CLINICAL TRIAL RANDOMIZATION DESIGN:
BLOCKED RANDOMIZED RESPONSE ADAPTIVE METHOD

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ABSTRACT
The blocked response adaptive randomization method combines the strengths of both blocked design and response adaptive methods. The SAS code of the our model divides study participants by the randomized blocked method, and then applies the response adaptive procedure to randomize study participants within each block. Through this randomization, the conflict between collective and individual ethics in clinical trial practices is balanced. We demonstrate how this SAS code can also be modified to incorporate other block randomization designs to mitigate covert biases.

INTRODUCTION
The Food and Drug Administration (FDA) requires that each potential treatment is clinically proven safe and effective prior to its release for general implementation. Randomized Clinical Trials (RCTs) are typically employed to serve this purpose. The process of randomization “tends to produce study groups comparable with respect to known and unknown risk factors, removes investigator bias in the allocation of participants, and guarantees that statistical tests will have valid significance levels” (Friedman et. al, 1998, p. 61). Thus, such randomization increases external validity, allowing researchers to generalize their findings to the general population.

Because clinical trials are “prospective studies comparing the effect and value of intervention[s] against a control in human beings” (Friedman et. al, 1998, p. 2), the ethical balance between collective and individual interest is an important issue in RCTs. Collective interest emphasizes public health benefits; whereas individual interest is concerned with the best benefit for the participant (Rosenberger et. al, 2002, Sect. 1.4). If emphasis were given to collective interest, then an individual’s chance to receive the most suitable care is often sacrificed in exchange for generalizable result for populace. Conversely, the generalizability of the clinical trial outcome is likewise diminished if participants were provided with the intervention that is most likely to be effective.

THE ALGORITHM

OVERVIEW
The SAS program first performs a randomized block allocation. Each incoming study participant has an equal probability of being assigned to one of two blocks (groups). Then within each block, the SAS code assigns a probability, P(XY), to each participant for treatment decision-making. This probability is compared to an adjusted probability, P(XYAR), to decide the treatment assignment for the participant. As each study participant is assigned to treatment A (Tx A) or treatment B (Tx B), a treatment outcome probability is then assigned to determine if the treatment is a success or failure.

While the blocked method achieves collective interest, the response adaptive method accomplishes individual interest. Thus, the blocked randomized response adaptive method balances the conflict between collective and individual ethics. The flow chart (Fig. 1) summarizes the steps involved in the blocked randomized response adaptive method.
The Blocked Method

/*Blocked Method*/
hold = numpt/2;
half = 0;
whole = 0;
blkprob = ranuni(658921);
IF (blkprob < 0.5 AND half LT hold)
  OR whole EQ hold
THEN DO;
  blk = 1;
  half + 1;
END;
ELSE DO;
  blk = 2;
  whole + 1;

(Corresponding Code on Left) Blocked randomization rids of the imbalance that occurs in simple randomization by assigning an equal number of study participants to each block (group). The SAS program first performs a randomized block allocation by assigning each incoming participant onto one of two blocks with equal probability.

The Response Adaptive Method

(Corresponding Code on Right) The response adaptive method adjusts treatment assignment probability for the next study participant by using “the information on participant response to intervention during the course of the trial” (Friedman et al., 1998, p. 72). Within each block, a probability is first assigned using a random number generator to each incoming participant for treatment decision-making [1]. This random probability is then compared to a continuously adjusted probability P(XYAR) that is calculated based on the preceding treatment outcomes [2]. Based on the comparison result, the study participant is assigned into Tx A or Tx B. Once the study participant is in a treatment, a treatment outcome probability is assigned to determine the success or failure of the treatment [3].

For demonstration, the Randomized Play-the-Winner (Wei & Durham, 1978) method is employed to perform the response adaptive treatment assignment. The procedure is as follows: a ball is drawn and replaced from an urn that contains \( \alpha \) balls representing Tx A and \( \beta \) balls representing Tx B. A success results in adding \( \beta \) balls representing that treatment; a failure results in adding \( \beta \) balls representing the opposite treatment. Thus, on the next draw, the probability of drawing a ball representing the treatment with more successes and less failure is increased. If previous study participants generally experience favorable outcome with the treatment, then subsequent participants would be more likely to receive the better treatment.

/*Response Adaptive Method*/
xy = ranuni(127597);
xyar=(alpha+beta*blklsa+beta*blk1fb) \[1\]
/(alpha+beta*(numblk1-1));
outcome = ranuni(973480);
IF xy < xyar THEN tx = 'A';
ELSE tx = 'B'; \[2\]
IF (tx = 'A' & outcome GT 0.6) THEN blklsa + 1;
ELSE IF (tx = 'A' & outcome LE 0.6) THEN blk1fa + 1;
ELSE IF (tx = 'B' & outcome GT 0.3) THEN blklsb + 1; \[3\]
ELSE IF (tx = 'B' & outcome LE 0.3) THEN blk1fb + 1;
OUTPUT;

EXAMPLE
For simplicity, the example makes the following assumptions:
\[\begin{align*}
\text{\# blocks} & \quad 2 \ (1 \ or \ 2) \\
\text{\# treatment types} & \quad 2 \ (A \ or \ B) \\
P(\text{Tx A is successful}) & \quad 0.4 \\
P(\text{Tx B is successful}) & \quad 0.7 \\
\alpha & \quad 5, \ \beta = 1
\end{align*}\]
where the probabilities, \( \alpha \) and \( \beta \) are adjustable parameters. The complete output is shown below for 20 study participants.
CONCLUSION
The blocked response adaptive randomization method integrates the strengths of its component randomization designs to mitigate the conflict between collective and individual ethics. Because the blocked method maintains the randomness of participant assignment into Tx A or Tx B, the results are generalizable to the public. The response adaptive method allows study participants to receive the most effective treatment by building upon outcomes of preceding treatments. The corresponding SAS code is written in such way that, the user can incorporate his/her desired blocked and response adaptive designs together.

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REFERENCES

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/*Blocked Randomized Response Adaptive Method*/

DATA BRRAM;
alpha = 5;
beta = 1;
blklsa = 0;
blklfa = 0;
blklsb = 0;
blklfb = 0;
numpt = 20;
half = 0;
hold = numpt/2;
whole = 0;
retain half whole;
DO pt = 1 to numpt;
/*Block Allocation*/
blkprob = ranuni(658921);
IF (blkprob < 0.5 AND half LT hold) OR whole EQ hold THEN DO;
   blk = 1;
   half + 1;
END;
ELSE DO;
   blk = 2;
   whole + 1;
END;
/*Response Adaptive Allocation for Block 1*/
IF blk = 1 THEN DO;
   numblk1 + 1;
   xy = ranuni(127597);
   xyar = (alpha+beta*blklsa+beta*blklfb)/(alpha+beta*(numblk1-1));
   outcome = ranuni(973480);
   IF xy < xyar THEN tx = 'A';
   ELSE tx = 'B';
   IF (tx = 'A' & outcome GT 0.6) THEN blklsa + 1;
   ELSE IF (tx = 'A' & outcome LE 0.6) THEN blklfa + 1;
   ELSE IF (tx = 'B' & outcome GT 0.3) THEN blklsb + 1;
   ELSE IF (tx = 'B' & outcome LE 0.3) THEN blklfb + 1;
OUTPUT;
END;
/*Response Adaptive Allocation for Block 2*/
IF blk = 2 THEN DO;
   numblk2 + 1;
   xx = ranuni(127597);
   xxar = (alpha+beta*blk2sa+beta*blk2fb)/(alpha+beta*(numblk2-1));
   outcome = ranuni(973480);
   IF xx < xxar THEN tx = 'A';
   ELSE tx = 'B';
   IF (tx = 'A' & outcome GT 0.6) THEN blk2sa + 1;
   ELSE IF (tx = 'A' & outcome LE 0.6) THEN blk2fa + 1;
   ELSE IF (tx = 'B' & outcome GT 0.3) THEN blk2sb + 1;
   ELSE IF (tx = 'B' & outcome LE 0.3) THEN blk2fb + 1;
OUTPUT;
END;