# Adaptive Randomization

# Designs

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#### Introduction and Background

Randomized clinical trials have been in practice since 1929 when Ronald Fisher implemented the first randomization scheme - the flip of a coin - in a tuberculosis trial<sup>1</sup>. Since then, randomization has become the standard for clinical trials because of the way it tends to equalize the treatment groups by balancing variables not under examination (often called confounding variables). Simple randomization (i.e. flipping a coin) was the only method in place for many years but then researchers noticed that for certain situations, this was not ideal. In clinical trials, the entire sample of patients is often not available at the time of randomization and patients must be randomized to a treatment group as they arrive in the trial. At the beginning stages of trials, or for trials with very small sample sizes ( $n < 100^2$ ), using simple randomization can cause an extreme imbalance among the treatment groups. Sometimes the number of patients assigned to each group may be very different, or the characteristics of the patients (possible covariates) may be very imbalanced among the treatment groups. These situations may lead to inflation of the error variance and may cause researchers to disregard a potentially significant treatment difference where one exists.

Since the mid-1900s, there has been an increase in biomedical research funding. Despite this increase, pharmaceutical development has NOT increased<sup>3</sup>. The cause of this plateau in pharmaceutical research is unknown, but researchers and investors have looked for opportunities to break through it. In 2006, the U.S. Food and Drug Administration published the *Critical Path Opportunities Report*, calling for researchers to advance the use of innovative trial design<sup>4</sup>. Since then, he F.D.A. has emphasized the use of prior information in clinical trial design, hoping that it will increase pharmaceutical productivity.

An adaptive design method is one such example using prior information in a clinical trial design<sup>5</sup>. The goal of an adaptive design is to maintain the integrity and validity of the study while giving the researcher flexibility in identifying the optimal treatment. An example of an adaptive design can be seen in a basic pharmaceutical trial. There are three phases of the overall trial to compare treatments, and experimenters use the information from the previous phase to make changes to the

<sup>&</sup>lt;sup>1</sup> Kang, Minsoo, Ragan, Brian G., and Park, Jae-Hyeon (2008)

<sup>&</sup>lt;sup>2</sup> Kang et. al (2008)

<sup>&</sup>lt;sup>3</sup> Chow, Shein-Chung, and Chang, Mark (2008)

<sup>&</sup>lt;sup>4</sup> Chow and Chang (2008)

<sup>&</sup>lt;sup>5</sup> Chow and Chang (2008)

subsequent phase before it begins.

Adaptive design methods have been in practice since the 1970s, but have become increasingly complex ever since. Adaptations can be made to either trial procedures (eligibility criteria, study dose, treatment duration, study endpoints, laboratory testing procedures, diagnostic procedures, criteria for evaluation, and assessment of clinical responses) or statistical procedures (randomization, study design, study objectives/hypotheses, sample size, data monitoring and interim analysis, statistical analysis plan, and methods for data analysis)<sup>6</sup>. Adaptive design methods reflect how medicine is actually practiced – once new information is learned, that knowledge must be applied to the current way things are accomplished. Within trials, there are many ethical and safety discussions to be had. This method also allows for better efficacy and ethicality checks in trials. With adaptive methods, differences that exist between treatments can be detected early and changes can be made to the trial concurrently, rather than waiting for the end of the study to check results. This provides researchers with a much more ethical way to investigate different treatments. However, once changes are made to a trial, it becomes difficult to provide estimates of the true treatment effects for each group. There is discussion on whether the results obtained from such trials are accurate and if they are still addressing the preliminary research question, or if the adaptations have changed the very nature of the trial.

A specific type of adaptive design is adaptive randomization, which changes the way in which patients are randomized into treatment groups. These designs can be further categorized as treatment adaptive, covariate adaptive and response adaptive randomization designs. The first two of the preceding designs are the primary focus of this paper; however it should be noted that there are many other genres of designs including group sequential, sample size re-estimation, drop-the-losers, biomarker-adaptive, adaptive treatment-switching, adaptive dose finding, adaptive-hypotheses, adaptive seamless phase II/III, and multiple adaptive designs.

#### The Biased Coin Design

The goal of the biased coin design is to balance the treatment group sample sizes as subjects enter the study sequentially and the total sample size of the experiment is not predetermined. This specific design was first introduced in a Hodgkin's disease

<sup>&</sup>lt;sup>6</sup> Chow and Chang (2008)

investigation by Efron in 1971<sup>7</sup>. This method is usually considered to balance the sample sizes between treatment groups<sup>8</sup>. The Biased Coin Design utilizes the principles of Friedman's Urn Model, in which an urn contains  $\alpha$  white balls and  $\alpha$  red balls to start<sup>9</sup>. A ball is drawn from the urn at random, determining the treatment group of the next patient, replaced and  $\beta$  balls of the opposite color are added to the urn. In the biased coin design, the probability that a new subject is assigned to either group is determined by the current balance in treatment group sample sizes. The difference in the treatment group sample sizes of the groups are currently balanced the probability that the next patient is assigned to group A is 0.50. If there are more patients in group B currently, the probability that the next patient is assigned to group A is a constant  $0 < \eta < 1$ . ( $\eta = 2/3$  has been shown to be optimal<sup>10</sup>.) The assignment probabilities for are summarized in Table 1(below).

Current Sample Size Balance	Probability of Assignment to Group A	Probability of Assignment to Group B
$D_N > 0$	$\frac{1}{3}$	$\frac{2}{3}$
$D_N = 0$	$\frac{1}{2}$	$\frac{1}{2}$
$D_N < 0$	$\frac{2}{3}$	$\frac{1}{3}$

#### Table 1: Assignment Probabilities for the Biased Coin Design

The biased coin design is easy to implement and attempts to create equal treatment groups by randomizing patients to the groups. While this method of adaptive randomization aims to balance the treatment group sample sizes while maintaining the randomization of each patient to a treatment group, it also has limitations. These include the inability to distinguish between a large imbalance and a small imbalance in group sample sizes. For example, the following situations have identical allocation probabilities: (1) group A has three patients, group B has one patient, and (2) group A has 16 patients while group B has 14 patients. Situation (1) has a larger imbalance in treatment group sample sizes so it would be more important to researchers to decrease that imbalance by assigning the next patient to group A. In situation (2) the treatment group sample sizes are nearly balanced and researchers may not be as

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<sup>&</sup>lt;sup>7</sup> Wei, L. J. (1977)

<sup>&</sup>lt;sup>8</sup> Chow, Shein-Chung, and Chang, Mark (2006)

<sup>&</sup>lt;sup>9</sup> Wei, L. J. (1977)

<sup>&</sup>lt;sup>10</sup> Efron, Bradley (1971)

concerned about the assigned group of the next patient. However, the biased coin design does not factor the severity of imbalance into the probability of assignment. The only factor that determines the probability of group assignment is the sign of  $D_N$ . If  $D_N$  is positive, the probability of assignment to group B is greater than that for group A, and vice versa when  $D_N$  is negative. This is the largest limitation of the biased coin design.

#### The Adaptive Biased Coin Design

The limitation of the biased coin design to detect the severity of the imbalance in treatment group sample sizes was a main influence in the creation and implementation of the adaptive biased coin design. The adaptive biased coin design was introduced in 1977 by Wei<sup>11</sup>, and is based on Friedman's Urn Model<sup>12</sup>. Similar to the biased coin D<sub>N</sub> is calculated preceding the arrival of the next patient. The difference is then scaled by the total sample size thus far, *n*. The ratio of difference to total sample size determines the assignment probabilities for the next patient. The probability that the next patient is assigned to group B is a monotone increasing function, *f*, of the ratio  $\frac{D_N}{n}$ . The probability of the next patient being assigned to group B is a monotone decreasing function, *g*, such that f+g=1. Thus, the severity of imbalance in treatment group sample sizes is taken into account. Choosing  $f = \frac{N_A}{n}$  has been shown to yield good designs, which makes  $g = \frac{N_B}{n}$  where N<sub>j</sub> is the number of subjects in group j. The probability functions are depicted in Figure 1 (below).





<sup>&</sup>lt;sup>11</sup> Wei, L. J. (1977)

<sup>&</sup>lt;sup>12</sup> Chow and Chang (2006)

Returning to the previous biased coin design examples, we see that the probability of assignment to group B has been scaled to 0.75 in situation (1), and scaled to 0.067 in situation (2). It is clear that this design balances sample sizes across treatment groups more effectively than the biased coin design, because it increases the probability of assignment to the group with fewer subjects in the cases of severe imbalance, and is guaranteed to achieve perfect balance for the first two assignments. A comparison of the sample size balancing qualities of basic randomization (CRD), the biased coin design (BCD 2/3) and the adaptive biased coin design (ABCD) are shown in Table 2 (below). (Note: for odd *n*, sample sizes within one of each other were considered to be in balance.) It is easy to see that for the first ten assignments, the adaptive biased coin design produces more balanced sample sizes across groups than the other two designs.

Probability of Balance (of Two Groups) after <i>n</i> Assignments									
Design					n				
	2	3	4	5	6	7	8	9	10
CRD	.500	.750	.375	.625	.313	.547	.273	.492	.246
BCD(2/3)	.667	.889	.593	.840	.560	.812	.541	.795	.530
ABCD	1	1	.667	.917	.550	.839	.479	.775	.430

Table 2: Comparison across Designs of the Probability of Equal Treatment Group Sample Sizes<sup>13</sup>

A SAS<sup>®</sup> macro has been implemented to perform adaptive biased coin randomization<sup>14</sup>. The macro takes the current sample sizes of two treatment groups and determines the assignment of the next patient based on the randomization scheme described above.

#### **Covariate Adaptive Randomization**

The previous two designs consider the primary goal of adaptation to be balancing the sample sizes of treatment groups. It is possible that there are other factors that the researcher wishes to keep balanced across treatment groups. For example, in a trial examining the efficacy of different blood pressure medications, it would be of interest to have nearly equal baseline blood pressures across the treatment groups. Covariate adaptive randomization aims to balance covariates (either quantitative or categorical) across treatment groups. There are many methods of covariate adaptive randomization; the one presented in this paper is the Frane method since it is the only

<sup>13</sup> Wei, L. J. (1977)

<sup>&</sup>lt;sup>14</sup> Code available in Appendix (p.11).

method that controls for quantitative covariates in addition to categorical ones<sup>15</sup>. Frane published this design, which aims to balance the treatment groups by assigning the next patient to a treatment group so that the imbalance among the covariates is the least, in 1998<sup>16</sup>. The method is described in Table 3 (below)<sup>17</sup>:

Step 1:	Temporarily assign the new patient to treatment group A.
Step 2:	Calculate the Pearson's $\chi^2$ Goodness-of-Fit test statistic for the covariate groups to which the new patient would belong.
Step 3:	Identify the maximum $\chi^2$ test statistic among all the covariate groups.
Step 4:	Remove the patient from group A and repeat steps 1 – 3 for all other treatment groups.
Step 5:	Identify the minimum $\chi^2$ test statistic over all the identified test statistics (one from each repetition of step 1 – 3).
Step 6:	Assign the new patient to the group for which the minimum $\chi^2$ test statistic was achieved.

 Table 3: Steps of Covariate Adaptive Randomization

Consider the following example:

The efficacy of two blood pressure reducing drugs is being compared in patients with high blood pressure, with consideration of the following covariates: baseline blood pressure (hypertensive or pre-hypertensive) and age (greater than or equal to 65 years or less than 65 years). The trial is summarized in Table 4 below.

<sup>15</sup> Kang et. al (2008)

<sup>16</sup> Frane, J.W. (1998)

<sup>&</sup>lt;sup>17</sup> This method describes the procedure for categorical covariates; a similar method would be used for quantitative covariates – instead of using  $\chi^2$  test statistics, use the p-value for a t-test and ANOVA.

Sample sizes for the first 20 patients				
		Drug A N <sub>A</sub> = 12	Drug B N <sub>B</sub> = 8	
Baseline Blood	Hypertensive	8	3	
Pressure	Pre-Hypertensive	4	5	
Age	$\geq$ 65 years	7	6	
	< 65 years	5	2	

 Table 4: Patient Characteristics
 for First 20 Patients in Trial

A new patient arrives at the trial who is hypertensive and less than 65 years of age. To determine to which treatment group this patient should be assigned, we first temporarily assign this new patient to group A, and calculate  $\chi^2$  Goodness-of-Fit test statistics for the number of hypertensive patients across groups A and B, and for the number of under-65-year-old patients across groups A and B. This process is demonstrated in Table 5 below.

	Drug A	Drug B	<b>X</b> <sup>2</sup>
Baseline Blood Pressure (Hypertensive)	9	3	3.0
Age ( < 65 years)	6	2	2.0

 Table 5: Calculating the Chi-Squared Test Statistics

We note that the largest  $\chi^2$  test statistic when we add the new patient to group A is 3. Repeating this process, assigning the patient to B, and calculating  $\chi^2$  test statistics, we determine that the largest  $\chi^2$  test statistic when the patient is assigned to group B is 1.33. Therefore the new patient should be assigned to group B, since there will be a smaller imbalance for the covariates when the patient is in group B.

This example utilizes Frane's covariate adaptive randomization method with two treatment groups and two binary categorical covariates. However, this method can be extended for more treatment groups and more covariates and covariate categories. Also, the researcher may predetermine the proportion of allocation for the treatment

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groups, if unequal treatment group sample sizes are desired. In our example above, we could specify that there should be twice as many patients on drug A as on drug B. This could be done for numerous reasons, including ethical reasons, if one drug is potentially more effective or more practically used than another.

Covariate adaptive randomization will balance the covariates across the treatment groups but there are some marked limitations of this design. Because this method determines the treatment group of the next patient, rather than increasing the probability of being randomly assigned to that treatment group (as seen in the adaptive biased coin design), selection bias is present. Researchers may be able to determine the treatment group assignment of the next patient based on the patient characteristics alone, which will lead to a more biased method than desired. Further investigation should consider randomizing patients with increased probability rather than directly determining the group assignment of the next patient.

A SAS<sup>®</sup> macro has been implemented to perform covariate adaptive randomization<sup>18</sup>. The macro requires inputting a data set of current patient characteristics similar to table 4 above.

#### Conclusion

The biased coin design, adaptive biased coin design and covariate adaptive randomization are specific designs aimed at balancing certain aspects of a clinical trial. The biased coin design and the adaptive biased coin design aim to balance treatment group sample sizes by assigning the next patient to the group with the smaller sample size with higher probability. The biased coin design uses a fixed probability to achieve this whereas the adaptive biased coin design determines the severity of the imbalance between treatment groups using the total sample size to scale the difference in treatment group sample sizes. The probability of assignment to a specific group in the adaptive biased coin design thus depends on the ratio of the difference in sample sizes between treatment groups to total sample size. Covariate randomization designs aim to balance the covariates across the treatment groups by assigning the next patient to the group that causes the smallest imbalance across the covariate groups.

All of these adaptive randomization designs provide researchers with alternatives to traditional randomization. However, the complicated probability structures involved in patient assignment to treatment groups makes estimating treatment effects more challenging than in traditional randomization designs. Often the traditional treatment

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<sup>&</sup>lt;sup>18</sup> Code available in Appendix (p.12)

effect estimates are used in these designs, but researchers should take caution that these estimates may not be accurate. More development is needed in methods to estimate treatment effects and variance.

### Appendix

```
Adaptive Biased Coin Design Macro Code
*** Adaptive Randomization Macro - using the adaptive biased coin design;
** f(x)=1-x <- probability of assignment to A;
** g(x)=x <- probability of assignment to B;
** where x = (diff in num of subjects in each trt)/(total num of subjects);
%macro ABCDrandomization(NumA, NumB);
       data Assignment;
        %let numer=%EVAL(&NumA-&NumB);
        %let denom=%EVAL(&NumA+&NumB);
        %let DiffRatio = %SYSEVALF(&numer/&denom);
        /* assign subject to B with probability x, A with prob 1-x */
        %let RandNum = 2*%SYSFUNC(ranuni(0))-1; %*uniform[-1,1] random var;
        %if %SYSEVALF(&RandNum <= &DiffRatio) %then %let Assign=B;
        %else %let Assign=A;
        /* create subject num var */
        %let AssignNum = %EVAL(&NumA+&NumB+1);
        groupA = \&NumA;
        groupB = \&NumB;
        newGroup = "&Assign";
        label groupA = "Number in treatment group A"
                    groupB = "Number in treatment group B"
                    newGroup = "Assignment for next subject is";
       run;
       proc print data=Assignment label noobs; run;
%mend ABCDrandomization;
```

#### **Covariate Adaptive Randomization Macro Code**

```
*** Covariate Adaptive Randomization Macro;
/* This is the data set for the current subjects in the trial */
/* Must be in this form */
data patdat;
input cov level group $ count;
datalines:
11A4
12A8
21A5
2 2 A 7
1 1 B 5
12B3
21B2
22B6
run;
%macro doit(TrtGrp=A,level1=2,level2=1);
/* increase counts for new patient */
 data freq;
  set patdat;
       if Group = "&TrtGrp" then do;
   if cov=1 and evel=\&evel1 then count = count + 1;
        if cov=2 and evel=\&evel2 then count = count + 1;
       end:
 run;
/* sort data by cov and level for proc freq */
 proc sort data=freq;
  by cov level;
run;
/* run goodness-of-fit (Note: can't use noprint option with ods output */
 proc freq data=freq;
  table group / CHISQ;
  weight count / ZEROS;
  by cov level;
  ods output OneWayChiSq = temp;
```

run;

```
/* get chi-square statistics for new patients cov values */
 data freq_&TrtGrp;
  set temp;
         if Name1 = "_PCHI_";
  if cov=1 and evel=\&evel1 then output;
  else if cov=2 and level=&level2 then output;
       keep cov level nValue1;
 run;
/* find highest chi-square statistic */
 data freq_&TrtGrp;
  set freq_&TrtGrp;
       retain highchi2 0;
  if nValue1 > highchi2 then highchi2=nValue1;
 run;
/* pick out highest chi-square statistic */
 proc sort data=freq_&TrtGrp;
   by descending highchi2;
 run;
 data freq_&TrtGrp;
  set freq_&TrtGrp;
  if _N_=1 then output;
       keep cov level highchi2;
 run;
%mend doit:
%macro CAR(cov1_val=2,cov2_val=1);
/* get highest chi-square statistics when we assign */
/* new subject to group A and group B */
%doit(TrtGrp=A,level1=&cov1_val,level2=&cov2_val);
%doit(TrtGrp=B,level1=&cov1_val,level2=&cov2_val);
/* combine output from macro calls above */
 data all:
 set freq_A (in=A) freq_B (in=B);
 GrpA = A;
```

```
GrpB = B;
 run;
/* find lowest chi-square for the two treatment groups */
 proc sort data=all;
 by highchi2;
 run;
/* print out the group assignment associated with the lowest chi-square statistic*/
 data all;
 set all;
 if _N = 1;
 if GrpA = 1 then TrtGrp="A";
 if GrpB = 1 then TrtGrp="B";
 cov1 = \&cov1_val;
 cov2 = \&cov2_val;
 label cov1 = "Next subject*has covariate 1*value"
               cov2 = "Next subject*has covariate 2*value"
               TrtGrp = "Assignment*for next*subject is";
 keep cov1 cov2 TrtGrp;
 run;
 proc print split="*" noobs; run;
%mend CAR;
```

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