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Risk Based Approach Applied to the Validation of Report Objects

Dipl.- Dok. Christoph Ziegler, F. Hoffmann – La Roche AG, Basel, Switzerland

ABSTRACT

Quality assurance (QA) is a key area within the reporting process of clinical trials. However, the level of QA activity quite often competes with resource and time considerations within the Biostatistics departments in the Pharmaceutical industry and is often seen as adding unnecessary paper work.

High quality reporting of clinical trials is essential, but resource aspects should also be taken into account. In order to combine both aspects and to present a defensible process and method, which ensures compliance with regulatory expectations a risk based approach can be applied to the validation of report objects. Good risk management results in reduction of efforts in low risk areas and increases the consistency within the Biostatistics departments. It allows resources to be deployed more effectively.

The risk based approach applied to the validation of report objects is a very effective way to define efficient generic methods to our validation processes. It reduces the overheads where appropriate and is a compliant process, which is endorsed by the regulatory authorities.

A general principle underlying a risk based approach is the fact, that any contribution (including the statistical reporting deliverables) harbors risk, which by no mean can entirely be eliminated. The goal of such an approach is to minimize risk and invest most where it can result in most harm. This principle needs to be understood and endorsed across all layers of an organization, since a successful implementation requires collaboration across various business domains that go beyond Biostatistics departments.

This paper is discussing requirements, benefits and challenges for deploying a risk based approach to validation strategies in statistical reporting.

INTRODUCTION

Regulatory authorities such as the Food and Drug Administration (FDA) recommend a risk based approach when it comes to the validation of report objects. Documents published by the FDA recommend that "*… the approach to validation be based on a justified and documented risk assessment and the potential of the system to affect product quality and safety as well as record integrity*" [1]. Also [2] and [3] recommend "…*an integration of software life cycle management and risk management activities. Based on the intended use and the safety risk associated with the software to be developed, the software developer should determine the specific approach, the combination of techniques to be used, and the level of effort to be applied"*.

In order to apply a risk based approach to the validation of report objects, the detailed processes needs to be reflected within local Standard Operating Procedures (SOPs), the technical background (programming environment / tools / systems) has to allow the implementation of such a concept and supportive documents / instruments need to be in place in order to fulfil a risk based approach within the statistical reporting department.

DEFINITION OF RISK

Risk is the combination of the probability of an error occurring and the severity of that error. This needs to be transferred to our daily work and to be reflected within the risk management in our reporting process. Risk management is the continuous process of analyzing, evaluating, controlling and monitoring risks that exist within our business processes. It is important to keep in mind that risk can change over time and might be perceived differently by others.

REPORT OBJECTS AND REPORTING EVENT

A report object is defined as any object which is sent outside the Biostatistics department, e.g. to regulatory agencies or to other departments within the company. A report object might be any type of data display or other output produced for delivery such as a summary output, a subject data listing, a dataset, a graph or any other file including clinical trial data in raw form or in a summarized way. Within this definition, two aspects being relevant to a risk based approach are hidden: The form and the destination of a report object are both contributing factors when it comes to the risk assessment of report objects.

A reporting event consists of one or more report objects and is defined as the delivery of report objects at a certain time. A clinical trial usually has more than one reporting event with different objectives, intended audiences and conclusions drawn thereof. Examples of reporting events are e.g. interim analysis, final analysis, deliverables to safety monitoring boards, a submission or deliverables for medical review. Also within this definition, aspects concerning a risk based approach are obvious: the type of the reporting event and the audience combined with the intent of use.

A comprehensive list of contributing factors to risk assessments is presented within the following chapter.

RISK ASSESSMENTS – LEVELS AND CONTRIBUTING FACTORS

When applying risk assessments to the statistical reporting of clinical trials, we can differ between

- the risk of the overall reporting event,
- the risk of the individual report objects (outputs) and
- the risk of the individual programs.

There are lot of different factors that contribute to risk assessments of programs, outputs and the reporting event. The risk assessment of a reporting event and of the individual report objects is a challenging team effort between programmers, statisticians and clinical science whereas the risk assessment of a program is driven by the programmers. The dependency between reporting event, report objects and programs also needs to be considered in the risk assessment.

It is probably the best way to define the categories of risk as low, medium and high. Any other classification would be over the top.

The risk assessment is done for all three levels (reporting event / report objects / programs). Due to the dependency between report object and underlying program(s), the risk of the program is of course at least as high as the highest risk level of the report object it produces. Figure 1 shows a summary of the risk assessments involved within a risk based approach. The level of risk assigned should then determine the method of validation (e.g. code review, double programming, unit testing etc), the method of the final check before the deliverables are sent out and the level of documentation.

Report Objects Risk Program Risk _____ Reporting Event Risk	LOW LOW / MEDIUM / HIGH	MEDIUM MEDIUM / HIGH	HIGH HIGH
LOW	Based on this matrix, the method of validation, the method of the final check before delivery and the level of documentation can be determined.		
MEDIUM			
HIGH			

Figure 1 Risk Assessment interaction

A great challenge is the level and the timing of the validation documentation. It could either be done when the main validation of a program is performed or at a very late stage, just before delivery, when the final check of the report objects is done. A combination is also possible. The level of detail should possibly go hand in hand with the assigned risk of a report object / reporting event / program.

RISK ASSESSMENT OF REPORTING EVENTS

When doing the risk assessment of a reporting event, four main contributing factors are suggested to be considered:

A. Type of Reporting Event

- Interim Analysis
- Final Analysis
- Data Safety Monitoring Board / Committee (DSMB / DSMC)
- Ad-Hoc Request
- Pooled Analysis (Integrated Summary of Safety / Efficacy (ISS / ISE))
- Exploratory Analysis
- Other

B. Audience of Reporting Event deliverables

- Company Internal – Study Team
  - Medical Science
  - Other
- Company Internal – Other
  - Upper Management
  - Other (e.g. Marketing)
- Company External
  - Health Authorities
  - DSMB / DSMC
  - Investigators
  - Other (e.g. Publications / Company Business Partners)

C. Intended Use of Reporting Event deliverables

- Filing (New Drug Application (NDA))
- Data Review / Assessment
- Control Patient‘s Safety
- Efficacy Purposes
- Other

D. Criticality of Data used for Reporting Event / Administrative Issues

- Importance of Clinical Trial / Project
- Early Reporting (e.g. first DSMB / filing) vs. Repetitive Reporting (e.g. regular DSMBs / additional Filing)
- Complexity of underlying Data ((analysis) datasets / (electronic) Case Report Form ((e)CRF) / Analysis / Report Objects / Programs)
- Data Quality aspects
- Other (e.g. experience of People (Staff / Clinical Research Organizations (CROs)) / Timelines of the Reporting Event / Standardization Level of Project Programming Environment)

RISK ASSESSMENT OF REPORT OBJECTS

The contributing factors of report objects risk assessment can be classified as follows:

A. Type of Report Object
- (Analysis) Datasets
- Summaries
- Listings
- Graphs
- Export files (e.g. EXCEL)
- Other

B. Importance of Report Object
- Key Report Object
- Non-Key Report Object

C. Data dependency
- Report Object run on sub-populations
- Report Object run on a subset of the data (e.g. cutoff-date)

D. Program in the background (validation level / complexity)
- Report Object produced with standard macros
- Report Object produced with standard reporting system
- Report Object produced with “normal” code
- Report Object produced with non-standard statistical software
- (or a combination)

RISK ASSESSMENT OF PROGRAMS

When doing the risk assessment of a program the following contributing factors are proposed to be considered:

A. Risk of corresponding Report Object(s)
- “the risk of the program is at least as high as the highest risk Report Object that the program makes”

B. Type of Program Code
- Program using standard macros
- Program using “normal” code
- Program using non-standard statistical software
- (or a combination)

C. Program Characteristics
- Amount of Lines of Code
- Amount of Macros called (Dependencies – Input / Output – Level of Documentation of called Macros)
- Amount of Data Derivation / Data Handling / Data Manipulation done
- Complexity of Code

D. Type of corresponding Report Object(s) / Functionality
- Analysis dataset
- Summary
- Listing
- Graph
- Export File (e.g. EXCEL)

- Helper Program (e.g. Macro performing specific Tasks)
- Format Program
- Initialization / Autoexec- Program

E. Criticality of underlying Data
- Standard (raw) Datasets used
- Analysis Datasets used
- CSV-files or other external Data used
- Pooling of Data from several Trials

F. Project Standards / Project Programming Environment
- Level of Project Programming Environment Standardization
- Reliability of Project Programming Environment (e.g. frequently used within the Project for many Reporting Events in the past)
- Level of Project Standards

G. Level of Program in Change Control System
- Reporting Event specific
- Protocol (Trial) specific
- Project specific

H. Origin of Program
- Newly developed
- Copied from other Protocol (Trial) / Project

I. Level underlying Specifications
- Stable / Final Specifications vs. Unstable / Draft Specifications
- Well written Specifications vs. Not well written Specifications

J. Management Decisions
- Decisions / Policies by Management on Risk Assignment (e.g. standard macros are validated → programs calling standard macros are therefore e.g. medium risk)

DECISION TREE

Based on the factors described above, a so-called informal "decision tree" could be set up (see Figure 2). E.g. (Risk Assessment of programs):

1) → Report Object Risk HIGH + normal code used + High Amount of Code Lines + Summary table + Pooling of Data from several Trials + Low Level of Project Programming Environment Standardization + project-level +… → high risk
2) → Report Object Risk LOW + standard macro used+ no Data Derivation done + Data Listing + no Pooling of Data from several Trials + High Level of Project Programming Environment Standardization + Reporting Event Level… → low risk

However, there is no black and white rule available. The contributing risk factors mentioned above are just things to consider and should not replace common sense.

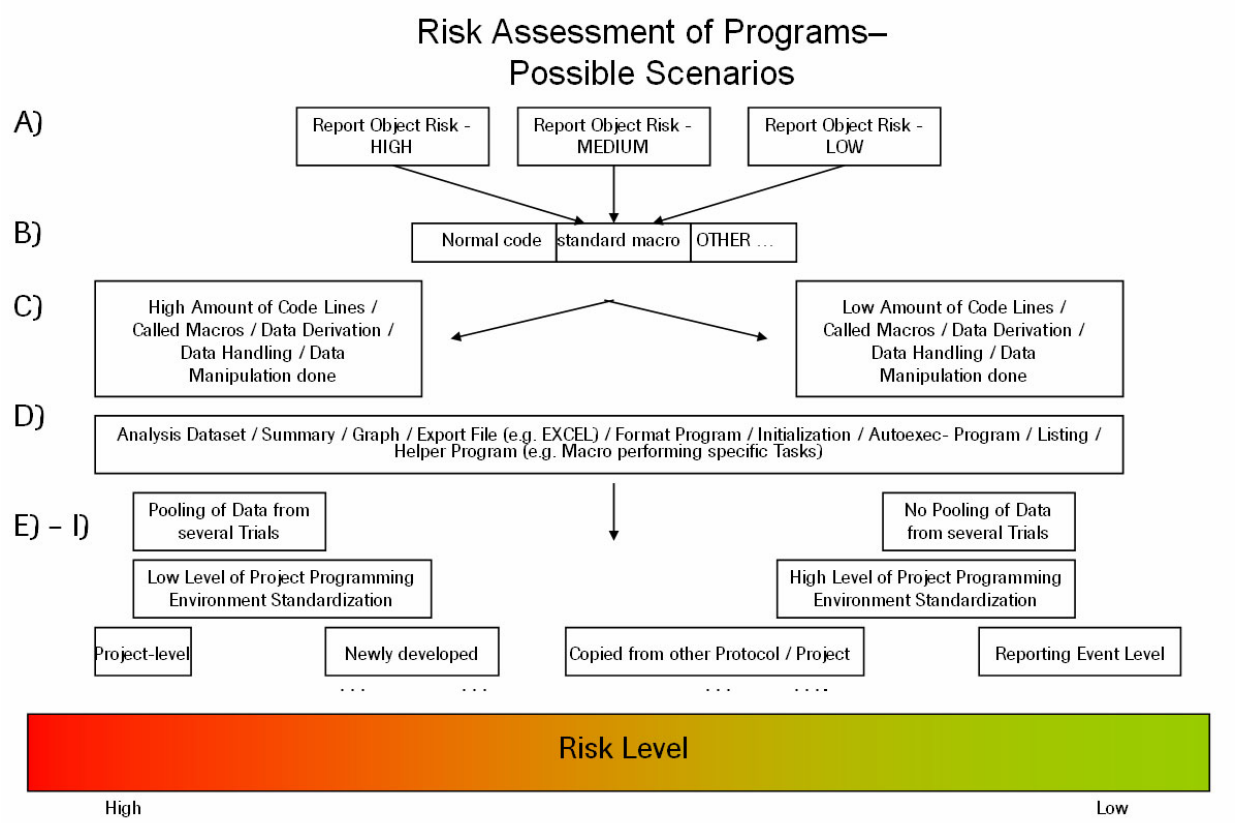

Figure 2 Decision Tree: Risk Assessment of Programs

PROCESSES / TECHNICAL BACKGROUND

The level of risk assessments agreed and approved by the project team will define the validation methods and techniques of programs, outputs and the level of formality that the reporting event should be reviewed at before the reporting event is sent outside the department / company. In order to implement the risk assessments the necessary processes and technical background (reporting environment) should be available.

REPORTING ENVIRONMENT

If possible, the reporting environment should be set up in a way that the risk assessment of programs / report objects / the reporting event can be done directly within the system. It is not recommended to do it externally (e.g. documents and / or excel sheets). Ideally, the risk assessment of programs should directly be done in the program change control system. For report objects where the targeted audience has been defined as internal in a company or for exploratory use, the risk assessment of report objects should be well visible on the report object itself. e.g. be mentioned within a standard footnote or within the title of the respective report object and the risk assessment of the reporting event itself should also be done directly within the reporting environment. The intended use of a report object can change and the originally applied risk which had been used as a basis for quality assurance may no longer apply. The above proposed approach ensures that the risk level and corresponding validation levels are reassessed before such a report object is for example sent externally. It also provides a mean to avoid that risk is set too conservative simply to cover for all eventualities, since once the report object has been delivered to customers it is nearly impossible to keep track of possible changes in their use. For report objects where the ultimate audience is company external, it should also be possible to hide the risk assessments to the audience (e.g. to health authorities), because it is an internal process.

COMMUNICATION PLAN

The intended use of report object deliverables is an important factor when it comes to risk assessment. Each reporting event has an intended use which is used to determine the risk. When delivering the report object(s) of a reporting event, it is important to communicate the intended use. If e.g. Clinical Science request a report object for unofficial internal review (medium or low risk), they are not allowed to use this report object for e.g. a publication or as a basis for important decisions (high risk). The communication plan is an important aspect to emphasize the intended use and to make customers aware that risk assessment related decisions were also based on the intended use.

PLAN TO DOCUMENT ALL QUALITY RELATED ASPECTS

It is recommended to have a central document where all quality related aspects of a reporting event are gathered. Important QA-related aspects are e.g.:

- The location of programs used for a reporting event within the company specific reporting environment
- All risk assessments including justifications (if not done within the reporting environment)
- Data related information
- Location of formal validation and change control (if no appropriate change control system is used)

The goal is to have all information concerning a reporting event at one central place. The challenge is how to deal with repetitive reporting events and so-called ad-hoc requests. In this case, more advanced document setups are needed.

RISK ASSESSMENT OF SINGLE REPORT OBJECTS VS RISK ASSESSMENT OF REPORT OBJECTS GROUPS

Risk assessment applied to report objects could be done on an individual basis. It is also possible to group report objects according to categories which is a lot easier. It is e.g. possible to say that all subject data listings are low risk or that all analysis datasets are in general high risk, because all analysis will be based on those dataset.

CONCLUSION / BENEFITS OF A RISK BASED APPROACH

The risk based approach applied to the validation of report objects is an effective way of validating report objects and underlying analysis programs. The approach reduces efforts in low risk areas and focuses the validation activities on high risk areas. Furthermore, the process is compliant with regulatory expectations and forces consistency within Biometrics departments.
However, in order to implement a risk based approach the necessary technical background should be in place. It has been shown that a lot of different risk factors are contributing to the risk of reporting event, report objects and programs. Assign risk to reporting events and report objects is a challenging team effort between programmers, statisticians and clinical science. In general, the risk based approach adds a lot of value to the validation process within Biometrics departments and allows dispatching resources where they matter most.

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CONTACT INFORMATION

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

Christoph Ziegler
F. Hoffmann – La Roche AG
Malzgasse 30, Bldg. 670/506
4070 Basel
+41 61 68 89200
christoph.ziegler@roche.com
www.roche.com