An Introduction to Adaptive Interventions and Sequential Multiple Assignment Randomized Trials

SOCIETY OF BEHAVIORAL MEDICINE ANNUAL MEETING 2022

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BALTIMORE, MD

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Introductions

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Agenda

Introduction (10 minutes)

- Course outline
- Goals for the course

Adaptive Interventions (40 minutes)

Questions and Discussion (10 minutes)

Sequential, Multiple-Assignment Randomized Trials (40 minutes)

Questions and Discussion (10 minutes)

Future Directions (10 minutes)

Learning Objectives

Learning Objective 1:

Learn about the key elements of adaptive interventions, situations when adaptive interventions are useful, and design considerations for adaptive interventions.

Learning Objective 2:

Learn about sequential multiple assignment randomized trials (SMARTs) and how they can be used to inform the development of high-quality adaptive interventions.

Agenda

Introduction (10 minutes)

Adaptive Interventions (40 minutes)

- What are adaptive interventions?
- Why use adaptive interventions?
- What are some design considerations for adaptive interventions?

Questions and Discussion (10 minutes)

Sequential, Multiple-Assignment Randomized Trials (40 minutes)

Questions and Discussion (10 minutes)

Future Directions (10 minutes)

What is an adaptive intervention?

An **adaptive intervention** (AI) is

- an *intervention* design that
- adapts the type, timing, intensity, or dose of treatment over time
- according to an individual's specific and changing needs

In practice, an adaptive intervention is a **sequence of decision rules** that can be used to guide how treatment can be adapted and readapted to an individual.

This sounds a lot like clinical practice!

Many other names: adaptive treatment strategy, individualized treatment rule, dynamic treatment regime(n), treatment algorithm, individualized intervention, …

An adaptive intervention is an *intervention design*, ***NOT*** an experimental design.

5 components of an adaptive intervention

Adaptive interventions consist of

1. Decision points
2. Tailoring variable(s)
3. Intervention options
4. Decision rule(s)
5. Proximal and distal outcomes

Example: Weight loss program for individuals with serious mental illness

Individuals with serious mental illness have a 2-3 times-higher mortality rate than the general population.

- Cardiovascular disease is the primary cause of death.

ACHIEVE is a lifestyle intervention delivered in psychiatric rehabilitation outpatient programs which consists of *group weight-management sessions*, *individual weight-management sessions*, and *group exercise sessions.*

- Shown in a clinical trial to significantly reduce weight over 18 months

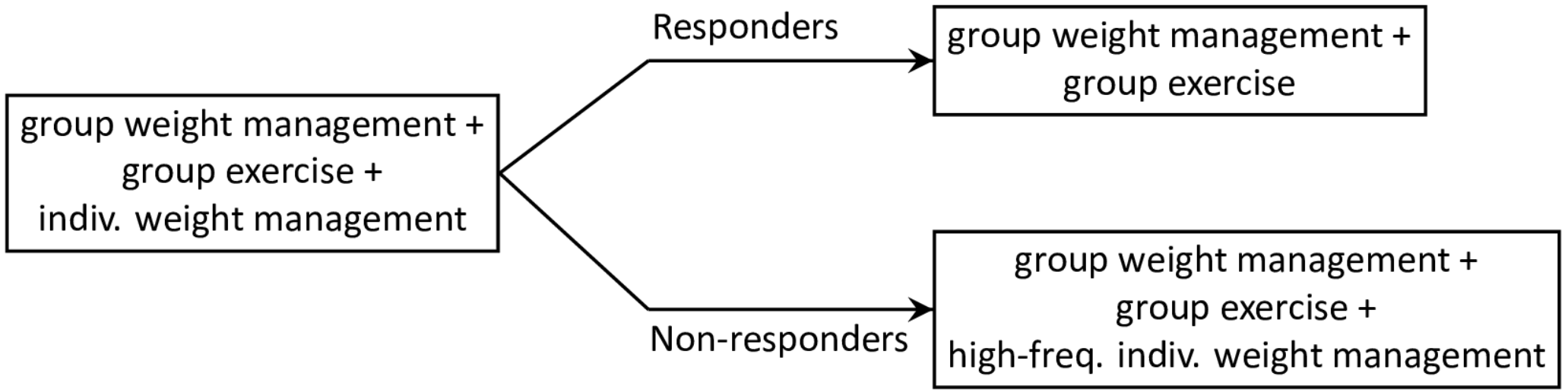
After 18 months, investigators observed meaningful heterogeneity in weight loss:

- 36.1% of participants did not lose any weight relative to baseline
- 18.5% of participants lost more than 10% of their baseline weight

Daumit, Gail L., et al. 2013. "A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness." *New England Journal of Medicine* 368 (17): 1594–1602. https://doi.org/10.1056/NEJMoa1214530.

Because of the heterogeneity in 18-month weight loss, we might consider an **adaptive** version of this **intervention** to address individuals' specific and changing needs.

Hypothetical example adaptive intervention: Weight loss program for individuals with serious mental illness



An individual is a *responder* if they have lost 5+ pounds in the first 6 months, and a *non-responder* otherwise.

Hypothetical example adaptive intervention: Weight loss program for individuals with serious mental illness

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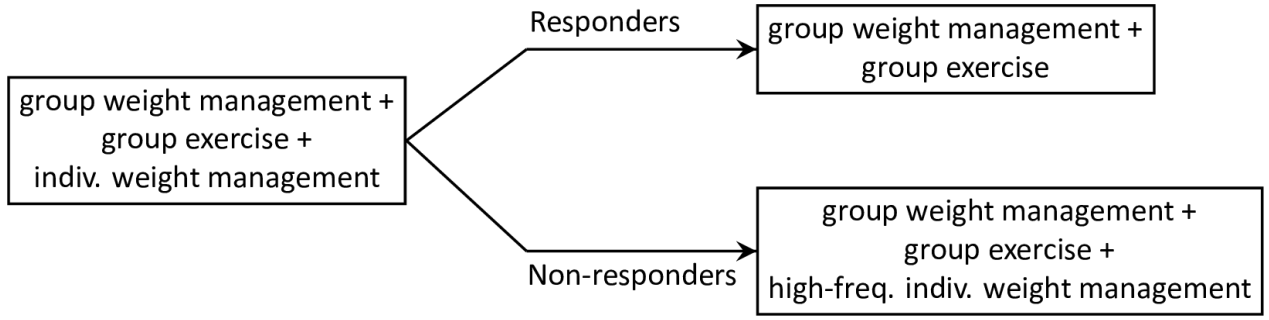
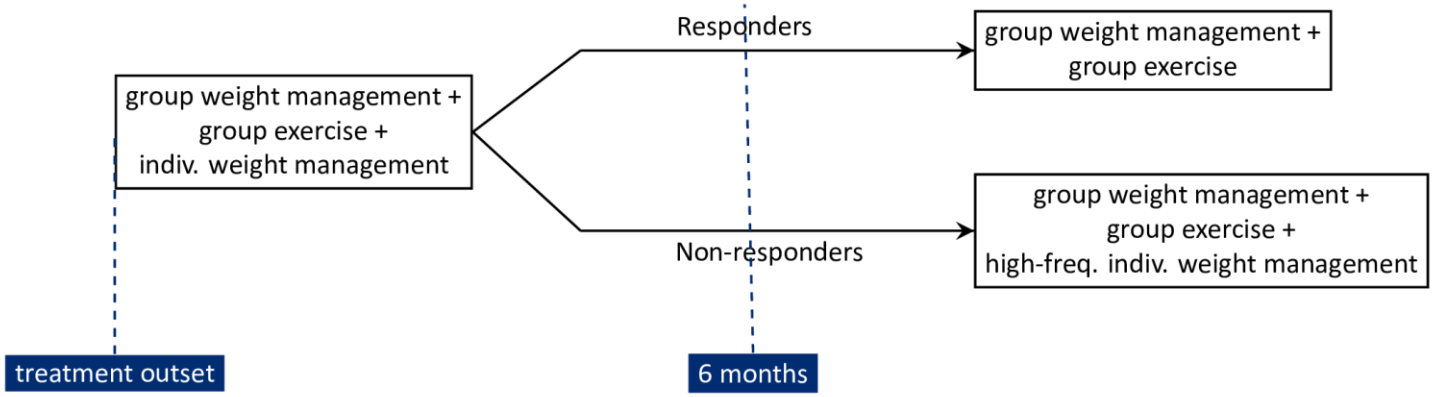


Hypothetical example adaptive intervention: **Decision Points**

A **decision point** is a time at which the intervention might be adapted to the individual.

Decision Point 1: Treatment outset – we decide how to initiate treatment

Decision Point 2: Month 6 – we decide how to modify treatment



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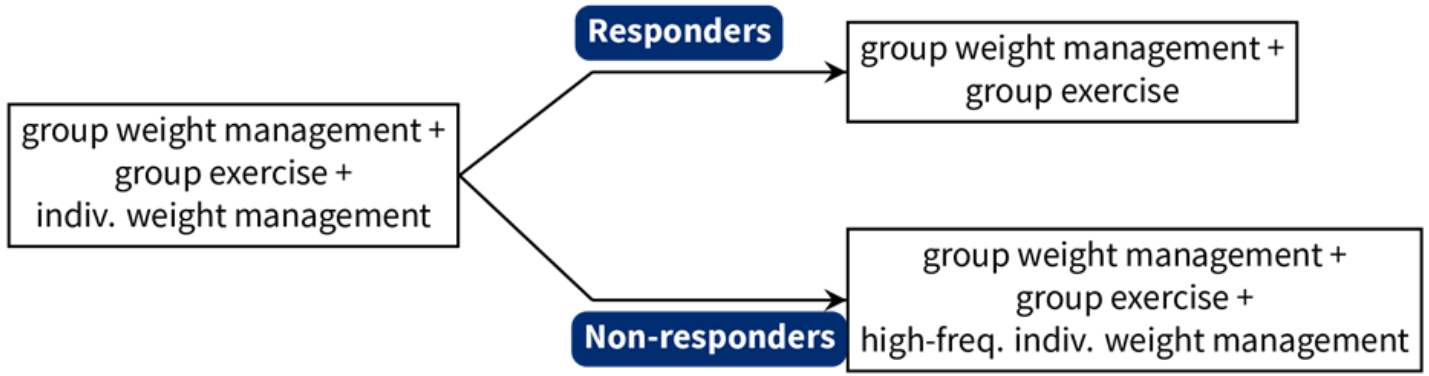
Hypothetical example adaptive intervention: **Tailoring Variable**

A **tailoring variable** is used to individualize treatment at each decision point.

- "Static": age, baseline risk, etc.
- "Dynamic": adherence to treatment, disease severity, etc.

The adaptive intervention recommends an intervention option for each level of the tailoring variable.



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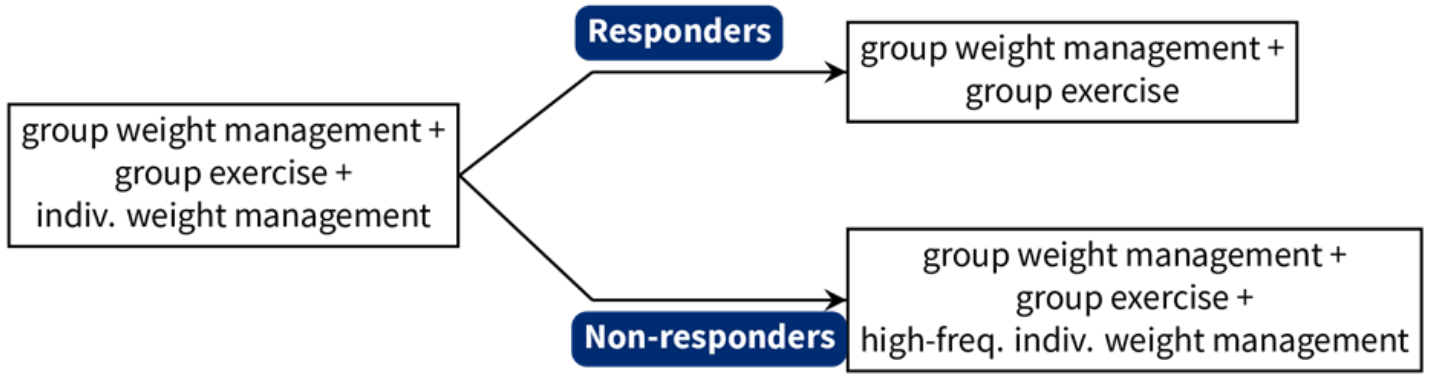
Hypothetical example adaptive intervention: **Tailoring Variable**

Here, the tailoring variable is **the amount of weight loss after 6 months on the intervention.**

≥ 5 lbs lost → responder

< 5 lbs lost → non-responder



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Some notes on tailoring variables

Tailoring variables should be *pre-specified* and *well-defined*.

Tailoring variables are **part of the intervention**!

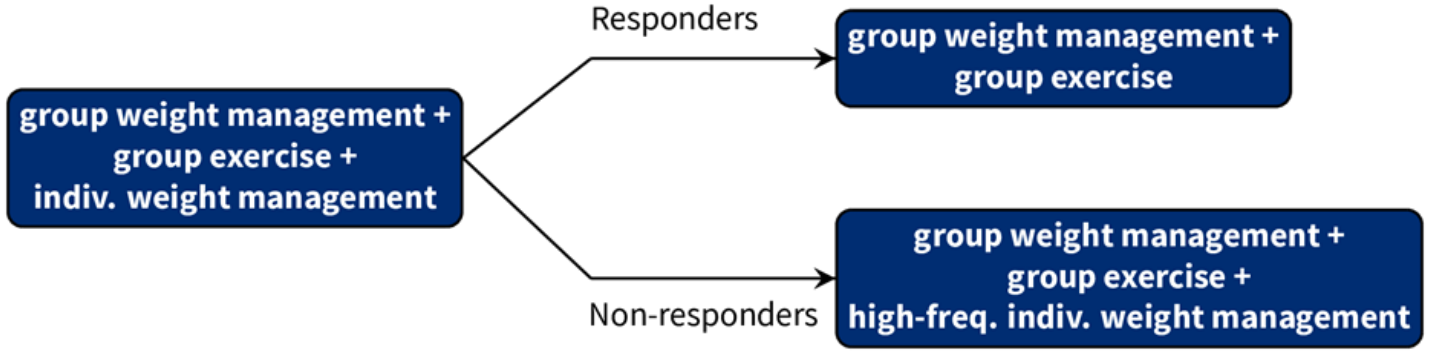
Should be based on *practical*, *ethical*, or *scientific* considerations.

- **Practical**: You might save more intense or costly intervention options for those who need it most (i.e., "non-responders").
- **Ethical**: You might have an ethical obligation to modify treatment for a particular subset of individuals
- **Scientific**: You might have empirical evidence suggesting that "responders" need a different type of intervention than do "non-responders"

Hypothetical example adaptive intervention: **Intervention Options**

Intervention options at each decision point might be aspects of treatment: type, intensity, dose, delivery method, timing, etc.

Here, intervention options are different combinations or frequencies of *individual weight management*, *group weight management*, and *group exercise*



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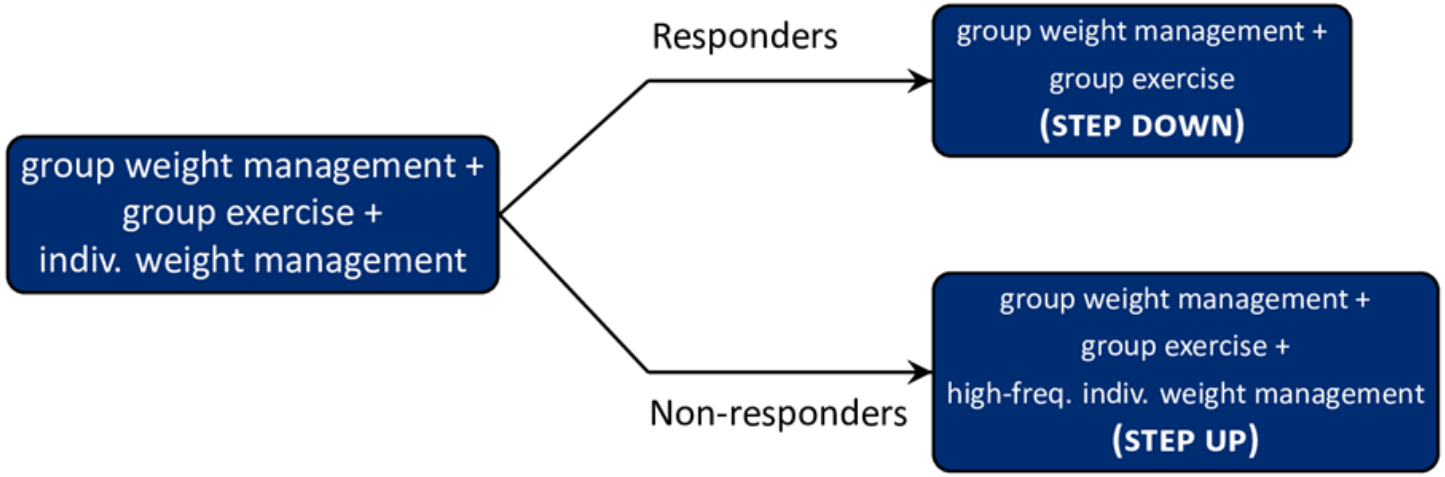
Hypothetical example adaptive intervention: **Intervention Options**

In later stages of the adaptive intervention, these might be *adaptation strategies*

e.g., “augment”, “intensify”, “stay the course”



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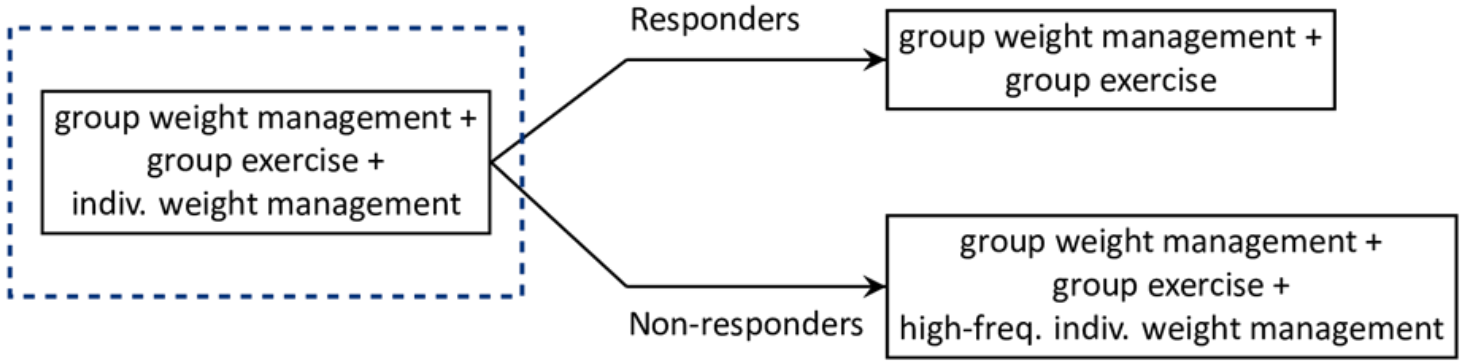
Hypothetical example adaptive intervention: **Decision Rules**

A **decision rule** recommends an *intervention option* for individuals at each decision point, possibly based on prior information (i.e., a tailoring variable)



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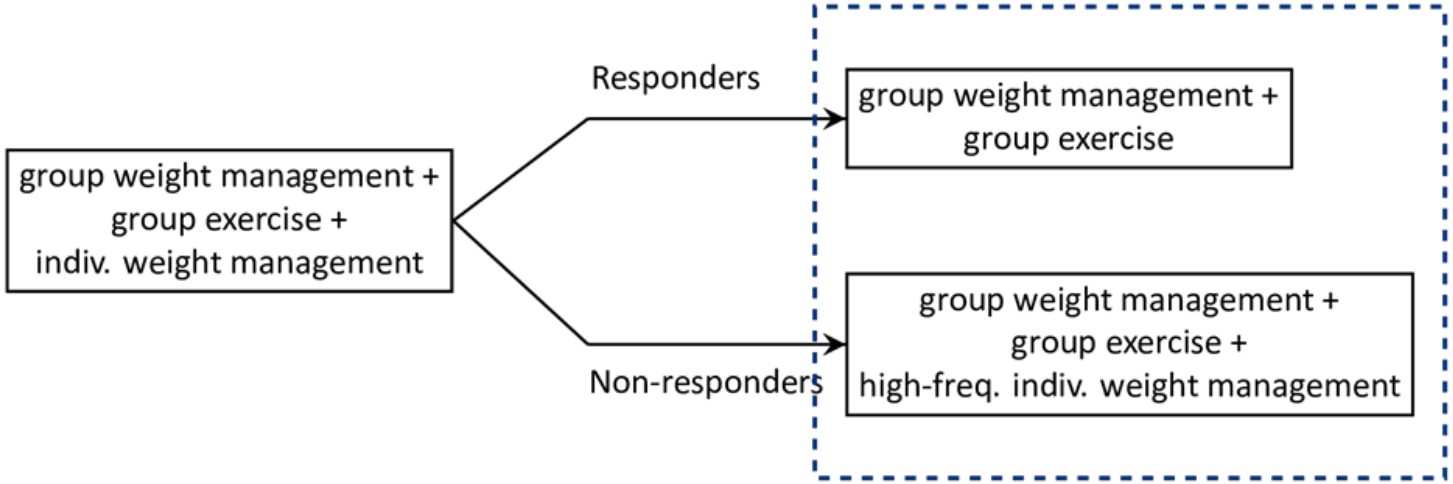

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Hypothetical example adaptive intervention: **Proximal and Distal Outcomes**

An adaptive intervention's design should be guided by both short-term (**proximal**) and long-term (**distal**) outcomes

Distal outcomes are the long-term goals of the adaptive intervention

- Long-term, example adaptive intervention should *reduce risk of cardiovascular disease*

Proximal outcomes are the near-term goals of the adaptive intervention; perhaps a mechanism by which we can achieve the distal outcome.

- Short-term, we want to lower risk of cardiovascular disease by helping participants *lose weight over 18 months*

Why use adaptive interventions?

HIGH **HETEROGENEITY** IN NEED FOR, OR RESPONSE TO, A PARTICULAR INTERVENTION

What works for one person may not work for another.

Need to:

- Detect early signs of intervention failure,
- Modify the intervention, and
- Work to prevent ultimate intervention failure.

Why use adaptive interventions?

INTERVENTION IS **BURDENSOME**

Interventions can be burdensome when participant required to invest significant time or effort.

Burden leads to non-adherence, reducing the likelihood of a positive intervention effect

Need to identify:

- Signs of burden
- How to modify intervention intensity based on signs of burden

Why use adaptive interventions?

INTERVENTION IS **COSTLY**

Certain treatments can be very expensive

Resources are often limited

Expensive interventions can be difficult to scale

May need to:

- Try less expensive intervention first, saving more costly intervention for those who need it
- Try most costly intervention up front and reduce intervention over time

Scientific questions about adaptive interventions

There are often unanswered questions about how to sequence and adapt interventions! These are typically related to

- relative effectiveness of different intervention options
- how intervention options work with/against each other
- relative effectiveness of different adaptive interventions

For example:

- Which treatment option should the adaptive intervention begin with?
- How should we modify treatment for initial non-responders?
- How should we modify treatment for initial responders?
- How do we define response/non-response?
- How should we time decision points?

Hypothetical scientific questions in the weight loss example

Should we start everyone on all three intervention components, or can we start with just the group components?

- Individual sessions require more resources of a facility

Which intervention components should be offered following the initial version of the intervention

- Can I step down the intensity of the intervention for six-month responders?
- Should I step up the intensity of the intervention for six-month non-responders?

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Sequential, Multiple-Assignment Randomized Trials (40 minutes)

- What are SMARTs and why are they useful?
- When should we consider a SMART?
- What are some principles for design and analysis of SMARTs?

Questions and Discussion (10 minutes)

Future Directions (10 minutes)

Recap: Adaptive Interventions

An **adaptive intervention** is a sequence of decision rules which make recommendations for treatment based on an individual's changing needs.

- Recommendations can be related to treatment type, timing, dose, etc.
- Adaptation is made according to a *tailoring variable* which captures ongoing information about the individual.

Scientific questions about adaptive interventions

Which treatment option should the adaptive intervention begin with?

How should we modify treatment for initial non-responders?

How should we modify treatment for initial responders?

How do we define response/non-response?

How should we time decision points?

An adaptive intervention is an *intervention design*, ***NOT*** an experimental design.

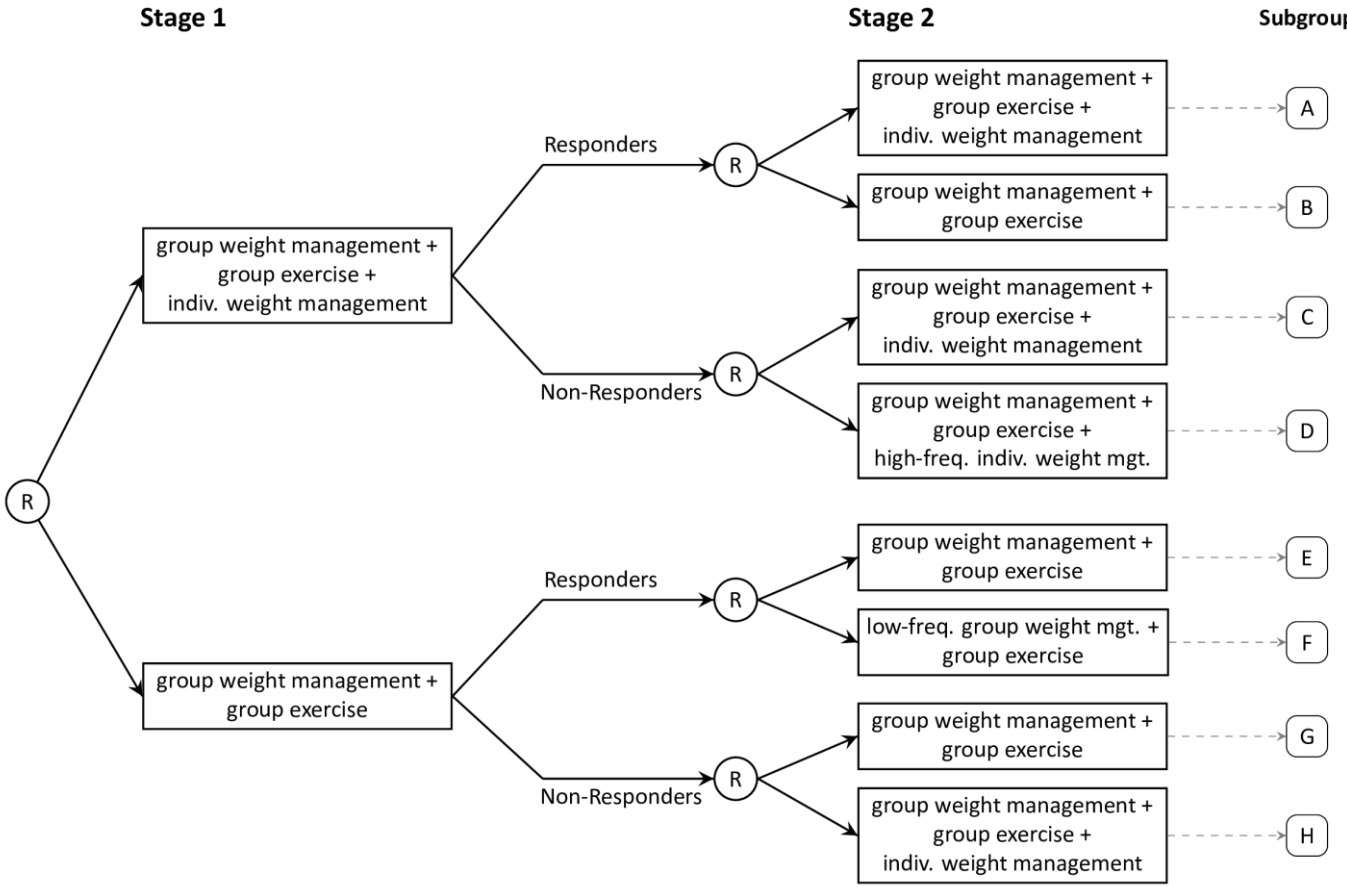
Sequential, **M**ultiple-**A**ssignment **R**andomized **T**rials (SMARTs)

A **sequential, multiple-assignment randomized trial (SMART)** is *one* type of randomized trial design that can be used to answer questions about multiple stages of an adaptive intervention.

The key feature of a SMART is that some (or all) participants are randomized more than once.

SMARTs are typically designed to construct effective adaptive interventions.

Hypothetical example: weight loss program for individuals with serious mental illness



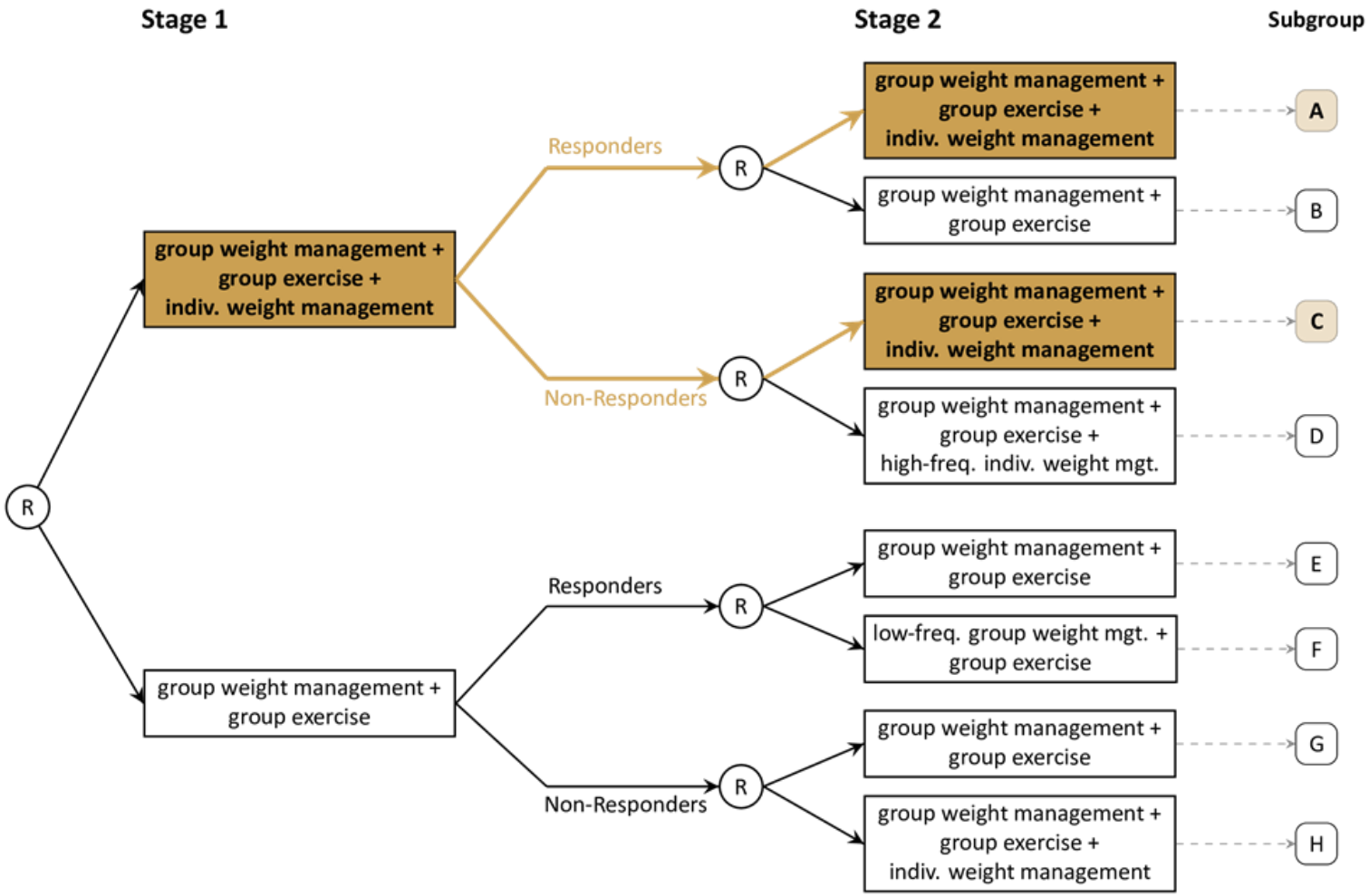
How does this SMART inform the development of an adaptive intervention?

Randomizations in a SMART correspond to open scientific questions related to the construction of an adaptive intervention.

In the previous example:

- First-stage randomization asks whether individual weight management is needed up-front
- Second randomization in responders asks whether first-stage treatment should be continued or stepped down
- Second randomization in non-responders asks whether first-stage treatment should be continued or stepped up

8 “embedded” adaptive interventions



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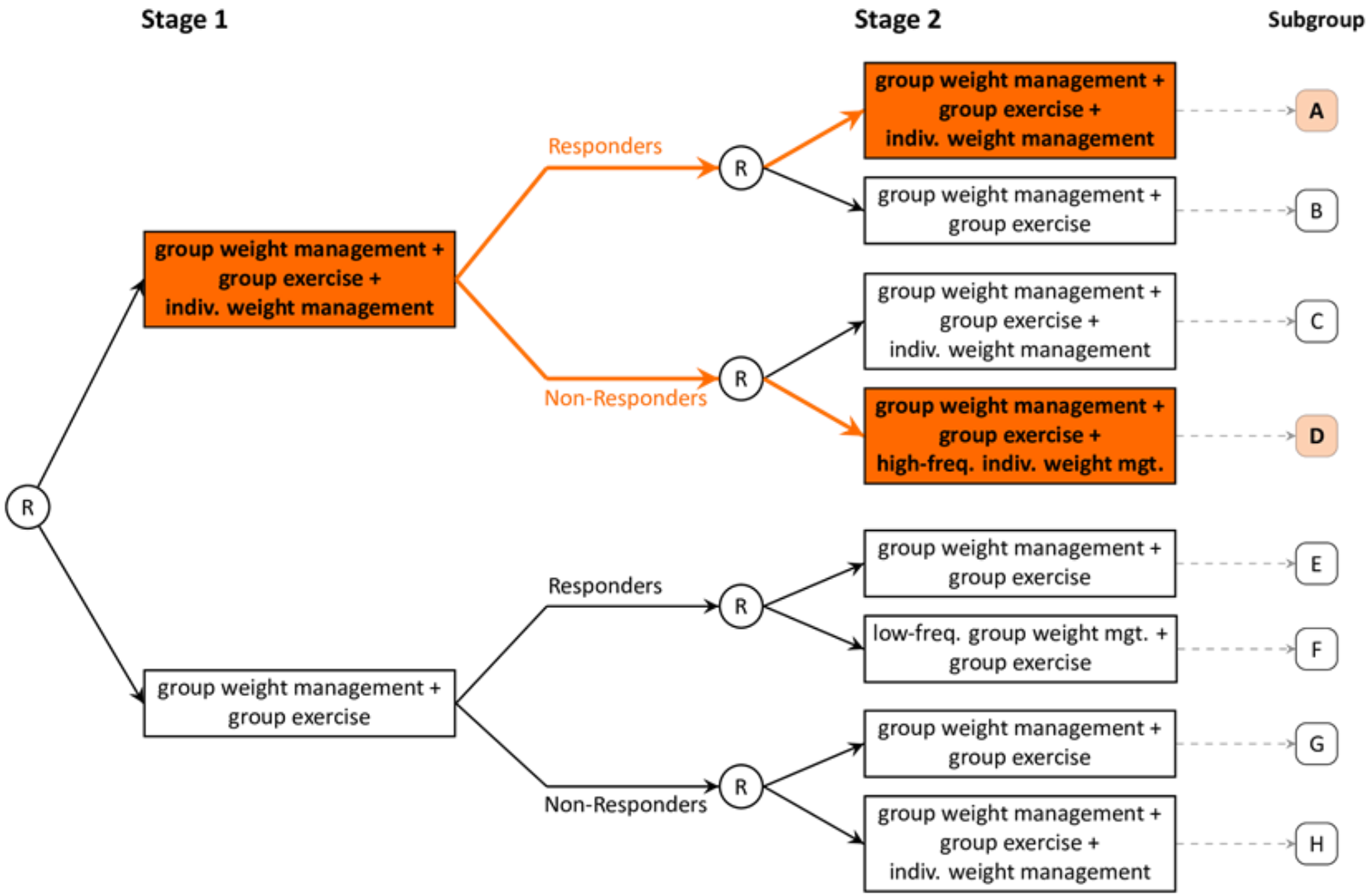

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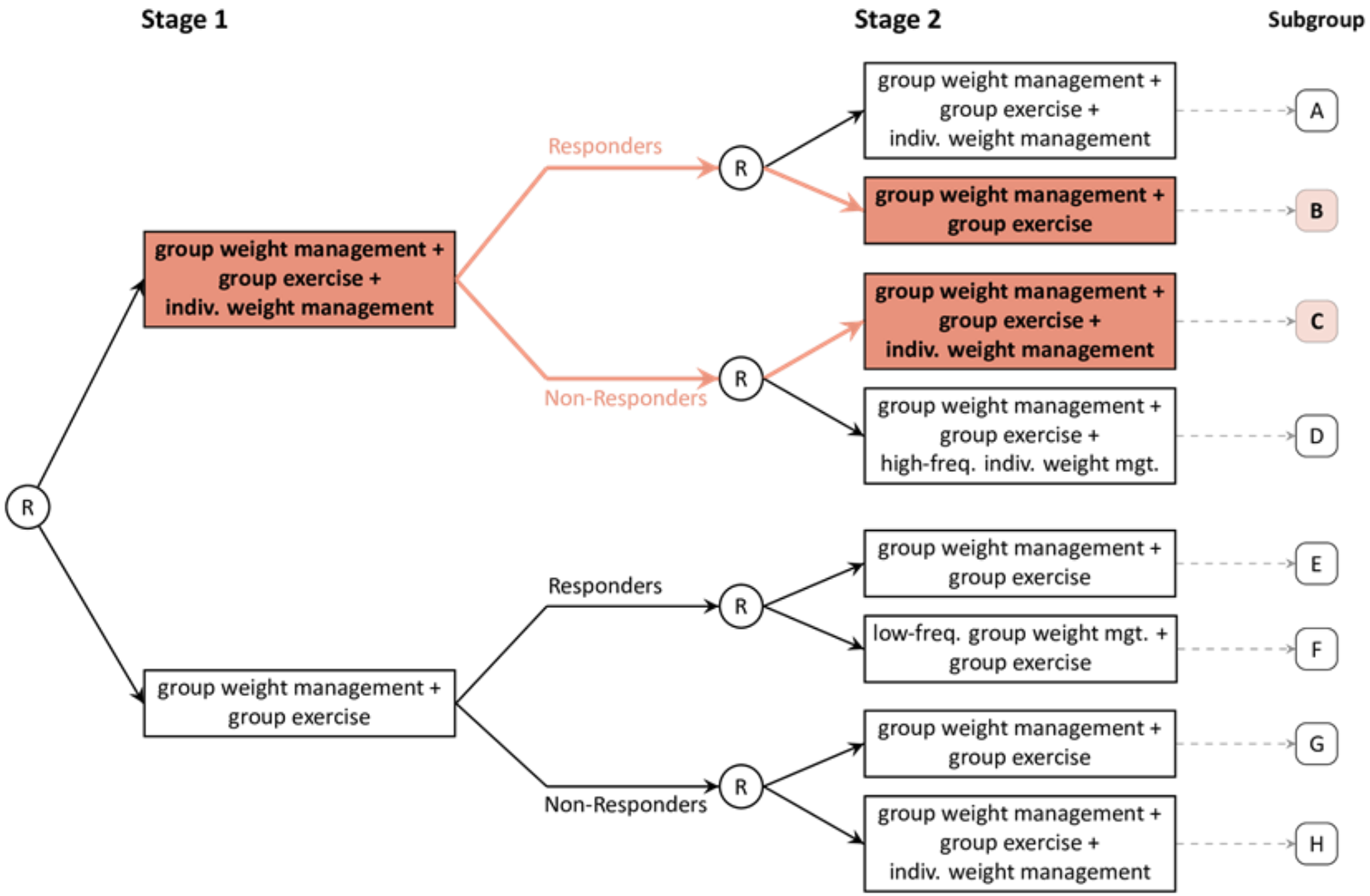

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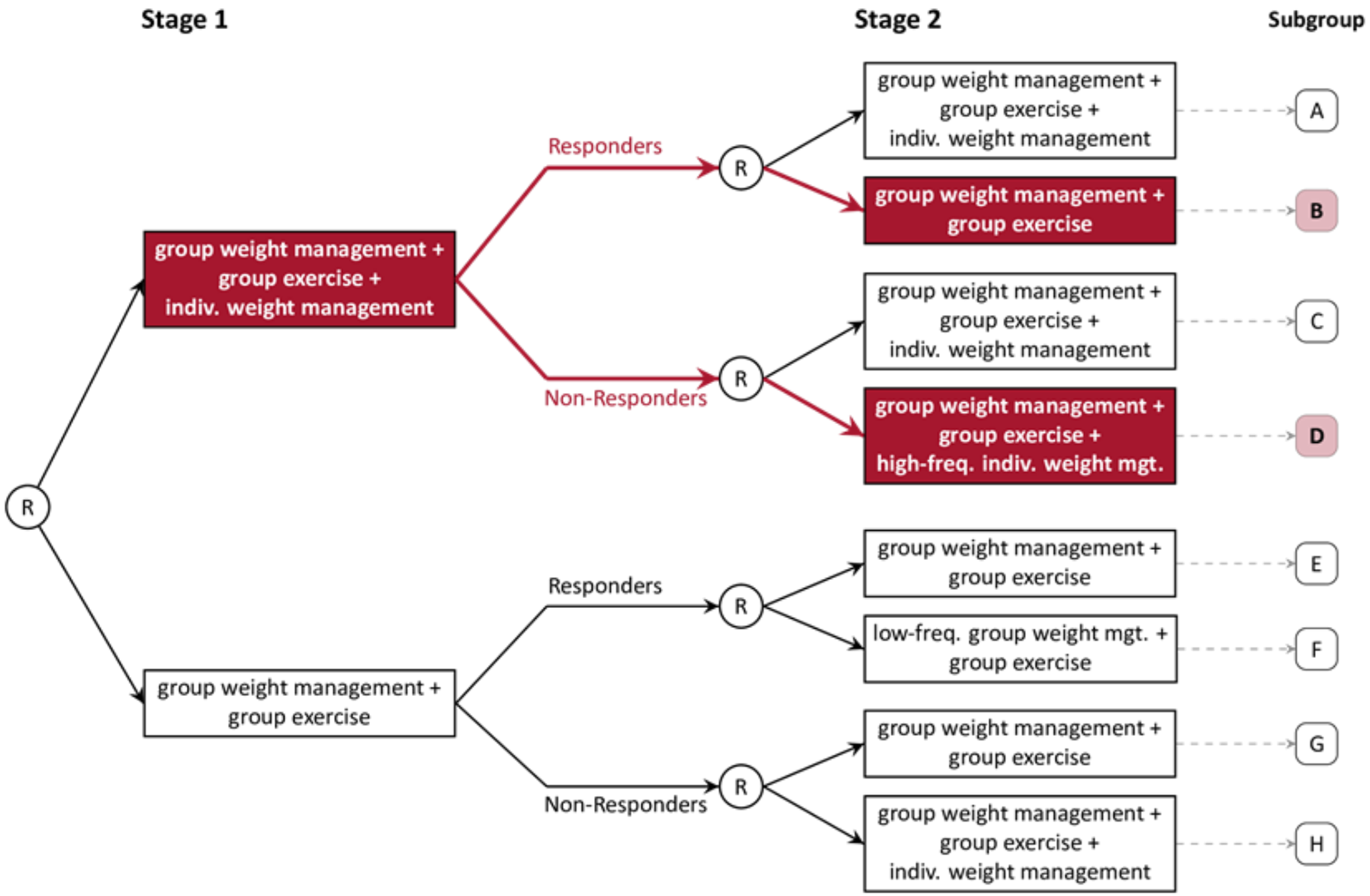

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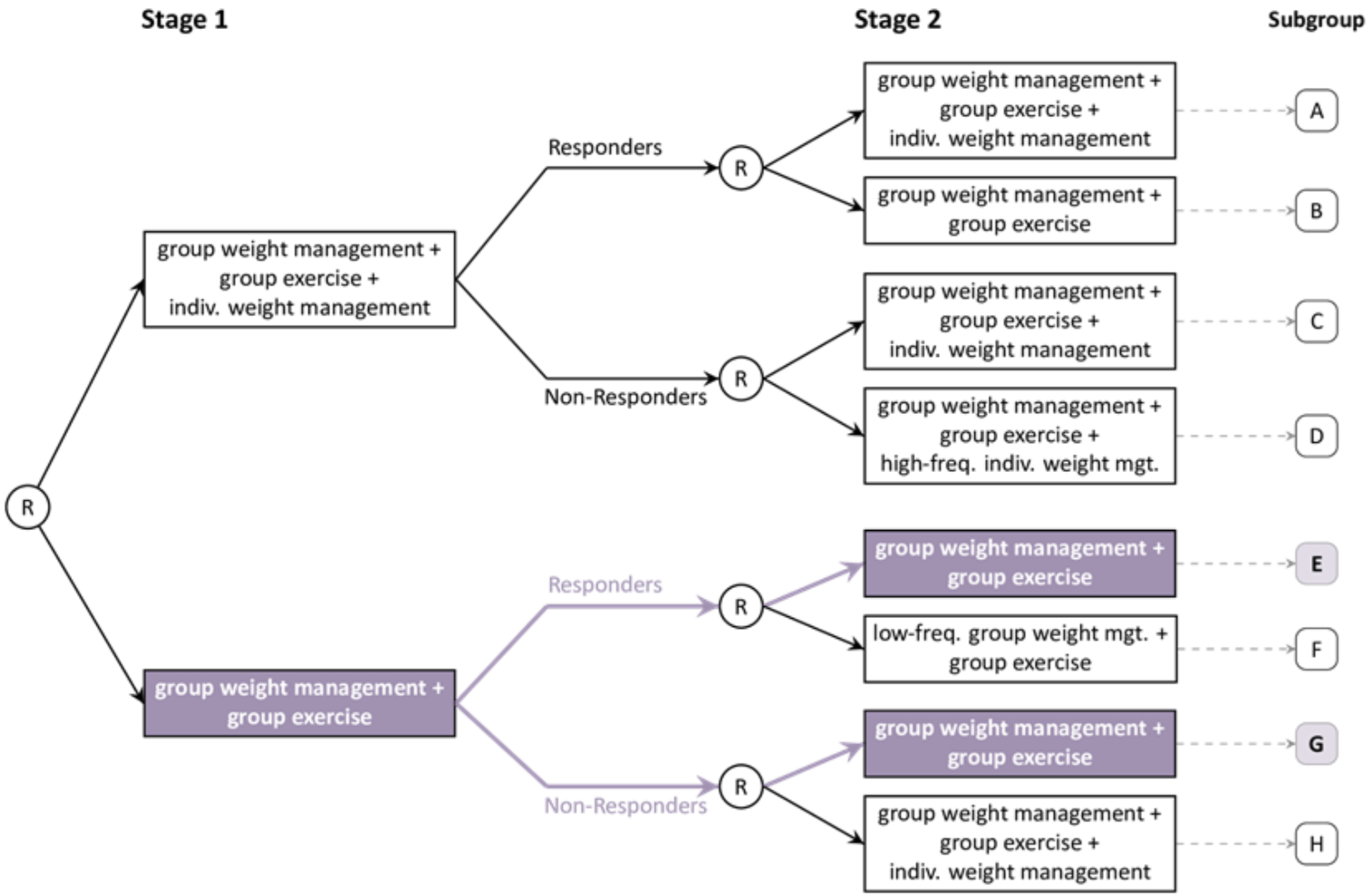

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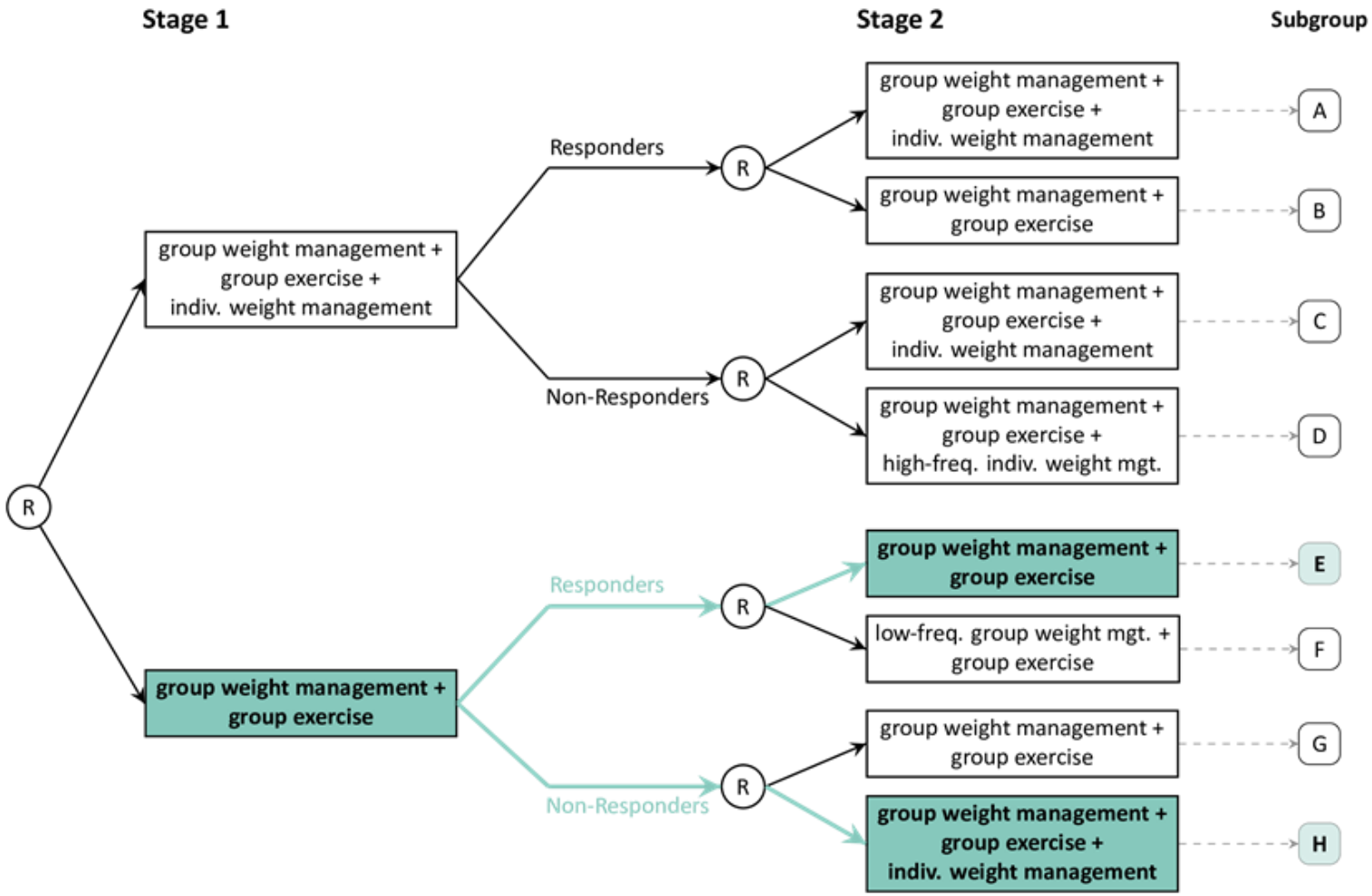

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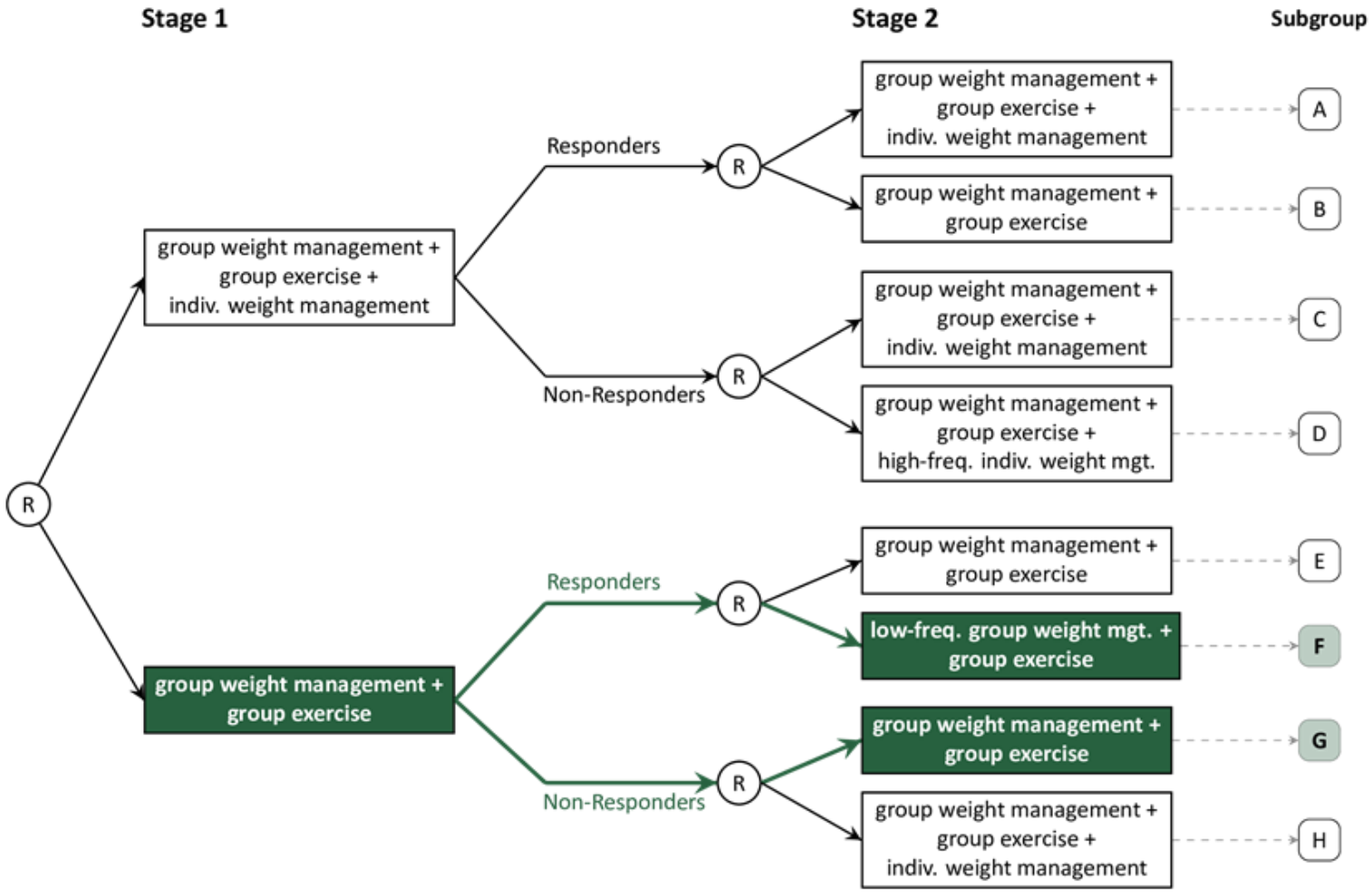

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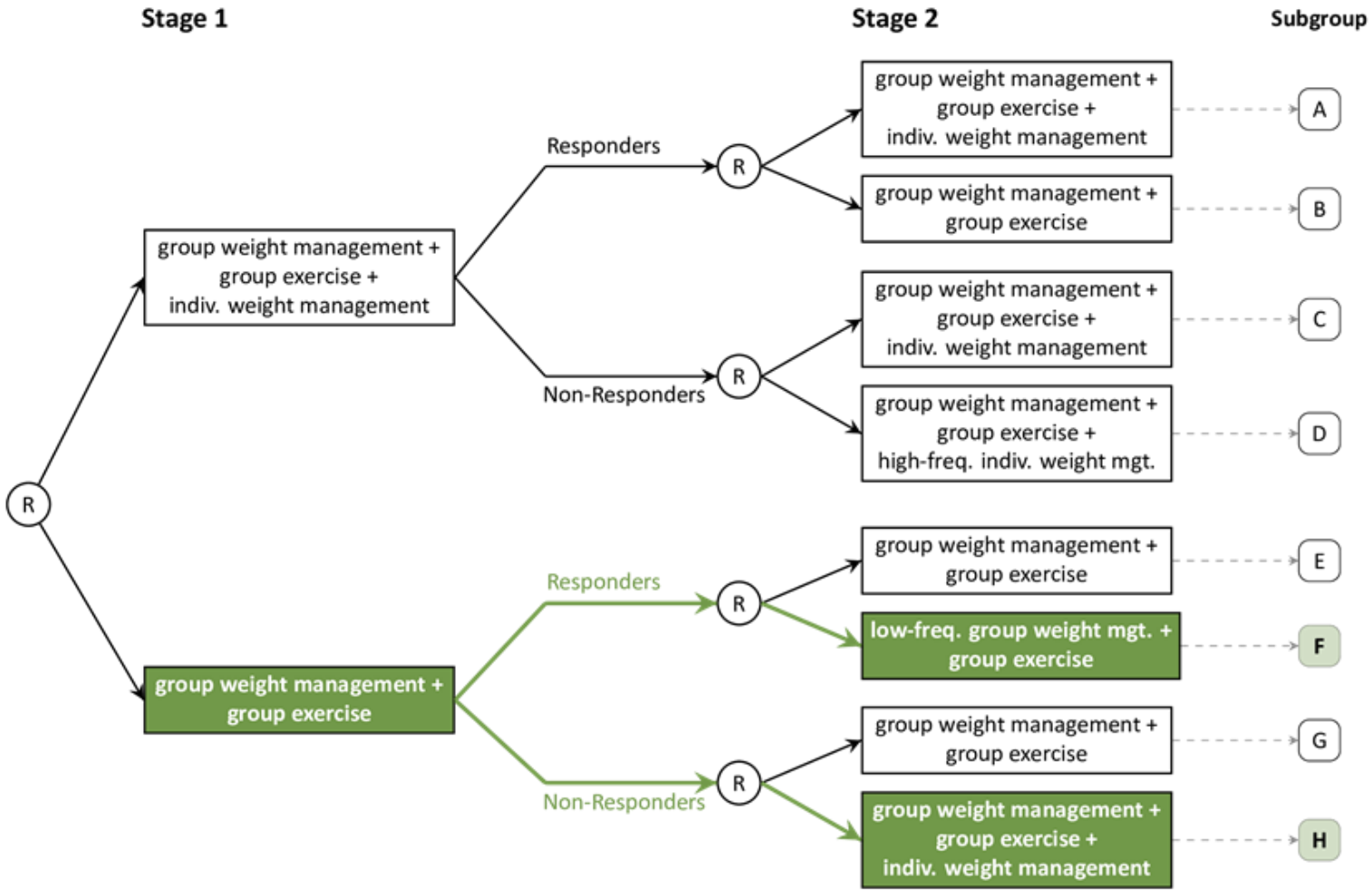


THIS IS A HYPOTHETICAL EXAMPLE

Do you need a SMART?

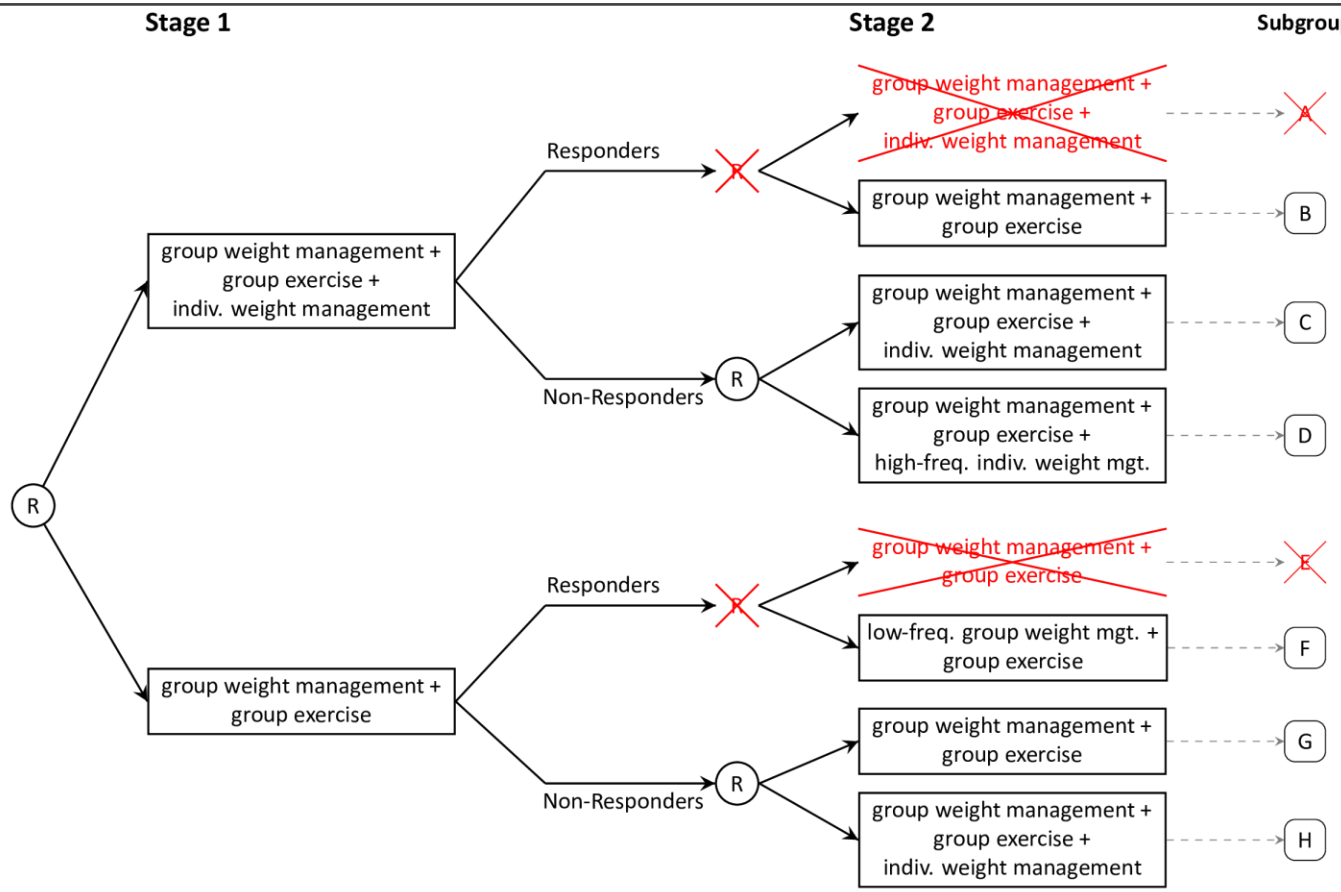
SMARTs are designed to answer questions about the development of high-quality adaptive interventions.

You might consider a SMART if…

- you want to develop an adaptive intervention,
- there are open questions preventing the construction of an effective adaptive intervention, *and*
- there are open questions at **multiple decision points** within an adaptive intervention

If any of the above are *not* true, you do not need a SMART!

Do you need a SMART if you know what to do for responders?



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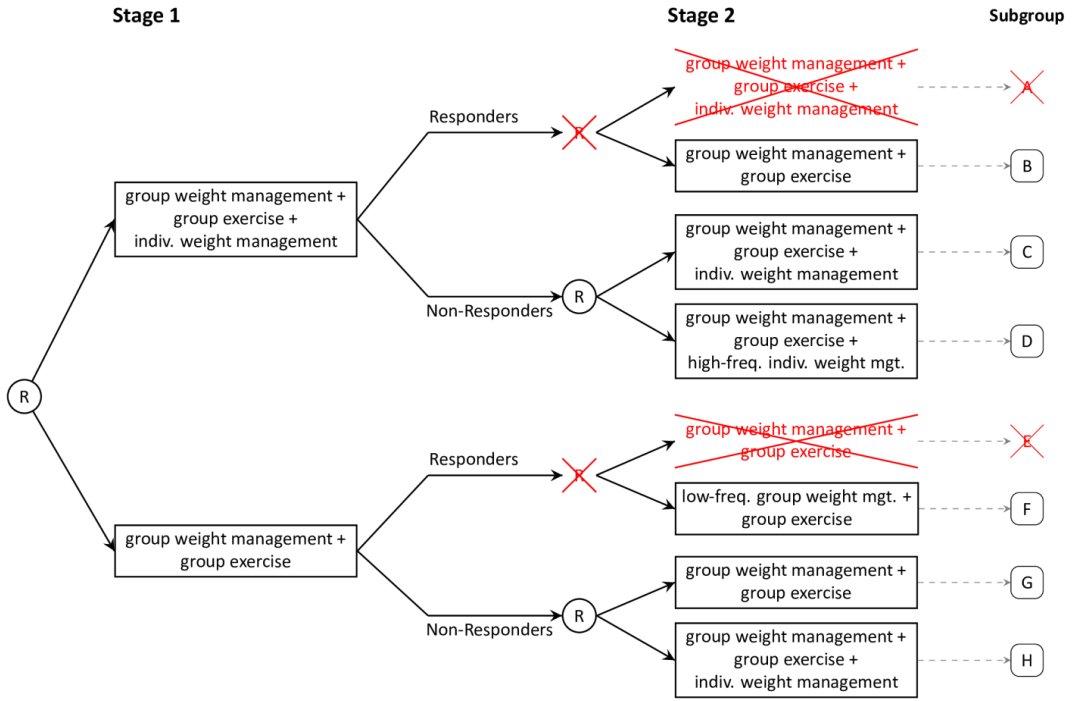
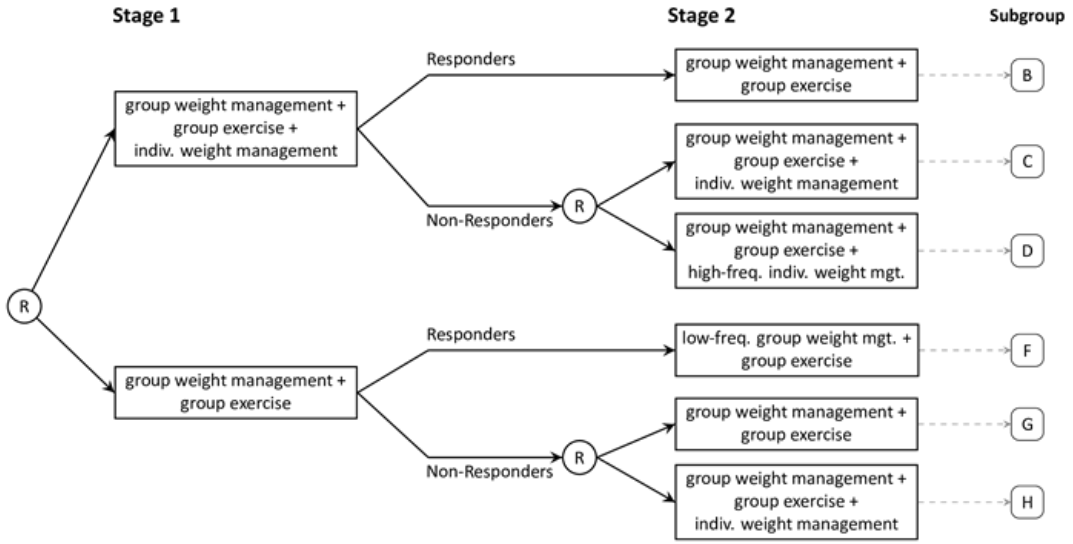


Still questions about *multiple stages* of an adaptive intervention:

- What should we do first?
- What should we do for non-responders?

Do you need a SMART if you know what to do for responders?



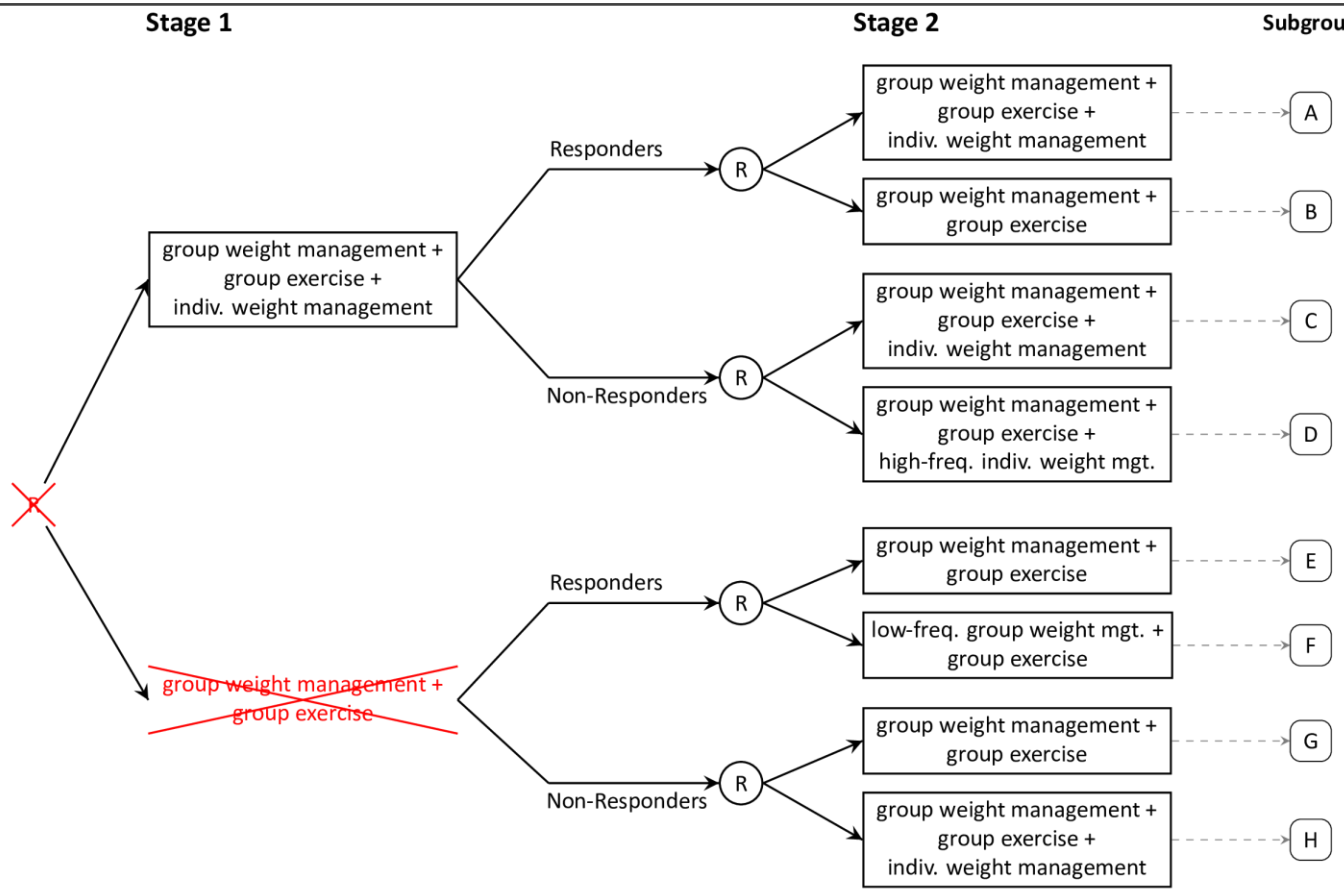
Still questions about *multiple stages* of an adaptive intervention:

- What should we do first?
- What should we do for non-responders?

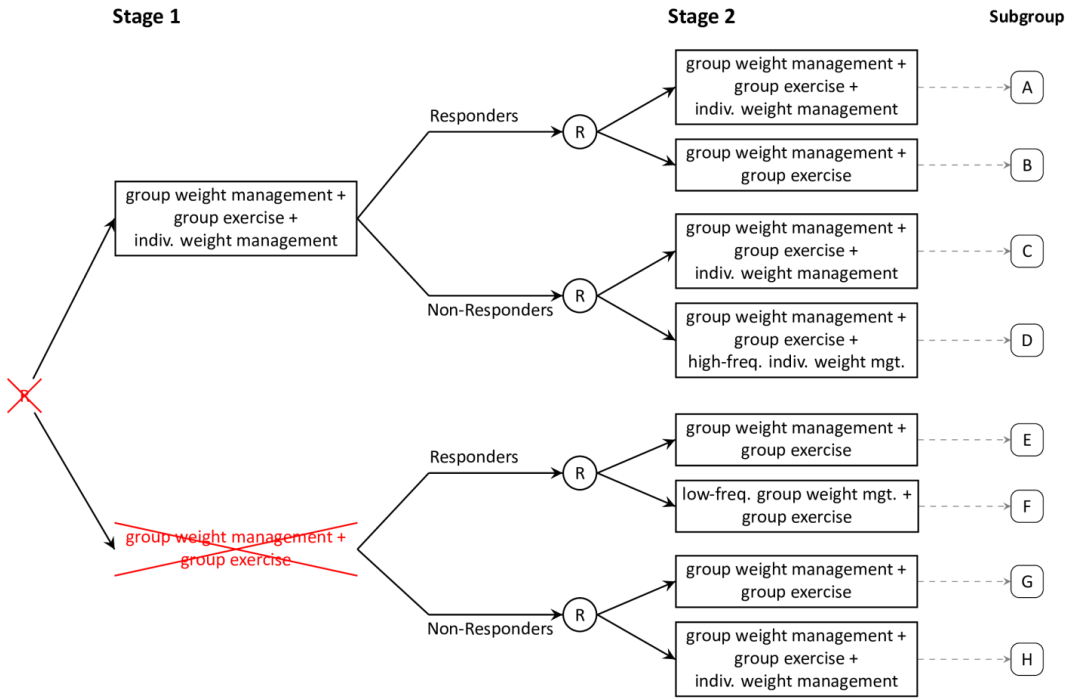
A SMART is appropriate here

- **Some** participants are randomized more than once

Do you need a SMART if you know what to do initially?



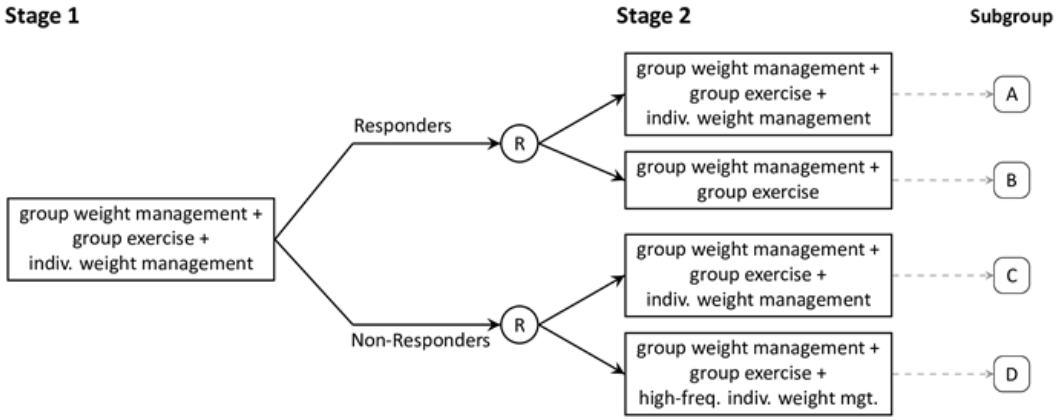
Do you need a SMART if you know what to do initially?



There are not questions about **multiple stages** of an adaptive intervention.

If there is no scientific question about how to initiate an adaptive intervention, we do not need the initial randomization.

Do you need a SMART if you know what to do initially?



We could instead design a trial with a run-in period on the initial intervention.

Randomization is still tailored, but there is only one.

- This is not a SMART!

Do you need a SMART?

Not all research on adaptive interventions requires a SMART

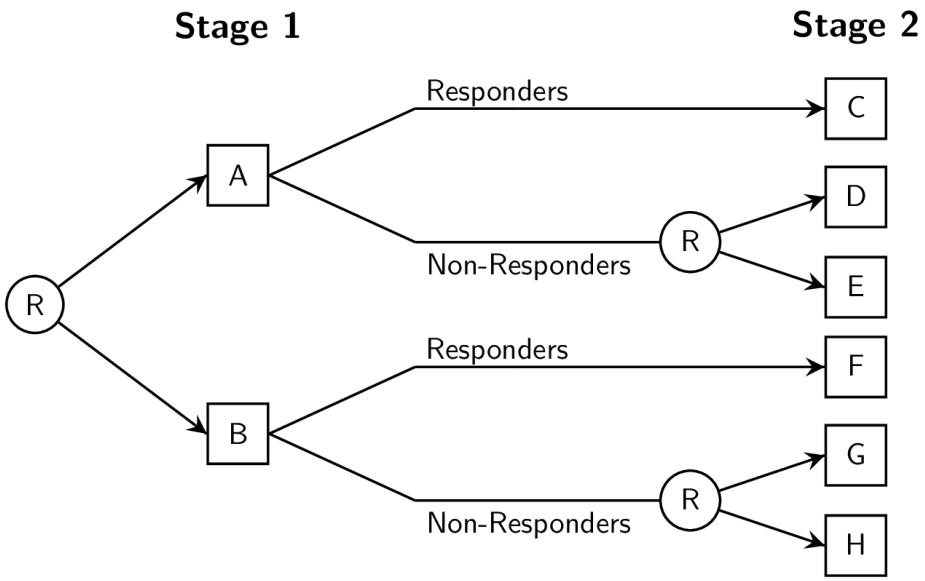
It may be appropriate to consider a “singly-randomized” alternative to a SMART

- See Almirall et al. (2018) for examples.

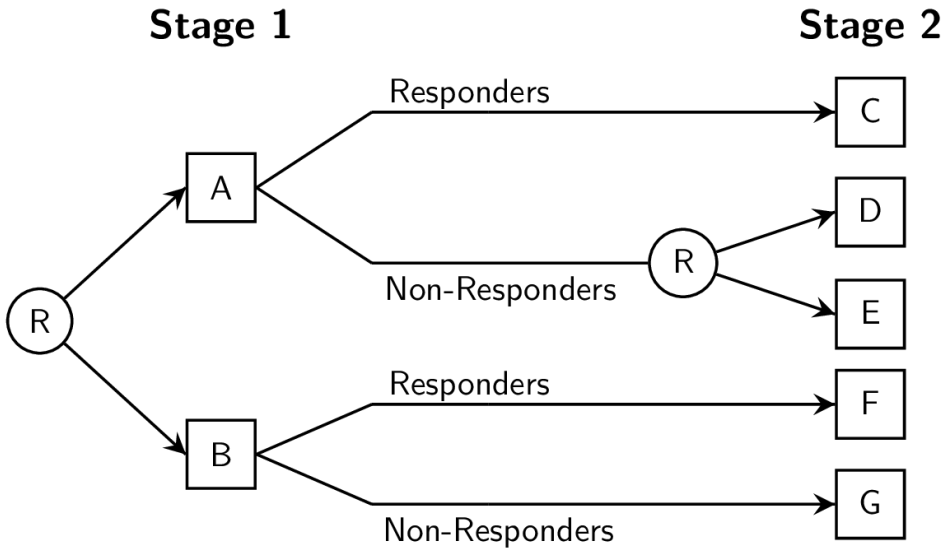
ALMIRALL, D., ET AL. 2018. “EXPERIMENTAL DESIGNS FOR RESEARCH ON ADAPTIVE INTERVENTIONS: SINGLY AND SEQUENTIALLY RANDOMIZED TRIALS.” IN OPTIMIZATION OF BEHAVIORAL, BIOBEHAVIORAL, AND BIOMEDICAL INTERVENTIONS: ADVANCED TOPICS, EDITED BY LINDA M. COLLINS AND KARI C. KUGLER, 89–120. STATISTICS FOR SOCIAL AND BEHAVIORAL SCIENCES. CHAM: SPRINGER INTERNATIONAL PUBLISHING. HTTPS://DOI.ORG/10.1007/978-3-319-91776-4_4.

Other SMART Designs

ONLY (NON-)RESPONDERS RE-RANDOMIZED



ONLY SOME (NON)-RESPONDERS RE-RANDOMIZED



Recap: What do we know so far?

So far, we've learned

- what an adaptive intervention is
- some scientific questions one might ask about developing an adaptive intervention
- an experimental design for addressing questions related to multiple-stages of the development of an adaptive intervention (SMART)
- when SMARTs may or may not be useful

Example

Where are the decision points?

What are the research questions?

How many embedded adaptive interventions?

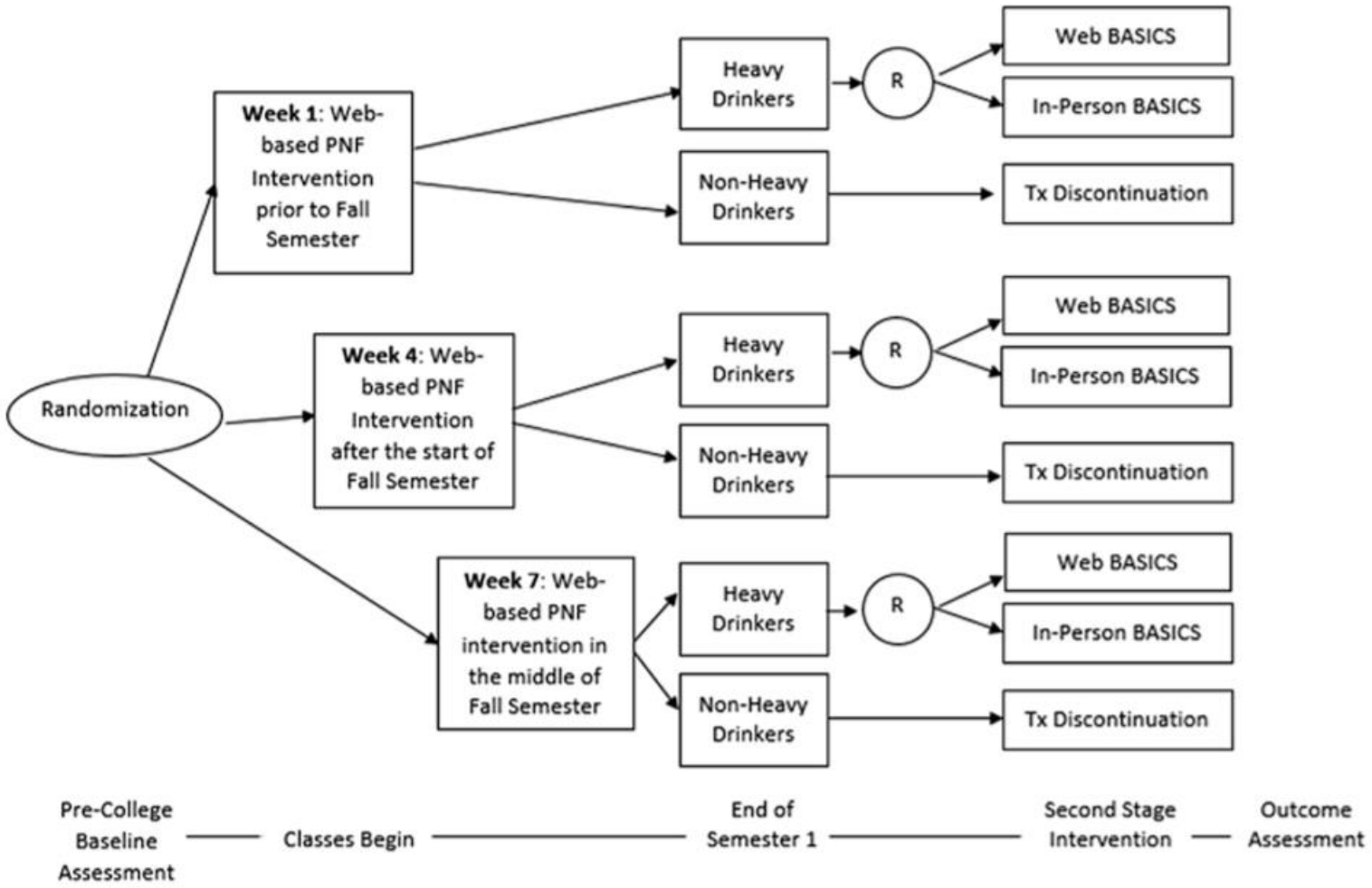
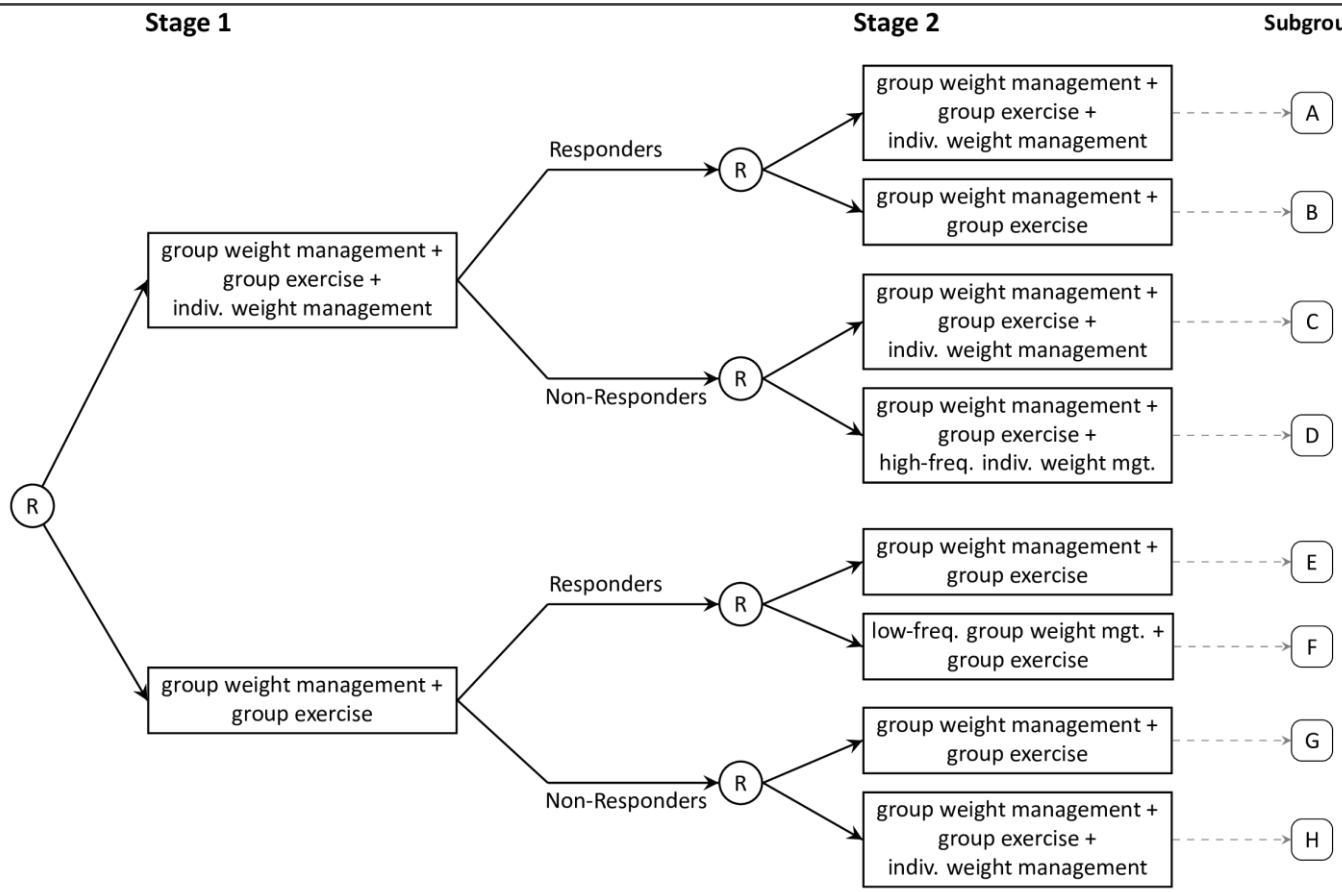


Fig. 17.4 SMART design for an adaptive preventive intervention pilot study for preventing heavy alcohol use in 1st-year college students (Patrick et al.)

Some Design and Analysis Considerations for SMARTs

Hypothetical example: weight loss program for individuals with serious mental illness



Tailoring Variables

Tailoring variables are often used to **restrict randomization** (i.e., recommend different intervention options to different subgroups of participants)

Tailoring variables should be **well-justified**: they're part of the embedded adaptive interventions!

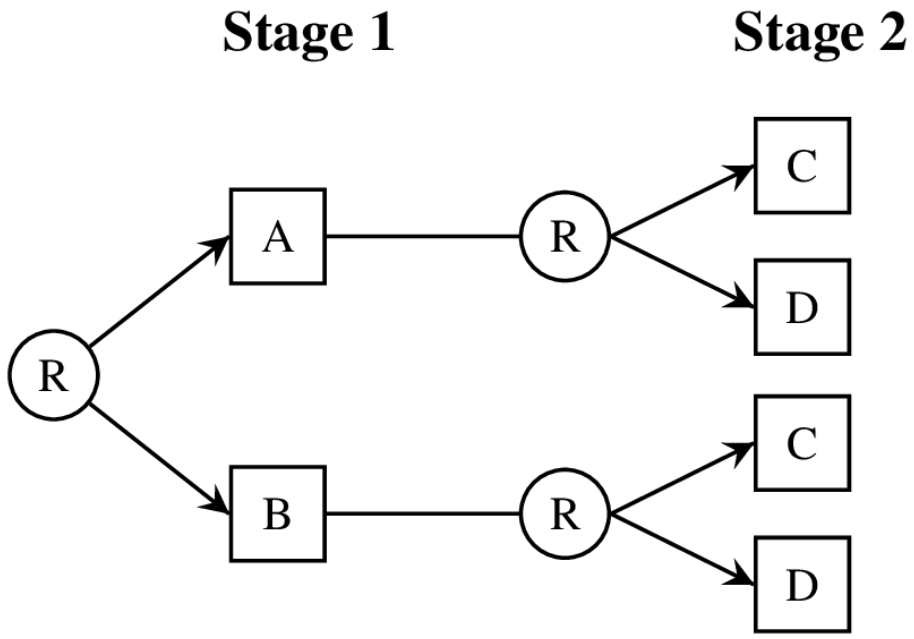
- Should be relatively easy to measure *in situ*
- Assignment should be systematic

Tailoring Variables

If you don't have strong scientific, practical, or ethical reasons for embedding a tailoring variable, you don't have to!

So-called *unrestricted* SMARTs don't embed tailoring variables

Secondary data analysis (e.g., Q-learning) can discover *candidate tailoring variables* for future work.



Primary & Secondary Aims

Just as the design of an adaptive intervention is guided by proximal & distal outcomes, so too is the design of a SMART.

Focus on a few scientific aims about developing a high-quality adaptive intervention.

Primary aims inform sample size and are usually comparisons of *groups of experimental conditions.*

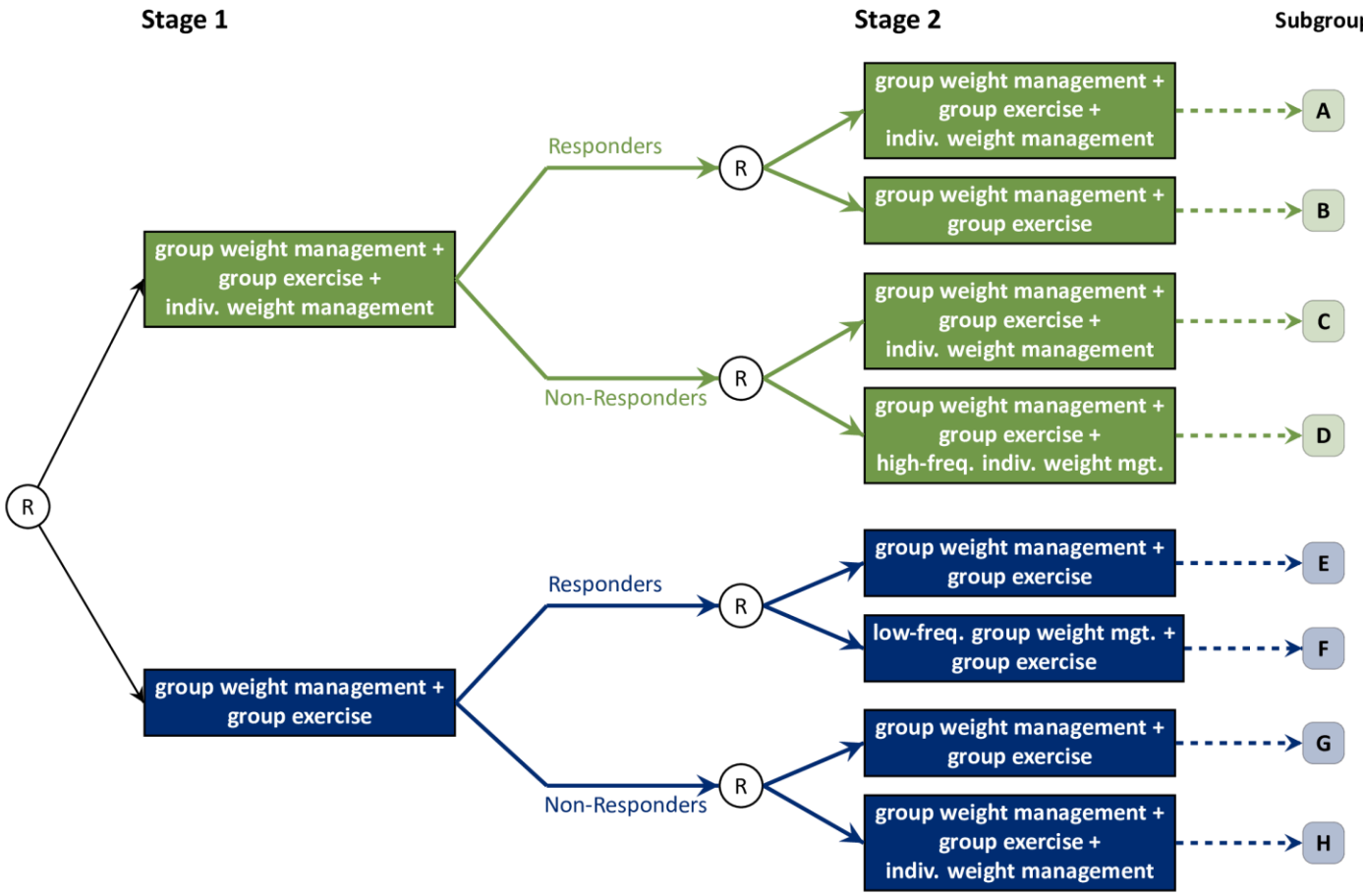
- Must be pre-planned and highly specific

Secondary aims can use rich data on treatment sequences to further inform more deeply-tailored adaptive interventions.

- May tolerate higher type-I error and lower power; flexible pre-specification

Common Primary Aims for SMARTs

COMPARE INITIAL INTERVENTION OPTIONS IN THE CONTEXT OF AN ADAPTIVE INTERVENTION



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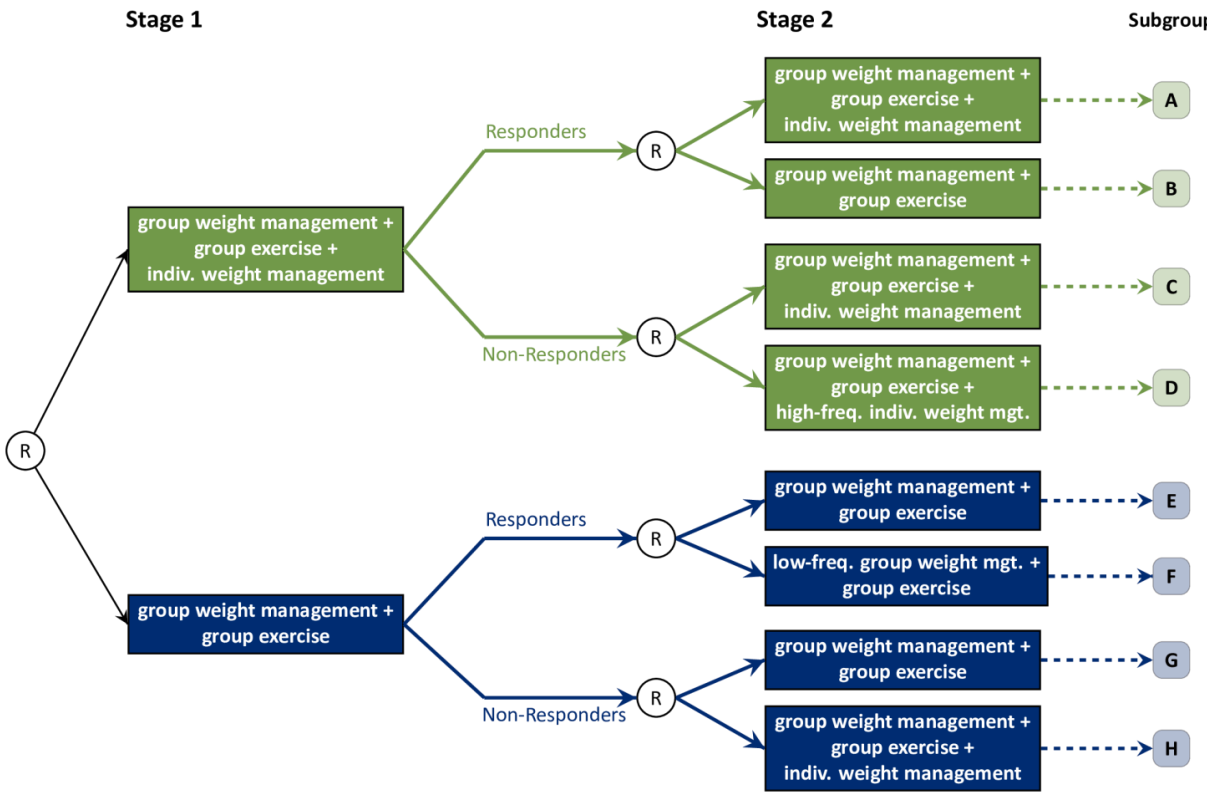


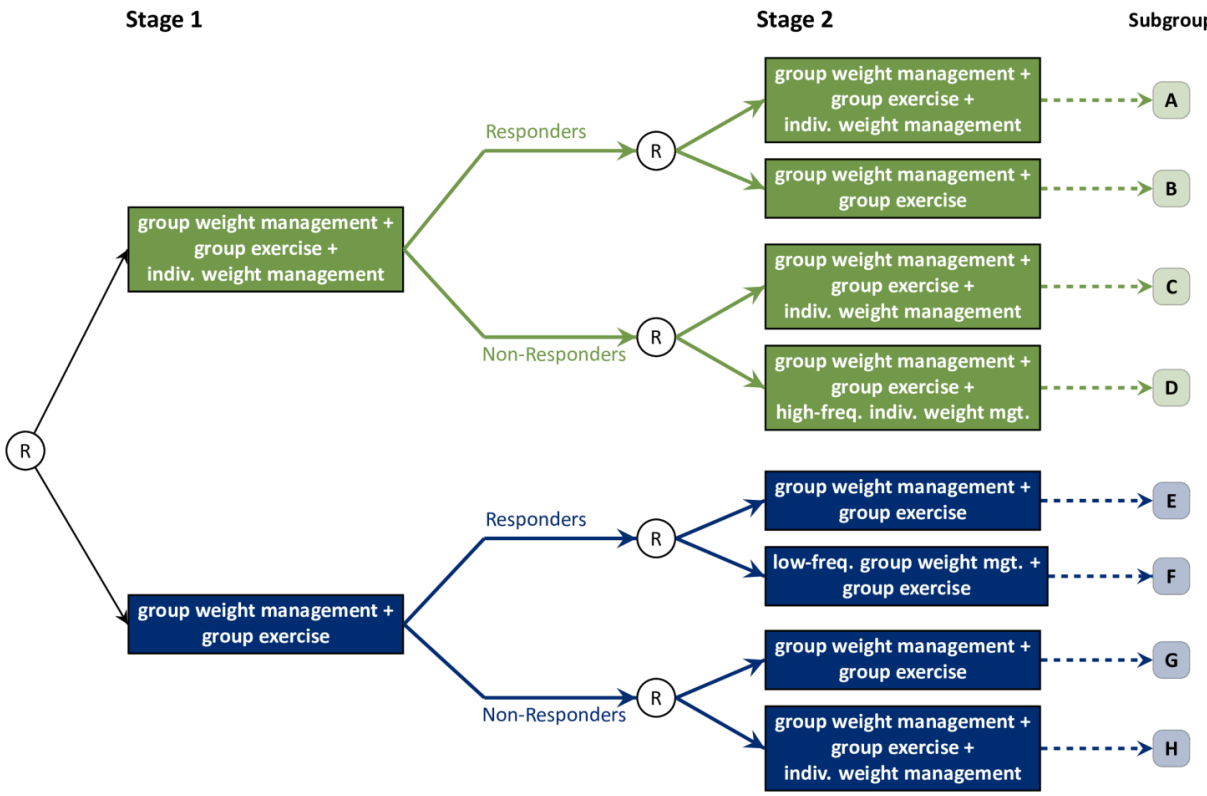
Hypothetical hypothesis:

> "Individuals who receive an adaptive weight-loss intervention which initially includes individual weight management sessions will lose more weight at 18 months, on average, than individuals who receive an adaptive weight-loss intervention that involves only group sessions."

Notice that the hypothesis is *in the context of adaptive interventions:* it "averages over" future treatment.

Common Primary Aims for SMARTs

COMPARE INITIAL INTERVENTION OPTIONS IN THE CONTEXT OF AN ADAPTIVE INTERVENTION



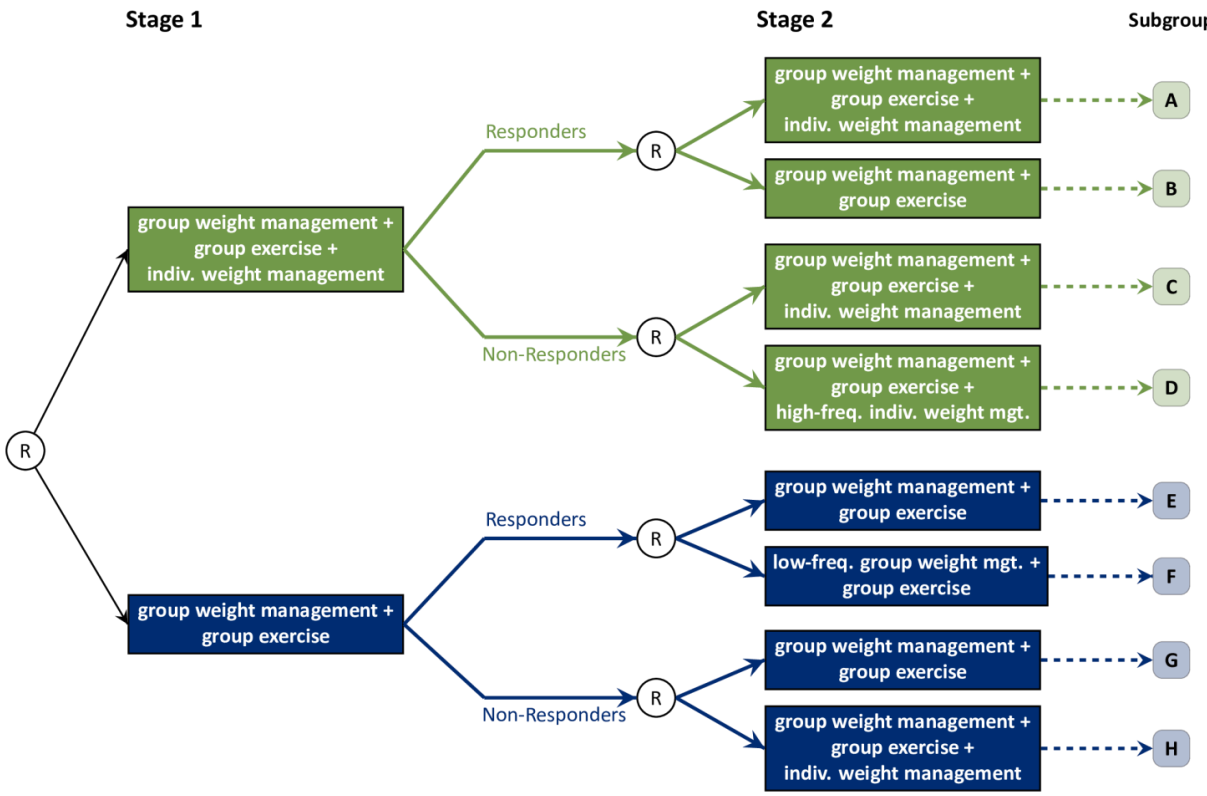
Analysis is a comparison of subgroups A, B, C, D vs. subgroups E, F, G, H.

- A two-group comparison!
- Can use standard methods (t-test, linear regression, etc.)

Sample size requirements are the same as for a two-arm trial.

Common Primary Aims for SMARTs

COMPARE INITIAL INTERVENTION OPTIONS IN THE CONTEXT OF AN ADAPTIVE INTERVENTION



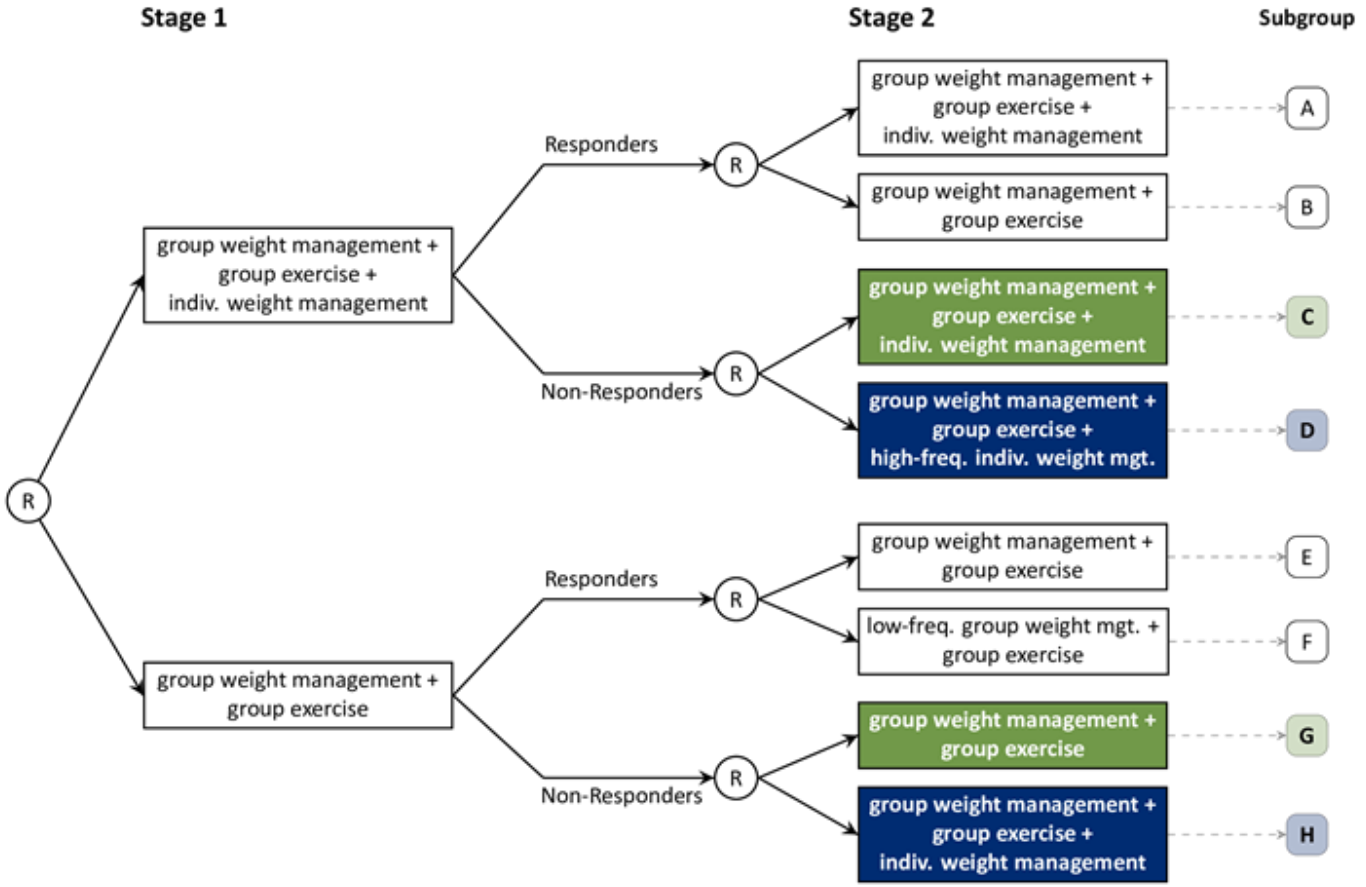
Sample size requirements are the same as for a two-arm trial.

$$n \geq \frac{4\left(z_{1-\frac{\alpha}{2}} + z_{1-\gamma}\right)^2}{\delta^2}$$

	80% power	90% power
$\delta = .3$	$n = 351$	$n = 469$
$\delta = .5$	$n = 128$	$n = 171$
$\delta = .8$	$n = 52$	$n = 68$

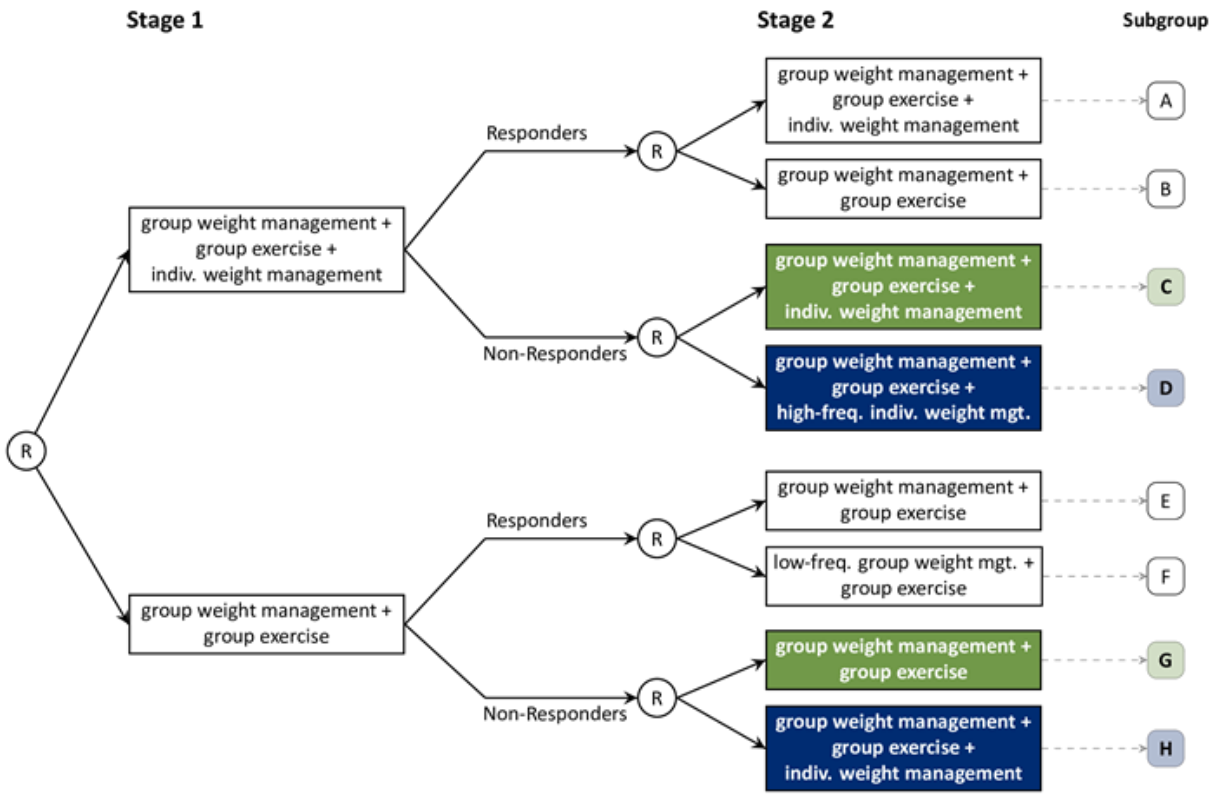
Common Primary Aims for SMARTs

COMPARE SECOND-STAGE INTERVENTION OPTIONS AMONG (NON-)RESPONDERS



Common Primary Aims for SMARTs

COMPARE SECOND-STAGE INTERVENTION OPTIONS AMONG (NON-)RESPONDERS



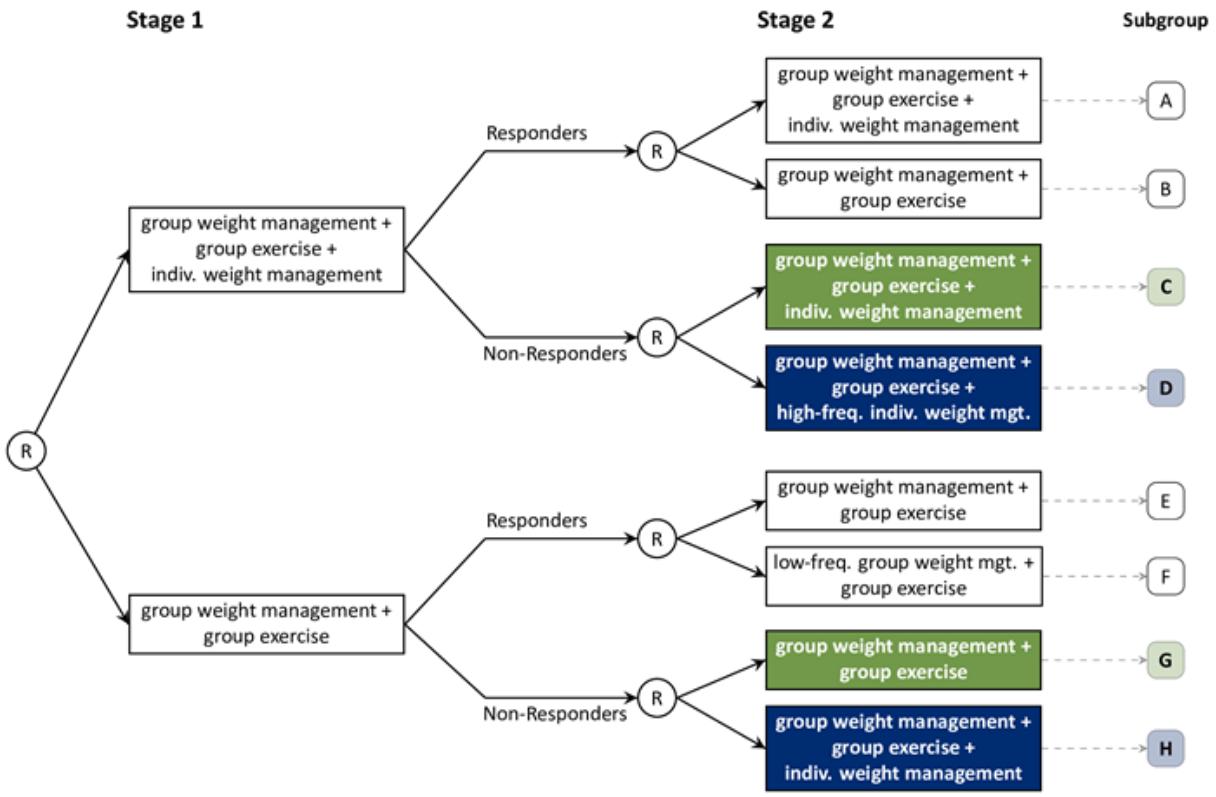
Hypothetical hypothesis:

> "Individuals who do not lose ≥ 5 lbs in the first 6 months of a weight-loss intervention will lose more weight at 18 months, on average, if their initial intervention is stepped up, compared to if they continued on the existing intervention."

Notice that the hypothesis is *in the context of adaptive interventions:* it "averages over" past treatment.

Common Primary Aims for SMARTs

COMPARE SECOND-STAGE INTERVENTION OPTIONS AMONG (NON-)RESPONDERS



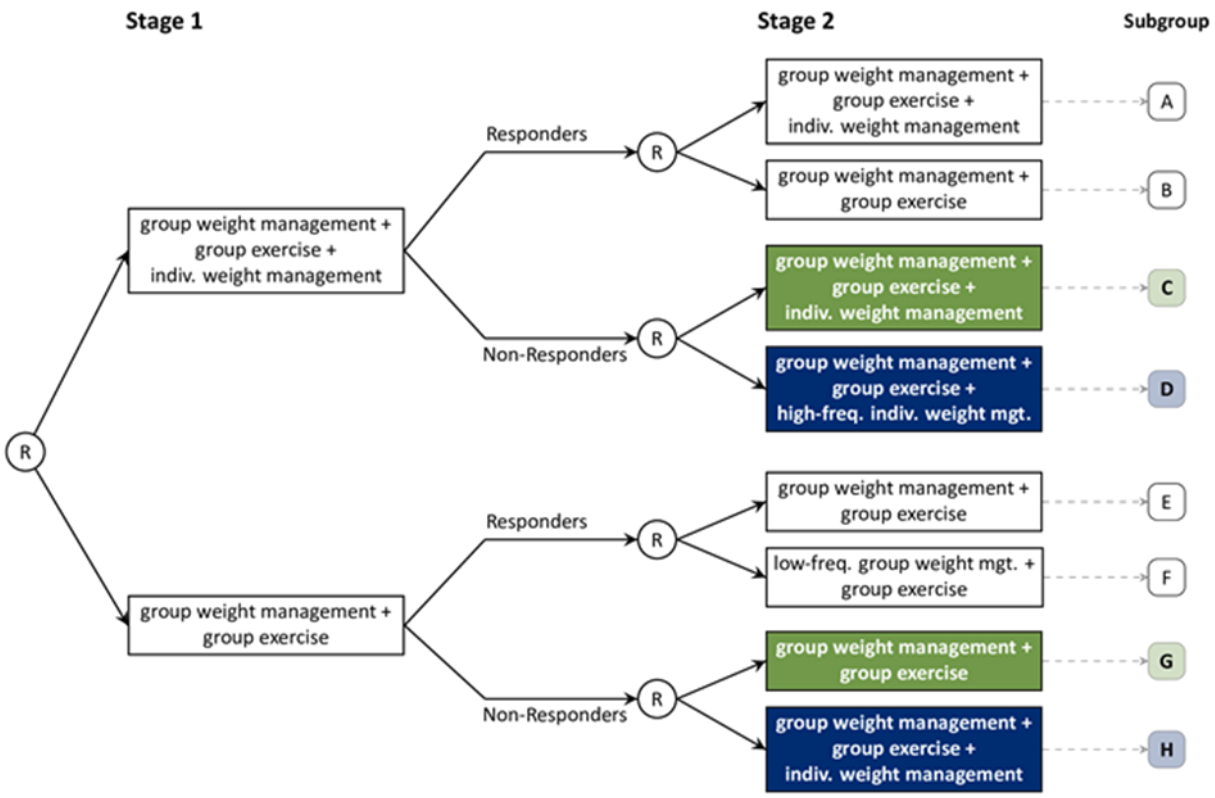
Analysis is a comparison of subgroups C & G vs. subgroups D & H.

- A two-group comparison among non-responders!
- Can use standard methods

Sample size requirements are the same as for a two-arm randomized trial, upweighted by (non-)response rate.

Common Primary Aims for SMARTs

COMPARE SECOND-STAGE INTERVENTION OPTIONS AMONG (NON-)RESPONDERS



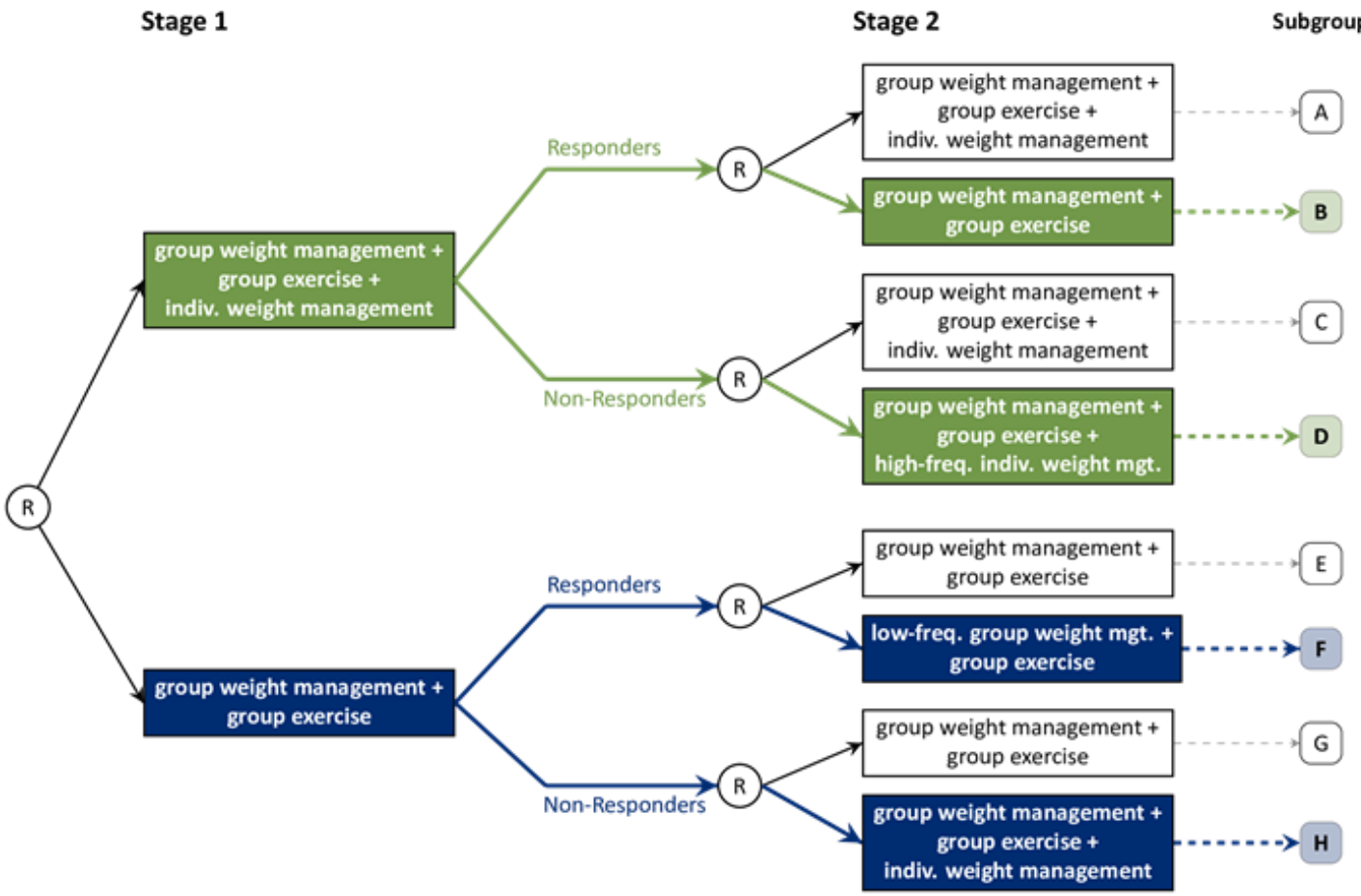
Sample size requirements are the same as for a two-arm trial.

$$n \geq \frac{4\left(z_{1-\frac{\alpha}{2}} + z_{1-\gamma}\right)^2}{\delta^2} \cdot \frac{1}{1 - P(R = 1)}$$

	80% power	90% power
$\delta = .3$	$n = 351/(1-r)$	$n = 469/(1-r)$
$\delta = .5$	$n = 128/(1-r)$	$n = 171/(1-r)$
$\delta = .8$	$n = 52/(1-r)$	$n = 68/(1-r)$

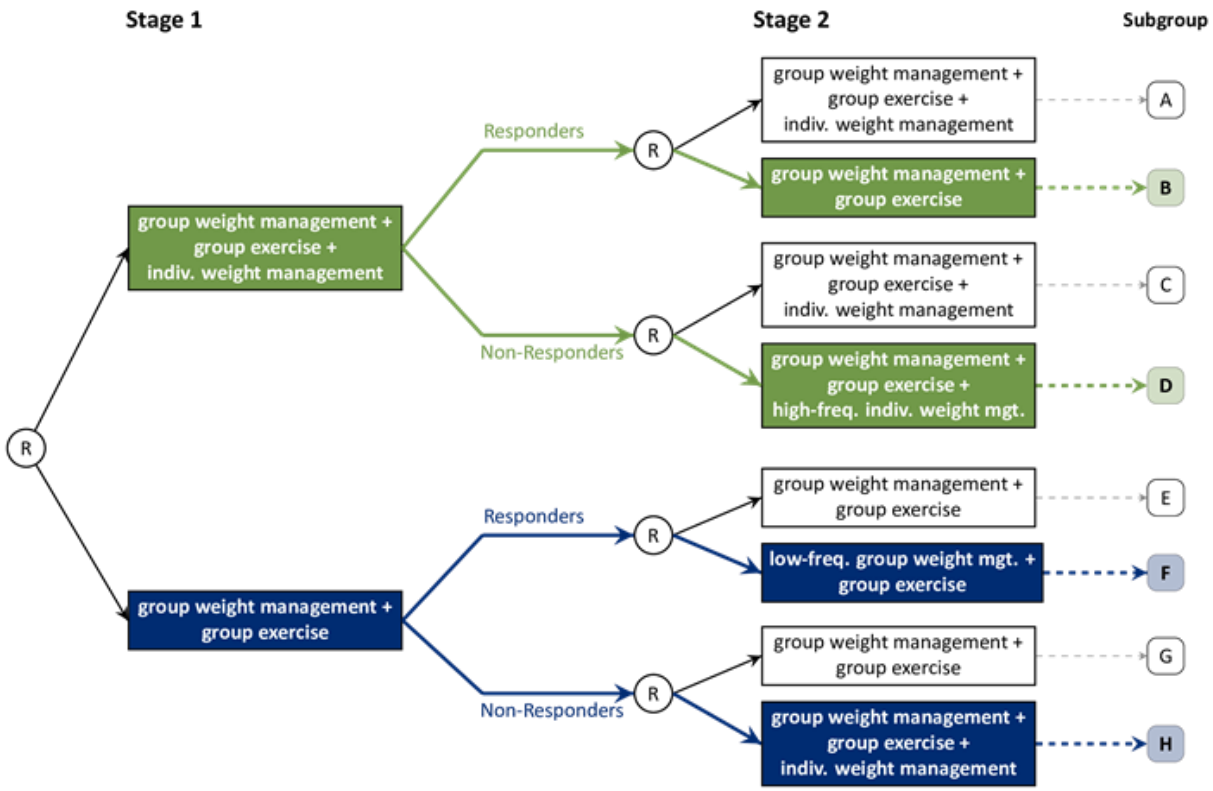
Common Primary Aims for SMARTs

COMPARE EMBEDDED ADAPTIVE INTERVENTIONS



Common Primary Aims for SMARTs

COMPARE EMBEDDED ADAPTIVE INTERVENTIONS

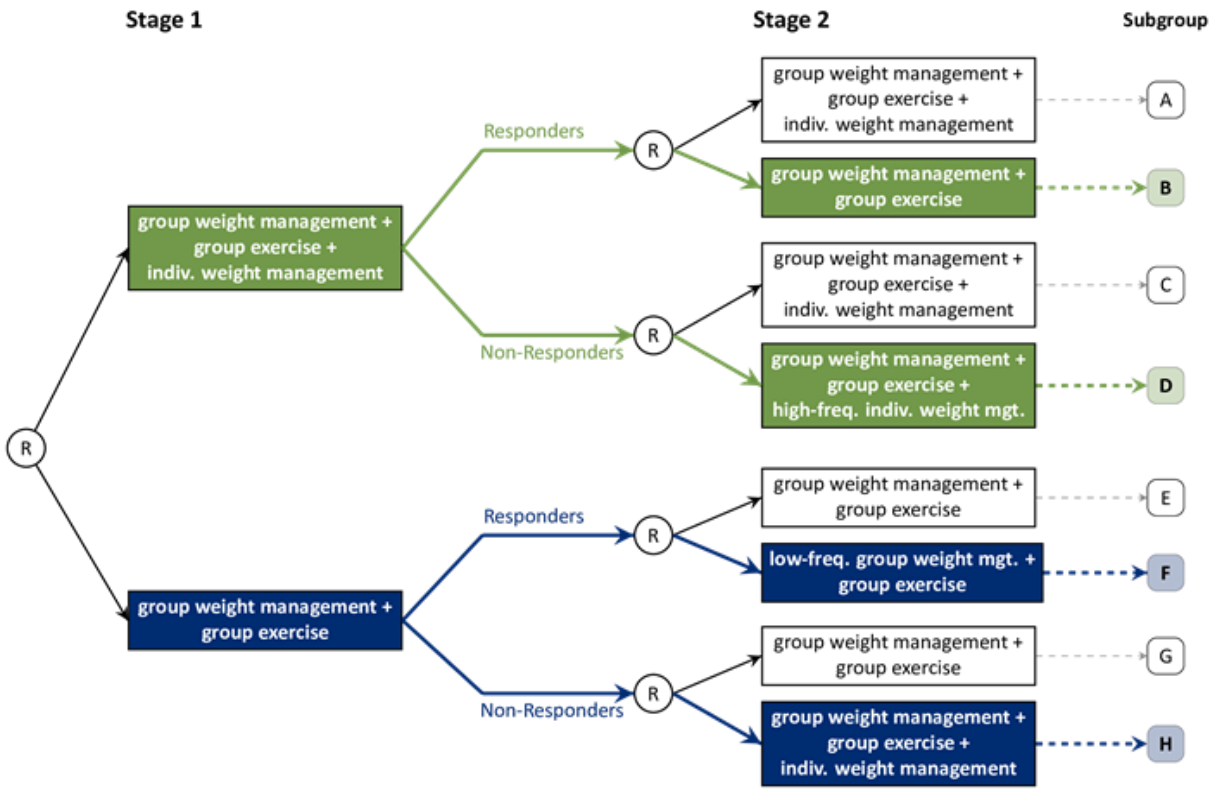


Hypothetical hypothesis:

> "Individuals who receive treatment according to the green adaptive intervention will lose more weight after 18 months, on average, compared to those treated according to the blue adaptive intervention."

Common Primary Aims for SMARTs

COMPARE EMBEDDED ADAPTIVE INTERVENTIONS

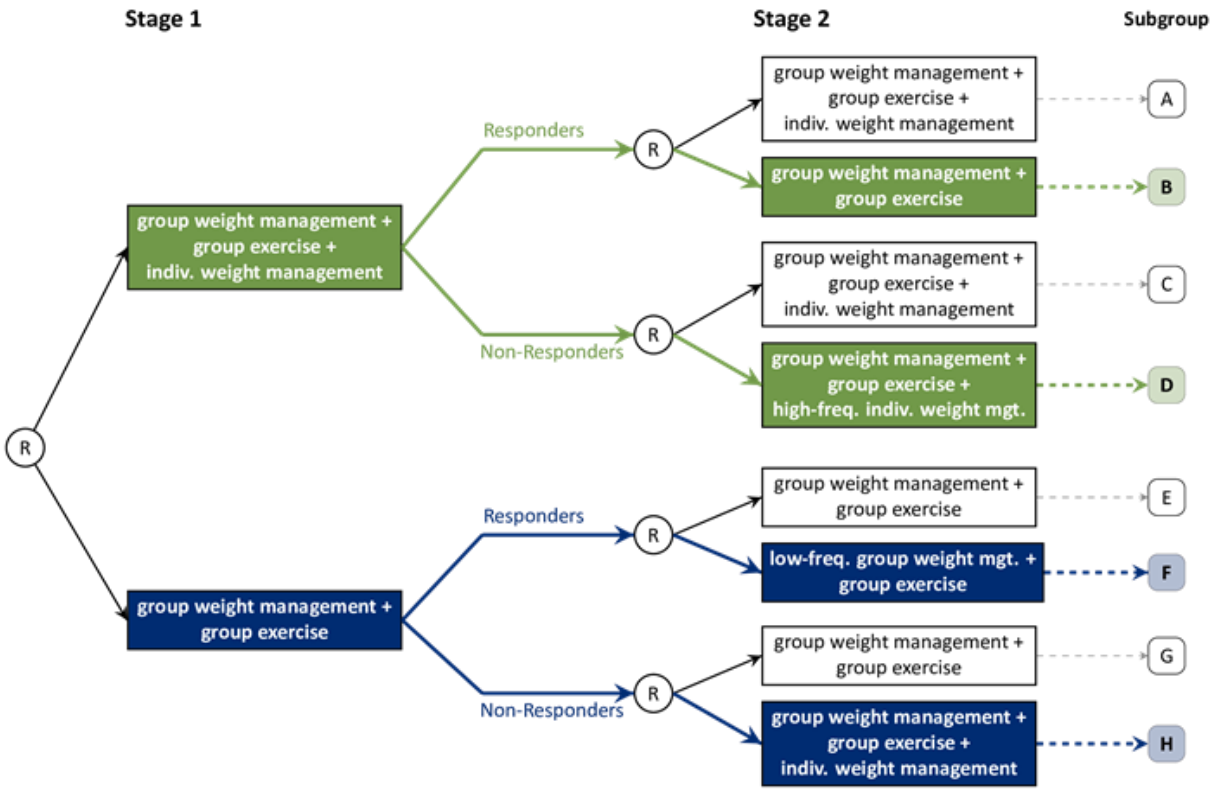


Analysis is a comparison of subgroups B & D vs. subgroups F & H.

- In general, need to account for unique design features of a SMART when comparing adaptive interventions.

Common Primary Aims for SMARTs

COMPARE EMBEDDED ADAPTIVE INTERVENTIONS

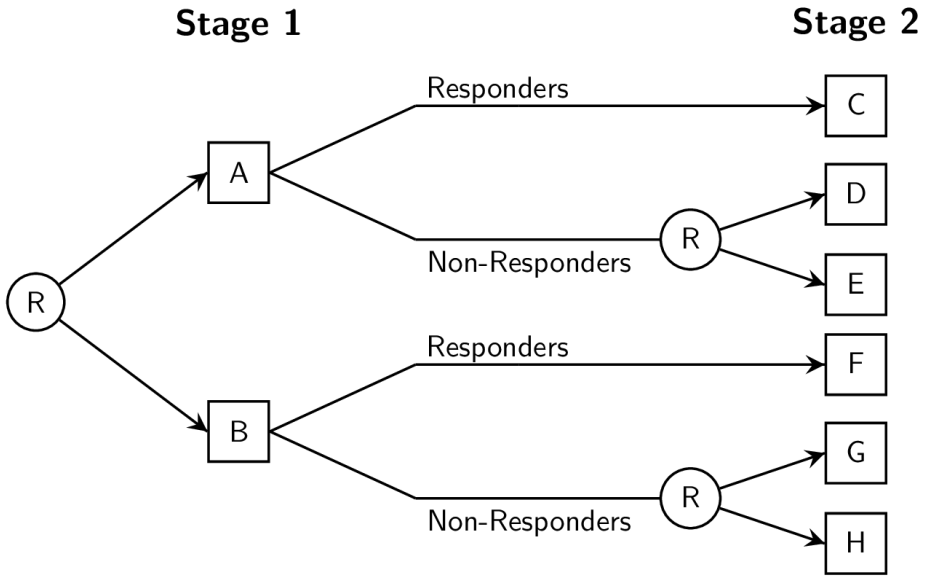


Sample size formulae available for many outcome types. For *this* design with a continuous outcome:

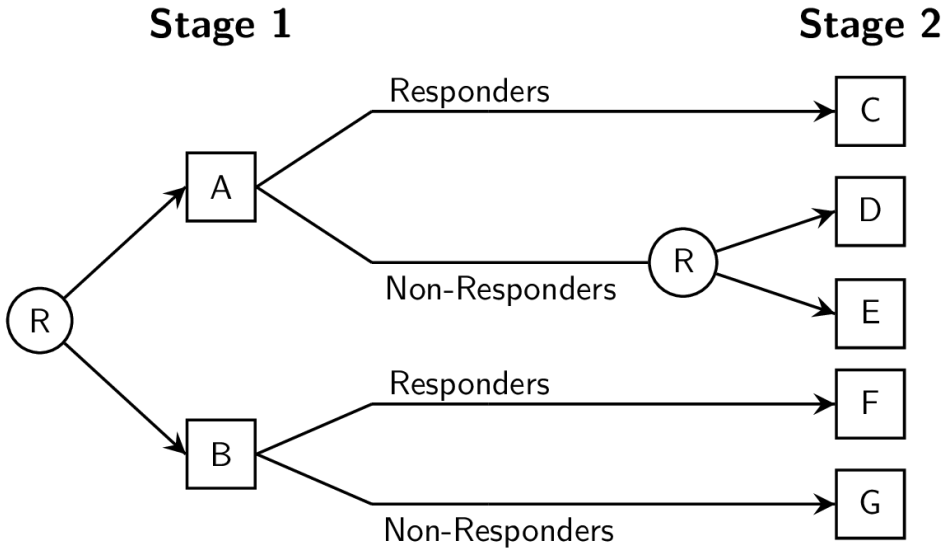
$$n \geq \frac{4\left(z_{1-\frac{\alpha}{2}} + z_{1-\gamma}\right)^2}{\delta^2} \cdot 2$$

	80% power	90% power
$\delta = .3$	$n = 702$	$n = 938$
$\delta = .5$	$n = 256$	$n = 342$
$\delta = .8$	$n = 104$	$n = 136$

Sample Size for Comparing Embedded Adaptive Interventions



$$n \geq \frac{4\left(z_{1-\frac{\alpha}{2}} + z_{1-\gamma}\right)^2}{\delta^2} \times (2 - r)^*$$



$$n \geq \frac{4\left(z_{1-\frac{\alpha}{2}} + z_{1-\gamma}\right)^2}{\delta^2} \times \left(\frac{3}{2} - r\right)$$

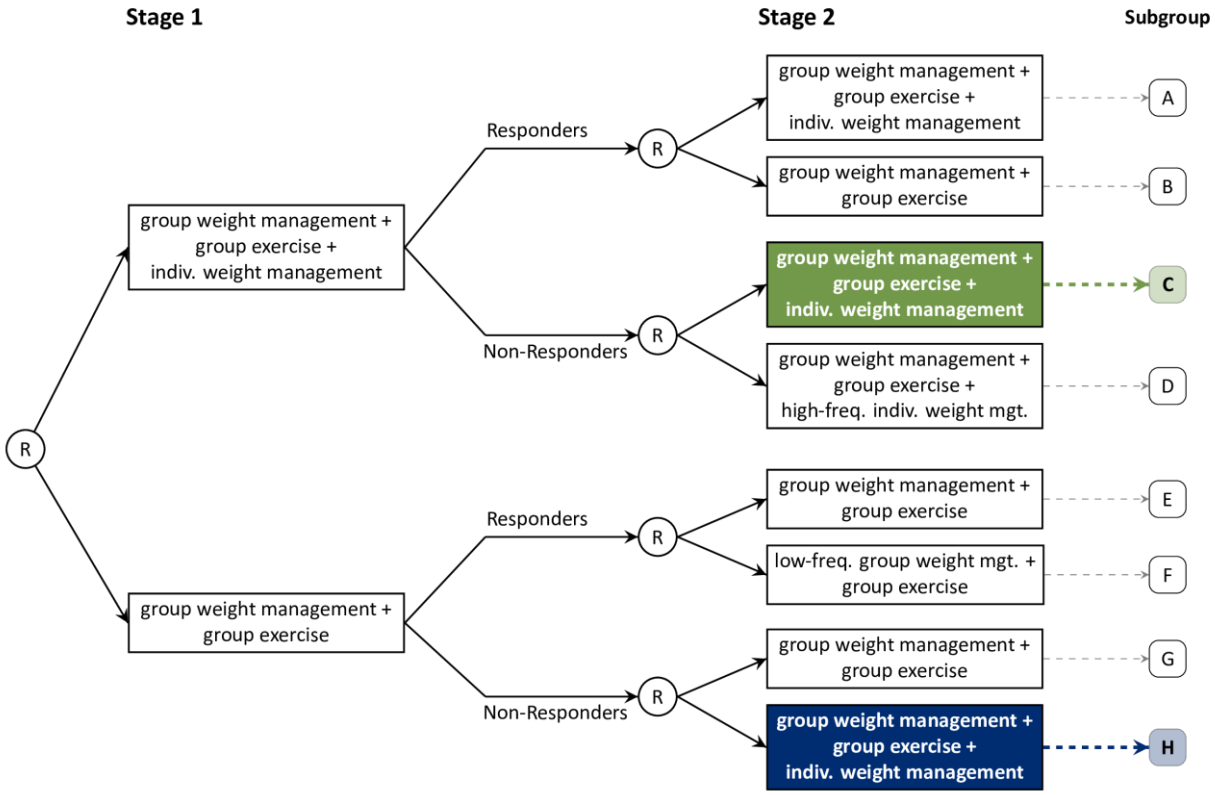
*IF RESPONSE RATE IS DIFFERENT BETWEEEN A & B, DESIGN EFFECT BECOMES $\left(2 - \frac{r_A + r_B}{2}\right)$

Questionable Primary Aims for SMARTs

COMPARE INDIVIDUAL SUBGROUPS OR EXPERIMENTAL CONDITIONS

Adaptive interventions recommend treatments for every level of the tailoring variable.

This is not a question about adaptive interventions and is not strong motivation for a SMART.

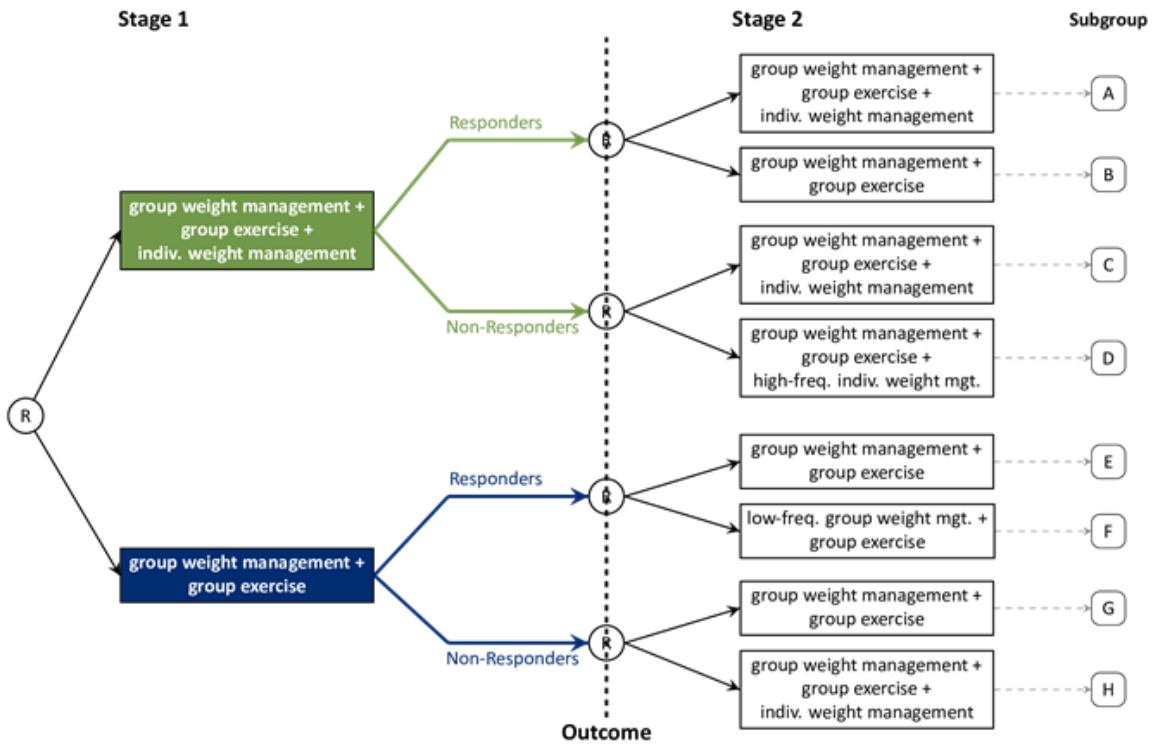


Questionable Primary Aims for SMARTs

COMPARE RESPONSE RATES TO FIRST-STAGE INTERVENTIONS

Not about adaptive interventions: ignores stage-2 treatment

Maybe an interesting secondary analysis, but is not strong motivation for a SMART.



Questionable Primary Aims for SMARTs

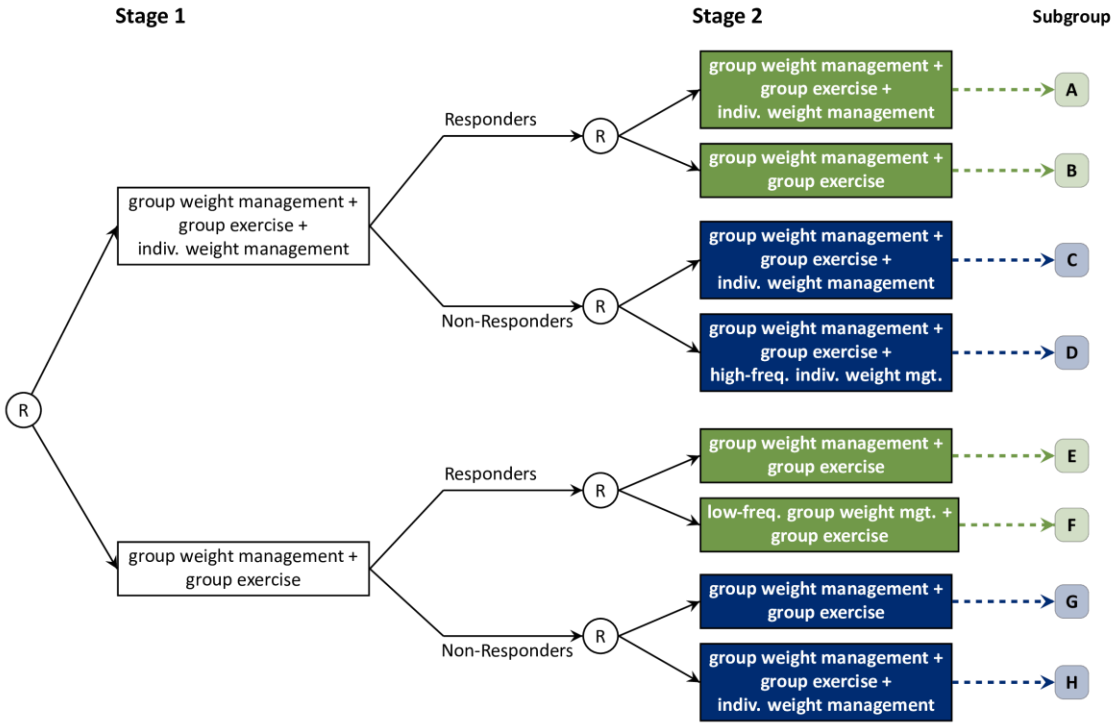
COMPARE RESPONDERS TO NON-RESPONDERS

This is a non-randomized comparison: we did not experimentally assign response status

Not really a question about adaptive interventions

- Adaptive interventions recommend treatments for *both* responders and non-responders

A non-randomized comparison does not motivate a randomized trial.

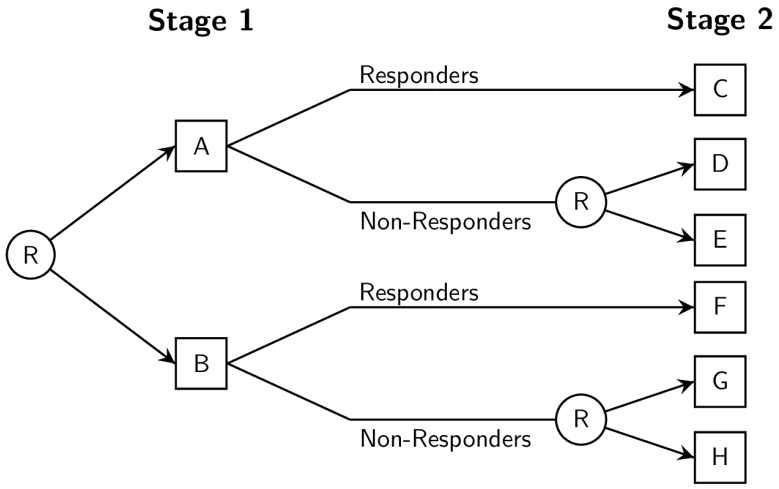


Why a SMART and not _____?

Not all research on adaptive interventions requires a SMART. We've seen some examples already.

When a SMART is an option, why might you choose to use it over something else?

Why a SMART and not multiple separate trials?



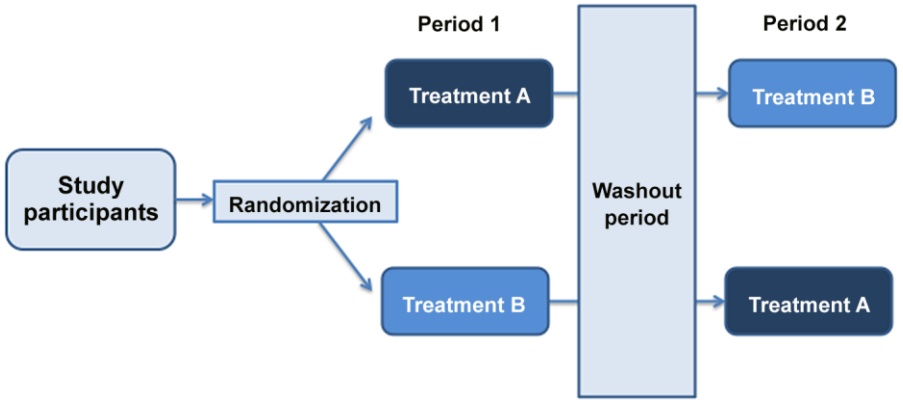
VS.

1. DELAYED EFFECTS
2. DROP-OUT
3. SELECTION EFFECTS
4. RICH DATA

Why a SMART and not a crossover trial?

In a **crossover trial**, participants start on one treatment then switch to another after a *washout period*.

The goal of a crossover trial is typically to evaluate the effects of standalone treatments – generally want to wash out any carryover effects.



Li, et al. (2015) *PLOS One*. https://doi.org/f8zws8

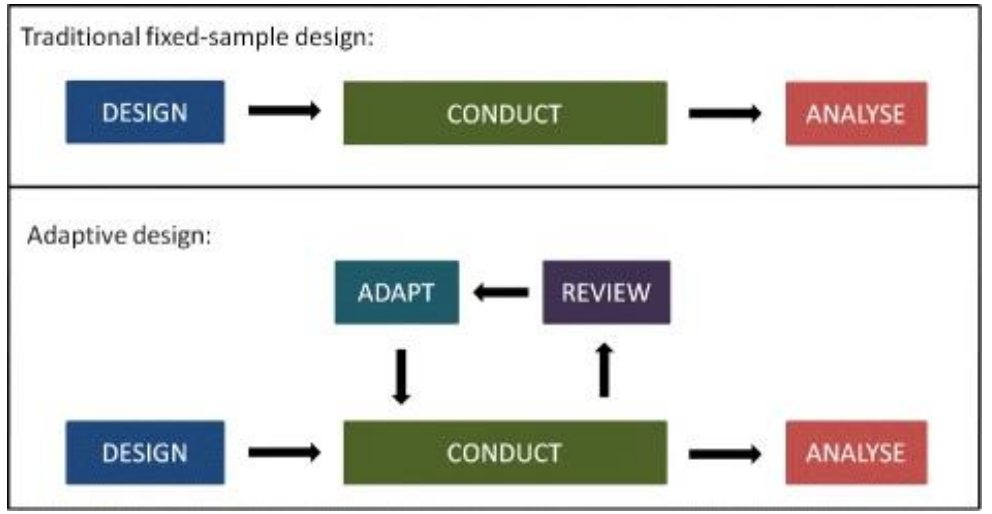
Why a SMART and not an adaptive trial?

An **adaptive trial** is a multistage study in which data collected throughout the trial is used to *modify features of the trial itself.*

- e.g., early stopping, dropping arms, modifying randomization probabilities, etc.

SMARTs are typically fixed designs: all participants move through every stage of the trial as it was initially designed.

In adaptive trials, the *trial* is adaptive. SMARTs are designed to address questions about *interventions* which are adaptive.



Pallmann, et al. (2018) *BMC Medicine*. https://doi.org/gc6jrz

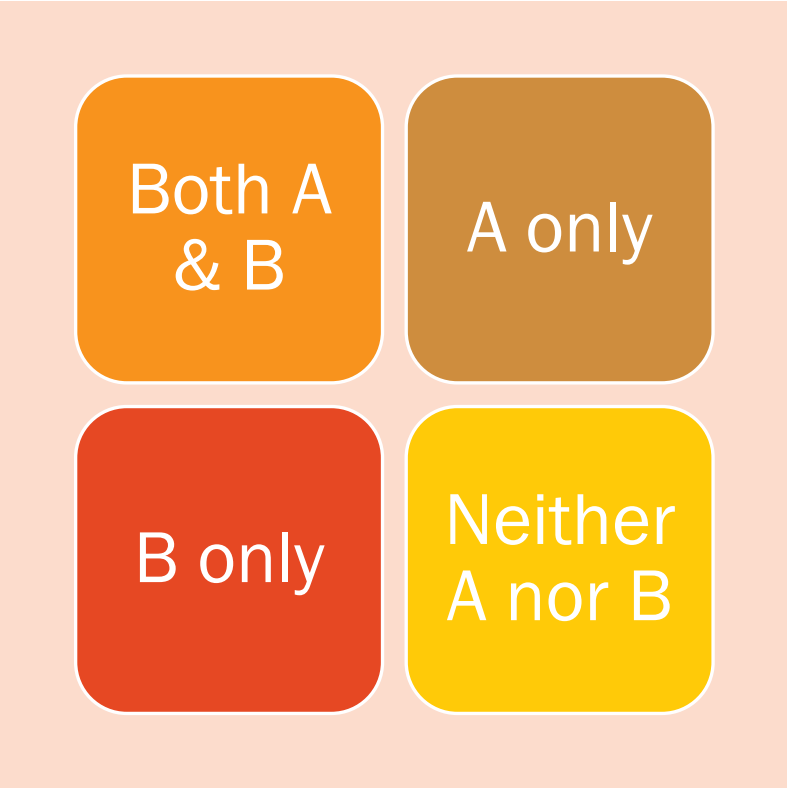
SEEWALD, N.J., ET AL. 2021. "SEQUENTIAL, MULTIPLE ASSIGNMENT, RANDOMIZED TRIALS (SMART)." IN PRINCIPLES AND PRACTICE OF CLINICAL TRIALS, EDITED BY STEVEN PIANTADOSI AND CURTIS L. MEINERT, 1–19. CHAM: SPRINGER INTERNATIONAL PUBLISHING. HTTPS://DOI.ORG/10.1007/978-3-319-52677-5_280-1.

Why a SMART and not a factorial trial?

In a factorial trial, two or more *factors* (each with 2+ *levels*) are crossed to create different experimental conditions.

SMARTs are conceptually similar to (fractional) factorial designs in which treatments are delivered *sequentially*.

- A *fractional factorial design* does not fully cross all levels of all factors



SEEWALD, N.J., ET AL. 2021. "SEQUENTIAL, MULTIPLE ASSIGNMENT, RANDOMIZED TRIALS (SMART)." IN PRINCIPLES AND PRACTICE OF CLINICAL TRIALS, EDITED BY STEVEN PIANTADOSI AND CURTIS L. MEINERT, 1–19. CHAM: SPRINGER INTERNATIONAL PUBLISHING. HTTPS://DOI.ORG/10.1007/978-3-319-52677-5_280-1.

Why a SMART and not a factorial trial?

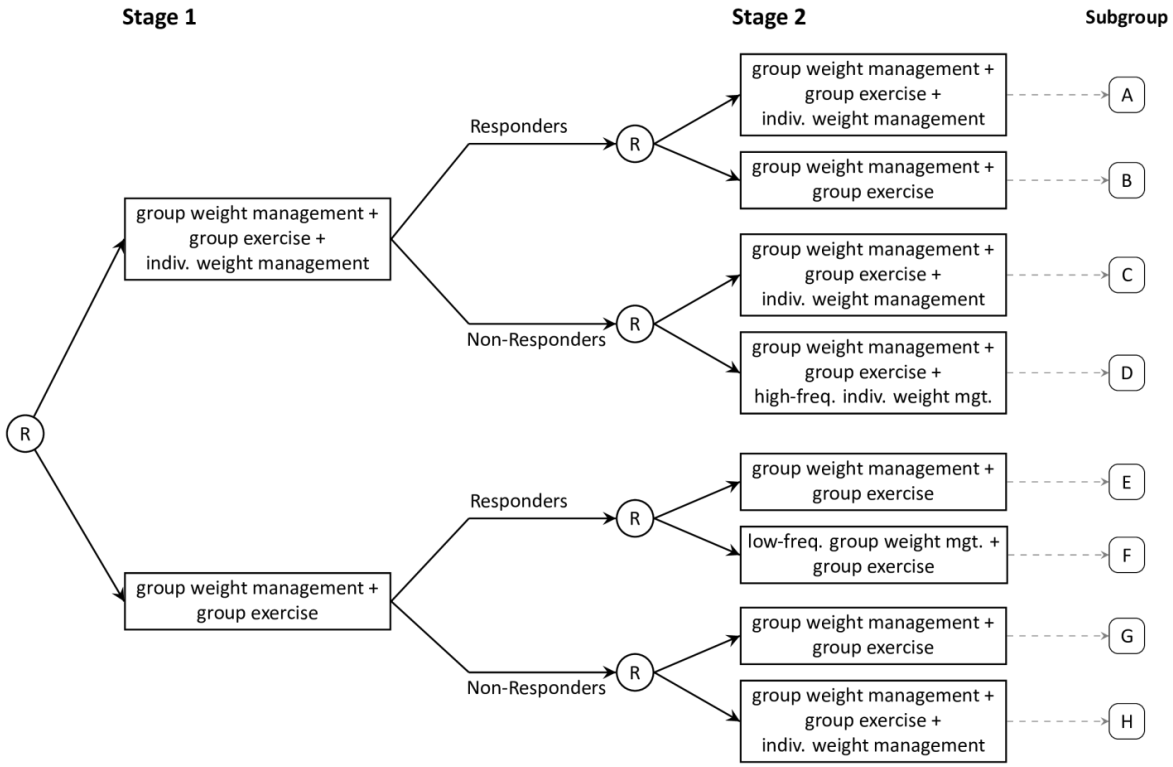
Our hypothetical SMART is similar to a (2 x 2 x 2) (fractional) factorial trial.

Factor 1: first-stage treatment options

Factor 2: second-stage tactic *for responders*

Factor 3: second stage tactic *for non-responders*

Factors 2 and 3 are restricted by the tailoring variable: a key difference from standard factorials!



SEEWALD, N.J., ET AL. 2021. "SEQUENTIAL, MULTIPLE ASSIGNMENT, RANDOMIZED TRIALS (SMART)." IN PRINCIPLES AND PRACTICE OF CLINICAL TRIALS, EDITED BY STEVEN PIANTADOSI AND CURTIS L. MEINERT, 1–19. CHAM: SPRINGER INTERNATIONAL PUBLISHING. HTTPS://DOI.ORG/10.1007/978-3-319-52677-5_280-1.

Agenda

Introduction (10 minutes)

Adaptive Interventions (40 minutes)

Questions and Discussion (10 minutes)

Sequential, Multiple-Assignment Randomized Trials (40 minutes)

Questions and Discussion (10 minutes)

Future Directions (10 minutes)

Agenda

Introduction (10 minutes)

Adaptive Interventions (40 minutes)

Questions and Discussion (10 minutes)

Sequential, Multiple-Assignment Randomized Trials (40 minutes)

Questions and Discussion (10 minutes)

Future Directions (10 minutes)

Methodological research is active and ongoing!

Recent developments:

- Methods for longitudinal outcomes measured over both stages of the SMART
  - Lu et al. (2016), Seewald et al. (2020), Seewald et al. (in progress)
- Non-inferiority and equivalence testing in SMARTs
  - Ghosh et al. (2020)
- Cluster-randomized SMARTs
  - Kilbourne et al. (2014), NeCamp et al. (2017), more to come from Almirall, Nahum-Shani, and collaborators.
- Causal mediation in adaptive interventions
  - Brincks et al. (in progress)

Get in touch!

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Resources and References

Sample size for comparing embedded adaptive interventions

- Continuous Outcomes
  - Oetting, A. I., et al. 2011. “Statistical Methodology for a SMART Design in the Development of Adaptive Treatment Strategies.” In *Causality and Psychopathology: Finding the Determinants of Disorders and Their Cures*, edited by P.E. Shrout, K.M. Keyes, and K. Ornstein, 179–205. New York: Oxford University Press.
  - Ogbagaber, S.B., J. Karp, and A.S. Wahed. 2016. “Design of Sequentially Randomized Trials for Testing Adaptive Treatment Strategies.” *Statistics in Medicine* 35 (6): 840–58. https://doi.org/10.1002/sim.6747.
- Continuous Longitudinal Outcomes
  - Seewald, N.J, K.M. Kidwell, I. Nahum-Shani, T. Wu, J.R. McKay, and D. Almirall. 2020. “Sample Size Considerations for Comparing Dynamic Treatment Regimens in a Sequential Multiple-Assignment Randomized Trial with a Continuous Longitudinal Outcome.” *Statistical Methods in Medical Research* 29 (7): 1891–1912. https://doi.org/10/gf85ss.
- Binary Outcomes
  - Kidwell, K.M., N.J. Seewald, Q. Tran, C. Kasari, and D. Almirall. 2018. “Design and Analysis Considerations for Comparing Dynamic Treatment Regimens with Binary Outcomes from Sequential Multiple Assignment Randomized Trials.” *Journal of Applied Statistics* 45 (9): 1628–51. https://doi.org/10.1080/02664763.2017.1386773.

Resources and References

Sample size for comparing embedded adaptive interventions

- Survival / Time-to-Event Outcomes
  - Feng, W., and A.S. Wahed. 2009. “Sample Size for Two-Stage Studies with Maintenance Therapy.” *Statistics in Medicine* 28 (15): 2028–41. https://doi.org/10.1002/sim.3593.
  - Li, Z., and S.A. Murphy. 2011. “Sample Size Formulae for Two-Stage Randomized Trials with Survival Outcomes.” *Biometrika* 98 (3): 503–18. https://doi.org/10.1093/biomet/asr019.
- Continuous Outcomes in a Cluster-Randomized SMART
  - NeCamp, T., A. Kilbourne, and D. Almirall. 2017. “Comparing Cluster-Level Dynamic Treatment Regimens Using Sequential, Multiple Assignment, Randomized Trials: Regression Estimation and Sample Size Considerations.” *Statistical Methods in Medical Research* 26 (4): 1572–89. https://doi.org/10.1177/0962280217708654.
- Find the Best Embedded Adaptive Intervention
  - Artman, W.J., I. Nahum-Shani, T. Wu, J.R. Mckay, and A. Ertefaie. 2018. “Power Analysis in a SMART Design: Sample Size Estimation for Determining the Best Embedded Dynamic Treatment Regime.” *Biostatistics*. https://doi.org/10/ggth75.

Resources and References

In-depth book on adaptive interventions and SMARTs

- Kosorok, M.R., and E.E.M. Moodie, eds. 2015. Adaptive Treatment Strategies in Practice: Planning Trials and Analyzing Data for Personalized Medicine. Philadelphia, PA: Society for Industrial and Applied Mathematics. https://doi.org/10.1137/1.9781611974188.

Overview of a variety of SMARTs in the field

- Lei, H., et al. "A 'SMART' Design for Building Individualized Treatment Sequences." Annual Review of Clinical Psychology 8, no. 1 (2012): 21–48. https://doi.org/10.1146/annurev-clinpsy-032511-143152.

Clear explanations of primary aim analysis in SMARTs

- Nahum-Shani, I., et al. 2012. "Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions." *Psychological Methods* 17 (4): 457–77. https://doi.org/10.1037/a0029372.

Resources and References

Analysis of Longitudinal Outcomes in SMARTs

- Lu, X., Nahum-Shani, I., Kasari, C., Lynch, K. G., Oslin, D. W., Pelham, W. E., Fabiano, G., & Almirall, D. (2016). Comparing dynamic treatment regimes using repeated-measures outcomes: Modeling considerations in SMART studies. *Statistics in Medicine*, *35*(10), 1595–1615. https://doi.org/10/gg2gxc

Noninferiority and Equivalence Testing in SMARTs

- Ghosh, P., Nahum-Shani, I., Spring, B., & Chakraborty, B. (2020). Noninferiority and equivalence tests in sequential, multiple assignment, randomized trials (SMARTs). *Psychological Methods*, *25*(2), 182–205. https://doi.org/10/ggtmgv

Example of Cluster-Randomized SMART

- Kilbourne, A. M., et al. (2014). Protocol: Adaptive Implementation of Effective Programs Trial (ADEPT): cluster randomized SMART trial comparing a standard versus enhanced implementation strategy to improve outcomes of a mood disorders program. *Implementation Science*, *9*(1), 132. https://doi.org/10/f6q9fc