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Choosing a Randomization Method in Balance

Introduction to Randomization

Drug Research and Development is facing many opportunities and challenges, not the least of which is improving the efficiency of clinical trial research. The structured, web-based interface of Medidata Rave and Balance provides a high level of control ensuring correctly executed randomization and aiding in the uniform collection of study data, while behind the scenes, the Randomized Study Treatment Management systems ensure efficient, and timely delivery of blinded supplies. Medidata Balance gives users flexibility to configure a randomization system to the needs of the clinical study. Users may configure Balance to traditional methods, such as:

- Stratified Permuted Block
- Uploaded user generated schedule (stratified or not)
- Complete Randomization (all treatment assignments made with the same probabilities)

You can also use Covariate Adjusted methods which assign treatments to reduce treatment imbalances within randomization factors. Medidata's configurable randomization algorithm, Dynamic Allocation (DA) allows one to choose:

- The degree of randomness (between completely random and deterministic).
- Which randomization factors to include (e.g., sex, severity group, etc.).
- Whether to balance within sites
- Whether to balance within strata (which are defined as all combinations of levels of randomization factors).
- The relative weight to be given to imbalances within each factor.

Furthermore, Response adaptive methods can be implemented by reconfiguring treatment allocations in Balance during an ongoing study. While treatments must be predefined, new allocations can be predefined prior to study start, or analytically determined as the study is in progress (for instance, as determined by an unblinded Data Monitoring committee, a third-party statistical analysis, or predefined performance criteria). Commonly used methods include:

- Dropping treatment arms
- Adding pre-defined treatment arms
- Changing treatment allocations during the study.

The covariate-adaptive algorithms in Balance are a superset of the methods of Minimization (Taves, 1974), and of Pocock & Simon (1975). In this document, Minimization refers to the Taves, 1974 algorithm, DA (Dynamic Allocation) refers to the Medidata Balance covariate adjusted algorithm, and PS refers to the Pocock-Simon algorithm.

Bias and Randomness

Randomness of a schedule is important to minimize allocation bias, selection bias, and to enables blinding of treatment to observers. Allocation bias is basically an uneven distribution of subjects of treatments over a factor that affects outcomes; since the existence of hidden variables can never be absolutely excluded, random assignment of treatments provides some assurance that a hidden (or known) factor will not bias the outcomes between treatment groups.

The Cochrane Collaboration broadly defines Selection Bias as: "...systematic differences between baseline characteristics of the groups that are compared." (Higgins, 2011). Generally it is a form of allocation bias and implies an observer might anticipate the next treatment allocation and influence the choice of next subject accordingly. Whether or not a sequence appears random can depend on the information available to an observer, so that, if the randomization assigns treatments based on allocations at all sites (e.g., non-center specific randomization), a local clinician could not predict the next treatment with certainty.

Blinding of observers to treatment helps ensure that patients in all treatment groups are treated identically regardless of treatment, as well as prevent observers from anticipating the next treatment based on past assignments; Often treatment is not blinded to observers because of study requirements, or accidently (e.g., because of distinct drug side effects).

Balance

In a formally designed experiment, one generally plans to have equal numbers of experimental units in each combination of experimental factor (either treatment or prognostic variables). When this is achieved, the effects of prognostic variables are orthogonal to the treatment effect, and precision is maximized. However, even in carefully controlled experimental conditions, this can be difficult to achieve, and in clinical studies, nearly impossible. In multicenter trials it is recognized that precision can be maximized when strongly prognostic factors and centers are both included as covariates in the analysis and treatments are balanced across those factors (Toowara, 2009)

For large studies the strong law of large numbers greatly reduces the likelihood of imbalances large enough to affect statistical power. However, even large studies effectively "contain" small studies in which balance becomes important: Often there subgroups of subjects of special interest, interim analyses of a fraction of the enrollment target, studies terminated early, embedded studies enrolling a subset of the larger study (such as for PK), or issues of credibility for non-statistical reasons (Toowara, 2009). Furthermore, the structure of some study designs require a balance between sequences of treatments. For instance:

- Cross-over designs require balance between sequences of treatments between periods (for example, a 4 treatment, 4 period cross-over design could require balance between up to 24 permutation sequences of treatments–or far fewer in a Williams design).
- Designs like Sequential Parallel Comparison Designs require with an initial randomization and a subsequent randomization for subsets of subjects by response status (e.g., placebo non-responders might be randomized to active treatments).
- Waitlist Control studies or Stepped Wedge designs which randomize subjects to a treatment arm which starts after a randomized length of time.

Tradeoff between Balance and Randomness

While balance within prognostic variables is desirable, it often comes with a price: predictability. If an observer knows (or can guess) previous treatment assignments, they can guess future assignments better than chance knowing that allocations will be balanced. "Exactly equal sample sizes in a randomized controlled trials contribute little to statistical power and potentially harm unpredictability, especially in non-double blinded trials that use permuted-block randomization" (Schulz, 2002).

With effective double blinding of treatment allocations, predicting future treatment assignments from the past assignments should not be possible. However, often double blinding is not feasible, or masking is incomplete: sometimes study drugs have distinct side effects, or complete blinding is impossible (as for acupuncture) or unethical (as for surgery). Even if participants do not know, or cannot accurately guess at, assignments, partial or inaccurate knowledge of treatment assignments can bias outcomes for some subjects.

General Dynamic Allocation

The primary randomization algorithm used in Medidata Balance is a covariate adjusted dynamic allocation method. Like other dynamic allocation methods, it contains:

- An imbalance measure expressing the distance between the target treatment allocation and an allocation of treatments within a subgroup of subjects.
- A scoring system to summarize and prioritize the treatment imbalances over all subgroups of subjects (e.g., over sites, randomization factors, strata, etc.)
- A selection method to assign a treatment to the next subject which will minimize the total imbalance score.

Imbalance Distance

As in most dynamic allocation algorithms, the imbalance distance function looks ahead to the imbalances resulting after the next subject is randomized (for each treatment), not the current imbalance at the time of randomization. For example, if there are two treatment arms A and B with a target allocation of (50%, 50%), and one subject is already allocated to arm A, the current allocation are 1:0, and after the next assignment, the imbalance after the next assignment will be either 2:0 (if assigned to A), or 1:1 (if assigned to B). Separate imbalance scores are calculated for each study treatment, which compute the imbalance that will result if that treatment were used in the next assignment.

Balance uses the relative marginal imbalance within sets of subjects as its distance measure. For a given subgroup of subjects G, the marginal imbalance for treatment X is simply the difference between the percent of subjects assigned to X within G and the target allocation. Other distance measures have been proposed, such as range, standard deviation and variance of the relative imbalance as either the number or percent of subjects within subgroups (McEntegart, 2003), however this measure has several advantages:

- It can be easily calculated for arbitrary target treatment allocations, such as those in unbalanced trial designs.
- It is easily understood.
- It prioritizes imbalances within small subgroups, since a single subject in a small subgroup affects the imbalance more than in large subgroups.
- Simulation show that average marginal imbalance over randomization factors and strata shows a strong correlation with the loss of efficiency, and substantially stronger correlation than a simple imbalance as count of subjects (Sweitzer, 2013).

Scoring

Scoring is a simple weighted sum of imbalances within each subgroup defined by the discrete values of randomization factors, with weights assigned by the user. The Randomization factors used in the imbalance calculations include:

- All subjects (i.e., the overall imbalance)
- Site (as recommended by ICH guidelines, (ICH E9, 1998)).
- User defined randomization factors (such as age group, sex, or region).
- Strata, which are all combinations of levels of the user defined randomization factors (note that site is not used in determining strata).

Imbalances for all subjects with a given value of a randomization factor is called a marginal imbalance. Since a subject belong to multiple subsets determined by randomization factors, assigning a treatment to a subjects affects multiple marginal imbalances. (Unlike stratified randomization, in which every subject belongs to exactly one stratum, and a treatment assignments only affects imbalance within that stratum).

The importance of each randomization factor in randomizing subjects is determined by weights a user assigns to each factor. and the same weights are used for each level of a factor,). The choice of weights gives Medidata Balance Dynamic Allocation considerable flexibility. Under conventional Stratified Permuted Block, only imbalances within strata are considered. By assigning all factor weights to zero except for strata, Dynamic Allocation can behave like a stratified randomization in which treatments are independently assigned between strata.

Under minimization (Taves) and conventional covariate adjusted algorithms (Pocock&Simon), only marginal imbalances are considered. By assigning factor weights of zero to strata and overall, DA can behave like these more conventional methods. By including both strata and marginal imbalances in the equation, Medidata Balance DA can avoid some of the limitations with both stratified and minimization based randomizations methods.

In stratified randomizations, strata with fewer subjects than the number of treatments cannot be balanced, and as Therneau (1993) observed: "With a sufficient number of factors, performance is actually worse than using an appropriate unstratified assignment method for the study. Studies that use stratified assignment should not attempt to balance on more than a few important predictors." Therneau's formula for the maximum number of strata is often stated as:

#Strata ← #Subjects / (2 x Treatment Block Size)

On the other hand, methods which only consider marginal imbalances (such as minimization) are prone to have imbalances within strata which can confound treatments and factor interactions (when strata are defined by combinations of randomization factors). In most cases when randomizing a new subject to a relatively large number of treatment factors and strata, or early in a study, the algorithm basically does the following:

- If treatment are balanced within a strata, the algorithm will assign treatment based on the overall or the marginal imbalances. This occurs when a strata is empty, or the strata already has treatments in the targeted allocation (if treatment allocations are equal).

- If treatments are imbalanced within a strata, the algorithm tends to assign the next treatment based on the strata imbalance. Because DA uses the relative imbalance within a set of subjects, the smaller numbers of subjects assigned to strata result in a single treatment assignment having a larger impact on the resulting subject imbalance.

In this way, the Medidata Balance algorithm tends to have advantages of both approaches. Strata with sufficient subjects are balanced across treatments, protecting the analysis against confounding treatment with interactive effects, while marginal imbalances are minimized protecting the analysis against confounding treatment with main effects.

Selection

Having scored each potential treatment assignment for the imbalance that would result, the next step is to select a treatment. Complete Randomization is at one extreme, in that it optimizes randomness while ignoring Balance. At the other extreme, Minimization (Taves, 1974) attempts to optimizes Balance with little regards to randomness. Restricted randomization methods attempt to have a balance between balance and randomness (in the case of permuted block randomization, this results in a mixture of random & non-random treatment assignments).

Without the random element, the Medidata algorithm is essentially Minimization, the version of Dynamic Allocation developed by Taves (1974), in which one simply choses the treatment that results in the least imbalance. If 2 or more assignments reduce the imbalance by the same amount (a tie), then one of those are chosen at random. Consequently, Minimization is not completely deterministic depending on the frequency of tied imbalances, although:

- The more randomization factors there are, the more terms there are in the scoring function and the fewer ties.
- As subjects are added, fewer ties occur because the denominators of the calculated imbalances become larger and are less likely to be equal
- Paradoxically, as the algorithm becomes more deterministic because of fewer tied choices, it becomes less predictable to an observer: such an observer would have to track values of all randomization factors for all subjects to accurately predict the next treatment assignment.

Medidata Balance Dynamic Allocation

The ICH E9 guideline recommends that: "Deterministic dynamic allocation procedures should be avoided and an appropriate element of randomisation should be incorporated for each treatment allocation." (ICH, 1998). The Balance DA algorithm provides 2 methods to make the algorithm more random, both based on a random biased coin method like that of the Pocock-Simon algorithm.

DACR Version 2

The DACR ("Dynamic Allocation-Complete Randomization") algorithm was implemented to address a limitation in the original version. When the target treatment allocations are unequal, and the randomness parameter is non-zero, there is a tendency for the actual treatment allocations to differ from the target. This issue with Pocock-Simon type biased coin randomization has been discussed by Han (2009) with a proposed solution. The DACR algorithm uses a simpler solution which provides other advantages as well.

First, note that the in the case of the unequal treatment allocation, Minimization converges to the target treatment allocation by design, while Complete Randomization converges by the law of large numbers. Consequently, if one alternated between the 2 methods of randomization, the sequence would still converge to the target allocation. The DA-CR algorithm randomly alternates between Minimization and Complete Randomization where the probability of using Complete Randomization is the parameter CRP (Complete Randomization Probability). CRP ranges from 0 (always use Minimization to maximize determinism) to 1 (only use Complete Randomization, to maximize randomness), as follows:

- With probability = CRP, use Complete Randomization for next treatment assignment
- Otherwise, use Minimization.
  - IF there are multiple treatment arms in the 1st Choice set, assign one at random.
  - ELSE Assign unique 1st Choice treatment to next subject

DAV1 Version 1

In the Balance's original version of Dynamic Allocation, potential treatment assignments are scored for imbalance and divided into three subsets:

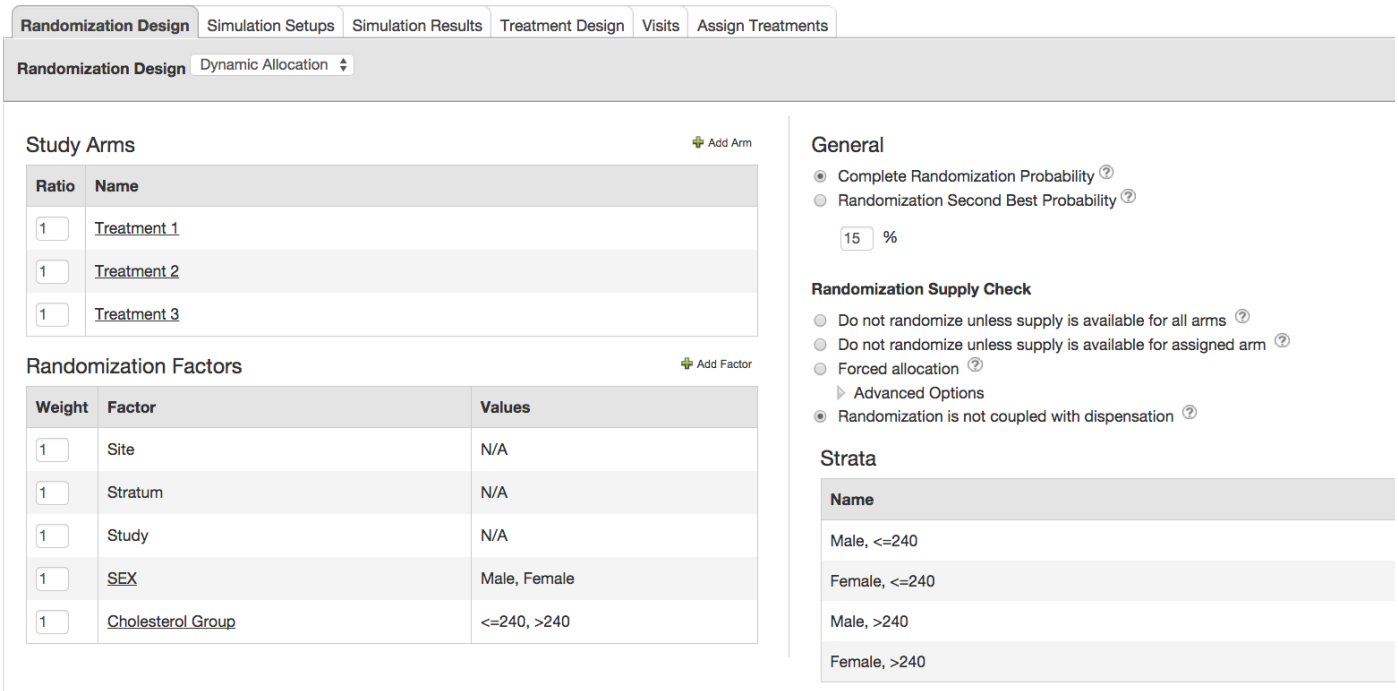
- The first-choice set: The subset of arms that result the least imbalance. This might be only one arm, multiple arms, or even all arms.
- The second-choice set: The subset of arms that provide the second least imbalance. This might not have any members, or it could have all but the first-choice set.
- All others arms.

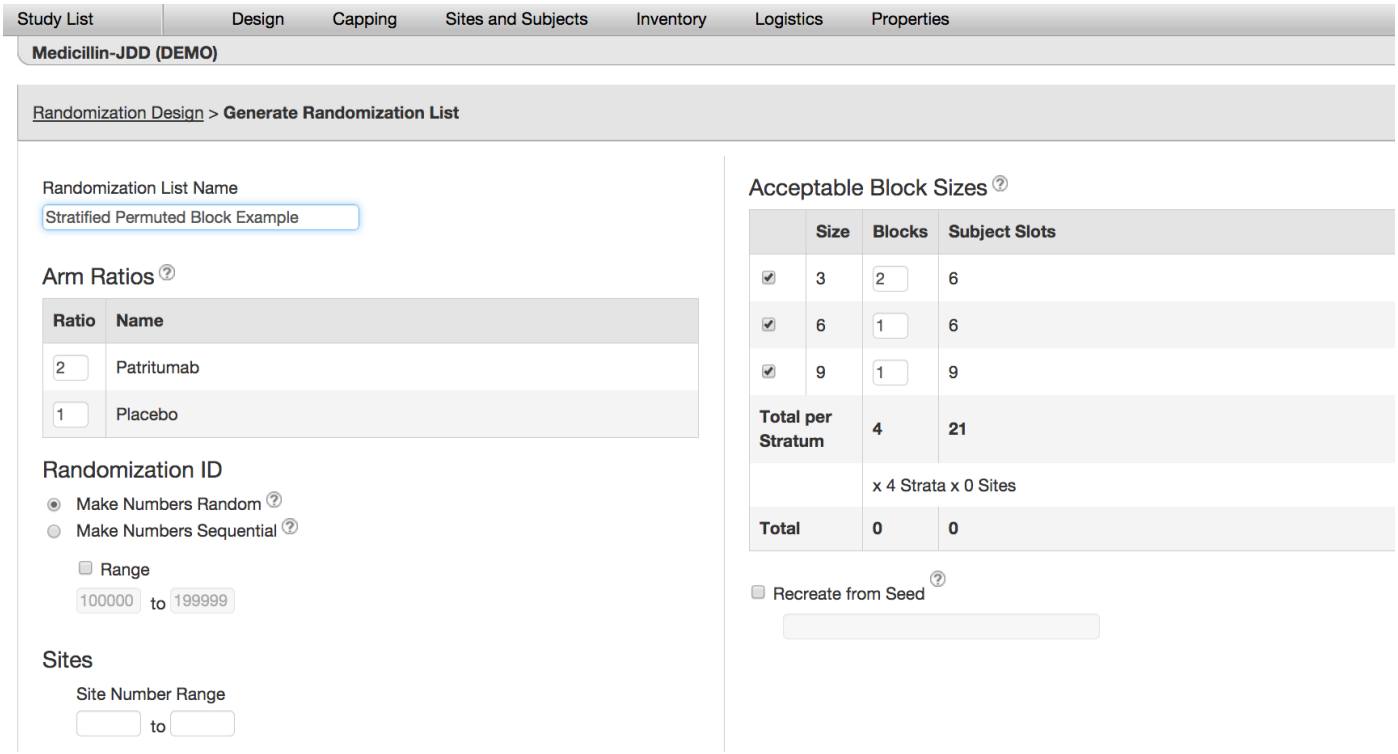
The random element parameter is called the Second-Best Probability (SBP), and it is the probability of assigning a subject to an arm from the Second-Choice set, instead of the First-Choice set (However, if there are multiple arms in the First-Choice set, the SBP is ignored and one of the First-Choice arms is chosen at random). Full details about DAv1 are found in Lebowitsch (2012).

Choosing DACR or DAv1

In a simple 2 arm, 1:1 randomization, both DACR and DAv1 yield the same results when CRP = 2 * SBP. However, when used for more treatment arms or for imbalanced arms, the DACR algorithm shows less selection bias than DAv1. As long as CRP is non-zero, any of the study treatments may be assigned to a new subject, while the DAv1 algorithm choses between the first and second choice treatment assignments, excluding any others.

DACR is the default algorithm for Randomization. After selecting "Dynamic Allocation" from the dropdown menu on the Randomization Design page (see below), the user is prompted to select to enter either the Complete Randomization Probability (for the DACR algorithm), or the Second Best Probability (for the DAv1 algorithm). For two treatment arms with equal allocation, the two algorithms are functionally identical (if CRP is twice SBP). However, for unequal allocations, or for more than 2 arms, DACR is preferred.





Other Methods

Medidata Balance gives two options to pre-allocate randomization schedules: To generate a permuted block randomization schedule, or to upload an externally generated schedule.

Stratified Permuted Block

Traditional Stratified Permuted Block randomizations are created with a user-friendly web interface (see below). Some features include:

- Creates permuted block randomization schedule before the start of study.
- Randomization seed optionally set by the user.
- Treatment arm ratios (Integer values)
- Random block sizes of 1, 2 or 3 times the minimum treatment block size.
- Randomization Strata generated from cross product of Factors and Sites
- Choice of Sequential or Random randomization identification numbers
- Option to pre-allocate of blocks to strata.

Once generated before the study begins, the schedule can be reviewed and stored.

Uploaded External Randomization Schedule

Another feature of Medidata Balance is the ability to upload externally generated randomization schedules. While the capabilities of the Dynamic Allocation and Stratified Permuted Block functions cover the large majority of randomization requirements, this feature provides an extra level of customization. Since the uploaded randomization schedules are static (i.e., generated and loaded prior to study start), they are non-adaptive (unlike DA). While they can be stratified, extra consideration must be given to the limitations thereof. Examples of applications include:

- Client may have preferred in-house systems for generating and maintaining randomization schedules.
- Multilevel permuted block structures. For example, a study may aim for 1:1:1 randomization of treatments A, B, and Placebo, but A and B each require distinct matching placebos, PA, and PB. A 2:2:1:1 randomization of treatments {A, B, PA, PB} is feasible as a 'superblock', composed of smaller blocks of 1:1:1 of {A, B, PA} or {A, B, PB} (this has been done with 5 treatment dose with 4 matching placebos).
- Factorial / Latin Squares designs: For example, permuted blocks could be created and assigned to strata so that treatments vary by position. E.g., 4 treatments in 4 permuted blocks of: ABCD, BADC, CDBA, DCAB when assigned to 4 strata will result a balanced distribution of treatments over time as well as between strata. Note that Dynamic Allocation will create randomization schedules with a similar structure if correctly configured.
- Brick Tunnel randomization as a modification of permuted blocks in which the final position in a permuted block is not always determined by the previous entries (Kuznetsova, 2013, 2011). This would avoid some of the predictability in permuted blocks.
- Randomization sequences which are generated and filtered to meet specific requirements, e.g., one may want a completely random sequence but eliminate runs of 3 or more of the same treatment., or may require at least 1 but no more than N subjects between occurrences of a specific treatment.
- A stratified permuted block randomization in which the frequency of permuted blocks are adjusted by their propensity for selection bias.

More About Dynamic Allocation

Dynamic Allocation as implemented in Medidata Balance provides distinct advantages over traditional Permuted Block randomization, and many other implementations of covariate adjusted methods.

Imbalance versus Predictability

Simulation studies comparing randomization methods have shown that minimization tends to be more adaptable and to work better in complex cases. For fewer patients or for more prognostic factors, imbalances within stratified randomization increased more than that for minimization" (Chabouis, 2015; Toorawa, 2009). Furthermore, there is trade-off between imbalance and predictability within all methods: One cannot have a method that is both perfectly random and perfectly balanced. (Chabouis, 2015; Sweitzer, 2013).

While the Medidata Balance DA algorithm is subject to the same constraints, the algorithm is flexible enough that it can be configured to behave very much like other methods. Increasing the CRP parameter creates a randomization schedule resembling Complete Randomization; Assigning a high weight to Strata results in a stratified randomization resembling stratified permuted block, without the periodic predictability at the end of blocks; Assigning a high weight to marginal imbalances results in a randomization schedule resembling Minimization or the Pocock-Simon algorithm; Intermediate values of the parameters can optimize the randomization to the expected characteristics of the study at hand. (Sweitzer, 2013).

Potential Selection Bias

The potential for selection bias with stratified permuted block randomization is well known, as later treatment assignments are determined by earlier treatment assignments. An unblinded observer can easily predict the last treatment assignment in a permuted block and following the simple rule of always guessing that the next treatment will be the one that best restore balance (the Blackwell-Hodges rule, Blackwell, 1957) can guess better than chance (50% correct), averaging about 75% correct for a 1:1 permuted block, 71% for a 2:2, and 68% for a 3:3. If block sizes vary as usually recommended, it would be more difficult to predict the last assignment within a block, but the average rate of guessing correctly would still be the average of the average correct for each block size.

In the worst case, covariate adjusted methods show similar predictability as stratified permuted block. (Indeed, Minimization by strata and a 1:1 permuted block randomization are essentially the same method, as the odd assignments are by chance, and the even assignments are the opposite choice). However, in the case when randomization is not double blind, DA gives more control over the potential selection bias.

- Permuted Blocks inherently have patterns of predictable and unpredictable treatment assignments, while every choice in DA is unpredictable. E.g., while every 4th assignment in a 2:2 Permuted Block randomization can be predicted from the previous 3, but as long as the randomness parameter is non-zero, no assignment can be predicted with certainty in DA.

- Assignments within Stratified Permuted Blocks depend entirely on the previous treatment assignments within the strata and an observer can partially predict the next treatment, while assignments in DA depend on treatment allocations across all strata. If stratified within center, an unblinded observer at the center can guess better than chance under stratified permuted block. However, with DA, assignments also depend on marginal imbalances within randomization factors between strata (centers). Not only would an observer not have that information, but the calculations too complex.

- Assignments within Permuted Blocks depend only the assignments within the same block, typically within the last 2, 4 or 6 randomized subjects; In the case of partial unblinding, an observer need only guess correctly the last few treatment assignments to increase selection bias.

Sample Implementation

A study of 720 subjects is planned using 20 sites. Because the indication and treatment involve sex hormones, an interaction with age (3 levels: Old, Middle, and Young) and sex is expected. The clinical study outline suggests stratifying the analysis by age, sex, and site, and proposes an interim analysis after 240 subjects. The initial plans are to use a permuted block randomization, stratifying on age, sex, and site, for a total of 120 strata with an average of 6 subjects per strata—enough for mixed block sizes of 2 or 4. Stratification by site is considered important because sites varied in clinical experience, patient population, and therapeutic specialization; hence treatment imbalances within sites can confound treatment and site effects. Stratification by sex & age is important because the indication and treatment affected sex hormones, hence another source of confounding.

After estimating from historical data the expected demographics and enrollment per site, it is estimated that sex and age strata would range from 10%-26% of total, i.e., from about 72 in the smallest strata (young males) to 185 in the largest (middle-aged females), while expected enrollment at sites range from 2% to 15% of total. Consequently, stratifying by all 3 factors was expected to result in a minimum strata size of 1 to 2 subjects in the final analysis, and 0 to 1 at the interim analysis. Consequently, the choices for a stratified permuted block randomization are:

- Stratify by all three factors results in many strata with only one subject, with little control of marginal imbalances. At the interim analysis, nearly half of strata have an odd number of subjects, hence inevitably imbalanced. Marginal treatment imbalances within sites and sex-age groups are likely to be less than would occur with complete randomization, but could be substantial at the interim analysis

- Stratify by age and sex, and ignore imbalances within sites. Stratum sizes at the interim are expected to range from 25 to 61, for which permuted blocks would ensure balance between treatments. Less than 5 subjects are expected at the smallest sites at the time of the interim analysis, for which there is a substantial risk of confounding treatment and site effects.

- Stratify by site and ignore imbalances within age-sex combinations. Permuted block randomization at each site would minimize imbalance and confounding between site and treatment. With at least 25 in each age-sex subgroup, the probability of large imbalances will be more limited than in sites. However, this would have a higher potential selection bias, since if an observer knows (or can guess) the assigned treatments at the site, they can predict some assignments.

Using Dynamic Allocation, all 3 factors can be used as randomization factors. Strata would be defined as combinations of Sex and Age, and imbalances within site included as a marginal imbalance. The algorithm would tend to balance treatments within small sites first (because a single subject has a larger impact on imbalance within a small group than a larger group), and within sex and age when balanced within site. Factor weights can be chosen so that more priority is given to sex and age factors as subjects accrue at a site. Predictability of assignments will be low throughout the study because of the cumulative impact of multiple factors:

- The randomness parameter CRP that guarantees every assignment is partially random.
- Treatment assignments at each site are affected by prior assignments at other sites. Even if an observer knows (or can guess) prior assignments at his site, he is unlikely to know them at the 19 other sites.
- In the beginning, the small numbers of subjects in site and strata will create many tied imbalances that will be randomly broken.
- As the study progresses, imbalances will tend to be small and difficult to calculate (or guess).
- In a permuted block randomization, an observer would only need to keep a simple tally of prior assignments within strata to better predict the next assignment. Under DA, he would also need to calculate all imbalances as a percent imbalance within each factor, and to know the weights associated with each factor.

Furthermore, the randomization can be optimized over time. The randomness parameter CRP can be set low prior to the interim analysis to maximize the power of the interim analysis, and set high after the interim analysis to increase randomness. This would also counterbalance any learning effects among observers guessing at treatment assignments: For example, if side effects are become apparent that can distinguish between treatment arms, clinicians might begin to guess past assignments and anticipate future ones. In this case, increasing the randomness parameter would reduce the potential selection bias.

Summary

Medidata Balance provides a flexible and configurable randomization system capable of creating both traditional and modern randomization algorithms, as well as uploading custom designed schedules. As it is fully integrated with the Medidata Rave EDC platform and randomized trial supply management, the potential for unblinding or data errors is minimized. Built-in simulation tools allow biostatisticians to test randomization configurations, and simulation results can be summarized within Balance or downloaded for further analysis. Medidata professional and statistical consulting services are available to aid in adopting Balance as an easy-to-use self service platform, and to help in meeting out-of-the-ordinary randomization requirements.

About Medidata

Medidata Solutions is the leading global provider of cloud-based solutions for clinical research in life sciences, transforming clinical development through its advanced applications and intelligent data analytics. The Medidata Clinical Cloud™ brings new levels of productivity and quality to the clinical testing of promising medical. treatments, from study design and planning through execution, management and reporting. We are committed to advancing the competitive and scientific goals of global customers, which include over 90% of the top 25 global pharmaceutical companies; innovative biotech, diagnostic and device firms; leading academic medical centers; and contract research organizations

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