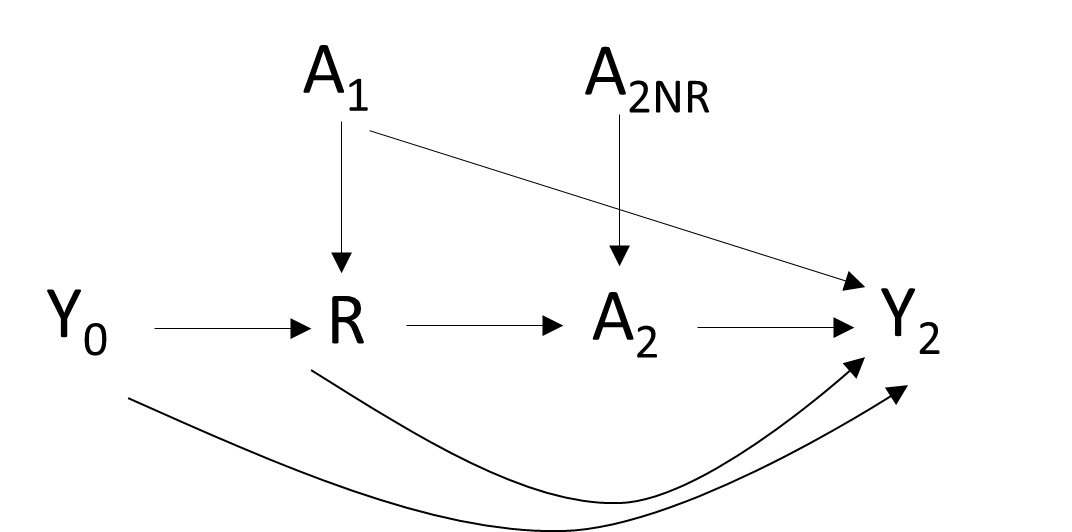
**Scenario and Notation for Simulation Study**

Suppose that the binary outcome at a given time point represents whether or not a desired event (e.g., negative drug test indicating abstinence for illicit drugs) is observed at that time point. Let be the outcome observed before initial treatment (i.e., pretest), observed at the beginning of stage 1. Suppose that the response status represents some healthy state or behavior, observed at the end of stage 1. Response status is likely to be positively correlated with , but they are assumed not deterministically related (i.e., it is not always the case that for all participants). For example, response status could be abstinence during the last week of stage 1. Let the posttest be the outcome observed at the end of stage two of treatment (e.g., negative test result at end of study). For convenience, is said to be observed at time 0, at time 1, and at time 2.

Suppose that a dichotomous treatment , coded as or , is assigned after is observed but before is observed (i.e., immediately after time 0). Suppose that has a slight beneficial effect, so that the conditional expected value of tends to be higher for participants randomized to than for participants randomized to . Also, suppose that for nonresponders only, a dichotomous treatment , coded as or , is assigned. This is a restricted SMART, i.e., only nonresponders are rerandomized. Again, suppose the level of is beneficial, and thus associated with a slightly higher probability for relative to . The simulation model can be represented in a directed acyclic graph (DAG) by constructing a recoded variable

.

For responders, is 0 by convention, indicating that it cannot have an effect; for nonresponders, . With this notation, the graph can be written as follows:



To follow convention, , , and above are coded as versus , while and are coded as versus . There are four candidate adaptive interventions (ADIs): , , , , , and , .

**Data-Generating Model**

**Elicitation or Calculation of Conditional Probabilities**

Suppose an investigator wants to estimate the expected value (i.e., outcome probability) of for an ADI , . In practice, contrasts between ADIs will be of interest. These contrasts could be expressed in terms of differences in probabilities, ratios of probabilities (risk ratios), or odds ratios. However, each of them is a function of the expected values of the ADIs.

There are three, non-equivalent ways to define this expected value of given , . The expectation can be conditional on and ,

or it can be conditional on only but can average over ,

or it can be marginal over both and ,

The third quantity is probably of greatest practical interest because it could be interpreted as applying on average to the target population as a whole if everyone were to receive the treatment. Depending on the investigator, either the second or third quantity might be easiest to elicit from substantive investigators. This paper has presented sample size and power formulas which use either the second or third quantity. The first quantity (fully conditional probability) is the most complicated and least intuitive. Unfortunately, it is this awkward quantity which must be specified in order to do a simulation. That is because a simulation requires a fully specified data-generating model (DGM) which tells how all of the variables are related to each other and which directly or indirectly provides a probability for every possible joint value for the variables.

This presents a small dilemma if we wish to use simulations to validate sample size or power formulas for a longitudinal SMART. It becomes necessary to “translate” from the fully conditional specification to at least a partly marginal specification. This is fairly easy if a linear link function is used in the DGM, but still feasible if a log or logistic link function is used.

**Converting Probabilities from a Linear Link Function**

Under the assumption that a linear models holds for the fully conditional probabilities , it becomes feasible to express the true value of the difference in marginal outcome probabilities between two regimens () and (), using only the coefficients of the fully conditional model. Specifically, suppose

Also suppose and . The fully conditional contrast between expected values under () and (), given and , is therefore

For example, the fully conditional probability difference between () and () is for responders or for nonresponders.

In contrast, the marginal final outcome probability difference does not depend on a specified value but on the response probability . Specifically,

For example, the marginal probability difference between () and () is . Note that in the fully conditional contrast is set to either 0 or 1, while and are probabilities between zero and one.

The decomposition of the contrast into four terms can be intuitively explained by saying that there are four ways in which the adaptive intervention can have an effect on : (1) indirectly by changing the proportion of responders, (2) directly by the effect of stage 1 treatment on expected regardless of response status, (3) directly by the effect of the stage 2 treatment on expected for nonresponders, or (4) directly by the interaction of stage 1 and stage 2 treatment for nonresponders. As an aside, this means that can be relevant even when comparing two regimens which prescribe the same . That is, even if , the third or fourth term above can still be nonzero, unless we also have . This is because, by increasing the proportion of responders, successful Stage One treatment can have the side effect of decreasing the proportion of individuals eligible to be affected by the Stage Two treatment option. In the special case where both and , then the contrast simplifies to the usual which would be expected in a factorial experiment. This complication is already a kind of noncollapsibility (i.e., does not cancel out even when it is not of interest), although it is still relatively tractable here because of the linear assumptions elsewhere in the model (i.e., at least cancels out by iterated expectation).

**Converting Probabilities from a Non-Linear Link Function**

Unfortunately, a linear model is often considered unrealistic for a binary outcome. Given a more realistic DGM with a log or logistic link function, it will no longer be feasible to express the causal effects in the marginal model in terms of the regression coefficients of the conditional model. However, the marginal probabilities can still be calculated indirectly from conditional probabilities.

First, notice that the marginal expectation is a weighted average over the distribution of and , i.e.,

Next, because and are each binary, we can use the definition of expected value to write this expectation as a weighted average of four quantities.

Thus, it is only necessary to specify the probability for , the model for given and , and finally the model for given all the other variables. The products of these three probabilities can be added, in order to calculate the marginal final outcome probability for an ADI as a weighted average. In our simulations, we use logistic link functions for the data-generating models, as described below.

**Data-Generating Model Parameters**

First, suppose

so that . That is, less than half the sample is abstinent at baseline.

Second, suppose

where and . Thus, the possible values of range from for participants who were non-abstinent at baseline and received the low level of , to for participants who were abstinent at baseline and received the high level of ).

Last, suppose that

where , , and . Thus, the possible values of range from (for someone who has not been abstinent at baseline, nor a responder, and who has received the weaker treatment at both stage) to (to someone who was abstinent at baseline, and received the high level of , and was a responder).

Suppose we are comparing two adaptive interventions, specifically to . We can use iterative expectations to calculate the true marginal probabilities of the regimens (which average over and ) from the fully conditional probabilities (which specify and ). First, the marginal response rates are calculated as

and

Next,

and

The probability difference is . Notice that this effect is not equal to , even though is the only randomized factor that differs between the arms. This is because the data-generating model was conditional on and , while the inference model of interest is not; it is not possible to simulate data directly from the marginal model.

Now that , , and have been obtained, power or sample size can be computed using the results in Kidwell et al (2019). That formula was based on a test of the log odds ratio, rather than directly on the probability difference, but the log odds ratio can be calculated from the two probabilities. Specifically

representing an odds ratio of about . The can be substituted into the Kidwell et al (2019) sample size formula for a desired power, say . Specifically,

> 2\*(((.8416+1.96)^2)/(1.0655^2)) \* ( (2-0.55)/(.615\*(1-.615)) + (2-.35)/(.355\*(1-.355)))

[1] 184.3168

where and are the marginal variances given treatment, is the significance level of the test, and and are normal quantiles.

These values also be substituted into the equivalent power formula for a given sample size, say, for ,

where is the cumulative normal distribution.

This shows that with the current approach, it is possible to simulate pretest-posttest binary SMART data and also use theoretical power formulas, so that the performance of the formulas can be checked empirically for this kind of data. The analysis of the simulated data need not use a linear link, because it was only required for a tractable data-generating function. It would be possible to compare the performance of the linear link, log-linear link, and logistic link, because although they are most suitable for use with different estimands (probability difference, log risk ratio, and log odds ratio), they test a logically equivalent null hypothesis.

**Log-Linear Data-Generating Model**

**Contrasts**

Suppose an investigator wishes to have adequate power for a significance test of the risk ratio, i.e., ratio of expected values on between a pair of candidate adaptive interventions denoted , and . As before in the linear model case, there are three, non-equivalent ways to operationalize this contrast. The contrast can be conditional on setting both and to the same value,

or it can be conditional on a particular value of only but average over ,

or it can be marginal over both and ,

A Monte Carlo simulation requires the parameters in the first version. The interests of substantive investigators are most likely to focus on the parameters in the third version, although the second might also be of interest. Therefore, it would be very convenient to have a way to relate these quantities to each other.

**Data-Generating Model Parameters**

Suppose the probabilities follow a set of log-linear models as follows. First, generate from

Second, generate from

where . This means that ranges from to .

Third, generate from

where This means that ranges from to .

Let and . Suppose an investigator wants to estimate the risk ratio

Then the log of the risk ratio is is

.

Can these terms be simplified? First, the marginal expectation is a weighted average over the distribution of and , i.e.,

Next, we know the expected value under the fully conditional model, i.e.,

Furthermore,, because and are each binary, we can use the definition of expected value to write this expectation as a weighted average of four quantities.

Thus, it is only necessary to specify the models for , , and finally , conditional on the variables that preceded each, and then to multiply and add probabilities accordingly, in order to calculate the marginal probability for an ADI . Unfortunately, no simple expression is gained when taking the ratio of the probabilities, or the difference of their logarithms; that is, very little will cancel out, because the probability of being a responder depends on treatment. However,