Common Misconceptions about Sequential Multiple Assignment Randomized Treatment (SMART) Research Designs

Misconception #1: Sample size calculations for a SMART design are complicated; and sample size requirements are prohibitively large.

- As with any randomized trial, sample size in a SMART is determined by the choice of primary aim.
- There are now a number of easy-to-use sample size calculators for data arising from a SMART, including for an end-of-study continuous outcome, an end-of-study binary outcome, a continuous repeated measures outcome, a survival outcome, and for data arising from a cluster-randomized SMART.
- Sample size requirements for a SMART may be smaller, similar, or larger than the sample size requirements for a standard trial design answering the same (or a similar) scientific question. This depends on the choice of primary aim, as well as the SMART and standard trial designs being compared.
- For example, the sample size calculation for a SMART with a primary aim that seeks to compare the effect of initial treatment is the same as the sample size calculation for a standard 2-arm RCT.

Misconception #2: All SMARTs require multiple-comparisons adjustments.

- As with any randomized trial, multiple-comparison adjustments are required when primary aim comparisons are made on multiple outcome measures, or when the primary aim involves multiple comparisons (e.g., two or more pairwise comparisons). SMARTs are no different in this respect.
- SMARTs differ from standard trial designs in that there are multiple randomizations. Multiple randomizations, however, does not imply that the primary aim makes multiple comparisons (making a multiple-comparison adjustment necessary).
- For example, an investigator might size a SMART to detect the effect of increased behavioral modification dose versus addition of medication among children who are non-responding to an initial ADHD treatment (a single comparison), but also have other randomized comparison (as secondary aims) that are not included as a comparison for purposes of this sample size calculation.

Misconception #3: All research on adaptive interventions require a SMART.

- Adaptive interventions are sequences of decision rules leading to individualized interventions (or intervention components). AIs represent an *intervention design*, not a *research design*.
- The use of a SMART research design implies an interest in answering questions related to adaptive interventions; however, the converse is not true. Not all research on adaptive interventions requires a SMART design.
- For example, a standard two-arm randomized trial can be used to compare outcomes between an adaptive intervention versus a suitable control condition (e.g., treatment as usual).
- In addition, SMARTs are just one type of research design that can be used to inform the development of adaptive interventions. Other designs are possible. For example, an enhanced non-responder trial (which is not a SMART) could be used to inform the development of adaptive interventions by examining how best to treat non-responders to an initial treatment.

Misconception #4: All SMARTs must include an embedded tailoring variable.

- SMARTs do not have to include an embedded tailoring variable.
- For example, an *unrestricted SMART* design can be used to (1) randomize all participants to two intervention options at stage 1, and (2) re-randomize all participants two intervention options at stage 2. In this example, the choice of stage 2 intervention is not dependent on (i.e., restricted based on) characteristics of the participant, the choice of assigned stage 1 intervention option, or any outcomes to stage 1 intervention.
- An unrestricted SMART design is often used in situations when there is no scientific, practical or ethical rationale for embedding a tailoring variable as part of the SMART.

Misconception #5: All aspects of an adaptive intervention must be randomized in a SMART.

- Not all aspects of an adaptive intervention require randomization in a SMART (or in any study of adaptive interventions).
- As with any randomized trial, a single SMART study might only answer a handful of questions related to the development or evaluation of an adaptive intervention.
- For example, consider a SMART which examines how best to intervene with children with autism who are slow-responders to a naturalistic intervention without a device (by randomizing these children to two intervention options) but does not randomize children who are slow-responders to the naturalistic intervention with a device (these children all received intensified intervention).

Misconception #6: SMARTs are a form of adaptive research design.

- An *adaptive research design* (a type of study design) is different from an *adaptive intervention design* (a type of intervention design). It is important not to conflate the intervention(s) and the study of the intervention(s).
- In *adaptive research designs*, modifications can be made to *study design* elements based on the results of a (pre-specified) interim data analysis. Such study design elements often include: sample size or the number of interventions being compared.
- For example, a standard 3-arm trial comparing three interventions might include an interim analysis using the first N/2 participants recruited in the study to determine if any one of the three interventions ought to be dropped from the study due to side-effects or toxicity. Here, the research design is potentially adapted but the study is not a SMART.
- By contrast, SMARTs are most often conducted as *fixed research designs* in that no changes to the study design are pre-specified. However, as described above, SMARTs are used to develop the best possible *adaptive intervention*. The study is fixed, but the interventions are adaptive.

Misconception #7: SMARTs never include a control group.

- A SMART may be designed to include a suitable control group.
- For example, one of the adaptive interventions embedded in a SMART might represent "business as usual" (i.e., a suitable control).

Misconception #8: SMARTs require multiple consents.

- SMARTs differ from standard trial designs in that a participant may be randomized multiple times. Multiple randomizations however, does not mean that a separate consent is required at each randomization point.
- As with any randomized trial, we recommend SMARTs employ a single *study consent* protocol with all participants prior to the initial randomization. The *study consent* protocol would include informing participants of all possible sequences of intervention components the participant might be assigned to during the course of the study.
- For example, consider a SMART that (1) randomizes children with ADHD to initial behavioral modification (BMOD) vs initial medication (MED), (2) continues initial intervention for children who are not identified as non-responders, and (3) re-randomizes non-responding children to increased intervention vs combined BMOD+MED. In this study, parents/children consent *once, up-front* (i.e., prior to the first randomization) to being part of the entire study (both stages of intervention) and to the possibility of receiving one of the four embedded adaptive interventions.

Misconception #9: SMARTs are susceptive to high levels of study drop-out.

- SMARTs are no more likely to produce high levels of study drop out than standard randomized trial designs.
- In fact, we find that researchers implementing SMART designs are reporting decreases in both treatment drop-out and study drop-out (relative to study designs they have used in the past). We conjecture that this is due to the focus on *adaptive interventions* in SMARTs (rather than the SMART design itself).
- For example, a participant may be less likely to drop-out of a study comparing two adaptive interventions—each of which includes potential changes in intervention components according to the participant's changing outcomes/severity, side effects, or risk of disengagement—versus a study comparing two fixed (i.e., non-adaptive) interventions.