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Quality Risk Radar for the Outsourcing of Clinical Trials
The Best Guide to Success

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"If birds can glide for long periods of time, then… why can't I ?"
- Orville Wright

Table of Contents

Abstract

A quality risk radar for clinical development is a vital means to ensure that trial activities are speedy and safe. Such a system enables the early identification and proactive mitigation of risk on planned development activities. Early identification allows for the intervention in running processes so that one can mitigate risks and maintain process integrity and momentum.

The quality risk radar consists of data collection tools that either automatically extract data from available databases or with undemanding tools assist participants to submit data without significantly increasing their monitoring or compliance burden. These data are fed into simple and adaptive analytics systems to traverse the complexity of the reporting, compliance and quality assurance requirements of clinical development. By doing so they derive useful insight to support risk management of the clinical development process. To ensure that the findings are meaningful, baseline assessment and benchmarking of the data permits the creation of boundaries within which clinical development process performance and integrity can be objectively assessed.

This paper presents the rationale for utilizing risk radar for the quality management of outsourced clinical trials and in so doing highlights how this facilitates regulatory compliance as well as better performance of prospective clinical trials. The paper strengthens its claims by drawing on experiences with quality risk radar systems and tools.

1 Quality Risk Radar: The Rationale

Within the clinical development domain, the operating model for many global pharmaceutical companies has been one of extensive outsourcing of clinical trials with up to 60% of Phase III trials being performed by CROs. Reasons for this have been to drive down the immense costs and improve process performance of clinical trials. However, the accountability for clinical trials and the responsibility for ensuring regulatory compliance does not transfer to the large number of partners such as trial site investigators, affiliates, and CROs. Responsibility remains with the sponsor of the trial. Given that many trials are outsourced, often on a global scale and commonly involves the management of up to 100 partners per trial, it is not uncommon that significant risks regularly arise due to the sheer scale and complexity of such an undertaking. However, traditional retrospective Quality Assurance (QA) audits result in findings after the fact. If these findings are sufficiently serious, they result in the exclusion of the data from statistical analysis, increasing cost and sometimes reducing the power of the study.

In order for this model to be successful, one requires the means to measure and assess risk in a geographically dispersed, culturally and operationally diverse environment. This implies the need for scalable processes that facilitate the sharing of data, which in turn, necessitates the implementation of data standards so that efficient and effective communication of risk assessments is possible. The information that is gleaned from these processes is most effectively and beneficially used to pro-actively correct existing problems while the trials are running and to influence the planning of prospective clinical trial activities. Typically, identified risks concerning ongoing trials are mitigated by defining corresponding actions that ensure the risk is either reduced or removed within a certain period. These mitigation actions form the basis for a risk mitigation plan that is implemented. Due to the great number of outsourcing partners and clinical studies it is imperative that risk radar systems and tools are deployed in order to cope with this risk management challenge.

2 Quality Risk Management

When applied to pharmaceutical industry Good Clinical Practices (GCP), quality risk management (QRM) is a systematic process for the assessment and control of risks during clinical development and the quality of drug development across the entire product lifecycle.

In this context, there are two generally accepted principles of pro-active quality risk management, namely:

- The evaluation of the risk to quality should be based on scientific knowledge, probability and ultimately link to the protection of the patient; and

- The level of effort, formality and documentation of the quality risk management process should be commensurate with the potential impact and level of risk.[1]

These principles are significant as they address the primary objective, evaluation basis and the rules that govern how much effort is appropriate for conducting a quality risk management process. The first principle clearly states that the primary objective of QRM is to protect the patient from hazards.

Moreover, it also points out that risk evaluation is a process that should be driven by one's understanding of the probability, severity and potential impact of the considered threat. As such, this must be an objective and data driven process. The second principle is important as it advises that the level of effort invested into controlling a risk should be proportional to the level of identified risk.

Risk is a measure of a one's inability to achieve certain objectives. It comprises two components: the probability of failing to achieve these objectives and the consequences of this failure. In order to ensure that a desired level of quality is maintained, quality risk management has to be current, based on frequent samples of data, and be adjustable when underlying baseline assumptions change.

This process involves the following major areas of activity:

- Risk Management Preparation
- Risk Assessment
- Risk Control
- Risk Review and Risk Baseline Adjustment

In Risk Management Preparation, one designs and implements the initial version of the operational quality risk management and data collection process. While doing this, one determines the sources of risk for the domain of concern and proceeds to categorize them as well as the frequency and statistical significance of the data that is available These sources of risk are then considered with respect to their potential impact, priority, likelihood of occurrence and duration of impact which provides the framework on which subsequent baseline assessments are made. With this information, a risk management strategy is specified.

Risk Assessment initiates the operational part of risk management. In this phase, the risks are identified, analyzed and ultimately assessed with respect to the risk framework with specific indicators for individual risks that was developed in Risk Management Preparation. This way, one is able to evaluate risks with appropriate scales and thereby consistently assess the corresponding impact and likelihood of occurrence. Indicators can be combined or adjusted to ensure that the threshold of signals they generate match normal operational variability and only trigger a signal when critical thresholds are exceeded. Where these data are not available from operational IT systems (for trial monitoring, adverse event reporting, trial management etc.) these data can be supplemented with structured questionnaires and web-based data collection tools.

Given that mistakes will happen, and all issues cannot be avoided, the second area of operational risk management is Risk Control. This involves the compilation and implementation of risk mitigation plans. More specifically, it entails the tracking, reporting, and mitigating of risk and the communication of these results throughout the organization. Risk reduction and management is the usual objective of risk control. However, in some cases it is advisable to accept a risk. It is not uncommon that a certain degree of residual risk remains after subjecting it to risk control and to the extent that the risk is at a moderate level, then it is acknowledged and accepted.

3 Quality Risk Radar Tools

Quality risk radar tools for clinical studies facilitate the efficient and effective execution of quality risk management within this context. In general these tools:

- Provide management with the information needed to make informed strategic and operational decisions
- Support the alignment of operations with corporate strategy
- Sustain accountability throughout the organization and all its service providers
- Improve productivity while maintaining high quality and meeting regulatory requirements

In particular, these tools store and use a risk baseline (determined during the Risk Management Preparation process) against which newly acquired data can be compared and evaluated. To make risk assessments regarding process performance, process integrity and regulatory compliance. As the underlying repository is enriched with data from new sources and the analytics systems mature, the range and sensitivity of the risk radar increases and the baseline and signal thresholds can be refined.

3.1 ADAMON Project

Furthermore, by creating risk-based tools that evaluate the content and planned design of the trials, it becomes possible to improve the design and the planned monitoring strategies before supervision of the trials commence. Quality risk radar tools of this variety supplement activities such as risk-based trial approval processes and supplement monitoring regimes and inspections by competent authorities of clinical trials by:

- Trial specific risk analysis
- Implementation of QM measures targeted to the risks identified
- Continuous interdisciplinary supervision
- Timely reaction to problems

An implementation of this approach is found in the ADAMON Project which was initiated in Germany and funded by the Federal Ministry of Education and Research (BMBF). The project name ADAMON is an acronym for: risk ADApted MONitoring strategies. In particular, the project addresses how one can best assure quality and patient safety in non-commercial clinical trials in which resources are limited. This project defined patient *risk* to be: the risk of non-compliance with the GCP objectives, namely to provide assurance that the rights, confidentiality and safety of the clinical trial subjects are maintained and that the data and reported results are credible.[2]

ADAMON carried out their trial specific risk analysis by answering the four questions 1) Who? 2) When? 3) Why? and 4) How? In particular, this meant that 1) the Study Team was addressed early on, i.e. 2) during the study preparation phase in order to 3) identify the trial specific risks and specify the quality assurance measures necessary to mitigate the identified risks and 4) with a structured questionnaire that was transparent and comprehensive that analyzed patient safety and data quality

with respect to key risk indicators (KRI) involving: study population, enrollment process, study therapies and other trial related procedures, sources of bias robustness of trial results.

An example of a question that addresses patient related risk is:

P1 Potentially vulnerable population?
a. Will a vulnerable population be included? No ☐ Yes ☐ If 'Yes': specify _____ If 'Yes': continue with b. *E.g., pregnant women, newborns and infants, geriatric patients, patients with cognitive or psychological disorders.* *Vulnerable populations may be exposed to higher risks, but this is not necessarily always the case.*
b. If the above indicator applies, does it mean a higher risk for the patient's safety and/or patient's rights, and/or the validity of results? No ☐ Yes, for patient's safety ☐ Yes, for patient's rights ☐ Yes, for data validity ☐ If 'Yes' was answered at least once, continue with c and d. Comments:_____ _
c. If at least one GCP objective is at risk, which quality management measures will be taken to control this risk? _____ _
d. If at least one GCP objective is at risk, does on-site monitoring independently contribute to quality management in conjunction with the other measures? No ☐ Yes ☐

Some insightful and valuable conclusions of their work are:

- Risk-based quality management does not necessarily mean reduced intensity of quality management measures, but quality management measures focused on trial-specific risks

- Risk-based quality management requires
    - Trial specific risk analysis
    - Implementation of mitigation actions targeting the identified risks
    - Continuous interdisciplinary supervision
    - Timely reaction to problems
    - Trial-specific training of the study team[3]

3.2 GCP Diagnostic Tool and MA Tracker

In the case of commercial clinical trials, other methods and tools have been employed in order to both assess and control risk. In order to assess the risks associated with the various clinical trial activities a so-called GCP Diagnostic Tool (GCP DT) was designed and used. The implemented tool is a structured questionnaire for country organizations of multi-national pharmaceutical companies to report on their capacity and capabilities to support local clinical development which enabled the identification and analysis of risks associated with the following areas:

- Data integrity
- Infrastructure and processes
- Communication effectiveness with headquarters

The objective of this questionnaire is to collect feedback on the GCP quality of globally dispersed affiliates of a pharmaceutical company without raising their workload or the level of effort of repeated monitoring. The tool enables a risk assessment based on consolidated data from simple and regular questionnaires completed by the affiliates. The GCP DT serves as an early warning system that feeds back areas of increased risk. Its main purpose is to empower the affiliates to assess their own risk exposure and to take mitigating actions where appropriate. Moreover, the results from the tool are used to recalibrate the underlying risk baseline on a periodic, usually annual basis.

After the GCP DT has assessed the identified risks to be either Low, Medium or High, then a second tool, namely Mitigation Action Tracker (MA Tracker) is used by the Quality Risk Specialists and the local GCP DT Coordinators for:

- Defining mitigation actions for all questions of the self assessment survey that were evaluated to be high risk
- Ensuring high quality mitigation actions definitions, by facilitating the review of defined mitigation actions
- Registering mitigation action implementations
- Ensuring that the risk of problematic areas are documented, tracked and sufficiently mitigated
    - By reviewing registered mitigation action implementations

A typical workflow associated with the defining and review of appropriate mitigation actions is shown in the following screen shots of the MA Tracker.

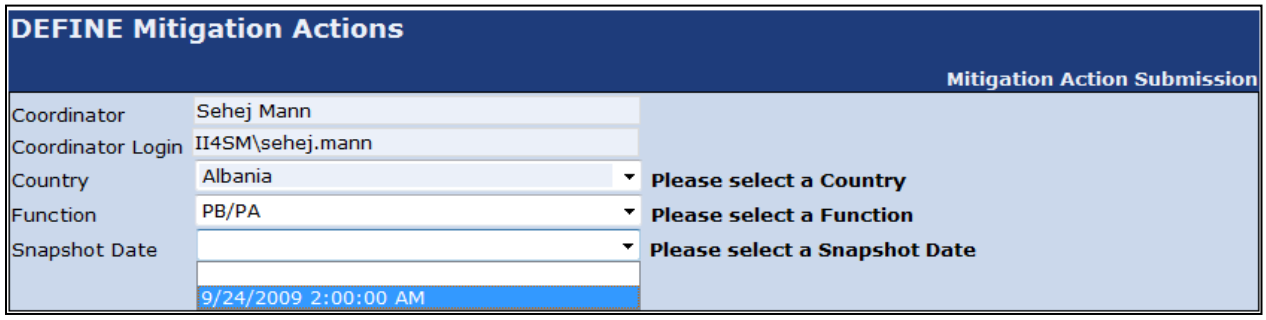

Illustration: Query Interface for Globally dispersed Affiliates

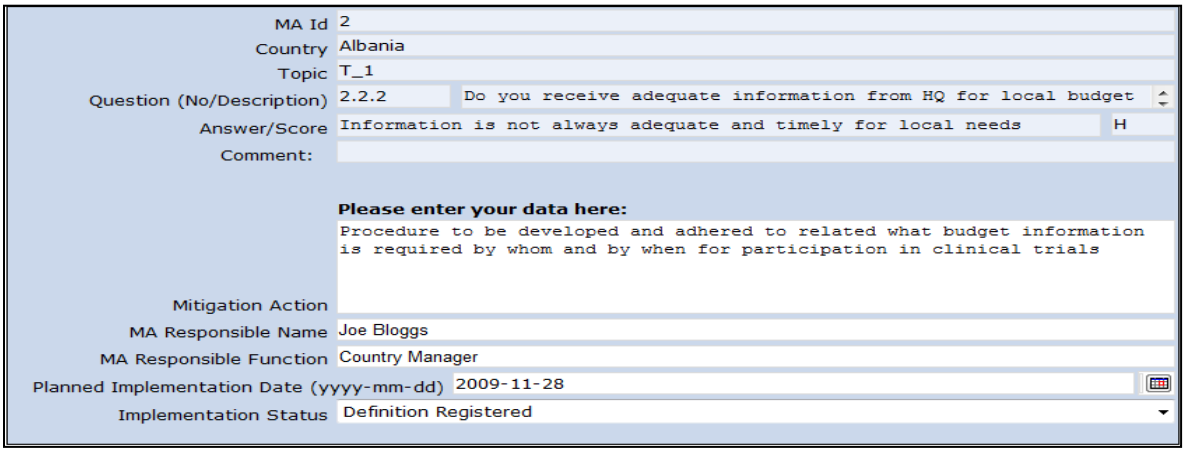

Illustration: MA Definition Entry Interface

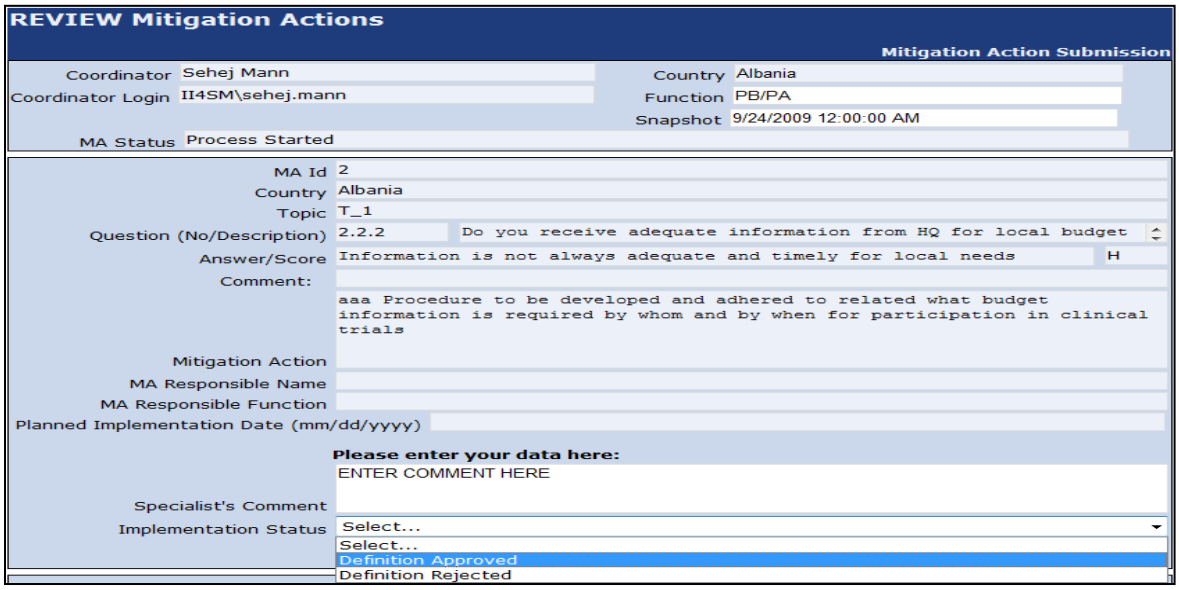

Illustration: Review and Quality Control of MA Definitions

3.3 Risk Communication

Given the global nature of today's clinical landscape, efficient and effective communication of risk assessments is paramount to ensuring that adequate time and resources are available for risk mitigation. One approach that has proven its effectiveness is the delivery of multiple levels and multiple dimensions of information that can be drilled down or across. An example of this is demonstrated in the following report snapshot that provides an overview of the risk status of clinical trial sites by region.

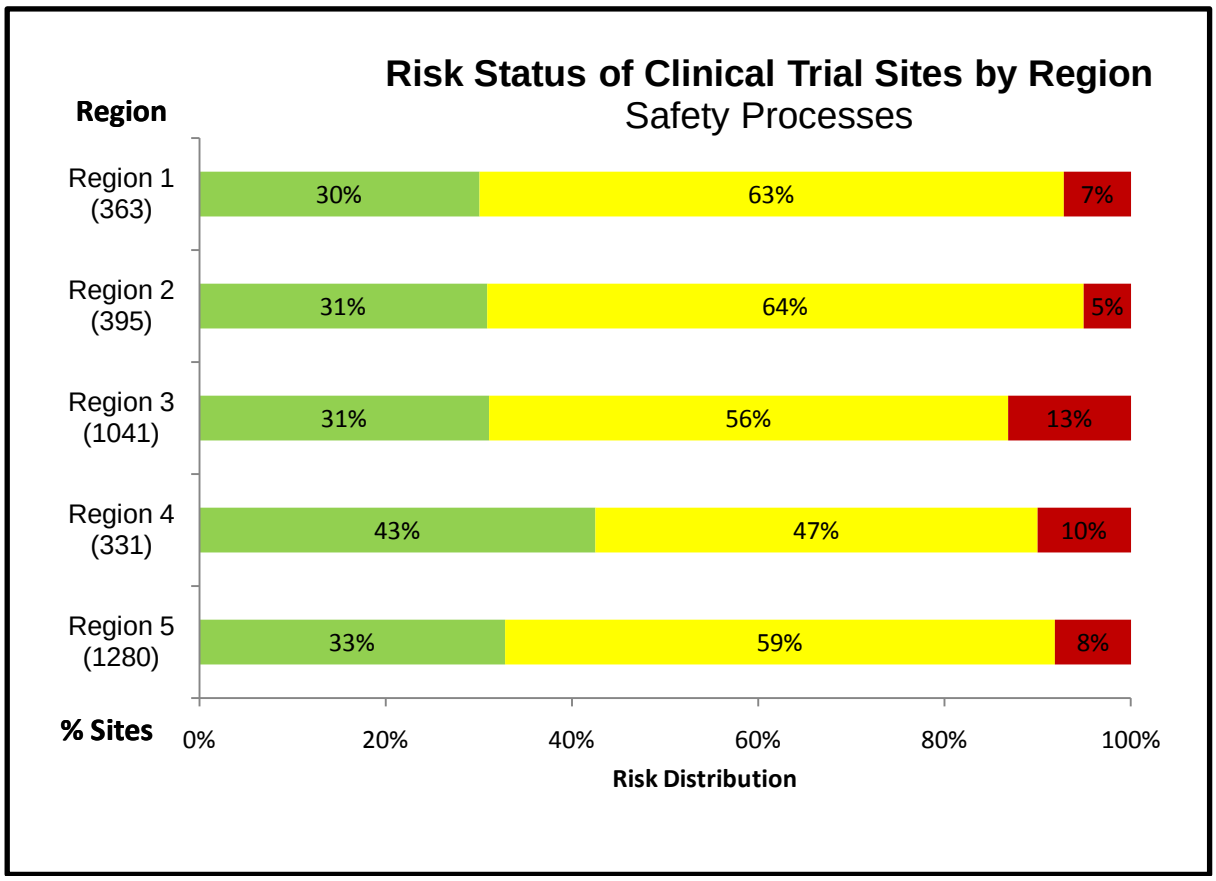

Illustration: Risk Status Overview Report by Region

After getting an overview of risk status as illustrated in the above report, an effective means of establishing the cause of certain risk signals is to drill down into the level of detail that is often provided by evaluating risk indicator signals (KRI signals) in a corresponding context. For example, once one sees that a given region is problematic, one can query the risk repository for the context, i.e. the studies, countries and sites in which KRI signals have been identified by the quality risk radar. An example of such a result in shown in the following report.

				KRI Signals				
Study	**Country**	**Site**	**Quality Risk Area**	KRI-1	KRI-2	KRI-3	KRI-4	KRI-5
Study 123	Country B	553	Safety Processes					
			Data Integrity					
		576	Data Integrity					
			Safety Processes					
		578	Data Integrity					
			Safety Processes					
	Country C	608	Data Integrity					
			Safety Processes					
		610	Data Integrity					
			Safety Processes					
		613	Data Integrity					
			Safety Processes					
		614	Data Integrity					
			Safety Processes					
		617	Data Integrity					
			Safety Processes					

Illustration: Risk Status Detail Report

4 Summary

In order to address the need to save cost and increase effectiveness of clinical trials, pharmaceutical companies can introduce quality risk radar tools into their ongoing efforts to manage the quality and integrity of their trials. These tools are designed to minimize the workload of staff, while increasing manifold the volume and quality of data for analysis. As seen with ADAMON, many of the indicators are evaluated at the time of design of the study, limitations of the design can be corrected before the start of the trial.

By automating the analysis and basing risk assessments within predetermined tolerances, the data that was collected can be filtered to provide an early indicator of those entities, sites or investigators that are not performing according to pre-agreed expectations. These early indicators can be distributed to the relevant functional managers to pro-actively alert the sites or investigators and provide training, resources or other assistance to avoid the problems from escalating. The use of these signals has been shown to result in the identification of critical issues six to twelve months before they could have been discovered by audits or other traditional means.

Additionally, these activities complement and help traditional auditors to focus their efforts on those organizations and entities that require review as well as giving them additional information for the planning of their audits.

By identifying process breaches and non-compliance before they result in risk exposure of patients or critical findings in audits, ongoing trial quality can be actively improved. This will result in less data being excluded during statistical analysis and tighter control of the large number of service providers.

5 Contact Information

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