

Beyond “Just fix it!” Application of Root Cause Analysis Methodology in SAS® Programming.

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ABSTRACT

“Just fix it, we have too much to do”- a common phrase heard in organizations and especially in SAS® programming departments. It is relatively easy to fix programming issues every time it occurs rather than look into why it occurred in the first place. The problem with this approach is that, there is a good chance that a similar issue may occur and not be caught next time resulting in compromising validity of deliverables. This is analogous to treating the symptom, every time it occurs and not looking deeper into figuring out the actual cause.

In order to prevent systemic programming issues occurring, it is essential to identify what, how and why an undesirable event occurred before taking steps to prevent it in the future. A systematic process of investigating and identifying root cause that can be controlled by programming/management team with an intention of preventing it in future, can be done through Root Cause Analysis (RCA). This paper discusses how we utilized principles of RCA in statistical programming and reporting to identify root cause(s) and came up with corrective and preventive action plan (CAPA) after an undesirable event in the form of an adverse event report with incorrect numbers was produced, passed validation and multiple review by study team, was submitted to regulatory authority before the issue was found.

INTRODUCTION

Clinical trials in today's world is an expensive, complex multi-disciplinary processes involving multiple partner entities working together to satisfy stringent regulations to improve patient lives by bringing innovative therapy to the market. Due to competitive nature of our industry, there is a push towards increasing efficiency in order to deliver on-time, on-budget accurate representation of clinical trial data to regulatory authorities. SAS® Programming departments play a crucial role in this process by providing data tabulations that help regulatory authorities make decision on approval of a drug or a device. An undesirable quality related event raises questions on accuracy of the data reported in a clinical trial. This paper discusses our approach for using the RCA methodology to investigate events of undesirable programming quality and provides a corrective intervention to prevent its future occurrence.

INTRODUCTION TO ROOT CAUSE ANALYSIS (RCA)

A root cause(s) is an underlying cause (hence the term 'Root') that primarily lead to an undesirable event that needs to be investigated. Generally, root cause is never obvious and a methodical investigation is required to 'dig' it out. The RCA is a structured investigation methodology (Figure 1) designed to identify and categorize root cause(s) of an undesirable event with an intention of implementing intervention to prevent it from reoccurring. In other words, it is a methodology used to identify 'What', 'How' and 'Why' an undesirable event occurs for an investigator to suggest workable, specific corrective action.

In order to be effective, The RCA investigation should focus on identifying root cause(s) that have following three characteristics.

1. Root cause need to be non-trivial and as specific as possible. A workable and effective corrective intervention can only be suggested and implemented if a specific root cause(s) is identified.
2. A root cause needs to be supported by collected data and people who are Subject Matter Experts (SME) on the processes associated with undesirable events.
3. Management should be able to take specific preventive action on an identified root cause. Any cause that cannot be controlled through specific intervention is of little value.

RCA is performed in three steps as illustrated in Figure 1. First we need to understand the issue being investigated, after which the specific issue needs to be defined and the participants familiar with the project including those who worked on it are assembled. A formal discussion/brainstorming session is

conducted to identify the cause(s) and circumstance that lead to this undesirable event. Once we obtain the required information, the second step involves analyzing the causes and circumstances using appropriate RCA tools like '5-Why', Fish-Bone diagram etc. to find actual root cause(s). After identifying root cause(s) the third step involves prioritizing causes based on which one more likely caused the issue and preparing a corrective and preventive action plan (CAPA) to remediate the issue at hand with measures to prevent similar issues in future.

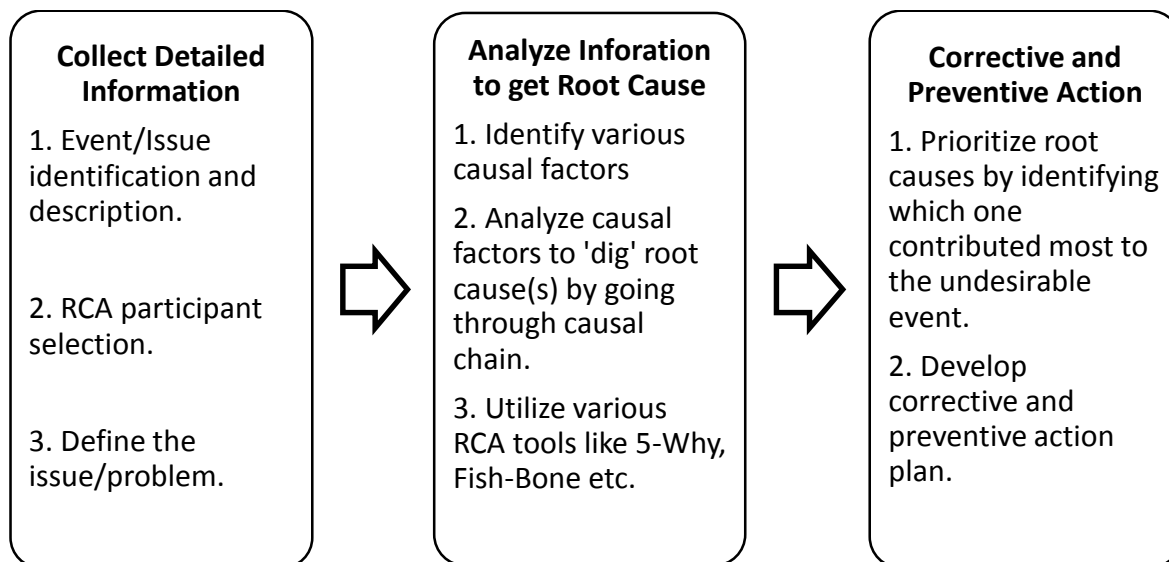


Figure 1. Basic steps involved in a Root Cause Analysis

ROOT CAUSE ANALYSIS APPLICATION IN CLINICAL TRIALS

Clinical trials are multi-disciplinary in nature and any nonconformity can potentially negatively impact the patient safety and wellbeing. It is in the best interest of both patients and sponsors that the regulatory authorities are provided with accurate and reliable reports of clinical trial analysis, for them to make decision about drug approval. Any non-conformities in accuracy/reliability of the reporting needs to be corrected with precautions to prevent the occurrence of non-conformities in future submissions. This makes RCA one of the best tools to be used here.

The RCA is generally done in response to a significant event. An event is categorized as significant if it can potentially impact patient safety, regulations dealing with confidentiality, data integrity or validity of clinical trial. A few relevant examples would be programming algorithm that may exclude certain adverse events, use invalid result in analysis, hardcoding and reporting that does not follow Food and Drug Administration (FDA) guidelines on representation of data for certain endpoints or compliance issue that may potentially result in Refuse to File (RTF) etc.

In order to illustrate how RCA can be applied to real life clinical trial analysis reporting issues, this paper describes an actual situation where we utilized RCA methodology to better understand the root cause and implemented corrective actions.

OUR ROOT CAUSE ANALYSIS

BACKGROUND

In a long term phase 3 pivotal clinical study we worked on, included a critical but non-standard safety table Incidence of exposure adjusted treatment emergent adverse event (Table 1). This table was programmed using data up to and including week 48 and was part of Clinical Study Reporting (CSR).

Table programming was completed using a snapshot of clean data that had to be programmatically cut-off at week 48 for each subject before table programming.

Table :1x.x.x.x

<Drug name> Protocol xyz123

Incidence of Exposure Adjusted Treatment Emergent Adverse Event Prior to Week 48 (Safety)

Num of subjects available for AE	Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)

System organ class			
MedDRA(V18.x) preferred term			
SOC term 1			
AE Preferred term1	x.x	x.x	x.x
AE Preferred term2	x.x	x.x	x.x
SOC term 2			
AE Preferred term1	x.x	x.x	x.x
AE Preferred term2	x.x	x.x	x.x
...			

Event counts are adjusted to 100 years of subject exposure.

Includes data up to 30 days after last dose of study drug.

Programming note: Exposure adjusted AE= (Duration of particular AE for all subject in the cohort/ treatment duration of all subjects in the treatment) x100.

Table 1: Table shell for treatment emergent AE exposure adjusted.

After the week 48 cut-off table was programmed and validated independently, it was sent to clinical study team for review. After review, this AE table was included in the CSR for regulatory submission.

Post CSR submission, during the review of another comparable study, it was observed that the exposure adjusted AE incidence rate in this table was much lower compared to a corresponding one in another comparable clinical study. It appeared that this particular table underestimated safety risk associated with the compound. Upon further investigation involving clinician, statistician and the programming teams it was found that the data cut-off till week 48 was only applied to adverse event data but not to the treatment data. In other words calculation of exposure adjusted AE had 48 week cut-off applied to numerator but not to the denominator which was summation of exposure duration for all the safety analysis subjects in respective treatment groups. Clinical study director, upon being informed of this incorrect AE table in CSR decided to conduct an in-depth investigation using RCA methodology as this non-conformity could potentially undermine safety profile of the drug.

ROOT CAUSE ANALYSIS PROCESS

Step 1: Collect Detailed Information.

To perform RCA, a team comprising of representatives selected along functional lines, involved in this clinical study analysis and reporting process including clinician, biostatistician, programming managers and primary programmer from both client and CRO's were selected by a RCA facilitator and tasked to investigate and collect information on circumstances and identify various causes for this non-conformity. It is essential to select appropriate people who have sound knowledge of the clinical trial analysis and reporting processes and are involved in its day-to-day operations for conducting meaningful investigation.

While investigating any root-cause, it is important for the RCA participants to agree upon and define the issue under investigation in unequivocal and specific terms. It is also mandatory for the team to develop a common understanding of circumstances that lead to the issue under investigation, before an effective solution can be proposed. The issue here was defined as *'A non-standard safety table (table that cannot be programmed using standardized re-useable, pre-defined macro) on incidence of exposure adjusted treatment emergent adverse event (AE) was programmed to summarize the AEs starting up to and including week 48, had incorrect summarization of treatment emergent AEs due to an error in calculation of exposure duration (denominator), was included in CSR submission after independent validation and multiple review by the study team'*. To increase clarity, specific guidelines from Programming/Statistics Standard Operation Procedure (SOP) that might not have been fully followed were also mentioned.

After the problem statement is clearly defined and understood by the team, severity and frequency of the issue needs to be assessed. Severity refers to how this issue impacted/or can potentially impact patient safety, data quality, compliance and validity of the clinical trial. The frequency refers to how common is this issue or issues similar in nature. Assessment of severity is generally done through input from people who have expertise in respective processes. The frequency assessment is quantitative in nature and hence done by going through related documentation in form of audit report or formal documents related to request for re-work. A frequent issue that can have severe impact needs to be given highest importance. In our assessment it was determined that this issue is moderately frequent and of moderate severity. However if we do not take preventive measure there can be severe potential impact.

To know about the circumstances and possible cause(s) of the above mentioned issue, a discussion was conducted on the lines of 'Who', 'What', 'When' and 'Where' this event happened. A discussion on 'Why' the nonconformity occurred helps us to identify the root cause(s) in next step.

Some of the points discussed during this step focused on circumstance and possible cause are in the following.

1. Originally, the table was not a part of the CSR submission and was added at a later stage creating time crunch, which may have impacted quality of deliverable (Post-Hoc table).
2. New programmer was assigned to program this table and he/she might not have enough background knowledge to fully understand data and its context.
3. Programmer(s) assumed this was an AE table and applied cut-off to AE data (numerator) and not the denominator (summation duration of treatment for all subjects in respective treatment group).
4. An existing report from other study was used as de-facto table shell here and there was no cut-off related programming note in it.
5. General assumption by programmer that one should follow the reference table and it is common practice in SAS® programming to use/modify existing code.
6. Code from previously existing report provided to programmer as de-facto shell was re-used after some modification. The issue arose due to misunderstanding of data that goes into table creation.
7. Table did not display denominator so it was not very intuitive for reviewers to spot inaccurate AE summarization here.
8. Validation (QC) programmer modified previously existing validation code from reference table that was used as table shell.

STEP2: Analyze for Root Cause(s).

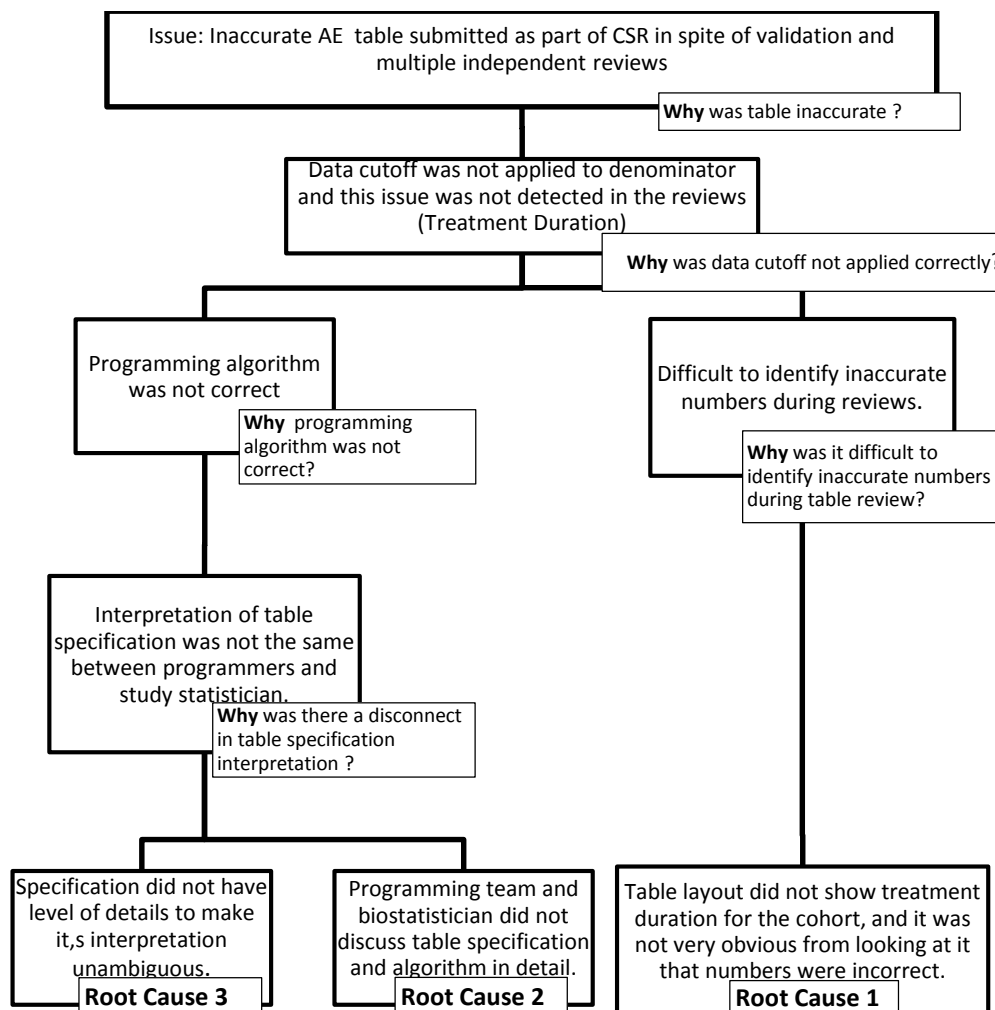
Once we have a good understanding of ‘WHO’, ‘WHAT’, ‘WHEN’ and ‘Where’ of a non-conformity, it is time to analyze ‘WHY’ it happened. Analyzing for root cause will provide answer to ‘WHY’ it happened. The root-cause can be analyzed using multiple tools, and an appropriate tool needs to be chosen depends upon the nature and complexity of non-conformity. Four of the most widely used tools are as following.

1. **5-WHY (Gemba Gembutsu):** This is most effective when dealing with human error involving people who are familiar with subject matter. 5-WHY typically is a practice of asking why an issue occurred 5 times through the causal chain to identify actual root cause.
2. **Cause and Effect Diagram (Fishbone or Ishikawa diagram):** This tool is generally used for complex RCA’s in which interaction between multiple processes and factors can contribute to a problem. A diagram that resembles bone structure in a fish in which issue is placed at the ‘head’ of the fish while major factors and processes are considered as main ‘Bone’. The causal chain starting from each main bone are represented as side bones.
3. **Fault tree analysis:** Fault tree analysis is a top-down deductive analysis in which a flowchart is used to methodically identify what caused non-conformity. Both human error and system failure can be accounted into this analysis.
4. **Difference analysis:** In this type of analysis, a comparative study of the circumstances in absence of issue versus presence of the issue are performed. Any recent changes in the processes are accounted, this method is generally more effective if failure occurs after any significant update to system or processes.

We choose the method ‘5-WHY’ as it is most appropriate for problems arising due to human factors or interaction and also people involved in clinical programming and reporting are familiar with the processes. ‘5-Why’ is an interactive- iterative process that involves asking why a problem occurred, if the answer to first ‘why’ does not provide root cause then a second round of questions (addressing ‘WHY’) is asked as a response to first ‘WHY’ . It is to be noted that using ‘WHY’ questioning five times is rule of thumb. Generally number of iterative questioning depends upon nature of the problem and how hard it is to identify root cause.

To better illustrate how we analyzed for root cause using ‘5-WHY’ technique, a flowchart (Flowchart 1) is included. After analysis, we were able to identify following three root causes.

1. Table layout (Table shell) did not display denominator values, if they were included, it would have been much more intuitive for reviewer/validator to identify error in the table.
Root Cause 1: *Table shell design was not very intuitive for reviewers to catch error.*
2. Lack of clarity in table specification as a table from another study was used as table shell. There was also disconnect between footnote of the table shell and what was intended to be communicated as programming guidance.
Root Cause 2: *Table Specification provided to programming team lacked clarity.*
3. It is not uncommon to have some ambiguity in specifications and it is expected that programming team would get clarity from study statistician/clinician before/during programming to avoid any misunderstandings. There was no attempt to get clarity and programmers assumed that it should be done as it was done in reference table rather than discuss specific nature of the data cut-off requirement.
Root Cause 3: *Programmers assumed code should be programmed as done previously (in reference table provided as shell) and did not seek further clarification.*



Flowchart 1: Flow chart showing investigation to determine root cause through ‘5-Why’ method.

STEP 3: Corrective and Preventive Action Plan (CAPA)

Once root cause was identified it is time to correct existing issue and put processes in place to prevent similar issue from occurring in future, and hence it is imperative that a corrective and preventive action (CAPA) is put in place. Corrective and Preventive Action is a two part action plan, corrective action is reactive in nature and is undertaken to eliminate existing cause of an issue or an undesirable event, while a preventative action plan refers to proactive action taken to eliminate cause of potential issue in future. CAPA should be as specific as possible and time-bound along with accountable persons/departments who take ownership of implementing it.

The following corrective action were implemented as per root cause analysis.

1. Table was updated with correct cutoff for both adverse event and treatment and validated.
2. Programming team checked algorithms for other outputs and either corrected or confirmed it being correct in reference to the week 48 cutoff data limit. Review focused on application of cutoff algorithm across all relevant outputs.
3. Table was replaced in week 48 CSR Amendment and CSR text was updated to reflect the change after review by study team.

Preventive actions involve improvement in processes along with ways to spot the problem quickly and increasing awareness among personals about potential pitfall arising of root cause(s). Our recommendation were as following.

1. Table shell for exposure adjusted AE's (Table 1) should be updated to include 'person year' which is sum of duration of treatment for all the subjects in years (denominator). This update to table shell layout will aid in identifying the cutoff related inaccuracies during validation or review.
2. Statistical Standard Operating Procedure (SOP) should be updated to mandate all non-standard Post-Hoc tables to have specific table shell before programming commencement. A quick approval processes should be set up for Post-Hoc table shells.
3. This case of week 48 data cutoff error was included in 'lesson learned' training for programming leads and an item was added to quality assurance checklist for exposure adjusted tables that need data cut-off.

CONCLUSION

In an era which emphasis on improved efficiency and higher degree of scrutiny in drug development by the regulatory authorities, quality related issues can lead to re-work, increase the submission related queries from the regulatory agencies, hamper relationships between pharmaceutical client and partner CRO and may potentially risk validity of clinical trials and hence compromise patient safety. In situation where an issue occurs repeatedly, it is essential to look beyond “just fix it” every time an issue occurs and instead focus on performing RCA analysis to identify to the root cause(s) of the event with an intention to eliminate the issue from future occurrence. Avoiding occurrence of systemic issue will improve efficiency of SAS® programming processes and in turn contribute to improving efficiency of drug development in terms of reduced risk and cost.

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