SMART TRIALS: DEVELOPING PERSONALIZED, ADAPTIVE INTERVENTIONS

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Learning objectives

1. Understand the basics of SMART designs
2. Decide whether SMART designs are right for your research
3. Be prepared for the first meeting with a statistician to collaboratively design your trial

What are SMART trials?

- Sequential Multiple Assignment Randomized Trials
- A type of study design developed to build and test adaptive interventions
- An adaptive intervention is a set of decision rules about when and how to modify interventions (e.g., switch, step-up, etc.)
- The goal is to evaluate treatment sequences and develop health interventions that are individualized and respond to patient needs
- SMART trials mimic clinical practice in that interventions are adjusted as needed, although they are randomized at each decision point
- The hallmark of a SMART trial is multiple randomized treatment assignments within a patient
- Designs are highly flexible, and therefore, can be challenging

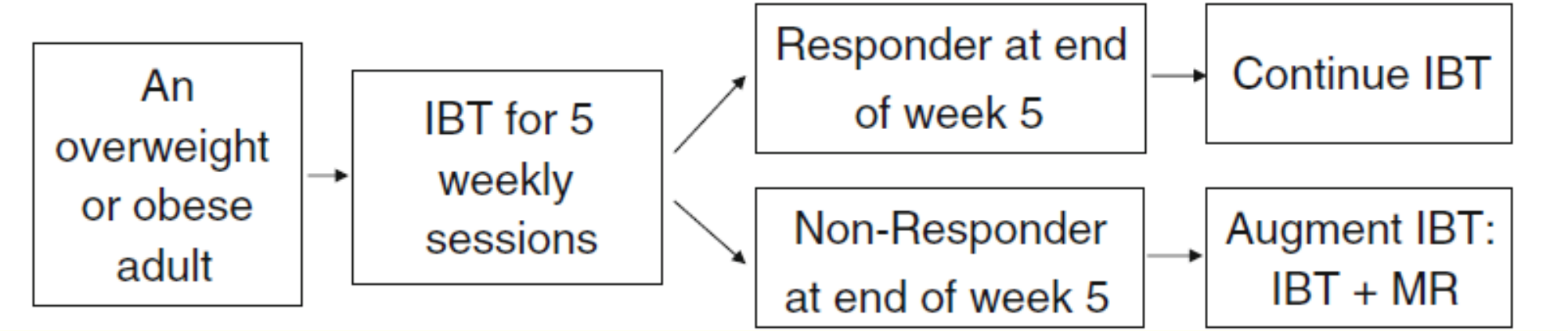
Why consider a SMART trial?

- SMART trials are ideal for settings where:
  - Patient outcomes are heterogeneous
  - Treatment goals change over time
  - There is a need to balance benefits and risks, cost, and burden of treatment
  - Effectiveness of therapies change over time
  - Comorbidities need to be considered in treatment algorithms
  - Relapse is possible
  - Maintaining adherence to treatment is difficult
- Design allows comparison of intervention options at different stages of treatment
- Data from SMART trials can be used to build tailored, personalized adaptive interventions
- Can evaluate interactions between treatments that would be missed in multiple single stage trials
- SMART trials are often used as part of the Multiphase Optimization Strategy (MOST) to optimize and evaluate multicomponent interventions

How do SMART trials work?

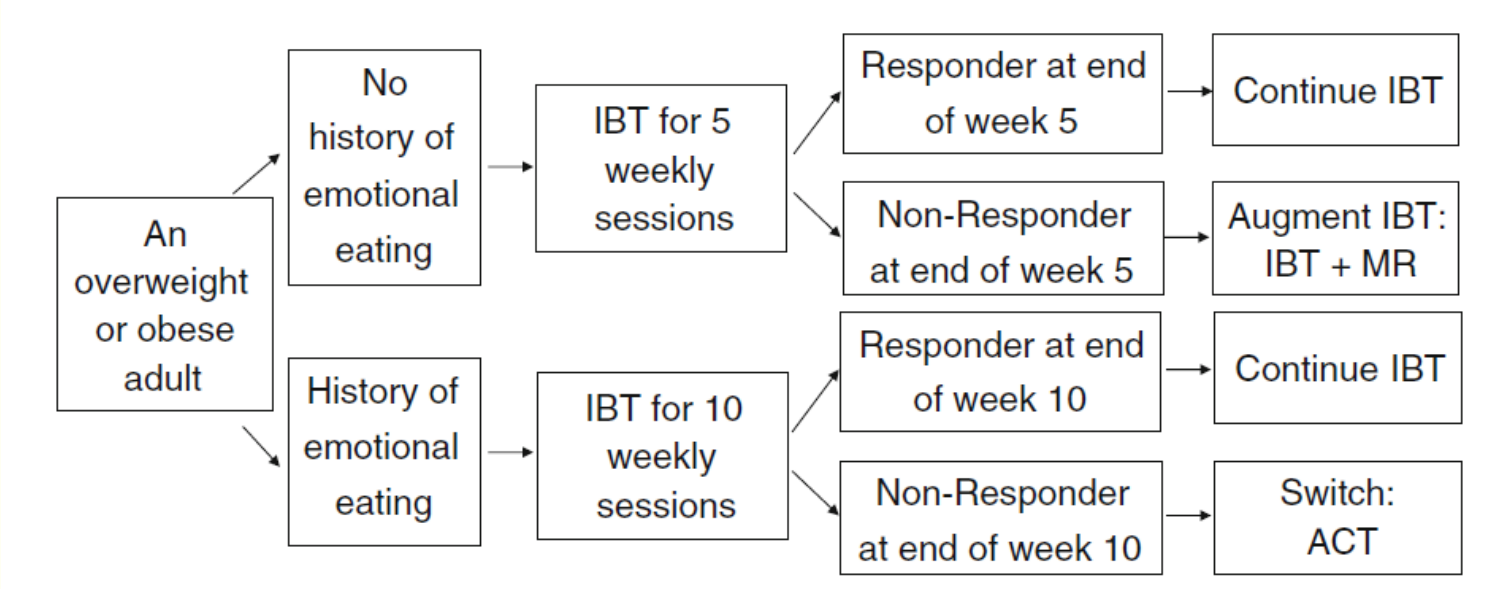
- At each of K≥2 decision points, the patient is randomized to one of the treatment options that are feasible given their history of treatments and response
- Critical design decisions:
  - Initial therapy
  - How long to wait to decide if therapy is effective?
  - How to determine if the therapy is effective?
  - What treatments to provide if the therapy is not effective?
- Primary tailoring variable is used to determine whether changes are needed
  - Needs to be a different outcome than the primary outcome of the trial
- All of these components (treatments, timing, tailoring variables) can be evaluated in a SMART, although a larger number of features to be evaluated increases sample size required

Example SMART (Almirall et al., 2014)



- Begin with individualized behavioral weight loss treatment (IBT)
- After 5 weeks, if the individual has lost ≥5 lbs (tailoring variable), continue on IBT
- Otherwise, augment IBT with meal replacements (MR)
- Note that a number of fixed treatment regimes (adaptive interventions) are embedded in the design

Example SMART (Almirall et al., 2014)



- Length of initial IBT determined by baseline characteristics
- Two tailoring variables: history of emotional eating and weight loss after 5 or 10 weeks
- For non-responders with history of emotional eating, switch to acceptance and commitment therapy (ACT)

Other study designs confused with SMART

- Adaptive clinical trials in which randomization probabilities change over time
- In SMART, randomization sequences are fixed (although it is possible to integrate adaptive randomization into a SMART)
- Cross-over trials in which a given patient receives all treatments
- The goal of a cross-over trial is to identify the single best treatment

SMART aims and hypotheses

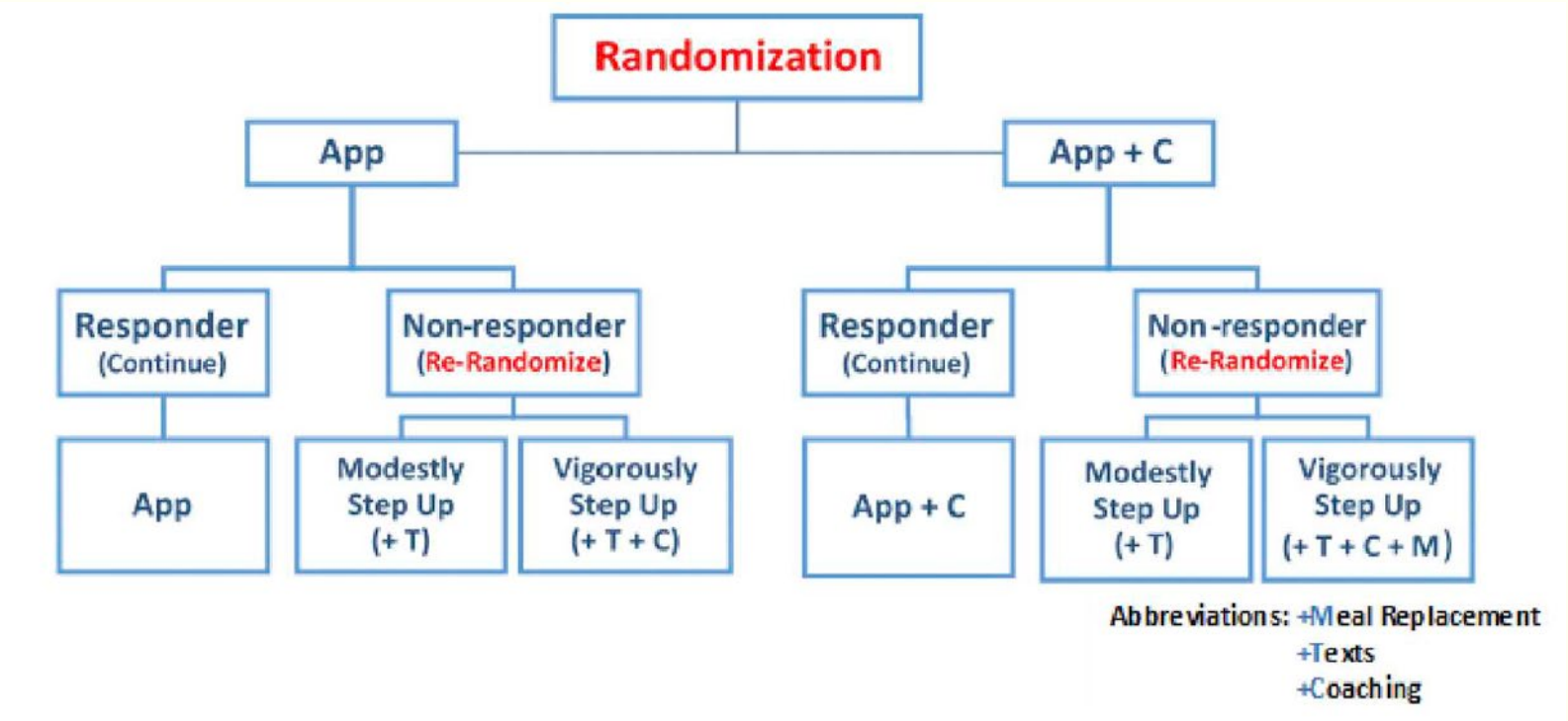
- A common concern about SMART designs is “sample splitting”
- Often, primary outcome involves pooling subjects across terminal nodes
- Main effect aim: comparing first or second stage options
  - Can use standard analytical techniques
- Embedded adaptive intervention aim: how do treatments at various stages interact?
  - Contrast two or more AI’s
  - Weighted analysis methods account for the fact that non-responders are randomized more often than responders
  - Replicate data for responders since they are consistent with multiple AI’s
- Optimization aim: identify the optimum sequence of treatments and tailoring variables
  - Normally a secondary aim, and the goal of a confirmatory trial

Typical SMART designs: “switch away from the loser”

- Develop a strategy for patients who fail to respond to a standard treatment
- Often all patients are assigned to the standard therapy first, and non-responders are randomized
- Several candidate treatments are tried sequentially and discontinued if no response
- Goal is to decrease time to response
- Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Rush et al., 2014)
  - All patients started on SSRI citalopram (CIT)
  - Responders continue on SSRI and were followed for 1 year
  - Non-responders entered series of RCTs
    - Level 2: 4 switch treatments (venlafaxine [VEN], sertraline [SER], bupoprion [BUP], cognitive therapy [CT]) plus 3 augmentation treatments (CIT+CT, CIT+BUP, CIT+buspirone [BUS])
    - Level 2a: if no response to CT, switch to BUP or VEN
    - Level 3: 2 switch (mirtazapine or nortriptyline) plus 2 augmentation options (lithium and thyroid hormone)

Typical SMART designs: stepped care

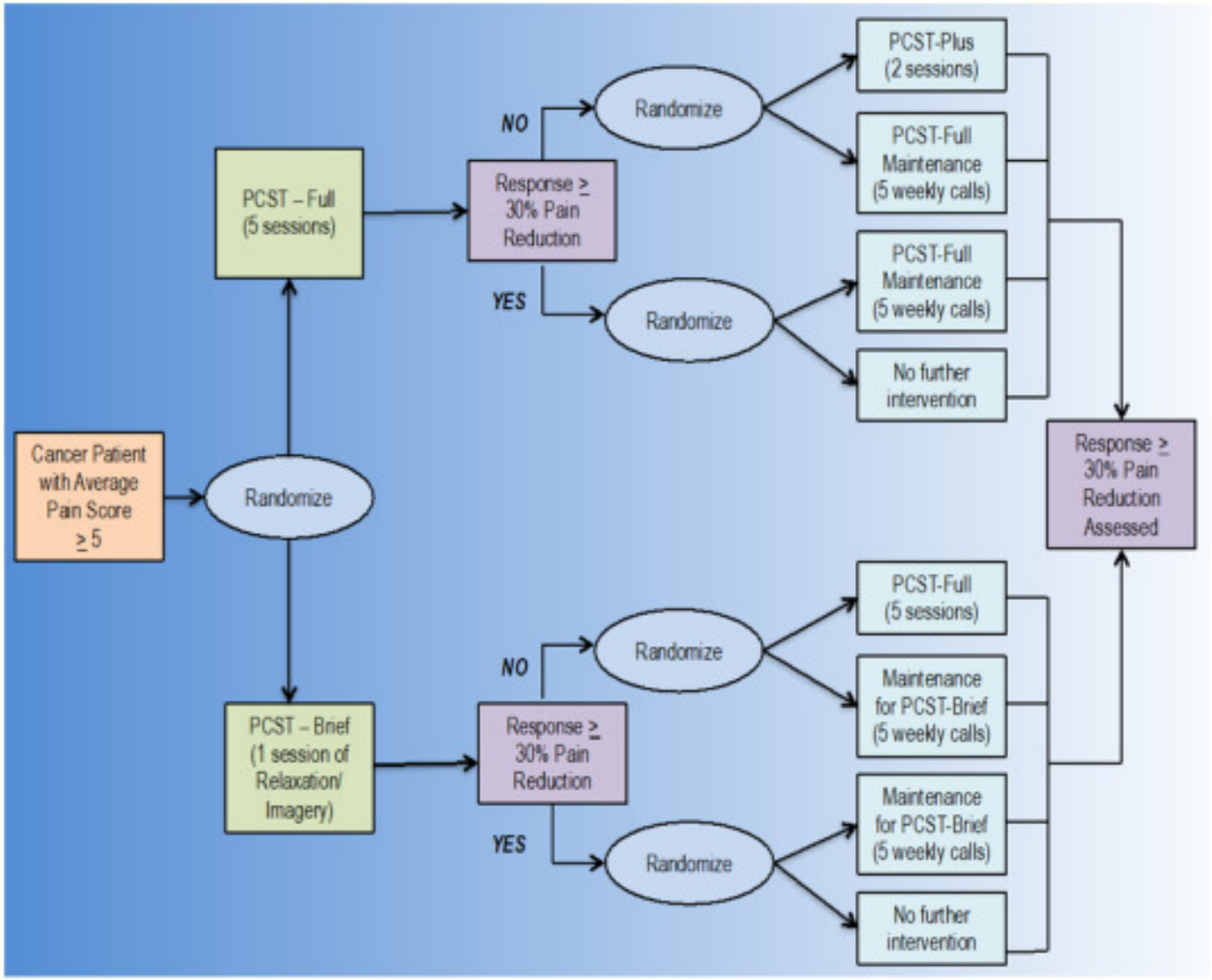
- Start with an inexpensive (cost, adverse events, burden) therapy and add more expensive treatments if needed
- Goal is to identify treatment regimes that produce improvements at the lowest cost
- SMART Weight Loss Management Study (Pfammatter et al., 2019)



Typical SMART designs: dose adjustment

- Identify optimal dosing regimes (either medication or other therapies)
- Consider either few doses (low/medium/high) or large/infinite number of doses
  - In the latter case, may need to make simplifying assumptions
- Pain Coping Skills Training in patients with breast cancer (Kelleher et al., 2017)

Typical SMART designs: dose adjustment



Challenges in SMART designs

- Identification of the tailoring variable and decision timing
  - If there is some evidence available, follow clinical practice
  - Can also randomize patients to combinations of treatments, decision times, and tailoring variables
  - If there are large cost or other constraints, prioritize patients most in need of treatment change
- Drop-out: some patients will not reach the entire sequence of decision points
  - Relatively little literature on this topic
- Missing data: need a pre-specified way of dealing with treatment changes if the primary tailoring variable is missing
  - E.g., assume missed visit = non-response, or classify patients as responders until proven otherwise
- Sample size
  - Combining many treatments, timings, tailoring variables can increase sample size
  - Can use a fractional factorial design in which some combinations are dropped – may not be able to estimate all interactions but this is often acceptable

Are SMART designs right for your research?

- Is your goal to develop and test adaptive, sequential, and/or multicomponent interventions or to identify the single best intervention?
- SMART trials are ideal for settings where:
  - Patient outcomes are heterogeneous
  - Treatment goals change over time
  - There is a need to balance benefits and risks, cost, and burden of treatment
  - Effectiveness of therapies change over time
  - Comorbidities need to be considered in treatment algorithms
  - Relapse is possible
  - Maintaining adherence to treatment is difficult
- Consider potential alternative designs
  - Evaluation of treatment “packages” – SMART designs allow you to “open the black box”
  - Multiple one-stage at a time trials – SMART designs reduce cohort effects and allow testing of interactions
  - Micro-randomized trials if there are many treatment decisions to be made on a fine time scale

Are SMART designs right for your research?

- Disadvantages of SMART designs
  - Complex, but often can be simplified
  - Requires collaboration with a statistician, but this is often the case with standard RCTs
  - Pharmaceutical companies may dislike head-to-head comparisons of drugs
- Wolbers and Helterbrand (2008) found that if the primary aim of a study is about the initial treatment and there is low probability of maintenance success, a one stage design is faster and more efficient
- However if both initial and maintenance treatment are of interest, a SMART design is more efficient
- Consider conducting a pilot study first (Almirall et al., 2014)
  - Demonstrate that the design is feasible and you have the necessary experience to conduct a SMART

For consideration prior to meeting with a statistician

- What are the pressing clinical questions to be answered?
  - Design the trial to answer those questions rather than determining which questions can be answered by a particular design
- What hypotheses are of primary interest?
  - SMART designs are often powered to compare first stage treatments – is that of primary interest?
  - Are there interactions you are willing to ignore to create a more efficient design?
- What are the key decision points and their timing?
  - Match clinical practice as much as possible
  - Optimal timing may be unknown, but could be considered in a follow-up study
- Identify the set of feasible treatment options at each stage
  - First stage treatments, maintenance treatments, salvage treatments
- Possible tailoring variables (different from primary outcome)

For consideration prior to meeting with a statistician

- Are there baseline characteristics that should be considered as tailoring variables?
- Is stratification desirable/necessary?
  - For example, in a trial of diabetes treatments, it may be helpful to ensure that the AI's are balanced with respect to diabetes duration
- If your goal is to compare first stage treatments, there are several ways to do this with respect to the second stage:
  - Marginalize over second stage: estimate the mean outcome in each of the first stage treatments averaging over the second stage (i.e., according to randomization probabilities in second stage)
  - Marginalize over standard of care: estimate the mean outcome in each of the first stage treatments assuming that patients receive second stage options according to current standard of care
  - Maximize over second stage: estimate the mean outcome in each of the first stage treatments assuming that patients received the optimal decision given their treatment history in the second stage

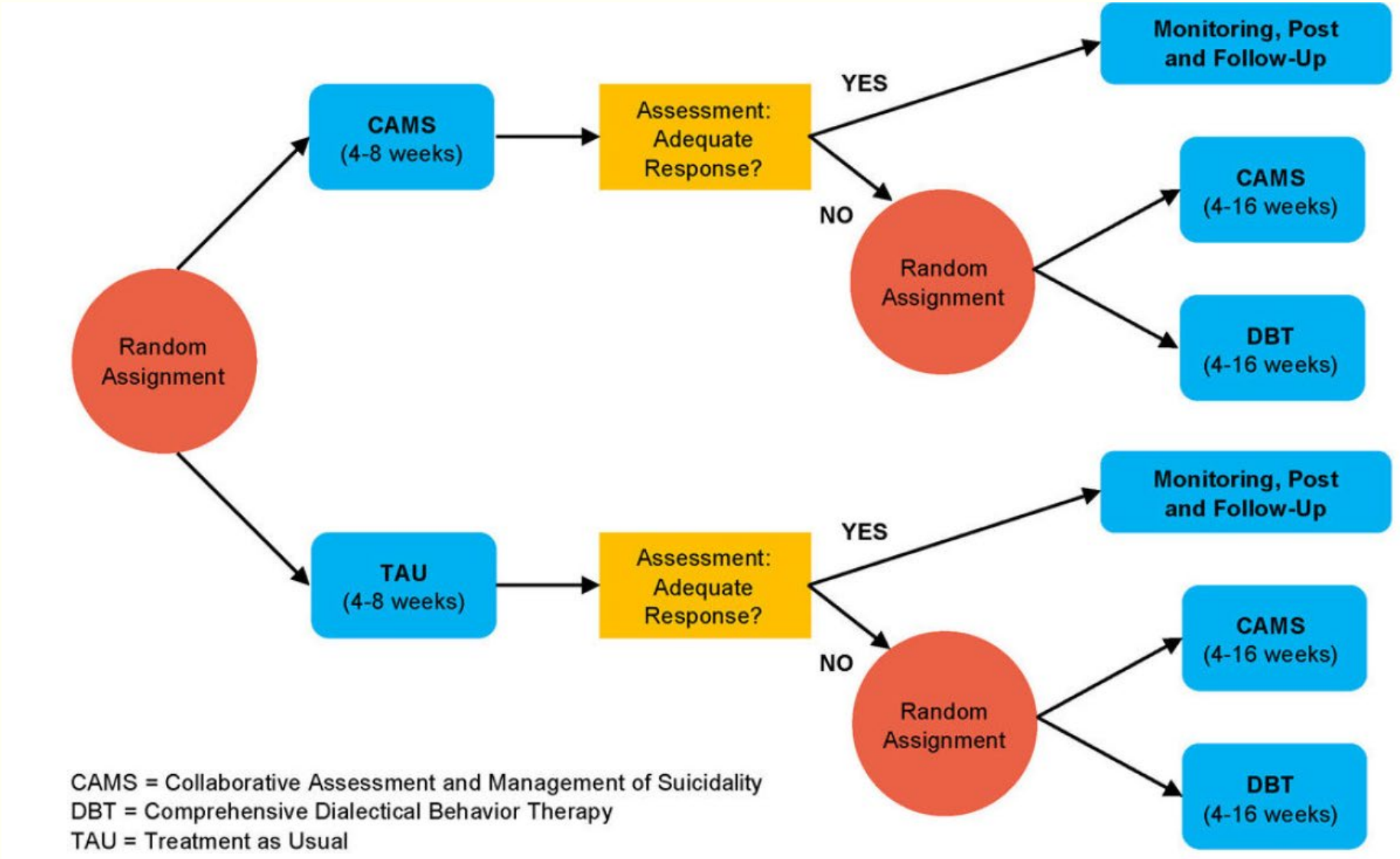
For consideration prior to meeting with a statistician

- Estimates needed for power calculations will depend on the design chosen
- Powering on main effects for first stage: power calculation will be similar to a standard RCT
  - Estimates of variability, differences between interventions in first stage
- Powering on main effects for second stage: need estimate of non-response rate
- Powering for embedded AI's: need estimate of differences between the AI's (e.g., best vs. second best)

Final example (Pistorello et al., 2017)

- Pilot study investigating adaptive treatment strategies for moderate to severe suicidal risk in college students
- Aims:
  - Determine feasibility (recruitment, clinician adherence to treatment)
  - Evaluate acceptability of adaptive strategies (attendance, drop-out, client and clinician satisfaction)
  - Examine how to measure and manage tailoring variable
- Interventions:
  - Treatment as usual (TAU)
  - Dialectical Behavior Therapy (DBT)
  - Collaborative Assessment and Management of Suicidality (CAMS)
- At stage 1, participants were randomized to CAMS or TAU
  - Adaptive biased-coin design to ensure equal group sizes and that groups were balanced on gender, presence of past suicide attempt, and current use of psychotropic medication

Final example (Pistorello et al., 2017)



Final example (Pistorello et al., 2017)

- Same therapist conducted stage 1 and 2 treatments to mirror clinical practice
- Recruitment, therapist adherence, and session attendance were satisfactory
- Participants reported liking the tailoring of the interventions to their needs
- Pilot study allowed modification of the primary tailoring variable
- Originally planned to use client self-report, but moved to counselor report
- Initial definition of resolution of suicide risk was a score of 0 on CCAPS suicidal thoughts question, but this was deemed unrealistic and unnecessary so modified to a reduction in intensity
- Another trial is planned to determine baseline characteristics of patients needing intensive multimodal treatments and in what sequence first line therapies should be offered

References/Resources

- The Methodology Center at Penn State: www.methodology.psu.edu
- Almirall D et al. 2014. Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research. Translational Behavioral Medicine 4(3): 260-274.
- Rush JA et al. 2004. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Controlled Clinical Trials 25(1): 119-142.
- Pfammatter AF et al. 2019. SMART: study protocol for sequential multiple assignment randomized controlled trial to optimize weight loss management. Contemporary Clinical Trials 82: 36-45.
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- Pistorello J et al. 2017. Developing adaptive treatment strategies to address suicidal risk in college students: a pilot sequential, multiple assignment, randomized trial. Archives of Suicide Research 22(4): 644-664.

Additional reading

- Kidwell KM. 2014. SMART designs in cancer research: past, present, and future. Clinical Trials 4: 445-456.
- Lei H et al. 2012. A SMART design for building individualized treatment sequences. Annual Review of Clinical Psychology 8: 21-48.
- Nahum-Shani I et al. 2012. Experimental design and primary data analysis methods for comparing adaptive interventions. Psychological Methods 17(4).
- (Statistically focused) Tsiatis et al. 2020. Dynamic treatment regimes: statistical methods for precision medicine. Chapman and Hall.