



International Institute **for** the Safety of Medicines

Quality Risk Radar
for the Outsourcing of Clinical Trials

The Best Guide to Success
(RG06)

October 2010

Objective:

This presentation addresses 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 clinical trials.

1. Quality Risk Radar: Identity, Parameters, Rationale
2. Quality Risk Management
3. Quality Risk Radar Tools
 - 3.1 GCP Diagnostic Tool and MA Tracker
 - 3.2 Risk Communication
4. Summary



- A Way of Life
 - That enables one to deal effectively with the challenges of a complex and dynamic environment while moving toward mid and long term goals

- A Composite of Tools and Methods
 - That are available to properly equip one for the long and demanding journey toward your goals

- Before applying these tools and methods you will have to answer a few questions...

- Where do you want to go, i.e. what do you want to achieve?



- What are the possible paths?



- What are the risks along these paths?



- How can you reliably identify these risks?



Conventional
Techniques



Modern Techniques

- What are the likely impacts of these risks?



- How will you mitigate/control these risks?



- How will you adapt
 - If a risk becomes actualized?
 - If your environment changes?

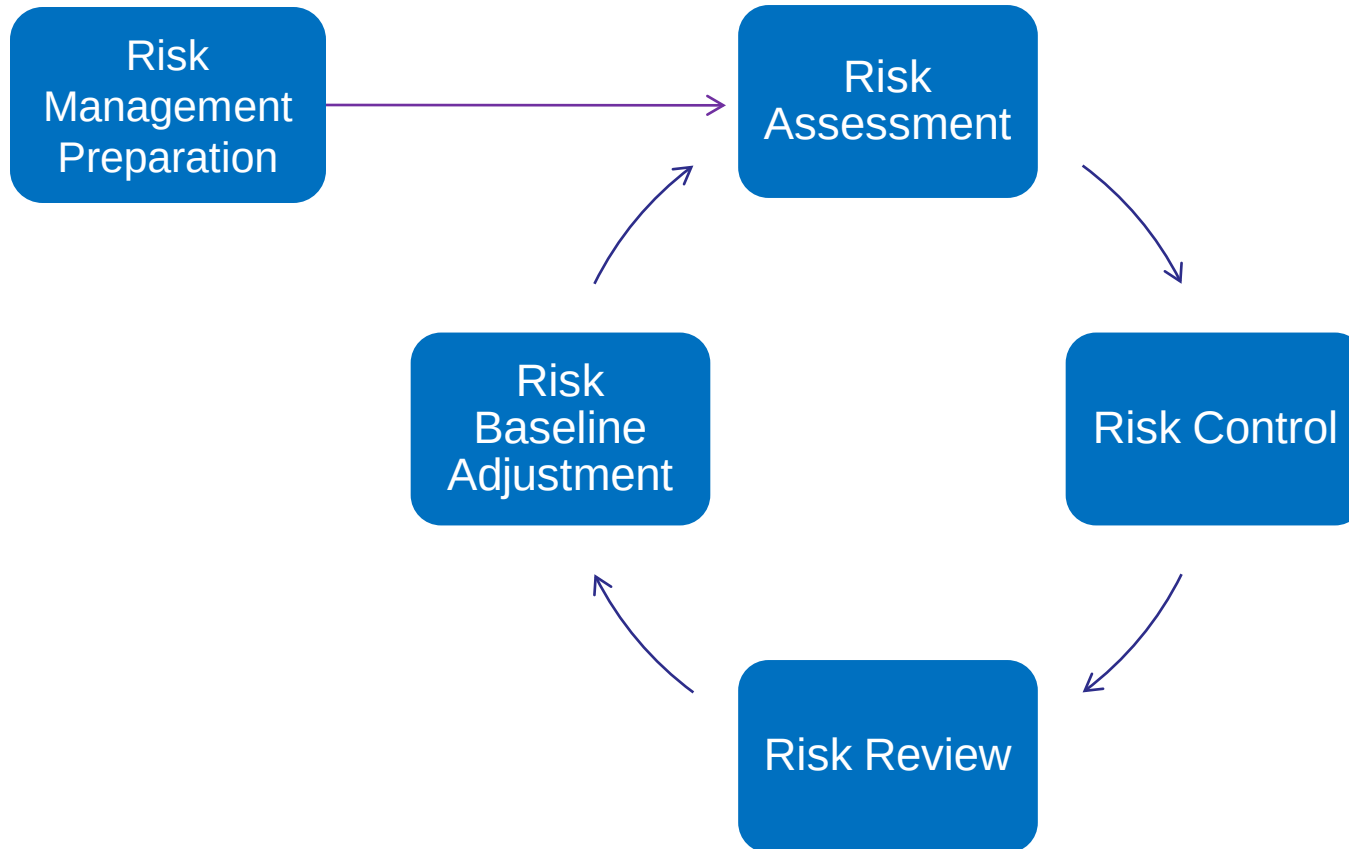


- The Operating Model
 - Extensive outsourcing of clinical trials
- Rationale
 - Cost reduction and process performance improvement of clinical trials
- Regulatory Constraints
 - Responsibility for regulatory compliance remains with sponsor
- Common Result
 - Due to scale and complexity, significant risks arise
 - Exclusion of data from statistical analysis, increasing cost and reduction of power of the study
- Conditions for Success
 - Means to measure and assess risk in a geographically dispersed, culturally and operationally diverse environment
 - Scalable processes that facilitate data sharing
 - Efficient and effective communication of risk assessments

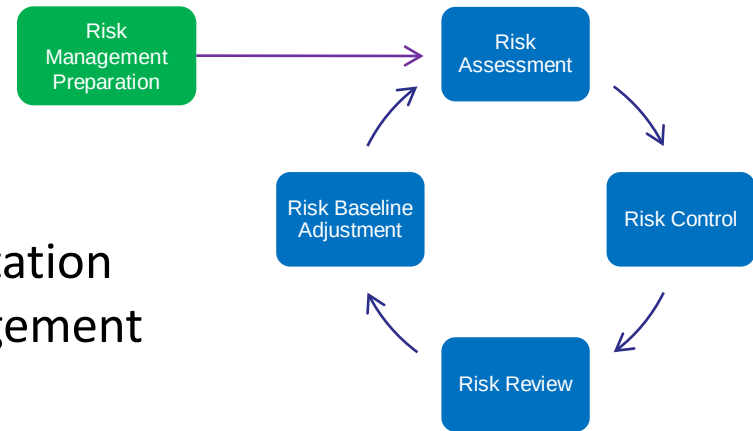
- When applied to Good Clinical Practices (GCP): QRM is defined as ...
 - Systematic process for the assessment and control of risks during clinical development and the quality of drug development across the entire product lifecycle

- Principles of pro-active QRM
 - The evaluation of the risk to quality should be based on scientific knowledge, probability and ultimately be linked to the protection of the patient
 - The level of effort, formality and documentation of the quality risk management process should be commensurate with the potential impact and level of risk¹

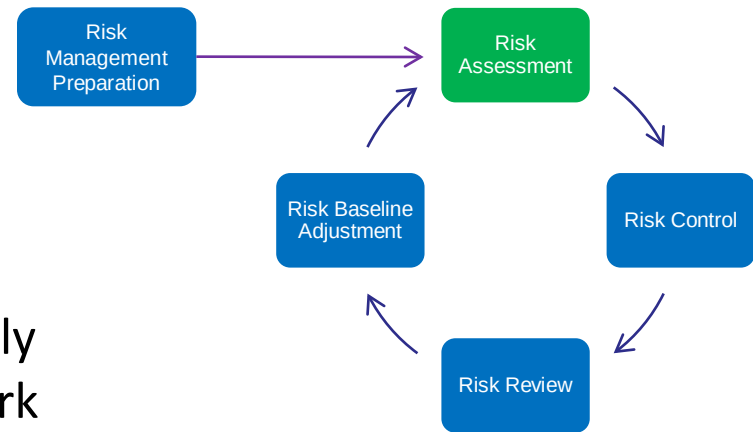
- Risk is a measure of a one's inability to achieve certain objectives
 - Component 1: the probability of failing to achieve these objectives
 - Component 2: the consequences of this failure



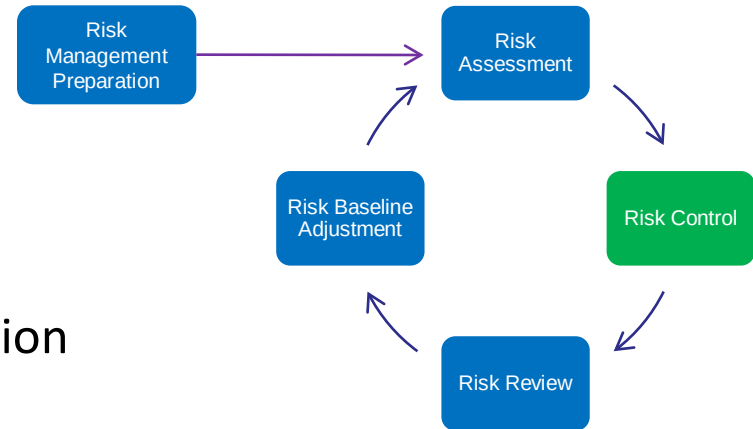
- In general, entails a design and implementation of 1st cut of operational quality risk management and data collection process
- Involves Risk Source Identification and Categorization
 - Potential Impact, Likelihood of Occurrence and Priority
- Provides risk framework for subsequent baseline assessments
- Results in a Risk Management Strategy



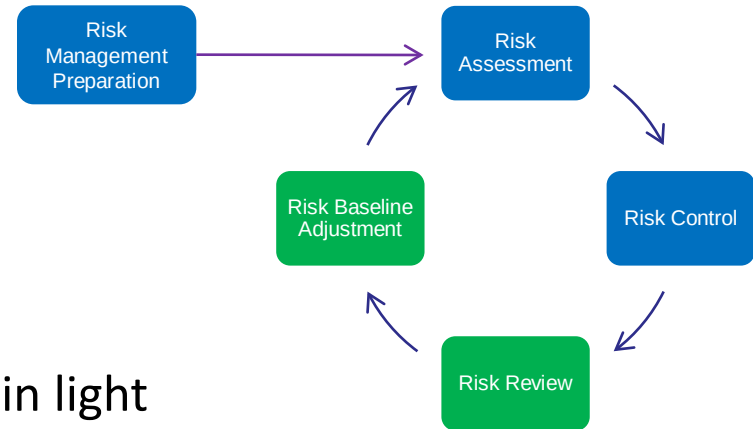
- Operational part of risk management
- Risks are identified, analyzed and ultimately assessed with respect to the risk framework with key risk indicators
- Thereby enabling consistent assessment of impact and likelihood of occurrence
- These data are usually extracted from operational IT systems (for trial monitoring, adverse event reporting, trial management etc.)
- Otherwise, are supplemented with structured questionnaires and web-based data collection tools

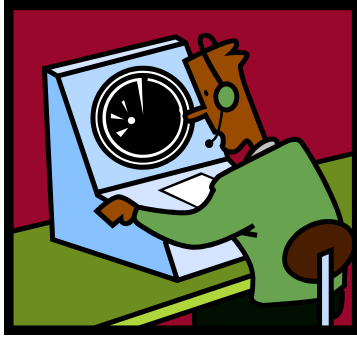


- 2nd Area of operational risk management
- Involves the compilation and implementation of risk mitigation plans
- Tracking, reporting and mitigating of risk and the communication of these results throughout the organization
- Usual objective of risk control: Risk reduction and management
- Residual Risk Acceptance



- A process to review or monitor events should be in place
- Results of risk control should be reviewed in light of new knowledge and experience
 - Verification of intended mitigations
 - Re-assessment of KRI threshold sensitivities
- Frequency of review should be based upon the level of risk
- Risk review results can translate into Risk Baseline Adjustments, e.g.
 - Introduction of new KRIs
 - Adjustment of KRI thresholds etc.





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

- In order to both assess and control risk structured questionnaire for country organizations of multi-national pharmaceutical companies to report on their capacity and capabilities to support local clinical development which enabled identification of following risks areas:
 - Data integrity
 - Infrastructure and processes
 - Communication effectiveness with headquarters
- Serves as an early warning system
- Empower the affiliates to assess their own risk exposure and to take mitigating actions where appropriate



- **After GCP DT has assessed risk impact, then Mitigation Action Tracker enables:**
 - Registration and review of mitigation action definitions for identified risks
 - Registration and review of mitigation action implementations
- A typical workflow of Defining and Reviewing of mitigation actions follows

DEFINE Mitigation Actions		Mitigation Action Submission
Coordinator	Sehej Mann	
Coordinator Login	II4SM\sehej.mann	
Country	Albania ▼	
Function	PB/PA ▼	
Snapshot Date	9/24/2009 2:00:00 AM ▼	

Query Interface for Globally dispersed Affiliates

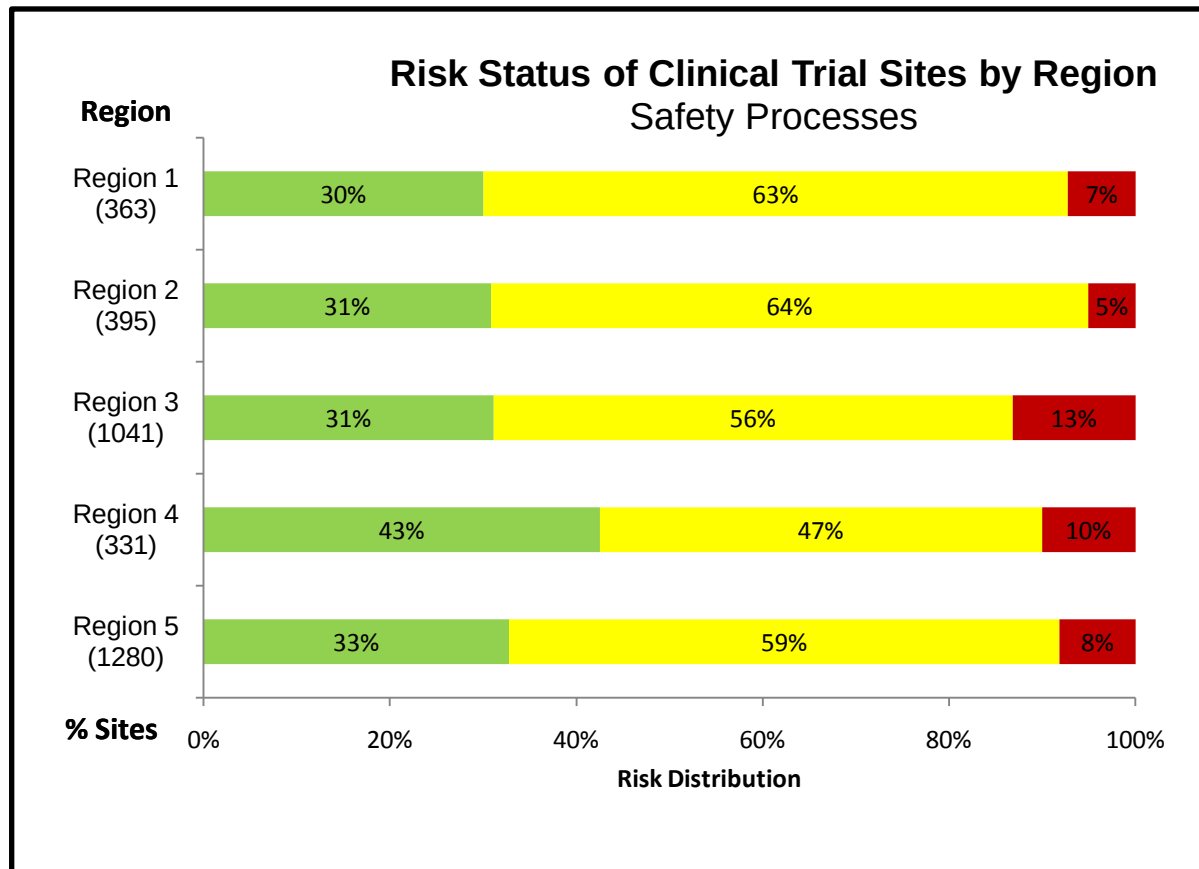
Mitigation Action Entry Interface

MA Id	2		
Country	Albania		
Topic	T_1		
Question (No/Description)	2.2.2	Do you receive adequate information from HQ for local budget	
Answer/Score	Information is not always adequate and timely for local needs		H
Comment:			
	Please enter your data here:		
	Procedure to be developed and adhered to related what budget information is required by whom and by when for participation in clinical trials		
Mitigation Action			
MA Responsible Name	Joe Bloggs		
MA Responsible Function	Country Manager		
Planned Implementation Date (yyyy-mm-dd)	2009-11-28		
Implementation Status	Definition Registered		

Quality Control of Mitigation Actions

REVIEW Mitigation Actions		Mitigation Action Submission	
Coordinator	Sehej Mann	Country	Albania
Coordinator Login	II4SM\sehej.mann	Function	PB/PA
		Snapshot	9/24/2009 12:00:00 AM
MA Status	Process Started		
MA Id	2		
Country	Albania		
Topic	T_1		
Question (No/Description)	2.2.2 Do you receive adequate information from HQ for local budget		
Answer/Score	Information is not always adequate and timely for local needs H		
Comment:	aaa Procedure to be developed and adhered to related what budget information is required by whom and by when for participation in clinical trials		
Mitigation Action			
MA Responsible Name			
MA Responsible Function			
Planned Implementation Date (mm/dd/yyyy)			
	Please enter your data here: ENTER COMMENT HERE		
Specialist's Comment			
Implementation Status	Select... Select... Definition Approved Definition Rejected		

- The global nature of today's clinical landscape requires efficient and effective communication of risk assessments
- An effective Information delivery approach: Multi-Level and Multi-Dimensional



■ From Overview to Cause of Risk Signals

- For example, once one sees that a given region is problematic, drill down into the level of detail of risk indicator signals and determine cause

Study	Country	Site	Quality Risk Area	KRI Signals				
				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					

Risk Status Detail Report

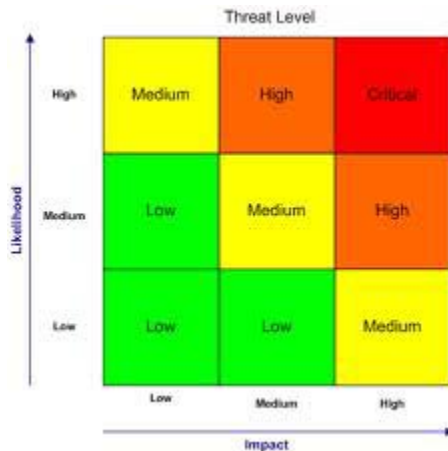
- Risk Maps also provide an effective overview on which studies are at risk of becoming non-compliant regarding Data Integrity

		Study 1	Study 2	Study 3	Study 4	Study 5
KRI	KRI Description					
1	CRF amendments					
3	Received vs. predicted pages					
4	Time from patient visit to DB					
5	Data entry errors					
6	Age of unresolved issues					

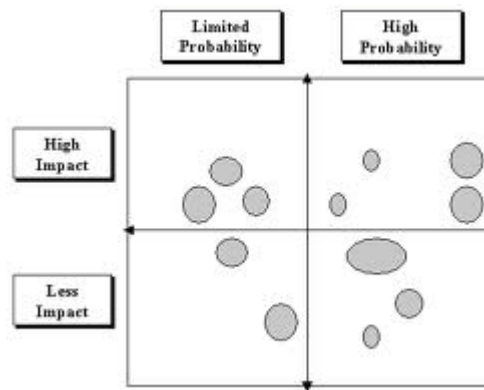
Data Integrity Risk Map

Risk Communication: Risk Maps

- Risk Maps provide a visual overview of your risk on a risk landscape
- They also facilitate the grouping of risk indicators



Impact	Risk Distribution		
Significant	S2 E2	E1 L3 T1	T2 TF1
Moderate		T3 F3 S3	
Minor	L1 F2	S1	E3
	Low	Medium	High
	Likelihood		



■ Annual Country Threshold Calculation Method

■ Motivation

- Same single threshold was used for the determination of Affiliate Drug Safety KRI signals for all affiliates (countries)
- Not flexible enough in certain cases
- This situation typically leads to an inordinate amounts of signals in affiliates that carry out only relatively small numbers of clinical studies

■ Objective

- Develop a method in which signal determination accommodates the wide range of number of clinical studies carried out among the affiliates and thereby is more sensitive to this diversity and consequently better measures the risk profile of each affiliate.

■ Result

- The calculation method was adapted to accommodate this new understanding

- 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 performance of their trials.
- 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.
- 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.
- 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.

- Your comments and questions are valued and encouraged. You can contact the authors at:

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- **¹ ICH Q9 QUALITY RISK MANAGEMENT**, an ICH Harmonised Tripartite Guideline, Current Step 4 version, 9 November 2005
- **² Risk analysis and risk-based quality management in noncommercial clinical trials**, Oana Brosteanu, Clinical Trial Center, University of Leipzig, Presentation at the 22nd Annual EuroMeeting, March 8-10, 2010 in Monaco



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