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Risk-based Program Validation for Clinical Trial Analysis and Reporting

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ABSTRACT

A risk-based approach to plan and execute the testing of programs used for statistical analysis of clinical trial data will allow Clinical Programmers to apply the principles of ICH Quality Risk Management (Q9) and E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1). This paper will explain how to conduct an evaluation of the risk to quality for each program during the requirements phase of development. In addition, this paper will explain how to ensure the testing activities are planned and conducted in a manner that ensures the level of effort to test a program is commensurate with the level of risk for that program. This risk-based approach allows programmers to vary the degree of testing rigor and ensures that testing activities are focused on analyses that are most critical and have the highest risk.

INTRODUCTION

Recent regulations encourage us to implement "improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and data integrity." [1] ICH GCP has set expectations that we utilize a quality-by-design, risk-based quality management in our clinical trial activities to achieve this. Clinical programmers can adopt a process to identify and prioritize risks as they plan and conduct validation activities for analysis programs.

The paper attempts to align validation activities for clinical trial analysis programs with ICH E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) and ICH Quality Risk Management (Q9) guidance to identify, assess, control, communicate, review and report risks related to program validation for clinical trial analyses. Taking a risk-based approach supports working efficiently while still ensuring high quality, accurate analysis of data.

The scope of this paper encompasses evaluation of the risks related to validating the quality of a clinical analysis program and the output it generates. Also in scope are risks related to the resources doing the programming. System level risks including software, computing platforms and vendors are out of scope as are trial leveling risks including data management related activities.

OVERVIEW

In clinical trials, risk can be defined as "the combination of the probability of occurrence of harm and the severity of that harm."[2]

Principles of quality risk management that should be considered when it comes to clinical program validation include the level of risk to quality and accuracy of our results and the protection of the patient linked to that accuracy as well as the level of effort that aligns with the risk.

The methods we use to validate programs and control the quality of our analyses must be aligned with the importance of the information being analyzed. We should avoid unnecessary complexity during validation. Our program requirements and validation process should be clear, concise and consistent. We must identify the analyses of data that are most critical to assure protection of subjects and the reliability of the study results. A good quality

[1] Guideline for Good Clinical Practice ICH. ICH E6 R2 § Addendum (2015)
[2] Quality Risk Management ICH Q9 § 1 (2005)

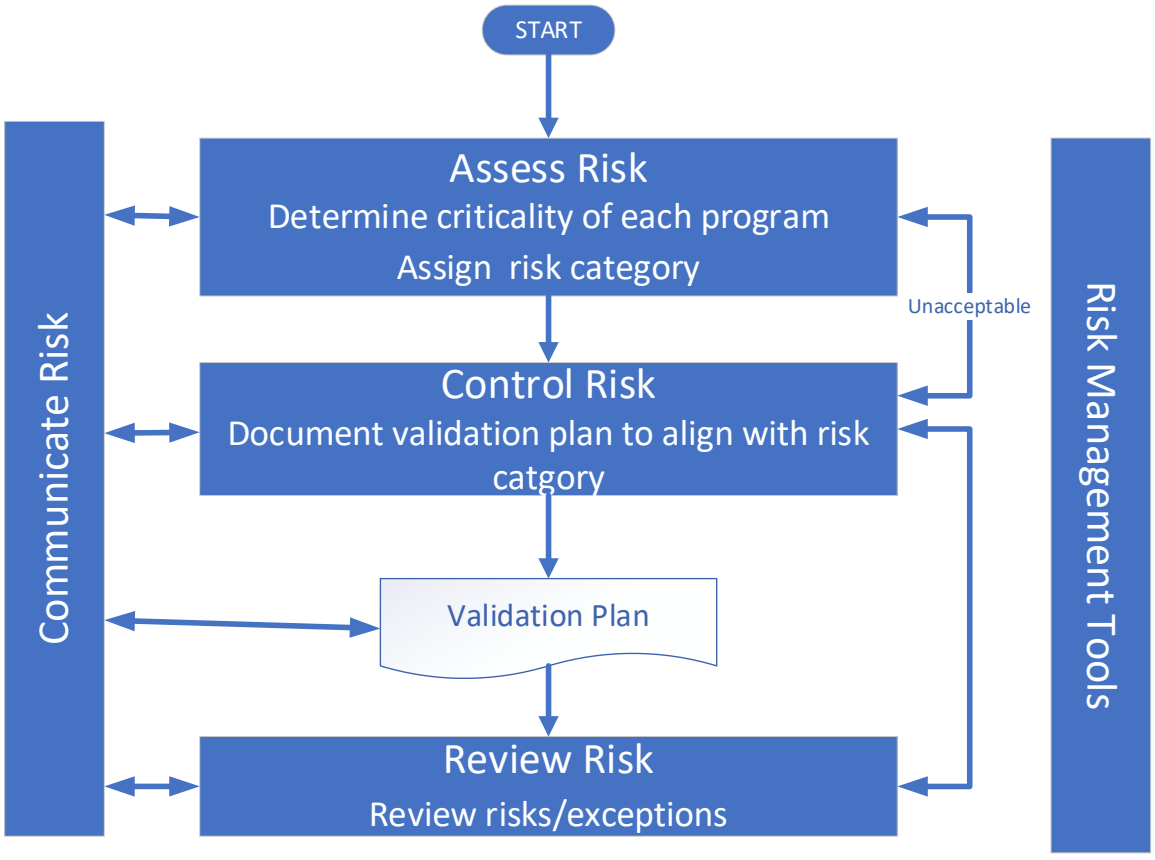
management process can ensure that clinical programmers are following a quality by design methodology. Applying a risk-based approach as we develop and validate our programs will allow us to focus validation activities on the most critical analyses to ensure that we accurately analyze the safety and efficacy of medications and ensure human subject protection.

For clinical programmers, in addition to patients, stakeholders can include, investigators, statisticians, clinicians, medical writers, government and industry regulators. While we need to ensure our risk-management supports all stakeholders, protecting the patient should be our primary focus when managing our risk to quality.

The statistician, clinician and clinical programmer must work as partners as they follow the risk management process and evaluate risks. When beginning a quality risk management process for clinical programming, the team must work to identify potential risks associated with each program including the potential harm or human health impact of the associated analyses. A leader and resources to support the process must be identified. The team should determine timing, outputs/deliverables and decision-making responsibilities.

Departmental guidelines to capture roles, responsibilities and risk assessment rules are strongly suggested. A template tracking tool which allows teams to assign criticality, document validation plans and capture exceptions and assessments will ensure consistency across projects.

Figure 1: Example of statistical programming quality risk management process



RISK IDENTIFICATION, ASSESSMENT AND EVALUATION

A team should identify quality risks that could impact programs and outputs used to analyze the safety and efficacy of a study drug. Risk assessment and evaluation of identified risks should take into consideration the likelihood of errors continuing, the impact of errors on the integrity of our results and the protection of human subjects. Program requirement specifications that are complete and clear are critical to allow the team to understand the risk associated with a particular program. The complexity of analysis programs and available resources should be considered.

Assessors must also understand resource impacts such as level of experience and number of resources available to support validation activities within required timelines.

Each program should be assigned to a risk category following evaluation of the program, outputs and resources. Complex programs; outputs for critical analyses and programs supported by less experienced staff should be identified. Critical data includes safety assessment as well as primary efficacy analyses. Standard programs used across multiple studies also should be considered as critical when first being developed.

Company defined risk categories are an important tool that will ensure consistency and proper assessment for each program. Guidelines for assigning risk categories should be documented and reviewed by senior staff or management.

Table 1: Example of Risk-based assessment to assign risk category

Risk Impact of Quality Issues	Risk Likelihood for Quality Issues to Occur		
	High: New logic, Complex algorithm, Use across areas, Major changes to critical derivations	**Medium:** TLFs with simple counts (n and %), Non-critical variable dataset changes, Minor changes to critical derivations (i.e. change 2 to 4 in algorithm) TLF changes	**Low:** Calling programs, Utility macros, Re-use of validated program, Minor updates to validated programs
High: Critical analysis, primary hypotheses for efficacy or safety, CSR/CTD analyses	**High**	**High**	**Medium**
Medium: Appendices, 2ndary/Exploratory analyses, Publications	**High**	**Medium**	**Medium**
Low: Non-submitted analyses, Cosmetic changes (labels, variable names, footnotes)	**Medium**	**Low**	**Low**

RISK CONTROL

Risk control for clinical programming is done by planning validation activities for each program to ensure the risk associated with each program is reduced to an acceptable level. This may include deciding to accept some risks. The effort to conduct required validation should be proportionate to the significance of the risk. Finding that balance can be a challenge to clinical programmers especially when resources are limited. Focusing resources on high-risk program validation is a way to meet this challenge.

Validation plans associated with each risk category should be documented. Pre-defined validation activities required for each risk category should be established. If no company guidance exists, management and senior programmers should review and approve plans. Training is an important factor in understanding the roles, responsibilities and criteria to identify risk controls. The plan should include a way to document and review exceptions that occur during validation.

Validation must be done to manage risk associated with the quality of analysis datasets, tables, listings and figures output by clinical programs. Validation ensures that program outputs accurately reflect the analysis plans to evaluate the safety and efficacy profile of a drug. The outputs must be easy to understand and should not be misleading. Validation activities can vary depending on the risk associated with a specific program. If there are issues found, the plan should identify what is acceptable (i.e. can a “warning” be ignored).

Table 2: Validation activities required per risk category example

Category	Required Validation/QC
High	• Developer testing activities ✦ • Statistical review of output with focus on complex derivations • Double independent coding of critical dataset/variables (list variables in plan) • User acceptance testing across multiple trials as appropriate • Clinical review of dry run TLFs • Independent code review ✦✦
Medium	• Developer testing activities ✦ • Statistical review of output • Clinical review of dry run TLFs • Independent code review ✦✦
Low	• QC of logs and output • Customer review of dry run TLFs • Cross table count checks • Compare to prior output for changes

✦ Developer testing activities include review of logs for errors and warnings; checking alignment of output with specifications; ensuring consistency of counts across tables and adherence to industry and company good programming practices (GPP).

✦✦ Independent code review needs should be determined for each program based on risk associated with programmer experience and complexity of code. It should be determined if the independent review is conducted by a statistician or a programmer. If risk is deemed to be acceptable, no code review is required.

RISK COMMUNICATION

Communication is critical to the success of risk management. Communication can occur at any stage in the process. The quality risk management plan should be available before programming begins and be updated as needed throughout the life of a trial to continue to evaluate risk and improve the quality of analyses. Newly identified risks, including process exceptions or known code issues must be documented. Communication of newly identified risks is not necessary for every issue. The severity and impact of the risk should be assessed to determine if it should be shared with others in the company or with a regulatory authority. Management and quality subject matter experts should always be involved if there is a need to share outside of one's department.

RISK REVIEW

Clinical programming groups must review and monitor the risk management plan and risk controls for deliverables they produce. An internal review of individual study validation activities by senior staff or management is recommended. A tool to document risk categories and validation plans that can also track validation activities and known exceptions is a great way to be able to do this. The original quality risk management criteria should be reviewed periodically to ensure it stays in alignment with pre-established risks and continues to be relevant as new knowledge and experience emerges. New risks can be added and risks that have low probability can be removed.

RISK REPORTING

The statistical programming quality management approach implemented in a trial should be captured and available for review, however there is no need to include this in the data quality assurance section of a clinical study report.

RISK METHODOLOGY – WHAT MIGHT BE USED BY CLINICAL PROGRAMMERS

Clinical Programmers can assess and manage risk to the quality of programs using a variety of methods including but not limited to:

- A check sheet or flow chart capturing plans and activities
- SAS code or utilities to check and/or compare outputs
- Utility to review logs for errors and warnings
- Utility to read validation folders and ensure all evidence is saved
- Tracking issues/re-runs of deliverables to evaluate quality
- Internal audits

CONCLUSION

Developing a quality risk management plan for validation of programs will ensure that the testing activities align with the risk associated with results analysis and that the effort to do the validation is commensurate with the level of risk. Developing standards for risk-based program categories with associated expected validation activities is a goal for industry collaborators to consider.

REFERENCES (HEADER 1)

Guideline for Good Clinical Practice ICH. ICH E6 R2 § Addendum (2015)

Quality Risk Management ICH E9 § 1 (2005)

CONTACT INFORMATION (HEADER 1)

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

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