Building Effective Adaptive Interventions in Mental Health Services Research

Nicholas J. Seewald, Ph.D.
Johns Hopkins University

Section A: Adaptive Interventions

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.

Five 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.

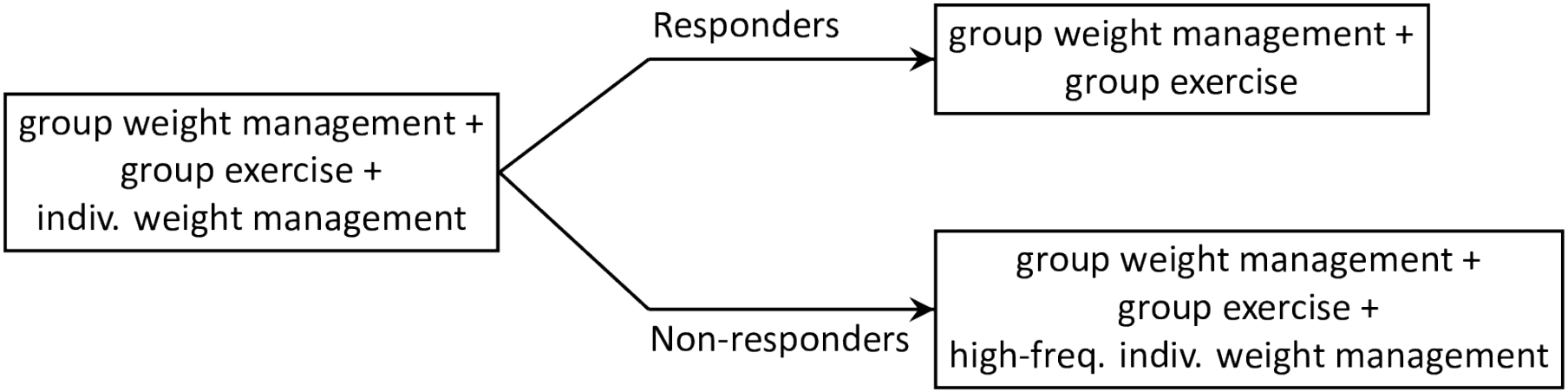
- **ACHIEVE** is a lifestyle intervention delivered in psychiatric rehabilitation outpatient programs which consists of *group weight-management sessions*, *individual weight-management sessions*, and *group exercise sessions.*
  - *S*hown in a clinical trial to significantly reduce weight over 18 months

- 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



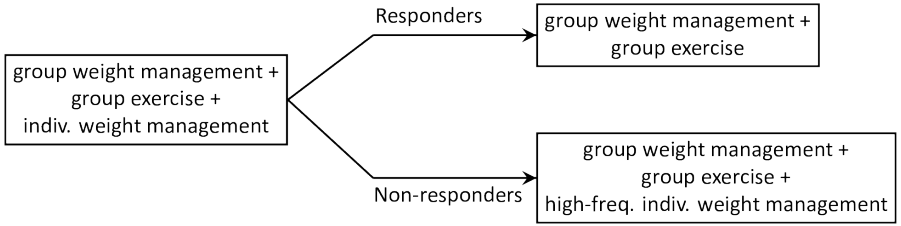
- An individual is a *responder* if they have lost 5+ pounds in the first 6 months, and a *non-responder* otherwise.

This is a hypothetical example.

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

- Adaptive interventions consist of

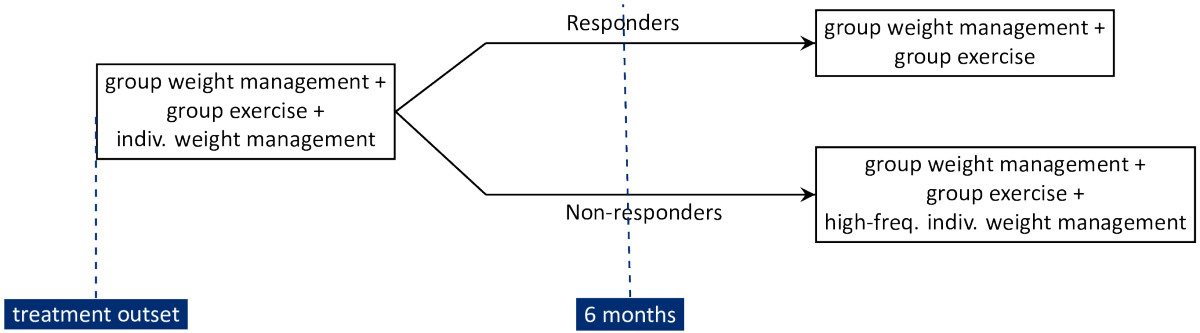
1. Decision points
2. Tailoring variable(s)
3. Intervention options
4. Decision rule(s)
5. Proximal and distal outcomes



This is a hypothetical example.

Hypothetical example adaptive intervention: Decision Points

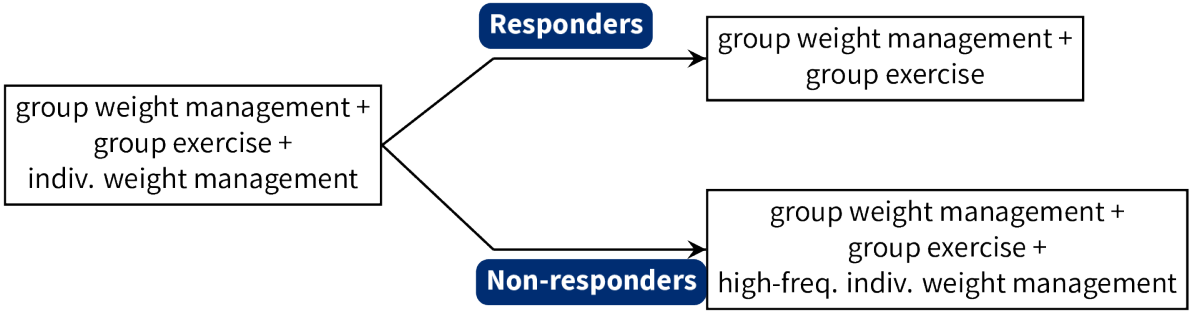
- A **decision point** is a time at which the intervention might be adapted to the individual.
- **Decision Point 1:** Treatment outset – we decide how to initiate treatment
- **Decision Point 2:** Month 6 – we decide how to modify treatment



This is a hypothetical example.

Hypothetical example adaptive intervention: Tailoring Variables

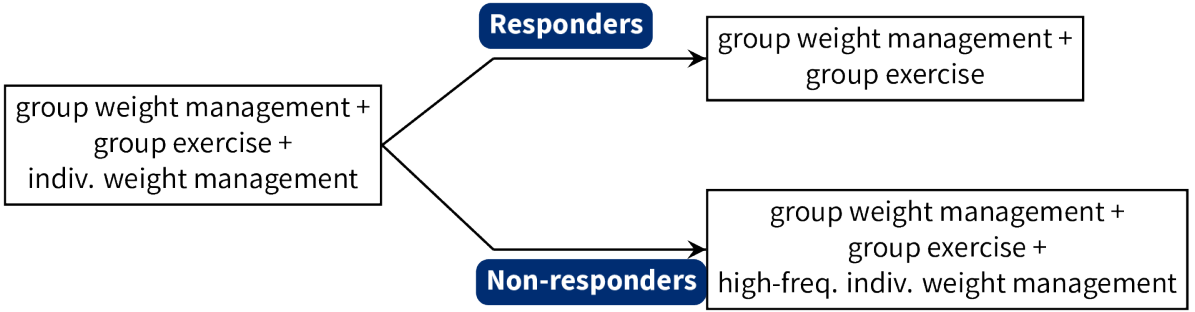
- A **tailoring variable** is used to individualize treatment at each decision point.
  - "Static": age, baseline risk, etc.
  - "Dynamic": adherence to treatment, disease severity, etc.
- The adaptive intervention recommends an intervention option for each level of the tailoring variable.



This is a hypothetical example.

Hypothetical example adaptive intervention: Tailoring Variables

- 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*



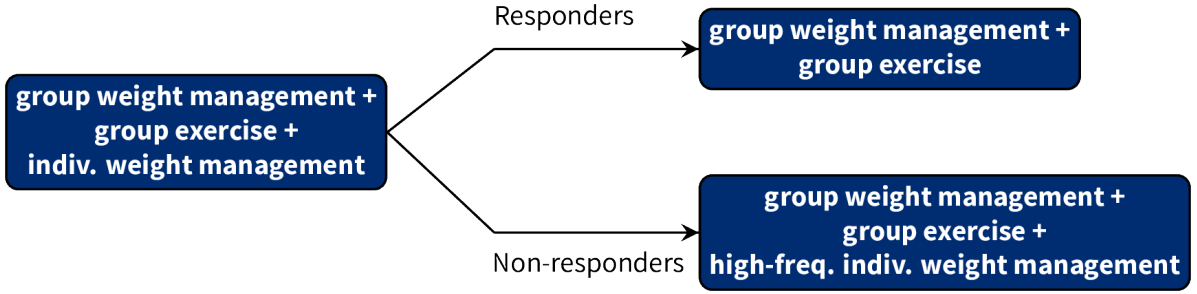
This is a hypothetical example.

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

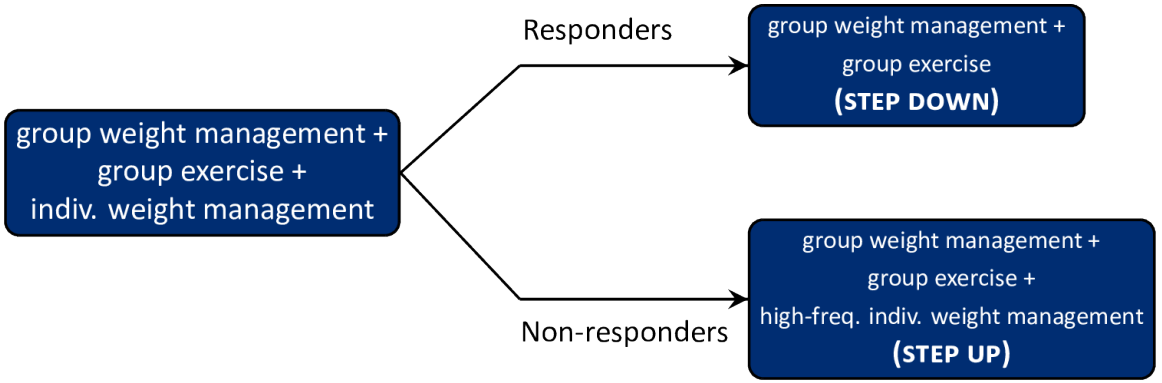
- **Intervention options** at each decision point might be aspects of treatment: type, intensity, dose, delivery method, timing, etc.
- Here, intervention options are different combinations/frequencies of *individual weight management*, *group weight management*, and *group exercise*



This is a hypothetical example.

Hypothetical example adaptive intervention: Intervention Options

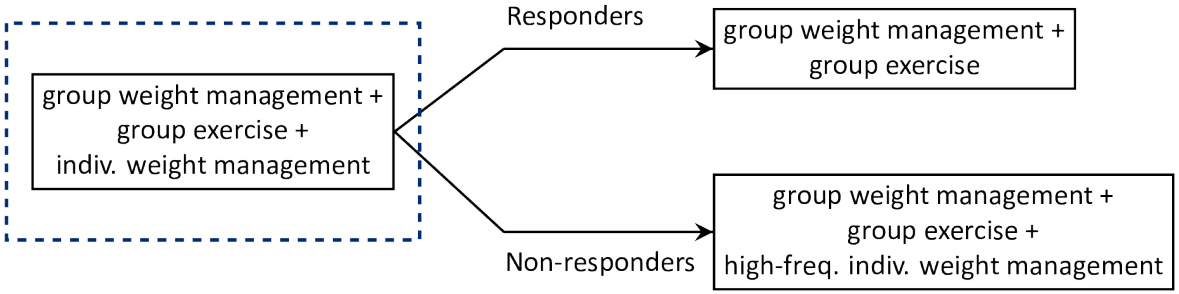
- In later stages of the adaptive intervention, these might be *adaptation strategies*
  - e.g., “augment”, “intensify”, “stay the course”



This is a hypothetical example.

Hypothetical example adaptive intervention: Decision Rules

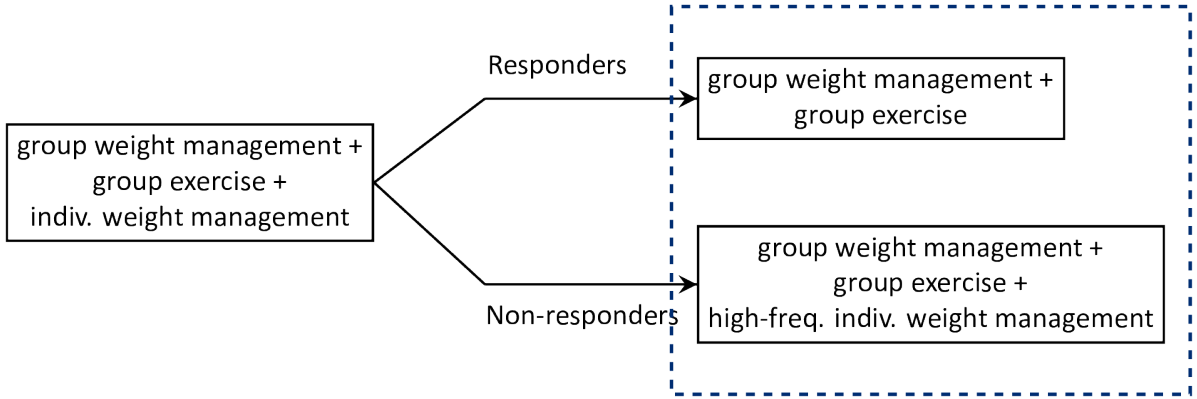
- A **decision rule** recommends an *intervention option* for individuals at each decision point, possibly based on prior information (i.e., a tailoring variable)



This is a hypothetical example.

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)



This is a hypothetical example.

Hypothetical example adaptive intervention: Proximal & 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*

This is a hypothetical example.

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?

In another section, we'll discuss an experimental design which can help answer these and more questions about the development of an adaptive intervention.

This is a hypothetical example.

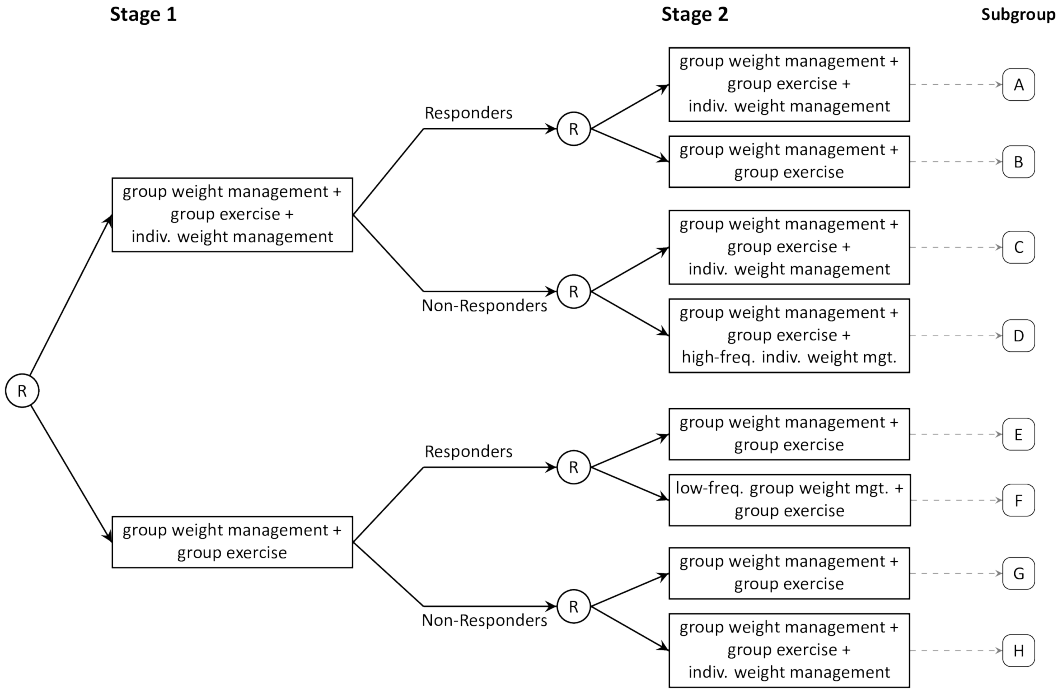
Section B: Sequential, Multiple-Assignment Randomized Trials (SMARTs)

Sequential, Multiple-Assignment Randomized Trials (SMARTs)

- A **sequential, multiple-assignment randomized trial (SMART)** is *one type* of randomized trial design that can be used to answer questions at multiple stages of the development of a high-quality adaptive intervention.

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

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



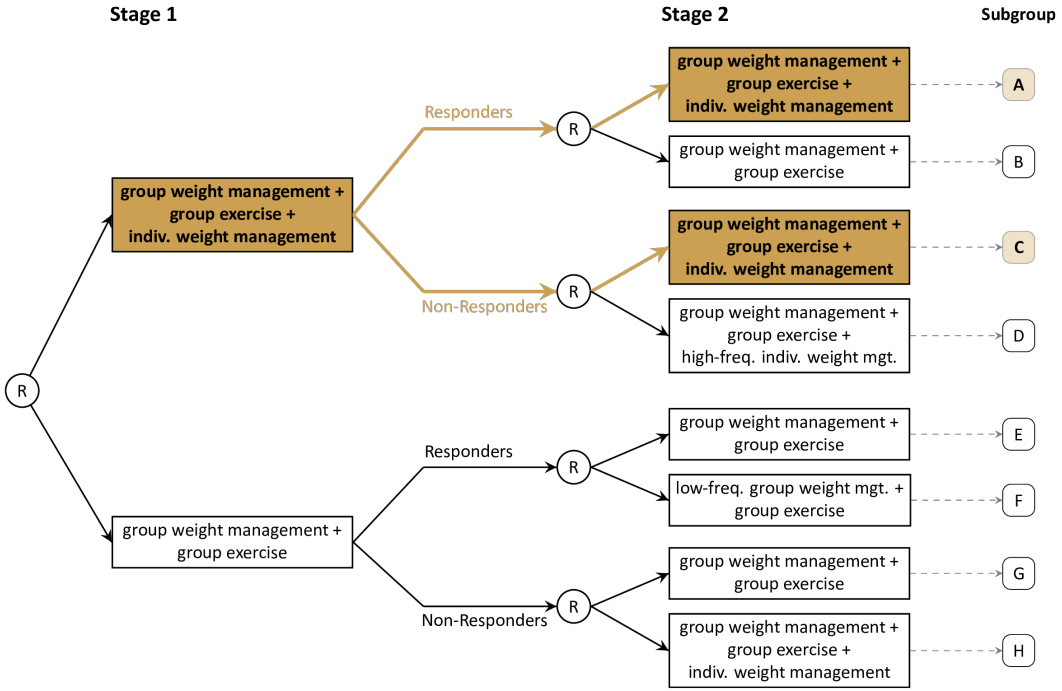
This is a hypothetical example.

How do SMARTs inform the development of adaptive interventions?

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

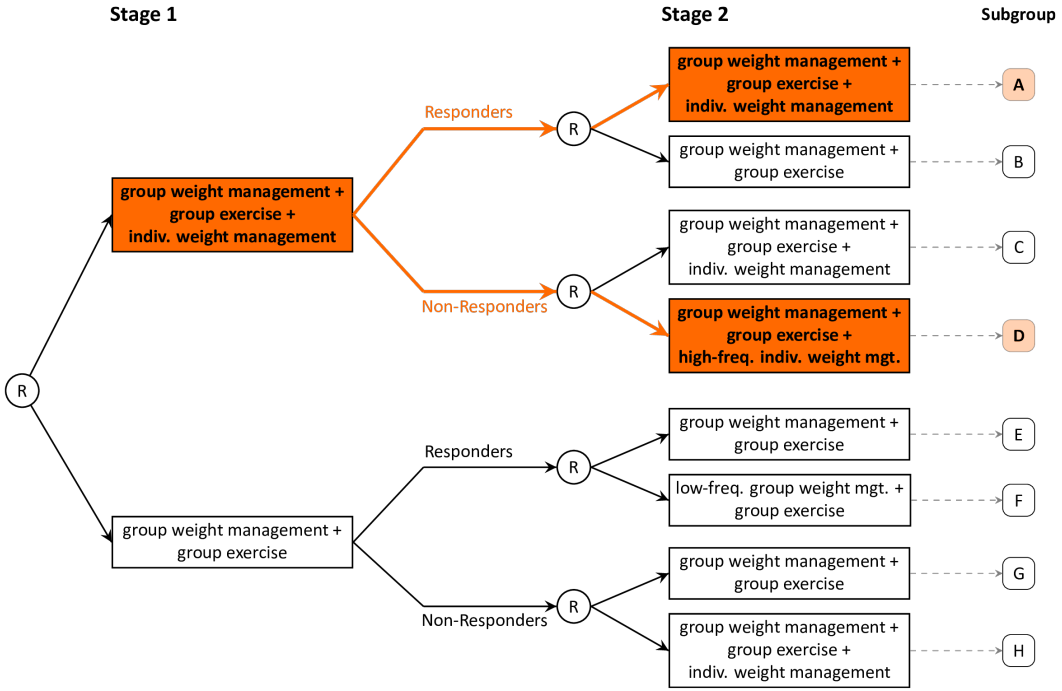
- In our example,
  - First randomization seeks to answer a question about whether individual weight management sessions are necessary up-front
  - Second randomization in *responders* investigates whether first-stage treatment should be continued or stepped *down*
  - Second randomization in *non-responders* investigates whether first-stage treatment should be continued or stepped *up*

8 AIs “embedded” in this SMART



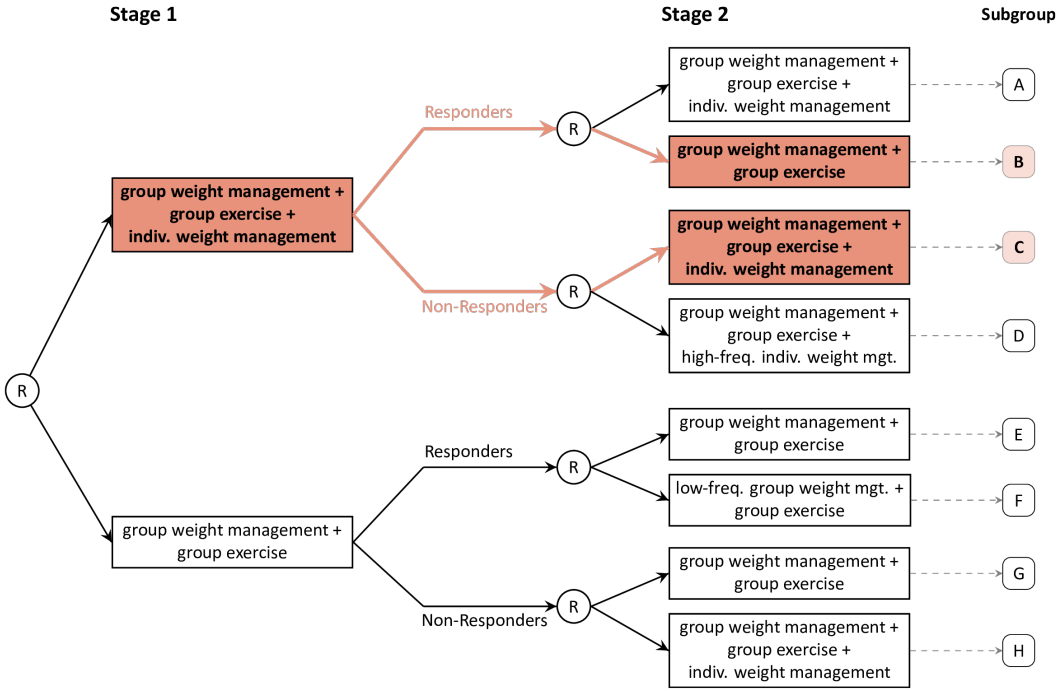
This is a hypothetical example.

8 AIs “embedded” in this SMART



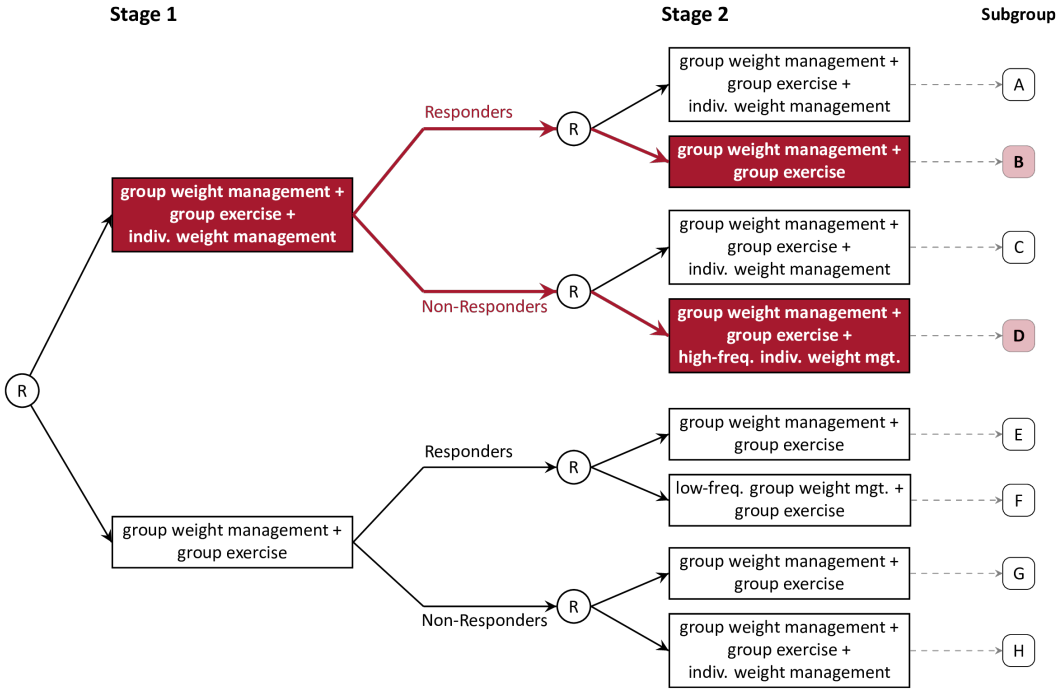
This is a hypothetical example.

8 AIs “embedded” in this SMART



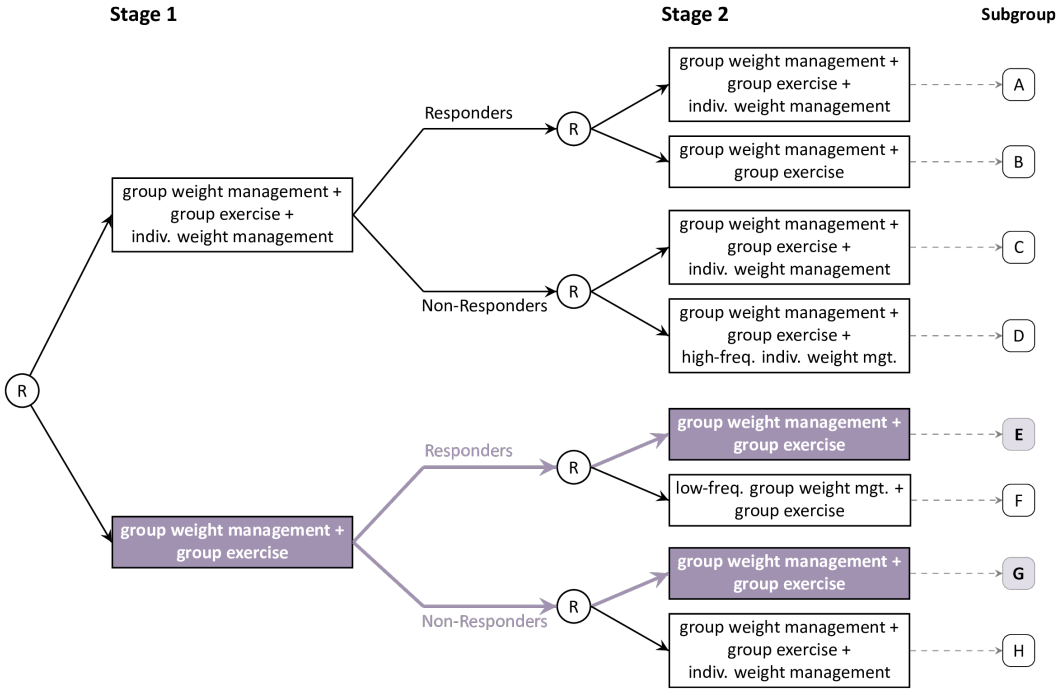
This is a hypothetical example.

8 AIs “embedded” in this SMART



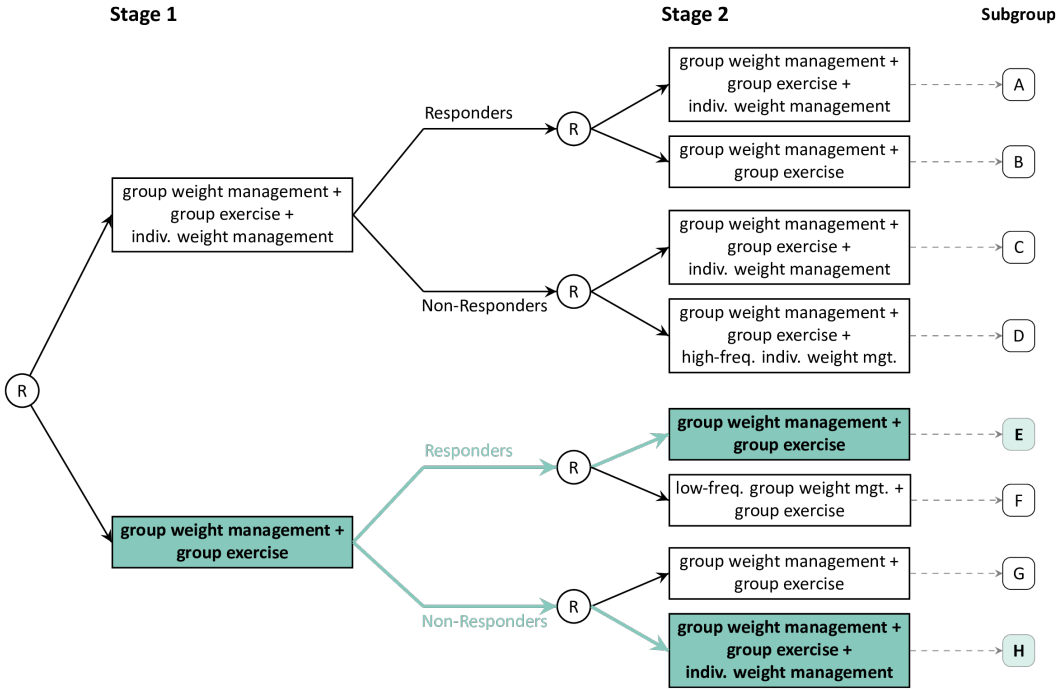
This is a hypothetical example.

8 AIs “embedded” in this SMART



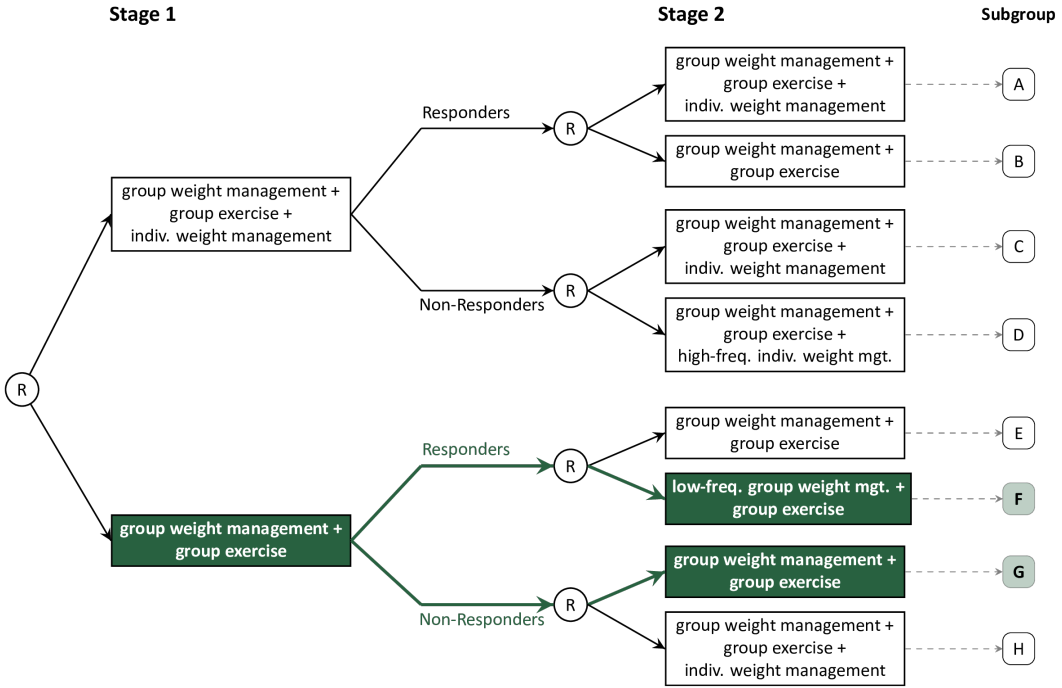
This is a hypothetical example.

8 AIs “embedded” in this SMART



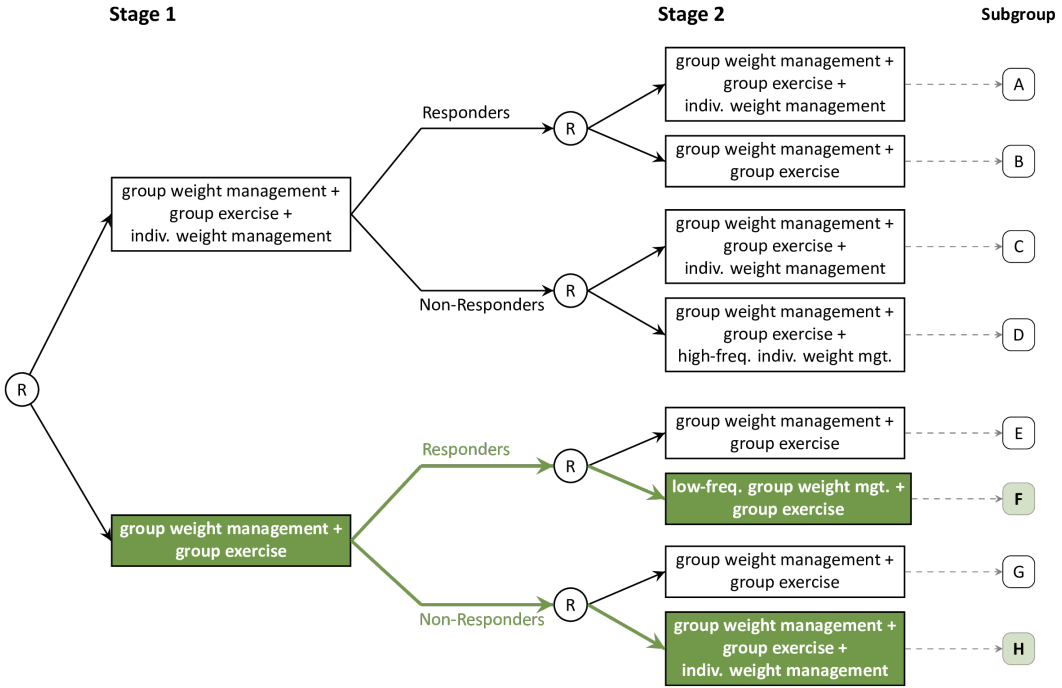
This is a hypothetical example.

8 AIs “embedded” in this SMART



This is a hypothetical example.

8 AIs “embedded” in this SMART



This is a hypothetical example.

Do I need a SMART?

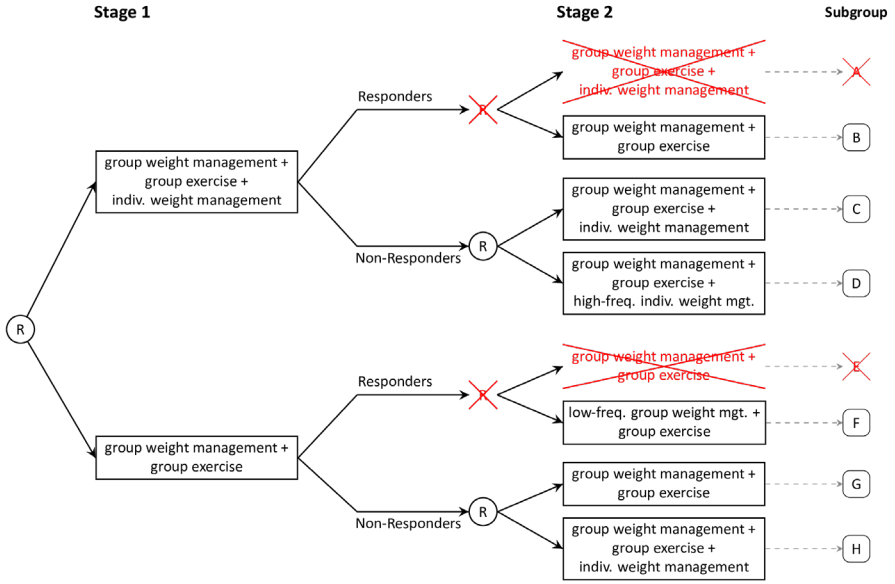
- SMARTs are designed to answer questions about the development of high-quality adaptive interventions.

- 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 I need a SMART?

What if we know what to do for responders?

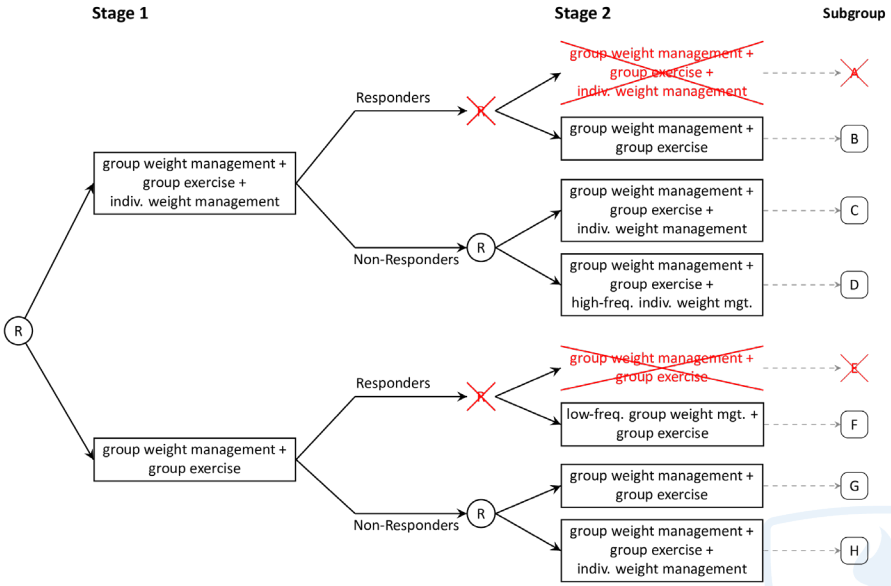


This is a hypothetical example.

Do I need a SMART?

What if we know what to do for responders?

- There are still questions about multiple stages of the development of an adaptive intervention
  - What should we do first?
  - What should we do for non-responders?

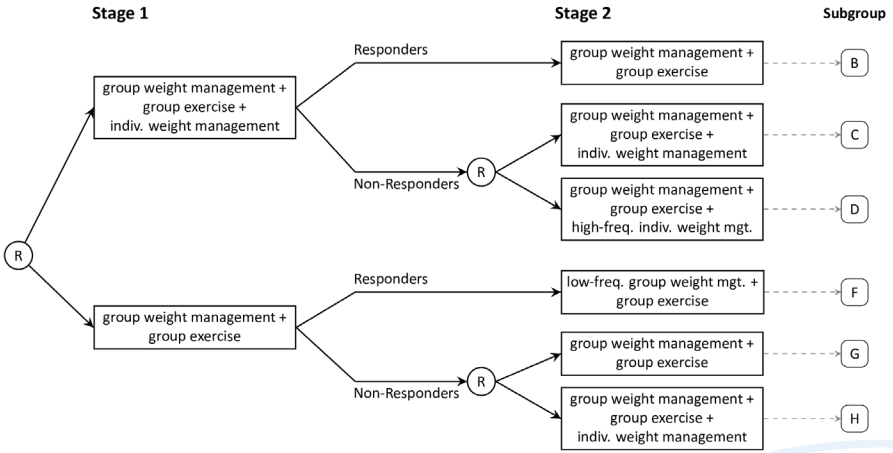


This is a hypothetical example.

Do I need a SMART?

What if we know what to do for responders?

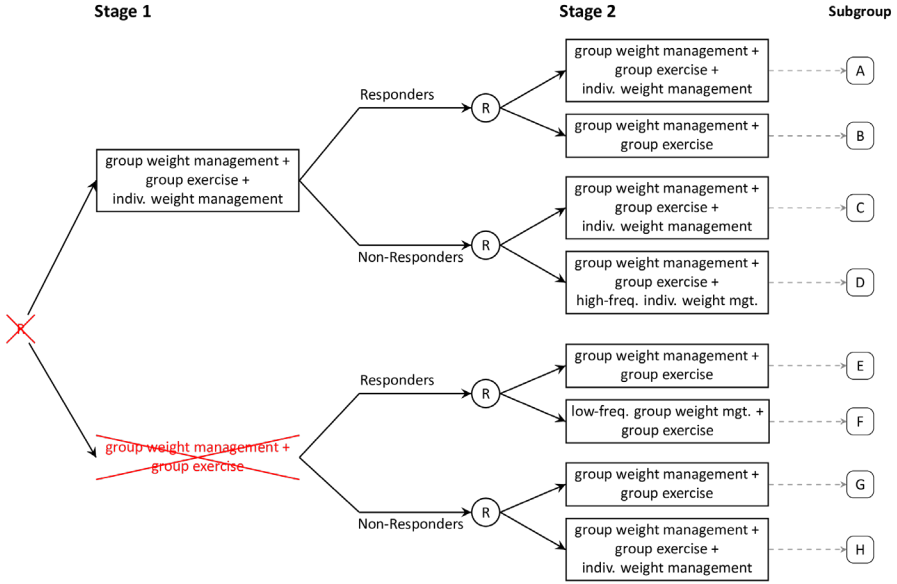
- There are still questions about multiple stages of the development of an adaptive intervention
  - What should we do first?
  - What should we do for non-responders?
- A SMART is appropriate here
  - *Some* participants are randomized twice



This is a hypothetical example.

Do I need a SMART?

What if we know what to do initially?

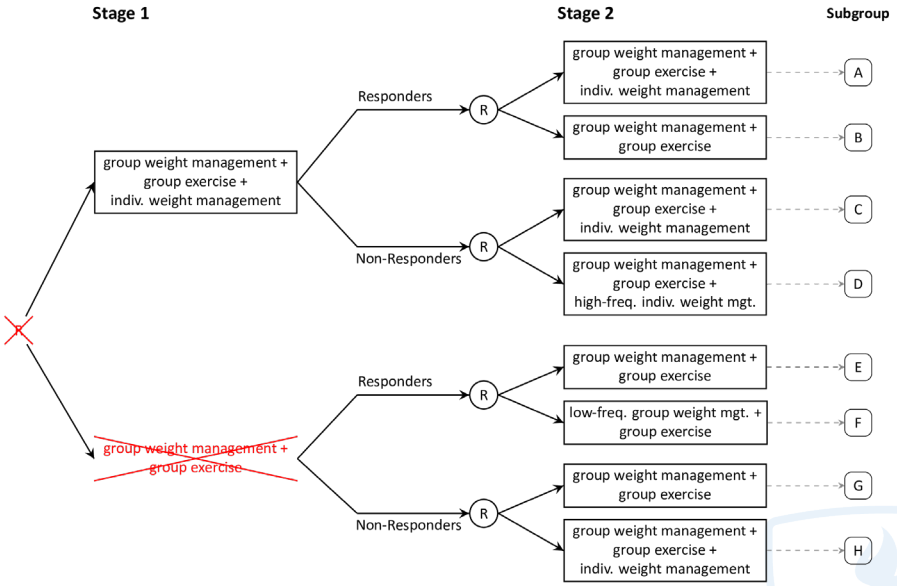


This is a hypothetical example.

Do I need a SMART?

What if we 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.

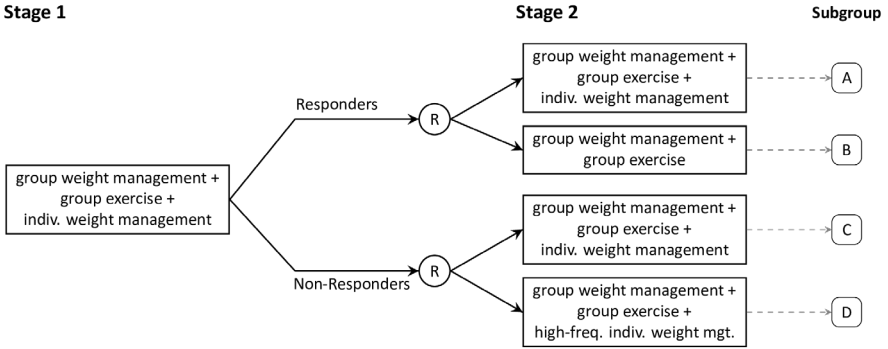


This is a hypothetical example.

Do I need a SMART?

What if we know what to do initially?

- We might instead run this trial with a run-in period on the initial intervention.
- This is **not** a SMART: all participants are randomized exactly once.



This is a hypothetical example.

Do I 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.

Recap: What do we know so far?

- So far in this training, 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

In another section, we'll discuss some principles which guide the design of a high-quality SMART.

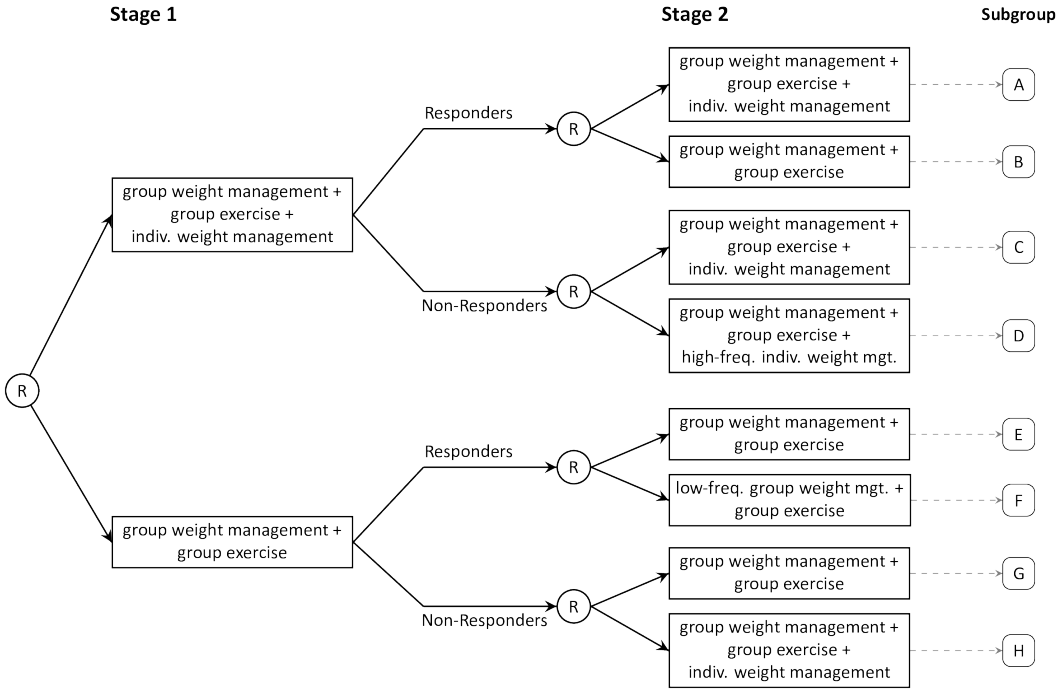
Section C: Design and Analysis Considerations for SMARTs

Sequential, Multiple-Assignment Randomized Trials (SMARTs)

- A **sequential, multiple-assignment randomized trial (SMART)** is *one type* of randomized trial design that can be used to answer questions at multiple stages of the development of a high-quality adaptive intervention.

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

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



This is a hypothetical example.

A small misconception

- Sometimes, SMARTs are referred to as “adaptive” trials. This is not necessarily correct.
  - An adaptive trial is a multistage study in which data collected throughout the trial is used to modify features of the trial itself
  - 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.

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.

Tailoring Variables

- Tailoring variables are often used to **restrict randomization** (recommend different intervention options to different subgroups of participants)
- Tailoring variables should be **well-justified**: remember, they're part of the embedded adaptive interventions
  - Should be relatively easy to measure *in situ*
  - Assignment should be systematic
- Secondary data analysis (Q-learning) can be used to discover "candidate" tailoring variables for future work or more deeply tailored adaptive interventions

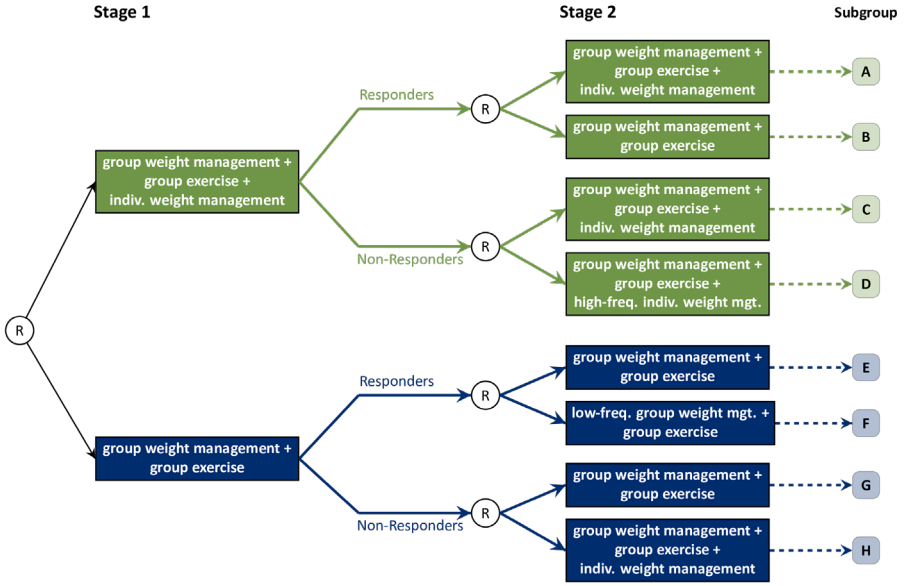
Nahum-Shani, I., et al. 2012. "Q-Learning: A Data Analysis Method for Constructing Adaptive Interventions." *Psychological Methods* 17 (4): 478–94. https://doi.org/10.1037/a0029373.

Primary & Secondary Aims

- Focus on a few scientific aims about developing a high-quality adaptive intervention.
- **Primary aim** informs sample size, commonly a comparison of groups of experimental conditions
  - Should be related to scientific questions about adaptive interventions
- **Secondary aims** can leverage rich data on treatment sequences to further inform more deeply-tailored adaptive interventions

Common Primary Aims for SMARTs

Compare initial intervention options in the context of an adaptive intervention



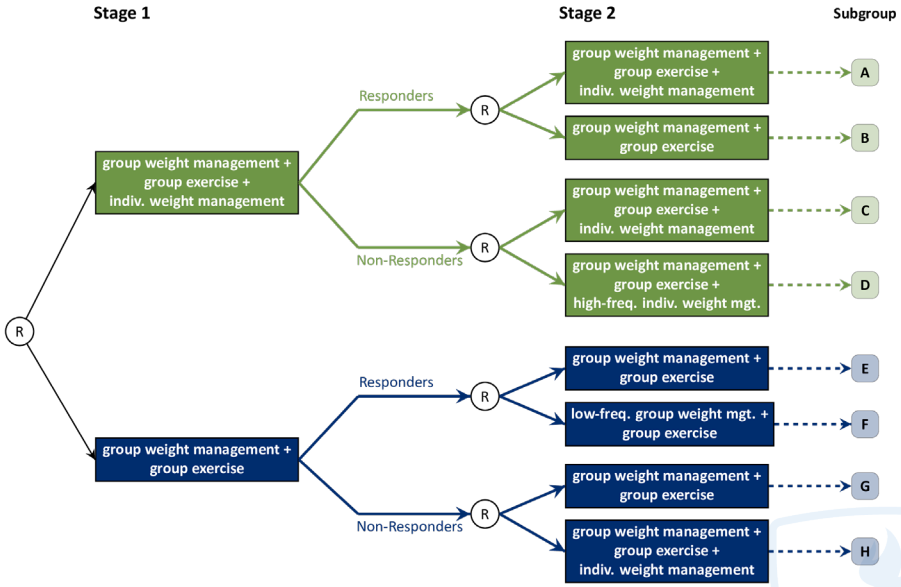
This is a hypothetical example.

Common Primary Aims for SMARTs

Compare initial intervention options in the context of an adaptive intervention

- 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.

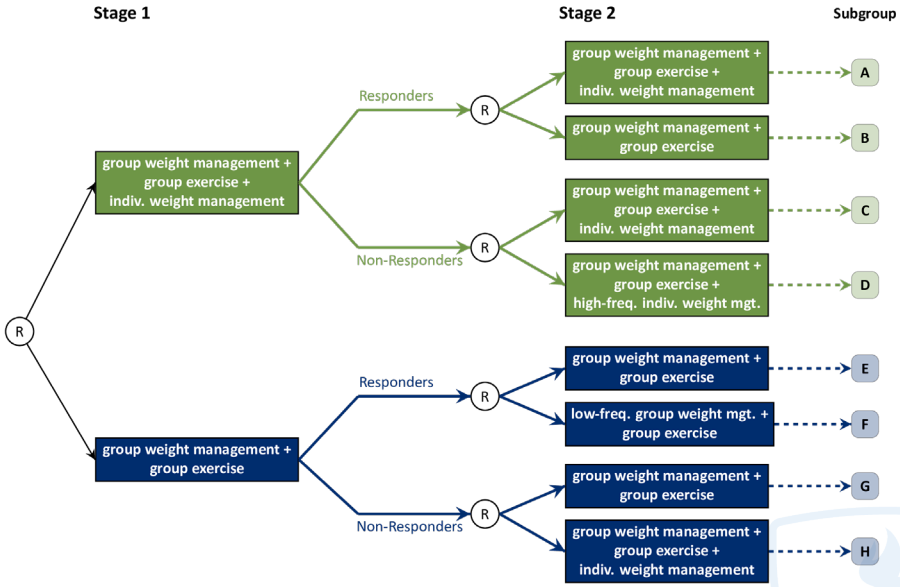


This is a hypothetical example.

Common Primary Aims for SMARTs

Compare initial intervention options in the context of an adaptive intervention

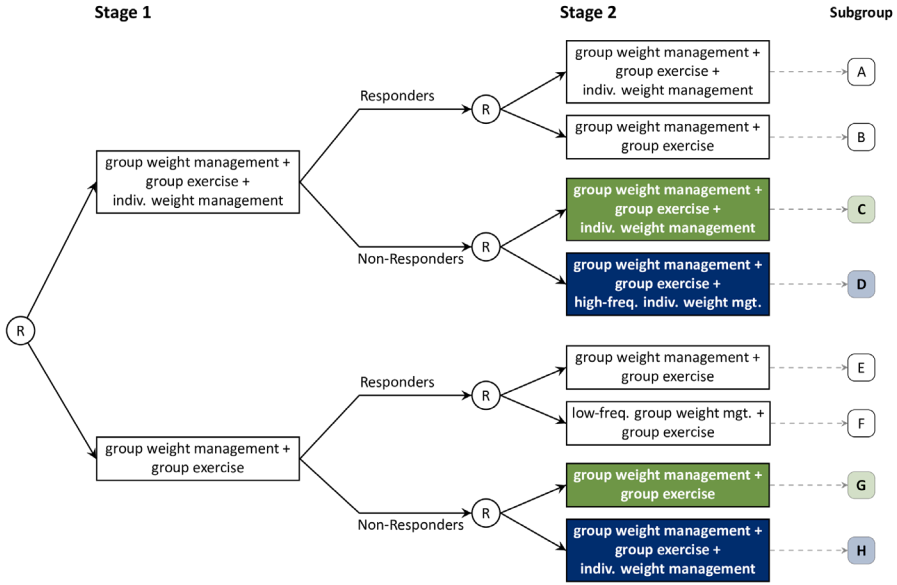
- Analysis is a comparison of subgroups A, B, C, D vs. subgroups E, F, G, H.
  - A two-group comparison!
  - Can use standard methods
- Sample size requirements are the same as for a two-arm randomized trial.



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.

Common Primary Aims for SMARTs

Compare second-stage intervention options among (non-)responders

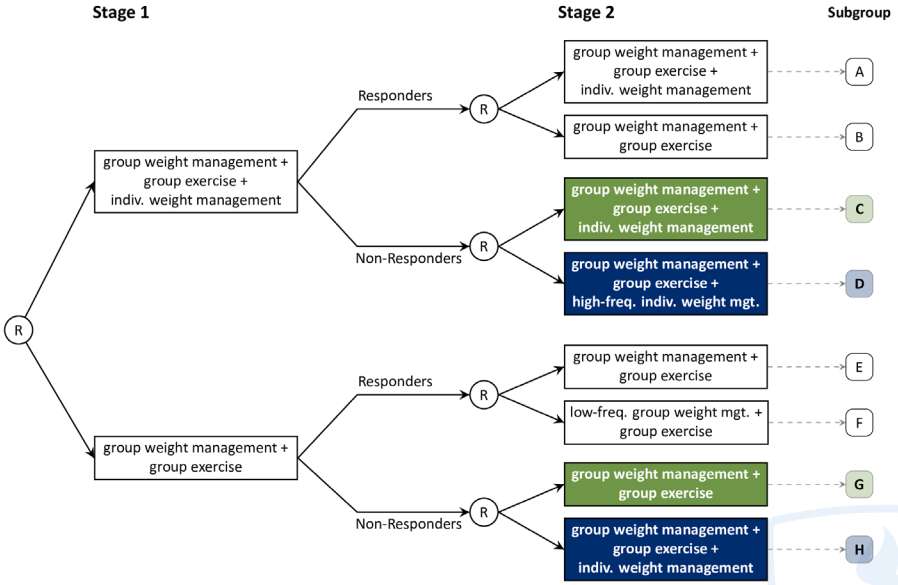


Common Primary Aims for SMARTs

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."

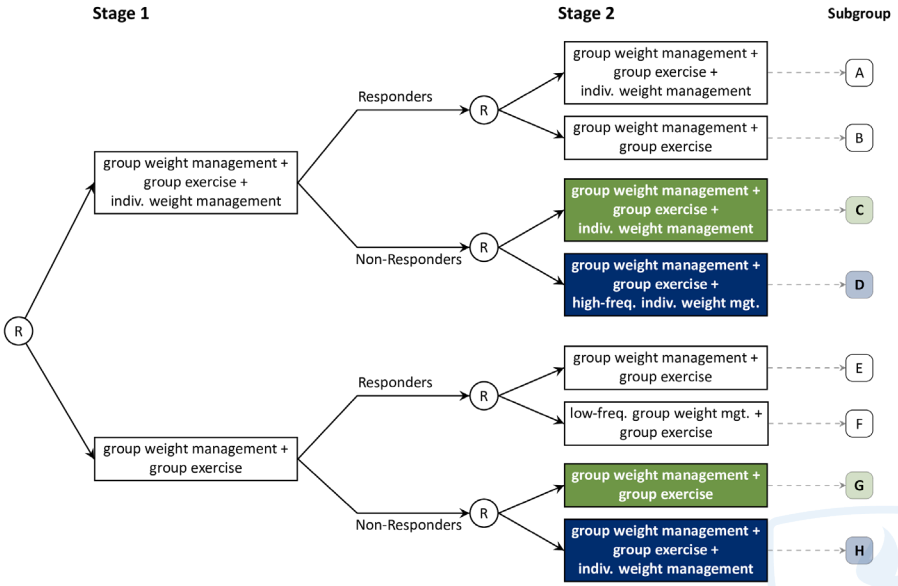
- Notice that the hypothesis is *in the context of adaptive interventions:* it "averages over" past treatment.



Common Primary Aims for SMARTs

Compare second-stage intervention options among (non-)responders

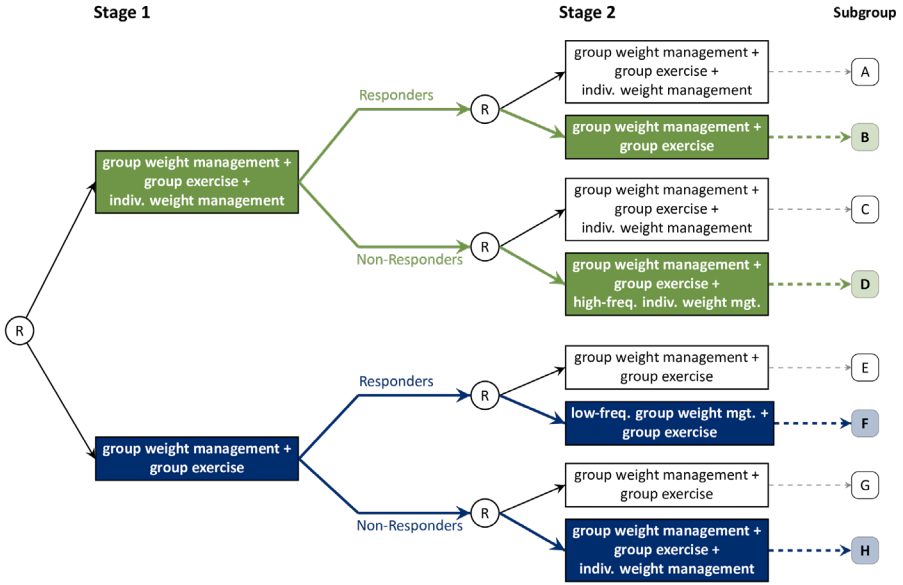
- Analysis is a comparison of subgroups C & G vs. subgroups D & H.
  - A two-group comparison among non-responders!
  - Can use standard methods
- Sample size requirements are the same as for a two-arm randomized trial, upweighted by non-response rate



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.

Common Primary Aims for SMARTs

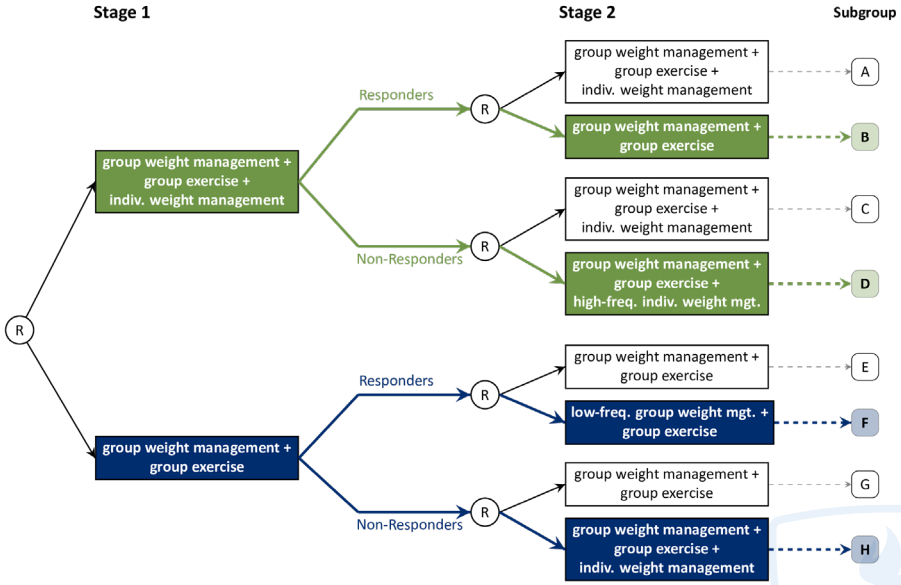
Compare two embedded adaptive interventions



Common Primary Aims for SMARTs

Compare two embedded adaptive interventions

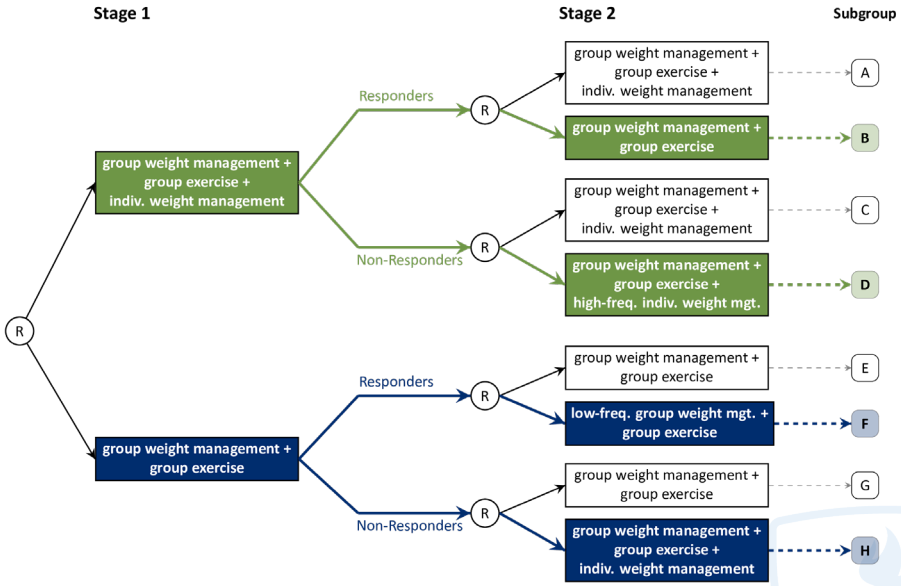
- Hypothetical hypothesis:
  "Individuals who receive an adaptive weight-loss intervention which begins with all three components, removes individual weight management sessions for responders and increases their intensity for non-responders will lose more weight at 18 months, on average, than those who receive an adaptive weight loss intervention which initially recommends only group components, then reduces frequency of group weight management sessions for responders and adds individual weight management sessions for non-responders."



Common Primary Aims for SMARTs

Compare two embedded adaptive interventions

- Analysis is slightly more complicated than previous example aims, but still very tractable (weighted regression).
- Sample size formulae are available for a variety of outcome types.

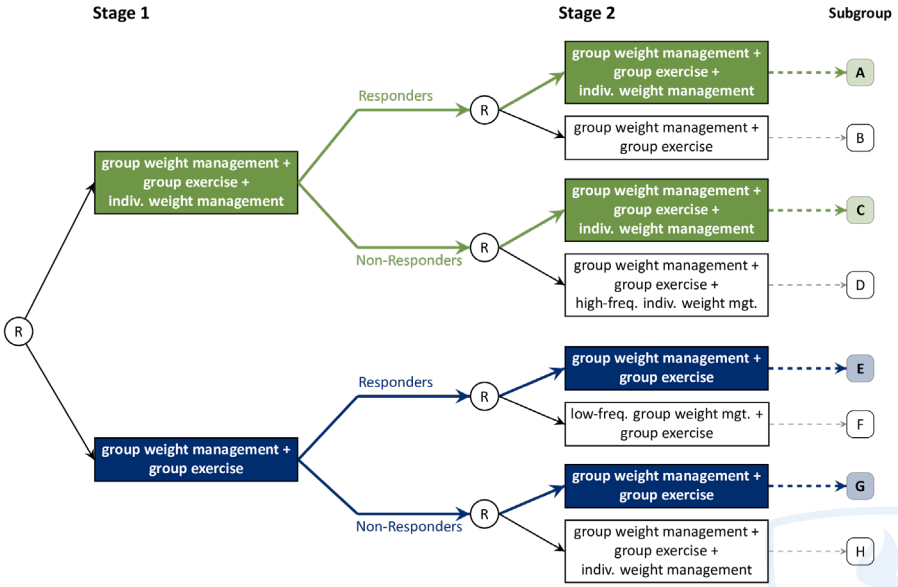


Nahum-Shani, I., et al. 2012. "Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions." *Psychological Methods* 17 (4): 457–77. https://doi.org/10.1037/a0029372.

Common Primary Aims for SMARTs

Compare two embedded adaptive interventions

- Notice that the highlighted adaptive interventions are not adaptive at all!
  - Responders and non-responders both continue the initial treatment: there is *no adaptation*!
- This SMART has an embedded RCT in it!
  - This is not necessary, but it is possible

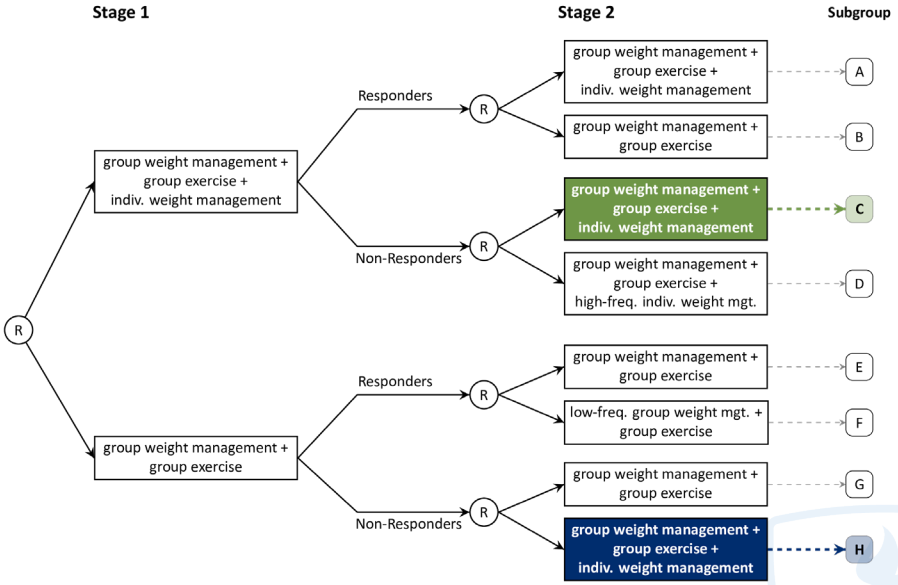


- Jones, H.E., et al. 2011. "Reinforcement-Based Treatment Improves the Maternal Treatment and Neonatal Outcomes of Pregnant Patients Enrolled in Comprehensive Care Treatment." *The American Journal on Addictions* 20 (3): 196–204. https://doi.org/10.1111/j.1521-0391.2011.00119.x.
- ClinicalTrials.gov Identifier NCT01177982

Questionable Primary Aims for SMARTs

Comparison of individual subgroups / experimental conditions

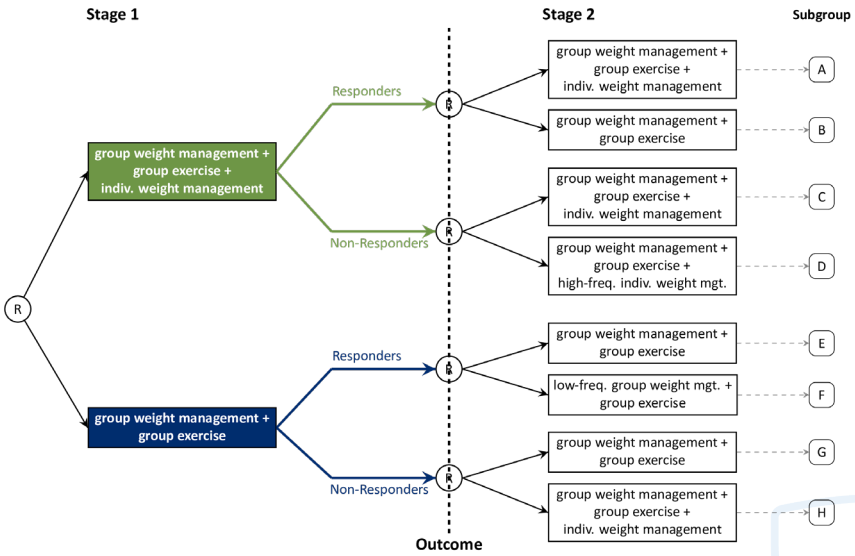
- Adaptive interventions recommend treatments for every level of the tailoring variable.
- This is not a question about adaptive interventions and is not strong motivation for a SMART.



Questionable Primary Aims for SMARTs

Comparison of response rates between first-stage intervention options

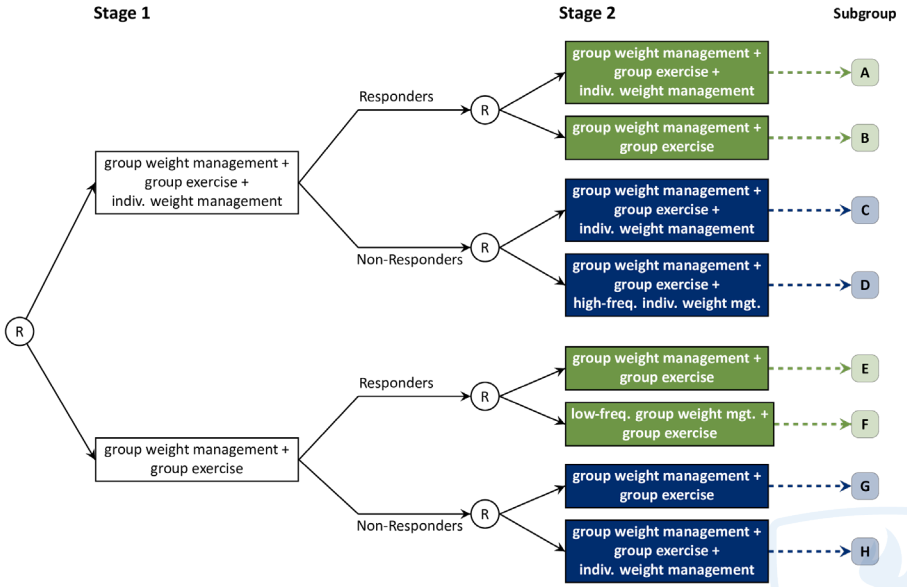
- Not really about adaptive interventions: ignores stage-2 treatment
- Maybe an interesting secondary analysis, but is not strong motivation for a SMART.



Questionable Primary Aims for SMARTs

Comparison of responders vs. 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.



Recap

- SMARTs are experimental designs which are used to address questions at multiple stages of the development of adaptive interventions
- Ultimately, the guiding principle of designing a SMART is “keep it simple”
- Primary aims of a SMART should be focused on developing adaptive interventions
- Sample size and analytic considerations for primary aims can often leverage familiar tools, and more advanced methods are available for more complex questions.