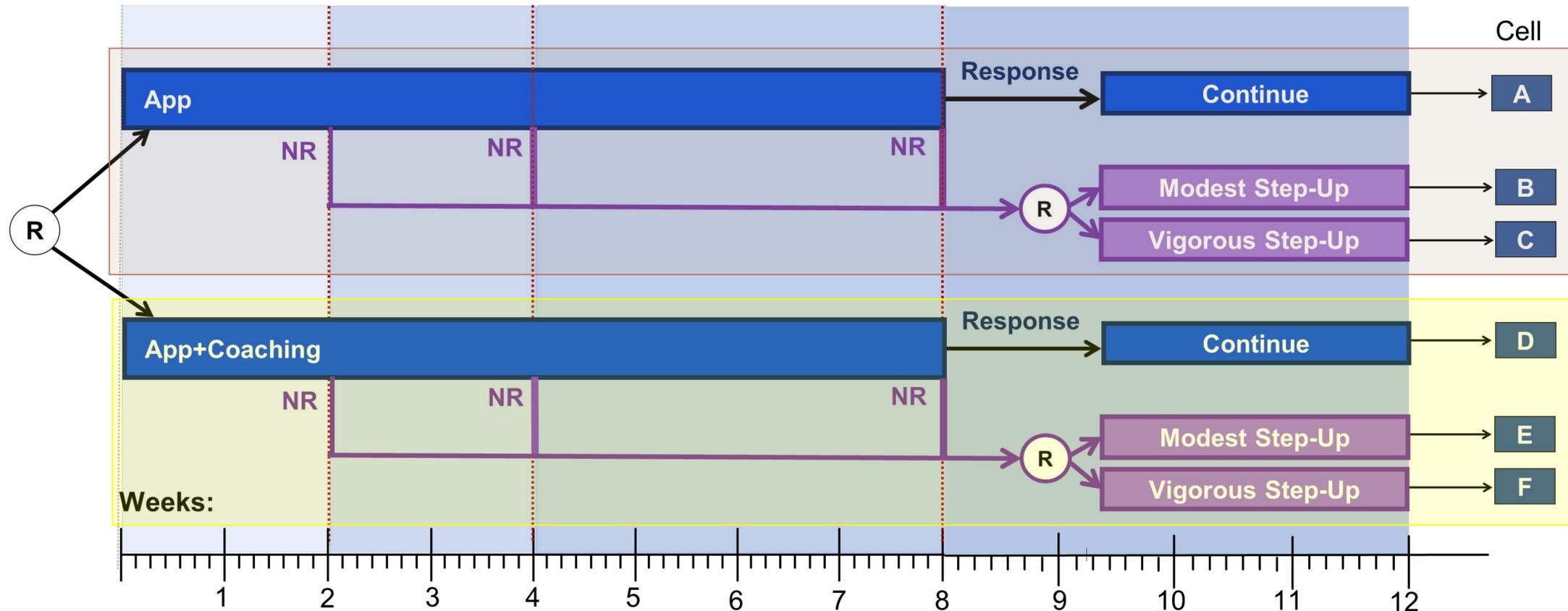
SMART Example

Weight Loss SMART

Aim Type 1: Main Effect of First-stage Intervention

What is the best initial intervention option in terms of weight loss at month 6:
App alone vs App + Coaching ?

Weight loss in overweight & obese adults



Primary Aim Hypothesis 1

Starting with App + Coaching will improve weight loss more than starting with App Alone

In this example, Aim Type 1 compares A+B+C vs D+E+F

The 3 most common primary aims in a SMART:

Aim Type 1. Main effect of initial intervention options

Aim Type 2. Main effect of subsequent intervention options

Aim Type 3. Compare embedded adaptive interventions



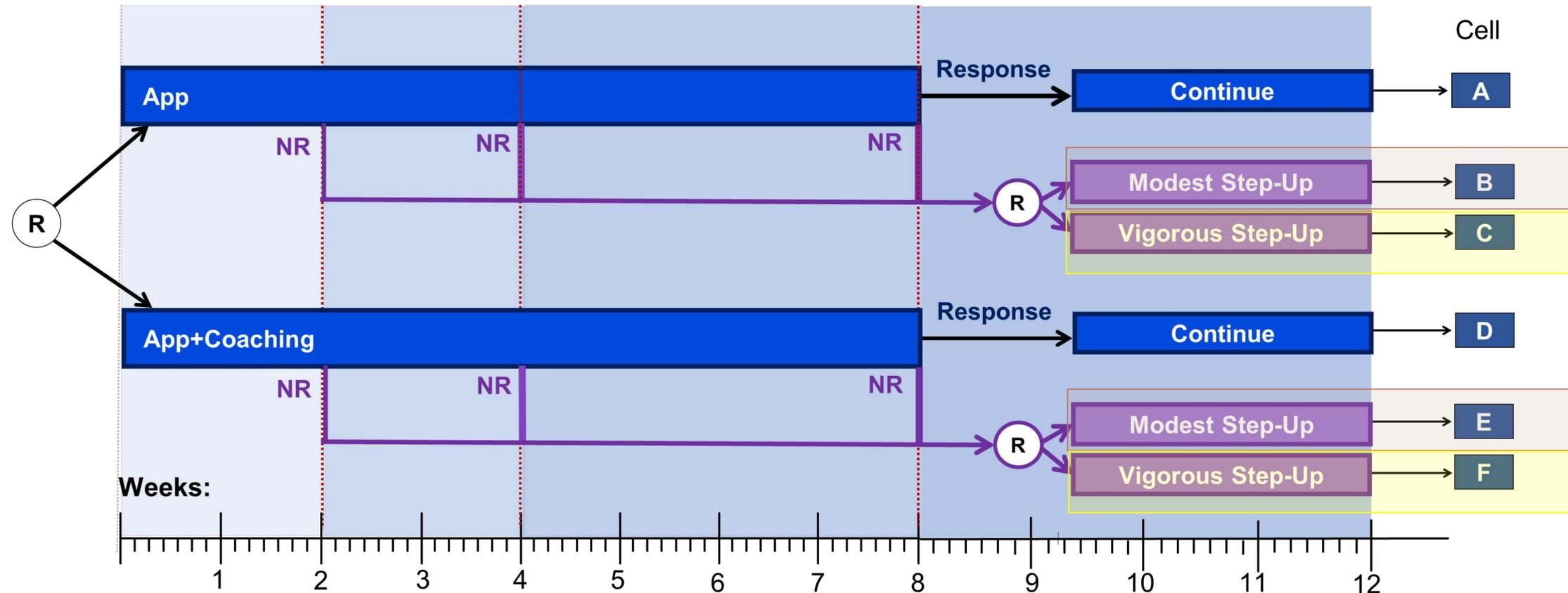
SMART Example

Weight Loss SMART

Aim Type 2: Main Effect of Second-stage Intervention

What is the best augmentation tactic for non-responders in terms of weight loss at month 6: Modest Step-Up vs Vigorous Step-Up?

Weight loss in overweight & obese adults



Primary Aim Hypothesis 2

Among non-responders, Vigorous Step-Up improves weight loss by month 6 more than Modest Step-Up.

In this example, Aim Type 2 compares B+E vs C+F

Note

As soon as you select a primary aim from among the 3 types, any one or more of the others can be secondary aims.

The 3 most common primary aims in a SMART:

Aim Type 1. Main effect of initial intervention options

Aim Type 2. Main effect of subsequent intervention options

Aim Type 3. Compare embedded adaptive interventions



SMART Example

Weight Loss SMART

Aim Type 3: Comparison of Adaptive Interventions

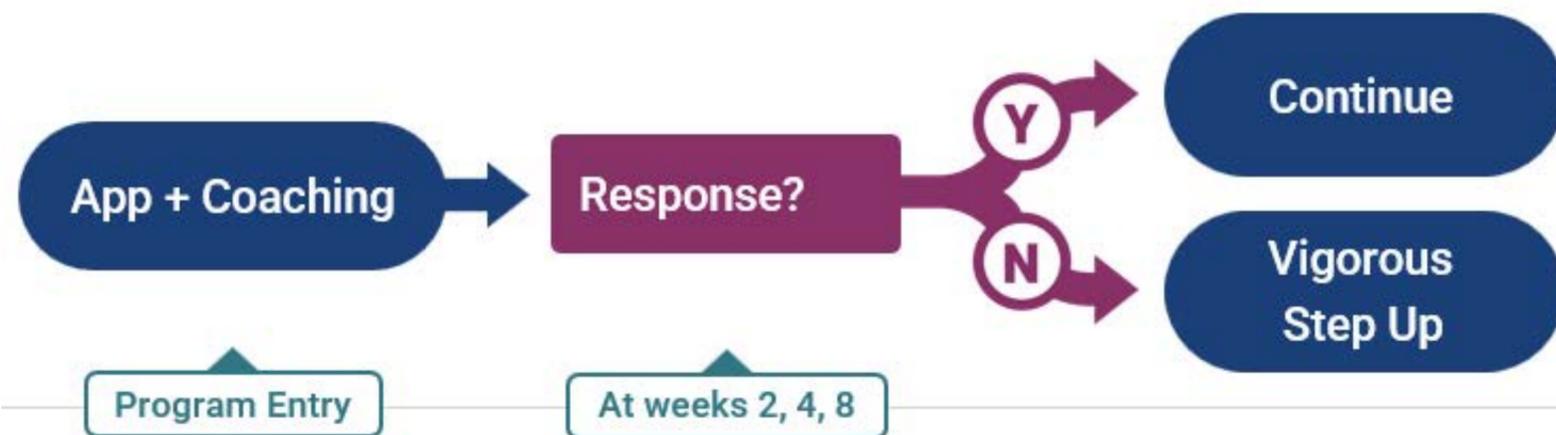
Is the adaptive intervention requiring the greatest resource investment better at improving weight loss by month 6 than the one requiring the least investment?

SMART Example

Weight Loss SMART

Aim Type 3: Comparison of Adaptive Interventions

Is the adaptive intervention requiring the greatest resource investment better at improving weight loss by month 6 than the one requiring the least investment?

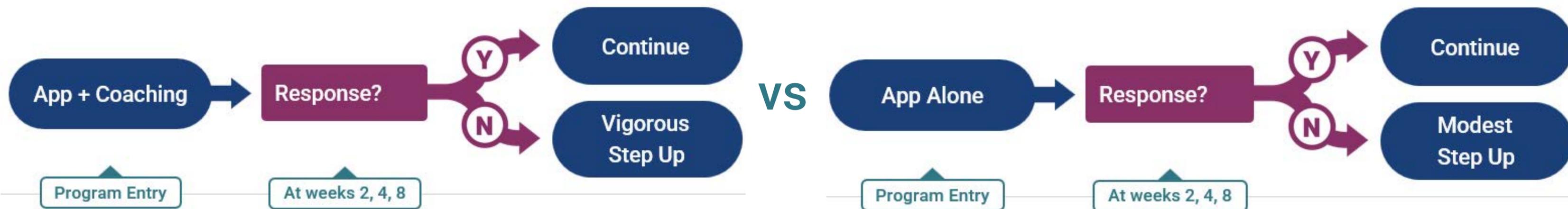


SMART Example

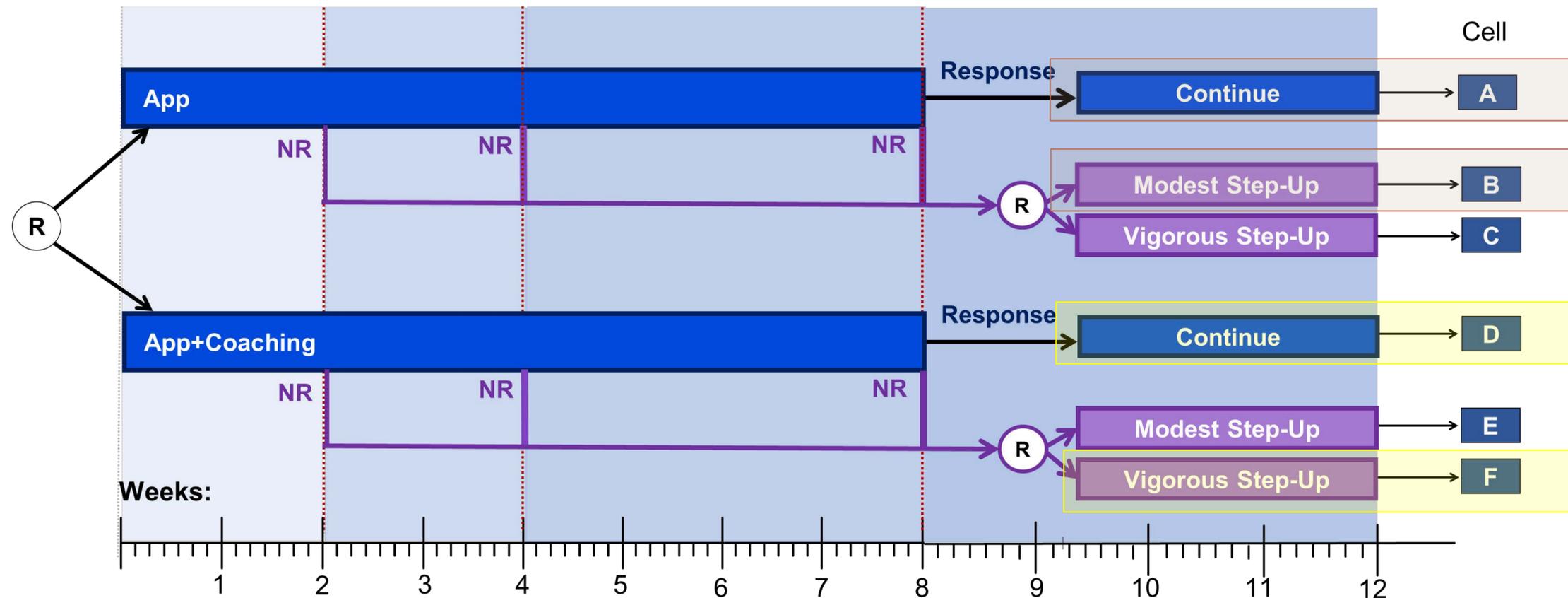
Weight Loss SMART

Aim Type 3: Comparison of Adaptive Interventions

Is the adaptive intervention requiring the greatest resource investment better at improving weight loss by month 6 than the one requiring the least investment?



Weight loss in overweight & obese adults



Primary Aim Hypothesis 3

The adaptive intervention that starts with App+Coaching and then steps up vigorously while containing for responders, improves weight loss more than the adaptive intervention that starts with App alone and then steps up modestly for non-responders while containing for responders

SMART Example

Weight Loss SMART

Aim Type 3: Comparison of Adaptive Interventions

	Stage 1	Tailoring Variable	Stage 2	Cell
1	App	Response Non-Response	Continue Modest Step-Up	A+B
2	App	Response Non-Response	Continue Vigorous Step-Up	A+C
3	App+C	Response Non-Response	Continue Modest Step-Up	D+E
4	App+C	Response Non-Response	Continue Vigorous Step-Up	D+F

The most common secondary aim in a SMART:

Aim Type 4. Construct a more deeply-tailored adaptive intervention

Additional Questions

Among non-responders, individuals who

- Gained weight will benefit more from Vigorous Step-Up
- Triggered a non-response early will benefit more from Modest Step-up

Why is this useful?

At each decision point

- Identify new candidate tailoring variables
- Identify new cut-points for decision rules



SMART Example

Weight Loss SMART

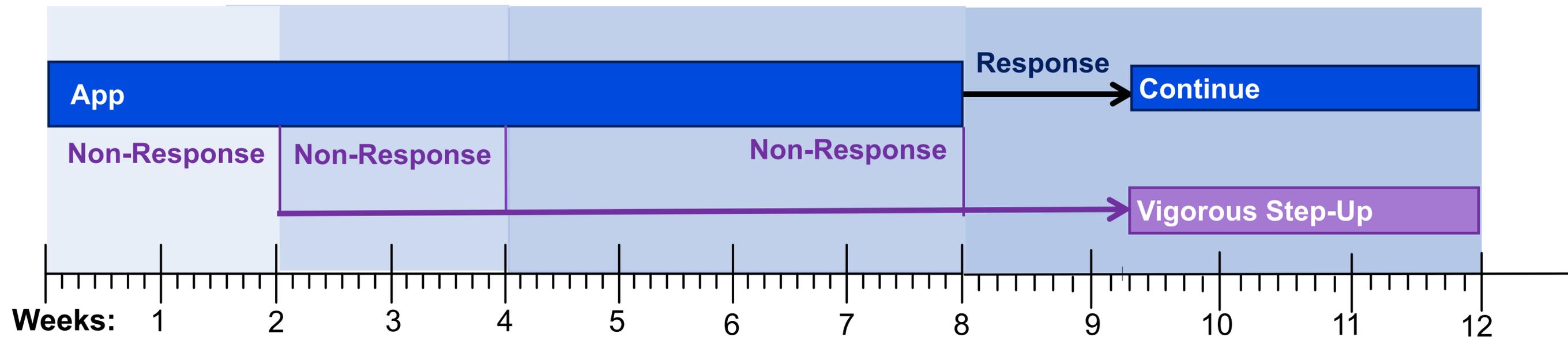
Aim Type 4

Secondary Aim 3. To construct a more richly individualized adaptive intervention by examining

- whether (a) baseline severity, or (b) baseline emotional eating; or (c) SES moderate the effect of initial App vs. App+Coaching; and
- whether, among non-responders, (d) magnitude of weight change; or (e) timing of transition to stage 2, moderate the effect of stepping-up Vigorously vs. Modestly.

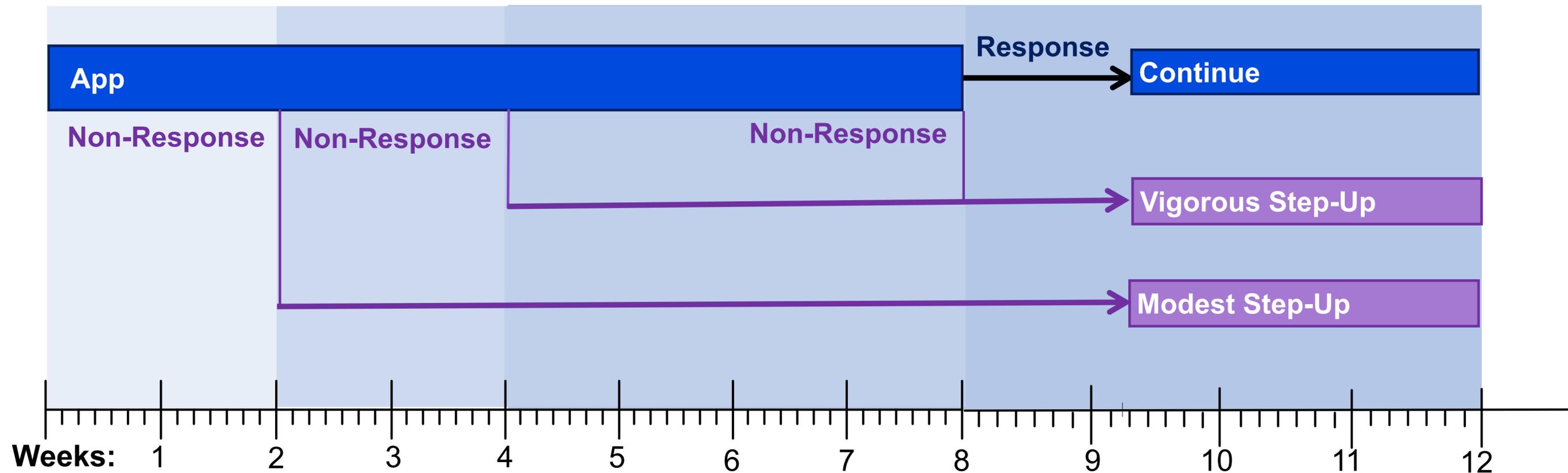
Example of a More Deeply Tailored AI

One tailoring variable: Response status



Example of a More Deeply Tailored AI

Two tailoring variables: Response status and timing of non-response



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What to know about SMART data analytic methods

Analytics for Aim Types 1 and 2

- You can use standard methods here, such as Linear Mixed Modeling
- Do not adjust for responder status when addressing Aim Type 1. This leads to causal collider bias.
- For the same reason, do not use standard methods to attempt answering Aim Types 1 and 2 simultaneously--that is, using a single analytic model.

What to know about SMART data analytic methods

Analytics for Aim Type 3

- Typical concerns include
 - Non-responders are under-represented in the sample mean
 - Responders contribute data to more than one embedded adaptive interventions,
- An accessible method to address these issues is called Weight and Replicate (W&R)
 - Weights correct for the under-representation of non-responders
 - Replication enables you to obtain all four sample means with one weighted analysis
 - This method also provides an estimate of the Between-stage Interaction Effect

Nahum-Shani, I. et al., (2012). Experimental design and primary data analysis methods for comparing adaptive interventions. *Psychological methods*, 17(4), 457.

What to know about SMART data analytic methods

Analytics for Aim Type 4

- Our website has code for a method known as Q-learning
 - Reinforcement learning method, borrowed from computer science
 - Intuitively: It is an extension of “moderated regression analysis” to data arising from a SMART that avoids the causal collider bias mentioned earlier
 - A key advantage is that it allows you to assess moderators of Stage 1 intervention, assuming that Stage 2 intervention has been set to optimal
 - A benefit of the approach linked on our website is that it produces appropriate Confidence Intervals

What to know about SMART data analytic methods

d3c code library: <https://d3c.isr.umich.edu/code-library/>

Code Library

Browse our library of open-source statistical software for the design, conduct, and analysis of intervention optimization trials.

Sequential, Multiple Assignment Randomized Trials [SMART]

➔ SMART Sample Size Calculation

➔ SMART Data Analysis

[Compare adaptive interventions in a SMART with a binary, longitudinal outcome \[Standard Least Squares Regression\]](#)

[Compare adaptive interventions in a SMART with a continuous, longitudinal outcome \[Standard Least Squares Regression\]](#)

[Compare adaptive interventions in a SMART with a continuous, longitudinal outcome \[Linear Mixed Modeling\]](#)

[Compare adaptive interventions in a SMART with a continuous end-of-study outcome \[Weighted & Replicated Least Squares Regression\]](#)

[Construct a more deeply-tailored adaptive intervention using data from a SMART \[Q-Learning Regression\]](#)

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SMART Sample Size Calculation

[Sample size for a SMART with a binary, longitudinal outcome](#)

[Sample size for a SMART with a continuous, longitudinal outcome](#)

[Sample size for a SMART with a binary or continuous end-of-study outcome](#)

[Sample size for a SMART with a longitudinal count outcome](#)

[Sample size for a clustered SMART with a continuous, end-of-study outcome](#)

SMART Data Analysis

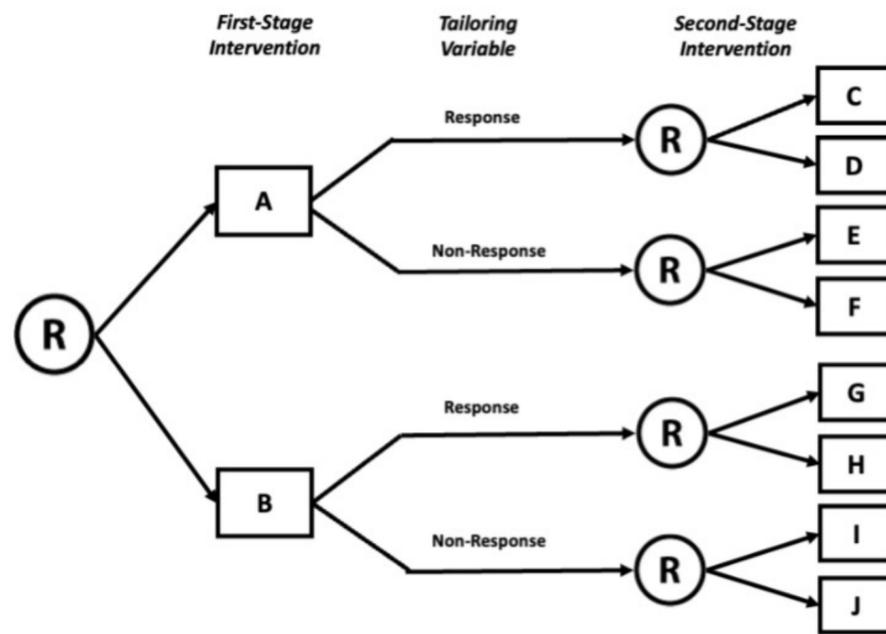
Clustered SMART Data Analysis

What to know about SMART sample size planning

Sample Size Calculator for SMARTs with Binary or Continuous Outcomes

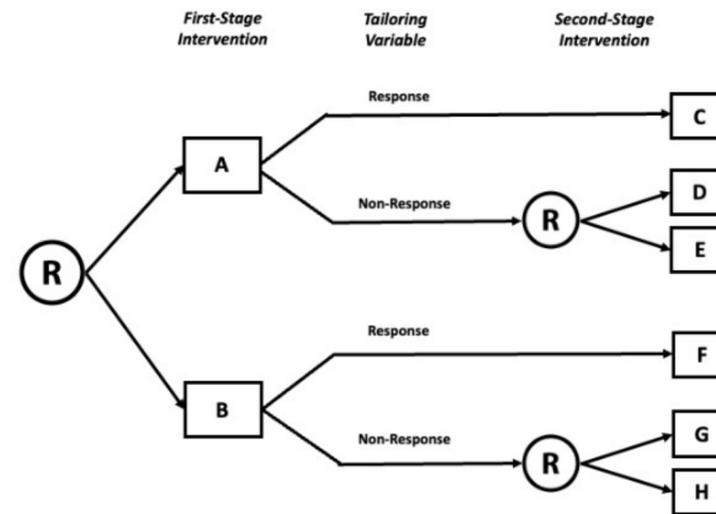
Get started by selecting one of three common designs.

The three designs below are commonly seen in the field. Click the button below it to get started.



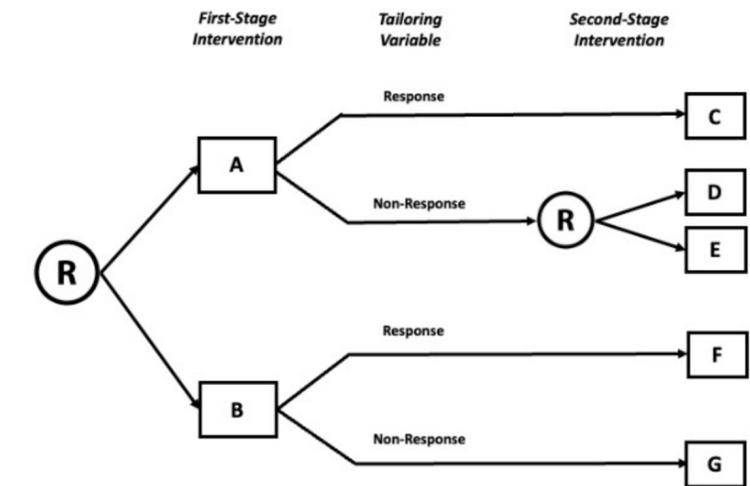
Use Design I

Both responders and non-responders to first-stage treatment are re-randomized. There are 8 embedded adaptive interventions: {A,C,E}, {A,C,F}, {A,D,E}, {A,D,F}, {B,G,I}, {B,G,J}, {B,H,I}, {B,H,J}. [Click here for an example from the field.](#)



Use Design II

Only non-responders to either first-stage treatment are re-randomized. There are 4 embedded adaptive interventions: {A,C,D}, {A,C,E}, {B,F,G}, {B,F,H}. [Click here for an example from the field.](#)



Use Design III

Only non-responders to a particular first-stage treatment are re-randomized. There are 3 embedded adaptive interventions: {A,C,D}, {A,C,E}, {B,F,G}. [Click here for an example from the field.](#)

What to know about SMART sample size planning

Is the **outcome** of interest binary or continuous?

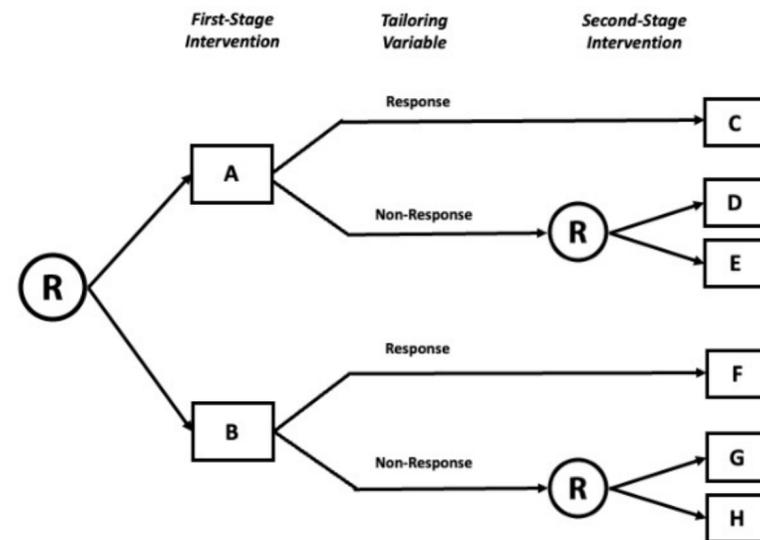
- Binary
- Continuous

What is your primary aim?

- Compare first-stage treatments as initial treatments in an adaptive intervention.
- Compare second-stage treatments among non-responders as secondary treatments in an adaptive intervention.
- Compare two embedded adaptive interventions with different first-stage treatments.

Which two **adaptive interventions** would you like to compare? Choose two from the menus below. The image below will change to highlight the AIs you select.

Reference Adaptive Intervention



Are you interested in finding sample size or power?

- Sample Size
- Power

Do you want to perform a one- or two-sided test?

- One-Sided
- Two-Sided

Comparison Adaptive Intervention

Please provide the **probability of response** to the first-stage intervention.

Concerning the primary outcome, please provide the **probability of success** for each of the AIs of interest.

Please select a Reference AI.

Please select a Comparison AI.

Type I Error (α):

Power of Trial ($1-\beta$):

Results

Please fill in the inputs required to receive an estimated sample size. The probability should be greater than 0.

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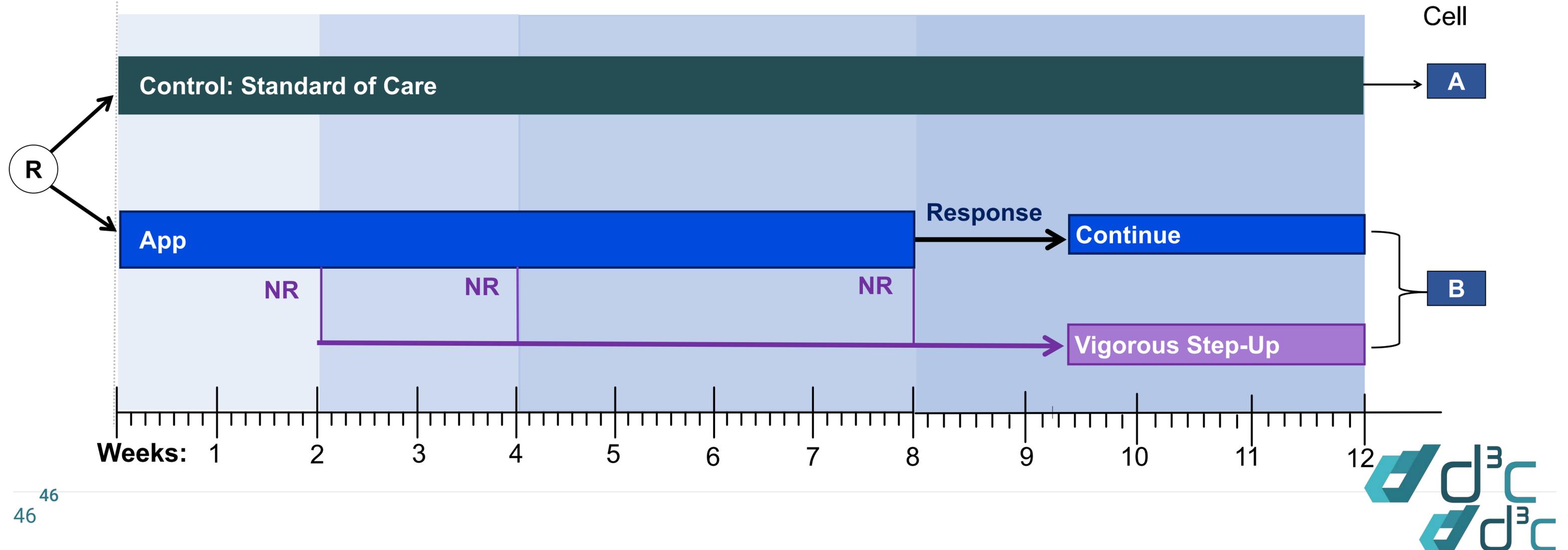
Frequently Asked Questions & Answers

The goal: engage you and help you generate additional questions

1. Go to Kahoot.it (we recommend using your phone)
2. Type in pin #
3. Select a nickname (not your real name)
4. Let's play

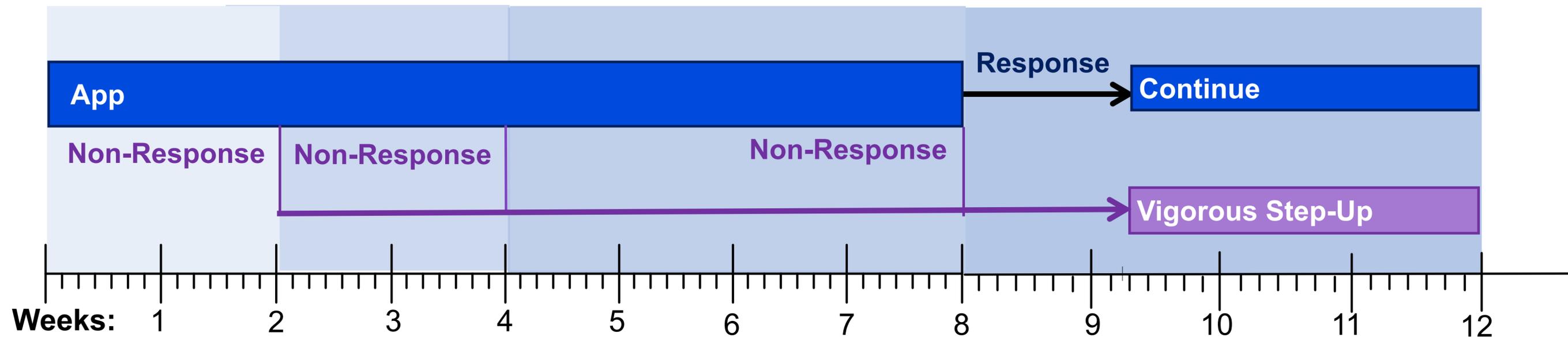
Q1: Does all research on adaptive interventions requires a SMART?

A1: No. The choice of randomized trial design depends on the scientific question. For example, if you are ready to evaluate an adaptive intervention (that you believe has been optimized), then you can use a standard two-arm randomized clinical trial.



Q2: The tailoring variable(s) embedded in a SMART does not have to be a research assessment.

A2: TRUE. In fact, in most cases, the embedded tailoring variable in a SMART should not be a research assessment. Recall that tailoring variables represent one of the components of an adaptive intervention. Yet, many research assessments are too burdensome to be used in actual practice settings.



Q3: Which of these two is the higher quality SMART design?

A3: SMART #2 is preferred. Recall that a tailoring variable is component of the adaptive intervention. Thus, we may want to avoid using research staff to collect tailoring variables because doing so can make it difficult to generalize the results of the SMART to actual practice settings.

SMART Design Consideration	SMART No. 1	Smart No. 2
Embedded tailoring variable is collected by:	Research Staff	Clinical Staff (e.g., nurses) Providing Intervention
Research assessments are collected by:	Research Staff	Research Staff

Q4: Which of these two is the higher quality SMART design?

A4: SMART #2 is preferred for those of us that are effectiveness scientists. The protocol used in SMART #1 can make it difficult to generalize the results of the SMART to actual practice settings.

Note that this study design principal is not specific to SMART designs. This is an important design principal in all effectiveness randomized trials.

SMART No. 1	A single retention and engagement protocol, with high quality incentives, is used to prevent study drop-out and to prevent treatment drop-out.
SMART No. 2	Two separate retention and engagement protocols are used as part of the SMART. The study retention protocol is deployed by research staff and the intervention retention protocol is deployed by clinical staff

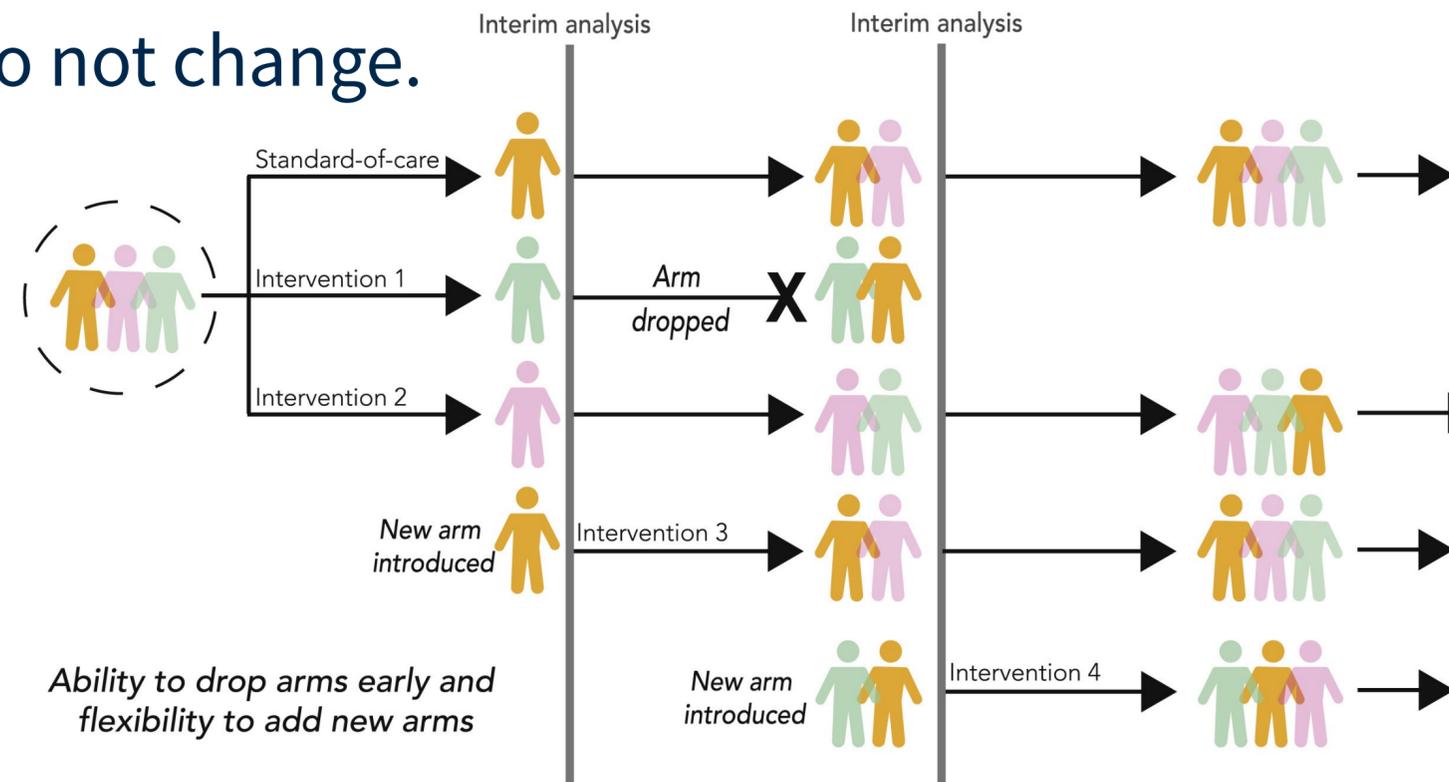
Q5: The SMART is an Adaptive Trial Design

A5: No. Adaptive Trial Design: A clinical trial design that allows adaptations or modifications to aspects of the trial while the study is still ongoing e.g., 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

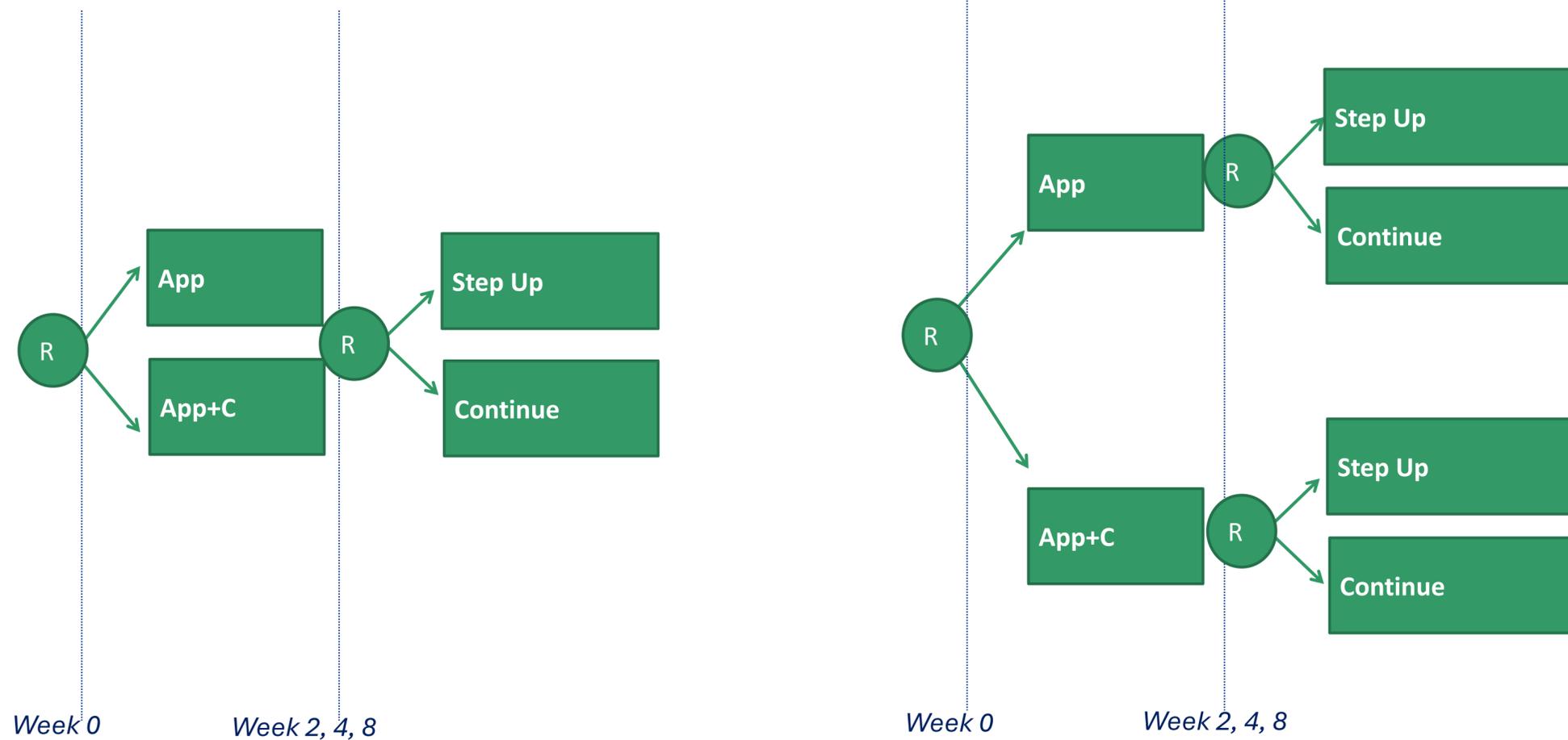
Design parameters are set a priori and do not change.

But the two concepts can be combined
(Cheung et al., 2015; Lee et al., 2015)



Q6: Is this a SMART?

A6: Yes. All participants are randomized more than once. This is a SMART although there is no embedded tailoring variable (e.g., response status).



Q&A

**Extra Slides
Beyond Here**

