

Questions/Concerns about SMART Studies during the June 11-12 Workshop

3 types of concerns were brought up about SMART: design, conduct, and data analysis concerns. A fourth category, miscellaneous, was used to classify additional concerns that did not fit into these 3 groups.

SMART Study Design Concerns	Possible Response
What is a good acronym for remembering the important pieces that go into a designing a SMART experimental study? For example, for standard RCTs, investigators often use the PICO strategy for helping remember steps to devising the research question: P = what is the Problem? Patient Population? I = what is the Intervention? C = what is the Control? O = what is the primary Outcome. Can you help me come up with something similar for SMART?	The overarching aim of a SMART, which is to build an adaptive intervention, is different from the overarching aim of an RCT, which is to confirm/evaluate that an (adaptive) intervention is efficacious. Therefore, the acronym for SMARTs should be different to reflect this. A possible acronym for SMARTs is PICTO: P = what is the Problem? Patient Population? I = what are the adaptive Intervention treatment options? (i.e., what is inside the treatment toolbox?) C = what are the Critical decisions in adaptive intervention development? T = what are the embedded and candidate Tailoring variables? O = what is the primary Outcome? Further, the use of the acronym PICTO will also remind us that it is often useful to come up with a picture or SMART-pictogram, showing the various critical decision points, treatment options at each decision point, and embedded tailoring variables, when thinking about the design of a SMART.
Do we need a control group in a SMART? Why didn't any of your examples include a control group?	The overarching goal of the SMART is to build an adaptive intervention (the specific aims of a SMART all generally support this overarching goal). Put in other words, SMARTs are about "evaluating the components" that go into an adaptive intervention rather than "evaluating the/an adaptive intervention itself" (e.g., versus a control). Since control groups are often used in experimental designs that seek to confirm/evaluate the efficacy of an (adaptive) intervention, their use is limited in the SMART. One place where control groups could be used in a SMART is if we think of evaluating a delay in treatment. In this case, SMART participants might be randomized initially to "watchful waiting" vs treatment A for an initial X weeks, before moving on to stage 2 treatment options. This might be used following graduation from an inpatient alcohol-addiction/weight-loss program, say, where investigators might be interested in understanding at what point in time to begin maintenance/aftercare treatment.
What is the difference between a classical randomized-clinical trial (RCT) and a SMART?	The goal of an RCT is to evaluate if one treatment arm is better than the other treatment arm. A treatment arm can be a control or standard care arm, a treatment arm can be a fully formed adaptive treatment strategy or a treatment arm may be a medication including the guidelines for how the

	dose of the medication is ramped up. In contrast, the goal of a SMART is to <i>build</i> an adaptive treatment strategy. To do this, the treatment components and the sequencing of these components are evaluated. SMART studies need to be followed by a classical RCT to evaluate the constructed adaptive treatment strategy (vs some standard of care, control or treatment as usual).
Can biomarkers be useful in the design of a SMART?	Yes. There is much interest right now in the use of biomarkers to aide in the development of individualized interventions. Since the aim of an adaptive intervention is to individualize treatment over time so as to improve long-term outcomes, and since the aim of a SMART is to build an adaptive intervention, there is a role for biomarkers in the design of SMARTs. For example, genetic information can be used to pinpoint who will benefit most from initial treatment A vs initial treatment B. In addition, other time-varying biomarkers such as brain imaging and blood/tissue samples could be used to help guide ongoing treatment decisions, such as how to treat non-responders to initial treatment.
Do we always re-randomize all participants in a SMART?	No. There are at least three reasons for this: First, for some values of an embedded tailoring variable, it may be obvious what treatment should be provided. In this case, we do not randomize participants: they all get that treatment. This might happen in cases where it is only feasible or ethical to provide one treatment for that type of individual. Second, in other cases, investigators simply are not interested in evaluating treatments for a certain type of participant. In this case, no randomization occurs because the investigator has deemed this as not being a critical decision to investigate. Third, if a very small proportion of the population exhibits a particular value on the embedded tailoring variable, re-randomization may not be justified since insufficient numbers will be available for comparison. (Of course, this third setting is dependent on the total number of participants in the study, the putative effect size of the treatment options available for this type of participant, and the public health significance of investigating what to do among participants of this type.)
What are some of the background	
SMART Study Conduct Concerns	Possible Response
How do we deal with treatment contamination issues in the conduct of a SMART?	Treatment contamination issues and other intervention quality control concerns are dealt with in a SMART in much the same way that they are dealt with in a standard RCT. That is, by producing highly-manualized treatment protocols, by preventing the same staff member from implementing the different types of treatment being compared, by training research staff adequately, by documenting all treatments that were offered, by measuring what other treatments were received by randomized participants, by videotaping a subset of the treatment sessions and ensuring adequate quality control, and by employing a “parking lot” or a similar structure during weekly/monthly team meetings for permitting staff to voice their concerns and suggested changes about the treatments being provided.

	One difference is that in a SMART all of this takes place in the context of sequenced treatments/interventions. Another difference is that the idea of contamination, itself, requires more careful thought in the design of a SMART. This is because what we typically think of contamination may, in fact, be something we want to take advantage of or may be something we want to investigate. For example, we may want to maximize the synergistic (positive) effects of first- and second-stage treatments, in which case using the same therapist in the first- and second-stage may be a treatment design consideration worth entertaining. It is equally possible to examine this as a critical question in the context of a SMART.
SMART Study Data Analysis Concerns	Possible Response
How do we deal with missing data in the analysis of data arising from a SMART?	We will not cover this during our workshop. See the following manuscript for multiple imputation strategies for dealing with missing data arising from a SMART: Shortreed, S.M., Laber, E., Stroup, T.S., Pineau, J., Murphy, S.A. "Multiple imputation for sequential multiple assignment randomized trials".
I am concerned over unequal sample sizes in the final subgroups/cells of a SMART.	First, this is correct: there will often be unequal sample sizes in the final subgroups/cells of a SMART. Indeed, the proportion of participants that end up in the final subgroups/cells of a SMART constitutes an outcome of the study (we do not know ahead of time how many people will end up in each subgroup/cell). Second, except in certain limited circumstances, we will rarely compare outcomes between participants in one final subgroup/cell vs another subgroup/cell. As in the analysis of factorial experimental designs (recall that the SMART is a type of factorial design), the primary and secondary aims of most SMARTs utilize analyses that collapse data across multiple subgroups/cells in their comparisons. Third, for all of the example randomized comparisons we discussed in the workshop, the two arms being compared will always have equal sample sizes.
SMART Study Miscellaneous Concerns	Possible Response
What is the role of clinical judgment in the development of an adaptive intervention?	The overarching goal of a SMART is to build an adaptive intervention. The ultimate product/output from a SMART, is a proposal for an optimal, individually-tailored, adaptive intervention. Our view is that such interventions will help guide/inform clinical judgment in practice.
I am still having trouble describing the main effect comparison of first-stage treatments in simple language (for example, for purposes of the specific aims page of a grant)?	There are various ways to state this primary aim: 1. What is the effect on Y of adaptive strategies beginning with A vs strategies beginning with B? 2. What is the effect on Y of starting with A vs starting with B? 3. In terms of Y, what is the best first-line treatment (A vs B), controlling for future treatment by design? 4. What is the effect of initial A vs initial B? 5. What is the main effect of A vs B? Regardless of how we choose to describe this aim in the abstract or specific aims page of the grant, in which there is

	limited room, the key is to describe the aim fully/clearly in the remaining sections of the grant. Often this is most clearly explained in the analysis section because it can be explained that this is a comparison of all participants who begin on treatment A vs all participants who begin on treatment B. In addition, there are other primary aims to choose from in the design of a SMART. In the workshop we went over 2 additional commonly used primary aims: (1) a comparison of two of the embedded adaptive interventions, and (2) a comparison of 2 tactics among non-responders to initial treatment.
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There was an additional question we did not understand so we could not answer.

It asked “What is the connection between background variables and analyses?”