Quality Risk Management for Clinical Trials

Use the data at your hands to manage risk in your clinical trials

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Funded by
Federal Ministry of Education and Research
BMBF 01KN1106

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Quality Risk Management (ICH Q9)

is a systematic process to

- capture,
- assess,
- control,
- monitor and
- communicate

risks.

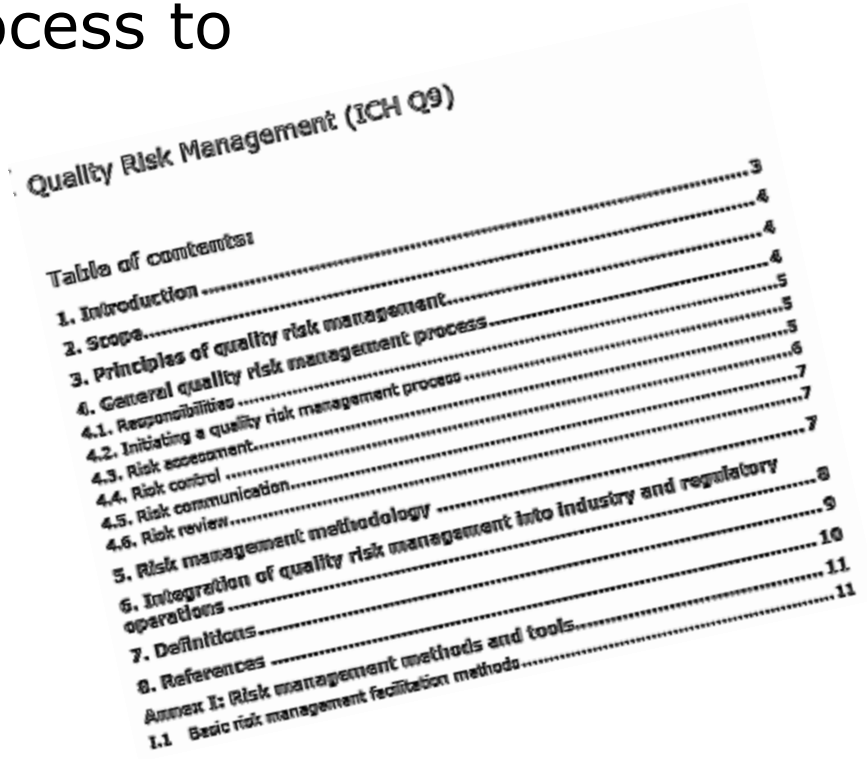
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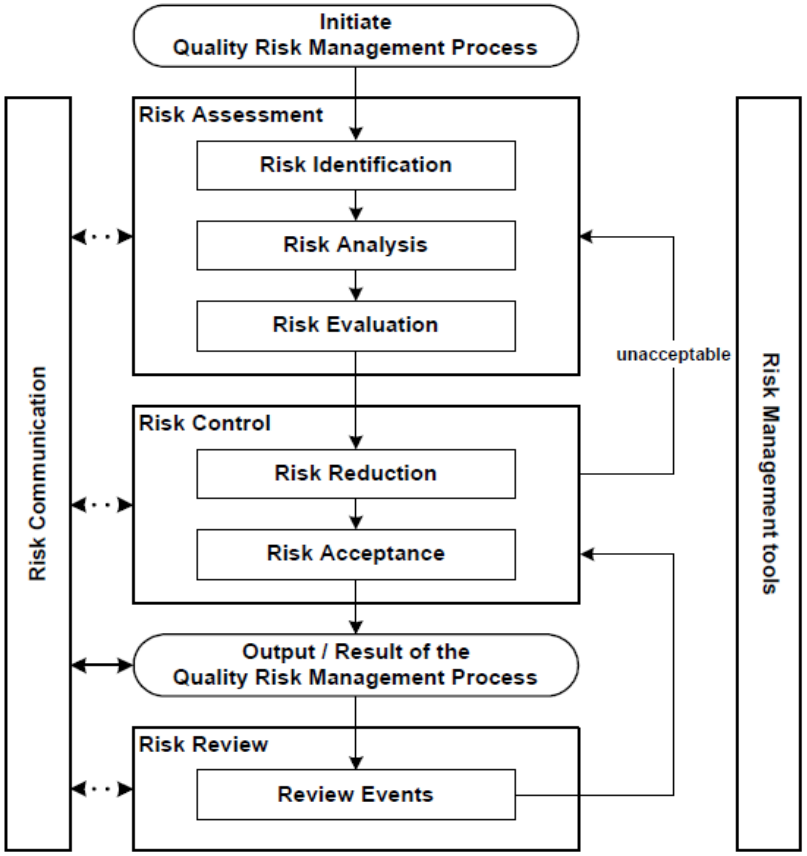
Figure 1: Overview of a typical Quality risk management process



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EMA/INS/GMP/79766/2011

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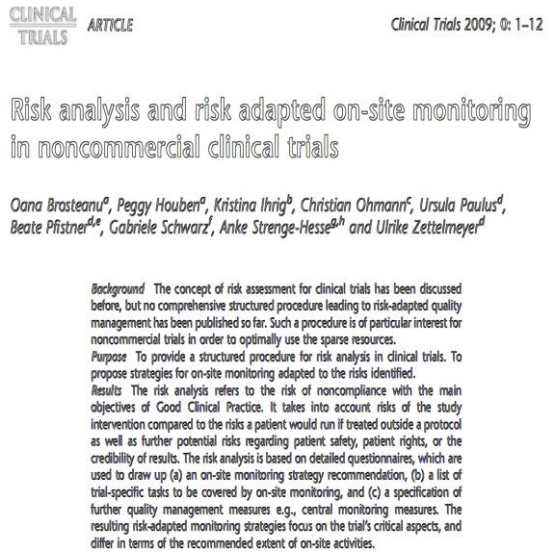
Example: Risk-adapted Monitoring

- ADAMON: Risk analysis and risk adapted on-site monitoring in non-commercial clinical trials
  - visit intervals are adjusted
  - selected data is checked
  - to assure
    - subject safety
    - scientific value
  - additional precautions are essential



CLINICAL TRIALS ARTICLE Clinical Trials 2009; 0: 1–12

Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials

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Background The concept of risk assessment for clinical trials has been discussed before, but no comprehensive structured procedure leading to risk-adapted quality management has been published so far. Such a procedure is of particular interest for noncommercial trials in order to optimally use the sparse resources.
Purpose To provide a structured procedure for risk analysis in clinical trials. To propose strategies for on-site monitoring adapted to the risks identified.
Results The risk analysis refers to the risk of noncompliance with the main objectives of Good Clinical Practice. It takes into account risks of the study intervention compared to the risks a patient would run if treated outside a protocol as well as further potential risks regarding patient safety, patient rights, or the credibility of results. The risk analysis is based on detailed questionnaires, which are used to draw up (a) an on-site monitoring strategy recommendation, (b) a list of trial-specific tasks to be covered by on-site monitoring, and (c) a specification of further quality management measures e.g., central monitoring measures. The resulting risk-adapted monitoring strategies focus on the trial's critical aspects, and differ in terms of the recommended extent of on-site activities.

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Approach

Define risk Indicators

- subject safety and scientific value
- assessment of potential danger

Evaluate risk-Indicators

- capture risk Indicators
- report according to potential danger

Act

- corrective and preventive actions

Define Risk Indicators

- What are the risks regarding subject safety and scientific value?
  - What might go wrong?
  - What is the likelihood (probability) it will go wrong?
  - What are the consequences (severity)?
- How can a change of risk profiles be detected as early as possible?
- What strategies / actions should be taken depending on the risk and potential danger?

Standard Risk Indicators

- Number of queries (total, per item; closed, open)
- Number of missing values (total, per item, per subject)
- Number of SAE/AE (total, per subject month)
- Contemporary documentation, subject visits and follow-ups on time
- Number of protocol deviations / violations (total, per subject)
- Assessments of the monitor(s) / project manager(s)

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Evaluate Risk Indicators

- Main observation units:
  - sites & subjects (over time)
- Standardized reference values:
  - per center,
  - per subject,
  - per subject-month,
  - per CRF page,
  - ...

Example: Queries

Site	Queries	Items	Queries/ Item
1	8	1725	0,46
2	20	3243	0,62
3	25	6070	0,41
4	54	5909	0,91
5	482	55368	0,87
6	74	9102	0,81
7	27	1747	1,55

Example: SAE

Site	Sbj.	SAE	SAE/ Sbj.	Sbj.-Month	SAE/ Sbj.-Month
1	1	1	1,00	5	0,20
2	2	0	0,00	7	0,00
3	6	5	0,83	11	0,45
4	3	1	0,33	8	0,13
5	31	27	0,87	76	0,36
6	5	4	0,80	9	0,44
7	1	0	0,00	3	0,00

Example: Protocol Deviations (PD)

Site	Sbj.	PD	PD/Pat	PD esc.	PD esc. / Sbj.
1	31	33	1,06	16	0,52
2	1	1	1,00	0	0,00
3	5	5	1,00	4	0,80
4	6	2	0,33	0	0,00
5	1	1	1,00	1	1,00
6	3	5	1,67	1	0,33
7	4	4	1,00	1	0,25

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Evaluate Risk Indicators

- Assessment: consider the context and take into account other information e.g. monitoring findings, DSMB reports

Act

- request clarification / correction by data management, monitor
- escalation to and initiation of a solution by project manager
  - "For Cause Visit"
  - additional training
  - …
- escalation to coordinating investigator, sponsor

Review

- Where the desired results achieved?
- Did any side effects occur?
- Adopt the approach if necessary.

Relevance

- required for risk-adapted monitoring strategies
- important for
  - the assessment of the trial performance and quality (overall and per site)
  - effective resource allocation
  - objective and effective audit planning
  - decisions regarding PP / ITT allocation

Precautions

- contemporary documentation
- timely collection, analysis and communication of risk indicators
- reporting and escalation routes
- trial-specific adjustment of parameters and measures

Experience

- quality is measurable and can be controlled
- cost is appropriate
- implementation is complex
- standardization and objectification of the processes / decisions is helpful
- findings / results are consistent compared to classic on-site monitoring
- abnormalities can be detected that are not found by on-site monitoring, only

Quality Risk Management is ...

- … a multidisciplinary task:
  - biometry
  - project management
  - data management
  - monitoring
  - …
- … a key element of risk-based quality management.
- ... a comprehensive tool for managing quality.

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Your questions are welcome.

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Protocol Deviations / Violations (Examples)

code	description	responsable
1	**informed consent**	
101	fabricated	MO
102	not available	MO
103	not dated by subject	MO
104	not signed by subject	MO
105	not signed by investigator	MO
106	signature date after date of randomization	MO, DM
107	wrong version used	MO
108	language not appropriate for subject	MO

Protocol Deviations / Violations (Examples)

code	description	responsable
3	**allocation / treatment / intervention**	
301	wrong allocation of subject	MO, DM
302	wrong subject-ID	MO, DM

5	**primary endpoint**	
501	data not collected	MO, DM
502	data partly collected	MO, DM
503	data incorrect	MO, DM
504	data not collected contemporary	MO, DM

Protocol Deviations / Violations (Examples)

code	description	responsable
4	**safety**	
401	SAE not reported	MO
402	SAE not reported on time	MO, SAE-B
403	SAE not reported correctly	MO, SAE-B
404	SAEs not reported or not reported on time	MO
405	SAEs Follow-up not performed or late	MO, SAE-B
406	AEs not reported or not reported accurately	MO

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Risk *– the combination of the probability of occurrence of harm and the severity of that harm* (ISO/IEC Guide 51)

Severity *– a measure of the possible consequences of a hazard*