PharmaSUG 2019 - Paper ST 259

Enhancing Randomization Methodology Decision-Making with SAS Simulations

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ABSTRACT

This paper will illustrate how SAS is an effective tool to conduct simulations for making data-driven randomization methodology decisions. SAS can be used to develop simulation programs to investigate the expected treatment balance and other randomization goals with comparing various randomization methods (stratified blocked randomization list, minimization, etc.) and associated parameters (block size, biased-coin probability, etc.).

A case study is provided to show how simulations can evaluate the expected treatment balance for different randomization methodologies / parameterizations being considered; and how simulations can investigate other randomization goals, such as minimum subjects required to be randomized at a site to ensure both treatment arms are represented.

This paper will illustrate how SAS simulation programs can be developed with configurable macros that are readily adapted for each individual protocol. Through including macros in the SAS simulation programs, different randomization design scenarios are efficiently simulated with minor macro variable updates to allow for swift delivery of statistically sound results. Incorporation of study-specific details (expected subject / strata distributions) can enhance the precision of the results. SAS macro programming allows for re-evaluation of varying subject distributions as means of testing the robustness of the simulation results.

Treatment balance for a clinical trial can be critical for establishing treatment effectiveness. The components of the randomization design that impact treatment balance (e.g., methodology, stratification factors / levels, block size, etc.) should be carefully considered at the protocol design stage. Simulation results can help make impactful design decisions to achieve the optimal treatment balance and randomization goals.

INTRODUCTION

Achieving treatment balance is essential to the success of your clinical trial. This is why your decision making regarding randomization methodology and associated parameterization is so important since these can impact the expected and observed treatment balance. Protocol sample size calculations and estimates on effect sizes are based on the assumption that exact treatment balance will be obtained according to the defined allocation ratio. Not achieving the required treatment balance in your study can impact your ability to accurately estimate the observed treatment effectiveness (in particular, for small sample sizes or at the sub-group level).

In clinical trials, common randomization methodologies include traditional blocked randomization (central, stratified) and Covariate Adaptive Randomization (CAR) (e.g., Pocock & Simon Minimization with biased-coin assignment *(1)*). Your choices that can affect expected treatment balance consist of stratification factor inclusion and block size(s) for traditional blocked randomization, and factor weight(s) and biased-coin probability(s) for CAR *(2, 3, 4)*. Determining the level of impact on expected treatment balance associated with each method and parameterization is informative for you in making these key decisions.

This paper demonstrates how you can use SAS to perform simulations for an in-depth investigation of the expected treatment balance for multiple scenarios to enable data-driven decision making *(5, 6)*. Via a case study, this paper illustrates the SAS Simulation Process for investigating impact to treatment balance for different randomization methodologies and parameterizations. Additionally, the paper shows how you can incorporate unique randomization goals for design analysis, such as figuring out the minimum number of subjects required to be randomized at a site to ensure both treatment arms are represented.

SIMULATION PROCESS

There are many factors you need to consider when making decisions on the protocol's randomization methodology and associated parameterization. For some protocol randomization designs, the impact on expected treatment balance cannot be easily understood, in which a more sophisticated approach is required to provide data-driven decision-making. SAS lends itself as a powerful tool for performing simulations, with also being able to generate tabulations and summaries within PDF reports to enable efficient result comparisons *(7)*.

When you use configurable, re-usable SAS macro programming, it allows for fast set-up to explore differences of the expected treatment balances across various randomization methodologies and associated parameterization scenarios. You can easily incorporate study-specific information, such as subject distributions, to mimic real-world scenarios (e.g. the expected proportion of subjects associated with different factor levels can be readily incorporated). To calculate the treatment imbalance, you can utilize the assigned treatments from the simulated subject sample data set for the Study and Stratum levels. Then when you generate many, for example 100,000 simulated subject data sets, it provides probability distributions for expected Study and Stratum treatment imbalances.

The process for generating these sample subject data sets (simulation process) can be summarized in three main steps:

1. Gather Study-Specific Information
2. Develop Study-Specific SAS Code
3. Analyze Results from Simulations

GATHERING STUDY-SPECIFIC INFORMATION

First you need to define the roles of the stakeholders participating in the process. Here, you are the Statistician who is performing the simulations. Within this role, you may be the SAS Simulation Programmer or Study Statistician within the Sponsor company itself or you may be with an outside party providing consultancy to the Study Statistician / Sponsor. This paper is written in the perspective that the Study Statistician is your key stakeholder and you are the SAS Simulation Programmer. Thus, you need to identify / work with the Study Statistician to gather the required information for this process.

As the SAS Simulation Programmer, a crucial component for you in this process is defining the study parameters for inclusion in the SAS Simulation Program. Specifically, you need to determine upfront the study's planned sample size, treatment groups and allocation ratio, stratification factors and their levels (with associated distributional assumptions). Although the study protocol will generally provide treatment / stratification factor information, a discussion with the Study Statistician will be beneficial.

Once you determine the study's core randomization design, you need to next understand the objectives and goals for the investigation. This is going to drive which design scenario(s) are needed.

For instance, some commons focuses of investigation are:

- Stratified Blocked Randomization vs. Covariate Adaptive Randomization
- Inclusion of Stratification Factor(s) (e.g., Site, Country, other)
- For Blocked Randomization, Selection of Block Size (e.g., Block Size 4 vs. Block Size 6), Block Size Design (Fixed Block Size 4 vs. Mixed Blocks of 4 and 6 in random order)
- For CAR, Biased-coin Probabilities (p = 0.70, 0.75, 0.80, 0.85) and Factor Weights

While several scenarios may be in envisioned at the start of discussions, you should be sure to limit the number of scenarios investigated initially (for instance, include at first only what is needed rather than what is 'nice to have'). Limiting the number of scenarios adds much needed focus to the review of the simulation's output. Configurable, re-useable SAS macro programing allows you to quickly perform iterations of the simulation process for the investigation of additional scenarios as needed. By following

this method, you may find that previously desired scenarios are invalid or not required, streamlining decision making for finalizing a study protocol.

Once the core design and initial scenarios for investigation are determined, you should next try to obtain estimates for expected subject distributions such as stratification, site, country, etc. to provide simulation results based on what is anticipated to occur in the actual study. The Study Statistician should liaise with other Sponsor key stakeholders (e.g., clinical, study / program manager[s]) to obtain realistic estimates (where available). These distributions may be estimated from earlier trials or even knowledge of site(s)' recruitment capabilities. If you are not able to obtain the expected distributions, you can still gain value from reviewing the results of a normal uniform distribution across stratification, sites, countries, etc. You can incorporate various distribution scenarios (e.g., based on equal / unequal distributions for stratification levels); these should be initially limited to a finite set of scenarios (e.g., 2 or 3) to explore whether the results are substantially impacted.

By the end of the information gathering sessions you, as the SAS Simulation Programmer, should have an understanding of:

- The Sample Size: N
- Treatment Arms and Allocation Ratio
- Stratification Factors and Levels
- Estimated Distributions of Stratification, Sites, Country (as applicable)
- 2 or 3 Specific Design Scenarios for Investigation of Impact to Treatment Arm Balance

DEVELOP STUDY-SPECIFIC SAS CODE

With the information gathering session complete, you now may begin developing the study-specific SAS Simulation Program. To be able to do this investigation, at a minimum you will need to develop your simulation code to do the following:

1. Randomly generate sample subject data sets with required variables (strata level, sites, other) per the study design (e.g., expected stratification or site enrollment distribution).
2. Randomly assign each subject record in the data set to a treatment arm per the randomization methodology (Stratified Blocked Randomization, CAR, etc.).
3. Calculate the treatment arm imbalances for study-level, strata-level, and other (e.g., site-level) based on the random assignments within the subject data set and provide in output report.

To calculate treatment imbalance, you need to find the difference between the numbers of subjects assigned to each treatment arm, relative to the treatment assignment ratio. For example:

- Assume the study has 2 treatments arms (**A**, **B**) that are allocated in a $\mathbf{R_A}$:$\mathbf{R_B}$ ratio.
- The number of subjects randomized to each treatment arm is $\boldsymbol{N_A}$ & $\boldsymbol{N_B}$ at the Study or Stratum level(s).
- Treatment imbalance can be calculated as:

  $\mathbf{|(R_B \times N_A) - (R_A \times N_B)|}$, in SAS this is calculated as:

```
STUDY_diff=RANGE(Ratio_B*Study_A,Ratio_A*Study_B);
```

In the case of studies with more than two treatment arms, the treatment imbalance can be obtained using the SAS RANGE function or through determining the maximum pairwise imbalance (accounting for the treatment ratios as above).

When you are first developing your SAS program, you need to perform the appropriate checks to ensure that the output meets the protocol assumptions. To do this, you can execute a single subject sample data set to confirm that the protocol assumptions for Sample Size, Treatment Assignment, and Stratification meet the expected total, assignment ratio, and distributions. A simple SAS Frequency

Procedure and Print Procedure helps you to verify the correct distributions and output of strata, treatment assignments, generated blocks (etc.):

```
PROC FREQ DATA=SIMULATION;
  TABLE Strata1 Strata2 StrataCode Treatment;
RUN;

PROC PRINT DATA=SIMULATION;
  VAR Subject StrataCode Treatment Block;
RUN;
```

Next, identify any hard-coded variables that you can convert into SAS macros variables. Macro coding allows you to easily incorporate study specific details and parameters for future use. Additional details for utilizing configurable, re-useable macro programming are addressed in the section (CONFIGURABLE (RE-USEABLE) MACRO PROGRAMMING) further below. Once you incorporate your macro variables, reiterate the above initial checks with the same initial parameters to confirm the output is identical.

After you are confident in your SAS program when applying on a single subject data set, you need to perform further checks across additional subject data sets (e.g., 5 or 10), with varying macro parameters, to confirm that the treatment assignments and treatment arm imbalance calculations are unique for each scenario's simulated subject data sets. At this point, you can be sure that your SAS program will deliver sound results across a larger set of simulated subject data sets (e.g., 100,000) for multiple settings of the simulation's parameters.

Finally, you can easily re-run based on alternative methods / parameters to enable comparison of results.

ANALYZE RESULTS FROM SIMULATIONS

Now that you have your code in place to perform the simulations, you need to program appropriate output, such as frequency tables, to be able to analyze the results. You can use the SAS Frequency Procedure to create tabulated summaries of the expected treatment imbalance based on the scenario's parameter settings. Examples of these results are shown below in Table 1 and Table 2 for the study-level and gender-level's treatment imbalance, respectfully. When you are reviewing these tables, look at the cumulative percentages to identify the treatment imbalance (STUDY_diff & GENDER_diff1) at the 90th and 95th percentiles for study-level and gender-level 1 for the specific scenario being investigated. For example, Table 1 below shows that you have an 89% chance of obtaining a study-level treatment imbalance of 4 or better and a 97.5% chance of obtaining a treatment imbalance of 6 or better.

The FREQ Procedure

STUDY_diff	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	24795	24.80	24795	24.80
2	41258	41.26	66053	66.05
4	22919	22.92	88972	88.97
6	8549	8.55	97521	97.52
8	2117	2.12	99638	99.64
10	325	0.33	99963	99.96
12	37	0.04	100000	100.00

Table 1: 100,000 Simulated Data Sets of 1,280 Subjects - Treatment Imbalance for Study-Level

The FREQ Procedure

GENDER_diff1	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	17634	17.63	17634	17.63
1	32038	32.04	49672	49.67
2	23995	24.00	73667	73.67
3	14707	14.71	88374	88.37
4	7387	7.39	95761	95.76
5	2963	2.96	98724	98.72
6	970	0.97	99694	99.69
7	255	0.26	99949	99.95
8	46	0.05	99995	100.00
9	5	0.01	100000	100.00

Table 2: 100,000 Simulated Data Sets of 1,280 Subjects - Treatment Imbalance for Gender-Level 1

You can compare and contrast the generated output across the different scenarios to quantify the gain and loss of expected treatment balance. Review this information together with the Study Statistician, highlighting any trends or differences across the varying designs. From here, together you may identify any additional scenarios warranting investigation based on initial findings.

Throughout this process, keep in mind that randomness is still required for any study's randomization design. When investigating treatment balance, the design parameters that yield the lowest treatment imbalance may not be the parameters that are selected for the actual study. For example, when investigating impact for different block sizes, it is obvious that a smaller block size will always yield the lowest treatment imbalance. However, you should recommend the selection of the largest block size that provides an acceptable treatment arm imbalance in effort to reduce predictability and selection bias.

As required, repeat the process to investigate alternative design scenarios.

CASE STUDY

As outlined above, the following case study shows how each of the simulation process steps would be executed within a real world example. Please note that the study design presented within this case study has been modified for confidentiality reasons, but remains representative of the actual simulation process and study design investigation.

CASE STUDY OVERVIEW

This is a Phase III, randomized, double blind, multi-center study to investigate the treatment effectiveness of a new active drug vs. placebo. 1,280 subjects are planned to be randomized to 2 treatment groups in a 1:1 ratio and stratified by Gender (Male, Female), Disease Severity (High, Low), and Age (≤12, >12 and <18, ≥18), (see Table 3). The case study incorporates 120 sites with varying enrollment expectations, (see Table 4).

The expected distributions came from underlying assumptions for subject recruitment. These expectations are not fixed and are allowed to vary between simulated subject data sets. However, a maximum of 10% of subjects (128) are allowed for the Age ≤12 stratification level. This is fixed in the simulations to mimic the protocol requirement.

Stratification Factor	Stratification Level	Expected Distribution
Gender	Male	40.0%
	Female	60.0%
Disease Severity	High	75.0%
	Low	25.0%
Age	≤12	10.0% (Capped)
	>12 and <18	35.0%
	≥18	55.0%

Table 3: Expected Stratification Distributions

Site Enrollment Level	Expected # of Sites	Average # of Subjects Per Site	Total Subjects
Low	40	4	160
Medium-low	30	9	270
Medium	30	15	450
High	20	20	400
Total:	**120**	**Total:**	**1,280**

Table 4: Expected Site Distributions

CASE STUDY: COMPARING DESIGNS AND PARAMETERS

The Study Statistician is interested in incorporating site stratification, but is concerned about the potential impact to the study-level treatment arm imbalance. The SAS simulation process needs to answer the question: what is the impact to treatment arm balance based on traditional stratified blocked randomization when including site as a stratification factor?

First, beginning with traditional stratified block randomization (with or without site stratification), the below parameters are incorporated for Stratified Blocked Rand:

- Block Size = 4, 6, 8
- Site Stratification:
    - Not Included (Site=No): 12 stratification levels
      (combination of Gender(x2), Disease severity(x2), Age(x3))
    - Included (Site=Yes): (up to) 1,440 stratification levels
      (combination of Gender(x2), Disease severity(x2), Age(x3), Site(x120))
      [Given 1,280 subjects will be randomized, not all 1,440 stratification levels will be utilized]

During the initial analysis, it is found that excluding site as a stratification factor yields acceptable treatment arm imbalance at the study-level (see Figure 1), while site stratification with blocked randomization severely impacts the expected study-level treatment imbalance. However, the Sponsor / study team is still interested in balancing treatment arms at the site-level, and wishes to further investigate the impact on treatment balance based on Covariate Adaptive Randomization methodology with the following parameters:

- Biased-coin probability value = 0.80
- Balancing Factors = Gender, Disease Severity, Age, and Site (with equal Factor Weights)

Figure 1 shows that the expected treatment imbalance at the study-level for Covariate Adaptive Randomization (minimization) yields acceptable study-level treatment imbalance. If site stratification is required, it is clear that utilizing Covariate Adaptive Randomization would help protect the study-level treatment balance.

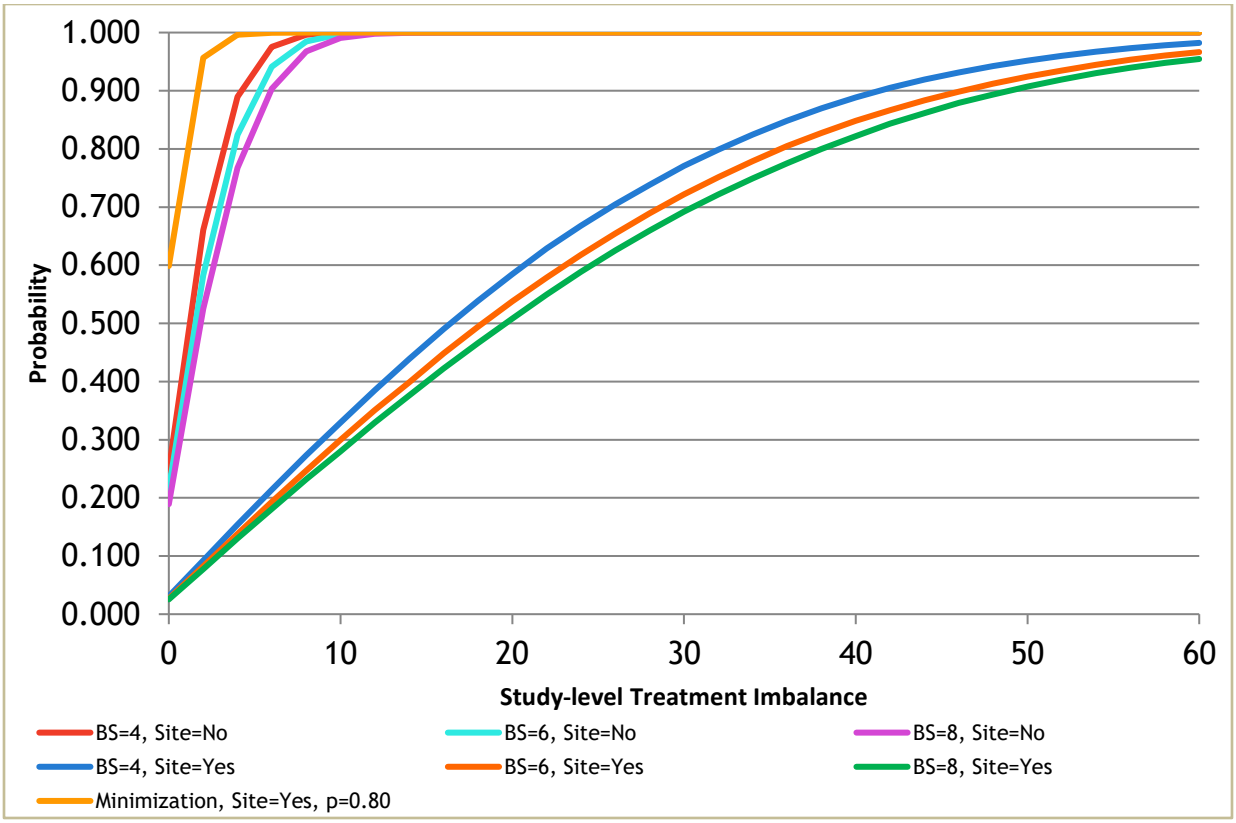

Figure 1: Cumulative Study-Level Treatment Imbalance Probabilities (N=100,000)

Without even performing simulations, you would expect that stratifying across 120 sites-levels via traditional blocked randomization list will impact the ability for treatment balance to be maintained at the study-level. Nevertheless, simulations allow you to actually quantify the impact on treatment imbalance, enabling data-driven decision making. Additionally, it is not immediately clear if there is any benefit / gain for site-level treatment arm balance itself when stratifying by sites via a traditional stratified blocked randomization or minimization method. The simulation results have to be closely examined to assess for this site-level impact for treatment balance across all scenarios. To demonstrate the site-level impact, Figure 2 includes the results for site-level treatment imbalance for the medium enrolling sites.

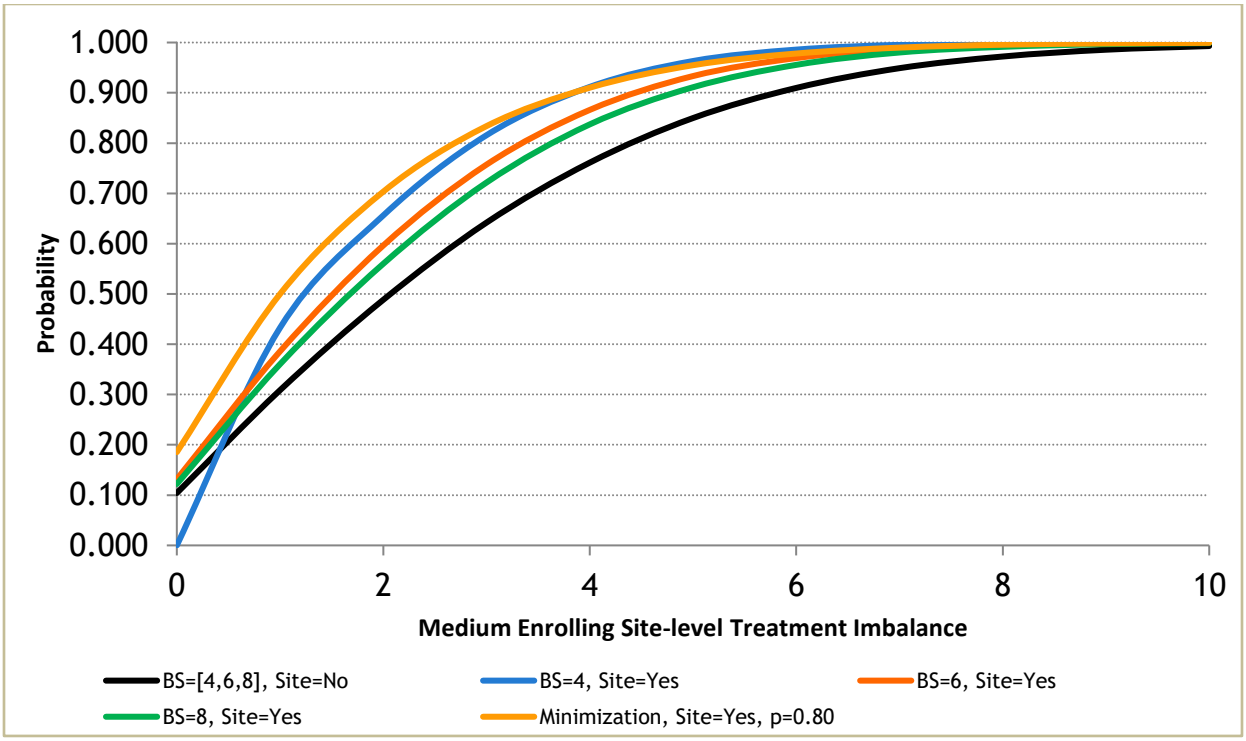

Figure 2: Cumulative Site-Level Treatment Imbalance Probabilities (N=100,000)

The expected site-level treatment imbalance is identical for blocked randomization excluding site stratification, regardless of block size (since site treatment arm assignments at each site are occurring randomly when site is not included as a factor). When including site stratification for blocked randomization, the simulations indicated that there is only some improvement of expected site-level treatment imbalance, with the greatest improvement for the smallest block size. However, this marginal improvement in site-level treatment imbalance comes with the loss of study-level treatment balance as detailed in Figure 1. The reason for only seeing a slight improvement for site-level treatment imbalance is due to the large number of participating sites where the balance is spread across 120 sites. If the study had a smaller number of Sites (e.g. 20 Sites), the difference of site-level treatment imbalance would be more apparent between site stratified and non-site stratified randomization designs.

The minimization approach showed similar results as for blocked randomization method with site stratification and BS=4. Overall for this example, minimization might be deemed optimal for protection of study-level and site-level treatment arm balance, but only in the case that site is required to be included as a stratification factor. During the simulation process, the Sponsor received feedback from the FDA stating that site stratification should not be included. This feedback is consistent with the regulatory guidance on randomization approaches where it is recommended that only clinically meaningful factors should be included within the stratification (2, 3).

Choosing the Randomization Design and Parametrization

With now having to exclude site stratification, the Study Statistician made the obvious choice to go with the traditional stratified blocked randomization method. However, the choice of block size, still needs to be selected. Reviewing the expected treatment imbalance at the study-level, gender-level, disease-level, and age-level helps with the selection of the appropriate block size.

Figure 3 shows the probability of treatment imbalance over 100,000 simulation runs (sample data sets), P(Imb=***x***) (where ***x***=0, 1, 2,..., 6) for Males:

- BS=4: P(Imb=0) = 17.63%, P(Imb=3) = 14.70%, P(Imb=6) = 0.97%
- BS=6: P(Imb=0) = 15.05%, P(Imb=3) = 15.88%, P(Imb=6) = 2.26%
- BS=8: P(Imb=0) = 13.20%, P(Imb=3) = 16.17%, P(Imb=6) = 3.66%

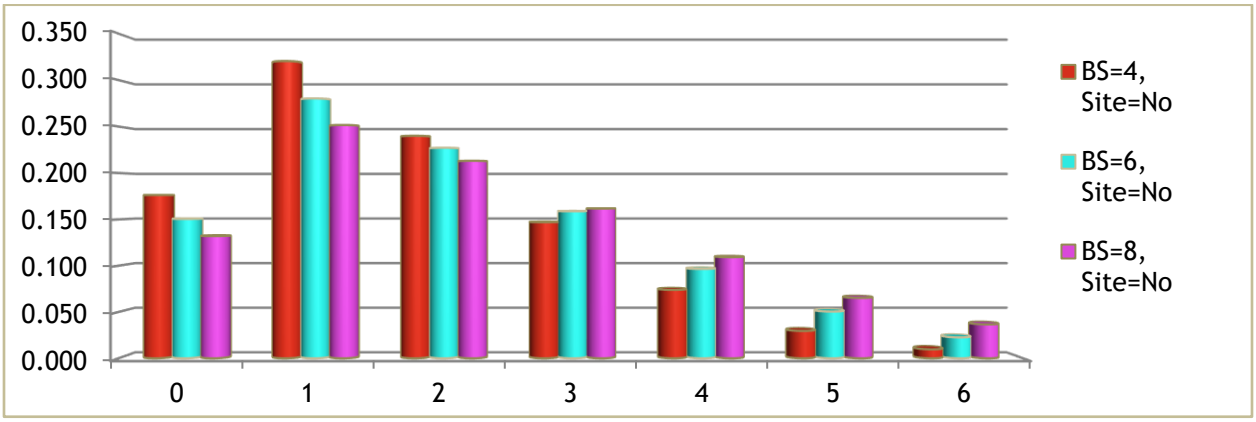

Figure 3: Gender = Male Treatment Imbalance Probabilities (N=100,000)

As expected, the results show a marginal treatment imbalance improvement as the block size is reduced. Similar trends are observed at the study-level, gender-levels (x2), disease severity-levels (x2), and age-levels (x3). It is clear that the smallest block size yields the lowest treatment imbalance, BUT the largest block size provides the lowest level of predictability. A block size of 6 is selected, since the Study Statistician determined it to be the largest block size that provides acceptable treatment imbalance across study and strata levels. This ensures that predictability is reduced as much as possible to protect against selection bias, while still maintaining acceptable treatment imbalance.

CASE STUDY: INVESTIGATING UNIQUE RANDOMIZATION GOALS

With the selection of randomization method and parameters made, the Study Statistician communicated that the clinical study team now wants to determine the minimum number of subjects a site needs to randomize to ensure that at least 1 subject is randomized to both treatment groups. This unique goal is required to establish the minimum site enrollment expectations for all participating sites when selecting participating sites for the study. Since treatment assignment will be random across all site levels, this can be examined through standard probability theory. Given a 1:1 treatment assignment ratio to treatments A and B, the following approach provides the probability that a site with *n* subjects has both treatment arms assigned:

- Let *n* be the number of subjects randomized at a site:
    - P(All *n* assigned to A) = P(All *n* assigned to B) = $(1/2)^n$
    - P(All *n* assigned to same Treatment Arm (A or B)) = $2x(1/2)^n$
- Therefore:
    - P(All Treatment Arms (A and B) being represented at a Site) = $1 - 2x(1/2)^n$

For a site enrolling 3 subjects, the probability that all subjects are assigned to either Treatment A or Treatment B is P(All Treatment Arms (A and B) being represented at a Site) = $1 - 2x(1/2)^3$ = **0.75**. This is illustrated further in Table 5 below.

Randomized at Site (*n*)	P(All on Treatment (A or B)) $(1/2)^n$	P(only A or B represented) $2x(1/2)^n$	P(Both A and B represented) $1-2x(1/2)^n$
1	0.50000000	1.00000000	0.00000000
2	0.25000000	0.50000000	0.50000000
3	0.12500000	0.25000000	0.75000000
4	0.06250000	0.12500000	0.87500000
5	0.03125000	0.06250000	0.93750000
6	0.01562500	0.03125000	0.96875000
7	0.00781250	0.01562500	0.98437500
8	0.00390625	0.00781250	0.99218750
9	0.00195313	0.00390625	0.99609375
10	0.00097656	0.00195313	0.99804688
⋮	⋮	⋮	⋮
18	0.00000381	0.00000763	0.99999237
19	0.00000191	0.00000381	0.99999619
20	0.00000095	0.00000191	0.99999809

Table 5: Theoretical Results (Minimum N Subjects for Site Enrollment)

Additional SAS coding can quickly and easily be incorporated into the original simulation program for the chosen parameterization (block size). The simulation output now includes frequencies for sites with subjects all randomized to same treatment group. The results yielded very similar probabilities to the theoretically derived probabilities (See Figure 4).

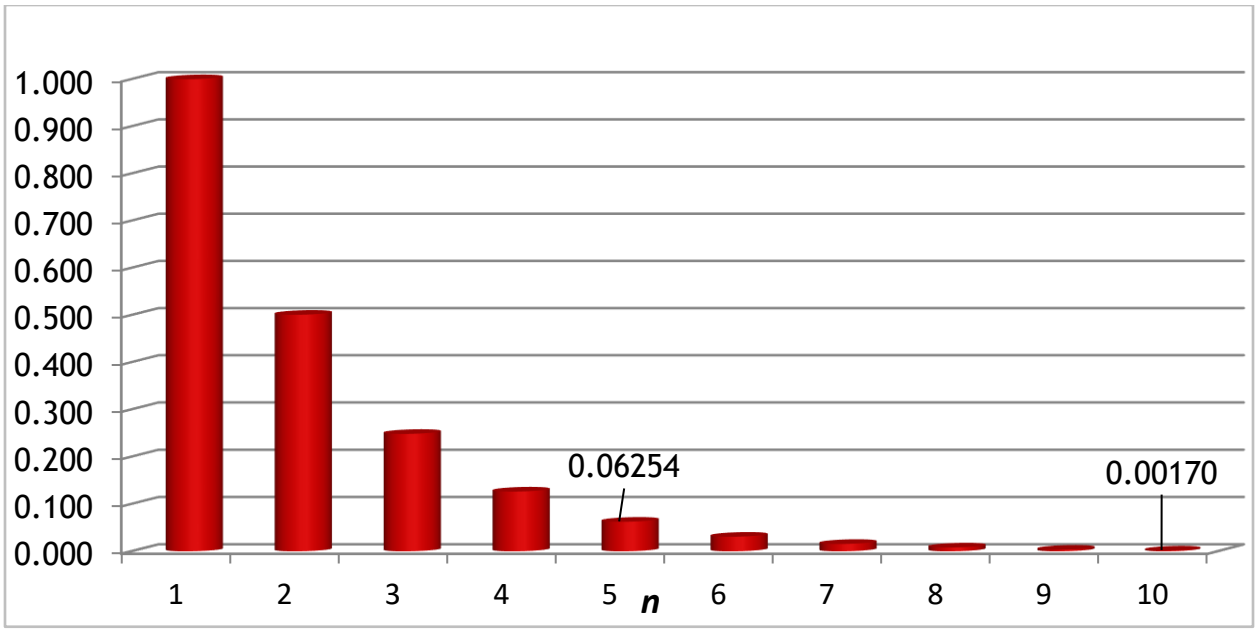

Figure 4: Proportion of Sites with n Randomized to Same Treatment

If an individual site randomizes a minimum of 5 subjects, there exists a (100-6.254)% = 93.746% chance that both treatment arms would be represented [corresponding theoretical probability = 0.93750]. If an individual site randomizes a minimum of 10 subjects, there exists a (100-0.170)% = 99.830% chance that both treatment arms would be represented [corresponding theoretical probability = 0.99805]. With this information in hand, the Study Statistician is able to make data-driven decisions for site enrollment requirements.

CONFIGURABLE (RE-USEABLE) MACRO PROGRAMMING

The case study illustrates how simulations through SAS can be used to explore the varying methodologies and parameterization, allowing the Study Statistician to make robust data-driven decisions on the randomization design. If SAS macro variable programing was not applied within the case study's simulation process, the process would have likely required excessive time and effort with needing multiple unique SAS programs to be put in place to explore all the scenarios and objectives as described above. Instead, the process was able to be executed efficiently and effectively with the use of SAS macro variable programing within a single SAS program, in setting the key parameters (e.g., block size, methodology, etc.) as macro variables outside of the main body of the SAS code. This enables parameters to be updated or even switched on or off based on the scenario being investigated, leaving the main body of the SAS code that creates the subject data sets and performs the random treatment arm assignment unchanged.

Once you have a SAS program that performs randomization simulations with SAS macro programming in place, you can easily adapt it for future protocols with different randomization design requirements. You can configure parameters (i.e., block size, number of treatments, treatment assignment ratio, stratification inclusion, subject distributions, starting seed used for random samples / treatment assignments, etc.) as macro variables. The case study's block size, sample distribution of the stratification factors (gender, disease, age, and site), and starting seed, are all configured as SAS macro variables. The %LET allows you to define these items at the beginning of your code for ease of switching between each scenario. Against each macro variable configuration, you can embed all options for each of the specific parameters within comments. For example, block size and the gender distribution are included as:

```
%LET BlockSize=4; /*4, 6, or 8*/

/*GENDER: MALE 40%, FEMALE 60%*/
%LET GENDER_p1=0.40; %LET GENDER_p2=0.60;
```

Within the body of the SAS code, the macro variables are utilized / called out. For instance, when randomly generating each of the stratification factor level's distributions, the body of the SAS code uses the SAS routine CALL RANUNI with the starting seed value and gender distribution probability value (as defined per the macro variable settings above) to assign gender levels within each subject data set record as follows:

```
%LET seed1=123456; /*define starting seed value */
CALL RANUNI(&seed1.,rnd_GENDER); /*randomly determines GENDER level 1 or 2*/
GENDER=1+(rnd_GENDER>(&GENDER_p1.));
```

When generating random samples and random treatment assignments within SAS simulations, you should always set and use a starting seed value. By setting a starting seed value (e.g., seed1=123456), can ensure that your results are repeatable within each scenario (subject sample distributions and treatment assignments) and are repeatable / comparable across the various scenarios (subject sample distributions).

For comparability across the various scenarios, you need to program the treatment imbalance calculations at the study-level and the stratum level to execute at the end of each iteration. You can do this by utilizing macro variables within arrays and DO Loops. To do this for each stratum, you would:

- Start by defining the number of levels within a macro variable:

```
/*Number of Stratification Levels*/
%LET n_STRATA=12; /*12 or 1,440*/
```

- Create an array with the number of elements equal to the number of stratum levels (defined by the macro variable above) multiplied by the number of treatment arms within the study. Each element within the array counts the number of subjects randomized to each treatment arm for each stratum:

```
/*(12 or 1,440) STRATA levels (x2 Treatments)*/
ARRAY n_TRT_STRATA{2*&n_STRATA.};
```

- Once the final subject has been simulated within each iteration, the stratum's treatment imbalance is calculated by using the array's count. For the case study above, i^{th} strata level, STRATA_diff{i}, is calculated based on either 12 or 1,440 stratification levels, with macro variable (above), array (above), and the DO Loop below:

```
/* Imbalances for each STRATA level between Treatments A and B */
DO i=1 to &n_STRATA.;
   STRATA_diff{i}=range(n_TRT_STRATA{2*(i-1)+1}, n_TRT_STRATA{2*(i-1)+2});
END;
```

- With the DO Loop above, the stratum-level treatment imbalance is calculated for each iteration of the simulation. When setting this up in your SAS code, ensure that all of these array counts and calculations are reset to 0 after each iteration. If the array counts / calculations are not reset to 0, then the next iteration's (simulated subject data set) treatment imbalance would still include the previous iteration's calculations.

When developing your configurable SAS simulation program(s), being able to identify parameters that can be converted and used as macro variables is a valuable skill. While this paper covers many uses of macro variables, you may discover more areas that you can include in your own simulation programs. When developing your own SAS simulation programs and conducting simulation investigations, you will quickly discover that effective macro programming is the key to being able to efficiently investigate various randomization design scenarios.

CONCLUSION

Obtaining acceptable treatment balance for a clinical trial is critical, as the resulting treatment effectiveness may be difficult to identify (power) if reasonable treatment balance is not achieved.

The use of simulations to explore the expected treatment balance provides the ability to make data-driven decisions in regard to the optimal randomization methodology and associated parameterization for a clinical protocol. Other considerations (i.e., regulatory guidance / expectations, impact on supplies, etc.) and collaboration amongst all key stake-holders (e.g., Study Statistician, Clinical Team, Study Manager, Supplies Team, etc.) is needed to ensure that realistic scenarios are investigated and that other non-statistical considerations are taken into account.

SAS Macro Simulation Programming lends itself to the quick and efficient exploration of multiple scenarios for the investigation of different randomization methodology parameterizations (e.g., fixed block sizes of 4 vs. 6, mixed/variable block sizes, etc.). The data produced from a single simulation run can be used as a representation of what might occur in the actual study (in terms of treatment assignment and resulting treatment balance). The data produced from running many simulations (e.g., 100,000) provides the ability to quantify the probability of observing specified treatment imbalance levels, both at the study level (overall) and for each stratification factor level.

For each scenario, within your SAS simulation program, you should be sure generate and save a scenario-specific output file that contains the critical treatment balance results. This way you would be able to quickly compare and contrast the outputted SAS results across the various scenarios being considered.

Wherever possible, you should perform the simulation exercise(s) based on real-world assumptions regarding expected subject distributions with respect to the key stratification factor level. Often these are 'best guesses' derived from previous clinical studies and/or from Sponsor key stakeholders. Once the randomization methodology and associated parameterization has been tentatively selected, you should run additional simulation scenarios based on different distributional assumptions to check the robustness of the observed simulation results. This can be quickly achieved by setting-up the SAS Macro Simulation Program with macros parameters for underlying distributional assumptions.

In conclusion, SAS Macro Simulation Programming can be a powerful and informative design tool to enable data-driven decision making regarding randomization methodology and associated parameterization.

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