ICH E6 (R2) How to Build a Sponsor Risk Management Program

Susan Leister, MBA, PhD, CQA, CSSBB

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Challenge Convention.
Exceed Expectations.

Course Objectives

- ❑ Discuss the ICH E6 (R2) updates for risk management
- ❑ Describe key elements of a Risk Management Program
- ❑ Describe how to conduct a risk assessment
- ❑ Discuss risk mitigation and reporting
- ❑ Discuss risk review and communication
- ❑ Discuss common pitfalls and solutions

Trainer Background

- ❑ >20 yrs QMS experience GCP, GLP, & GMP
- ❑ Consulted globally for numerous sponsor risk management programs & procedures

Q&A

How many of you have read the new ICH E6 (R2) update?

Have any of you established or participated in establishing a Risk Management Program?

Topic 1:
ICH E6 (R2) Updates for Risk Management

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Need for a Sponsor Risk Management Program

Revision to ICH E6 biggest drivers

- **Develop efficient and effective trial designs**
- **Evaluations & decisions based on facts, not opinions**
- **Helps deal with trial complexity**
- **Improve data reliability**
- **Focus on prevention**

Need for a Risk-Based Approach

Directs the Sponsor's limited resources to the higher risk areas

Focused on prevention

Process improvement vs QC

Reduces potential regulatory inspection findings

Helps manage non-compliant sites/vendors/contractors

Allows more coverage of critical areas in the same amount of time

Goal of ICH E6 (R2) Revision

"…to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results."

Revision of ICH E6

Increase In Scale, Complexity & Cost

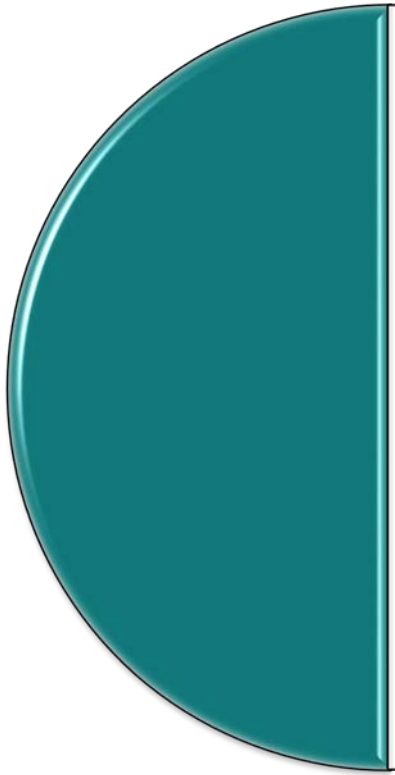
Evolution Of Technology & Risk Management Processes

Increase In Electronic Data Collection

Increase Clinical Trial Quality & Efficiency

Sponsor Responsibilities

ICH E6 (R2) Section 5.0

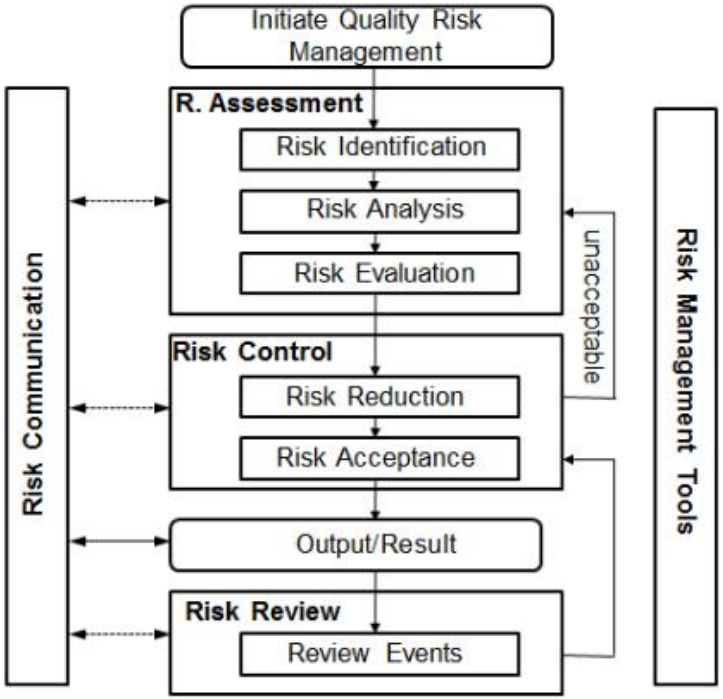


Quality Management: Sponsor Focus

- Implement a system to manage quality throughout all stages of the trial
  - Design, conduct, record, evaluate, report, and archive
- Focus on essential trial activities
  - HSP & data reliability
- Risk-based approach
  - Method is proportionate to inherent risk
- Operational feasibility
  - Avoid complex forms and processes
  - KISS principle

Overview of a Risk Management Program

ICH Q9



ICH E6 (R2) Risk Based Approach (5.0)

- ❑ Critical Process & Data Identification
- ❑ Identification Of The Risk
  - System Level & Trial Level
- ❑ Evaluate The Risk
  - Likelihood, Impact & Detectability
- ❑ Control The Risk
- ❑ Communicate The Risk
- ❑ Periodic Review Of Risks (Not A One Time Process)
- ❑ Reporting Risks

Let’s Discuss

Why do we need a quality management system with a risk-based focus?

Things to Consider

A risk based QMS helps focus and identify potential issues early on.

Identifying risks early have a better chance of being mitigated and controlled, therefore being proactive rather then reactive to managing risk to the subjects, quality and the trial data.

A QMS is a living system.

As more knowledge/experience is obtained during the lifecycle of a trial, there are processes in place to aid in continual improvement.

Definition of Risk

Risk Definition

ICH Q9

The combination of the *probability* of occurrence of harm and the *severity* of that harm.

Understanding Organization and Context

ISO 31000

It is important to evaluate and understand both the external and internal context of the organization.

Why?

The context can significantly influence the design of the framework.

External & Internal Influences

ISO 31000

External Factors:

Range could be International/National/Regional/Local

- Social & Cultural
- Political
- Legal & Regulatory
- Financial
- Technological
- Economic

Internal Factors:

- Organizational Objectives
- Quality System
- Resources
- Relationships with Stakeholders
- Organization's Culture
- Form and Extent of Contractual Relationships

Risk-Based Quality Management Focus

ICH E6 (R2)

- Trial activities essential to ensuring human subject protection and the reliability of trial results
- Risk based approach will focus on protocols prior to study start
- Understand major risks within a protocol prior to launch aids in adequate planning and mitigation of risks before they become a problem

Topic 2:
Key Elements for a Successful Risk Management Program

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Management Mandate and Commitment

ISO 31000

Let’s Discuss

What are the consequences of a risk management program that lacks commitment?

Effective Change Management

John Kotter's 8 Steps to Successful Change Management

Who are Stakeholders?

ISO 31000

Person or organization that can affect, be affected by, or perceive themselves to be affected by a decision or activity.

For example, a decision maker can be a stakeholder.

Benefits of Stakeholder Involvement

Ensure quality and compliance.

Promote Human Subject protection & data integrity.

Provide organizational & operational oversight.

Advocate on behalf of the risk.

Recommended Structure for a Risk Management Program

Risk Management Procedure

Organization's statement of overall intentions and directions to be taken for risk management.

(definition from ISO 31000)

Purpose/Scope within your organization

- What you want to accomplish by having a risk program

How will the company manage/ measure risk?

- Clear goals/objectives to meet

Who will do what?

- Roles and responsibilities

Risk Management Procedure

Other items to consider including:

- Conflict of interest statement
- Measurement of effectiveness
- Reporting Process
- Storage/archive plans

Topic 3:
How to Conduct a Risk Assessment

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Q&A

Have you participated in a formal risk identification process?

Why Identify Critical Processes and Data?

ICH E6 (R2) 5.0.1

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

Risk Identification Process

What is it?

- A process of systematically identifying potential risks.

When do we start identifying risks? (EARLY ON!)

- During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

What are critical areas?

- Processes, Data, Human Subject Protection

What is meant by Risk Identification?

ICH Q9

Risk identification is a systematic use of information to identify issues referring to the risk question or problem description.

Risk identification addresses the question

“What might go wrong?”

Including identifying possible consequences.

Why Identify Risks?

ICH E6 (R2)

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

Sponsor Risk Based Quality Management System

ICH E6 (R2)

Topics to Consider

- Protocol design, operational design and execution
- Participant safety
- Trial management
- Pre/non-clinical and test article development
- Data management
- Biometrics and statistical analysis
- Pharmaco-vigilance
- Quality control (QC)
- Quality assurance (QA)
- CRO Vendors: Development Operations, Specialty Vendors

System Level

EMA Reflection Paper 4.1.1

Organization structures

(ex: communication plan)

Organization responsibilities

(ex: contractors)

Quality systems and processes

(ex: SOPs)

Facilities and computerized systems

(ex: IVRS)

Personnel

(ex: training program)

Compliance performance

(ex: inspection outcome)

Regulatory framework

(ex: registrational approval)

Protocol Level

EMA Reflection Paper 4.1.2

Investigational drug product

(ex: accountability logs)

Trial design and protocol specific requirements

(ex: trial population)

Project management

(ex: timelines)

Resources

(ex: staffing needs)

Training

(ex: GCP or protocol)

Equipment

(ex: lab testing)

Procedures/ methods

(ex: specialty lab testing)

Let’s Discuss

Consider a situation where the backup and recovery program has not been properly established and tested for a safety monitoring computer system.

What are the potential impacts at a system level?

Protocol Summary

Title	Evaluation of Efficacy and Safety of rapid hormonal cycling (RHC) vs RHC + EndroCream for the treatment of Severe Empathy Withdrawal
Description of Study Design	This is a Phase I, 2-arm open-label clinical trial of standard of care rapid hormonal cycling (RHC) vs RHC + EndroCream as treatment for IGR-confirmed Severe Empathy Withdrawal

Exercise #1 Risk Identification

Protocol Summary Risk Identification

As one group, use the protocol summary document provided to identify three potential risks for further evaluation at the protocol level.

Establishing Risk Indicators, Quality Tolerance Limits, and Thresholds

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Risk Indicators & Thresholds

Risk Indicator

Risk indicators are metrics used to monitor identified risk exposures over time

Threshold

A pre-determined level, point, or value (e.g., number, %, range) associated with a Risk Indicator that indicates the need for a follow-up action

Risk Indicator Categories and Examples
Critical Success Factors

Safety
- Outliers/trends in number of adverse events per subject visit/site

Investigational Product
- Incidence of temperature excursions

Recruitment & Discontinuation
- Number of screen failures compared to average across sites

Issue Management
- Number of deviations per subject visit/site compared to average across sites

Data Quality
- Abnormal trend or lack of variability in data

On-Site Workload
- Amount of data outstanding for verification or review

Essential Documents
- Missing/Late documents

Staffing, Facilities, Supplies
- Staff turn-over

Thresholds, Example Enrollment Dropout Rate

Thresholds	Examples of Actions
+/- 3% more/less than the average reported enrollment dropout rate (Green)	No action Review data remotely
+/- 3.1 to 10% more/less than the average report dropout rate (Yellow)	Assess data remotely Call the site Visit the site
Greater than 11% of the average reported dropout rate (Red)	Visit the site Audit site

Identification of Risk Indicators

Risk Register

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What is a Risk Register?

Document that provides structure for cataloging, tracking, and reporting on risk events.

It is a living document.

Captures risk assessment data in a quantitative or qualitative manner for impact, likelihood, and detectability.

Also known as a risk log.

Why Have a Risk Register?

Common location for operational data to show how risk management has evolved over time, and allows you to analyze and trend high risks, areas that need more oversight, and help with process improvements to achieve overall compliance.

Benefits of a Risk Register

- Facilitates proactive risk identification & documentation.
- Facilitates risk mitigation.
- Captures the lifecycle of risks in a uniform manner
- Provides project planning documentation.
- Helps in communication to all stakeholders.
- Promotes continuous improvement.

Updating/Reviewing the Risk Register

Why do it?

- Keep the document as a living document (current)

When do I update the risk register?

- When changes occur

How do you track it?

- Document the updates (version control)

Drives the development of the final risk control/risk mitigation strategy

What is RPN (Risk Priority Number)?

R = Impact of the event [10 being most severe, 1 being very minimal if any impact]

P= Likelihood of the event occurring [10 it will happen, 1 very little chance it will happen]

N = Detection: The chance the event would not be detected before the user was aware [10 it would go undetected, 1 it would be obvious as soon as the event occurred]

Formula of all three multiplied together to equal one number.

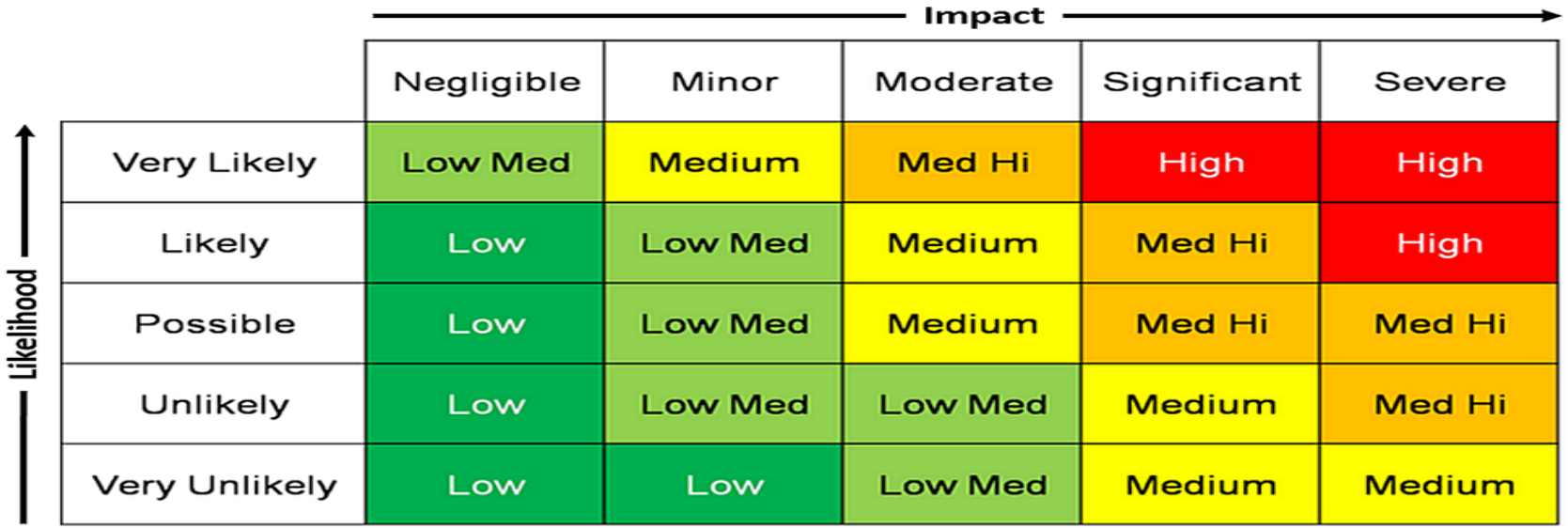
Risk Matrix (3 x 3 grid)

This matrix provides risk acceptance criteria and simple rules for risk treatment.

	Severity		
Likelihood	**Minor**	**Moderate**	**Major**
Likely	*acceptable* add controls		*unacceptable* don't go
Possible		*acceptable* add controls	
Unlikely	*acceptable* routine procedure		*acceptable* add controls

Risk Assessment Matrix (5 x 5 grid)

The risk assessment matrix is the tool that can be used to prioritize and develop an effective risk strategy.



	Negligible	Minor	Moderate	Significant	Severe
Very Likely	Low Med	Medium	Med Hi	High	High
Likely	Low	Low Med	Medium	Med Hi	High
Possible	Low	Low Med	Medium	Med Hi	Med Hi
Unlikely	Low	Low Med	Low Med	Medium	Med Hi
Very Unlikely	Low	Low	Low Med	Medium	Medium

Topic 4:
Evaluating Risks

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Sponsor Risk Based Quality Management System

ICH E6 (R2)

ICH E6 R2: Risk Evaluation (Sponsor)

The sponsor should evaluate the identified risks, against existing risk controls by considering:

(a) The ***likelihood*** of errors occurring,

(b) The extent to which such errors would be ***detectable***,

(c) The ***impact*** of such errors on human subject protection and reliability of trial results.

All Risks Are Not Created Equal

Recognize there is some level of risk inherent to all activities

Understand that risks vary in their significance

Understand that it is not possible to eliminate every risk in clinical studies

Risk Evaluation

Risk evaluation compares the identified and analyzed risk against given risk criteria.

Risk evaluations consider the strength of evidence for all three of the fundamental questions.

1. *What is the likelihood it will happen?*
2. *What is the impact if it happens?*
3. *What are the chances it will be detected?*

Definition: Likelihood

ICH E6 (R2)

The likelihood of errors occurring.

May be understood as the chance the risk may occur.

Evaluating Likelihood

Ask

What is the likelihood that the risk will become an issue?

Score	Descriptor	Frequency
1	Very Low	This will probably never happen.
2	Low	Do not expect it to happen/recur, but it is possible it may do so.
3	Medium	Might happen or recur occasionally.
4	High	Will probably happen/recur, but it is not a persisting issue/circumstances.
5	Very High	Will happen/recur, possibly frequently.

Definition: Detectability

ICH E6 (R2)

The extent to which such errors would be identified.

Evaluating Detectability

Ask

Can the risk be detected in time before it becomes a systemic issue?

Score	Detection	Criteria
1	Very High	Very high chance of detection.
2	High	High chance of detection.
3	Medium	Medium chance of detection.
4	Low	Low chance of detection.
5	Very Low	Very low chance of detection.

Definition: Impact

ICH E6 (R2)

The effect of errors on human subject protection and the reliability of trial results.

Evaluating Impact

Ask: *How will the risk impact patient safety, product quality, and/or trial results?*

Score	Impact	Criteria
1	Very Low	The event ***has a very low likelihood of impact*** on HSP, product quality and/or reliability of the trial results.
2	Low	The event ***has a low likelihood of impact*** on HSP, product quality and/or reliability of the trial results.
3	Medium	The event ***most likely will impact*** HSP, product quality and/or reliability of the trial results.
4	High	The event ***has a high likelihood of impact*** on HSP, product quality and/or reliability of the trial results.
5	Very High	The event ***has a very high likelihood of impact*** on HSP, product quality and/or reliability of the trial results.

Exercise #2

Risk Evaluation Using a Quantitative Scale

As one group let’s assess the impact, likelihood, and detectability using the quantitative scale for 3 risks identified from the protocol summary.

Tips for Risk Prioritization

Prioritization of risks should:

- Orient risks to meet the objectives of GCP and scientific objectives of the clinical trial.
- Establish priorities at study planning and preparation.
- Priorities should be reflective of the trial documents, and associated resources.

Topic 5: Risk Control & Mitigation

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Sponsor Risk Based Quality Management System

ICH E6 (R2)

Definition: Risk Control

A risk control is a decision to manage a risk.

- Controls may include any policy, procedure, practice, process, technology, technique, method, or device that modifies or manages risk.

Risk Control & the Sponsor

ICH E6 (R2)

The *sponsor* should decide which risks to reduce and/or which risks to accept.

- The approach used to reduce risk to an *acceptable level should be proportionate* to the significance of the risk.
- *Risk reduction activities* may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Risk Control

EMA Reflection Paper

Focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being mitigated or accepted?

Risk Control Example

If an organization has a new Phase 3 international study and some of the sites are remote so they will use paper CRFs the long term maintenance and storage of the records after the close of the study is an identified risk.

Prior to the study start, the Sponsor works with the PI and sites to determine the minimum data required in the CRFs along with a long-term data storage plan.

The Sponsor is controlling the identified risk by risk reduction.

Threat Strategies

Strategy	Description	Example
Avoidance	**Ensuring that no matter what happens there is no way the risk will hurt your clinical trial, system, human subjects, data integrity, or organization.**	Not conduct high risk protocol for new indication which organization has no experience with the population
Acceptance	**The act of inaction. Clearly document decision.**	Staff complete training late
Mitigation	**-Ensuring there is a lower likelihood that a threat event will occur. -Or ensuring that if the threat comes to pass the amount at stake is not as severe as it would have been without the action.**	Use Software as a Service for data management to mitigate the system downtime
Risk Transfer	**Shifting the ownership and responsibility for a threat (risk) to another party.**	Contracting clinical monitoring to a CRO (partial transfer)

Threat Strategies

Avoidance

when the risk is too great

Acceptance

most common strategy for threats

when the threat can be managed if it happens

when the risk is external & unpredictable

Transfer

Rare for a complete transfer

Mitigation & transfer tend to be the most expensive

Exercise #3 Risk Control

As one group, let's select a high risk identified from exercises 1 & 2. Let's discuss a mitigation strategy to reduce the overall risk.

If time permits we will rescore the risk.

Let’s Discuss

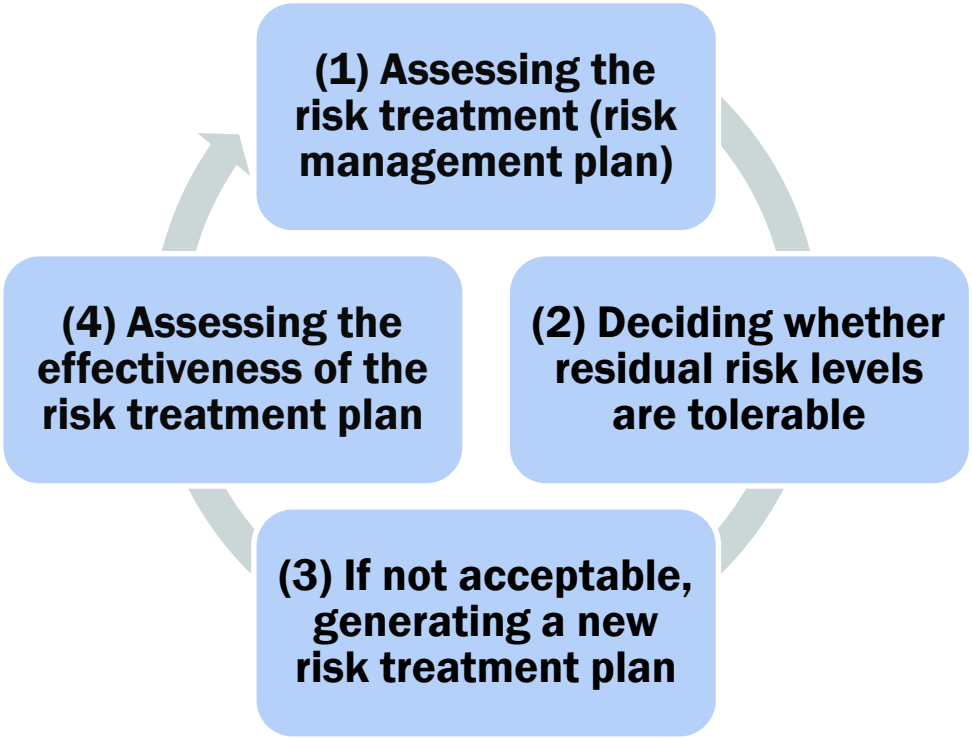
An organization wants to start a new phase 3 international study and there are new regulations related to insurance for subjects over the age of 65.

To minimize this potential risk, the clinical team should review the insurance requirements in each country.

What else would you suggest to help reduce the risk?

Cyclical Process of Risk Treatment

ISO 31000



Selection of Risk Treatment Options

Take into account:

- **Balance of costs and efforts of implementation**
- **Risks where risk treatment is not justifiable on economic grounds (cost for the investigator)**
- **Different stakeholders and subject matter experts involved in the decision of treatment action(s)**
- **Combining several actions to increase efficiency**
- **Secondary risks**

Topic 6:
Reviewing and Communicating Risks

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Sponsor Risk Based Quality Management System

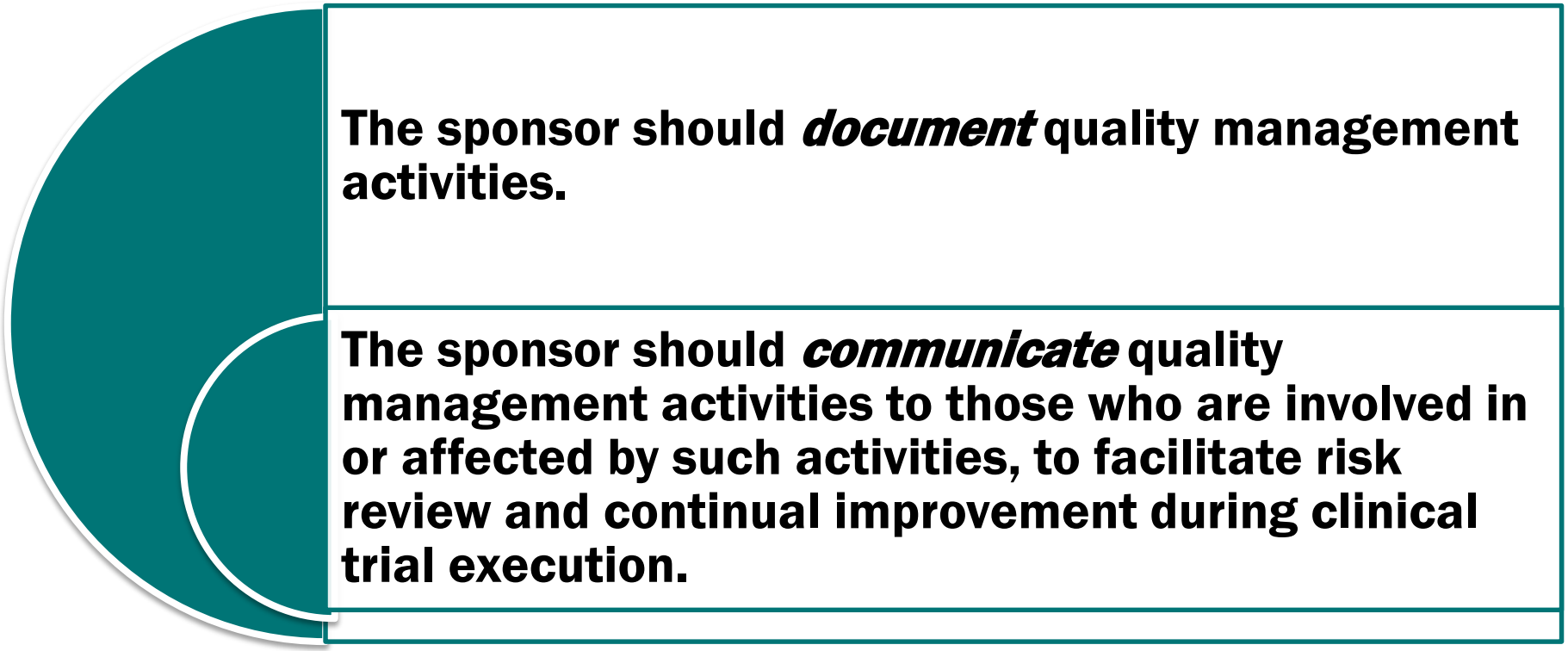
ICH E6 (R2)

What is Risk Communication?

Risk communication **is the sharing of information about risk and risk management between the decision makers and others.**

Continual and iterative processes that an organization Continual and iterative processes that an organization conducts to provide, share or obtain information and to engage in dialogue with stakeholders regarding the management of risk.

Risk Communication and ICH E6 R2 (5.0.5)



Periodic Risk Review

ICH E6 (R2)

The sponsor should *periodically review risk control measures* to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

(Section 5.0.6)

Following ICH E6 R2

Consider that ICH E6 is recommending several actions to be taken regarding risk reviews

- **Periodically assess**
- **Evaluate continued effectiveness of quality management activities**
  - *Monitor risks and if they continue to remain effective controlling risks, risk mitigation plans and the process for managing their implementation*
- **Consider changes due to new information**
  - *Continuous improvement opportunities*

Frequency: Scheduled Reviews

Guidance for a *scheduled* frequency of risk reviews should be stated in the risk management plan.

- **Examples of frequency are:**
  - **Weekly**
  - **Monthly**
  - **Quarterly**
  - **Yearly**
  - **By study milestone**

Frequency: Unscheduled Reviews

The risk management plan should provide guidance of when *unscheduled* risk reviews should be performed. Consider the following:

Whenever a risk event is triggered or occurs. • ***(GCP example: Exceeds QTL for Protocol Deviations)***	**Prior to a go/no go decision.** • ***(GCP example: Dose escalation study with Cohorts)***	**Major changes or updates to the risk.** • ***(GCP example: protocol amendment, major changes to organization's SOP, regulation change)***

Examples: Tasks for Risk Review Team

Retire/close **a risk whose ability to impact the project has elapsed**

Retire/close **a risk whose residual impact on the project is deemed to have reached an acceptable level**

Team should discuss any risks where the response actions are not being carried out effectively or the impact is increasing. If these cannot be resolved they should be escalated

Topic 7:
Reporting Risks

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Sponsor Risk Based Quality Management System

ICH E6 (R2)

Risk Reporting and ICH GCP E6

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

Following ICH GCP E6

Consider that ICH GCP E6 (R2) section 5.0.7 is recommending several items be included in the clinical study report (CSR):

- **A description of the quality management approach implemented in the trial**
- **A summary of the important deviations from the predefined quality tolerance limits**
- **A summary of remedial actions taken**

Risk Reporting: Example

In section 9.6, a description of data quality assurance and systems used should be included to address the “quality management approach” implemented.

The intent is to show credibility of the study results by describing methods of data collection that are accurate, consistent, complete and reliable.

For example, training sessions, monitoring, data checking and verification, centralized procedures in the case of a multicenter study, audits, and documentation used to control procedures (instruction manuals) should be described. Keep in mind, most, if not all of this information is already in the protocol.

Topic 8:
Challenges with Risk Programs

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Stakeholder/Team Challenges

Resources & Time management	**Risk averse**	**Balancing cost and measures taken**
Understanding context	**Shared understanding**	**Incomplete knowledge**

Executive Management Challenges

Communication Issues

Risk terminology

Fact vs. opinion

Roles and responsibilities

Communication Issues

- Someone Focusing on a Personal Agenda
- Experiencing Information Overload
- Getting Distracted by Emotional Noise
- Stereotyping and Generalizing
- Assuming Similar Interpretations
- Jumping to Conclusions

Conclusion

We discussed the following:

- ❑ updates to ICH E6 (R2) associated with risk management,
- ❑ key elements of a Risk Management Program,
- ❑ how to conduct a risk assessment,
- ❑ risk mitigation and reporting,
- ❑ risk review and communication, and
- ❑ some common pitfalls and solutions with risk management programs.

Questions

References

- ISO 31000:2009 Risk Management Principles and Guidelines
- ICH Q9 Quality Risk Management
- ICH GCP E6 (R2), Integrated Addendum to Good Clinical Practice
- EMA Reflection Paper on Risk Based Quality Management in Clinical Trials
- EMA Reflection Paper on Risk Based Quality Management in Clinical Trials, Annex 1

Contact information

For further questions:

Susan Leister, MBA, PhD, CQA, CSSBB

Vice President, Quality & Compliance

Technical Resources International, Inc.

sleister@tech-res.com