

Author: Eva R. Miller, Ph.D., Associate Director, Biostatistics

Introduction

The classic challenge of developing new medical treatments while minimizing patient safety risk is nothing new to the pharmaceutical industry. However, due to steeply rising drug development costs and escalating patient safety concerns, there is increasing pressure on pharmaceutical companies and industry thought leaders to reexamine traditional clinical trial techniques and increase the efficiency and safety of the clinical trial process.

One way to address the challenges that are receiving significant attention from pharmaceutical companies, regulatory agencies, and industry thought leaders is adaptive trial design. Adaptive trial design refers to a conceptual clinical trial methodology which allows for modifications to take place after the trial has started without compromising the scientific method. Examples of adaptive trial modifications include

- Balancing based upon probabilistic baseline covariate adaptive randomization (PBCAR),
- Combining phases I and II,
- Dropping a treatment arm,
- Modifying the sample size, or
- Simply stopping a study early for success or failure.

For all forms of adaptive design the critical distinction to maintaining the research perspective is that the decision-making rules governing the adaptation must be clearly stated in the protocol.

Each of these adaptive design techniques revolves around the core mission of allowing clinicians to maximize the safety and efficacy information that is generated from each subject. This mission is especially critical where small available patient populations make maintaining balance among treatments for the analysis population and subgroups especially challenging, such as studies involving:

- Rare conditions,
- Terminally ill patients,
- Medical device studies,
- Surgical procedure studies
- Studies of orphaned drugs,
- Studies with many smaller population subgroups and
- Studies terminated early.

By applying PBCAR, a form of adaptive design, better balance can be achieved in small study situations than is possible using simple randomization or traditional minimization techniques. This is different from the minimization techniques introduced in the 1970's, in that some element of chance is applied to every randomization decision, not just for tie-breaking decisions. This is an important distinction because the PBCAR methodology is probabilistic, as specified in the ICH E9 guidelines, rather than deterministic.

This paper will demonstrate a modified Pocock-Simon design that includes some element of chance in every randomization decision. This method is especially appropriate if blinding is not feasible, eg, in a surgical trial or medical device trial. Another related technique is the Adaptive Biased Urn Randomization (ABUR) method described by Schouten.¹⁸ This article also presents an example of the application of this method for a rare medical condition.

Ongoing debate on minimization techniques

As has been clearly documented in the literature, simple stratified randomization is of limited utility if many strata result in too few subjects per stratum.¹⁻⁴ With PBCAR, consideration is given to the hierarchy of balancing decisions or the weights of prognostic factors. Hierarchical ordering of prognostic factors or weights of factors may be derived from clinical judgment, previous clinical trials or preliminary data. Much consideration goes into determining the appropriate random adaptive algorithm. Atkinson⁵ aptly stated: **“too small a response to imbalance could lead to nearly random experimentation with a lack of balance in the completed experiment.”**

There is a vigorous ongoing debate about the appropriateness of uses of minimization techniques including its ‘probabilistic variants’. Senn⁶⁻⁹ has argued vigorously against minimization techniques, which he does not consider superior to simple or stratified randomization. Senn describes minimization as **“not based on the theory of experimental design and works on an *ad hoc* algorithm that adds together apples and pears”**. Senn considers Atkinson’s optimal design technique^{5,10} to be superior to minimization because it is **“based upon sound and logical statistical principles.”**⁶

Day, Grouin and Lewis,¹¹ who contributed to the Committee for Proprietary Medicinal Products (CPMP) position on minimization, consider that **“the scientific community is not of one mind regarding the use of covariate-adaptive randomization procedures”**. They also point out that direct linkage between randomization and method of statistical analysis is a critical underpinning of sound clinical research design, and that analytical approaches for minimization are still an open question.

The argument for probabilistic minimization techniques is posed convincingly by Buyse and McEntegart.¹² Some of their points include:

- A view that the CPMP claims that dynamic methods such as minimization **“remain highly controversial”** is unfair because it ignores recent methodological literature that encourages wider use of minimization.^{13, 14}
- Since the method of minimization considers individual factor levels separately from each other, a larger number of factors can be considered than in a stratified randomization design.
- For studies employing minimization techniques, the appropriate analytical approach is still an open question: whether conventional asymptotic tests can be used for analysis, or whether ‘re-randomization’ tests reflecting the order in which patients with different baseline characteristics entered the trial must be employed.
- It has been questioned whether minimization can actually create imbalances with respect to unknown prognostic factors, but this concern has been refuted as Aickin¹⁵ showed conclusively that dynamic randomization was at least as good as simple randomization.
- **“An article in a leading medical journal describes minimization as the platinum standard for clinical trials without drawing any adverse response.”**¹⁶

Regulatory authorities in the USA are beginning to consider the benefits of using PBCAR techniques.¹⁷ Balancing on covariates tends to decrease the variance of estimates of these covariates, and improves the efficiency of the treatment effect estimate. PBCAR is best implemented using a phone or internet-based interactive clinical technology in today’s research and regulatory environment.

Development of a random adaptive algorithm

When designing a study, the principal investigator and clinical trial statistician determine the primary efficacy endpoint, the appropriate study population and the analytical model. In determining the random adaptive algorithm to best support the statistical analysis, the clinical trial statistician considers the statistical methodology, or ‘model statement’, to be used for the primary efficacy variable. Prognostic factors are incorporated into the random adaptive algorithm in a parallel design to the planned statistical analyses. The randomization design must support the planned statistical

analysis.¹⁹ In order to ensure that the intended randomization objectives will be met, each random adaptive algorithm requires an extensive series of planning, simulation testing and verification steps.

After the primary efficacy endpoint and analytical model are determined, the appropriate factors to include in the random adaptive algorithm must be established. As a starting point, information about prognostic factors can be derived from clinical judgment, previous studies or historical values reported in clinical literature. After prognostic factors (at baseline) are chosen, decisions need to be made about:

- The nature of the statistical methodological framework,
- The priority or weight given to each factor within the decision-making rule (even deciding not to use weights actually means that all factors are weighted equally), and
- The choice of proportional assignments among treatment groups.

The contributions of the prognostic factors, their hierarchical structure and/or their weighting, and how these impact balance must be thoroughly tested. A good statistical textbook presentation of randomization algorithm design considerations is presented by Rosenberger and Lachin.²⁰ Currently, there is no set of rules for the statistician to use to develop the single definitive random adaptive algorithm or decision making rule; therefore, a goodly amount of thought and work goes into this process for each clinical trial protocol. An adaptive randomization algorithm that follows either a classical or Bayesian theoretical framework is clearly delineated through simulation testing. It is generally agreed that the algorithm selected must demonstrate a high level of convergence for the balancing criteria.

Once the design of the randomization strategy has been established, the development group works directly with the study team to develop system requirements for the random adaptive algorithm. The author recommends simulation testing during the development phase of the random adaptive algorithm system module, in order to:

- Address the robustness of the random adaptive algorithm to conditions not under the researcher's control, especially the order in which the subjects enrol.¹ The random adaptive algorithm must accommodate this variation. 'Re-sequencing' is a technique for reordering seeded data in a simulation data-set and checking the resultant balances while holding the random adaptive algorithm and random numbers constant. As many as 1000 iterations are tested and the algorithm must demonstrate convergence of balance on the relevant prognostic factors.
- Verify the degree to which chance alone will alter the overall balance and the balance for strata or subgroups. This may be accomplished by using multiple randomization schedules against the same simulation data set. Some authors refer to this as 're-randomization'.
- Test the contributions of the prognostic factors, their hierarchical structure and/or their weighting, and how these impact upon balance.

Should clinical trial statistician decide that too much variation is occurring based upon re-randomization or re-sequencing results during 'black box' testing, areas for possible reconsideration are:

1. If a boundary is placed on $|q_1 - q_2| \leq b$ (where q_1 = the number of subjects assigned to treatment 1, q_2 = the number of subjects assigned to treatment 2, and b = boundary value), as the boundary value increases, more treatment assignments will be based upon later steps in the hierarchy.
2. Hierarchical steps in the adaptive randomization algorithm may be changed.
3. Prognostic factors may be added or eliminated from the adaptive randomization algorithm.
4. If weights are used among prognostic factors, these may be altered.
5. To assure that every treatment determination is based upon an element of randomization, 'weighted-coin' decisions are stated with a maximum of 0.90 in any treatment arm; these weights may be adjusted.

During the development phase of the random adaptive module within the Interactive Voice Response (IVR) or Electronic Data Capture (EDC) system, simulation testing is used to validate the appropriate implementation of the random adaptive algorithm.

Randomization reports are designed to facilitate the decision-making process by showing resultant balances overall and for subgroups or strata. Also, individual listings of subjects randomized (in simulations and later in the live study) show the stratification factors of the subjects, the randomization counts upon which the treatment assignment was made, the random number, the probabilities, and the logical decision making rules (in footnotes).

The Randomization Logic (balanced coin or weighted coin and weighted in what direction), Randomization Logic Probability Outcome (statements showing the treatment assignment based upon the random number value) and Randomization Probabilities (decision in relation to the random number value) on the reports allow for a complete audit trail for each patient randomized and an accurate assessment of the robustness of the random adaptive algorithm.

After a clinical trial is completed (or stopped), it is possible to hypothetically re-sequence the subjects and run through the random adaptive algorithm used in the IVR or EDC system to verify the specificity of the overall treatment assignment balance among treatment groups, the balance within hierarchical steps in the random adaptive algorithm, and the balances for subgroups or strata.

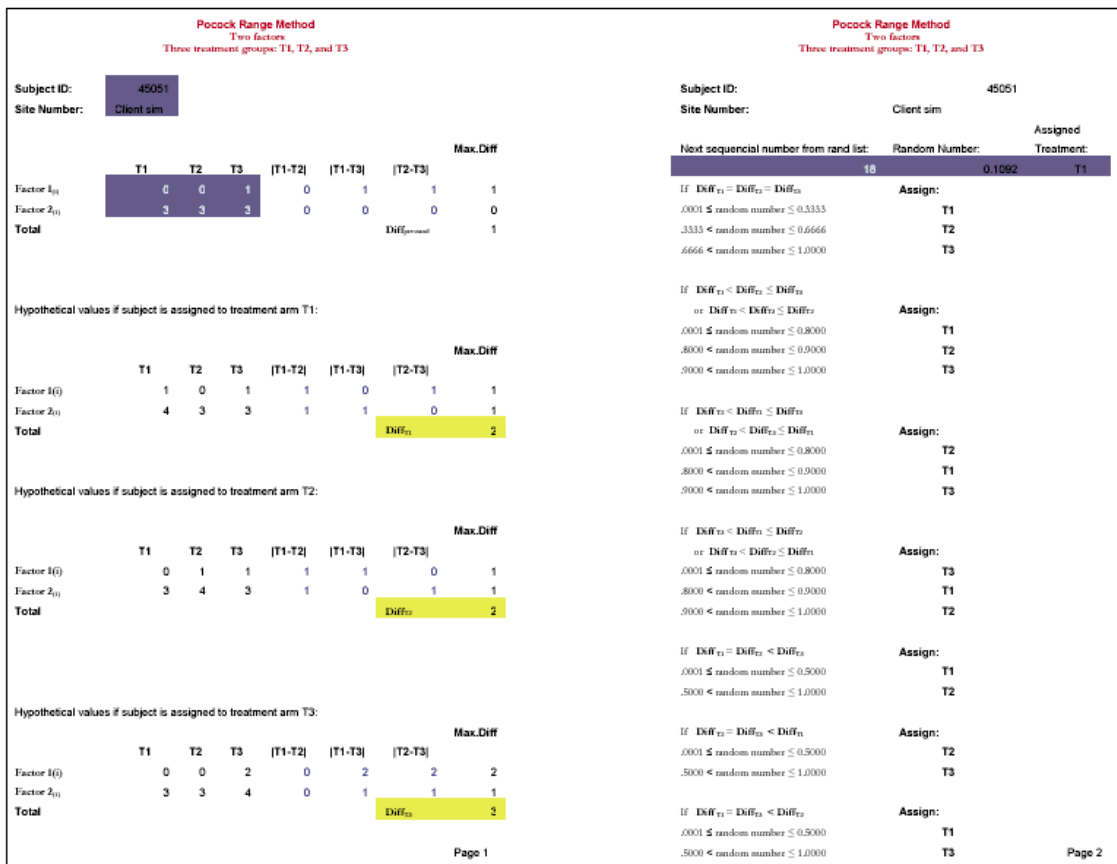


Fig. 1 Screenshot illustration on individual treatment assignment

Simple case study: Modified Pocock-Simon method

Pocock and Simon, classical theoretical statisticians, developed a general procedure for treatment assignment which concentrates on minimizing imbalances in the distribution of subjects to treatment groups within the levels of each prognostic factor.¹ The method involves determining the amount of imbalance for each of the prognostic factors, hypothetically assigning the next subject to each treatment group, and then assigning that subject to the treatment group which will minimize the treatment assignment imbalances. The original statement of the minimization method was deterministic, in that random number values were only used in tie-breaking situations. Modified Pocock-Simon methodology is recommended here, in which every randomization decision is dependent on a random number and the maximum probability of treatment assignment possible for

any specific treatment group assignment is 0.90. This is an illustration of a probabilistic baseline adaptive randomization.

This example of a Pocock and Simon’s ‘range’ method was designed to support a clinical study with two stratifying factors: Factor 1 (with four levels) and Factor 2 (with two levels). The study had three treatment groups: active drug at two dose levels (referred to as T1 and T2) and a comparator, T3. The sample size for this study was approximately 1000 subjects. There were more than 25 investigational sites, but site was not a stratifying factor. Sampling was without replacement.

Assignment of subjects to treatments in this study applied a weighted coin approach, with a maximum probability component of 0.80. The treatment allocation resulting in the smaller overall measure of imbalance is performed with probability $p=0.80$. This allocation scheme focuses on achieving an approximate balance with respect to the predefined factors, while also including a random component that tends to balance arms generally with respect to any other prognostic factors.

Randomisation assignments are generally made by an automated system, which is written in TSQL and functions on an SQL platform. A spreadsheet illustrating an individual treatment assignment, which helps users to follow the logic within the protocol-specific adaptive randomization algorithm, and may be used to check randomization assignments derived from the automated system, is shown in Figure 1. (Full-size versions of all figures presented in paper are provided in the PDF version of article, which is accessible via the ODIN engine in the “Information services” section of the CRfocus website - www.crfocus.org.)

Using the spreadsheet, the user would input subject identifiers, randomization counts corresponding to the subject’s Factor levels, and the random number. The spreadsheet automatically computes the D or Diff pre-randomization and Diff for hypothetical assignment to each treatment group. The user then checks the appropriate logical decision-making rule and assigns the treatment based upon the decision-making rule with the associated random number.

A summary report for a simulation using this random adaptive algorithm is shown in Figure 2. The example reflects 53 randomization transactions and the balance achieved for the study overall and for each of the two factors. The example also demonstrates that subjects do not necessarily present with balanced levels of each factor: Factor 1, level 1 has 39 subjects, while Factor 1, level 4 has 3 subjects.

A randomization report listing each randomization (usually 9 or 10 per page, but three on the example shown) is in Figure 3. This report would serve as an audit trail of each randomization transaction in a live clinical trial, since it is possible to trace the randomization decision given the subject ID, factor values and levels, random number, randomization counts and Diff values for each hypothetical assignment to treatment group. The logical decision-making probability statements, which are random adaptive algorithm specific, are in the footnote of each page of the report.

Figure 2
Pocock Range Method
Two stratifying factors
Three treatment groups

RandCounts Simulation

Simulation Number: 1						
Summary of Counts by Stratification Factor						
Factor 2	Treatment Arm	Overall Factor 1	Factor 1 Level 1	Factor 1 Level 2	Factor 1 Level 3	Factor 1 Level 4
Factor 2, Level 1	T1	12	8	2	1	1
Factor 2, Level 1	T2	12	8	2	2	0
Factor 2, Level 1	T3	12	9	1	0	2
Total: Factor 2 Level 1		36	25	5	3	3
Factor 2	Treatment Arm	Overall Factor 1	Factor 1 Level 1	Factor 1 Level 2	Factor 1 Level 3	Factor 1 Level 4
Factor 2, Level 2	T1	6	5	0	1	0
Factor 2, Level 2	T2	6	6	0	0	0
Factor 2, Level 2	T3	5	3	1	1	0
Total: Factor 2 Level 2		17	14	1	2	0
	Total	Overall Factor 1	Factor 1 Level 1	Factor 1 Level 2	Factor 1 Level 3	Factor 1 Level 4
	53	53	39	6	5	3
	Total T1	Total T2	Total T3			
	18	18	17			

Pocock Range Method														Two stratifying factors Three treatment groups		
RandCounts Simulation														Simulation Number: 1		
Summary of Simulation Number: 1																
SubjectID	TxArm	Random Number	Value Factor 2	Level Factor 2	Value Factor 1	Level Factor 1	Count Values Before Rand						Diff T1	Diff T2	Diff T3	
							T1 Factor 1	T1 Factor 2	T2 Factor 1	T2 Factor 2	T3 Factor 1	T3 Factor 2				
00005033	1	0.1330	6.6	1	18	1	3	2	4	1	4	2	2	2	4	
00018010	2	0.3576	4.1	1	37.3	3	0	2	0	1	2	3	1	3		
00085001	1	0.6737	5.3	1	21.4	1	3	2	4	2	4	2	1	3	3	

If $\text{Diff}_{T1} = \text{Diff}_{T2} = \text{Diff}_{T3}$.0001 ≤ random number ≤ 0.3333 .3333 ≤ random number ≤ 0.6666 .6666 ≤ random number ≤ 1.0000 Assign: T1, T2, T3	If $\text{Diff}_{T1} < \text{Diff}_{T2} \leq \text{Diff}_{T3}$ or $\text{Diff}_{T2} < \text{Diff}_{T3} \leq \text{Diff}_{T1}$.0001 ≤ random number ≤ 0.8000 .8000 ≤ random number ≤ 0.9000 .9000 ≤ random number ≤ 1.0000 Assign: T2, T1, T3	If $\text{Diff}_{T1} = \text{Diff}_{T2} < \text{Diff}_{T3}$.0001 ≤ random number ≤ 0.5000 .5000 ≤ random number ≤ 1.0000 Assign: T1, T2
If $\text{Diff}_{T1} < \text{Diff}_{T2} \leq \text{Diff}_{T3}$ or $\text{Diff}_{T2} < \text{Diff}_{T3} \leq \text{Diff}_{T1}$.0001 ≤ random number ≤ 0.8000 .8000 ≤ random number ≤ 0.9000 .9000 ≤ random number ≤ 1.0000 Assign: T1, T2, T3	If $\text{Diff}_{T2} < \text{Diff}_{T1} \leq \text{Diff}_{T3}$ or $\text{Diff}_{T1} < \text{Diff}_{T3} \leq \text{Diff}_{T2}$.0001 ≤ random number ≤ 0.8000 .8000 ≤ random number ≤ 0.9000 .9000 ≤ random number ≤ 1.0000 Assign: T3, T1, T2	If $\text{Diff}_{T2} = \text{Diff}_{T3} < \text{Diff}_{T1}$.0001 ≤ random number ≤ 0.5000 .5000 ≤ random number ≤ 1.0000 Assign: T2, T3
	If $\text{Diff}_{T1} = \text{Diff}_{T2} < \text{Diff}_{T3}$.0001 ≤ random number ≤ 0.5000 .5000 ≤ random number ≤ 1.0000 Assign: T1, T3	

icti Randomization-Logic-Probability-Tx-Assignment Key

Fig. 3 Randomization report listing details of each randomization transaction.

Advanced case study: ABUR

Urn randomization was introduced by Wei,²¹⁻²³ a Bayesian statistical theorist. In urn randomization, the assignment of probabilities is adapted to the degree of imbalance in relation to the number of patients already entered into the trial. Schoeten¹⁸ describes an even more flexible urn model than that described by Wei. Schoeten’s model, called biased urn randomization, is especially useful because it is appropriate for small sample sizes and when blinding is not feasible.

Schoeten’s method of biased urn randomization is randomization without replacement, where:

- s = number of balls (chances) for each treatment group at study start,
- x = extra balls (chances) for each of the treatment group not selected after each randomization
- g = number of treatment groups in the clinical trial

The integers s and x must be chosen such that there never can be a negative number of balls in the urn. In addition, care must be taken in the selection of s and x such that it is not possible to predict the next patient treatment assignment, given previous treatment assignments.

In our example, for three treatment groups (g = 3 with s = 0 and x = 1), Schoeten’s formula of:

$$p_i = \frac{s + (N - n_i)x - n_i}{gs + N(g-1)x - n_i}$$

reflecting the number of balls for one treatment type divided by the total number of balls in the urn after N drawings, reduces to:

$$p_i = \frac{N - 2 n_i}{N}$$

A crucial point is that the total number of balls in the urn after N drawings is independent of the balls that have been drawn, so unpredictability is maintained.

The example discussed here was for a rare medical condition; the clinical trial had three treatment groups representing different dose levels of the active study drug. Given the rare medical condition, the total anticipated sample size was small (under 50 subjects). The design called for one continuous factor (Factor 1) with two levels to be considered. The design is particularly interesting because it required attenuation of a second continuous factor (Factor 2) for clinical considerations: only treatments A and B were administered to patients in the highest level of Factor 2, while only treatments B and C were administered to patients in the lowest level of Factor 2. Balancing was not required for Factor 2; it was used to accomplish the desired clinical dose regulated attenuation. Balance within this randomization design was achieved overall and for Factor 1.

If the number of patients in the study within the same Factor 1 stratum as the patient to be randomized > 0. Find the probability of assigning Treatment A:	Find the probability of assigning Treatment B where there are patients within the same Factor 1 stratum.	Find the probability of assigning Treatment C where there are patients within the same Factor 1 stratum.
A – Number of treatments minus 1	A – Number of treatments minus 1	A – Number of treatments minus 1
B – A multiplied by x	B – A multiplied by x	B – A multiplied by x
C – B minus 1	C – B minus 1	C – B minus 1
D – Number of treatments multiplied by s	D – Number of treatments multiplied by s	D – Number of treatments multiplied by s
E – D divided by the number of patients in the study within the same Factor 1 stratum as the patient to be randomized	E – D divided by the number of patients in the study within the same Factor 1 stratum as the patient to be randomized	E – D divided by the number of patients in the study within the same Factor 1 stratum as the patient to be randomized
F – C plus E	F – C plus E	F – C plus E
G – x plus 1	G – x plus 1	G – x plus 1
H – G divided by F	H – G divided by F	H – G divided by F
I – Number of patients assigned to Treatment A in the study (within the same Factor 1 stratum as the patient to be randomized) divided by the number of patients in the study (within the same Factor 1 stratum as the patient to be randomized)	I – Number of patients assigned to Treatment B in the study (within the same Factor 1 stratum as the patient to be randomized) divided by the number of patients in the study (within the same Factor 1 stratum as the patient to be randomized)	I – Number of patients assigned to Treatment C in the study (within the same Factor 1 stratum as the patient to be randomized) divided by the number of patients in the study (within the same Factor 1 stratum as the patient to be randomized)
J – 1 divided by number of treatments	J – 1 divided by number of treatments	J – 1 divided by number of treatments
K – J minus 1	K – J minus 1	K – J minus 1
L – K multiplied by H	L – K multiplied by H	L – K multiplied by H
P _i – J plus L	P _i – J plus L	P _i – J plus L
If P _i < 0, set P _i = 0.1	If P _i < 0, set P _i = 0.1	If P _i < 0, set P _i = 0.1
P _i – probability of assigning treatment A	P _i – probability of assigning treatment B	P _i – probability of assigning treatment C

The algorithm is stated as follows:

- Let $s = 0$ = the number of chances to get each treatment at study start (ie, balls in the urn for each treatment).
- Let $x = 1$ = the number of extra chances added to the urn after each randomization for each treatment type not selected.

After determining P_a , P_b and P_c , perform appropriate clinical attenuation of treatment groups:

- If Factor 2 stratum is low, then determine P^b and P^a :
 $P^a = 0$
 $P^b = P_b + (P_b * (P_a / (P_b + P_c)))$
- If Factor 2 stratum is high, then determine P^a and P^c :
 $P^a = P_a + (P_a * (P_c / (P_a + P_b)))$
 $P^c = 0$

To standardize the final notation before programming:

- If Factor 2 stratum is middle:
 $P^{''a} = (P_a / (P_a + P_b + P_c))$
 $P^{''b} = (P_b / (P_a + P_b + P_c))$
 $P^{''c} = (P_c / (P_a + P_b + P_c))$
 $(P^{''a} + P^{''b} + P^{''c}) = 1$
- If Factor 2 stratum is low or high:
 $P^{''a} = (P^a / (P_a + P_b + P_c))$
 $P^{''b} = (P^b / (P_a + P_b + P_c))$
 $P^{''c} = (P^c / (P_a + P_b + P_c))$
 $(P^{''a} + P^{''b} + P^{''c}) = 1$

An excerpt from a spreadsheet illustrating an individual treatment assignment is shown on Figure 4. As the user inputs the randomization counts for subjects already in the study (or simulation) with the same Factor 1 level, the spreadsheet automatically computes the probability boundaries: P^a, P^b, and P^c for the three levels of Factor 2. The user then checks the appropriate logical decision-making rule and assigns treatment based upon the decision-making rule with the associated random number.

A summary report for a simulation using this random adaptive algorithm is shown in Figure 5. The example reflects 36 randomization Report Run Date/Time: DD-
MMM-YYYY, H:MIN pm EST transactions and balance achieved for the study overall and for each level of Factor 1. Factor 2 is a controlling factor related to clinical requirements for assignment of clinically appropriate dose groups (Treatment arms A and B for Factor 2, high level, all treatment arms for Factor 2, middle level and Treatment arms B and C for Factor 2, low level). Subjects will not necessarily present with balanced levels of each factor. In this example, Factor 1 is balanced with 18 subjects in each of the two strata. For Factor 2, 1 patient presented with low level, 27 patients with middle level, and 8 patients with high level. If an individual clinical trial requires certain numbers of

Adaptive Randomization Using Urn Method
Attenuated Example with Two Factors, Factor 1 and Factor 2
Three Treatment Groups Represent Different Levels of Active Drug

RandCounts Simulation

Simulation Number: 2

Summary of Counts by Stratification Factor

Factor 1: Stratum 1	Treatment Arm	Factor 2			
		Overall	Low	Middle	High
	A	6	0	5	1
	B	6	0	4	2
	C	6	1	5	0
Total Stratum 1		18	1	14	3

Factor 1: Stratum 2	Treatment Arm	Factor 2			
		Overall	Low	Middle	High
	A	6	0	3	3
	B	7	0	5	2
	C	5	0	5	0
Total Stratum 2		18	0	13	5

	Total A	Total B	Total C	Grand Total
	12	13	11	36

Fig. 5 Summary report for a simulation using this random adaptive algorithm.

Adaptive Randomization Using Urn Randomization Methodology
Attenuated Example with Two Factors, Factor 1 and Factor 2
Three Treatment Groups Representing Different Levels of Active Drug

Note to file: from Simulation 2

Subject ID: 111112049

Site Number: 22

g# = 0
x# = 1

Treatment

	A	B	C
Factor 2: Low level		1	8
Factor 2: Middle level	9	8	7
Factor 2: High level	9	8	

Treatment

	A	B	C
Factor 2: Middle level	2	2	2
A#	2	2	2
B#	1	1	1
C#	0	0	0
D#	0	0	0
E#	1	1	1
F#	2	2	2
G#	2	2	2
H#	0.375	0.3125	0.3125
I#	0.3333	0.3333	0.3333
J#	-0.0417	0.0208	0.0208
K#	-0.0833	0.0417	0.0417
L#	0.2500	0.3750	0.3750
neg. corrected P _(i)	0.25	0.375	0.375
P ^a _(i)	0.25	0.375	0.375

Adaptive Randomization Using Urn Randomization Methodology
Attenuated Example with Two Factors, Factor 1 and Factor 2
Three Treatment Groups Representing Different Levels of Active Drug

Subject ID: 1

Site Number: 22

Next sequential number from rand list: 520

If A = B = C = 0

0.0001	\$ random number < 0.3333
0.3333	\$ random number < 0.6667
0.6667	\$ random number < 1.0000

Factor 2: Low level

0.0001	\$ random number ≤ 0.5000
0.5000	\$ random number < 1.0000

Factor 2: Middle level

0.0001	\$ random number < 0.2500
0.2500	\$ random number < 0.6250
0.6250	\$ random number < 1.0000

Factor 2: High level

0.0001	\$ random number < 0.4000
0.4000	\$ random number < 1.0000

Fig. 4 Excerpt from a spreadsheet illustrating an individual treatment assignment.

patients per baseline factor level, the system can utilize ceilings or caps to stop enrollment of patients with certain baseline characteristics beyond the sample frame caps.

An excerpt from a randomization report, listing each randomization is presented in Figure 6. This report would serve as an audit trail of each randomization decision in a live clinical trial since it is possible to trace the randomization decision given the subject ID, factor values and levels, random number, randomization counts, P^a, P^b and P^c boundary values for each treatment group. The logical decision-making probability statements, which are random adaptive algorithm-specific, are in the footnote of each page of the report.

Conclusions

Baseline adaptive randomization approaches are flexible, easy to customize for specific clinical trial statistical designs, and easy to implement within IVR or EDC systems. They are especially valuable in clinical trials of small and moderate sample size and studies in which subgroup analyses are planned. It is very important to conduct thorough simulation testing on a random adaptive algorithm before implementation because there is no single definitive algorithm for each clinical trial protocol. A random adaptive algorithm for which simulation testing resulted in a high degree of convergence, regardless of the random number schedule, the order of patients enrolling in the study, or the background characteristics of the simulated subjects, can be used with confidence.

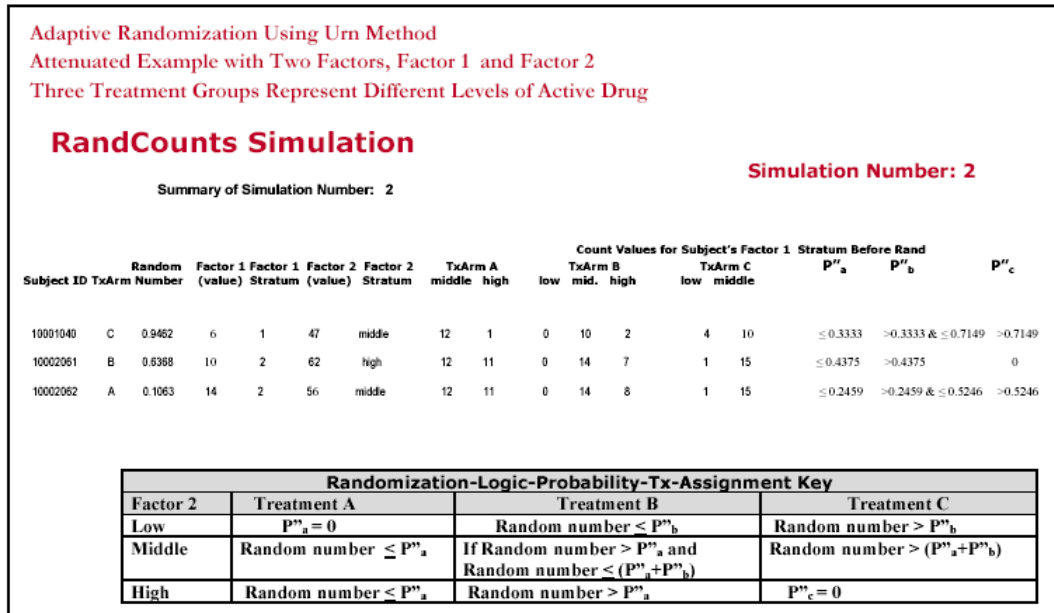


Fig. 6 Excerpt from a randomization report, listing each randomization.

In view of the lively statistical debate about the appropriateness of minimization techniques for subject allocation, it is highly recommended to incorporate the subject allocation procedure into the clinical trial protocol (including the actual probabilistic baseline random adaptive algorithm within an appendix) along with the planned analytical approach and to submit these for regulatory review and approval before undertaking the clinical trial. While planning and implementing, probabilistic baseline adaptive randomization does require significant effort, the benefit that is achieved by maximizing the safety and efficacy information generated from each subject results in a high return on investment.

Eva R Miller (eva.miller@icti-global.com) is Manager of Biostatistics, Interactive Clinical Technologies Incorporated (ICTI), Yardley, PA, USA. Interactive Clinical Technologies Incorporated (ICTI) has been implementing adaptive randomization designs in clinical trials since 1999 and has participated in over 75 adaptive randomization studies of varying complexity.

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