PhUSE 2016

Paper RG04

What auditors want

Cedric Marchand, Cytel Inc., Geneva, Switzerland
Angelo Tinazzi, Cytel Inc., Geneva, Switzerland

ABSTRACT

The aim of this presentation is to share some practical experiences on a number of audits we received at Cytel for our Biometrics activities with particular focus to Statistical Programming. We will make an overview of key items verified and requests made by the auditors.

INTRODUCTION

Ever since the finalization of the ICH GCP guideline in 1996, it was clear that the regulatory authorities would no longer accept that the investigator site was the only target for high-quality standards in a clinical trial and therefore the handling, transformation and analysis of clinical data is of equal importance.

All these processes require rigorous execution and GCP describes the need and importance of a clear "trail" for any clinical trial, moreover it described the importance of the audit of the study.

The role of the Quality Assurance (QA) in this process is to ensure, by independently auditing, that the clinical data presented and interpreted in the Clinical Study Report (CSR) reflects a true picture of what took place in the trial.

It must be remembered that QA auditing is not Quality Control (QC) and the responsibility for all trial activities related to data, must remain with the operational team. The QA group is responsible for taking 'snapshots' of the study at acritical times and places.

Good programming practice for analysis, reporting and data manipulations, addresses topics such as readability, portability, data integrity and efficiency, and very often these practices are restricted to SAS programming. However establishing such a practice is not enough and 'proof' that these practices together with other standard procedures (SOPs and guidance) are followed is what really matters to an auditor.

WHAT IS AN AUDIT

As per GCP "An audit is a Systematic and Independent examination of trial activities and documents to determine whether the evaluated trial activities were conducted, the 'clinical' data were recorded, analysed and accurately reported according to the protocol, sponsor SOPs, GCP, and the applicable regulatory requirement(s)".

We can classify audits into two main categories: internal vs external. While internal audits are usually conducted by the QA department of the company itself or by external consultants, external audits are audits performed by the sponsor (i.e. to vendors) or by regulatory agencies (in this case we talk about inspections).

External audits can be of two type, Pre-contractual audit i.e. vendor Qualification, and Routine Audit, aimed to verify an ongoing activity or activities that have been delivered / closed. Depending on the focus of the audit, the audit can be a "Database audit", an Independent verification of analysis results or an "Audit of Clinical Study Report", and furthermore a "Vendor qualification".

HOW AN AUDIT IS CONDUCTED

All aspects of an audit are covered by the above GCP definition.

All audits should be conducted according to a pre-defined schedule (audit plan) and the main scope should be recorded in the resulting audit report.

An audit plan should define how the audit will be conducted by listing key items that the auditor will review such as SOPs, the management and staff qualification, study files, IT services.

WHAT AUDITORS ARE LOOKING FOR

Auditors will look for "Documented Evidence" about study activities were carried out by qualified individuals, that established policies and procedures were followed, obligations have been fulfilled as stated in contract and they will verify the data integrity and validity by carefully reviewing study data (accuracy and accessibility) and confirming that they are reliable and trustworthy. There could be a finding for example if a specific process is not covered by any procedure, or if during the interview of the study personnel some violations/deviations are admitted while answering to the auditor questions. Furthermore evidence is sought in the study documentation (i.e. Trial Master File) or in any electronic study documents and in the way they are organised (i.e. if standard folder organization should be followed).

PREPARATION PERSPECTIVE AND GETTING PREPARED

Audits can occur at any time with short notice and therefore we have to accept the "inevitability" of audits and assume they will occur at most inopportune time. We need to make everything that is possible to be ready for the audit and therefore having a set of procedures governing audits, and include positions on potentially controversial issues. We need to train and designate audit coordinators to serve as hosts at each audit and analyse results of each audit to determine how program can be strengthened for future.

Furthermore, we need to get prepared by reviewing procedure for audit, by assigning an Audit Coordinator, by assembling organizational documents in one place, by procuring a conference room for the length of the audit and reserve "backroom" workspace for the entire audit

Documentation needs to be ready and available for the reviewer, such as an organization chart, employee training files including Job Descriptions and CVs, vendor list, SOPs, any documents specific to the project/trial object of the audit (i.e. work order, team list, trial documentation including Statistical Analysis Plan, reports, etc.).

Key staff might be interviewed to assess process and the auditor may ask the same question to different people in different ways trying to get conflicting answers; the staff need to be prepared, look professional by behaving in a professional and polite manner, possibly prepare a short presentation and never take observations, if any, personally. Typical questions are "What is your role for this study?", "What responsibilities does this role have?", "How do you know how to do your job?", "What happens if you need to deviate from a SOP?", "Where do you store your study related documents?", "How do you QC your work?".

An audit is a team effort and it is not a single responsibility neither of the project manager nor the audit coordinator. Audits require some preparatory work and we need to make sure that key personnel are made available and prepared for the audit, meaning knowing how to "behave" (i.e. assume a friendly, cooperative attitude, do not overdo it and avoid creating an adversary relationship, guess and don't lie) and review pertinent policies (i.e. programming SOPs),

OUTCOME OF AN AUDIT

At the end of the audit the auditor usually gives an overall summary of the outcome of the audit. This is in anticipation of what will be included in the audit report. The audit report will then address issues found during the audit and classify them as follows[1]:

- Critical: any condition, practice or process that adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable and will result in a failure of the audit (or submission if that's the outcome of an inspection from the regulatory agencies). Bad quality of the data and absence of source documents are examples of critical findings;
- Major: any condition, practice or process that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data. Depending on the deviation, major finding could also result in a failure of the audit. An inaccurate QC or validation documentation are examples of major findings;
- Minor: any condition, practice or process that would not be expected to adversely affect the right, safety or well-being of the subjects and/or the quality and integrity of data. Minor findings are usually not causing the audit to fail but if many minor findings are detected, the sum might be equal to a major finding with its consequences; Minors findings, if observed, will require improvement in the practices and practices (the auditor might suggest what and how to improve). An outdated SOP and incomplete training records are examples of minor findings.

Urgent issues and serious concerns are communicated in an expedited manner.

In response to the audit report a Corrective Actions and Preventive Actions (CAPA) and its calendar needs to be implemented by the audited entity. The CAPA should contain the action(s) that is/are intended to take (or has already taken) to address the findings and their timeline; it is important that the intended actions are feasible. *Corrective Actions* are issues requiring immediate correction, while *Preventive Actions* are typically changes in SOPs to prevent an observation to occur again or potential issues to occur in the future.

Furthermore, relevant documentation needs to be provided as evidence that the corrective and preventive actions were executed and that an effectiveness check shows the preventive action is successful.

AUDIT IN STATISTICAL PROGRAMMING DEPARTMENT

A key GCP requirement states that ***any transformation of data must be documented and methods must be validated***.

Therefore a key objective of the audit is how programs are validated and if procedures are available. These procedures should specify validation approaches/strategies (i.e. review source code, double programming, etc.). Moreover it should include how programming logs are checked and errors, warnings and suspicious notes are handled.

Auditors will check that procedural documents are available and adequate for all statistical programming related activities; for example the programming and validation of SDTM/ADaM/TLFs and any other relevant documentation such as the Reviewer Guide and the QC and Validation process and its documentation.

[1] "Classification and analysis of the GCP inspection findings of GCP inspections conducted at the request of the CHMP", INS/GCP/46309/2012, December 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500178525.pdf

All activities need to be documented (if it's not documented it didn't happen!); this includes proper documentation and "justification" of any deviations of the standard processes i.e. Deviation recorded with a Note to File in the project documentation to explain what happened, why and actions taken, if applicable.

With regards to 'transformation', all derivations need to be properly and accurately documented. This means you need to describe the algorithm used step by step and not simply copying for example the SAS code from the program you have created to make the derivation. Programming guidelines and other standard conventions are expected. These guidelines defining Good Programming Practice (for SAS or other programming language) will be assessed and SAS programs might be also audited. For example, the header of a SAS program might be the object of an observation if the author and the objective is not clearly stated.

If macro libraries are available and used for programming, evidence of their validation needs to be provided and documentation of their use needs also to be available.

The auditor will also ask and verify procedures for folders and file organization and how we make sure these are accessed by only authorised personnel, such as the programmers assigned to the ask. Furthermore, they may ask how the status of a SAS program is maintained and how production, or primary area, is kept "independent" from the QC area.

THE CYTEL EXPERIENCE

Over the last 5 years Cytel underwent several sponsor audits, either for vendor selection or for auditing the activities of a running project.

We have been indirectly involved with some agency inspections received by the sponsor of some of the studies we have analysed, and the type of items requested and reviewed by the auditors were very similar to those requested during sponsor audits.

Cytel, on average, hosts 10 sponsor audits per year, either for project specific or vendor qualification.

TRIAL PROJECT MANAGEMENT

The entire programming task is supported by appropriate project management documentation. This includes, but it is not limited to, project milestones, a team list that includes start and end dates for each member, which SOPs (Cytel or sponsor) are followed, corresponding training log, communication plan including escalation and issues resolution, and an ongoing list of open actions and issues. Minutes of meetings where important decisions have been taken were also sought by the auditors.

PROGRAMMING PROJECT MANAGEMENT AND DOCUMENTATION

The focus of auditors is to ensure that programming function staff adhered to the defined processes. This process adherence is often measured in terms of maintenance of process documentation and timely actions taken by programming staff over the course of trial.

Review of programming documentation is an aspect where auditors focus. Auditors not only check that the Cytel SOPs have been correctly applied during the conduct of the study but they may also spot inconsistencies across different document i.e. protocol vs SAP date inconsistency.

Auditors usually will not question the validation methods used provided that it follows standard approaches defined in any available SOPs. Auditors usually seek a validation plan where all planned outputs (SDTM Datasets, ADaM Dataset, TLFs) are listed and the level of QC to be applied together with assigned programmer is reported.

Cytel has this activity covered in its standard process together with a standard template for program tracking (the 'Programming Spreadsheet') and also the Programming Master File, a document where additional details such as input requirements and their location (i.e. study protocol, SAP, aCRF, etc.) are listed. The Programming Master File serves also as a place to document the main deviations or any particular detail related to programming that could be not documented elsewhere, such as reference to other external documents where more details are provided like the previously mentioned step by step complex algorithm. This document also lists all the programming and biostatistics personnel involved in the task and it formally 'certifies' that the programming personnel received the appropriate information specific to the trial and task required.

Issue tracking, regardless if it is done with an excel file or with a more sophisticated systems such as JIRA, should be available and accurately completed. The programming team should ensure that all open issues at the end of the programming activity have been solved. If not, an appropriate justification needs to be provided. Any open issue or any closed issue with unclear solution will constitute a major finding if detected by the auditor.

INDEPENDENCY OF PRODUCTION AND QC PROGRAMMING

Programming teams should use a standard folder structure. For example, it could be structured as follows:

- projects organized by sponsor, compound/indication, study and then task;
- within the task level, production and QC have separate directories with the same folder structure for all types of statistical outputs (i.e. SDTM datasets, ADAM datasets, Tables, Figures, Listings, etc.);
- access to each project is regulated through a documented IT access control.

QC programmers must investigate on reasons for discrepancies, provide and discuss with the primary programmer possible solution to solve any discrepancies found.

Auditors also verified and sought for proof that biostatisticians were always in the loop when required to clarify any doubt resulting from the QC process and that formal review and approval of each delivered item is documented.

The team managers should develop training material for emphasizing and discussing with both statistical programmers and biostatisticians the key aspects for “Independency in the QC process of programming outputs”. This includes the entire programming development life-cycle, from initial assessment of analysis requirements to the final production, validation and revision. This includes:

- Reviewing key points of all applicable SOPs;
- Clarifying differences between QC and Validation of Programs;
- Listing all possible input specifications to be used;
- Outputs specifications and their review;
- When to use and when not to use standard tools i.e. most of the standard tools can be only used by the primary programmer only;
- Recommended methods of QC for each type of output;
- How to make an independent QC/Review and how to handle discrepancies and their resolution.

The dos and don’ts were also discussed:

The dos:

- Question the relevance of specifications;
- Carefully review the output you produce (visually);
- Review your own code to ensure clarity;
- Add comments in your own code for traceability;
- Check all your log files for notes, errors and warnings;
- In case of discrepancy, the QC programmer must look for an explanation before contacting the primary programmer;
- Inform the biostatistician of all recommended decisions related to derivation rules.

The don’ts:

- Don’t copy code from the primary programmer’s program, or vice-versa;
- Don’t “try to match” with the primary programmer’s output: the objective is to find errors;
- Don’t expect that QC programmer will correct your code;
- Don’t assume that the specifications are entirely correct.

Furthermore, to make production and QC programming independent as much possible, it is preferable if programmers could only make use of specifications provided in the SAP and any Output Shells document (if available), together with other ‘ancillary’ or input document such as the study protocol and the annotated CRF. For example, for programming an ADaM dataset usually the lead programmer makes an assessment of required ADaM datasets and their structure. This assessment includes variables to be created and their attributes and any detail on specific ADaM structure such as including derived records; however, at this stage, details on how variables should be programmed are not provided (for example which source datasets/variables need to be used, the algorithm to be used and so on). This is for example the approach we follow at Cytel and we believe that with such approach we can reach the maximum level of independence between the lead and QC programmers. In that the programmer will need to “think more” and not simply try to apply specifications. In other words we want to avoid the situation where the QC programmer simply tries to repeat and match ‘at any cost’ that which the primary programmer has produced.

The auditors were ‘convinced’ that the approach applied by Cytel is appropriate, especially from the ‘scientific’ point of view.

EMPLOYEE AND TRAINING FILE AND PROOF OF THEIR COMPETENCIES

As per GCP section 2.8 e*ach individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)*. To be able to prove this, employee have an up-to-date curriculum vitae as well as other relevant documentation showing evidence of any training received on relevant SOPs and any other documentation showing regular update on relevant topic such as new regulations, programming, etc. These items together with the review of the Job Description are the first aspect reviewed by the auditor and very often can be the object of a finding.

To emphasize and document that training/experience can be acquired “on the job”, Cytel developed a function-specific training checklist to document that managers have evaluated the ability of their team members to perform certain activities. These function-specific checklists are completed for each team member and reviewed and updated annually during objective setting and performance review season and reflected in the employee’s training record. This is also applicable to contractors and needs to be activated as soon as possible when a new employee joins the company.

The appendix contains an example of a competencies checklist specific for the programming role. The level of competency for each identified item is assessed and graded by the manager together with the employee. Also, a development plan is identified for each item where this is required.

INSPECTION READINESS

Every employee needs to be aware and stressed on the fact that inspection by a health or regularity agency could occur at any time, thus documentation of programming is not an ‘ending’ process and documentation should be prepared and updated during the course of the trial/task. Cytel runs regular training to continuously warn employees about the need to have documents and data prepared at all times and how this could affect the quality review during

an inspection. During this training Cytel employees are also prepared to receive an inspection so that if exposed to an inspection the employee knows what to expect, how to prepare for it and most importantly, how to behave.

REGULAR INTERNAL AUDIT

Inspections/audit readiness can be also improved by the QA department running regular internal quality audits. At Cytel during the last two years we increased the amount of internal quality audits and their frequency. Our goal is to perform an internal quality audit of all high risk projects and prioritise internal quality audits of medium and low risk projects.

Internal quality audits are not only a way of checking that we have everything needed and that activities are performed as per Cytel process/SOPs, but it is also a good opportunity to train and re-train people on the process with real examples.

CONCLUSION

Auditors want to verify that access to the project files and working documents are restricted to the project team (provide evidence this is true at all times) and that the team consists of appropriately experienced and properly trained individuals. Auditors are also looking for consistency in documentation, clearly specifying when QC programming is completed and peer or statistical reviews are done (Who, when, and by what method). Other concerns from auditors include the validation status of all software and programs being run for a study, and the qualification of all third party vendors providing a service to the project (i.e. EDC vendors, independent offsite datacentres etc.).

Audits, especially when performed internally with regular frequency, are a useful tool to constantly assess and qualify the performance of the processes defined within a company and can lead to improving and building better practices and procedures.

All team members, including statistical programmers, need to be aware (not worried) that audits can happen at any time and therefore being responsible for their deliverables and how they could affect the success of the trial if not properly handled and documented according to defined procedures (have documents and data prepared at all times!).

REFERENCES

[1] Vincent J. Amoruccio, «Could Have, Would Have, Should Have! Adopting Good Programming Standards, Not Practices, to Survive An Audit» *PharmaSUG*, 2012.

[2] Woo, Wayne, «Building a Controlled Statistical Programming Environment» *WUSS*, 2013.

[3] «Quality Assurance: Best Practices in Clinical SAS® Programming» *NESUG*, 2012.

[4] Uwe Haag, «Audits in Biostatistics & Programming Background, Conduct & Common Findings» *PhUSE SDE Germany*, 2016.

[5] ICH, «Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidances», 1996.

[6] PhUSE WG, «Good Programming Practice», http://www.phusewiki.org/wiki/index.php?title=Good_Programming_Practice, 2015

ACKNOWLEDGMENTS

We would like to thank Sebastien Gerin, Meredith Alm and Dean Shults for their help in reviewing, correcting and improving the paper.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Your comments and questions are valued and encouraged. Contact the author at:
Cedric Marchand / Angelo Tinazzi
Cytel Inc.
Route de Prè-Bois 20
1215 Geneva – Switzerland
Email: cedric.marchand@cytel.com / angelo.tinazzi@cytel.com
Web: www.cytel.com

APPENDIX

PROGRAMMING COMPETENCIES CHECKLIST

Programming Competencies Checklist

DOCUMENT REVIEW HISTORY

Version	Section Changed	Change Made	Date
New	n/a	Initial issuance of document	1-Apr-2016

This functional checklist is meant to document the assessment of the skills required to perform the duties related to the specific function.

The line manager is responsible for filling this checklist for each employee in his/her team in the 3 weeks after start of employment and then once a year.

This assessment can be used as a basis for the technical development plan of each employee. It can be used to evaluate whether an employee can be given certain technical tasks and the level of oversight and mentoring needed for the good performance of a given task.

Instructions:

- In the attached matrix, tick the columns reflecting the past training or past experience of the employee.
- Concerning the development plan, only tick the relevant competencies on which the employee should focus in the next 12 months.
- Sign and file the checklist in the training log of the employee.

Date of Assessment:		
Employee Name:	Employee signature	Date (DD-MMM-YYYY)
Manager Name	Manager signature	Date (DD-MMM-YYYY)

	Never Exposed	Occasional Use	Frequent Use	Expert	Development Plan for the next 12 months
SAS Programming					
Essential Data Manipulation Technique: - Creation of SAS variables - Sub-set of data - Combination of datasets (merge, set...) - Simple SAS macro variable - ODS Statement - …	☐	☐	☐	☐	☐
Advanced Data Manipulation Technique - Control SAS data set input and output, - SQL technique, - Summarize, read, and write different types of data, - Perform DO loop and SAS array processing, - Advanced SAS macro programs - Customize Proc report, advanced ODS statement technique …	☐	☐	☐	☐	☐
Tables Reporting	☐	☐	☐	☐	☐
Listing Reporting	☐	☐	☐	☐	☐
Figures Production	☐	☐	☐	☐	☐
CDISC					
SDTM	☐	☐	☐	☐	☐
ADaM	☐	☐	☐	☐	☐
Define.xml/pdf and Reviewer Guide	☐	☐	☐	☐	☐
Open CDISC Report	☐	☐	☐	☐	☐

		Never Exposed	Occasional Use	Frequent Use	Expert	Development Plan for the next 12 months
Statistics						
	Descriptive Statistics - Categorical - counts and frequencies - Continuous - descriptive statistics (median, mean, SD, quartiles…) - Confidence Interval	☐	☐	☐	☐	☐
	Inferential Statistics - Standard statistic test (chi-2, Student, t-test, Fisher, Kolmogorov-Smirnov…) - Correlation - Simple Regression Model	☐	☐	☐	☐	☐
	Complex Inferential Statistics: - Survival Anaylsis - Cox Model - ANCOVA - Mixed Model - Complex Regression Model	☐	☐	☐	☐	☐
Clinical Trial - Regulatory Document						
	ICH E3, E9	☐	☐	☐	☐	☐
	Chapter 21 of the US Code of Federal Regulation - Part 11	☐	☐	☐	☐	☐
	FDA PORTABLE DOCUMENT FORMAT (PDF) SPECIFICATIONS	☐	☐	☐	☐	☐
	FDA STUDY DATA TECHNICAL CONFORMANCE GUIDE	☐	☐	☐	☐	☐
	eCTD - TECHNICAL CONFORMANCE GUIDE	☐	☐	☐	☐	☐
Others						
	PK/PD Data	☐	☐	☐	☐	☐
	NONMEM Datasets	☐	☐	☐	☐	☐
	e-sub services (clinical.trial.gov…)	☐	☐	☐	☐	☐
	Project Management (lead programmer role, manage budget, Interaction with DM and Biostat)	☐	☐	☐	☐	☐
Additional compentencies and comments						