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APPLYING SQC TO ADVERSE EVENT REPORT PROCESSING FUNCTION IN PHARMACOVIGILANCE: MANAGING THE QUALITY OF DATA ENTRY IN THE DATABASE

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ABSTRACT Statistical Quality Control (SQC) is widely applied in many industries, but its use in adverse event report (AER) processing in pharmacovigilance (PV) has been limited. We advocate implementation of SQC application model for data entry in PV considering the fact that the data is utilized for analysis of a drug's performance and to submit individual and aggregate reports to regulatory authorities. Considering the impact of quality of data on the decision making, it is extremely important to manage the quality of data in a safety database. There are 5 steps in application of SQC; define, measure, analyze, improve and control. In this report, we explain how to apply Six Sigma to AER processing in Pharmacovigilance. We also present a benchtop method for implementation of SQC at any case processing operation. SQC is important now than ever because the data entry work can be outsourced.

KEYWORDS : Six Sigma, Pharmacovigilance, Adverse Event Report, Data Entry, Statistical Quality Control

Introduction:

Quality control and process control in pharmacovigilance systems has gained importance since globalization of the adverse event case processing operations. Requirements have been defined and made public by the US FDA and the EMA following the 2010 pharmacovigilance legislation (guideline on GVP in 16 modules, published modules came into effect 02 July 2012). Statistical Quality Control is an established tool in manufacturing industry which is used to monitor systems and to determine the causal relationship between input variables and output to maintain and improve the quality of a product or a service. Acceptance sampling is an integral part of statistical quality control (SQC) implementation and it is used in manufacturing industry to support "accept or reject" decisions. Acceptance sampling consists of relatively small number measurements taken from the process under examination. The measurements are used to generate the statistical evidence to gain an understanding of the quality of process 1.

There are multiple functions in Pharmacovigilance; collection of Adverse Events (AE) from Clinical Trials or collection of AE from Post-Marketing Surveillance (PMS), Case Registration (CR), Data Entry (DE), Medical Review (MR), Quality Check (QC), Submission to FDA/ EMA or other regulatory authorities, processing of information from Observational Studies, conduct of Non Trial Activities, etc. Even after one has taken sufficient measures to maintain these processes in strict adherence to SOPs, the quality of data could be affected by inaccurate Data Entry (DE). Quality of Benefit-risk evaluation of a medicinal product is directly dependent on the quality of data in the safety database. Any serious errors in the database will affect the judgment of benefit risk evaluation. As the process of Benefit- Risk evaluation is further leaning towards a cumulative approach; accumulation of errors in the database will have a natural error inducing pull effect on the Benefit-Risk evaluation. In this article, we would like to focus only on the process of data entry/ case processing which is a core process that determines the accuracy and consistency of a database.

Adverse event case processing is also a proven bottleneck in maintaining the timelines required for submission to regulatory authorities. DE also requires large number of human resource and Cost Effectiveness is usually achieved by outsourcing the function to an international data processing company. A company must make sure not to affect the quality of DE while reducing the costs. What parameters a company can utilize to monitor the function of Data Entry? What parameters can it use to improve the Quality of Data and also provide an assurance to the regulatory authorities about the quality of information in its database?

Need for SQC in Pharmacovigilance (PV):

European Medicines agency has recently published Good Pharmacovigilance Modules to encourage public understanding and compliance to PV 2. Reflecting on the importance of quality management, first module is devoted to PV systems and their quality systems. It states that organizations should have performance indicators, quality objectives and methods for monitoring the efficiency of the PV system and methods of monitoring the efficient operation of the quality system (in particular its ability to fulfill the quality objectives) should be included in the documentation. EU guidelines also state that quality system should also include records to demonstrate the deficiencies and deviations from the established quality system are monitored, corrective and preventive actions have been taken, solutions have been applied to deviations or deficiencies and the effectiveness of the actions taken has been verified"[2].

As per the 'Guidance for industry- Good Pharmacovigilance Practices and Epidemiological Assessments' by US FDA, the quality of the reports is critical for accurate evaluation of potential relationship between the product and adverse events 3. US FDA has also provided 'Guidance for Industry, Oversight of Clinical Investigations- A Risk-Based Approach to Monitoring'. In this document, FDA mentions two methods of monitoring; on-site monitoring and Centralized Monitoring. On-site monitoring can identify data entry errors due to discrepancies between the source documents and case report forms (CRF) and missing data in source documents and CRFs 4. What if there are errors in the data entry? What if that one important Concomitant Disease was not added into the database? What is that one important Co-suspect was not added into the database? There is a need for a method to monitor and prevent the errors introduced during the manual entry of clinical data into the database. US FDA guidance also states that FDA encourages centralized monitoring, which involves data management personnel and statisticians at a remote location other than the site of clinical investigation.

Besides all the questions mentioned previously, we raise another important question, "Is it possible to detect and accurately quantify the errors in the data entry at the study site by conducting an analysis of data at the centralized location?" It would be extremely helpful if we could make a statement about the validity of data and support it by some statistical analysis (95% Confidence Interval or 99 % Confidence Interval).

The recent trends of globalization and computerization have revolutionized the processes in data processing and data management. With help from large database management solutions, it has become possible to reduce costs and save time in

data entry operations in PV. Companies, which outsource the function of AER processing to a contract organization, can use SQC to assure desired quality of AER data entry for PV. There has been much stress on the application of complex data mining techniques to the clinical data in the database but there has been little focus on applying statistical methods to maintain the quality of data entry itself.

The process of Six Sigma quality management may seem daunting to small pharmaceutical set-ups because of their limited resources. At the same time, big pharmaceutical companies face the challenge of processing a large amount of data. Lindquist (2004) has correctly suggested that the quality management in pharmacovigilance depends on quality planning, quality control, quality assurance and quality improvements [5]. In a holistic approach to maximize quality of data in the database, we advocate application of Six Sigma statistical quality control to the process. It can save time, money and overall resources while improving the quality of subsequent data analysis and aggregate reports. Software cannot understand the accuracy of the data fields in medical sense and edit check programs in the software are usually beyond the control of the end-user. Thus, Quality Management Personnel have limited access to parameters that could be used for quality management. However, if the qualitative data in adverse event case processing could be converted to quantitative parameters, then a statistical quality control method (SQC) could be implemented with success. This can be easily done by simply measuring quality of each case on a numerical scale up to 100. This process is no different than grading a test paper with descriptive answers. Maximum score would be 100 % when there is no mistake in the case data. The data fields can be scored with the exact same weight or if a specific data field is of more importance then that field can be given extra weight in calculating the score.

AER Processing and quality review:

AER processing function starts from reception of the information about an adverse event. Depending on the seriousness of the report, AER data is entered into the database and distributed to regulatory authorities as a 7 day/ 15 day reports or submitted in an aggregate report at a specified reporting frequency. Quality review team has the responsibility to take AER samples from the database and note errors, send feedback to the processing personnel, correct the errors in the database and suggest Corrective and Preventive Actions (CAPA) to prevent similar errors in future. CAPAs may include modifications in training modules and SOPs.

Figure 1: AER Processing Workflow

Application of SQC to AER processing:

There are five steps in implementation of Six Sigma SQC; Define, Measure, Analyze, Improve and Control.

1. Define: In this phase, desired quality and participants (stakeholders) are defined. Defining quality of AER processing is a critical step for success of the six sigma application. Based on our experience, each processed AER can be graded on a pre-defined scale, by giving specific score to each correctly processed data field. The entered data is compared with the source documents and quality of work is assessed. A desired quality is defined as a range of minimum acceptable score or Lower Specification Limit (LSL). This stage is also critical when the focus of risk monitoring is a specific serious adverse event.

2. Measure: In this phase, the current quality of the data in the database is measured. A few statistical tests are run to establish the quality of entire database with mathematical certainty.

3. Analyze: A qualitative and/or quantitative evaluation is developed to assess of how changes to system inputs affect system outputs. Changes can be made in SOPs and training modules, frequency of training modules, follow-up methods, documentation methods, screens or data entry capture forms, and building system checks to monitor the clock date, intensive investigator training on reporting etc.

4. Improve: Based on the analysis made in the previous step, recommendations are made to increase the quality of the work. The changes that increase the quality of system output are implemented.

5. Control: Confirmation and documentation of the SQC process is completed. Regular acceptance sampling is conducted to confirm the quality of the process. It is important to plot the performance and make sure that the process is shifted at least 1.5 standard deviations to the left of target (average population mean).

Figure 2: SQC in AER Processing

Benchtop Application of SQC to data entry in Pharmacovigilance:

1. Define Phase:

Desired minimal quality of the data in the database is defined as "μ". The participants in the process are the quality review team, triage personnel, data entry team, training group, statistics group, AER submission and distribution team, etc.

2. Measure Phase:

Step 1: Convert Qualitative AER Data into meaningful Quantitative Data.

Random AER samples are chosen from the database and errors are noted (errors in data entry, missing relevant data from source documents, incorrect coding of suspect product or events or history, error in following required SOP or errors in documentation). See figure 3 for a representative scale. Grading step can be customized as per internal requirements. For example, for an IND product, one can give extra importance (additional points) to adverse event field (putting extra weight on a specific field) which ensures more scrutiny to that field in mathematical logic. Even a small error in data entry in this field will tilt overall score of the mean AER quality in a bigger way.

Step 2: Statistical Tests

Determine the quality of AER processing function with a 95 % confidence interval. Check the quality of AER by running a single sample t test. You can also take another sample and run a two sample t-test.

1. Calculate the average quality score (sample mean x) and sample standard deviation (s) from a sample of 30 AERs. If the sample size needs to be less than 30, use the t- statistic. If the sample size is more than 30, use Z-statistic.

2. Find the standard error of the mean (standard deviation of the mean or SEM). SEM is given by formula $SEM = s/\sqrt{n}$

3. Confidence interval is given by the following formula.

At 95 % C. I. = $(x + 1.96 * SEM, x - 1.96 * SEM)$

Note: If desired Confidence level (α=0.01) is 99 %, Z value is 2.58.

Take another sample of same size and run a two sample t- test.

All of these tests can be easily performed in Microsoft Excel ® without need of formulae. To run a t-test in Excel ®, use the function TTEST.

3. Analyze Phase:

Quality is measured when changes are made in training modules, frequency of training, maximal time to enter an AER into database, workstations distribution, resource allocation and other input variables etc.

4. Improve Phase:
Based on the analysis made in Analyze phase, resources are allocated optimally, workstations are given optimal time to process specific function, and improvements are implemented.

5. Control Phase:
The quality management process is monitored on a regular basis, quality is plotted on a chart and process is controlled to the left of the desired target. When a process is allowed to run without continuous monitoring, (even after optimization) it loses quality with time and shifts to the right on the curve. To avoid this phenomenon (also known as 1.5 sigma shift), process is always monitored and continuously kept on the left of the desired target. This is the goal of six sigma implementation. Various input factors like number of resources used, number of year of education of human resources, number of years of experience of human resources, primary language of human resources can also be used in Regression Analysis to explore the relationships of these factors with the quality score of the database. Maintaining this Quality Score, a real time indicator for the quality of a safety database will be a Goal for Future Pharmacovigilance Systems.

Conclusion:
SQC can prevent deviation of any process from the desired quality. To apply SQC to data entry in pharmacovigilance, qualitative data from adverse event AER reports can be converted into meaningful quantitative data. Quantitative data can be analyzed to check the quality of data entered into a database. Applying SQC to data entry practice is essential to assure regulatory authorities about the accuracy of the data entry. Simple statistical tests can confirm the quality of data in the database and provide timely insight into quality of data entry function.

A few benefits of SQC
1. SQC can be used by a Contract Research Organization or the Client to monitor the work.

a. A client who outsources work to a data processing unit can ask an exact level of performance and use the quality review standard to monitor the quality of work.

b. Statistical analysis can show exactly which area of work may need additional training/ resources/ correction.

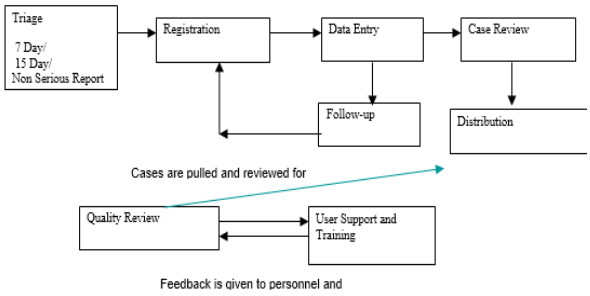
2. SQC helps to focus the efforts on exactly required amount of work and leads to best resource utilization and provides statistical support to any arguments made by the quality review group /department, which may want to add or change training modules.

3. Company is always prepared for an internal audit of quality or an inspection at any point of time. Company will have statistical assurance of quality of presented data available for any regulatory body inspection.

4. In particular, a continuous SQC quality management system will be helpful even for direct data entry at the clinical study sites. In a direct data entry system, data is entered into the database at the study site, which has its merit in saving the costs and time but one of the major concerns of direct data entry would be improper data entry.

Conflicts of Interest:
The authors report no conflicts of interest. The authors alone are responsible for content and writing of the article.

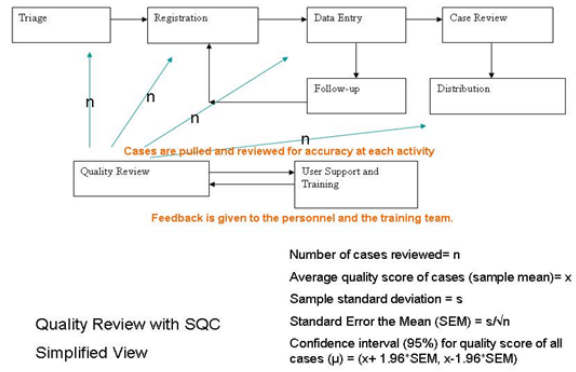
Figure 1:



AER Processing Workflow

AER (AER) is received (via phone/ internet/ direct report/ literature report) and assessed for its seriousness at Triage. AER report is registered in the database and forwarded for Data Entry. After careful Follow-ups and Medical Review AER is submitted to regulatory authorities individually or in an aggregate report. Quality review team functions by reviewing some of the AERs from the database and provides input to User support and Training team.

Figure 2:



Adding SQC, to quality review process, each function can be analyzed for its accuracy. The real difference in Quality Review with SQC is the statistical assurance provided by the methods in SQC. An exact number of AERs are reviewed so that the average quality of entire database can be predicted with more than 95 % confidence.

Figure: 3

Module/ Screen	Name of the Field	Points
AER Information/ Screen 1	Country	1
	Source	1
	Date of Report	2
	Clock Date	1
	Reporter	1
	AER ID	1
	Study ID	1
Demographic Information	Patient Initials	1
	Gender	1
	Age	1
	Date Of Birth	1
Medical History	Pre-existing Conditions	1
	Surgical History	1

	Medication History	1
Suspect Medications	Suspect Medication(s)	4
	Cosuspect Medications	4
	Dosage	1
	Route of Administration	1
	Indications	1
	Start Date	1
	Stop Date	1
Adverse Events	Adverse Event(s)	4
	Coded Correctly?	1
	Seriousness Assessed Correctly?	1
	Causal Relationship Assessment	1
	Start Date	1
	Dates of Hospitalization	1
	Resolved?	1
	Stop Date	1
Causality Assessment	Dechallenge	1
	Rechallenge	1
	Laboratory Tests	1
	Autopsy Results	1
	Causality comment	2
		1
Documentation	Follow-up Attempts Documented	1
	Audit Trail correct?	1
	All Relevant Data Entered?	2
	Total	50

References

1. Allen TT. Introduction to Engineering Statistics and Six Sigma: Statistical Quality Control and Design of Experiments and Systems. Springer Verlag; 2006.
2. Agency EM. Guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems. 20-Feb-2012 2012.
3. FDA. Good Pharmacovigilance Practices. 2005.
4. FDA. Guidance for Industry Oversight of Clinical Investigations —A Risk-Based Approach to Monitoring August 2013 2013.
5. Lindquist M. Data quality management in pharmacovigilance. Drug Safety. 2004;27(12):857-870.
6. Qual Manag Health Care. 2010 Jul-Sep;19(3):211-25. doi: 10.1097/QMH.0b013e3181eb140e. Assessing the evidence of Six Sigma and Lean in the health care industry. DelliFraine JL1, Langabeer JR 2nd, Nembhard IM.
7. Qual Manag Health Care. 2013 Jul-Sep;22(3):210-23. doi: 10.1097/QMH.0b013e31829a838e. The use of six sigma in health care management: are we using it to its full potential? DelliFraine JL1, Wang Z, McCaughey D, Langabeer JR 2nd, Erwin CO.