Is Your Study Balanced, as you had Planned?

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Abstract

Randomization coupled with maintaining the blind form the gold standard for minimizing the bias within the clinical trial. The scientific integrity of the trial greatly depends on adherence to the randomization schedule. To be sure that no biases are introduced, randomization procedures must be precise. Clinicians and statisticians who conduct studies and report results depend upon timely, accurate and clean data. While the trial is being conducted, trial statisticians may encounter any number of data discrepancies. These discrepancies can greatly impact the final analyses. Logistical and operational considerations in the actual practice of randomization and study conduct can provide opportunities to correct common errors that could otherwise compromise study validity.

Over the course of nine months a collection of misrandomization cases and resolutions were documented. Case studies of "misrandomization events" showed a comprehensive amount of data discrepancies that arose during the actual practice of randomization. These misrandomization events were characterized as: (1) Misclassification of subject stratifying information, (2) Screen failed subjects continuing to the randomization phase, (3) Incorrect treatments administered to randomized subjects, and (4) Multiple randomizations of the same subject.

Involving the trial statistician in management of misrandomization events as they unfolded, while maintaining the blind, offered the trial statistician the opportunity to work with the clinical trial study team to minimize the likelihood of recurrence of these same errors within the study.

Key Words: Randomization, balance, intent to treat, analysis, misrandomization

1. Introduction

Randomization coupled with maintaining the blind form the gold standard for minimizing the bias within the clinical trial. A well-conducted randomized clinical trial aims to avoid bias by using random assignment of subjects to treatment groups, basing analyses on all randomised subjects, and ensuring quality control standards throughout the study. The scientific integrity of the trial greatly depends on adherence to the randomization schedule as a trial may be said to be properly randomized, but the adequacy of the randomization can only be verified by checking the data from individual subjects (Pouge, 1998). It is well documented that there is standard methodology for implementing and following a randomization schedule. The randomization schedule should be followed in such a manner that the next subject to be randomized into a trial should receive the treatment corresponding to the next free number in the appropriate randomization schedule (in the respective stratum, if randomization is stratified) (ICH E9, 1998). In other words, the randomization list should be followed in sequential order, with no backfilling of records in order to maintain the true intent of study randomness. Furthermore, treatment allocation determined by the randomization schedule should be followed.

In practice, the integrity of the randomization schedule can become compromised by 'misrandomizations' especially if correct statistical methodology is not used to address these issues in randomization. The study design of a clinical trial may be flawless but subject outcomes may be misinterpreted due to errors in the practice of randomization. Sections 5.1 and 5.2 of the ICH E6(R1) guidelines list principles for data quality assurance and quality control stating that quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly (Smith, 2009). These control measures would be implemented to prevent protocol violations and protocol deviations (major or minor) from introducing bias to the clinical trial that can ultimately lead to the demise of the trial. It is especially important to minimize the incidence of protocol violations of the entry criteria, non-compliance, withdrawals, losses to follow-up, missing data and other deviations from the protocol, and also to minimize their impact on the subsequent analyses (ICH E9, 1998).

Many sponsors now conduct randomization procedures through the use of an Interactive Voice/Web Response System (IVRS/IWRS). While this automated technology provides credible audit trails and a program environment that assures adherence to the randomization schedule, control measures are often needed to address misrandomizations that occur due to human error (McEntegart, 2003). The sponsor should ensure that the systems used for electronic data handling and/or remote electronic data systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of actual transactions (i.e., maintain an audit trail, data trail, edit trail). If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data (Smith, 2009). While these opportunities to correct randomization errors before they compromise the analysis of subject data are allowed, it is especially important to minimize the incidence of protocol violations of the entry criteria, non-compliance, withdrawals, losses to follow-up, missing data and other deviations from the protocol, and also to minimize their impact on the subsequent analyses (ICH E9, 1998).

The frequency and type of protocol violations, missing values, and other problems should be documented in the clinical study report and their potential influence on the trial results should be described. It is the sponsor's obligation to be able to report these protocol violations and major and minor protocol deviations in the clinical study report (ICH E9, 1998). If these data discrepancies are not reported in the correct manner, fraud may be implied especially if subject data are modified to meet eligibility criteria or shortcuts were taken in obtaining subject outcome data, and that in extreme cases of fraud, data may have been completely fabricated. This requires that all modifications to subject randomization data be made in consultation with the trial statistician using statistically valid methodology in order to maintain the blind and uphold scientific integrity (Smith, 2009).

In practice, RCTs are commonly afflicted by errors to subject data and often it is difficult to gauge the effectiveness of the randomization without a detailed analysis of the randomization transactions. Often, the actual randomization is performed by clinical site staff that may not be aware of the statistical requirements around randomization practice. In addition to 'misrandomizations' that may occur at clinical sites, there is a potential to react to correct these errors immediately. This can lead to removal, deletion or modification of randomization transactions that is not warranted. By reporting possible protocol violations and major and minor protocol deviations that pertain to randomization to the trial statistician, we offer the opportunity to correct the randomization errors with limited consequence.

As the use of adaptive trial designs increases, we see innovative applications of randomization and drug supplies management within IVR/IWR systems. Adaptive trial designs necessitate increased randomization management including schedule generation, schedule management, randomization monitoring and statistical support/consultation. Caps may also be used to control subgroups. Depending on the complexity of the adaptation, certain levels of monitoring are required to ensure successful randomization implementation at any point in the study is achieved (He et al, 2012). This increased management is also necessary for the management of misrandomizations. For example, the management of erroneous randomizations will depend on the nature of the adaptation. The trial statistician must weigh factors such as dynamic randomization, the dropping of treatment arms from one randomization stage to another or the use of multiple randomization lists containing different drug ratios. The ability to maintain the study blind and overall integrity hinges on making appropriate modifications to subject randomization schemes, including drug ratios, identification of treatment groups, and appropriate drug dispensation in accordance with study design.

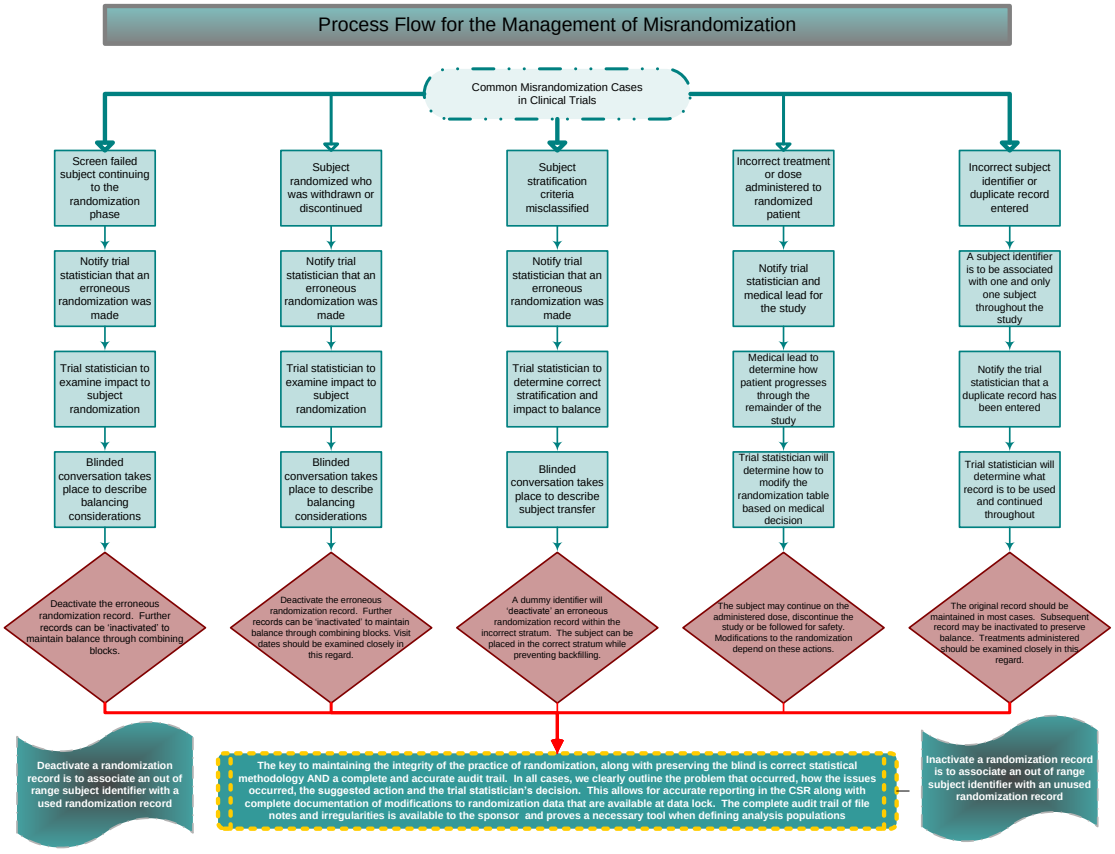
As a result of timely error reporting, sound error correction and detailed audit trails, sponsors can easily maintain a metric of site performance along with study irregularities. This provides the opportunity to re-educate underperforming sites or in worse case, close the site due to noncompliance with screening and/or randomization procedures. This also provides a database that contains clearly defined analysis populations (intent to treat, modified intent to treat, safety, per protocol, as treated, efficacy, etc.) throughout the course of the trial in an effort to mitigate risk at the point of analysis (final and/or interim) and reduce imbalances for comparable populations and subgroups.

2. Methods

Over the course of nine months in industry, a collection of misrandomization cases and resolutions were documented. These cases covered from Phase 1 through Phase 4 clinical trials encompassing a wide range of therapeutic areas. These cases show the complexity of statistical issues within the subject and pack randomization tables of the interactive voice response system. Each case contains a summary of events along with corrective action and flagged fields to ease identification of misrandomization cases, and study populations (such as ITT, mITT, per protocol, safety, evaluable).

In each case, the trial statistician was informed, in a timely manner, of the nature of the error and other supporting information such number of randomization transactions performed since the error was recorded and treatment information if the administered treatment differed from the randomization schedule (Figure 1). Overall study balance would be discussed upon request as this information could potentially be unblinding. Usually, the conversations had with the trial statistician were blinded in nature. In the rare case the conversation needed to contain unblinded information, the trial statistician had the option to delegate an unblinded team member to participate.

Figure 1: The process to successful data modification is outlined in a flow chart for the use in Standard Operating Procedure (SOP). This flow chart provides sponsors a quick reference for the handling of the most common misrandomization cases which ultimately leads to consultation with the trial statistician.



The trial statistician was considered to have full domain of the processing of the misrandomizations and all corrective actions were documented in a note to file (signed by the trial statistician) and the studies irregularity report. This report Serves as a transmittal for the tabular data from the IVRS at data lock and simplifies the identification of possible protocol violations and deviations (to be kept at below 5% of the randomized subjects). This information is used in the identification of study populations as defined in the Statistical Analysis Plan such as intent to treat, modified intent to treat, per protocol, evaluable, safety, etc.

There were instances when randomization was closed for a short period of time in order to implement corrective action(s). All details of the electronic change were documented within the system to complete the full audit trail.

The collection of misrandomization data was observed and classified into common error types. In all cases the site number was recorded along with the nature of the error. At any time, the sponsor could request the study irregularities report which would contain a full listing of all screening and randomization related potential protocol violations and protocol deviations (major and minor) on a site level.

2.1 Limitations

Only a subset of misrandomization cases are known to be reported due to the fact that misrandomization cases can only be discovered by notification of the incident from the clinical site and subsequent follow up from sponsor staff. It is thus assumed that cases may go unreported or there are global procedures within a study that no modifications to randomization data will be made. Furthermore, our ability to quantify the extent of misrandomization cases within a frame of reference is limited to those estimated randomization transaction within each study. The extent of each error's impact to the randomization schedule is to be determined by the trial statistician and in all cases the suggested action of the trial statistician was documented and followed.

3. Results

Results were compiled by clinical study phase (Table 1). Over a period of nine months there were a total of 90 'misrandomization' cases reported. The majority of randomization errors were reported during the large, quick enrolling phase 3 trials. The greatest ratio of error events to total randomization transactions are found in the phase 1 trials. Given the total numbers of randomization transactions, these rates of error are very low, especially in Phase 3 trials.

TABLE 1: Randomization errors reported by clinical and site staff over a period of 9 months (March 2011-November 2011). Table one shows the number of randomization transactions recorded as a sum of the unique studies and the total events reported as randomization errors.

Study Phase	Unique Studies	Total Rand. Transactions	Total Error Events	Percent
1	4	445	4	0.90%
2	17	4015	34	0.85%
3	35	35063	50	0.14%
4	2	1279	2	0.16%
Totals	58	40357	90	0.21%

The 'misrandomization' cases were reported to a firewalled unblinded randomization group within the company. The cases were reported to the group in order to obtain guidance on how to best alleviate the impact of the error to the overall study integrity and minimize the likelihood of recurrence. Furthermore, statistical guidance was requested as to how to best approach the study team and what solutions to offer. From these reports we are able to classify the types of 'misrandomization' errors (Table 2).

Study Phase	Stratification Error	Screening Error	Duplication Error	Treatment Error	Other
1	3	0	0	0	1
2	8	9	2	10	5
3	24	6	5	4	11
4	2	0	0	0	0
Total	37	15	7	14	17

As a result of the corrective action, a note to file was completed to document the action along with any supporting details. The notes to file were filed in the study project files and are powerful means of audit as they contain the reason(s) for the error occurrences, the suggested corrective action(s) directed by the trial statistician and the actions taken by the IVRS provider to modify or correct the randomization schedule.

4. Discussion

4.1 Misclassification of Subject Stratifying Information

The common misclassification of subject stratifying error occurs when a patient's covariate baseline information is entered into the IVR system in error. For example, a male could be entered into the system as a female and the randomization transaction could still be completed.

Stratified randomization is intended to create groups of subjects that are similar with regard to baseline characteristics that influence prognosis (known and unknown) other than the treatment being considered. This is an attempt to alleviate failures of simple, non-stratified randomization, such as the inability to assign the compared treatments to equal numbers of subjects. Moreover, simple randomization can fail if it creates treated groups of subjects that are unbalanced for critical features that are known or suspected to affect prognosis. Significant imbalance is most likely to happen in small trials where chance may result in sicker subjects being in one treatment arm than in another (Kernan et al, 1996). These failures can be propagated by the randomization of subjects into improper stratification levels.

Inaccurate stratification reporting can directly impact the randomized treatment assignment and therefore impact the intent to treat population. Although a treatment assignment should never be changed after a subject has been randomized, properly classifying the subject within the randomization table can prove beneficial at the point of data analysis. In such cases we offer the trial statistician the ability to move the subject into the correct stratification level from the incorrectly assigned level. This is a time sensitive decision that should be made prior to the randomization of any further subjects.

The methodology around this data modification preserves the treatment balance within the respective stratification levels by the use of a 'dummy' subject identifier. To preserve the details of randomization transaction and a complete audit trail of all randomization events, the record is neither removed nor deleted. The original record associated with the subject in the incorrect stratification level is deactivated using an out of range subject identifier and the subject is then placed in the correct stratification level that is associated with the same treatment to which the subject was originally assigned. This adheres to regulatory guidelines while providing the opportunity to classify the subject correctly. Furthermore, we offer the trial statistician the opportunity to inactivate further records within the original stratification level, usually collapsing two blocks into one, due to balancing implications that can result from data modification. For example, in a 1:1 treatment ratio, we consequently create imbalance in the original stratification level due to the inactivation of that record. In a permuted block design we can simply perform a similar modification to an unused treatment record for the opposite treatment, thus maintaining the correct treatment ratio within the stratum.

4.2 Screen Failed Subjects Continuing to Randomization

A trial auditor should be able to use the enrolment dataset to reconstruct the trial's process of allocating treatments to subjects and the analysis should reflect this. Randomization specifications or system requirements rarely explain to trial personnel what to do if investigators provide incorrect information when enrolling participants such has incorrect lab values pertaining to screening requirements (Downs et al, 2010).

A common problem which arises is how to handle a subject that has been entered into the randomization phase after being deemed a screen fail. For example, if a subject is entered into the system with an incorrect (i.e. data entry error or calculation error) lab value that qualifies the subject for randomization the subject is part of the intent to treat population. Given this information in a timely fashion we can notify the trial statistician and provide the possibility of deactivating this randomization transaction. At this point the trial statistician can advise the study team on how to further classify the subject. Furthermore balancing considerations can be made according to the corrective actions taken to classify the subject. The subject should not be treated and should be removed from the study classified as a screen failure.

4.3 Multiple Randomizations of the Same Subject

The next subject to be randomised into a trial should always receive the treatment corresponding to the next free number in the appropriate randomization schedule (in the respective stratum, if randomization is stratified). The appropriate number and associated treatment for the next subject should only be allocated when entry of that subject to the randomized part of the trial has been confirmed (ICH E9, 1998). This guideline is compromised when trial staff performs multiple randomizations of the same subject.

For example, a site may enter subject data into the randomization system in error. Instead of reporting the error and continuing with the same transaction, the site staff has the ability to back completely out of the system and record a new transaction regardless of a completed randomization. This results in a duplicate randomization transaction for the same subject and complicates analysis. In these cases it is imperative to maintain the original record for the subject as entered into the system. Each human subject can have one and only one unique subject identifier and it is the first one to be assigned in the study in the case of multiple assignments. Once again complete audit trails should be

maintained preserving each transaction and identifying the corrective action. Thus use of 'dummy' subject identifiers is helpful when deactivating the subsequent randomization transactions.

4.4 Incorrect Treatments or dose(s) Administered to Randomized Subjects

The intent-to-treat analysis provides the most realistic and unbiased answer to the more relevant question of clinical effectiveness. Also, the analysis can be considered unbiased when all randomized patients are included in the analysis to the extent dictated by the original design (Lachin, 2000). Complications arise when patients are randomized to one treatment and dispensed another treatment. This scenario is particularly more complicated when there a subsequent treatment follow up visits and a single dosing is made in error or when the study design involves planned crossovers or other dependent re-randomization procedures. Furthermore, if these cases are not handled properly, the study blind may be compromised due to the nature of the error. The ultimate decision regarding how to proceed with the patient in the study should be made by the clinical lead and followed up with the trial statistician in order to make sure that the patient can be defined clearly in the appropriate analysis population (as intent to treat, modified intent to treat, , per protocol, efficacy, and safety).

The most important issue concerning treatment allocation errors is patient safety. For example, a treatment allocation error can be made such that a patient receives an unsafe treatment or dose allocation due to a calculation error of laboratory information. In other words, the IVR/IWR system is validated to prevent these misallocations but the element of human error can never guarantee this. It is important for the provider of the IVR/IWR system to report these errors to the study medical lead and statistician in a timely manner. Only the study medical lead should make the decision regarding how the patient should be treated and whether the patient should continue in the study. In our experience we have seen the medical lead continue the patient on the treatment or dose that was last administered, continue the patient on the originally randomized treatment, stop all treatment but continue the patient for safety or discontinue the patient from the study completely. Each of these decisions has analysis consequences so it is at this point when consultation is made with the trial statistician in order to set flags in the randomization database such that the proper population classifications are given to the subject.

Protecting the blind when a patient is given the wrong treatment is often a challenge due to the nature of the error. For example, in order for the study clinical lead to make the most informed decision it is often necessary for treatment unmasking. Thus, it is important that the initial design is such that when a single unblinding is made further potential unblinding in minimized. This can be made possible by utilizing double randomization within the pack randomization lists such that a single kit number can never be associated with a treatment arm. For example, if kits are shipped in numerical order and an allocation error occurs such that a single kit is unblinded, further assumptions can be made about previous and subsequent kits (McEntegart et al, 2005). Further considerations should be made to conceal treatment identification from the trial statistician. By providing a follow up note to file in blinded format a full and complete audit trail can be kept with limited unblinding information.

4.5 Conclusions

Properly defined analyses populations constructed by adequate randomization and blinding techniques provide powerful tools in the scientific decision making process. If the practice of randomization is compromised, the proportion of subjects allocated to the treatment groups may differ quite substantially, especially when trial size is small or moderate. Chow and Shao (2003) set forth the theoretical framework for quantitatively studying the effect of treatment mix-up in the randomization code. They showed that an adequately powered test (80%) that suffers a 5% treatment code mix-up will have a power reduction of 9.2%. Furthermore, a 10% occurrence of treatment mix-up will reduce the power of the same test by 18.6%. That is, a small or moderate proportion of randomization code mix-ups may seriously affect the probability of detecting the treatment effect when such an effect exists (Chow, 2011).

A CROs experience over a 9 month period has proven that randomization mix-ups occur as we collected and analyzed a total of 90 individual events. While this rate of occurrence only accounted for .21% of all randomization transactions across all of the studies analyzed, it is still important to analyze the deviations on a per study and per incident basis as the individual deviations are reported as a ratio of the study sample size. By addressing these deviations to the randomization schedules, we helped to minimize treatment imbalances while helping to offset the loss of study power.

While international guidance's for clinical trials such as the International Conference on Harmonization E9, Statistical Procedures for Clinical Trials, outline procedures for adhering to randomization schedules, they do not provide framework for dealing with specific errors encountered in the practice and implementation of randomization. Logistical considerations must be made on a case by case basis which is the domain of the trial statistician. Some protocols do have specific information on management of some of the types of misrandomizations. Protocol specific decisions must be made when weighing the effects of the errors on the randomization and the overall treatment balance. These considerations can often provide a means of modification to the randomization scheme without undermining the scientific integrity of the trial.

Methods for the management of misrandomizations in clinical trials are not yet standardized. Some are of the opinion that no correction be made to investigator or site errors in the randomization process and to study drug allocation records. Manual corrections to randomization systems, no matter how well intended, are often incorrectly applied and it is far better to live with errors than to seek to correct them (Farina, 2010). In some cases it may be beneficial not to make any modifications to the randomization schedule but other cases may warrant modifications.

By involving the trial statistician in management of misrandomization events as they unfolded, while maintaining the blind, we offered the trial statistician the opportunity to work with the clinical trial study team to minimize the likelihood of recurrence of these same errors within the study.

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