Intro to the Multiphase Optimization Strategy (MOST) Framework for Intervention Science

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Outline

1. What is MOST and why should I care to learn about!
2. Set up the framing of MOST with a fun example.
3. Compare MOST to class treatment package approach
4. Overview of MOST and its three phases
5. Resource management principle and optimization criterion
6. Review of optimization trials – Not all technical details.
    1. Factorial designs – Why and how
    2. SMART designs – Why and how
    3. Other designs
7. Conclusions

What is MOST?

- An engineering-inspired framework

AP: Paul Sakuma

- Goal of MOST: To optimize multi-component behavioral & bio-behavioral interventions.
  - Components - *Any aspects of an intervention that can be separated out for study –* ***Your ingredients!***

NIMH and OBSSR Priorities

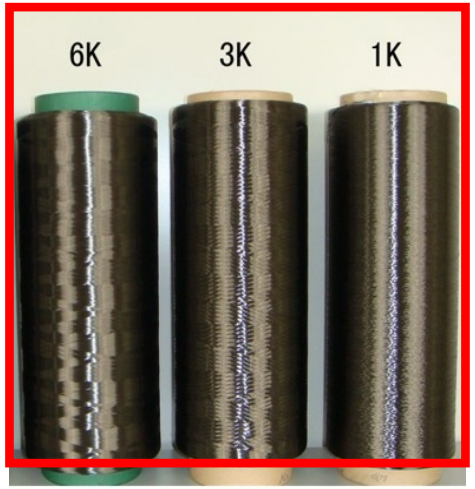
- Priority 3.2:…**tailor existing** and **new interventions** to optimize outcomes.

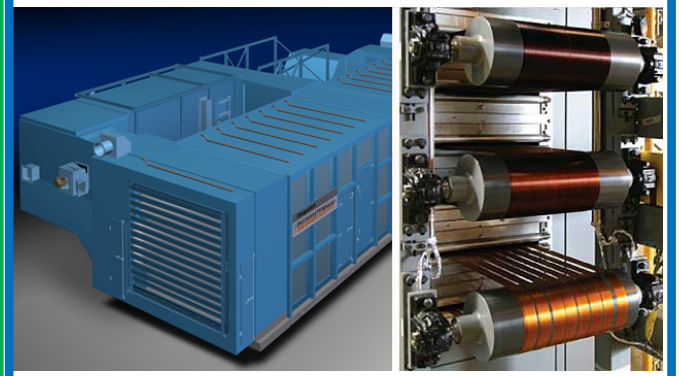
- **Develop and refine alt. research designs…analytic approaches…to test precise interventions.**
  - …prospectively incorporate tailoring variables into participant assignment algorithms…
  - .employ sequential randomization and iterative evaluation of treatment effects to test prescriptive interventions (e.g., MOST/SMART adaptive treatment designs).

- **New interventions** that take into account clinical data, biomarkers, behavioral markers…**from passive sensing of naturalistic behaviors**, **patient response history**.

An example to prime the engineer in you - 1988

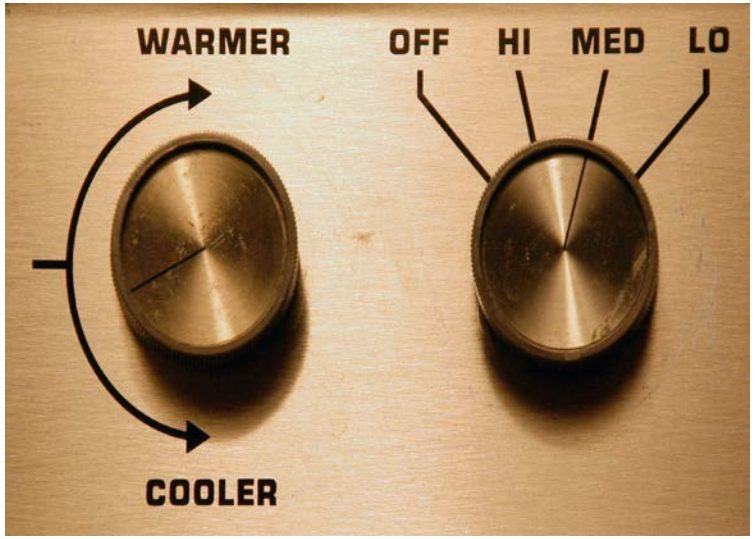
- **Goal**: Produce stronger, lighter, and cheaper carbon fiber bike.
- 4 Components to carbon fiber production:
  1. **Filaments**: 6K vs. 1K bundle
  2. **Oven temp**: high vs. low
  3. **Heating time**: long vs. short
  4. **Electrically-charged water**: strong versus weak





Example continued

- *If a behavioral scientist was making a bike, how do they hypothesize their components?*
    1. Filaments: 6K or 1K?
    2. Oven temp: Higher or lower?
    3. Heating time: Long or shorter?
    4. Electrical charge: Stronger or weaker?



- H1: More, higher, longer, stronger > less, lower, shorter, weaker
    1. Filaments: 6K is better than 1K;
    2. Oven temp: Higher better than lower;
    3. Heating time: Longer better than shorter;
    4. Electrical charge: Stronger better than weaker.

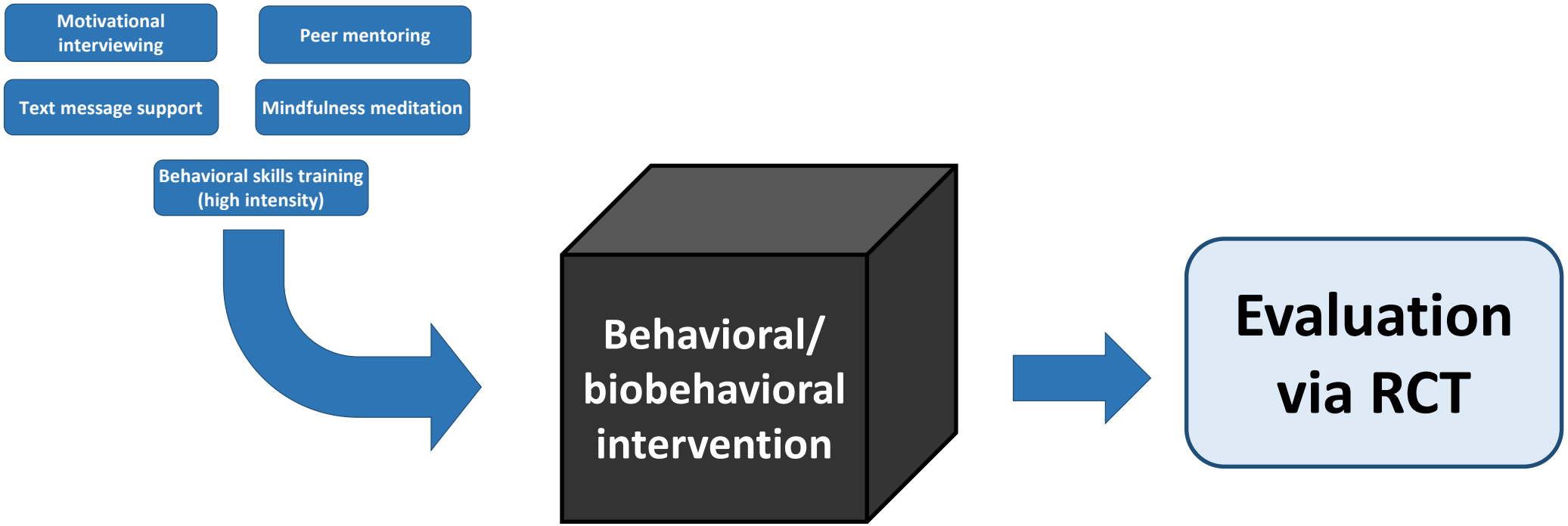
- Success! Your bike is better! But why?
- Failure ☹ - Your bikes is worse. But why?

Classic Treatment Package Approach

- **Turn everything to "high" in multi-component behavioral interventions**
  - Motivation interviewing
  - Peer support
  - Text message support
  - Behavioral skills training
  - Mental Health training

1. Design interventions by turning each component to "11."
2. Combine;
3. Compare to control group via RCT.
   - Possibly conduct post-hoc analyses.
   - Limitations in mediation analyses to identify "active ingredients" or mechanisms.

Classic Treatment Package Approach



There is nothing wrong with doing the CTP using an RCT!

How does MOST differs from the classic treatment approach and the role of the RCT?

MOST, CTP and the RCT

- **A few notes on MOST:**
  - **MOST does NOT replace (or demonize) the RCT!** Nothing wrong with doing the classic treatment approach – just recognize the limitations.
  - **The RCT is part of MOST in the evaluation phase.**
  - MOST is NOT an off-the-shelf framework applied identically for every project.
  - MOST is NOT a study design!
  - MOST recognizes the role of theory, formative research, mediation analyses, but argues it has its place in preparation phase.

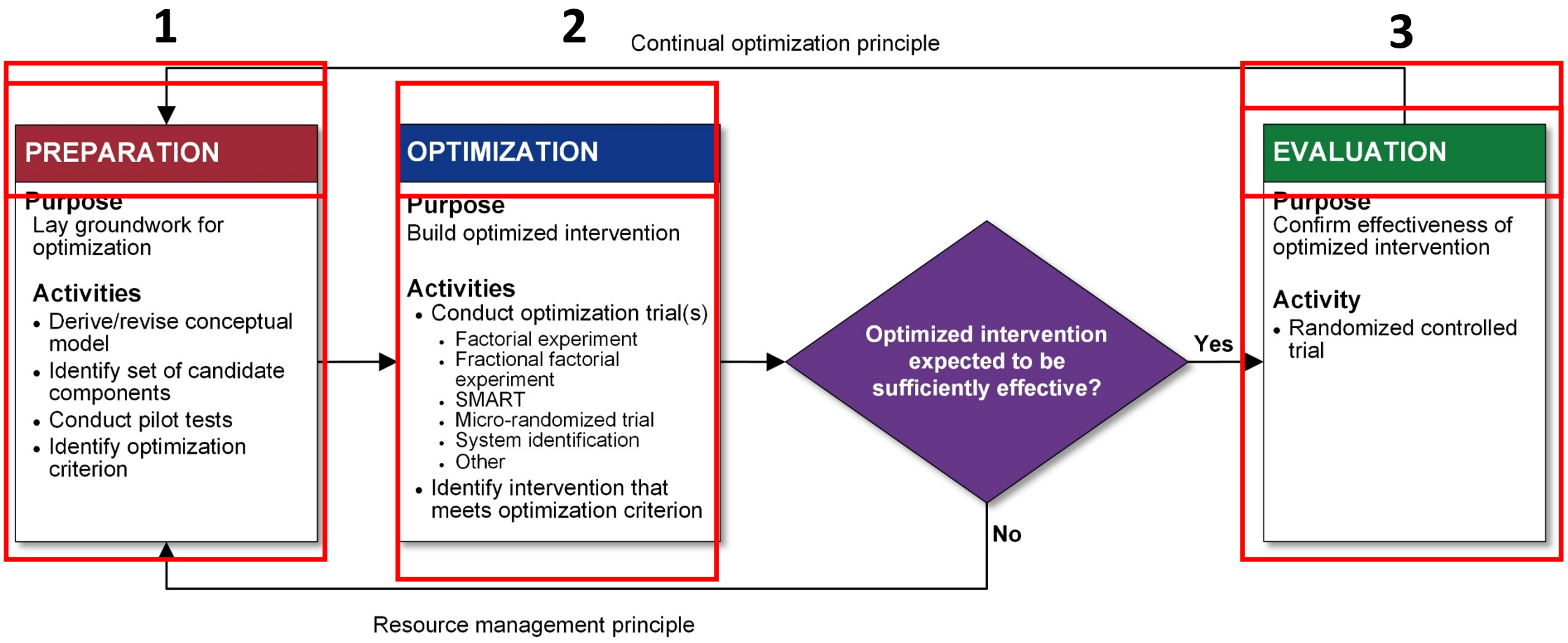
- **In the CTP, when you get a stat. significant result, you can't know…**
  - which components make positive contributions to overall effect;
  - whether one component has an impact on the effect of another;
  - whether a component's contribution offsets its cost;
  - whether all the components are really needed; and
  - how to make the intervention more effective, efficient, and scalable

MOST, CTP and The RCT Continued

- The CTP also can't tell you…
  - whether any components are worth retaining for future studies or scale up;
  - whether one component had a negative effect that offset the positive effect of others; or
  - specifically, what went wrong and how to do it better the next time!

- A definition – Intervention Science the "application of scientific and mathematical principles to practical ends, such as the design, manufacture, and operation of efficient and economical Programs Interventions, and Models

MOST is a framework, not a design.



Definitions: Starting Point

- **Components** - *Any aspects of an intervention that can be separated out for study – **Your ingredients!***

1. **Intervention content -** e.g., topics in a curriculum, homework
2. **Tool to promote adherence to intervention or behavior -** e.g., reminder phone calls or text messages
3. **Strategy to maintain high fidelity -** e.g., enhanced teacher training

- **WIP Eg.** – Does peer navigation (or NOT) for education and facilitation of MAT for PLWH who also inject drugs reduce drug use?

Key Definitions in MOST

- **Effectiveness** - Extent to which the intervention does more good than harm "under real-world conditions" (Flay, 1986).
  - Focus is on effectiveness here as that is the goal.

- **Efficiency** - Extent to which the intervention avoids wasting time, money, or other valuable resources.
  - e.g., 3-session ART readiness classes.

- **Economy** - Extent to which intervention is effective without exceeding budgetary constraints, and offers a good value.
  - e.g., effect sizes and clinical significance.

- **Scalability** - Extent to which the intervention can be implemented widely with fidelity.
  - e.g., pragmatic clinical trials – how much has to change to do the intervention in standard practice?

What does “optimization” mean in MOST?

- …process of identifying an intervention that provides the best expected outcome obtainable within key constraints imposed by the need for efficiency, economy, and/or scalability.

- 1. Best expected outcome – What is worth doing? Is the value good? Do people care about your outcome?
  - Implicit is the goal that we want to move the science forward!

- 2. Key constraints:
  - Does the intervention avoid wasting participant or staff time? (Efficiency)
  - Does it avoid wasting money? (sessions that few people attend?) (Efficiency)
  - How much data does it costs to do this on a participant’s phone? (Economy)
  - How burdensome or expensive is training and oversight? (Scalability)

Resource management principle

- You, the researcher, must always seek to make the best and most efficient use of available resources when obtaining scientific information!

- ANY experimental design is OK as long as it is the most efficient one!

Resource management principle (RMP)

- **Rationale for RMP**: Let's conduct a giant (e.g., 64-arm) RCT and test every possible combination of all behavioral intervention components – It would be definitive, but no way we could every power it!

- The RMP argues to instead, do a study that…
  - gives you the most information;
  - produces the most reliable information; and
  - move your field forward in the fastest way possible.

- The RMP helps you decide what information most important, and target resources in this area.

Resource management principle

- What are the resources you have now? That's your starting point!

Continual optimization principle

PREPARATION

Purpose
Lay groundwork for optimization

Activities
- Derive/revise conceptual model
- Identify set of candidate components
- Conduct pilot tests
- Identify optimization criterion

OPTIMIZATION

Purpose
Build optimized intervention

Activities
- Conduct optimization trial(s)
  - Factorial experiment
  - Fractional factorial experiment
  - SMART
  - Micro-randomized trial
  - System identification
  - Other
- Identify intervention that meets optimization criterion

Optimized intervention expected to be sufficiently effective?

Yes

No

EVALUATION

Purpose
Confirm effectiveness of optimized intervention

Activity
- Randomized controlled trial

Resource management principle

How can MOST improve the following study?

Real-World Example of Limitations of the CTP

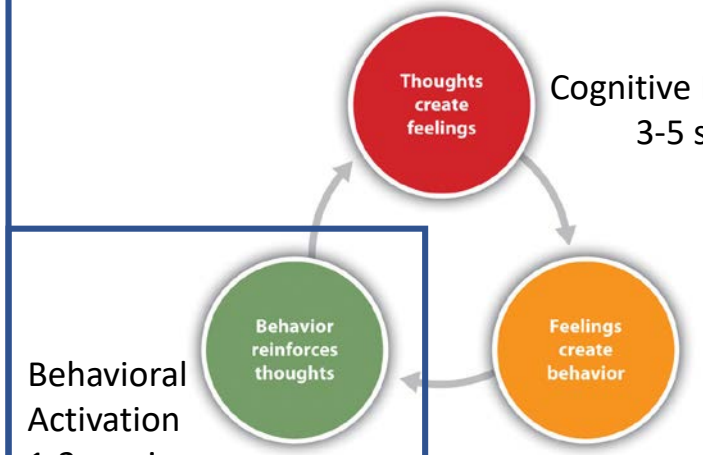
- NIMH R34 – A 40-person RCT testing CBT-AD against TAU.

1. All therapist were at least MA level
2. Paid consultants for oversight
3. Paid $20 per session to participants
4. Paid $5 fee per referral from staff
5. Rented office space at clinic.

- Reductions in self-reported depression, not blinded assessments.
- Improvements in self-reported adherence, not EDM.
- What caused these findings?
- How do we improve it?

1. Life-Steps
2. Cultural Exploration

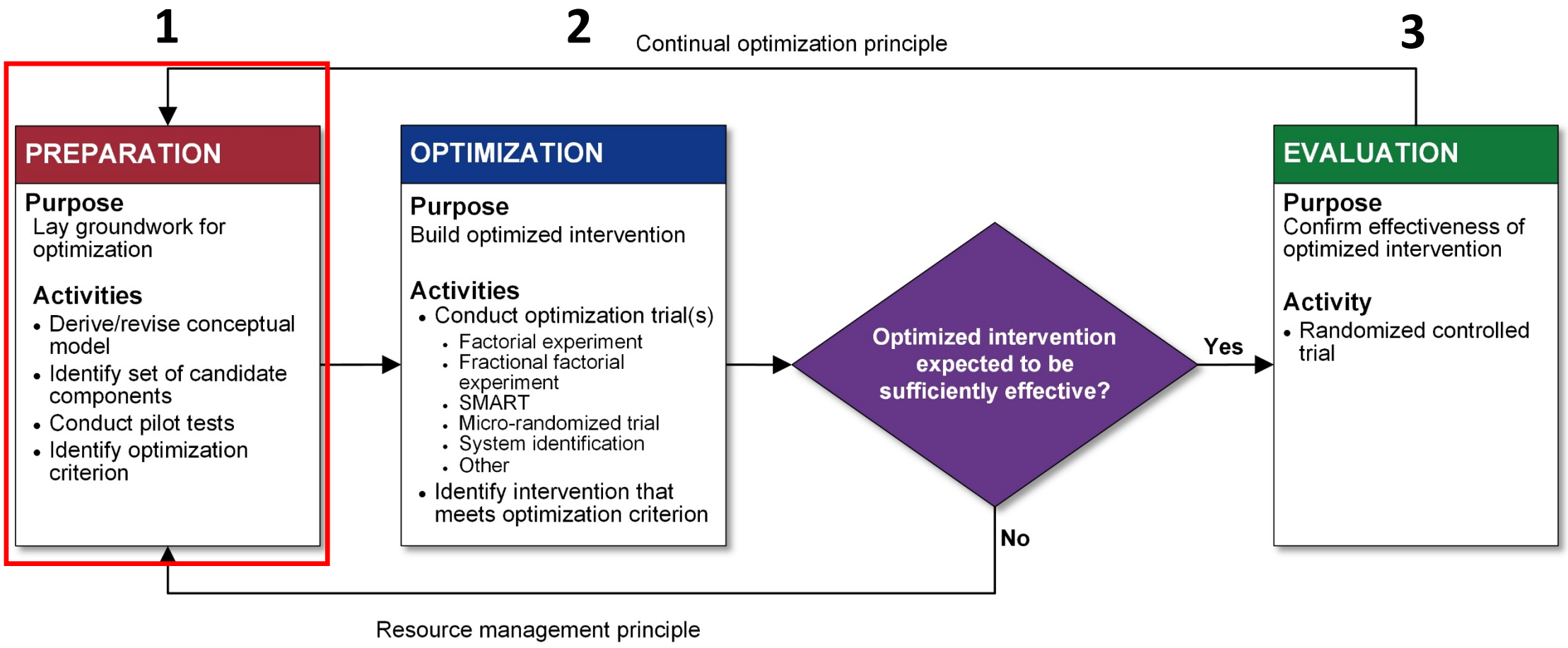
3. CBT-AD



4. Adherence Reminder

1. Sound on/off
2. Come in monthly/weekly

MOST is a framework, not a design.



Preparation Phase

1. Developing a detailed conceptual model.
   - How does the intervention change behavior?
   - Conceptual model is a blueprint, it is living, open to revisions.
   - Theory based – more than 1 can be used – How does X affect Y?
2. Selecting candidate components – What do you want to test that is efficient, economical, etc.
   - Pilot test – acceptability, feasibility of protocols, training, etc.

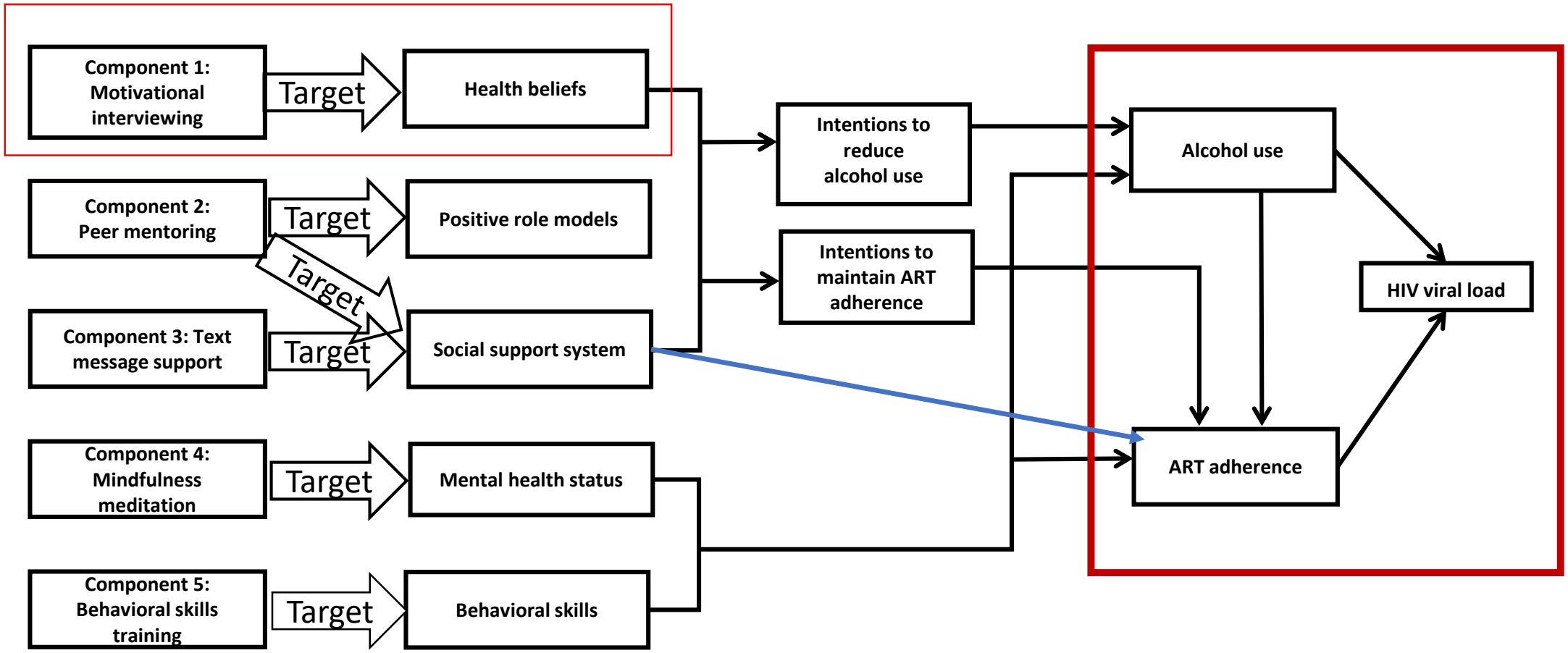
3. Identifying an optimization criterion – Explicit conditions of your intervention that make it best use of resources and worth investment.
   1. Thresholds – Does a component make the cut?

Optimization Criterion (OC)

- You must draw a conceptual map, state your RMP, and define your OC.
- State explicitly the conditions you will not break from!
- Best expected outcome – Is your outcome worth it?
  - Clinical significance versus statistical significance.
  - Reductions in depression scores, or reductions in depression from moderate to mild?
- Key Constraints:
  - Money, time, other resources
  - E.g., **An internet-delivered intervention that can be completed in under 30 minutes?**
  - E.g., **An intervention delivered for under $75 dollars that increases the odds, 2-fold, of keeping the next HIV appointment.**
    - Costs of outreach to find and reschedule next missed visit is $100.

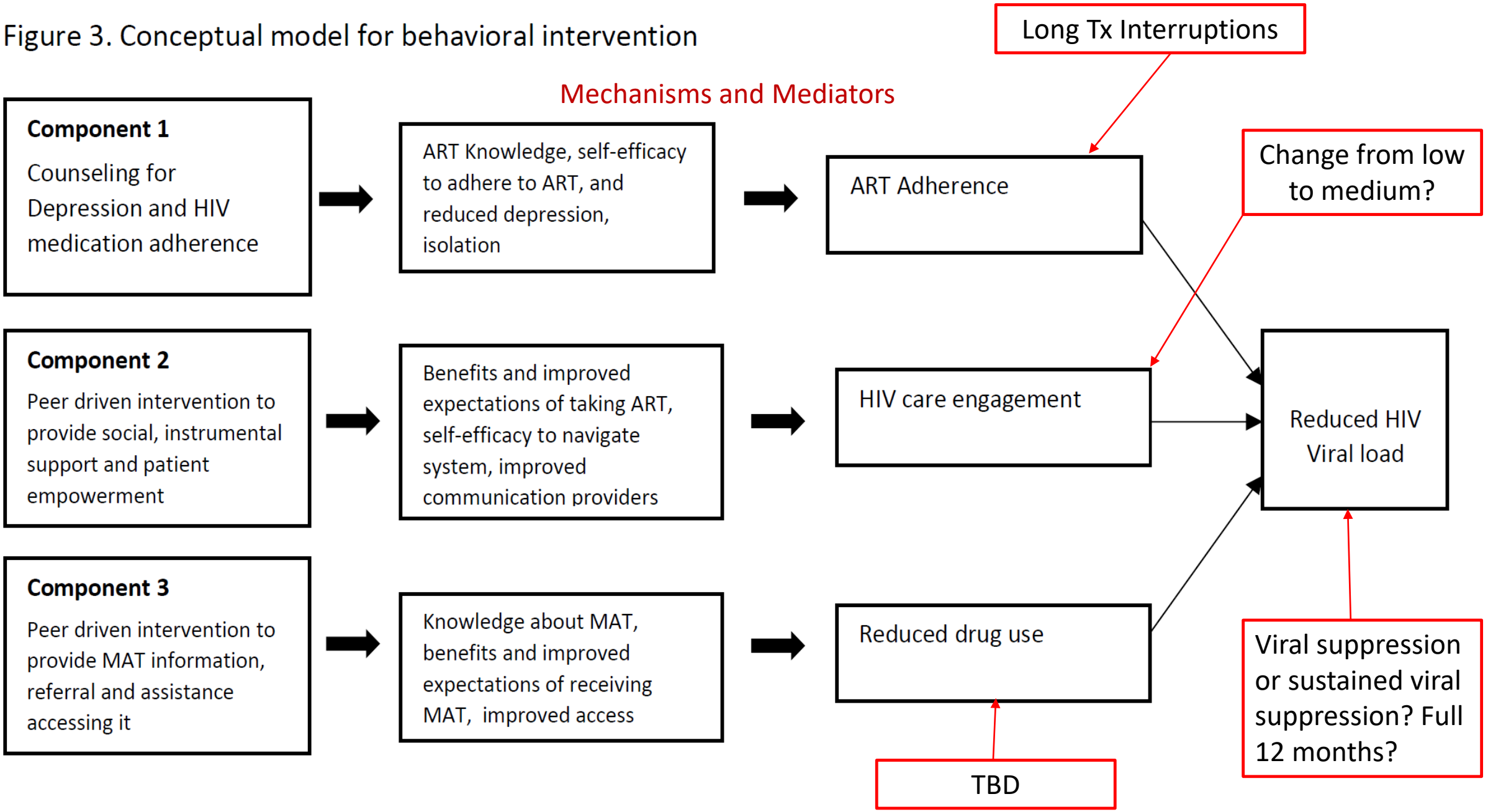
Conceptual Model (blue print)

- It is living and each component should focus on one causal variable.



- *Best expected outcome on adherence for no more than $500 and less than 10 hours of intervention exposure*.

Figure 3. Conceptual model for behavioral intervention



Preparation Phase Summary

- Decide on how much new research is needed for each component?
  - **Do you need pilot testing?**
  - R01 or R34?
  - E.g., Study in Cd. Juárez – **What has been done and can we sell there is no need for pilot testing?**
  - **Make the investment claim! (R01 funding to optimize).**
- Identify all key constraints – Participant and researcher time.

- State your resource management principle – You will NOT include components or move forward unless X1 and X^n are met!
  - While may not be useful for your personal gain, this is how science moves forward.

- Draw your conceptual map, peer review it, make known to reviewers that it will change – that is the point of optimization!

- Pick a study design that is efficient, economical and scalable!

The Optimization Phase

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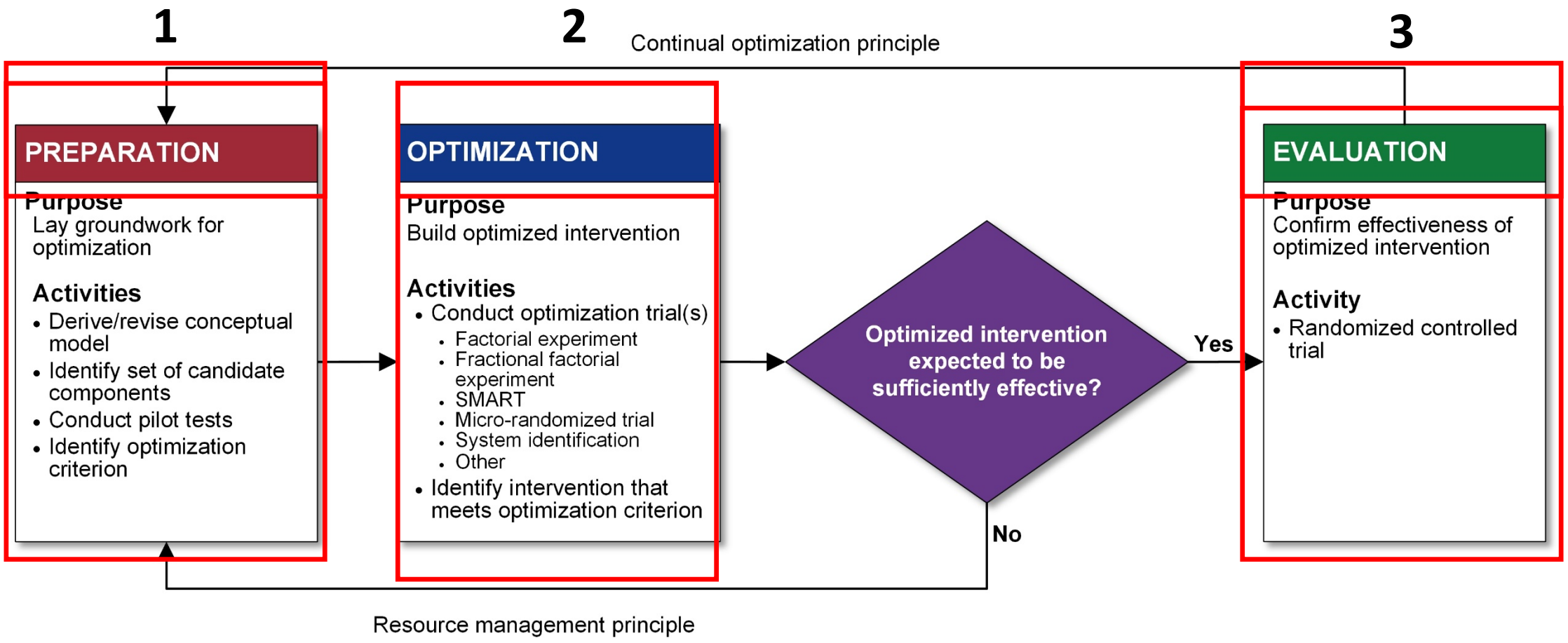
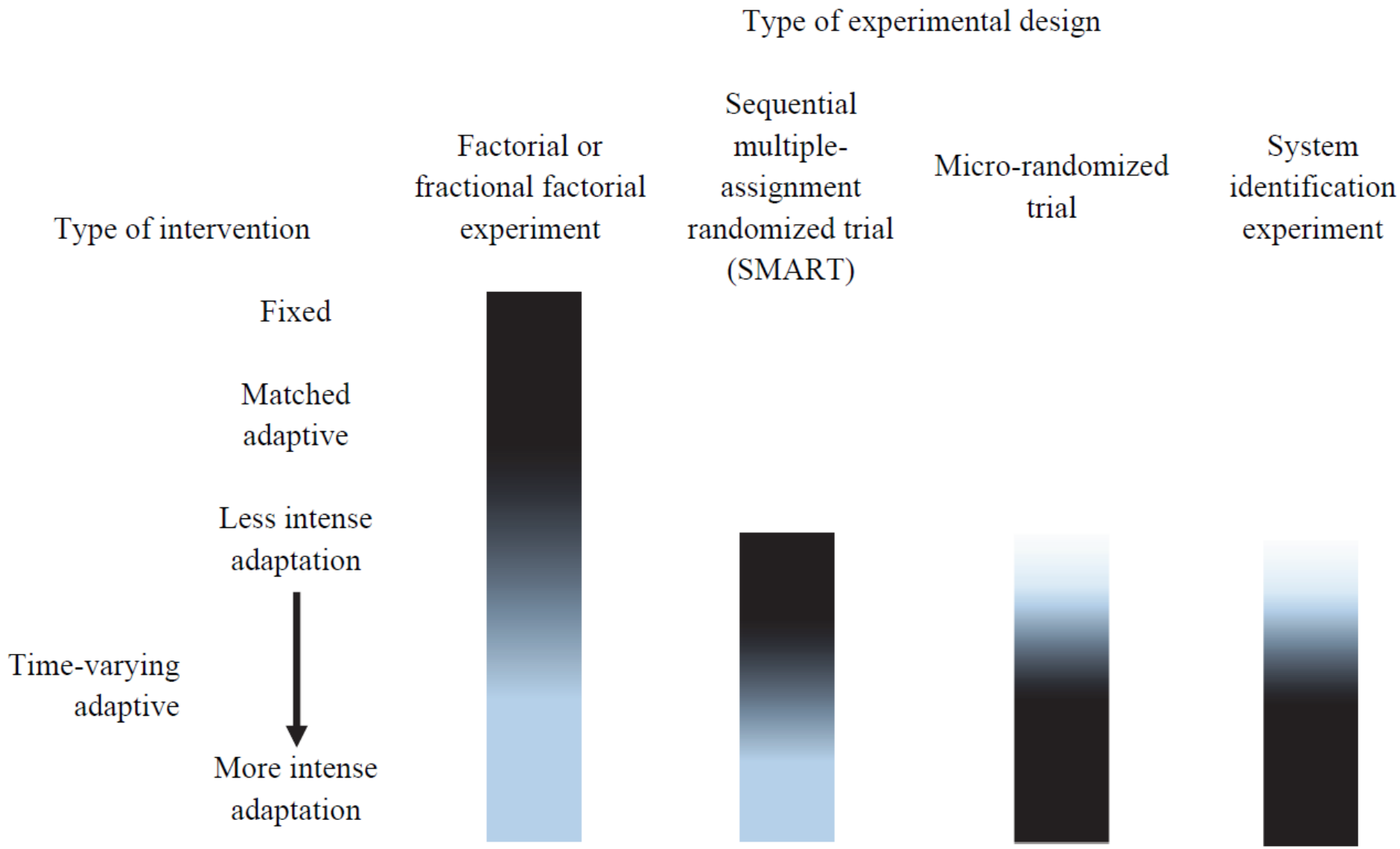


Likely relevance of various types of experimental designs for optimization of different types of interventions



Combining components into a multi-component intervention

Factorial Designs

- Goal is to identify best components and their levels.
  - Start with On/off rather than low, med. and high – why?
  - Not one component versus another.
  - Not combination of each other.
- Identify effect sizes.
- Identify how components affects each other – Improve, no effect, suppress.
- Collect ALL information to make a decision!

Experimental condition	Factor A	Factor B	Factor C	Factor D
1	No	No	No	No
2	No	No	No	Yes
3	No	No	Yes	No
4	No	No	Yes	Yes
5	No	Yes	No	No
6	No	Yes	No	Yes
7	No	Yes	Yes	No
8	No	Yes	Yes	Yes
9	Yes	No	No	No
10	Yes	No	No	Yes
11	Yes	No	Yes	No
12	Yes	No	Yes	Yes
13	Yes	Yes	No	No
14	Yes	Yes	No	Yes
15	Yes	Yes	Yes	No
16	Yes	Yes	Yes	Yes

Notes on Factorial Designs

- They are efficient
- Factorial designs can be more powerful because each factor has its own control when balanced.
- Not discussed, but you can do more with less than comparing Treatment A against a control.
- MAIN EFFECT OF FACTOR A is mean of conditions 1-8 vs. mean of conditions 9-16

Experimental condition	Factor A	Factor B	Factor C	Factor D
1	No	No	No	No
2	No	No	No	Yes
3	No	No	Yes	No
4	No	No	Yes	Yes
5	No	Yes	No	No
6	No	Yes	No	Yes
7	No	Yes	Yes	No
8	No	Yes	Yes	Yes
9	Yes	No	No	No
10	Yes	No	No	Yes
11	Yes	No	Yes	No
12	Yes	No	Yes	Yes
13	Yes	Yes	No	No
14	Yes	Yes	No	Yes
15	Yes	Yes	Yes	No
16	Yes	Yes	Yes	Yes

- MAIN EFFECT OF FACTOR B is mean of conditions 5—8 and 13—16 vs. mean of conditions 1—4 and 9—12

Experimental condition	Factor A	Factor B	Factor C	Factor D
1	No	No	No	No
2	No	No	No	Yes
3	No	No	Yes	No
4	No	No	Yes	Yes
5	No	Yes	No	No
6	No	Yes	No	Yes
7	No	Yes	Yes	No
8	No	Yes	Yes	Yes
9	Yes	No	No	No
10	Yes	No	No	Yes
11	Yes	No	Yes	No
12	Yes	No	Yes	Yes
13	Yes	Yes	No	No
14	Yes	Yes	No	Yes
15	Yes	Yes	Yes	No
16	Yes	Yes	Yes	Yes

- MAIN EFFECT OF FACTOR C is mean of conditions 3,4,7,8,11,12,15, and 16 vs. mean of conditions 1,2,5,6,9,10, 13, and 14

Experimental condition	Factor A	Factor B	Factor C	Factor D
1	No	No	No	No
2	No	No	No	Yes
3	No	No	Yes	No
4	No	No	Yes	Yes
5	No	Yes	No	No
6	No	Yes	No	Yes
7	No	Yes	Yes	No
8	No	Yes	Yes	Yes
9	Yes	No	No	No
10	Yes	No	No	Yes
11	Yes	No	Yes	No
12	Yes	No	Yes	Yes
13	Yes	Yes	No	No
14	Yes	Yes	No	Yes
15	Yes	Yes	Yes	No
16	Yes	Yes	Yes	Yes

- MAIN EFFECT OF FACTOR D is mean of conditions 1,3,5,7,9,11,13,15 vs. mean of conditions 2,4,6,8,10,12,14,16

Experimental condition	Factor A	Factor B	Factor C	Factor D
1	No	No	No	No
2	No	No	No	Yes
3	No	No	Yes	No
4	No	No	Yes	Yes
5	No	Yes	No	No
6	No	Yes	No	Yes
7	No	Yes	Yes	No
8	No	Yes	Yes	Yes
9	Yes	No	No	No
10	Yes	No	No	Yes
11	Yes	No	Yes	No
12	Yes	No	Yes	Yes
13	Yes	Yes	No	No
14	Yes	Yes	No	Yes
15	Yes	Yes	Yes	No
16	Yes	Yes	Yes	Yes

But you love component X…

Keep it!

You just can't estimate it!

Last step is estimation of effects and plotting them.

		Factorial Experiment			
Experimental Condition (Cell)	Information about effects of alcohol	*MI*	*PEER*	*TEXT*	*n*
1	Yes	No	No	No	40
2	Yes	No	No	Yes	40
3	Yes	No	Yes	No	40
4	Yes	No	Yes	Yes	40
5	Yes	Yes	No	No	40
6	Yes	Yes	No	Yes	40
7	Yes	Yes	Yes	No	40
8	Yes	Yes	Yes	Yes	40

The Conclusion-vs-Decision Priority

- Philosophical principles to getting starting – Goal is to make decisions about what to keep.

- **Conclusion-priority**: Does the effect exists?
  - Need sufficient power to detect the effect if it is there, whatever the size
  - Hypothesis test may result in "We do not know."
  - "Science court" demands use of traditional α.

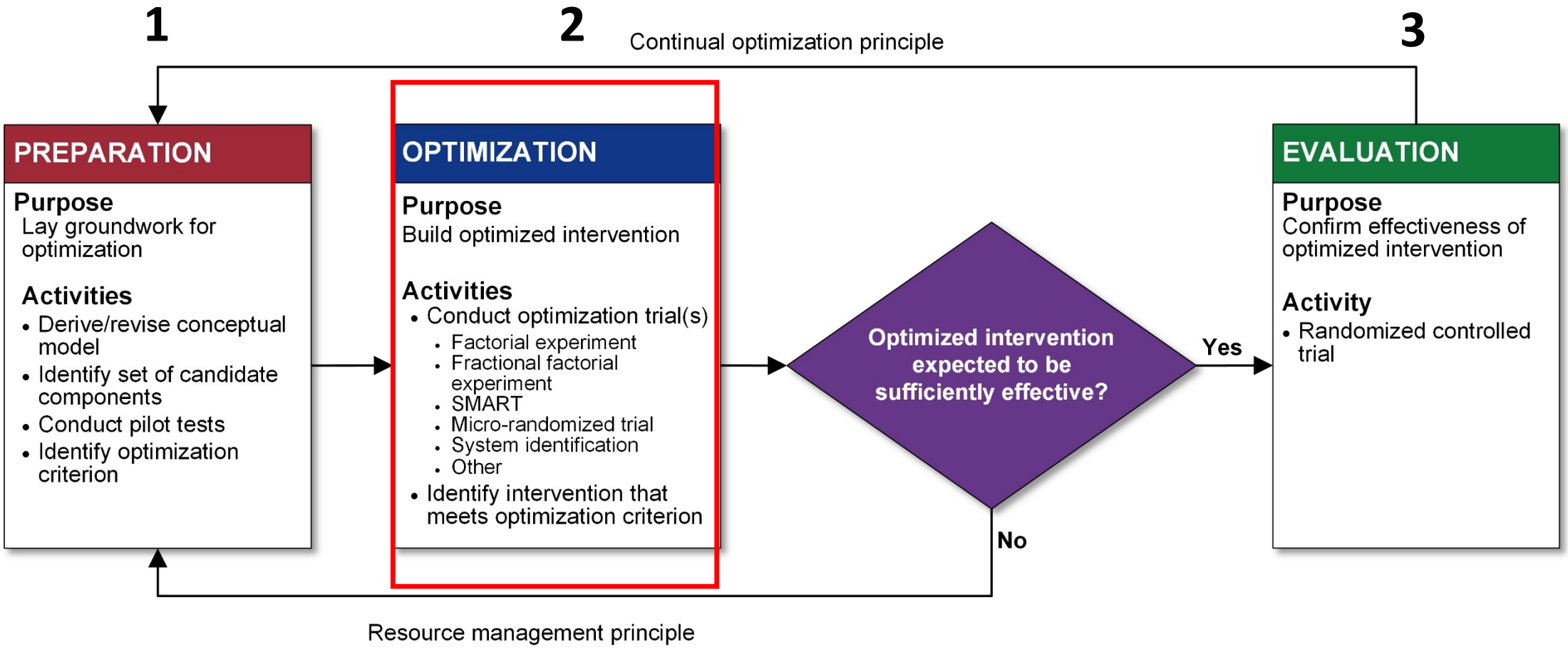
- **Decision-priority**: Decide on components/component levels!
  - Need sufficient power to provide a solid basis for decision-making
  - "We don't know" not an option – Does not tell you what to keep?
  - Investigator may strategically increase α to increase power (e.g., $p < .10$) if component has an effect but not stat. significant by science court.

- Decide on what your effect size is and how this fits with your decision priority.
- Do the study, and plot the graphs.

Overview of Factorial Designs

- **Based on conceptual map for a multi-component intervention** – what components affect the outcome through a single mediator?
- Factorial designs are more efficient as each factor has its own control.
- Decide what size of an effect is not necessarily needed for stat. significance, but clinical significance and worth the value
  - Best expected outcome as defined in your resource management principle.
  - Remember, you are building a product like an engineer.
- When components fail, you can screen out or go back, revise and re-optimize.
- Not discussed but worth reading:
  - Fractional factorial designs when you have many components
  - Multi-level components when data are clustered

MOST is a framework, not a design.



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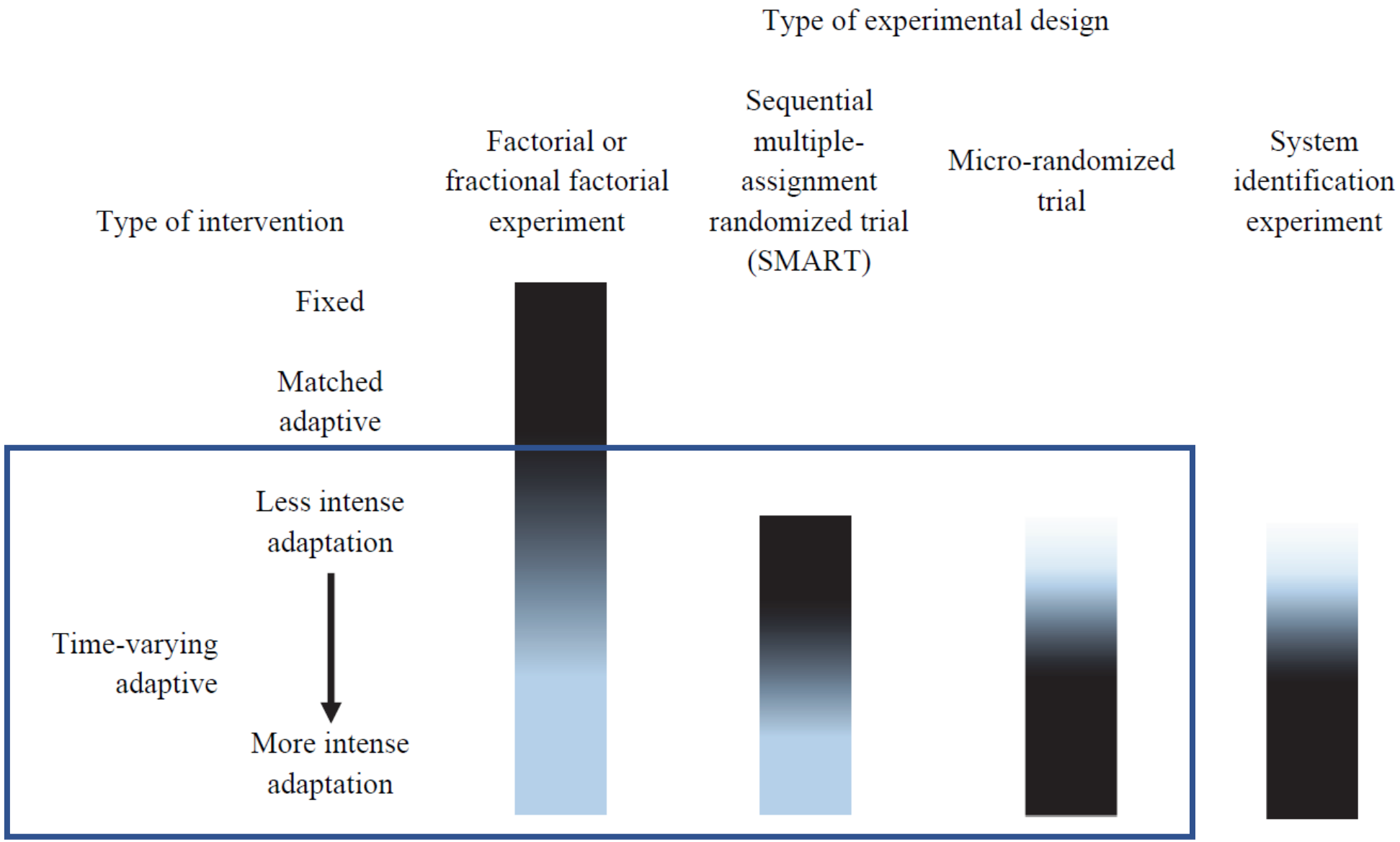


Adaptive Intervention

- **Outcome of interest** – HIV care engagement, depression, adherence, smoking, diet, exercise, etc.

- **Question 1** - Does Tx A work better than Tx B at improving the outcome?
  - Not does Tx A work better than control, it is thinking about how people respond different to different treatments.
  - **Does it help to start with low versus high dose? I think so!**

- **Question 2 –** What to do when Tx A works? What to do when patient doesn't respond to Tx A?

Adaptive Interventions

- CTP is typically “fixed” – all people get same thing, ideally.
- Adaptive interventions – people get interventions based on decision rules.
- You use alternative designs to build adaptive interventions.

- **My argument** – Will everyone receive the same exact benefit from your intervention?

- **Past experience – CBT R34** – Wasted resources on training, materials, etc., for sessions that no one attended or attended but required foundational knowledge that we had no time to improve.
  - Qual data would show otherwise – Problem-solving sessions.

Adaptive Interventions

- **Matched adaptive** – Heavy smokers get X amount of nicotine replacement at start versus intermittent smokers get X amount at the start.

- **Time-varying adaptive** – Interventions changes over time based on how participant responds.
  - What guides “changes” or ”adaptations” are decision rules based on evidence!
  - Tailoring variables – Intermediate outcome that is used to decide if and how to adapt.

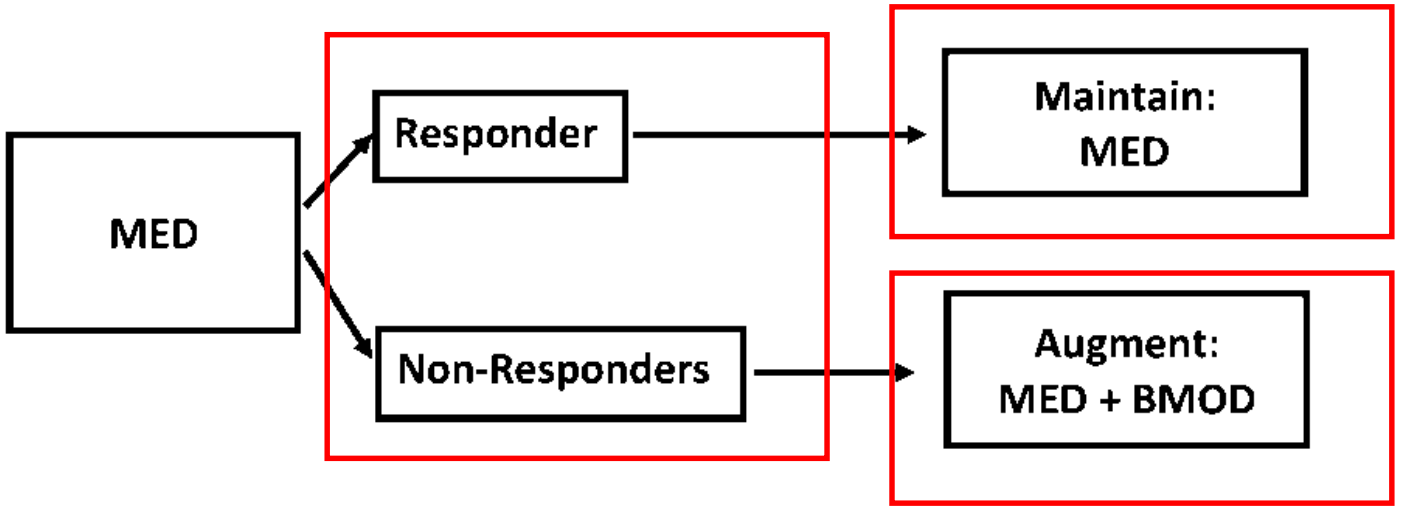
- Grant tip - Adaptive intervention described like basic medical treatment.
  - Patient X has condition A
  - Prescribe treatment A, report back **one week later**.
  - No change in condition A, make a decision:
    - Wait it out, maybe delayed benefit.
    - Augment, maybe add something, possibly higher dose.
    - Switch, treatment A does not work so go to treatment B.

Adaptive Interventions

- Example Continued – You give basic medical histories to providers – this informs how they prescribe treatment.
  - **New interventions** that take into account clinical data, biomarkers, behavioral markers…
- **Implicit assumptions of fixed interventions**:
  - To maximize the probability of offering enough for everyone, the intervention has components that people do not need, or is more intense than some people need.
    - If a participant does not need the extra stuff/added intensity, getting it will not diminish that participant's outcome.
  - There will be variability across people in response to the intervention
    - Some people may not respond, but that won't be dealt with in THIS intervention
- Adaptive interventions – Intervention that works for all people, the right type and the right dose, no more, no less.

Elements of simple adaptive intervention

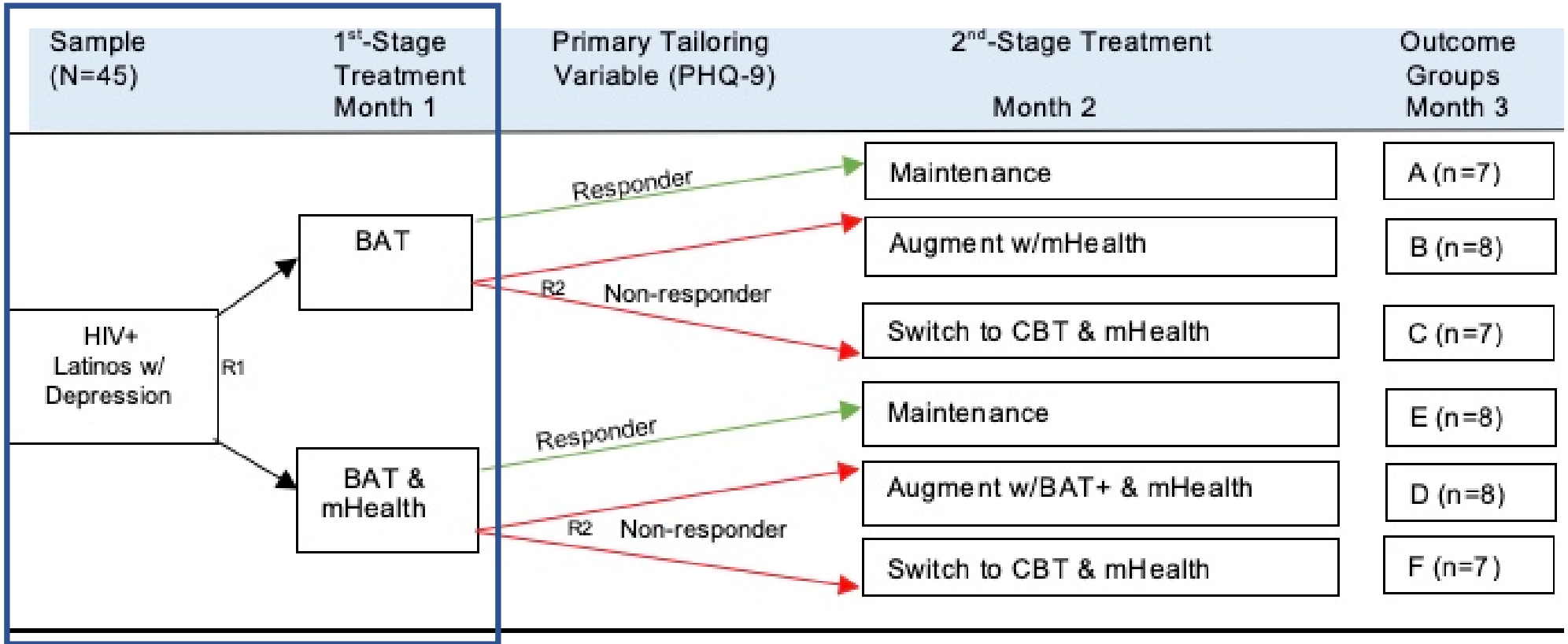
ADHD in children ages 6 – 12



- Response status measured monthly by the teacher
  - Based on two measures: Non-response if: Impairment Rating Scale ≥ 1 domain & Individualized Targeted Behaviors < 75% **(Tailoring Variable)**

Current Project

- **Fixed Intervention** – Combine CBT + mHealth + HIV care engagement components into one.
- **Adaptive Intervention** – Use a **sequential multiple assignment randomized trial** (SMART) to build the adaptive intervention.
- **Sample** – HIV + Latinos w/mild-to-moderate depression – Why?
- **1st Stage Tx** – Behavioral Activation or Behavioral Activation + mHealth – Why?



SMART

- SMARTs are a part of the optimization phase in MOST – same as factorial designs.
- SMARTs build the decision rules for your adaptive intervention.
- A SMART is just an randomized optimization trial with multiple stages
  - Each stage has a decision point
  - Randomization/re-randomization takes place at decision points
  - Real-time randomization versus matched

- Same as with other designs, the goal is to get all information needed to maximize effectiveness, efficiency, economical value, and that can be scaled up.

SMART

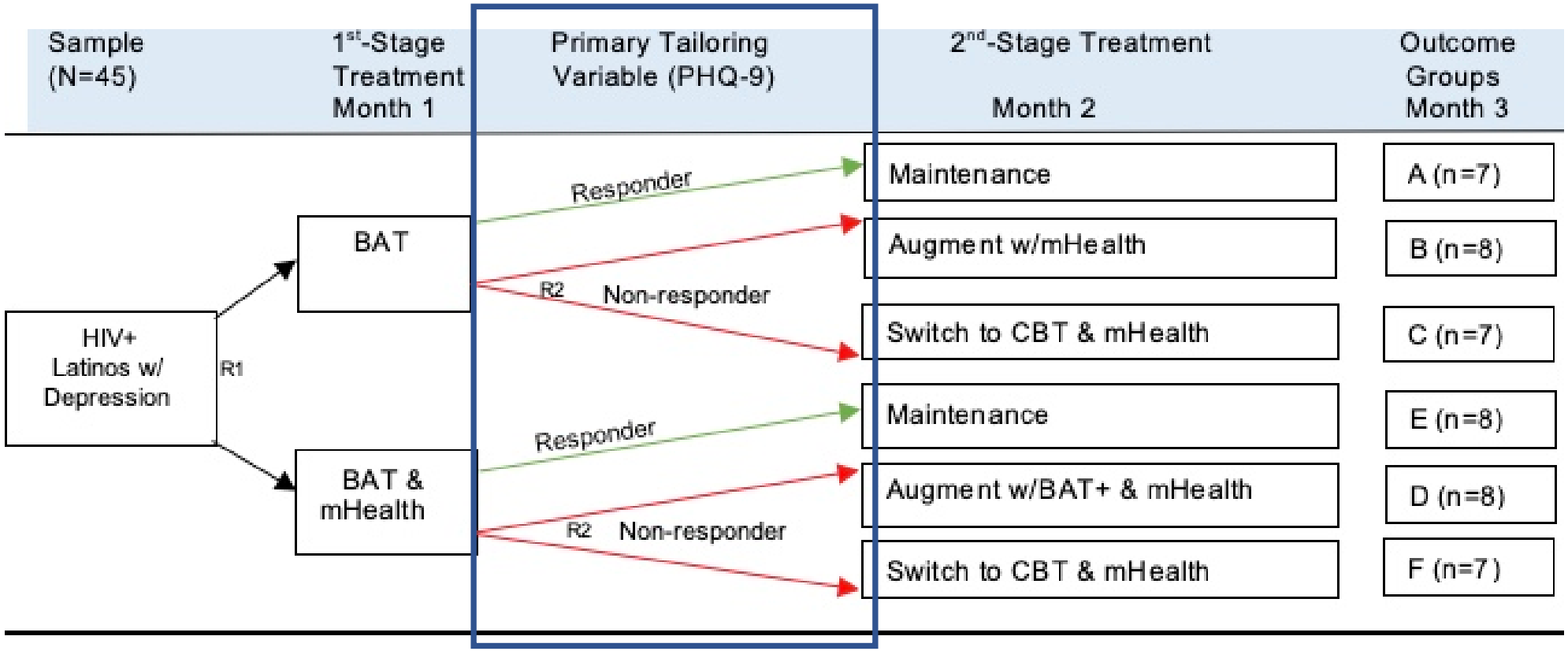
- Do you need a SMART?

- Are there multiple possible solutions to one problem?
  - Eg., Comorbid problems – What to treat first? Drug use or depression intervention?

- Do you think some people need more vs. less of an intervention?
  - “low intensity” versus “high intensity”

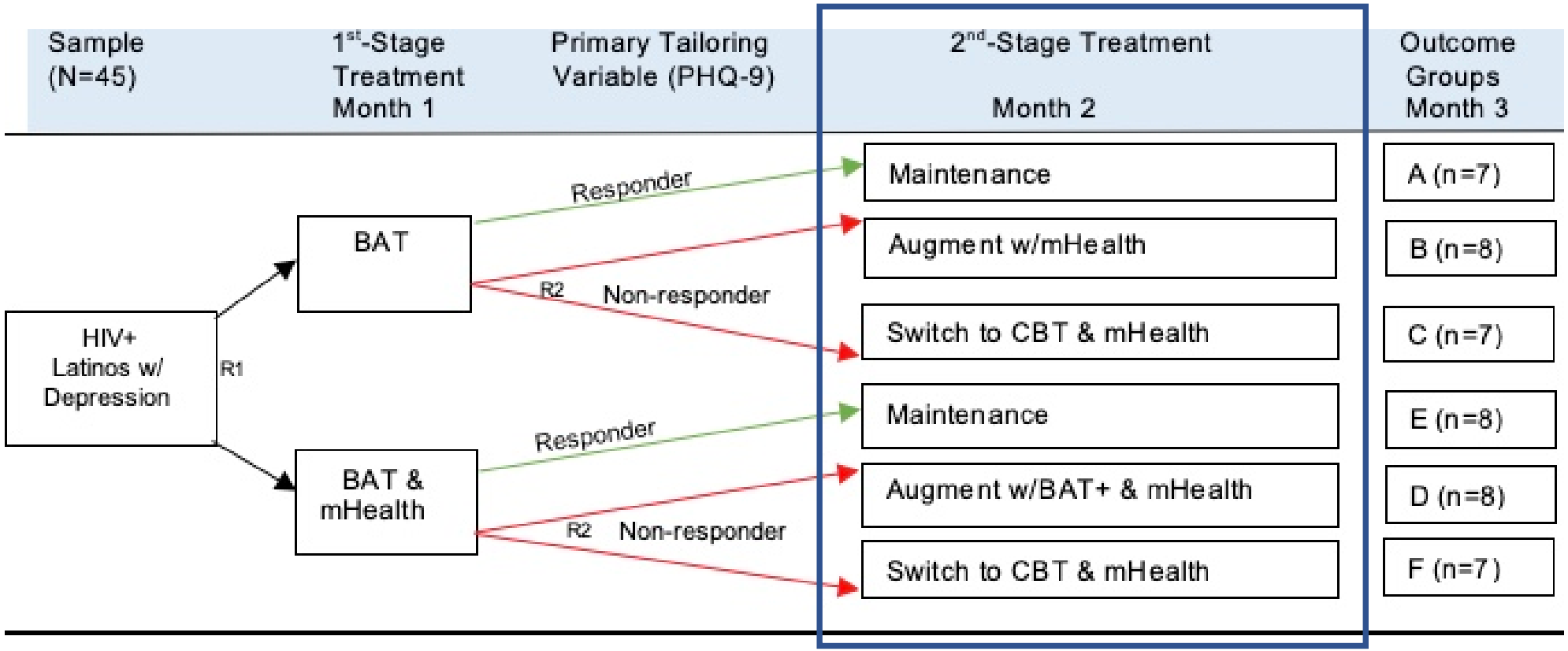
Current Project

- Decision when, whether, and how to adapt.
- **Decision Point** – One month – Why? Early detection in RCT.
  - You estimate “non-response rate” from literature.
- **Tailoring variable** – PHQ-9 – Classification from moderate to mild (deemed high value) – based on this, participants are considered “responder” and “non-responders.”



Current Project

- Based on decision rules, you decide whether to maintain, augment or switch - **This is called the 2nd stage treatment**.
- Based on response status, we asked a few questions:
  - BAT failed, add mHealth or switch to CBT to provide more robust content.
  - BAT and mHealth failed, add booster session or switch to CBT to provide more robust content.



Overview of Adaptive Intervention

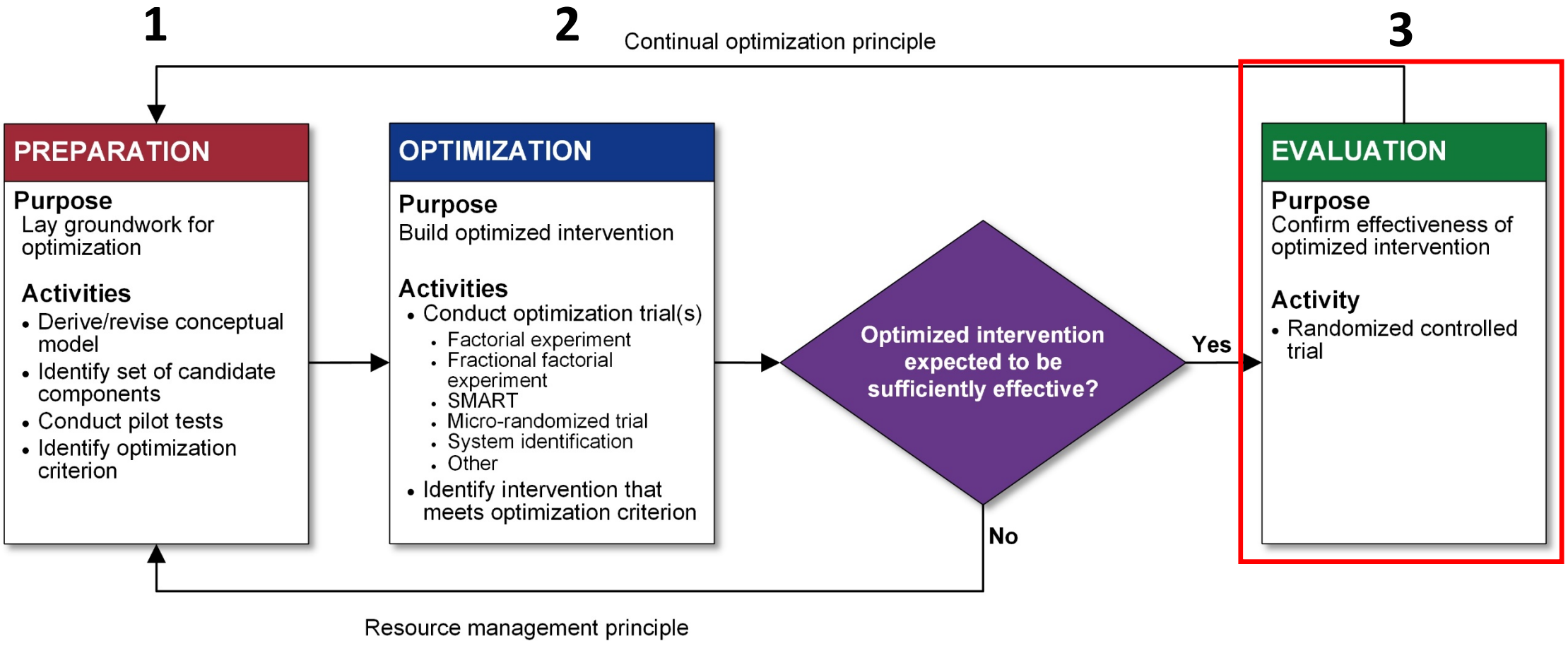
- It is not a design, the design is a SMART that gives you evidence for your key elements:
  - **Decision points** – Time frame – how long to stay in Tx A?
  - **Tailoring variable** – What change in the outcome is worthy of classifying "responders"?
    - Is it of high value?
  - **1st/2nd stage treatments** – What do you do when Tx A fails or succeeds?
  - Non-adherence/engaged problems – What do you do if people "don't engage with study?

Other designs linked to mHealth devices

- **Just-in-Time Adaptive Interventions (JITAI)** – Intervention delivered when needed where-ever needed.
  - Track, inquire, and intervene.
  - Text participant for urges for smoking, if urge reported, text back an intervention.

- **Micro-randomized Trials** – Participants randomized hundreds/thousands of times – Does intervention effects vary by time and individuals context?

MOST is a framework, not a design.



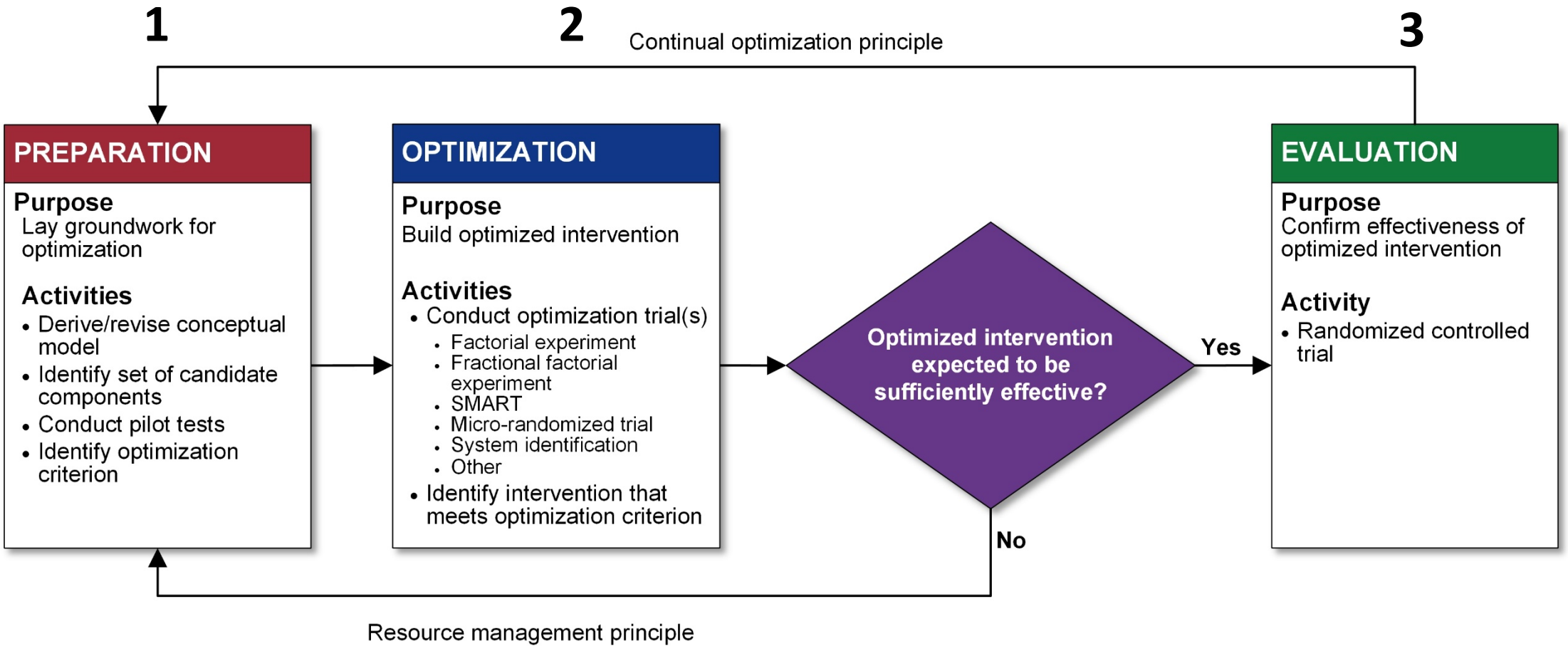
Evaluation Phase

- **Continual optimization principle – Don't release product unless it is ready, re-optimize.**
  - Unless a reviewer demands an RCT.

- **Factorial design** – You have evidence that X components combined produce Y – which is effective, efficient, scalable and economical as shown in your optimization trial.
  - Combination intervention A versus control – RCT
  - E.g., counseling, peer support, and mHealth will change behavior in this way.

- **Adaptive Intervention** - You have evidence that your decision rules for sequencing treatments for condition A is effective, efficient, scalable and economical as shown in your optimization trial.
  - Decision rules that guide whether, when and how to adapt are tested against a control in a RCT.
  - E.g., *Start with Tx A, go to C if responds, go to B if no response, monitor, switch to D.*

MOST is a framework, not a design.



Final Comments

- There are technical and statistical requirements as there are with all study designs.
- MOST is actually still a work-in-progress – There's discussion about how to handle other types of questions.
- MOST and Implementation Science – Some overlap and some disagreements.

Thank You & Questions?