Presented by

Daniel Almirall, PhD

Pilot Randomized Trials in the Context of Adaptive Interventions

Including Pilot SMARTs

Module 7 45 min

Outline

What is a pilot trial? (what is it not?)

Situating pilot trials as Preparation for Success and your Place in the Process

Tips: What to do in a Pilot SMART?

Sample Size for Pilot SMARTs

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For brevity, "Pilot Trial" is used in place of "Pilot Randomized Trial"

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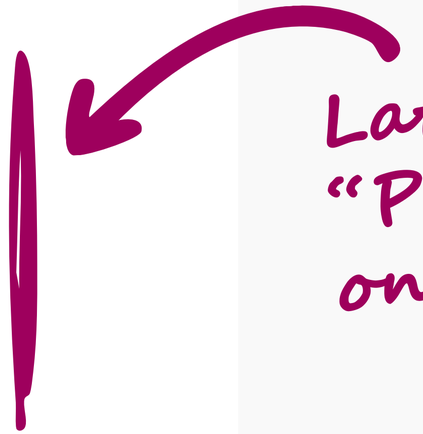
Tips: What to do in a Pilot SMART?

Sample Size for Pilot SMARTs



Later, I focus on a "Pilot SMART" which is one type of "Pilot Trial"

A Pilot Trial is

A small-scale randomized trial that is explicitly designed to prepare for a successful, full-scale randomized trial.

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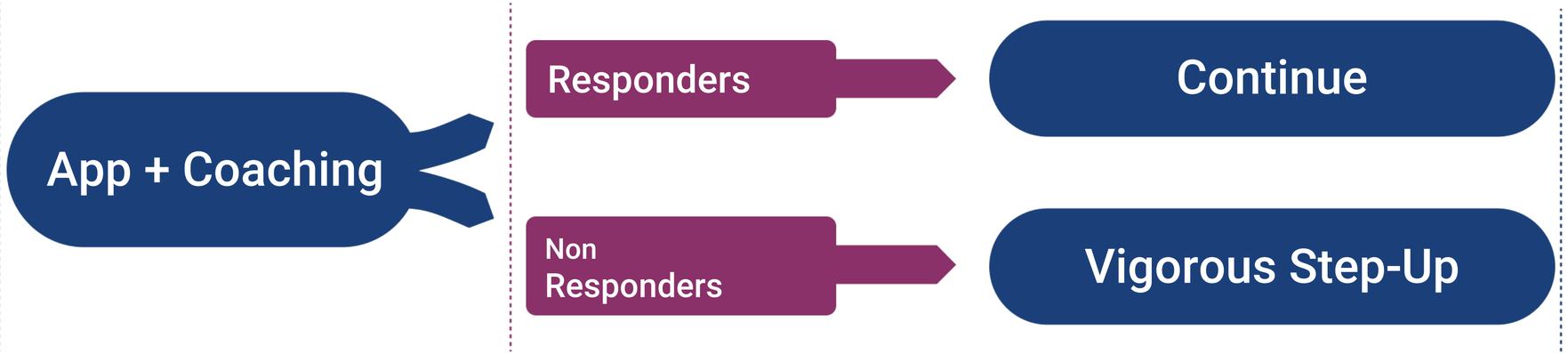
A Pilot Trial is not…

An adaptive intervention, such as:



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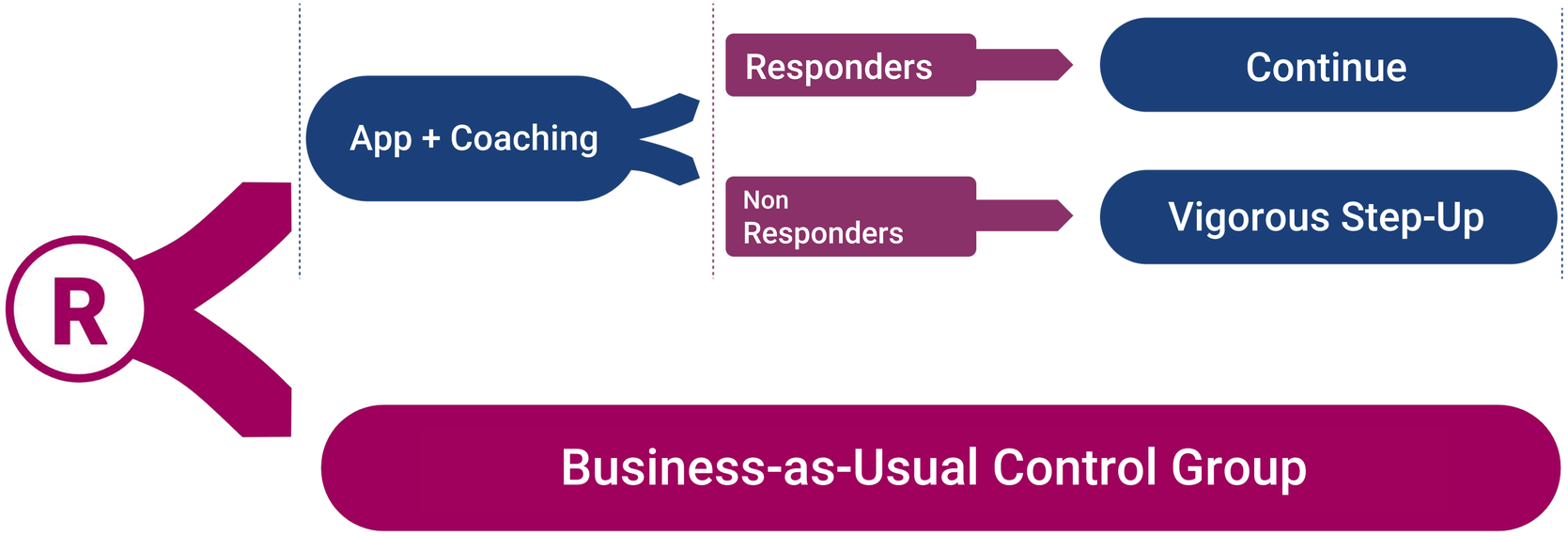
A Pilot Trial is not…

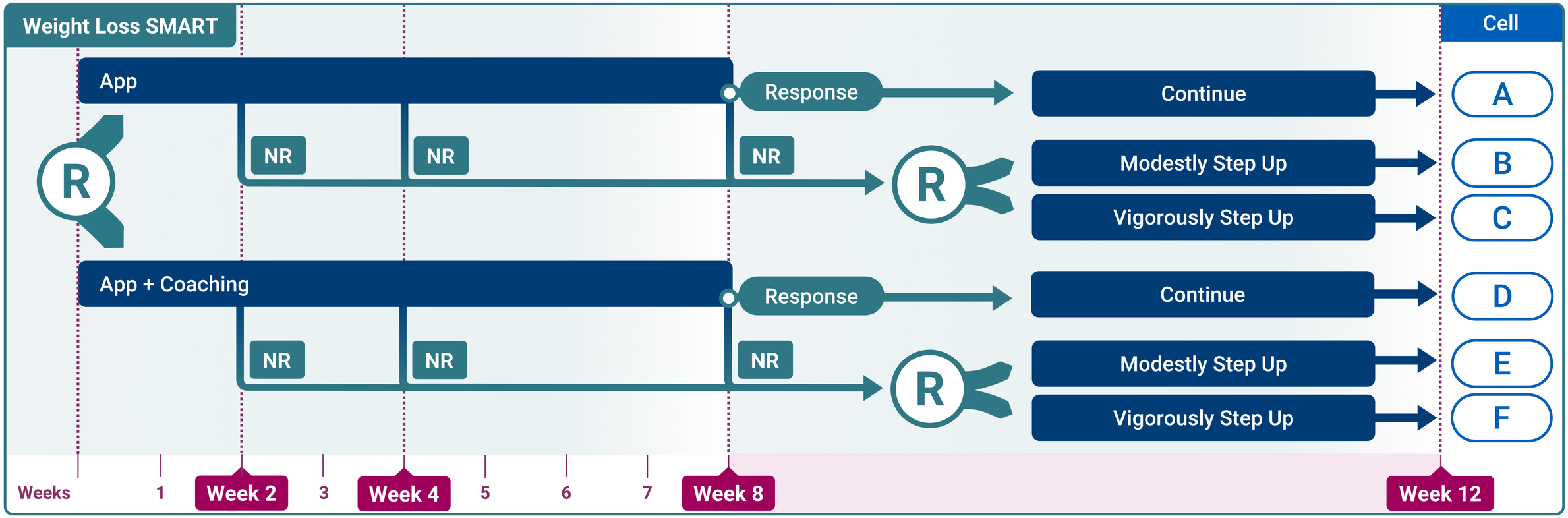
A full-scale evaluation/confirmatory randomized trial, such as:



Primary Aim: To test if an adaptive intervention that (i) starts with DTT, (ii) continues with DTT for responders, and (iii) augments with JASPER for slower responders differs from business-as-usual (control) on average change in socially communicative utterances over 16wks.

A Pilot Trial is not…

A full-scale optimization randomized trial, such as the Weight Loss SMART



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NR = Non-Response

A Pilot Trial is

A small-scale randomized trial that is explicitly designed to prepare for a successful, full-scale randomized trial.

What is a successful, full-scale trial?

A successful full-scale trial is one in which you were able to answer all your scientific questions rigorously and reproducibly. This means that:

- **Intervention Success** Interventionists were able to deliver, with high fidelity, all (components) of the intervention, as pre-planned; i.e., as described in the intervention protocol

- **Research Success** The researchers were able to conduct (and analyze) the full-scale trial, as pre-planned; i.e., as described in the study protocol

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- **Don't Conflate Intervention and Research** We ensure that, from the perspective of the participants in the full-scale trial, there is a clear distinction between intervention activities versus research activities; i.e., the intervention protocol is distinct from the research protocol

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Key idea that is nuanced.
We'll return to this. Meanwhile...

What is a successful, full-scale trial?

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- **Research Success** The researchers were able to conduct (and analyze) the full-scale trial, as pre-planned; i.e., as described in the study protocol

A successful full-scale trial is not a trial in which

- The researcher finds **clinically** or **statistically significant** treatment effects

Outline

What is a pilot trial? (what is it not?)

Situating pilot trials as Preparation for Success and your Place in the Process

Tips: What to do in a Pilot SMART?

Sample Size for Pilot SMARTs

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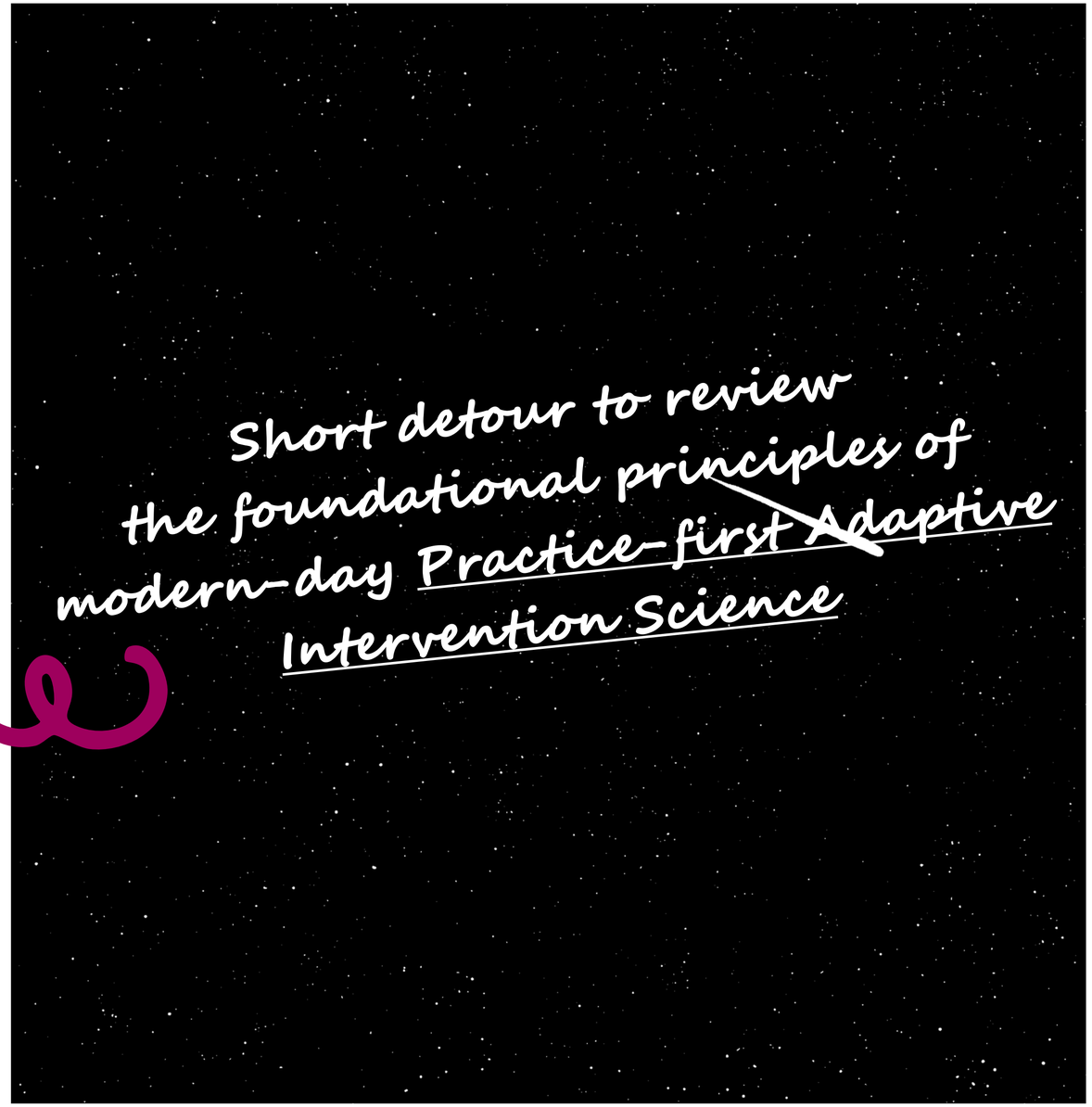

Practice-first Adaptive Intervention Science

1

What is the adaptive intervention design, as envisioned in practice?

2

What are the scientific questions?

3

What is the appropriate trial design?

Practice-first Adaptive Intervention Science

Adaptive Intervention

1

What is the adaptive intervention design, as envisioned in practice?

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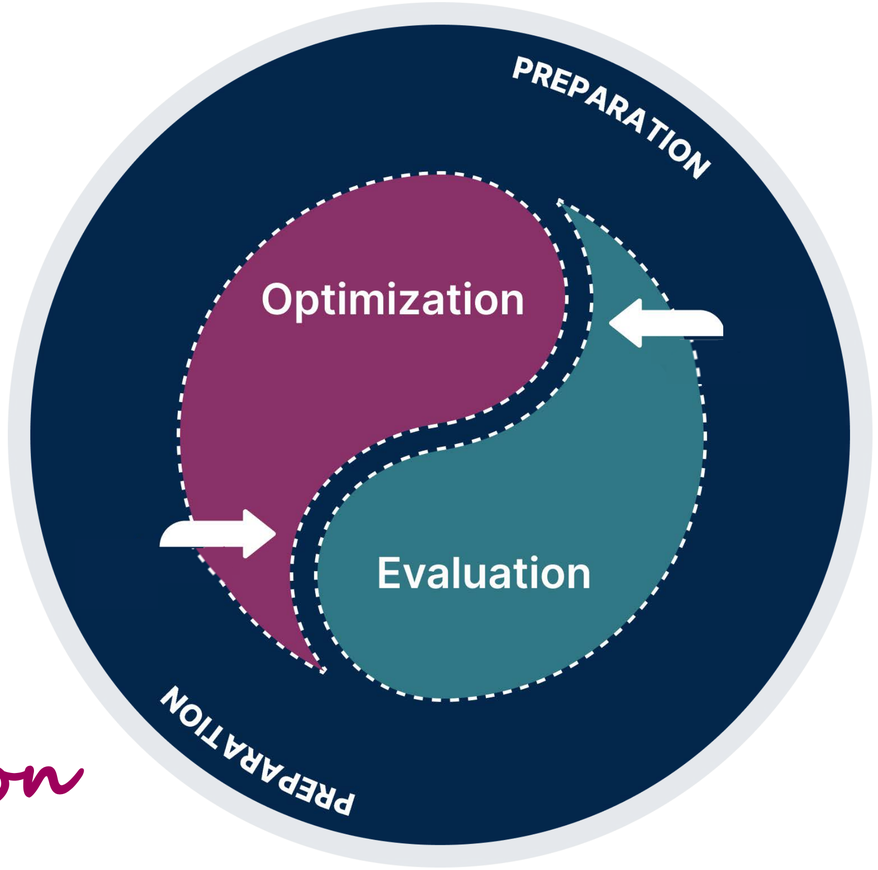
Practice-first Adaptive Intervention Science

1 What is the adaptive intervention design, as envisioned in practice?

Just-in-time adaptive intervention (JITAI)

2 What are the scientific questions?



3 What is the appropriate trial design?

Practice-first Adaptive Intervention Science

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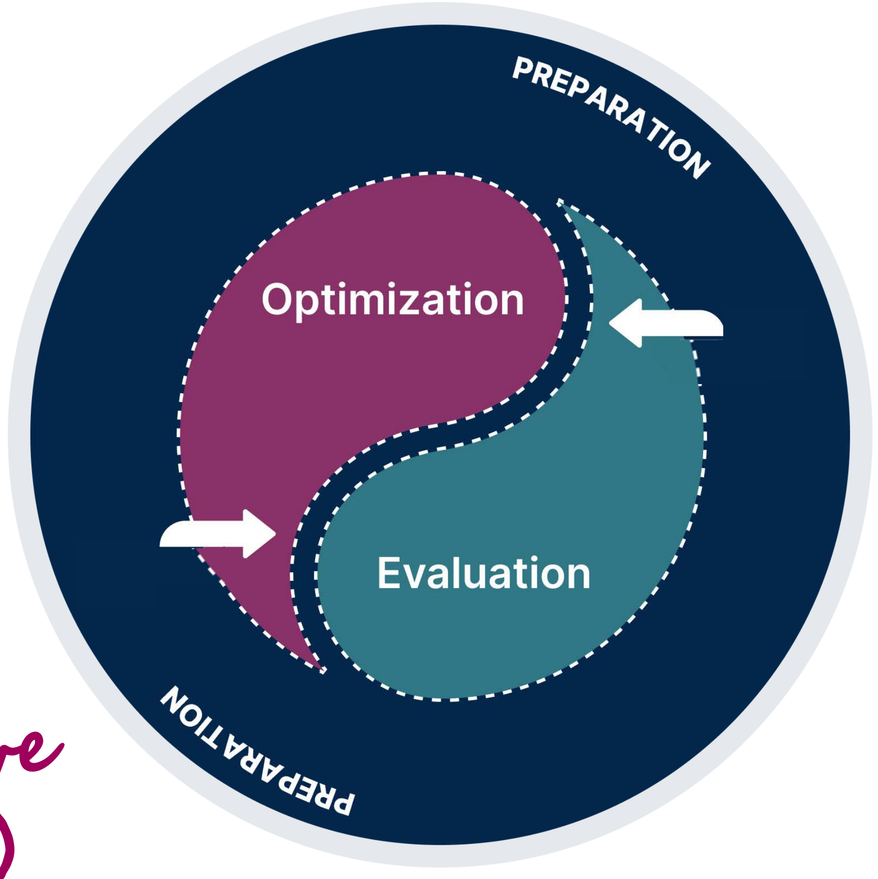


3

What is the appropriate trial design?

Multimodal adaptive intervention (MADI)

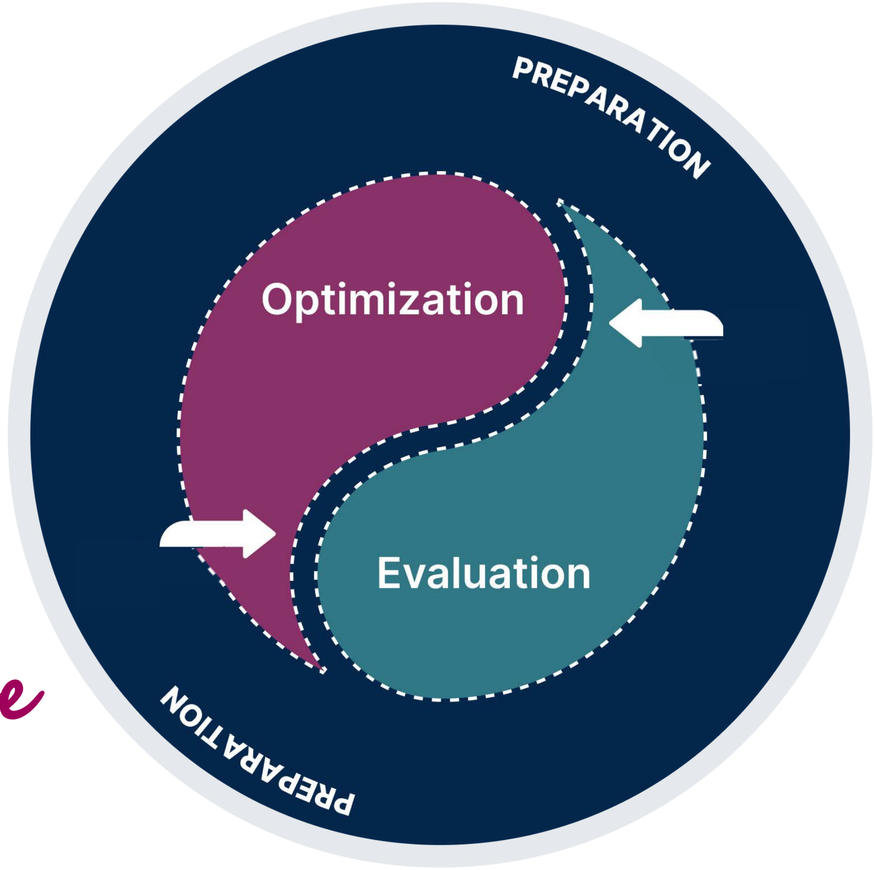
Practice-first Adaptive Intervention Science

1

What is the adaptive intervention design, as envisioned in practice?

2

What are the scientific questions?



3

What is the appropriate trial design?

Multilevel Adaptive Implementation Strategy (MAISY)

Practice-first Adaptive Intervention Science

Personalized JITAI (pJITAI)

1

What is the adaptive intervention design, as envisioned in practice?

2 What are the scientific questions?

3

What is the appropriate trial design?

Practice-first Adaptive Intervention Science

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What is the adaptive intervention design, as envisioned in practice?

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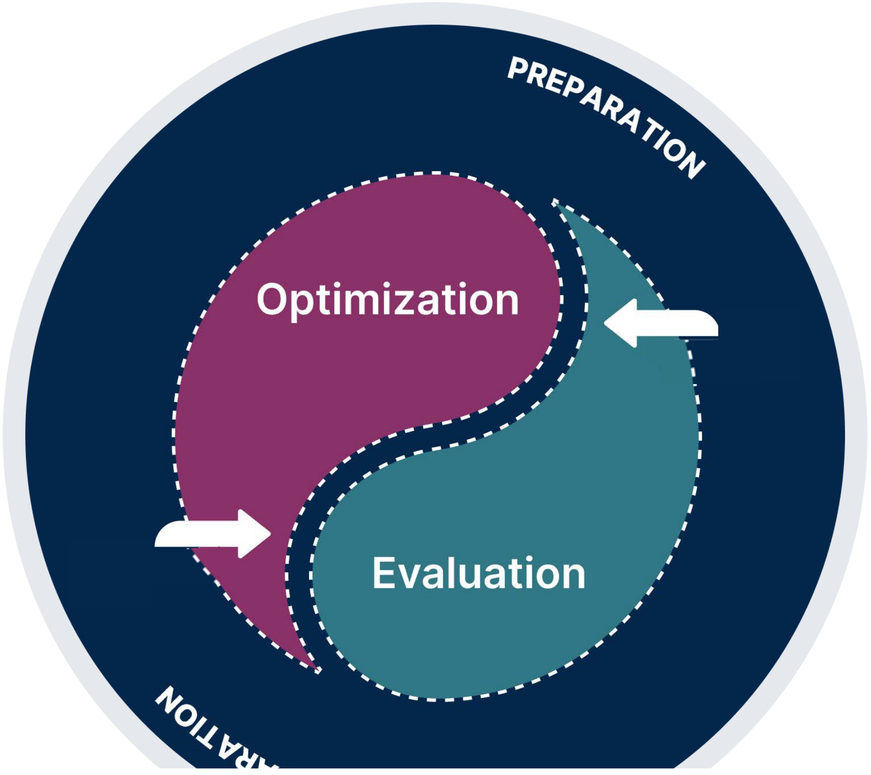
What are the scientific questions?



3

What is the appropriate trial design?

In (2), most effectiveness intervention scientists will begin by asking either a set of **Optimization** questions or an **Evaluation** question.

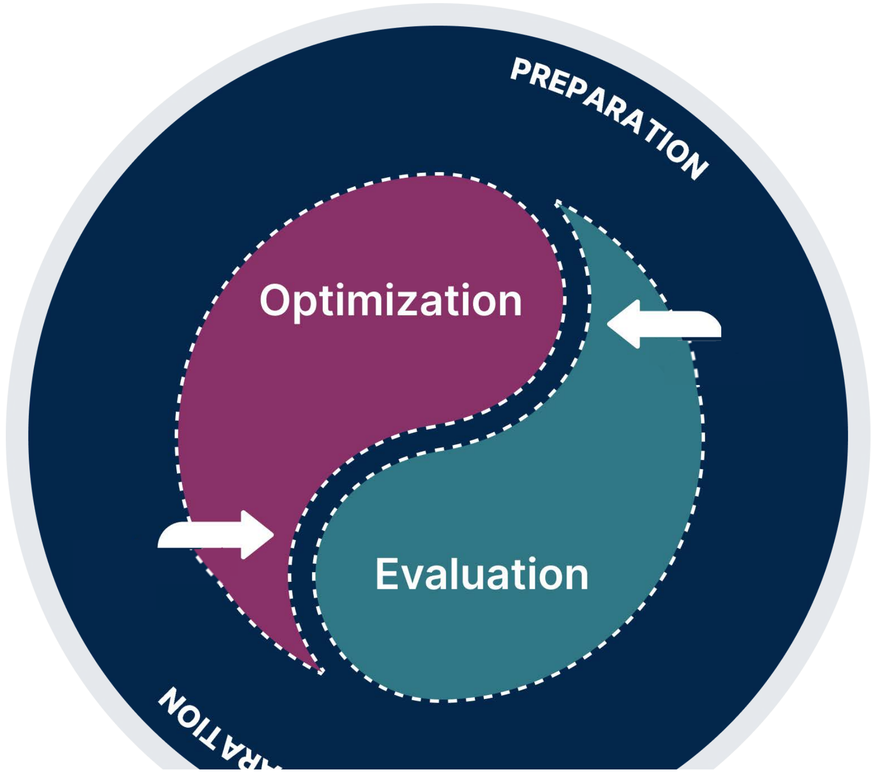
Practice-first Adaptive Intervention Science

1

What is the adaptive intervention design, as envisioned in practice?

2

What are the scientific questions?



3

What is the appropriate trial design?

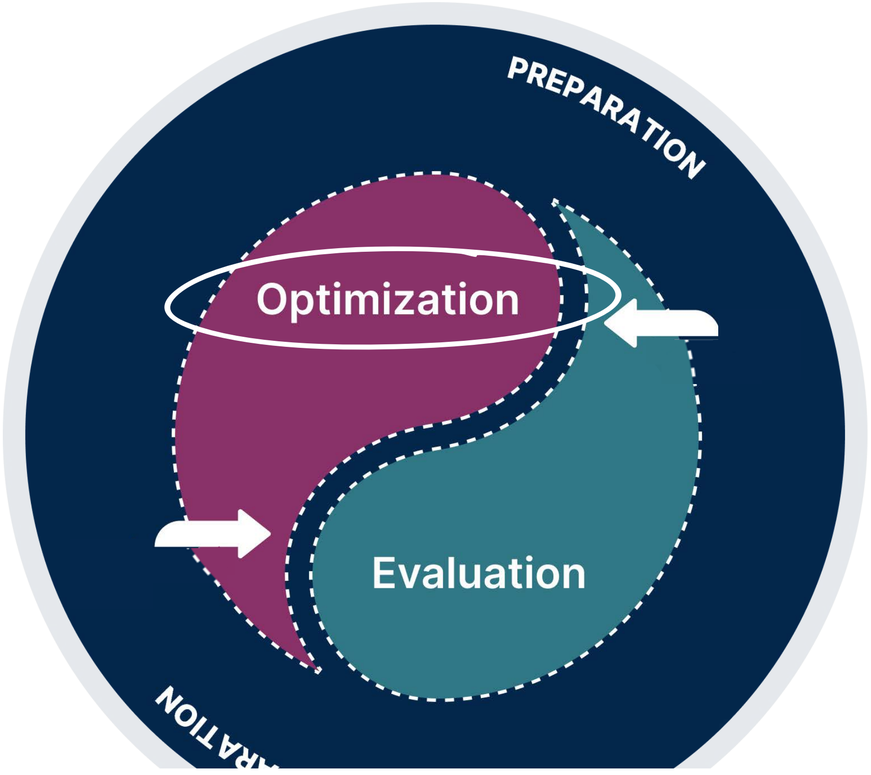
And, once (1) and (2) are known, the appropriate trial design (3) falls into place.

Example 1

Practice-first Adaptive Intervention Science

Adaptive Intervention

2 What are the scientific questions?



SMART

1 What is the adaptive intervention design, as envisioned in practice?

3 What is the appropriate trial design?

And, once (1) and (2) are known, the appropriate trial design (3) falls into place.

To answer **Optimization** questions across 2+ decision points in a **Clinical Adaptive Intervention**, you're likely to use a **SMART**.

Example 2

Practice-first Adaptive Intervention Science

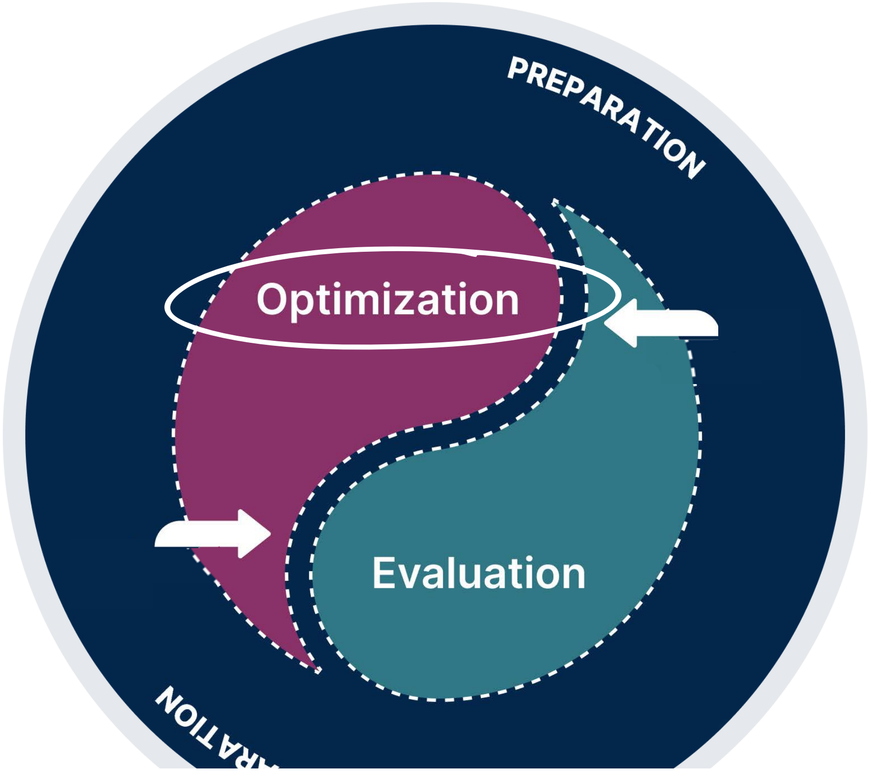
JITAI

1

What is the adaptive intervention design, as envisioned in practice?

2

What are the scientific questions?



MRT

3

What is the appropriate trial design?

And, once (1) and (2) are known, the appropriate trial design (3) falls into place.

To answer **Optimization** questions across 2+ decision points in an **JITAI**, you're likely to use an **MRT**.

Example 3

Practice-first Adaptive Intervention Science

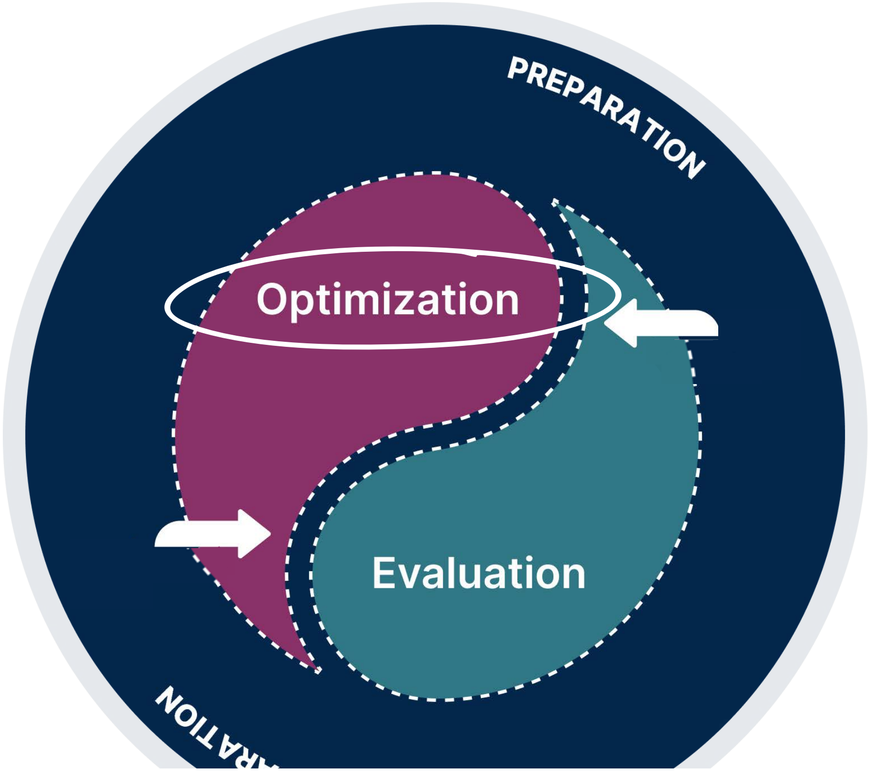
MAISY

1

What is the adaptive intervention design, as envisioned in practice?

2

What are the scientific questions?



Multilevel SMART

3

What is the appropriate trial design?

And, once (1) and (2) are known, the appropriate trial design (3) falls into place.

To answer **Optimization** questions at 2+ decision points across 2+ levels of a MAISY, you're likely to use a **Multilevel SMART**.

Example 4

Practice-first Adaptive Intervention Science

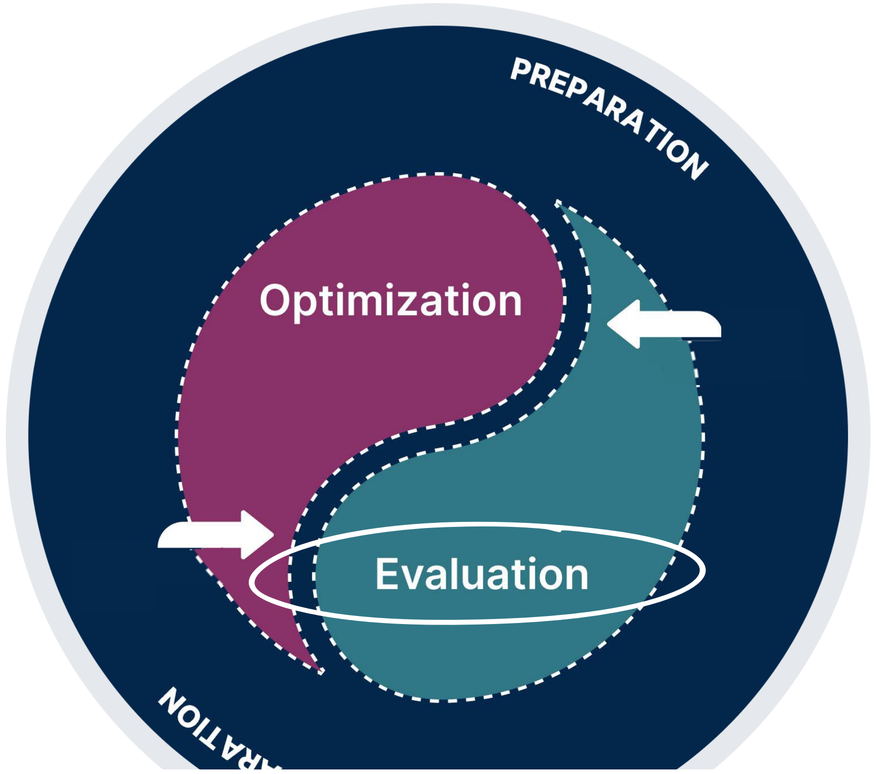
Any type

1

What is the adaptive intervention design, as envisioned in practice?

2

What are the scientific questions?



Confirmatory RCT

3

What is the appropriate trial design?

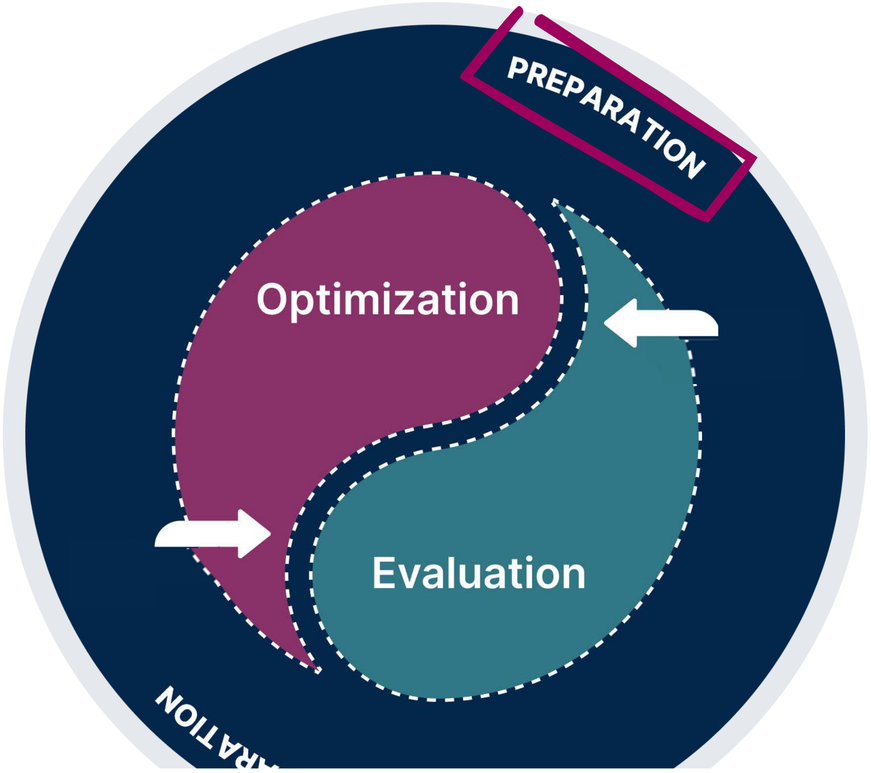
And, once (1) and (2) are known, the appropriate trial design (3) falls into place.

To **Evaluate** an Adaptive Intervention of any type, you're likely to use a **Confirmatory RCT**.

Practice-first Adaptive Intervention Science

However…

2 **What are the scientific questions?**



1

What is the adaptive intervention design, as envisioned in practice?

3

What is the appropriate trial design?

Some of you may have important Preparation Questions that you need answers to before embarking on a successful, full-scale optimization or evaluation trial.

Practice-first Adaptive Intervention Science

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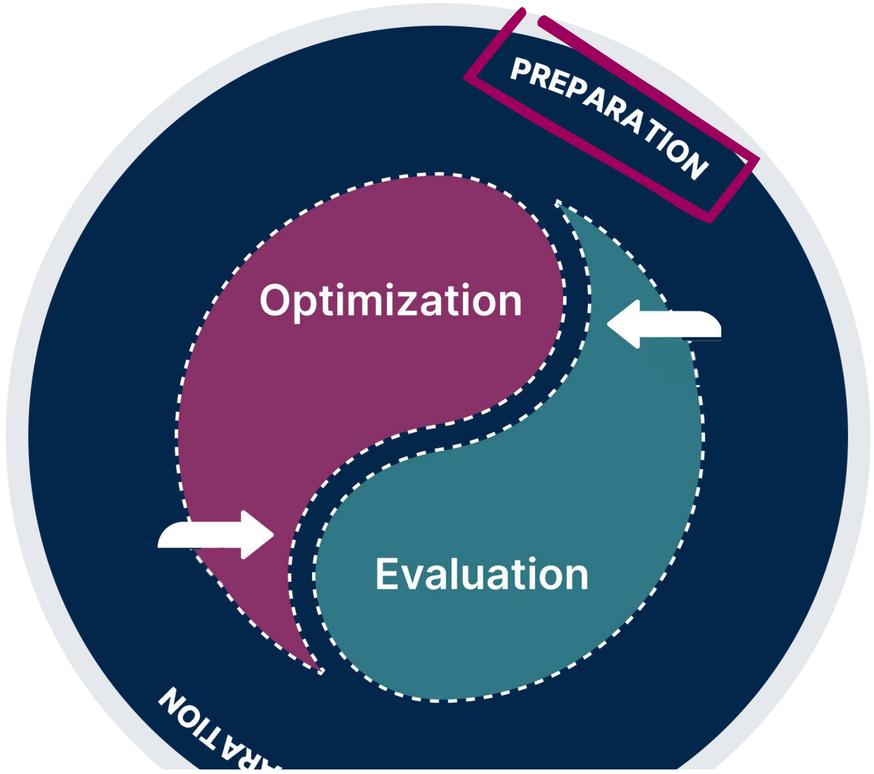
What are the scientific questions?



Pilot Trials

3

What is the appropriate trial design?

A Pilot Trial is a small-scale randomized trial explicitly designed to prepare for a successful, full-scale Optimization or Evaluation Randomized Trial.

References

Collins, L. M. (2018). Optimization of behavioral, biobehavioral, and biomedical interventions. *Springer.* These are 2 back-to-back books.

Almirall, D., Nahum-Shani, I., Wang, L., & Kasari, C. (2018). Experimental designs for research on adaptive interventions: Singly and sequentially randomized trials. *Optimization of behavioral, biobehavioral, and biomedical interventions: Advanced topics*, 89-120. Part of Collins' second book.

Collins, L. M., Nahum-Shani, I., & Almirall, D. (2014). Optimization of behavioral dynamic treatment regimens based on the sequential, multiple assignment, randomized trial (SMART). *Clinical Trials*, *11*(4), 426-434.

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Tips: What to do in a Pilot SMART?

Sample Size for Pilot SMARTs

Example 1

Practice-first Adaptive Intervention Science

Adaptive Intervention

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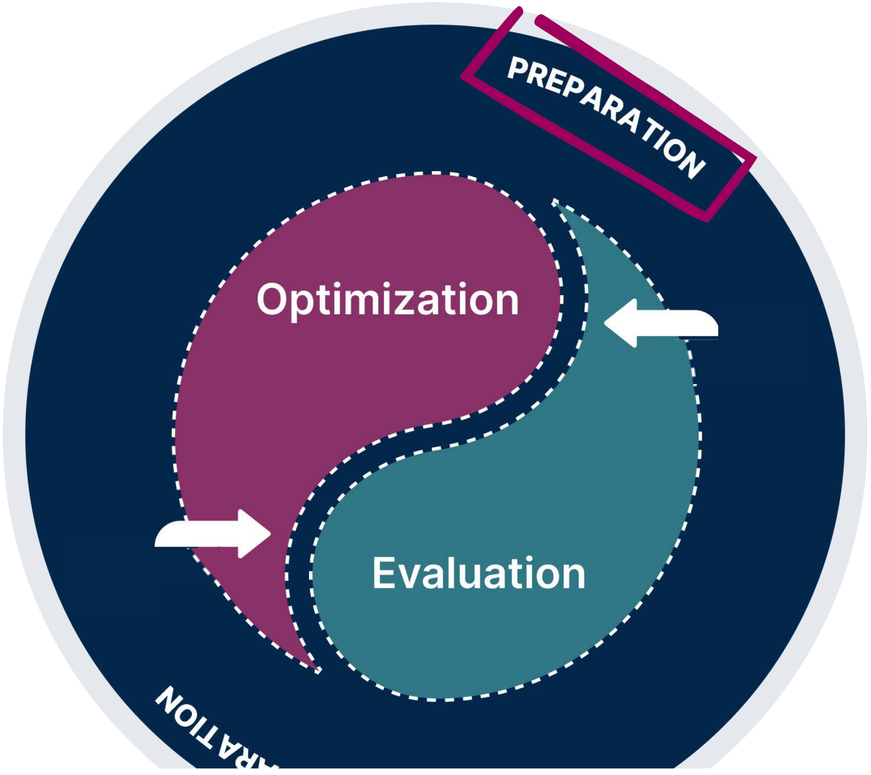
What are the scientific questions?



SMART

3

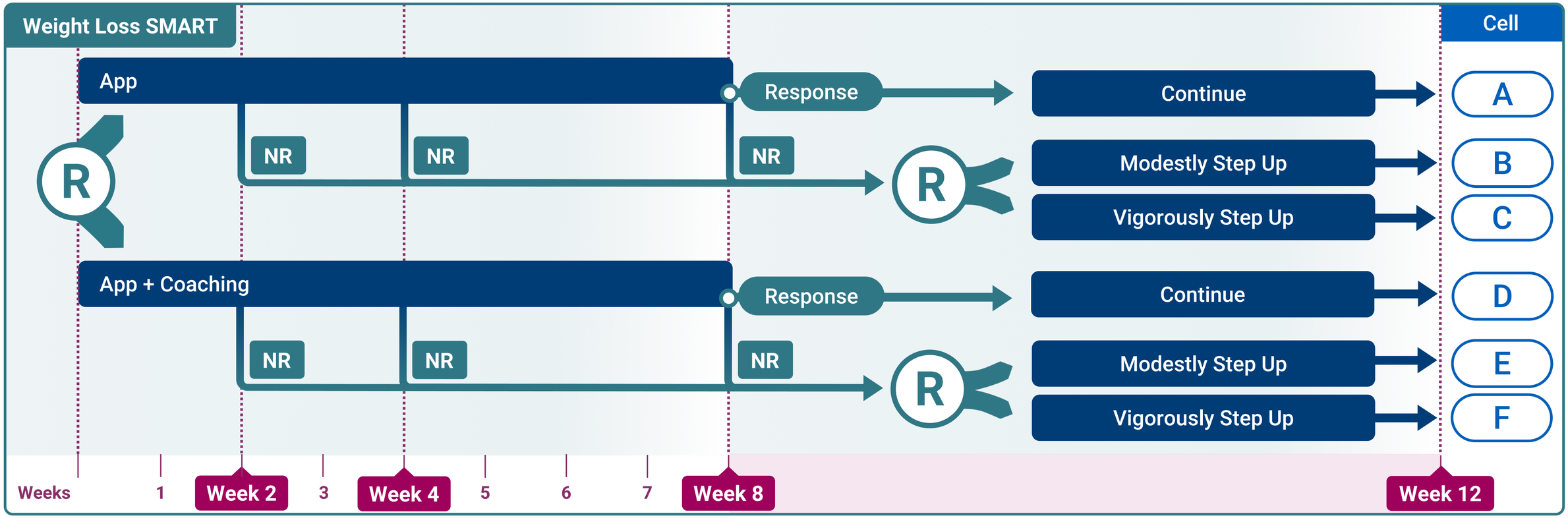
What is the appropriate trial design?

We suppose the following for the remainder of this presentation:

To answer **Optimization** questions across 2+ decision points
in a **Clinical Adaptive Intervention**, you're likely to use a **SMART**.

We are going to use the Weight Loss SMART as the motivating example.

A full-scale optimization randomized trial, such as the Weight Loss SMART



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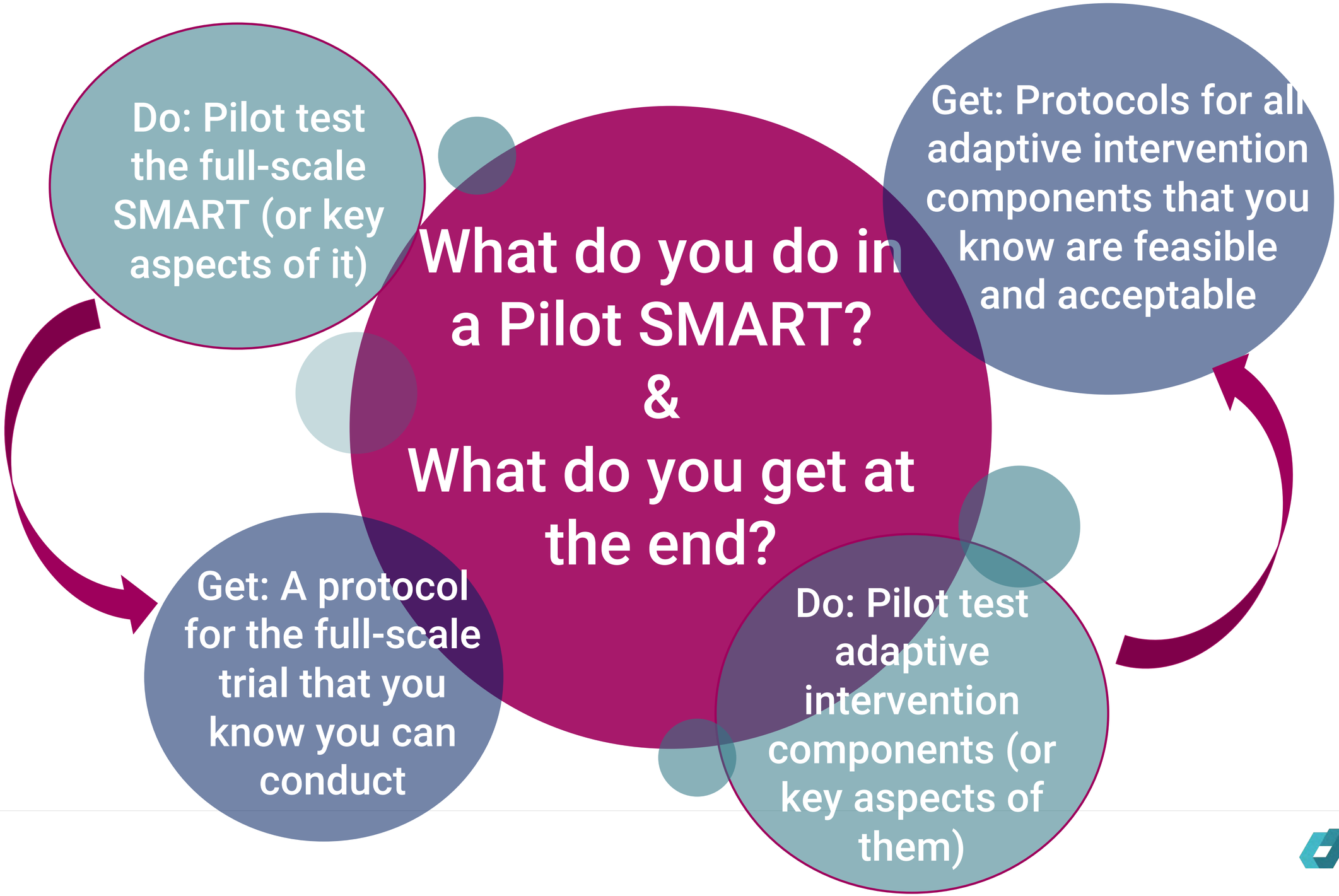
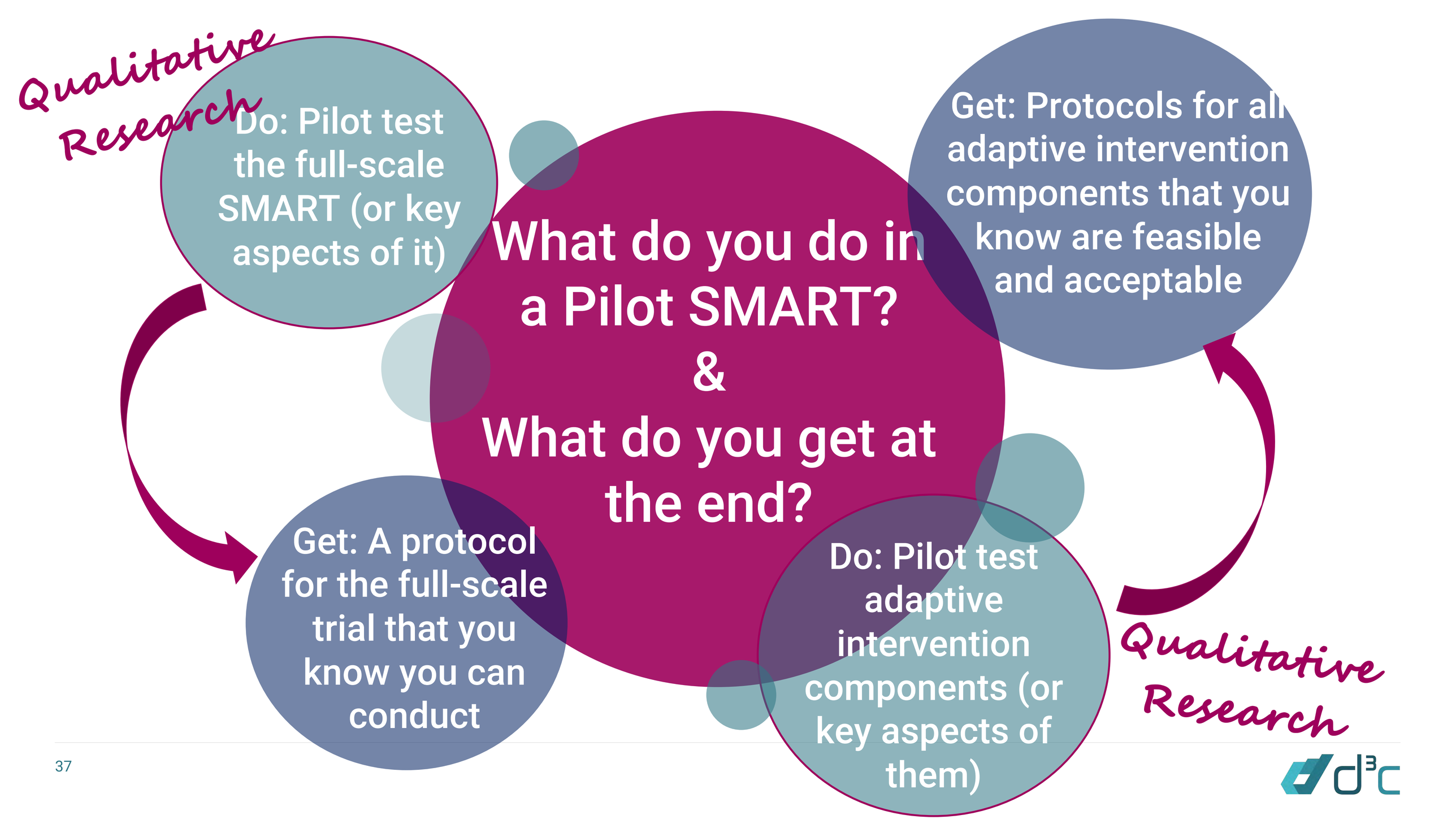
NR = Non-Response

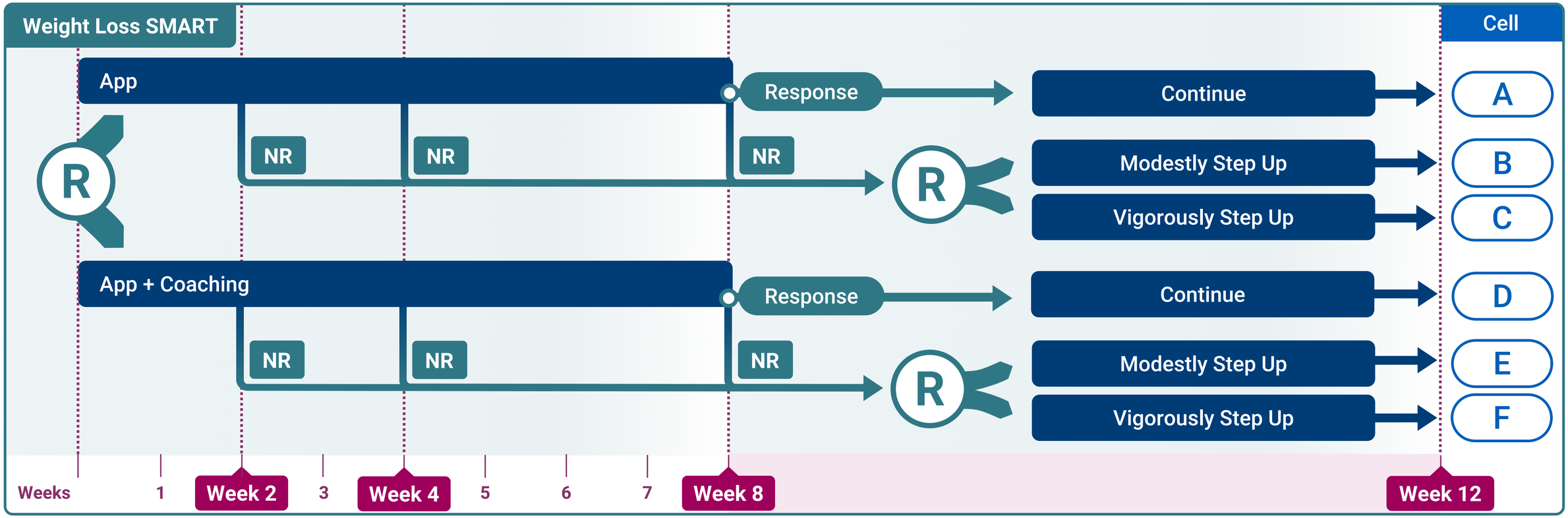
A Pilot SMART is

A small-scale SMART that is explicitly **designed to prepare for a successful, full-scale SMART**.


Do: Pilot test the full-scale SMART (or key aspects of it)
Get: Protocols for all adaptive intervention components that you know are feasible and acceptable
What do you do in a Pilot SMART?
&
What do you get at the end?
Get: A protocol for the full-scale trial that you know you can conduct
Do: Pilot test adaptive intervention components (or key aspects of them)


Qualitative Research
Do: Pilot test the full-scale SMART (or key aspects of it)
What do you do in a Pilot SMART?
&
What do you get at the end?
Get: Protocols for all adaptive intervention components that you know are feasible and acceptable
Get: A protocol for the full-scale trial that you know you can conduct
Do: Pilot test adaptive intervention components (or key aspects of them)
Qualitative Research

Qualitative Research in the Context of the Proposed SMART



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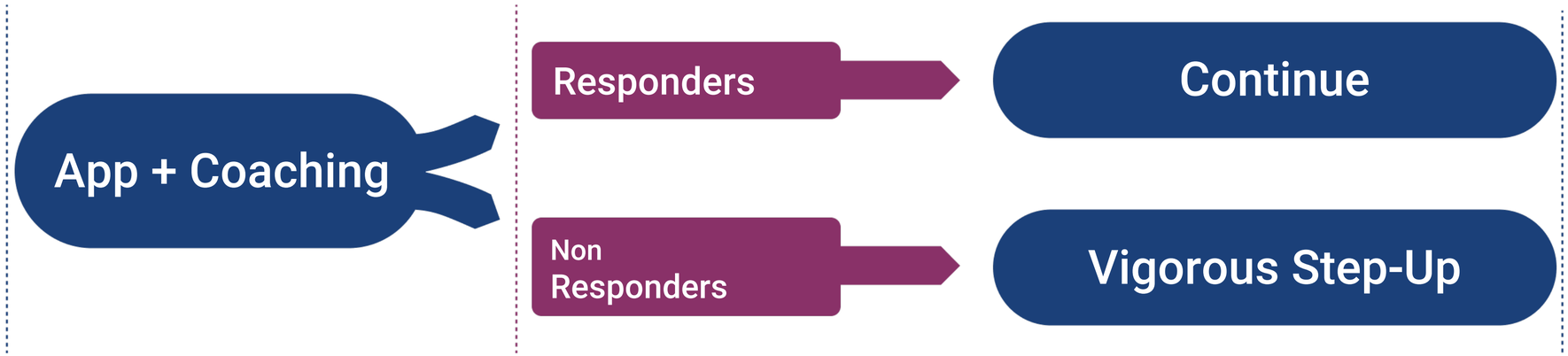
When Designing a Pilot SMART

Make Two Separate Lists of Things That Could go Wrong

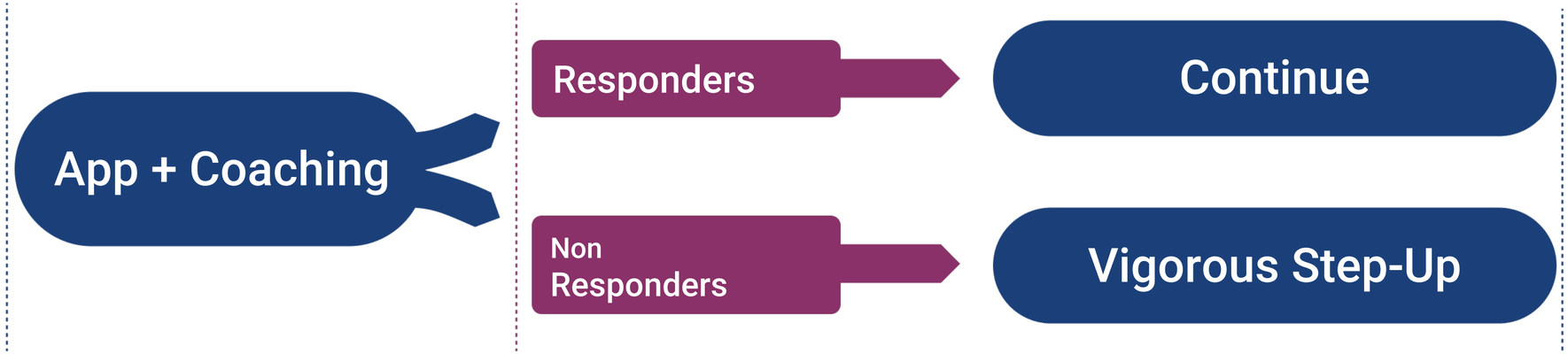
Intervention Protocol (actions of therapist to patients)	• Do you have a plan for common contingencies that arose during intervention (e.g., how did you classify a patient who did not show up to give the data on the embedded tailoring variable)? • Address feasibility/acceptability concerns from therapists (e.g., interventionist insists on classifying certain patients as non-responders, tailoring variable measures too burdensome, therapists had trouble with conversations when transitioning to next stage of treatment,)? • …from patients (e.g., infeasible to finish all sessions, treatment engagement protocol too burdensome)? • Therapist able to collect the top 1-2 candidate tailoring variables to explore in the secondary/tertiary aims? Did therapists
SMART Protocol (actions of researchers to participants + therapists)	• Did anything go wrong during screening procedures, consent procedures, research incentives, and research data collection)? Were these activities perceived (by participants) to be distinct from therapy? • Are you confident you can hit your recruitment targets during the full-scale SMART? • Did anything go wrong with therapy quality assurance protocol for monitoring and addressing fidelity drift? • Were you able to stratify your sequential randomizations? • Did your quant team write, test and practice the computer code to analyze the data from the SMART?

Example Considerations Related to Intervention Components



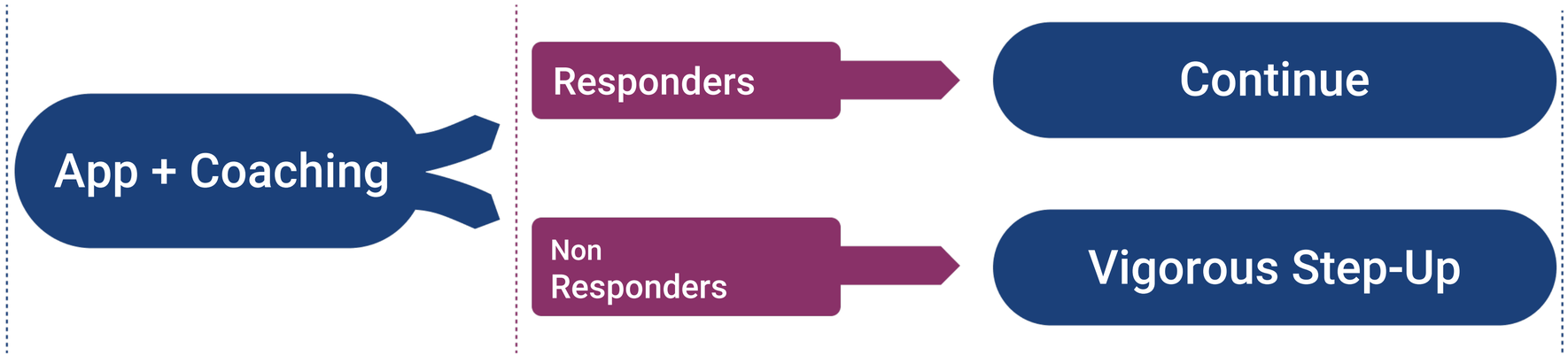
- Do you have a plan for common contingencies that arose during intervention (e.g., how did you classify a patient who did not show up to give the data on the embedded tailoring variable)?

Example Considerations Related to Intervention Components



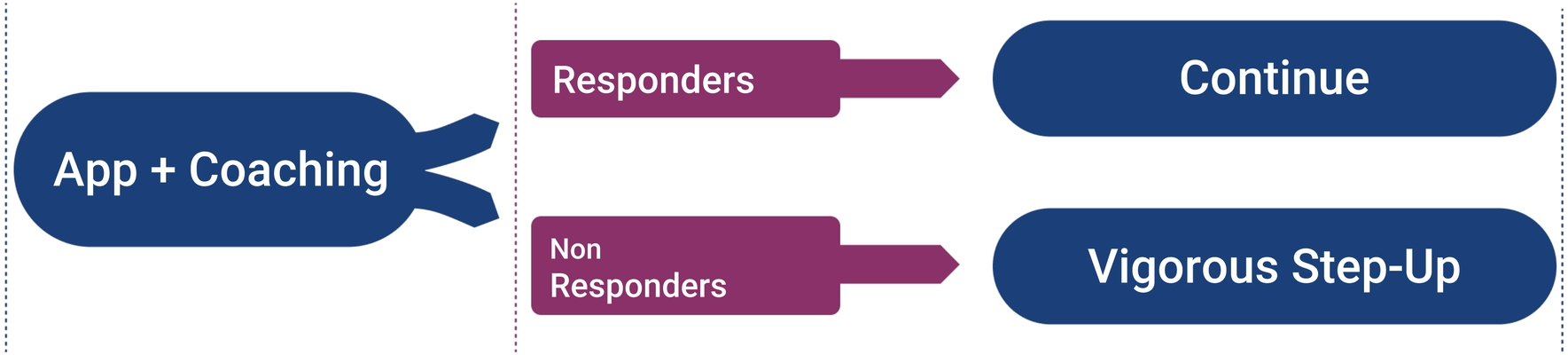
- Address feasibility/acceptability concerns from therapists (e.g., interventionist insists on classifying certain patients as non-responders, tailoring variable measures too burdensome, therapists had trouble with conversations when transitioning to next stage of treatment,)?
- …from patients (e.g., infeasible to finish all sessions, treatment engagement protocol too burdensome)?

Example Considerations Related to Intervention Components



- Therapist able to collect the top 1-2 candidate tailoring variables to explore in the secondary/tertiary aims?

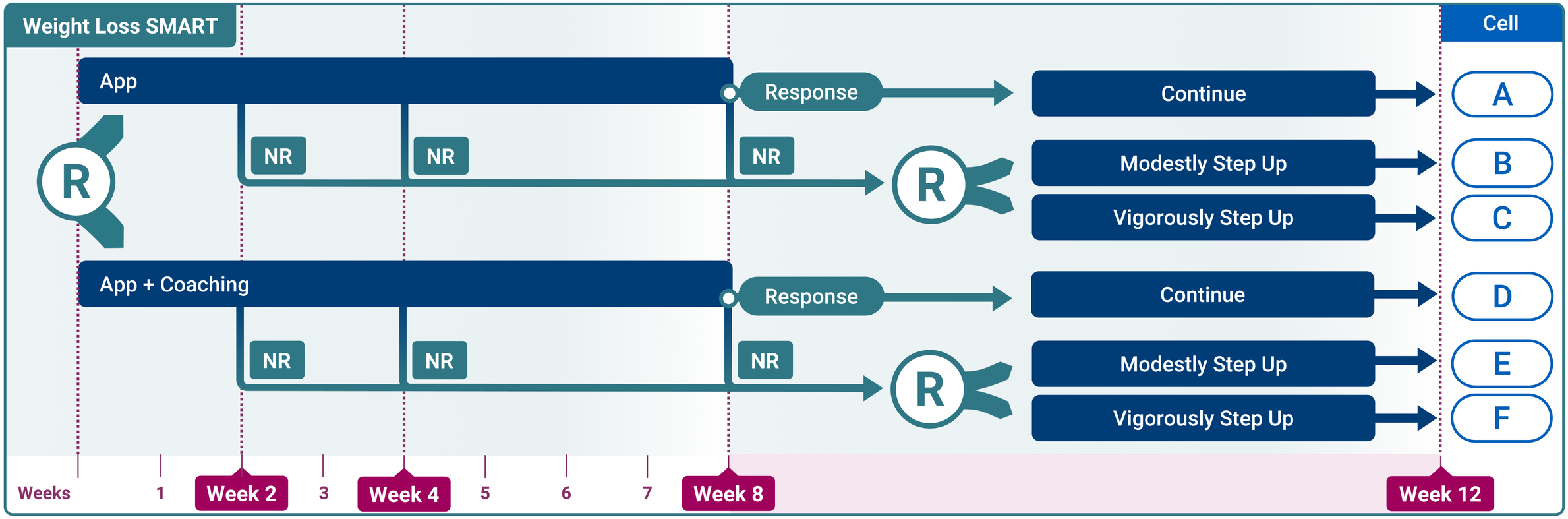
Example Considerations Related to Intervention Components



- Do you have a plan for common contingencies that arose during intervention (e.g., how did you classify a patient who did not show up to give the data on the embedded tailoring variable)?
- Address feasibility/acceptability concerns from therapists (e.g., interventionist insists on classifying certain patients as non-responders, tailoring variable measures too burdensome, therapists had trouble with conversations when transitioning to next stage of treatment,)?
- …from patients (e.g., infeasible to finish all sessions, treatment engagement protocol too burdensome)?
- Therapist able to collect the top 1-2 candidate tailoring variables to explore in the secondary/tertiary aims?

Example Considerations Related to Intervention Components

Did anything go wrong during screening procedures, consent procedures, research incentives, and research data collection? Were these activities perceived (by participants) to be distinct from therapy?



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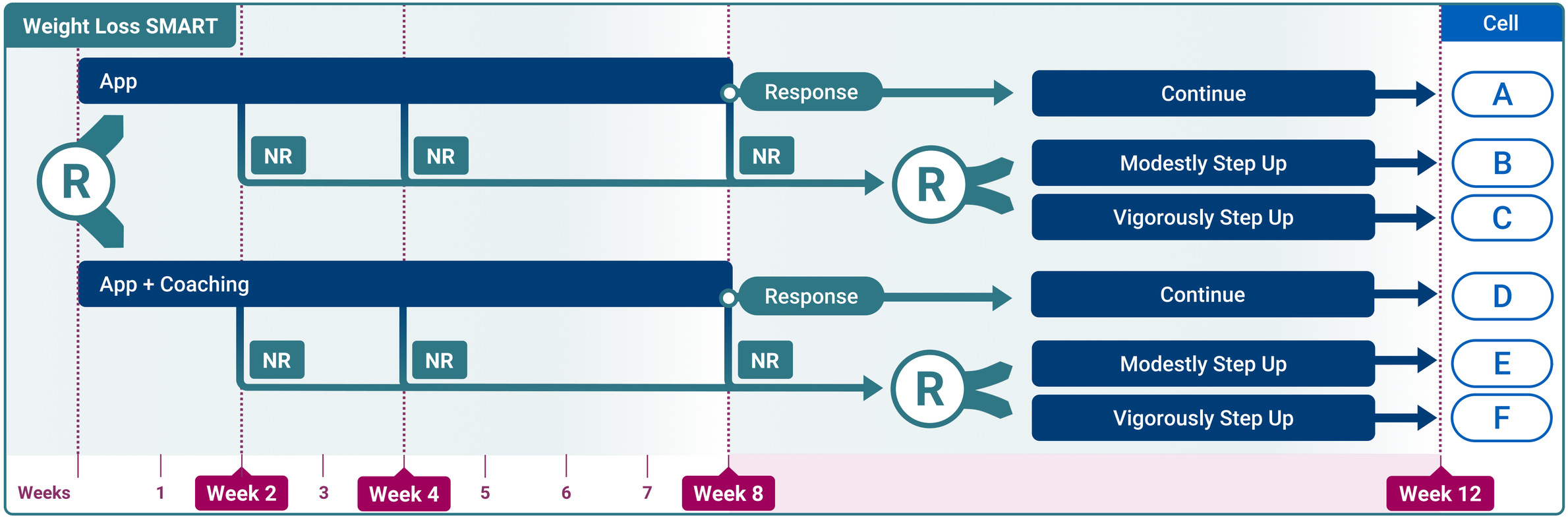
NR = Non-Response

Example Considerations Related to Intervention Components

Are you confident you can hit your recruitment targets during the full-scale SMART?



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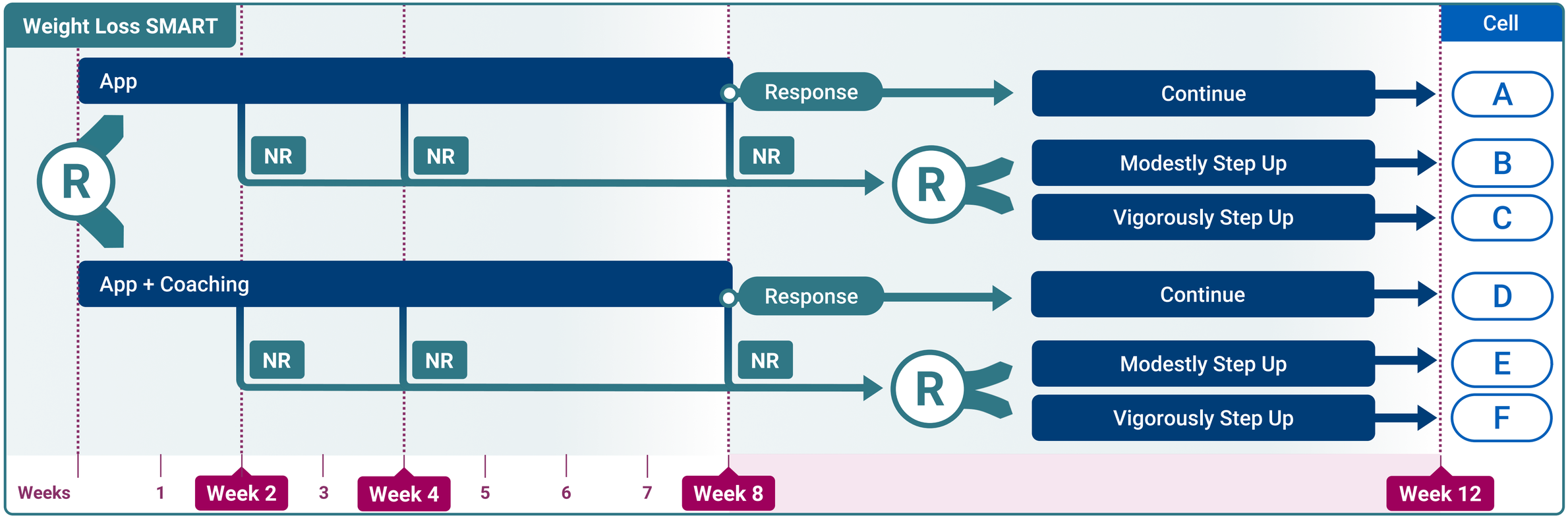
Example Considerations Related to Intervention Components

Did anything go wrong with therapy quality assurance protocol for monitoring and addressing fidelity drift?



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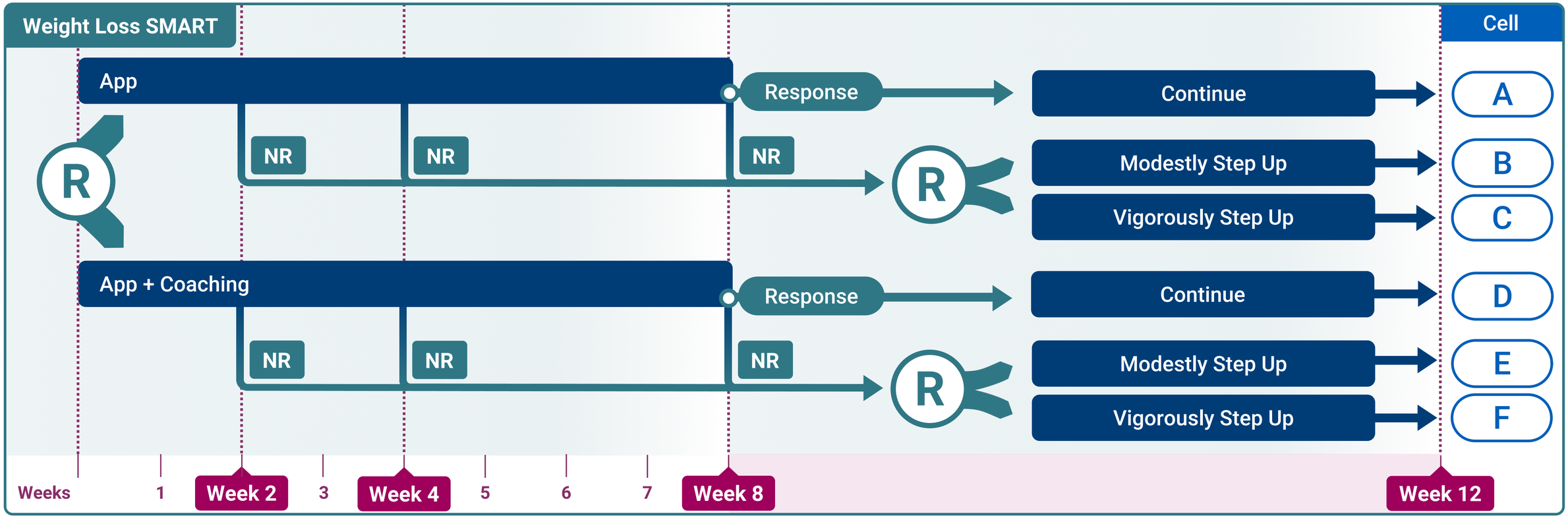
Example Considerations Related to Intervention Components

Were you able to stratify your sequential randomizations?



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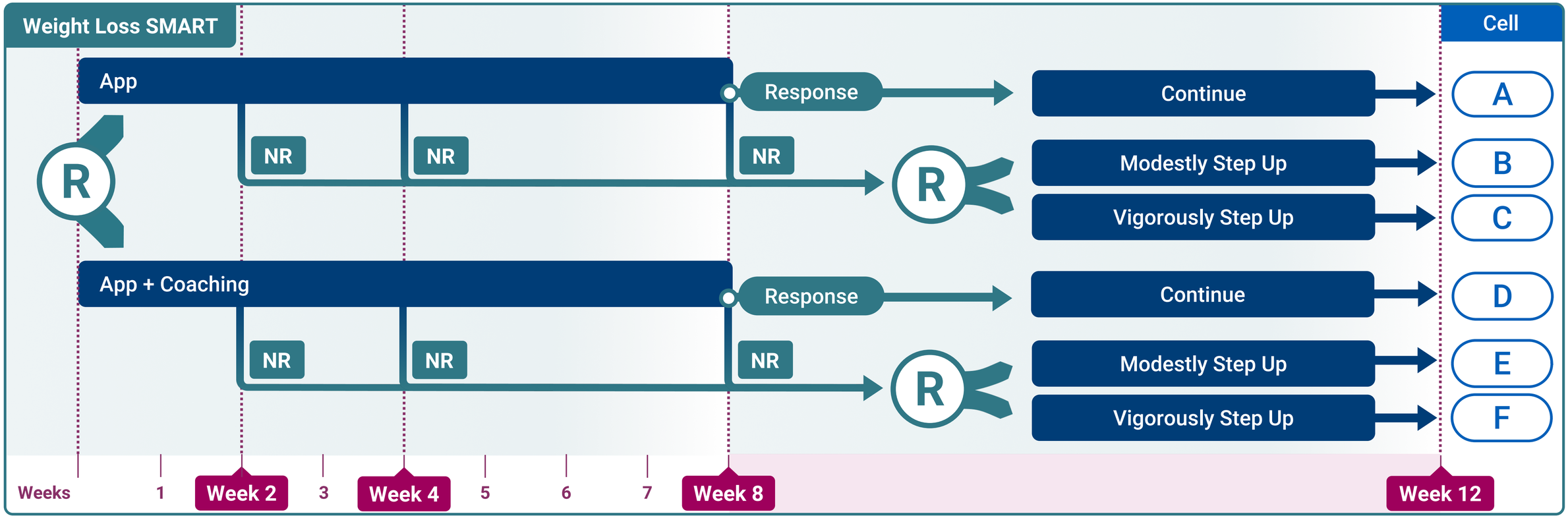
Example Considerations Related to Intervention Components

Did your quant team write, test, and practice the computer code to analyze the data from the SMART?



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References

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Outline

What is a pilot trial? (what is it not?)

Situating pilot trials as Preparation for Success and your Place in the Process

Tips: What to do in a Pilot SMART?

Sample Size for Pilot SMARTs

Sample Size for a Pilot SMART

Approach 1

Ensure research team can implement and assess feasibility and acceptability of all aspects of the the SMART (and within each “treatment path”)

Scientists chooses

m = number of students in each treatment path

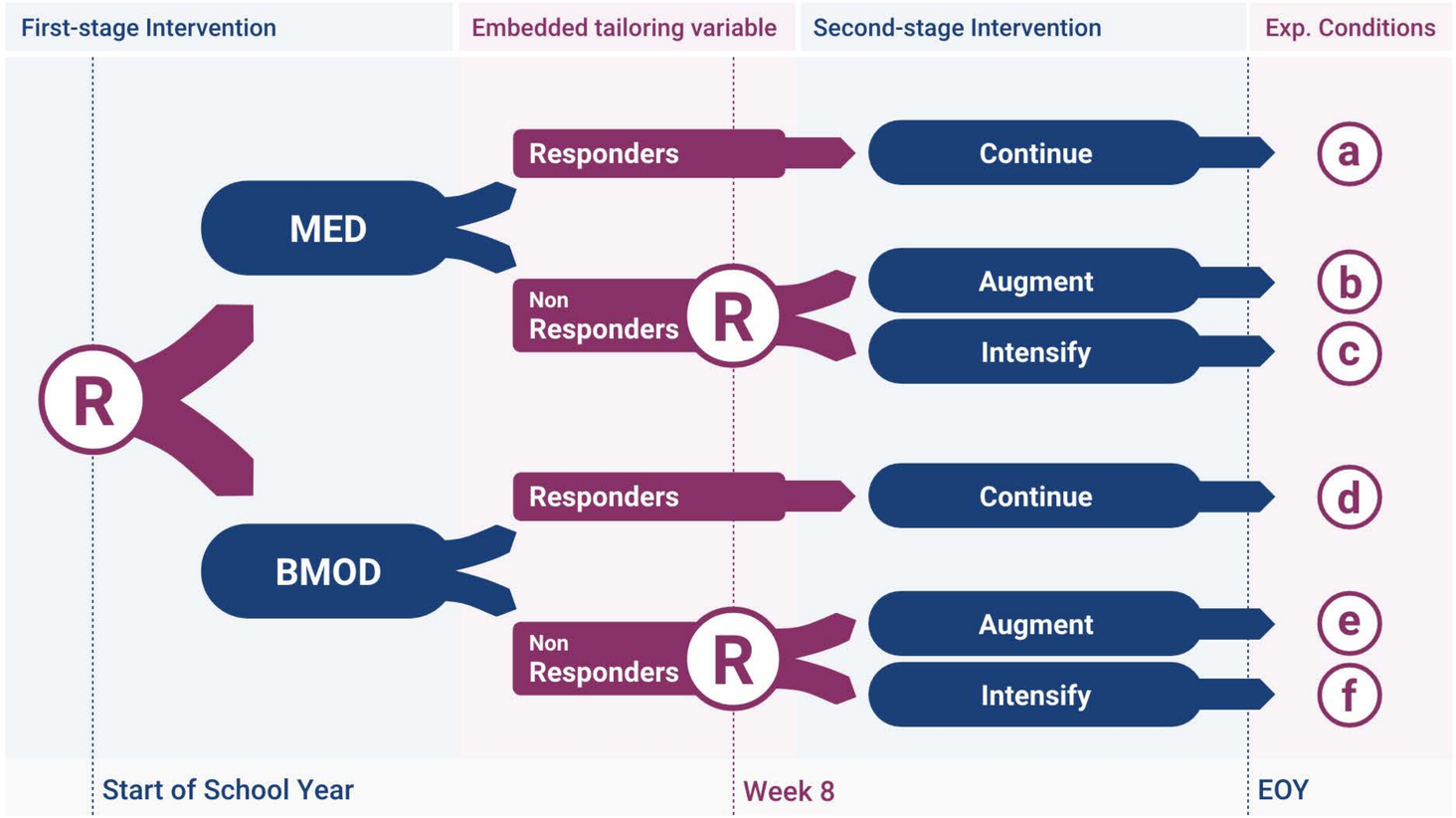
k = Pr (actual number of students in each path ≥ m)

q = anticipated non-response rate

Method provides total sample size N for the Pilot SMART

Approach 1

Ensure research team can implement and assess feasibility and acceptability of all aspects of the the SMART and the “treatment paths” (a-f) that make up the embedded AIs



Approach 1

Ensure research team can implement and assess feasibility and acceptability of all aspects of the the SMART and the “treatment paths” (a-f) that make up the embedded AIs

N	q = anticipated non-response rate						
	0.35	0.40	0.45	0.50	0.55	0.60	0.65
k = 0.85							
m = 2	44	38	34	30	26	24	22
m = 3	58	50	44	40	36	32	28
m = 4	72	62	54	48	44	40	36
m = 5	86	74	66	58	52	48	42

Sample Size for a Pilot SMART

Approach 2

To obtain an estimate of overall non-response rate with a given margin of error (i.e., choose N to have a specific amount of precision in the estimate)

- Confidence interval method (point precision)
  Use this if there is poor information about non-response rate

Scientists chooses

moe = margin of error

$1 - \alpha$ = coverage probability for confidence interval

q = anticipated non-response rate

Method provides total sample size N for the Pilot SMART

Sample Size for a Pilot SMART

Approach 2

Example: 1-α = 95%, moe = 0.10, q=0.50, requires N=100

To obtain an estimate of overall non-response rate with a given margin of error (i.e., choose N to have a specific amount of precision in the estimate)

- Confidence interval method (point precision)
  Use this if there is poor information about non-response rate

Scientists chooses

moe = margin of error

$1 - \alpha$ = coverage probability for confidence interval

q = anticipated non-response rate

Method provides total sample size N for the Pilot SMART

References

Almirall D, Compton SN, Gunlicks-Stoessel M, Duan N, Murphy SA (2012). Designing a Pilot SMART for Developing an Adaptive Treatment Strategy. Statistics in Medicine

Kim, H. & Almirall, D. (2016). A sample size calculator for SMART pilot studies, SIAM Undergraduate Research Journal, Vol. 9 (Undergraduate honors thesis).

Updated formulae (and for a variety of SMART designs) available at d3c.isr.umich.edu/code-library

Q&A