

Using SAS Simulations to determine appropriate Block Size for Subject Randomization Lists

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ABSTRACT

ICH E9 (Regulatory) guideline specifies that the minimum block size should be avoided for the generation of Randomization lists to avoid predictability / selection bias and to avoid full or partial unblinding to treatment assignment. Additionally, knowledge of the block size used within the Randomization list should be restricted (typically known by Sponsor Biostatistician only). However, in reality Sponsor Biostatisticians repeatedly utilize the **same** (default) block size for list generation (e.g. always use a block size of 4 for x2 treatments with equal allocation ratio) and/or utilize the minimum block size.

While Treatment balance for a clinical trial can be critical for establishing effectiveness, perfect Treatment balance is not required. The goal of randomization is to maintain the integrity of the study (keeping study blind, avoiding bias) and to achieve acceptable balance. Simulation results can provide data-driven results to show that acceptable balance can be achieved with alternative block size designs.

Case study examples will demonstrate how simulations can evaluate expected treatment balance for alternative block size designs. Through use of SAS macro programming, different randomization block size designs can be efficiently simulated through minor macro updates, allowing for quick delivery of statistically robust results.

This paper will illustrate how SAS is an effective simulation tool to provide evidence that different block size designs / parameters can yield acceptable balance without having to use the minimum or most common / default block size.

INTRODUCTION

Bias may seriously compromise your ability to draw any valid conclusions from a clinical trial. Randomization and blinding are the clinical trials' most important defenses against bias in ensuring the validity of trial conclusions (1, 2). However, how you design the randomization scheme directly impacts both its ability to protect from bias, and its ability to achieve an equal amount of subjects assigned to each treatment group (i.e. treatment balance). If you use a completely random ordered list of treatment assignments, it can help avoid predictability (as long as the list is kept blinded), but can also introduce risk of treatment imbalance. Consequently, if treatment balance is not achieved, that impedes your ability to draw valid conclusions. Utilizing a blocked randomization scheme helps to ensure treatment balance is maintained, but the inappropriate choice in block size can introduce the risk of predictability / selection bias. Thus, it is important that you choose block size(s) with care: select block size(s) that both provides acceptable treatment balance and sufficient protection from selection bias.

In this paper, we outline the ICH E9 guidelines for blocked randomization and show you how SAS can help you make block size selections with data-driven evidence. Via a case study, this paper demonstrates how SAS macro simulation programming is an effective tool in investigating appropriate block size designs recommended by the ICH E9 guidelines including larger fixed block sizes and multi-block sizes (mixed-block).

BLOCK SIZE SELECTION

Clearly, you should not take the choice of block size lightly, since it plays a critical role in treatment balance and randomness. Many are familiar with the ICH E9 guidance (1) (regulatory perspective), which indicates that a minimum block size should not be used for the generation of Randomization lists (to avoid predictability / selection bias and to avoid full or partial unblinding to treatment assignment). Occasionally, the minimum block size is still utilized, which increases the potential for selection bias with allowing treatment assignments to be highly predictable.

For those studies that comply with the ICH E9 guidance (1) and do not use the minimum block size, the most common approach is to go one size up from the minimum possible block size (e.g., 4 for x2 treatments in 1:1 ratio). This is likely since Sponsor Statisticians are focusing only on treatment balance, with consistently choosing a common / default block size (or even worse - the minimum!), when larger blocks could actually be used to provide acceptable balance for analysis.

If you select the same common / default block size routinely, then it introduces the risk for the block size to be easily guessed. Study personnel that manage many studies with similar randomization designs may be able to catch on to the fact that the randomization lists continuously to use the same common block size. This risk can exist in double blind studies, but is more apparent within open label studies, since knowledge of the previous treatment assignments can make the block size even easier to detect. In open label studies, if using the same block time after time, or if enrollment is high and block size is relatively small, the block size can easily be determined at the site. When block size is known in open label studies, the final treatment assignment in a block can be guessed based on previously viewed assignments. This introduces clear risk of selection bias potentially being introduced into the study, and therefore, makes block size selection for open label studies extremely important.

The ICH E9 guidance (1, p.13) further states that “care should be taken to choose block lengths that are sufficiently short to limit possible imbalance, but that are long enough to avoid predictability towards the end of the sequence in a block. Investigators and other relevant staff should generally be blind to the block length; the use of two or more block lengths, randomly selected for each block, can achieve the same purpose.” Thus, in considering the design of the randomization list, the block size(s) selected should be kept blinded and large / random enough to protect from selection bias, while still maintaining acceptable treatment balance. Alternative blocking approaches, such as slightly larger blocks (e.g. 6, 8) are often overlooked without reasonable evidence against their usage. If there is a real concern with large fixed block sizes, evaluations can be made for customized blocking, such as mixed / variable block sizes.

If you utilize mixed block sizes, it can provide a compromise between using a larger block size together with a common block size. Different block sizes may be included randomly throughout the entire list, or within a more controlled approach by including sub-blocks within a larger block (i.e. within a large block of 10, include sub-blocks of 4 and 6). These sub-blocks can be ordered randomly or fixed within each larger block based on a study’s need. Fixed ordering of sub-blocks may be preferred for specific study needs, such as if balance needs to be controlled for an early interim analysis. Random ordering of different sub-block sizes within a larger block provides further protection against any possibility of guessing treatment assignments, as it would be difficult to identify which block size is ‘in play’.

Alternative block sizes are likely often not considered if there is not any evidence to support that the balance would be maintained. Going through a SAS simulation process can provide you with the data-driven evidence you need to validate (or invalidate) different blocking designs for any protocol design.

SAS MACRO SIMULATIONS

SIMULATION PROCESS OVERVIEW

The main purpose of the simulations covered within this paper is selection of the block size parameters. First, let’s define the roles of the stakeholders within this process. This paper is written in the perspective that the Sponsor Statistician is your key stakeholder (who will be confirming the blocking parameter(s)), while you have the role of the Simulation Statistician / Programmer.

As demonstrated in Venner et al. (3), SAS is an effective tool in identifying optimal randomization design parameters for any given protocol. This paper mainly focuses on the block size parameter(s) and how alternative blocking approaches can be recommended to Sponsor Statistician that initially aims to use the common / default or minimum block size. Fortunately, SAS macro programming is an efficient resource for this evaluation, since it can provide robust and reliable results swiftly to help guide the decision making with regards to block size choice. The overall guidelines for creating your own SAS macro simulation program are specified within Venner et al. (3), but here in this paper, we are going to review how even more can be accomplished via SAS to help ease any concerns the Sponsor Statistician has with using alternative block sizes / approaches.

As a refresher, the goal of the SAS simulation exercise is to evaluate the impact that differing design parameters (e.g., block size, strata factor inclusions, capping, etc.) may have on the expected treatment balance across Study and Stratification levels. This is done by generating a large number of subject treatment assignment datasets (typically 100,000), based on protocol treatment assignment and enrollment expectations (e.g., N subjects, N treatments, treatment ratio, and stratification distributions). Generating these large datasets with different parameterizations (here - block size) obtains the frequencies and probabilities of obtaining perfect treatment balance, slight / acceptable imbalance, or large imbalance for each design scenario.

With proper SAS macro programming, statisticians can quickly and efficiently evaluate the impact on expected treatment balance for several randomization design parameters. Through a case study, we show you how SAS macro simulation programming can also be used to remove concerns for use of larger block sizes. Conversely, the simulation results may provide the data driven evidence to justify that the common block size indeed required for your study.

Before you begin developing any SAS program, it is important to understand the Sponsor Statistician's intention for utilizing either the common block size or minimum block size. For instance, the Statistician may have concerns with treatment balance mid-study (for interim analysis purposes), or may have had a poor experience / outcome with a previous study that utilized a larger block size. Alternatively, the Sponsor Statistician may be over-looking other block sizes (e.g., 6), or not realize that a mixed block approach could be implemented with a larger and smaller block appearing randomly within the list. Understanding Sponsor Statistician's concerns can help you with recommending the block design parameters to include within the SAS simulations.

RECOMMENDED SAS SIMULATION PROGRAMMING

The method for developing your own SAS simulation programming is summarized in our previous paper (Venner et al., (3)), which only included a fixed block design (for top level purposes). The simulations within this current paper require this programming to be expanded to account for a more complex blocking approaches with mixed / variable block sizes. In reviewing our previous SAS simulation code, we can identify ways to enhance the program to allow for the mixed block size design.

For example, a single macro parameter was previously utilized for fixed block of sizes 4, 6, and 8. Now, we wish to show additional evidence for mixed, variable block sizes. To do this, we need to rethink how the block size macro variables are specified and called within our program. One solution is to have multiple 'switches' and block sizes within our code; i.e.:

```
%LET FixedBlockSize=4; /*Fixed Blocks: 2, 4, 6, 8, or 10*/
%LET MixedBlockSize1=4; /*Sub-Block1: 2, 4, 6, 8, or 10*/
%LET MixedBlockSize2=6; /*Sub-Block2: 2, 4, 6, 8, or 10*/
%LET BlockDesign=Fixed; /*Fixed or Mixed*/
if &BlockDesign. = Fixed then do;
/*Treatment Assignment within a Fixed Block Size*/
end;
if &BlockDesign. = Mixed then do;
/*Treatment Assignment within Mixed Block Sizes*/
end;
```

As shown above, a total of 4 macro parameters are required to account for the mixed block design. One to set the fixed block size, 2 to contain the mixed block sizes, and a final 'switch' macro variable to specify whether the fixed or mixed block coding should be utilized for the simulation run. While this may be suitable, it can become cumbersome when navigating through running different block size parameters and designs.

A much more efficient coding technique is to simply use our block size parameters for both specifying block size and using as a switch between fixed / mixed SAS coding:

```
%LET BlockSize1=4; /*Block1: 2, 4, 6, 8, or 10*/
%LET BlockSize2=6; /*Block2: =6 or =0 if fixed blocks*/
if &BlockSize2. = 0 then do; /* Fixed block size*/
/* If Block2 = 0 then utilize Fixed Block Treatment Assignments*/
end;
if &BlockSize2. NE 0 then do; /* Mixed block size*/
/* If Block2 is not 0 then utilize Mixed Blocks Treatment Assignments*/
end;
```

Using the element that a second block size is not required for fixed blocks allows us to reduce the number of parameters we need to revise when executing our simulation program. We now only need to keep track of 2 macro parameters when we wish to execute a fixed or mixed block simulation run. When customizing your previously used code, you may find other instances where you plan to add additional macro variables when the information is already included within existing macro variables. It is important to limit the number of macro variables you are including, otherwise you may find yourself executing SAS with values in your parameters that are not compatible. When you use a high number of macro variables, the validation of your SAS macro simulation program may become quite extensive, and degrade the level of efficiency.

To expand the SAS simulation code for the mixed block design, including an additional CALL RANUNI allows us to randomly select the starting sub-block (=4 or 6) within each larger block of size 10. An array called B_SIZE will keep track of the current block size in play for each stratification level:

```
ARRAY B_SIZE{10}; /* Stores current block size in-play for x10 STRATA */
seed1=111111; /* define starting seed value */
/* Randomly select (50:50) first block to be 4 or 6 */
CALL RANUNI(seed1,rnd_block_size);
B_SIZE{STRATA}=4+2*(rnd_block_size>0.5);
```

Mastering arrays is a key component in any SAS simulation program, since an array lets you keep track of treatment assignments or blocking information during the execution of the data step generating the subject trial datasets. The above array, B_SIZE, is a simple one-dimensional array that is used to identify the current block size in play for the mixed-block design. Utilization of multi-dimensional arrays offers a more sophisticated approach of keeping track of information across more than one dimension. For example, to track treatments assigned across strata, the array n_Trт_Strata is defined as:

```
/* 2 Treatments, 10 STRATA levels */
ARRAY n_Trт_Strata{2,10}
n_Trт1_Strata1-n_Trт1_Strata10 /*Treatment 1: Strata=1-10*/
n_Trт2_Strata1-n_Trт2_Strata10 /*Treatment 2: Strata=1-10*/;
```

To increment the count of treatments assigned for a subject in the dataset, you can include both the treatment indicator (Trт_Ind = 1 or 2), as well as the strata code (strata = 1-10):

```
n_Trт_Strata{TRT_IND,STRATA}+1;
```

Treatment imbalance calculations are then performed once the final subject in a simulated trial run has been assigned treatment. A 'do loop' is utilized together with the multi-dimensional array to determine the value of STRATA_diff:

```
do i=1 to 10;  
  STRATA_diff{i}=range(n_Trtr_Strata{1,i},n_Trtr_Strata{2,i});  
end;
```

Being able to condense the number of macro variables and manage array usage within your code are 2 key components to effective SAS simulation programming. Macros, while helpful, need to be limited to including only those that add actual value within your programming. Arrays are the backbone to your simulation program, as they keep track of valuable information to allow you to include mixed blocks and treatment imbalance calculations. Smart macro programming, along with keen array usage, helps you with both the validation and execution of your SAS simulation program, and to allow for customizations such as mixed block sizes to be adapted easily within your code as demonstrated above.

CASE STUDY

As outlined above, the following case study shows how SAS simulations can help you identify alternative block sizes that can be utilized in place of the minimum block size or common block size. 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 II, randomized, open label, 3-center study to investigate the treatment effectiveness of a new active drug vs. placebo. N=126 subjects are planned to be randomized to 2 treatment groups in a 1:1 ratio, with stratification factors: Age (<50yrs, >=50-<60yrs, >=60-<65yrs, >=65-<70yrs, >=70yrs) and Gender (Male, Female) (see Table 1). The Sponsor Statistician provided the expected distributions based on underlying assumptions for subject recruitment. These expected distributions are not fixed and are allowed to vary between simulated subject data sets.

Stratification Factor	Stratification Level	Expected Distribution
Age	<50yrs	25.0%
	>=50-<60yrs	25.0%
	>=60-<65yrs	15.0%
	>=65-<70yrs	15.0%
	>=70yrs	20.0%
Gender	Male	50.0%
	Female	50.0%

Table 1: Expected Stratification Distributions

BLOCK SIZE CHOICES

With 10 stratification levels (5 Age levels * 2 Gender levels) and a small sample size, the Sponsor Statistician is interested in using either the minimum block size (2!), or the common / default block size of 4. After raising regulatory concerns with use of minimum block size (especially for an open label study), the Sponsor Statistician is agreeable that a block size of 2 may not be the best option. Since the Randomization list is shared across only 3 centers, an additional concern is raised for site personnel's ability in identifying block size based on their observations of previous treatment assignments.

While the Sponsor Statistician agrees that there is a chance for the block size to be identified if using a block of 4, the Statistician is more concerned with treatment balance if using a larger block size(s). However, larger fixed block sizes 6, 8 or 10 or mixed blocks of 4 and 6 within larger blocks of size 10 may still yield acceptable balance. The Sponsor Statistician is curious how the larger block sizes (6, 8 or 10) compared to the complex mixed blocking approach performs with regards to expected treatment balance.

Through SAS simulations we will answer this question: what is the impact to treatment arm balance based on stratified blocked randomization when block size is not equal to 2 or 4? To do this, we will generate simulations based on the case study protocol overview with fixed block sizes 2, 4, 6, 8, 10, and mixed blocks of 4 and 6 within larger blocks of size 10.

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

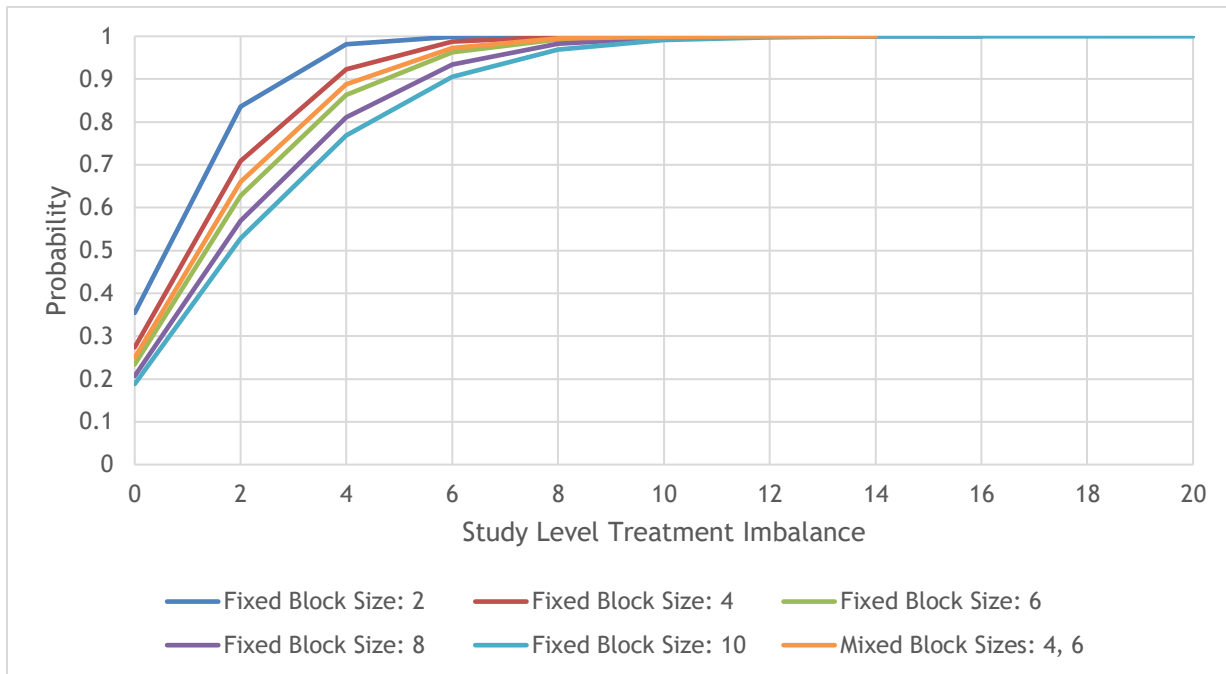


Figure 1 above shows the expected study level treatment imbalance across the 6 blocking designs. It is easy to see how imbalance overall is impacted as fixed block sizes are increased. As you would expect, a block size of 2 has the clear advantage, since it will control treatment balance for every 2 subjects within strata, while a block size of 10 provides the largest treatment imbalances. Like you may have guessed, the mixed block approach falls right between the fixed block size 4 and fixed block of size 6. Across 100,000 simulated trial runs, in looking at the 95th percentile, treatment imbalance is expected to be as good as 6 or better for block sizes 4, 6 and mixed blocks, while blocks of 8 and 10 show study imbalance as 8 or better. The Sponsor Statistician was surprised that the treatment imbalance for a block size of 10 did not differ significantly from that of a block size of 4. However, seeing that the maximum possible treatment imbalances for block size 8 and 10 is as large as 20 was enough evidence for the Sponsor Statistician to rule these 2 block sizes out.

A CLOSER LOOK AT IMPACT TO STRATIFICATION BALANCE

The Sponsor Statistician agrees that the study level balance does look acceptable for a fixed block size of 6, but still wants to review the impact to stratification. In reviewing the fixed block of 4, fixed block of 6, and mixed blocks of 4 and 6, it is easy to see how the mixed block approach provides a middle ground for expected treatment balance between the x2 fixed block sizes. The following figures provide the evidence on how the mixed blocks approach provides balance within the middle ground for this case study.

Figure 2 shows the probability of treatment imbalance over 100,000 simulation runs (sample data sets), $P(\text{Imb}=x)$ (where $x=0, 1, 2, \dots, 4$) for Age: <50yrs:

- Fixed BS=4: $P(\text{Imb}=0) = 30.07\%$, $P(\text{Imb}=2) = 19.38\%$, $P(\text{Imb}=4) = 0.39\%$
- Fixed BS=6: $P(\text{Imb}=0) = 25.98\%$, $P(\text{Imb}=2) = 22.18\%$, $P(\text{Imb}=4) = 1.67\%$
- Mixed BS=4,6: $P(\text{Imb}=0) = 27.40\%$, $P(\text{Imb}=2) = 21.34\%$, $P(\text{Imb}=4) = 1.10\%$

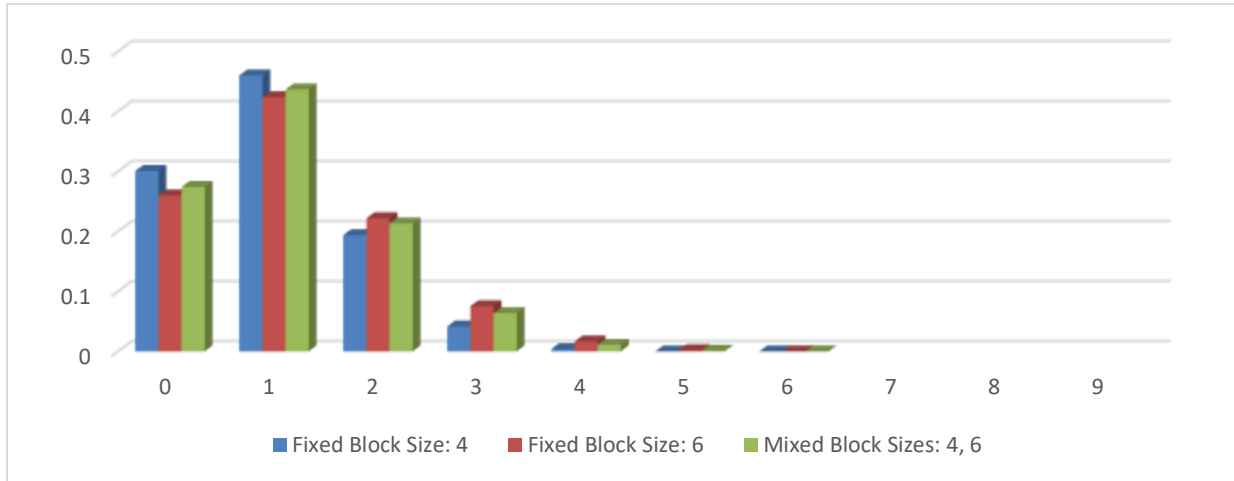


Figure 2: Age: <50yrs Treatment Imbalance Probabilities (N=100,000)

Figure 3 shows the probability of treatment imbalance over 100,000 simulation runs (sample data sets), $P(\text{Imb}=x)$ (where $x=0, 1, 2, \dots, 6$) for Gender: Males:

- Fixed BS=4: $P(\text{Imb}=0) = 19.35\%$, $P(\text{Imb}=3) = 13.48\%$, $P(\text{Imb}=6) = 0.47\%$
- Fixed BS=6: $P(\text{Imb}=0) = 16.63\%$, $P(\text{Imb}=3) = 15.30\%$, $P(\text{Imb}=6) = 1.51\%$
- Mixed BS=4,6: $P(\text{Imb}=0) = 17.39\%$, $P(\text{Imb}=3) = 14.63\%$, $P(\text{Imb}=6) = 1.04\%$

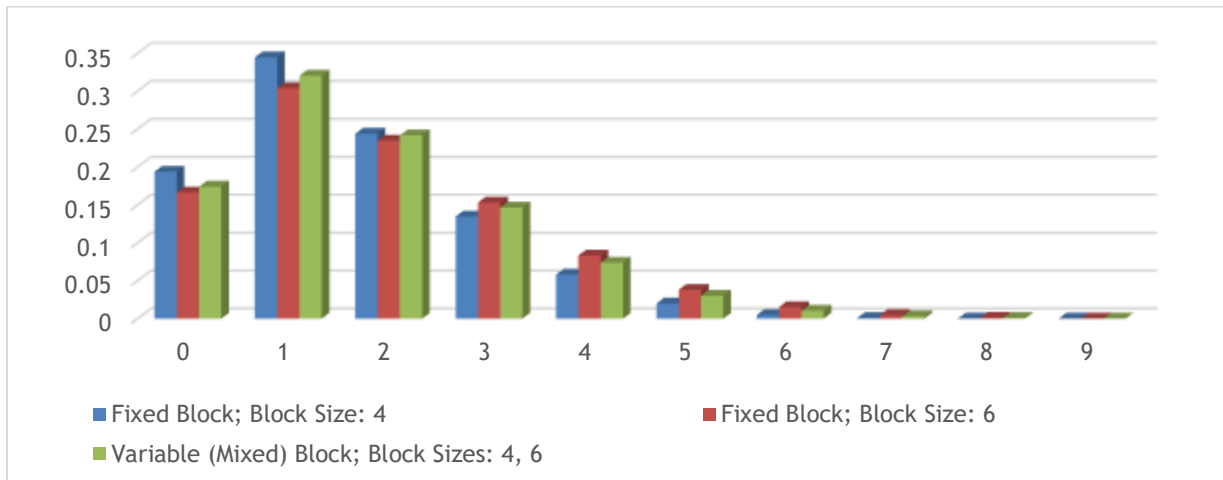


Figure 3: Gender: Male Treatment Imbalance Probabilities (N=100,000)

Figure 4 shows the probability of treatment imbalance over 100,000 simulation runs (sample data sets), $P(\text{Imb}=\mathbf{x})$ (where $\mathbf{x}=0, 1, 2, 3$) for Stratum 1: AGE: <50yrs; GENDER: Male:

- Fixed BS=4: $P(\text{Imb}=0) = 41.98\%$, $P(\text{Imb}=1) = 49.56\%$, $P(\text{Imb}=2) = 8.46\%$, $P(\text{Imb}=3) = 0.00\%$
- Fixed BS=6: $P(\text{Imb}=0) = 36.97\%$, $P(\text{Imb}=1) = 47.95\%$, $P(\text{Imb}=2) = 13.47\%$, $P(\text{Imb}=3) = 1.61\%$
- Mixed BS=4,6: $P(\text{Imb}=0) = 38.82\%$, $P(\text{Imb}=1) = 48.56\%$, $P(\text{Imb}=2) = 11.62\%$, $P(\text{Imb}=3) = 1.00\%$

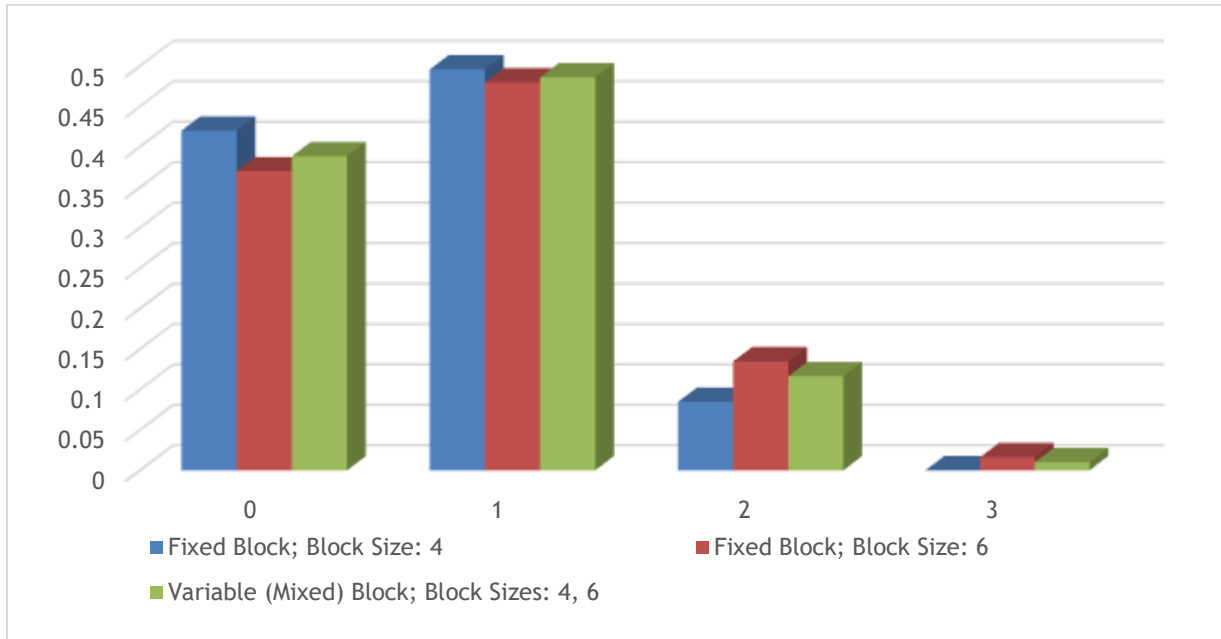


Figure 4: Stratum 1: AGE: <50yrs; GENDER: Male Treatment Imbalance Probabilities (N=100,000)

As expected, the results for stratification within the figures above show a marginal treatment imbalance improvement as the block size is reduced from 6 to 4, with the mixed-block approach falling right in between the two fixed block designs. Similar trends are observed at the study-level, age levels (x5), gender levels (x2), and strata levels (x10). It is clear that the common / default block size of 4 yields the lowest treatment imbalance, but the Sponsor Statistician is now aware that for open label studies, larger block sizes are recommended to avoid predictability of treatment assignment at the end of each block.

In looking at the results of the block size of 6, you can see that it provides acceptable balance. However, there may still be some concern that this block size could potentially be identified with predictability introduced. The mixed block approach provides additional randomness to the list design while providing slightly better treatment balance than the fixed block of 6. Because of this, the Sponsor Statistician selects the mixed blocks of 4 and 6 within larger block of size 10 as the blocking approach for the study. The simulations results provided the data-driven evidence that the Sponsor Statistician needed to make this critical decision with confidence that this mixed block approach reduces predictability of treatment arm assignment, while also maintaining acceptable treatment balance.

CONCLUSION

In reading through this paper, you are now aware that making the block size decision is critical, since it not only has impact on the treatment balance, but also on the predictability of the treatment assignments (level of protection against selection bias). While many Sponsor Statisticians follow the general ICH E9 guidance (1) of avoiding the minimum block size, the majority likely use a common / default block size (e.g. using the first available non-minimum fixed block size which would be 4 for 2

treatments with 1:1 ratio). Since the block size should be kept as a blind parameter, constantly using the same block size removes any claim that it remains unknown to the wider study team (leaving the study susceptible to selection bias).

The decision of using the common / default block size is ultimately driven by the study's treatment balance requirements, where the smallest possible (non-minimum) block size would obviously yield the best treatment balance results. Since this is obvious, no evaluations (to examine alternative block size options) are performed when making this decision to use the common / default block size. As demonstrated in this paper within the case study, you can see that evaluation can be effectively done through SAS simulations. When you incorporate SAS macro programming in your simulation code, you can make this process easy and efficient to execute various parameters (i.e. block size options).

Since the block size choice impacts both the study's treatment balance and susceptibility to selection bias, the choice should be evaluated against data-driven evidence. Using SAS simulations with macro programming enables you to efficiently and effectively perform the evaluation on which block size design would provide you with both acceptable balance while also limiting the predictability.

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