Treatment Adaptive Biased Coin Randomization:
Generating Randomization Sequences in SAS®
Adaptive Biased Coin Randomization: Generating Randomization Sequences in SAS®
Gary Foster and Lehana Thabane
McMaster University, Hamilton, Ontario, Canada

OBJECTIVES

• use SAS® code to generate randomization sequences based on the adaptive biased coin design (ABCD)
• sequence must have approximate balance in treatment groups
• sequence can be used to randomize participants in a parallel groups RCTs with 2, 3, or 4 groups
• maximum tolerable imbalance between groups can be specifiable
• must maintain a close to chance level of predictability for group assignments throughout the sequence
• sequences must be reproducible
• must be able to implement sequence in a central randomization server

INTRODUCTION

Simple Randomization (SR)
• each participant is assigned to a treatment group with a fixed probability
• can lead to significant imbalances in the number of participants assigned to groups

Permuted Block Design (PBD)
• assures balance in treatment groups at the end of each block and at the end of the trial
• it comes at the cost of being more predictable compared to SR
• highly susceptible to selection bias

Treatment Adaptive Biased Coin Design (ABCD)
• evolving from the work of Efron (1971), the earliest reference describing this method is Lei (1977)
• utilizes group allocation information from all previously randomized participants to determine the probability of the next participant being randomized to each treatment group
• more likely to be randomized to a group with fewer previously allocated participants
• more likely to progress toward balance than in SR
• user can specify maximum tolerable imbalance (MTI)
• predictability of treatment group is lower than that of the PBD but higher than that of SR (Wei & Lachin, 1988)

Colavincenzo (2013) developed a SAS® macro using the ABCD approach to generate a single allocation when summary information about previous allocations was passed to the macro.

MACRO INVOCATION

To generate a randomization sequence simply invoke the ABCD macro (example below):

```
%ABCD(120,11,2,94661,5)
```

The macro requires five inputs:

- Input 1: specify the total number of patients in the trial
- Input 2: specify the number of patients in the initial block of the sequence
- Input 3: specify the number of treatment groups (2, 3, or 4)
- Input 4: enter the random number generator seed
- Input 5: specify the MTI

- this example specifies a two treatment group trial with a total of 120 patients
- MTI is set to |5|, therefore the maximum group imbalance cannot exceed |5|

To randomly generate a random number seed use the data step below. Enter the resulting seed number as Input 4 in the %ABCD() invocation statement.

```
data seed;
  seed=round(ranuni(0)*1000000);
run;
proc print data=seed noobs;run;
```
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RESULTS

• generate a 2 group sequence with %ABCD(120,11,2.94661,500) (effectively no MTI)
• plot the difference in group allocations by sequence position, see Figure 1
• at the end of the sequence the difference in the number of patients randomized to groups A and B is 12
• relatively large imbalance in groups due to the random walk process
• Figure 2 shows how the probability of being selected for group A changes as a function of sequence position
• probability of B being selected is equal to 1- the probability of A being selected.
• in simple randomization the cut-point would be fixed at 0.5
• In ABCD it fluctuates most at the beginning of the sequence and tends to converge to 0.5 as balance is achieved

RESULTS (cont’d)

• generate a 2 group sequence with %ABCD(120,11,2.94661,5) (MTI = |5|)
• the difference in the number of patients randomized to groups A and B never exceeds |5|
• plot of difference by sequence position is shown in Figure 3
• Figures 1 and 3 are identical up to sequence position 54 where the lower MTI bound is first encountered
• at the end of the sequence the groups were not exactly balanced, difference of 4
• Figure 4 plots the probability of group A being selected as a function of sequence position

Summary:

Figure 1

Comparison | 1st position diff = |5| | # times diff = |5| | # times diff > |5| | Last position diff = |5| | Difference at end of sequence | Guessing Correctly in balance % | Guessing Correctly in imbalance % |
--- | --- | --- | --- | --- | --- | --- | --- | --- |
A vs B | 54 | 6 | 58 | 120 | 12 | 46.2 | 50.5 |

Figure 2

Summary:

Figure 3

Comparison | 1st position diff = |5| | # times diff = |5| | # times diff > |5| | Last position diff = |5| | Difference at end of sequence | Guessing Correctly in balance % | Guessing Correctly in imbalance % |
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
A vs B | 54 | 5 | 0 | 115 | 4 | 54.6 | 59.2 |
Results (cont’d)

• generate a 3 group sequence with %ABCD(240,11,3,94661,500) (effectively no MTI)

• Figure 5 plots the difference in group allocations by sequence position

• at the end of the sequence the difference in the number of patients randomized to groups was either 1 or 2

• Figure 6 plots probability cut-points as a function of sequence position for this sequence. There are two cut-points for a three group trial. If the random number is less than or equal to cut-point A (blue line) then group A would be assigned, if it is greater than cut-point A and less than or equal to cut-point B then group B would be assigned, and if it is greater than cut-point B then group C would be assigned.

Figure 5

Summary:

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Results (cont’d)

• generate a 3 group sequence with %ABCD(240,11,3,94661,5) (MTI = |5|)

• The difference in the number of patients randomized to groups A, B and C can never exceed |5|

• a plot of this difference by sequence position is shown in Figure 7

• at the end of the sequence the groups were not exactly balanced

• Figure 8 plots the probability cut-points as a function of sequence position
Two group sequence without MTI
- imbalance in treatment groups at end of sequence equals 12
- there were 12 instances when exact balance occurred
- balance occurred last at sequence position 40
- guessing correct percentage is close to chance
- there were no deterministic randomizations

Two group sequence with MTI = 5
- imbalance at the end of the sequence equals 4
- exact balance occurred 21 times in sequence
- sequence with MTI was superior on all three metrics
- it is more likely that the MTI sequence will produce a smaller imbalance at the end of the sequence
- guessing correct percentage is much better when there is imbalance
- only five (4.2%) randomizations were deterministic

Three group sequence without MTI
- balance in treatment groups at the end of the sequence was excellent
- exact balance among three treatment groups during sequence occurred four times
- guessing correctly was better than chance (overall percentage was 38.3%)

Three group sequence with MTI = 5
- balance in treatment groups at the end of the sequence was excellent
- exact balance among three treatment groups during sequence occurred six times
- guessing correctly was better than chance (overall percentage was 40.4%)
- there were many deterministic randomizations

CONCLUSIONS
- we present a method to generate reproducible randomization sequences based on the ABCD design
- user is able to specify MTI
- sequence can be used in a central randomization server
- can be used to randomize patients into parallel groups RCT with 2, 3, or 4 treatment groups
- the two group sequence with MTI = 5 was superior to the sequence without MTI

If sequences generated with the ABCD design are implemented properly and the MTI is unknown to the person randomizing study participants, the predictability of the sequence is lower than in sequences created by the permuted block design.

REFERENCES

CONTACT INFORMATION
Your comments and questions are valued and encouraged. Contact the author at:
Gary Foster
fosterg@mcmaster.ca