PharmaSUG 2022 - Paper SI-164

Quality Gates: An Overview from Clinical SAS® Programming Perspective

Nagadip Rao and Pavan Jupelli, Eliassen Group

ABSTRACT

Clinical trials are conducted in pursuit to answer a clinical research question, by generating relevant data, and analyzing it in order to validate an initial hypothesis. Data quality, thorough data analysis, and reporting, plays a critical role in determining our confidence in clinical trial outcomes.

An endower like clinical trial, which involves complex multi-disciplinary processes, with partner entities spanning across the globe, working together under stringent regulations to generate relevant data and perform data analysis, assuring quality is not trivial task. In an attempt to improve clinical trial data and analysis quality there are many techniques utilized over the years, one such technique which is successfully utilized across multiple industries is quality gate (QG's) approach.

QG's are formal quality checklist evaluations done on intermediate milestone deliverables and related documentation at predetermined milestone checkpoints against pre-defined criteria's in a clinical study process flow. The purpose of QG is to get an intermediate assessment of quality and reduce/eliminate any potential risks by facilitating early detection, discussion and resolution of identified issues. Clinical SAS® programming plays a vital role in execution of clinical trial projects. The quality of programming deliverables have considerable impact on overall quality of clinical trial results, and hence are assessed during QG's, in case, if QG's are planned for a given clinical trial.

This paper provides an overview of QG's in clinical trial projects from a clinical trial programming perspective and discusses key practical aspects and benefits of incorporation of QG's into overall programming processes.

INTRODUCTION

Clinical trials are complex projects with multiple departments/partners and stake holders across the globe working to generate and analyze data in order to answer clinical research question. Credibility of clinical research outcome depends primarily on quality of data generated and its analysis. In a complex multidisciplinary project like clinical trial, it is essential to assess quality throughout project lifecycle so that any quality issues can be fixed at the source. One of the method data quality can be improved is by using Quality gate (QG) approach. Quality gates approach has been successfully applied across various industries both manufacturing and service based for improving overall quality of product or services. QG's facilitate early detection, discussion and resolution of issues and problems through a collaborative effort to improve overall quality of the data, analysis and hence clinical trial outcome. A clinical trial project utilizing quality gates ensures that needs of downstream activities are meet through a formal, disciplined checklist evaluation at project milestones. A good example would be going through QG ensures that programming deliverables meet needs of medical writers. QG's also provide better visibility of project progression to stakeholders though out project lifecycle.

This paper provides an overview of application of QG methodology in clinical trials projects with primary focus on its impact on clinical SAS® programming activities and deliverables.

INTRODUCTION TO QUALITY GATES

"Quality Gate is a checkpoint consisting of a set of predesigned quality criteria that a project must meet in order to proceed from one stage of its life cycle to the next. Quality Gates thus serve as amendments to milestones and deliverables which meet predefined quality benchmarks" < Ref Schneider(2004)>.

The concept of QG was initially introduced in 1986 as a part of Quality Management System in European Union in order to optimize cost, functionality and quality of a product during product development processes with an intention of improving overall quality in automobile industry. Over the

years utilization of QG methodology spread across multiple industries in both manufacturing and service. Currently QG approach is widely used in information technology as part of SDLC (Software development life cycle) in an attempt to increase software quality.

In general, a project is broken down into multiple sequential phases or milestones. Then, a formal quality checkpoint or a quality gate is placed between end of one phase and beginning of next phase. At each QG, project execution up to end of current milestone is assessed using pre-defined checklist criteria's for 'Fit for Purpose' till just completed milestone in the project. A decision is made based on this QG assessment if project can proceed to next phase or certain issues need to be resolved before start of next phase. In other words, a project after completion of a milestone has to pass through 'Gate' before starting next phase towards achieving subsequent milestone. Generally, QG's are located before project milestones that are dependent on the outcome of a previous milestone, particularly where potential trouble spots need to be addressed and resolved in order to prevent it from being carried into next milestone and so on.

QUALITY GATES IN CLINICAL TRIALS

A typical clinical trial project activities can be broadly separated into three different stages based on timing of FSLV (first subject first visit) and LSLV (Last subject last visit) as illustrated in Figure 1. Activities associated with three stages are described in the following.

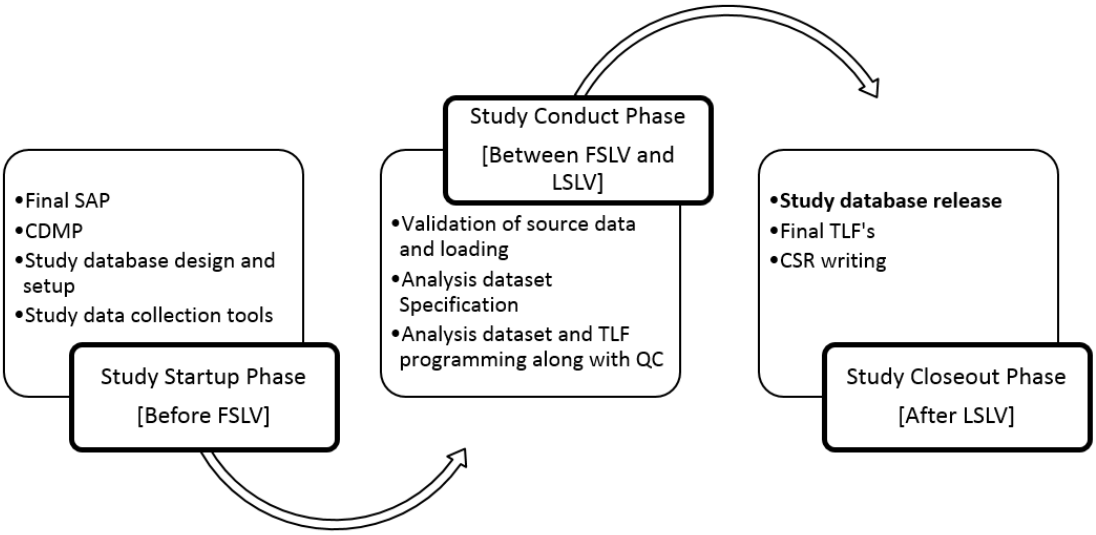

Figure 1: Clinical trial activities by overall subject visits schedule

Setup or Startup Stage: Clinical study setup stage refers to activities undertaken before first subject first visit occurs (FSFV). Some of these activities include finalization of study protocol and SAP (statistical analysis plan). Database related activities like design and set up of database along with finalization of data collection tools and data management plan etc...

Conduct Stage: Clinical study conduct stage occurs between FSFV and LSLV. During this stage source data is cleaned, loaded and periodically refreshed. Clinical SAS® programming specs are finalized and programs are developed for analysis datasets creation and reporting along with testing them. Test run of TLF's (tables, listings and figures) takes places and any changes requested by team are resolved. It is expected that by the end of conduct stage programs are ready for post database release final run.

Closeout Stage: Clinical study closeout stage starts after LSLV and includes clinical study closing activities like un-blinding (if needed) and database release, final TLF run and Clinical Study Report (CSR) writing by medical writing team.

In a clinical study project, successful completion of above mentioned three stages of activities require achievement of five project milestones. A quality gate marks end of a milestone in a project after which project needs to go though 'gate' before it can proceed towards next milestone. Each QG 'Pass' provides assurance that all the appropriate work required are completed and reviewed as per standard operating procedures (SOP) and project can proceed towards next milestone. QG at each milestone needs to have specific focus, gate entry and exit criteria's. In clinical trial projects, first QG focus on database activation related activities, second on activities related to data quality and its analysis, reporting operational planning, third on data quality and programming code readiness, forth on programming final deliverables and fifth focusing on comprehensive clinical study report and other submission activities. Placement of QG's in a clinical study are shown in below figure 2.

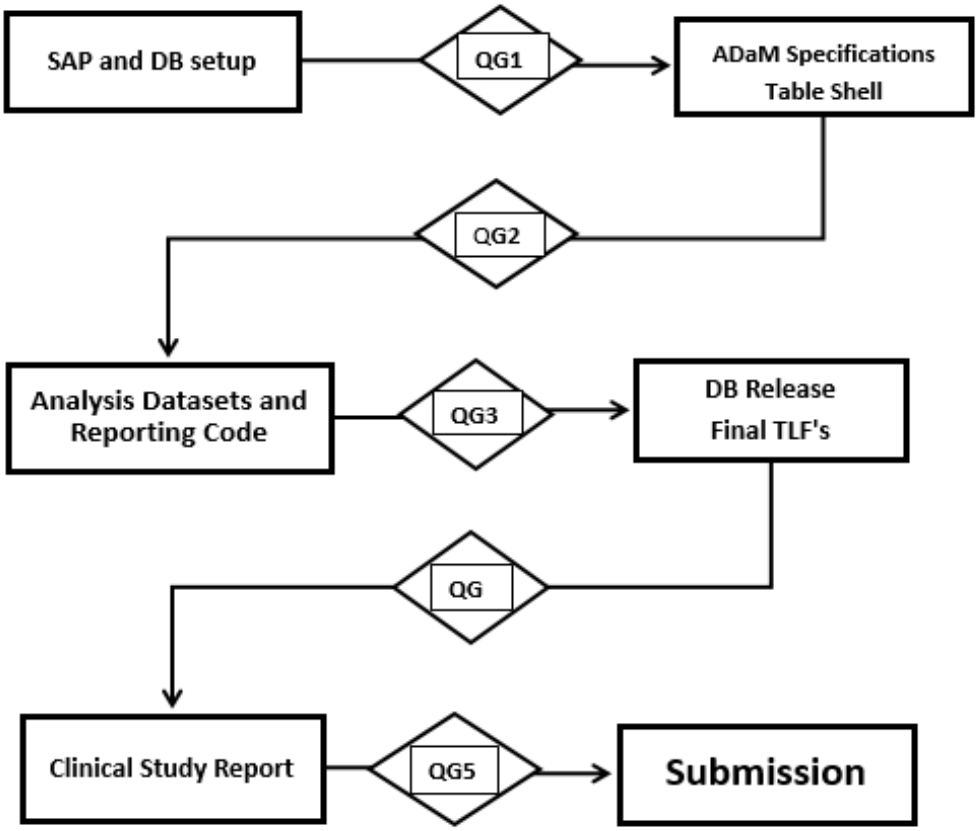

Figure 2: Quality Gate Placement in Clinical Study

A brief description of all five quality gates from Clinical SAS® programming's perspective is provided in the following.

Quality Gate 1 (QG1): Purpose of QG1 is to ensure clinical study processes is at a stage where database can be activated, this QG is placed before FSLV and database activation. Clinical study

protocol, SAP are complete and are correctly translated into data capture specification, in other words correct data is going to be collected and is consistent with requirements presented in Clinical study protocol and SAP. Clinical study has to pass QG1 before the database is accessible to the investigational sites and also trial subjects. Clinical SAS® programming department is generally not involved in QG1 as our role at this point in a study is just limited to review of SAP, CRF etc.
A general list documents completed and approved or completed up to FSFV time point provided in the following are to be submitted for QG1. These documents are submitted and reviewed as part of QG1 before a clinical study passes through QG1.

1. Final clinical trial Protocol
2. Statistical Analysis Plan
3. CRF and Annotated CRF
4. Data management and data integrity documentations
5. Data review specifications along with proposed edit checks

Quality Gate 2 (QG2): QG2 occurs just after clinical trial database is activated and before actual programming commencement. QG2 ensures final SAP is translated correctly into analysis dataset and programming specifications and approved by study statistician. List of Tables (LoT) and table shells are approved and final, SDTM mapping specifications are complete and randomization code administrator generates blinded code. The main purpose of QG2 is to ensure that Clinical SAS® programmers have correct instructions and can start writing codes that is in alignment with clinical study requirement. SAS® programming department's involvement here is to make appropriate resourcing is in place to start programming and LoT is aligned with SAP. Programming team needs to work with study statistician to develop analysis dataset specifications and programming lead needs to make sure table shells facilitate programming efficiency, utilizing pre-existing macros as much as possible.

QG2 requires submission of all the updated documents which were part of QG1 along with following additional documents for review

1. Final list of tables (LoT)
2. Table shells
3. Analysis dataset specifications approved by statistician
4. Programmer and validation programmer assignment spreadsheet
5. QC template describing proposed QC method for each of TLF and analysis datasets and template to capture QC comments and resolutions for each TLF and analysis dataset
6. Specification related to SDTM mapping if applicable

In a nutshell, purpose of QG2 is to check if programmers know what/how to program correctly from SAP.

Quality Gate 3 (QG3): QG3 occurs after all the scheduled test run, review of TLF's is completed but before database release or in other words after conclusion of study conduct activities. QG3's evaluates if study database is complete and programming code is validated and ready for post database release final run. QG3 needs to be successfully cleared before commencement of unbinding activities (if needed) and database release. Programming team has critical role in passage of QG3 as focus is on correct translation of SAP into programming codes along with validation and resolution of comments from TLF test runs (Blinded Data Reviews). It is expected that before a clinical study is submitted for QG3, LSLV has occurred and all the data is reconciled in database and complete. All data related quarries are resolved and programming code is validated and final along with associated documentation. Programming specifications are final and consistent with final programming codes and all the test run (BDR) comments are discussed, resolved and documented. Protocol deviation (PD) listing in draft form is generated.

QG3 requires submission of all the updated version documents that were part of QG2 along with following general list of additional documents for review

1. Updated LoT along with revision history
2. TLF's (Blinded if applicable)
3. Programming QC documentation
4. Documentation of test run (BDRs) conduct along with comments and resolution
5. Updated programming documentations like analysis dataset specifications with applicable amendments approved by study statistician
6. Data review and issue resolution documentation
7. Draft PD listing along with deviation criteria
8. Patient evaluability listings

Quality Gate 4 (QG4): Clinical study deliverables has to pass QG4 after DB release before final TLF's can be officially incorporated into CSR (clinical study report) or safety reviews. Primary focus of QG4 is final programming deliverables and related activities. It is expected that by the time deliverables are submitted for QG4, DB is unblinded and released as per SOP guidelines. Randomization processes is appropriately followed and unblinded treatment codes are incorporated into final TLF's. All TLF's are run on final unblinded data and validated along with requested changes by study team are addressed. Programming and validation documentations are final and complete QC sign-off are complete. Clinician and statistician has approved final TLF's. Final PD listing is complete.

QG4 requires submission of all the updated version documents that were part of QG3 along with following additional documents for review.

1. Final LoT
2. Final TLF bundle
3. Final programming QC documentation along with signatures
4. Patient Profiles
5. Documentation of final programming specifications
6. Final QC documentation along with sign-off's
7. Randomization approval document from statistician if needed
8. Final TLF approval sign-off's from statistician and clinician
9. Final protocol deviation listing along with deviation criteria

Quality Gate 5 (QG5): QG5 is the final QG in a clinical study process and primarily deals with clinical study reporting activities. Clinical study deliverables pass through QG5 after the CSR has been reviewed and agreed with the study team and, updated following a documented quality checks. At this stage in clinical study, involvement of programming team's is nonexistent or minimal as these activities are downstream from finalization of programming deliverables. QG5 evaluates if final CSR accurately reports clinical study objectives, results and conclusion. QA audit readiness is also checked.

QG5 requires submission of all the updated version documents that were part of QG4 along with following additional documents for review

1. Safety narrative plan and it's QC documentation
2. Important PD and it's QC documentation
3. Final CSR along with synopsis
4. Documentation of knowledge transfer discussions
5. Institutional Review Boards (IRBs)/Independent Ethics committees (IEC) checklists
6. QA audit readiness related documentation

Difference between Quality Checks (QC's) and Quality Gate (QG's)

All Clinical SAS® Programmers are very familiar with QC as it is integral part of our job. Table in the following provides difference between QC and QG.

Table 1: QC vs QG

	QC	QG
Purpose	The purpose of a QC is to ensure analysis datasets, and TLF's are compliant with the specification(s), numerically accurate and descriptions (title and footnote) corresponds to information presented in the clinical reports	QG's are predefined milestone checkpoints where synchronization of processes are checked to make sure collective set of deliverables are 'fit for purpose' till that point
Scope	Scope of QC is within each function e.g., Programming does QC of TLF's or analysis datasets by double programming and Data management by edit checks.	QG's are an attempt to look into multiple functions at a given milestone. E.g., all programming, data management and statistics deliverables are cross checked for completeness and synchronization.
Method	Method of QC varies by function, we in programming do double programming, peer review etc.	Independent checklist assessment done at predefined milestones. Completeness of corresponding processes across multiple functionalities are assessed independently. Documents are crosschecked. E.g., TLF's against LoT against Table shells.
Timing and Personals	QC is done in parallel or just after a deliverable item like table is programmed. QC personals are required to have same skills and work with same requirements as main programmer	QG is performed after completion of a study milestone before next milestone gets a go-ahead. QG review is done by statistician, clinician and operational SME.
Nature	QC is more in-depth and rigorous assessment of Analysis dataset and TLF's. Purpose of QC is to assess particular TLF or analysis dataset for correctness and compliance with intention of it's specification independently.	QG is a relatively quick assessment in checklist format. Purpose of QG is to get an overall assessment of how project is proceeding

QUALITY GATES IMPLEMENTATION

QUALITY GATE CONDUCT

Quality gates are relatively quick predefined checklist evaluations to assess if set of related deliverables are fit for purpose, in alignment with one another and have appropriate documentation. Evaluation is done by team of independent Subject Matter Experts (SME's) with clearly defined roles and responsibilities. Decision to incorporate QG evaluation needs to be taken at the time of study activities planning.

There are five steps in conduct of QG as shown in the figure 3 and described in the following.

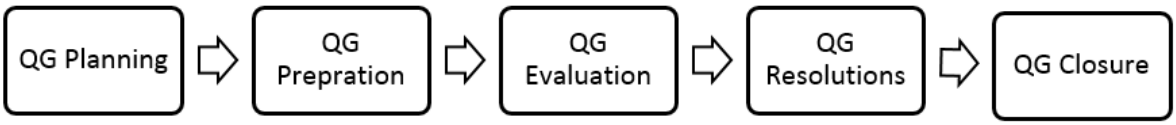

Figure 3: QG conduct 5 steps

1. **QG Planning:** Planning for incorporation of QG reviews is generally done during study activities planning stage. Planning includes verification of QG timeline from study operational team leads including programming lead. Roles and responsibilities are defined in each operational teams on designated primary point of contact for QG related activities like making sure correct documents are posted etc. Project management incorporates QG activities in timeline planning.

2. **QG Preparation:** QG perpetration refers to activities that occurs before a clinical study enters in to QG evaluation. These activities involves QG facilitator requesting relevant departments involved in current study milestone to submit required documents, and once all the required documents are submitted he/she schedules official QG review meeting. QG evaluators are required to review submitted key documents and meet with different operational team representatives, who provide an overview of submitted documents.

3. **QG evaluation:** QG evaluation consists of formal review of submitted documents and deliverables by SME reviewers, details of which are provided in the following. At the end of QG evaluation reviewer communicate overall Pass/Fail response to facilitator who consolidates reviews and provides feedback to operational teams and stakeholders.

4. **QG Resolution:** If a clinical study fails the QG, result from review along with identified issues that need resolution is communicated with appropriate operational team(s) representative. It is responsibility of operations teams to resolve identified issues and re-submit it for the same QG review so study can pass QG.

5. **QG Closure:** If study clears QG because reviewers provide overall ‘Pass’ result then QG facilitator ensures documentations related to QG review and identified issue resolution is complete and closes QG. Clinical study can proceed towards next project milestone.

QUALITY GATE EVALUATION

A QG evaluation team compromises of QG facilitator who is point of contact and also responsible for smooth and efficient conduct of these targeted reviews. Reviewers, whose number depends on size and complexity of clinical study undergoing QG, coordinate with QG facilitator. A clinical study passing through QG goes through three different types of reviews, reviewers who are called ‘Gatekeepers’ in quality (aka SME’s) who are trained in QG process from relevant background. Three different types of QG reviews are described in the following and illustrated in Figure 4.

A QG review consists of evaluation of a clinical study documentation and deliverables for appropriateness and completeness up to the current milestone from statistical, clinical and operational perspective. A brief description of each of these are in the following

1. Statistical QG review- This review consists of checklist evaluation by statistician, who assesses submitted deliverables and associated documentations, if they aligned with statistical purpose of the study and correct processes are followed as per relevant SOP. A statistical review for

example in QG4 (Final TLF) checks if TLF's support the study's statistical objectives and align with specifications

2. Clinical QG review- Clinical review consists of checklist evaluation by QG Clinician from clinical perspective for alignment of study processes followed and deliverables up to current milestone for fitness of purpose. A clinical review for example, in QG4 checks for clarity of safety conclusion and if it is understandable by independent reviewer.

3. Operational review- Operational review involves reviewers from multiple backgrounds including DM, Pharmacological, programming etc. evaluating documents and deliverables up to completed milestone. E.g., from DM perspective it is checked if CRF is consistent with Protocol and SAP and schedule of activities are appropriately captured. Data points are available for correct visits and time points. Correct versions of questioners are used as defined in protocol etc. Data standards and CRF are consistent. Focus of operational review is to assess quality deliverables and to make sure SOP is followed. Selected QG checklist criteria's used in programming operational review are described in the following.

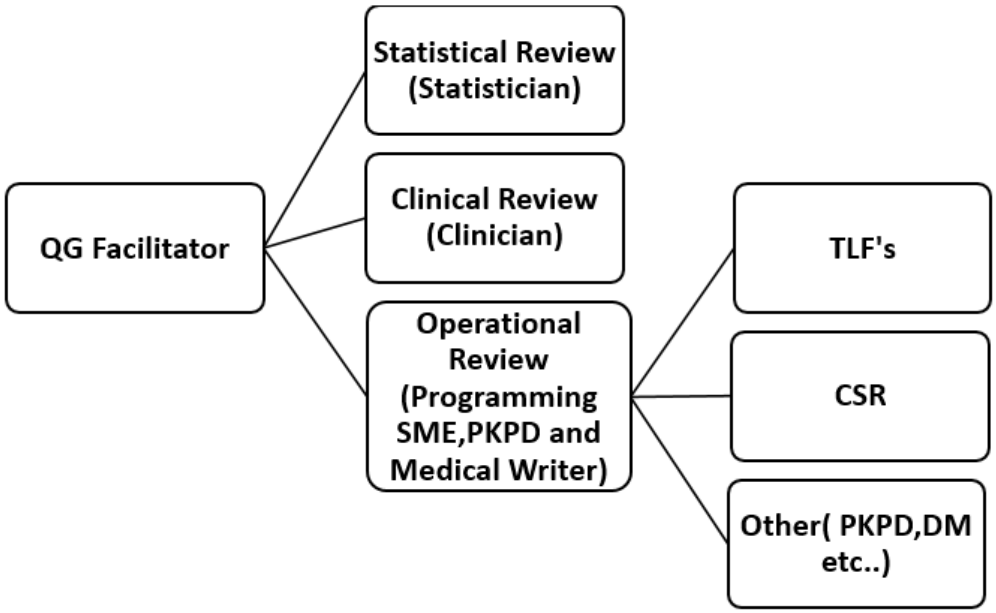

Figure 4: QG Review and Reviewers

A description of some of the QG checklist review items in programming operational review are described in the following.

QG2:

1. List of Tables (LoT) is completely satisfies analysis reporting requirement of the study and consistent with SAP and approved by statistician and clinician
2. Table numbering is compliant with ICH guidelines
3. Table shells are consistent with standard reporting macro template or marked for nonstandard programming
4. Analysis dataset specifications are complete, satisfies clinical study analysis reporting requirements and approved by study statistician

QG3:

1. Test run (or BDR) review of TLF's was conducted and issues have been discussed, documented and resolved.
2. All TLF's are generated as per LoT and any revision of LoT or TLF is clearly documented
3. Independent QC of TLF's and analysis datasets are complete, QC comments and resolutions are documented on standard template
4. Execution timestamps of analysis datasets, TLF's and QC program are consistent
5. Amendments to analysis dataset specifications are approved by study statistician

QG4:

1. All TLF's are produced from final LoT
2. Titles and footnotes are accurate along with source data reference date
3. Discontinuation due to adverse events are consistent across tables and any disconnect is documented
4. Treatment code is accurate and statistician approved it's application
5. Patient profiles are generated as per specifications

QG Feedback and Resolution

QG's are pre-specified checklist criteria evaluations, reviewer evaluate submitted documents and deliverables against each checklist criteria and provide response by selecting appropriate response (that 'confirms', 'does not confirm', 'Not Applicable' or 'Not Assessed'). It is to be noted here that checklist criteria's are always same irrespective of study design or study phase. Any checklist item that does not get satisfactory evaluation or 'Confirm' response mandates explanation by reviewer. An overall assessment in the form of 'Pass', 'Fail' is provided by each of the QG reviewer separately to QG facilitator.

QG Facilitator documents and provides stakeholders and operational teams, a formal document which includes checklists used for assessment and final outcome of QG. An overall QG 'Pass' means all required documents are present and each of the checklist criteria received 'confirm' response from reviewers. If a study failed QG, formal review documentation includes summarization of reason for QG failure. QG failure is due to one of the following reasons

1. Missing or incorrect/incomplete required documentation or provided documentation that are inconsistent with each other or does not match project deliverables cause QG failure. E.g., Analysis dataset specifications inconsistent with SAP or actual analysis performed.

2. 'Does not confirm' assessment by QG evaluators for any of the checklist criteria due to identified issues in clinical study processes or related documentation. E.g., mismatch between date of programming and validation in QC documentation.

It is responsibility of operational teams to come up with remediation in an agreed upon timeline so that QG can be re-assessed against same set of criteria's. Number of attempts a clinical study took to pass QG is formally documented.

Programming Related QG failures

Clinical SAS® programming activities have a major impact on quality of clinical study outcome and hence it is essential that our deliverables and documentations pass QG.

A few of the common reason why QG failure we experienced that can be related to programming operation are mentioned in the following.

1. Mismatch/Missing between TFL's and LoT
2. Incomplete QC documentation with missing comments/findings or mismatching dates

3. Errors in TFL's
4. Inconsistency between table content and footnotes describing them
5. Updates to analysis datasets not described in Specifications
6. Documentation issues

In review of QG's done on 20 clinical studies we found that 17 of these studies needed some form of remediation to pass QG4 that was related to programming

1. Documentation issues related to submission of incomplete version, missing/incorrect dates and timestamp inconsistency were found in 4 studies
2. 6 studies had inconsistency between table content and footnotes describing them
3. TLF mismatch was found in 5 of the studies
4. Discrepancy without explanation in discontinued subject count were found in 4 studies.

CONCLUSION

Quality Gates improve the overall quality level of the submissions by Facilitate early detection of issues and errors; Focus on meeting the needs of the regulatory agencies; Prevent future delays to approvals of NDA applications by injecting quality throughout the development process.

CONTACT INFORMATION

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

Nagadip Rao
Eliassen Group
NRao@eliassen.com

Pavan Jupelli
Eliassen Group
PJupelli@eliassen.com