Possible Scenarios to Address Issues on Non-clinical Studies for ATMPs

CAT/Stakeholders Workshop
London 12/Jan/2012

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Introduction – Eucomed and the Medical Device Experience

- Medical Device Manufacturers have been using Risk Management for many years.
- The goal is to address , calculate and reduce any foreseeable unwanted risk to the patient that may arise from the use of the product BEFORE it is marketed.
- Various standards have been written to help manufacturers manage the risk. ISO 14971 represents the gold standard for medical device manufacturers in terms of risk management.
- We believe that the principles described in the ISO14971 standard may help ATMP manufacturers to address and lower risks in a non-clinical scenario.

Risk Management

Intended Use, Risk, Harm, Hazard, Hazardous Situation, Risk Analysis, Risk Management, Risk, Risk Mitigation, Residual Risk, Overall Residual Risk, FTA, FMEA, Risk related to device, clinical procedure, concomitant treatment.

Product Risk Management

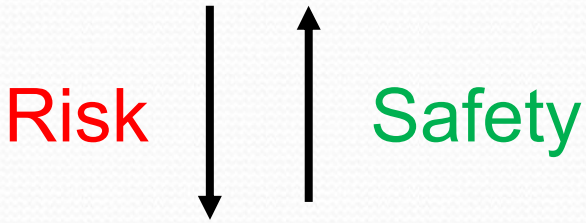
Scope Presentation:

- Not Project Risk
- Not Business Risk
- Patient/User Risk of Harm

Although, the risk of harm may directly affect project and business risk.

Product Risk Management

In general, the risk of harm is the inverse of safety.



Safety increases as risk of harm decreases

- Safety - freedom from unacceptable risk of harm.
- Concerned only with future possibilities.
- If there is certainty, there is no risk of harm.

- *If there is no use, there is no risk of harm*

Product Risk Management

- What does Safe mean?
  - Safety does not mean zero risk. It means it is free from any unacceptable risk and/or it is considered to have a Benefit that outweighs the Risk

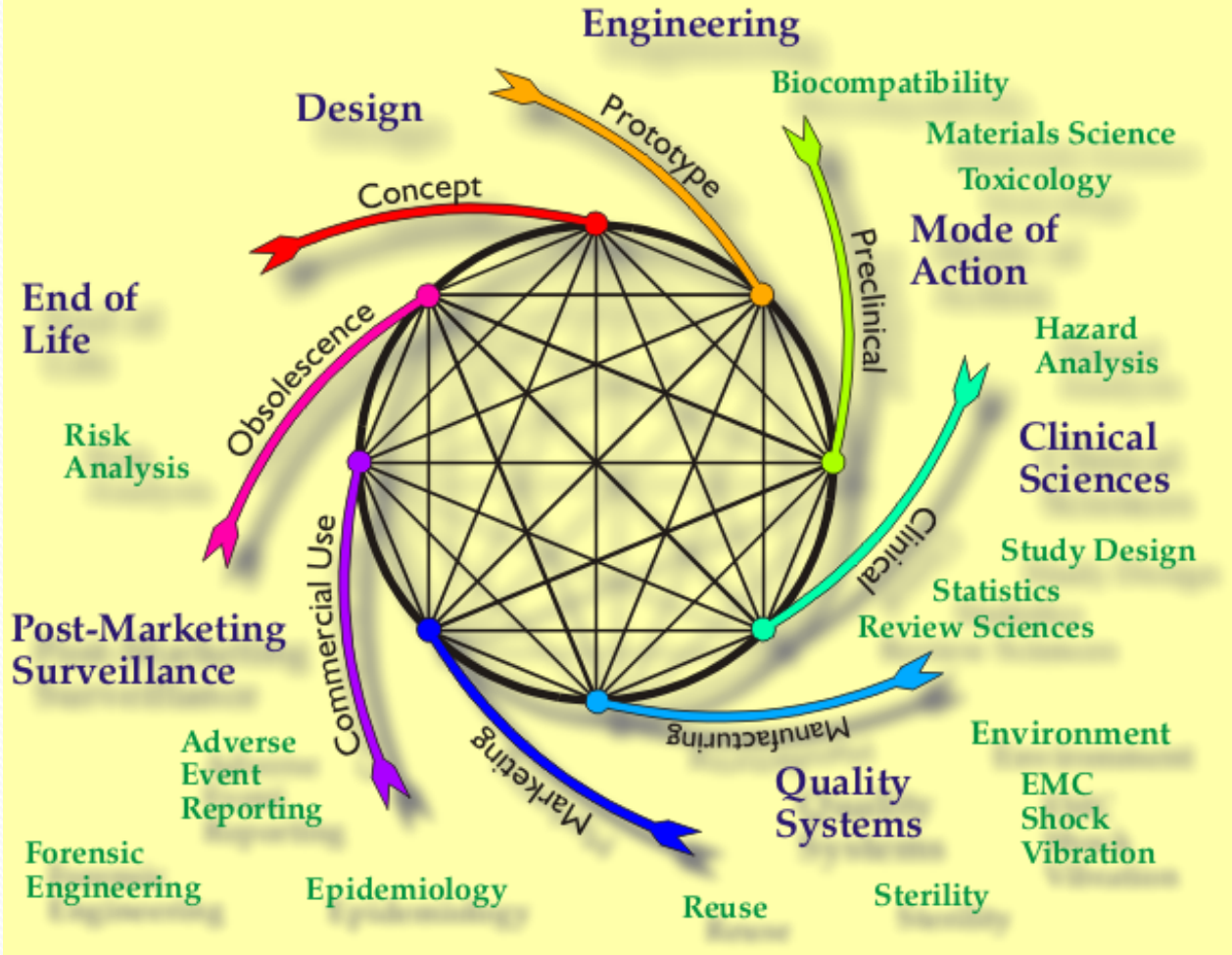
- Why is Risk Management needed?
  - Need some system to measure or weigh risk, with defined criteria on acceptability and/or action → Process, approach, and evidence that due diligence was done and overall residual risk to the patient is deemed acceptable.

Product Risk Management

- Risk Management

Systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, and controlling risk

EN ISO 14971:2009



Some Definitions

- **Risk** – Combination of the probability of occurrence of harm and the severity of that harm.
- **Harm** – Physical injury or damage to health of people, or damage to property or the environment.
- **Hazard** – Potential source of harm.
- **Hazardous situation** – Circumstance in which people, property, or the environment are exposed to one or more hazard(s).
- **Safety** - Freedom from unacceptable risk of harm

EN ISO 14971:2009

Hazard, Harm?

- **Hazard** = icy sidewalk
- **Hazardous situation** = Person walks on an icy sidewalk
- **Harm** = broken leg

Example of Scaffold forTissue Engineered Product

- **Hazard** = Incompatibility Host-Cells or scaffold material
- **Hazardous situation** = implant of inadequate cells
- **Harm** = critical patient injury and ineffective therapy/rejection of combination device

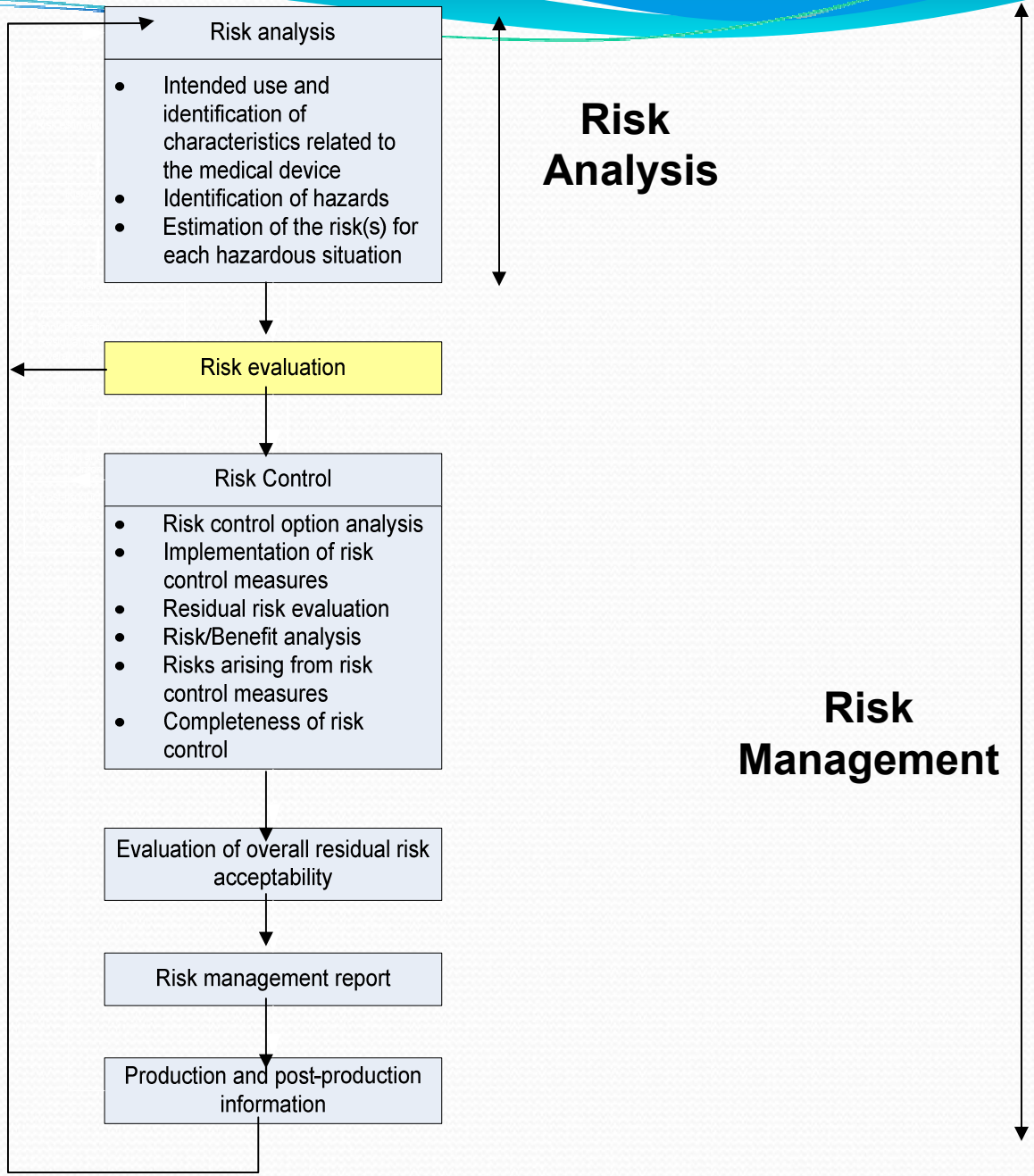
ISO 14971:2009

More Definitions

- **Risk analysis** – Systematic use of available information to identify hazards and to estimate the risk.
- **Risk evaluation** – process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk
- **Risk control** – process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels.

ISO 14971:2009

ISO 14971 Risk Management Process



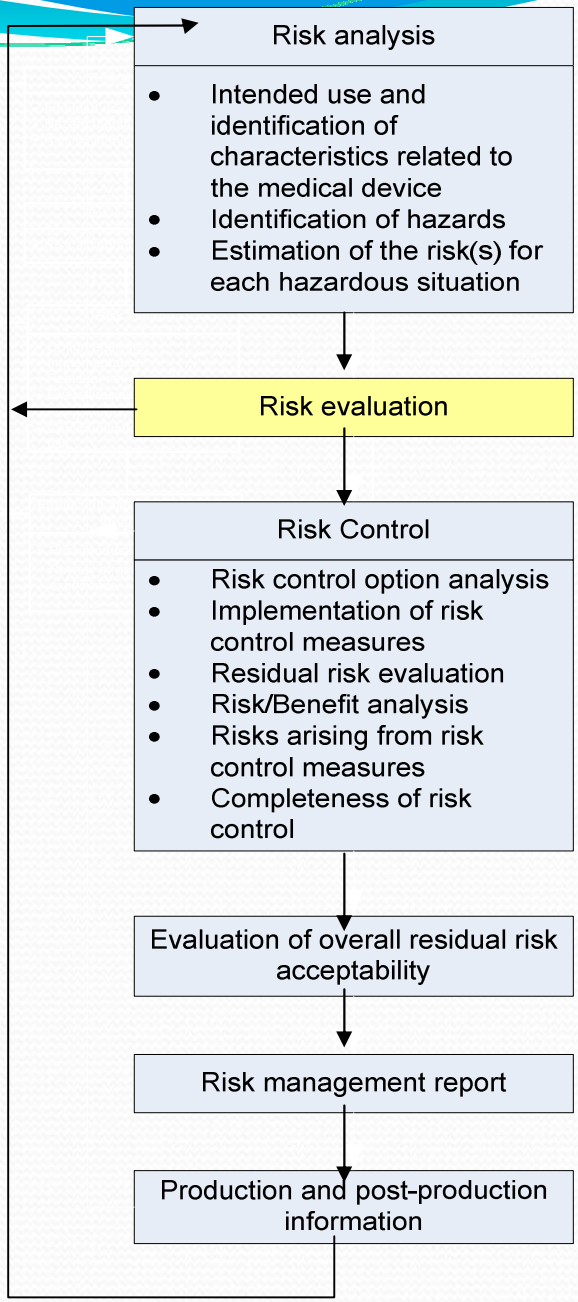
Risk Management Planning

A Risk Management Plan requires:

- Scope - identify and describe the medical device and the life-cycle phases for which the plan is applicable
- Allocation of resources / responsibilities
- Requirements for review of risk management activities
- Criteria for risk acceptability
- Verification activities
- Production and post-production monitoring

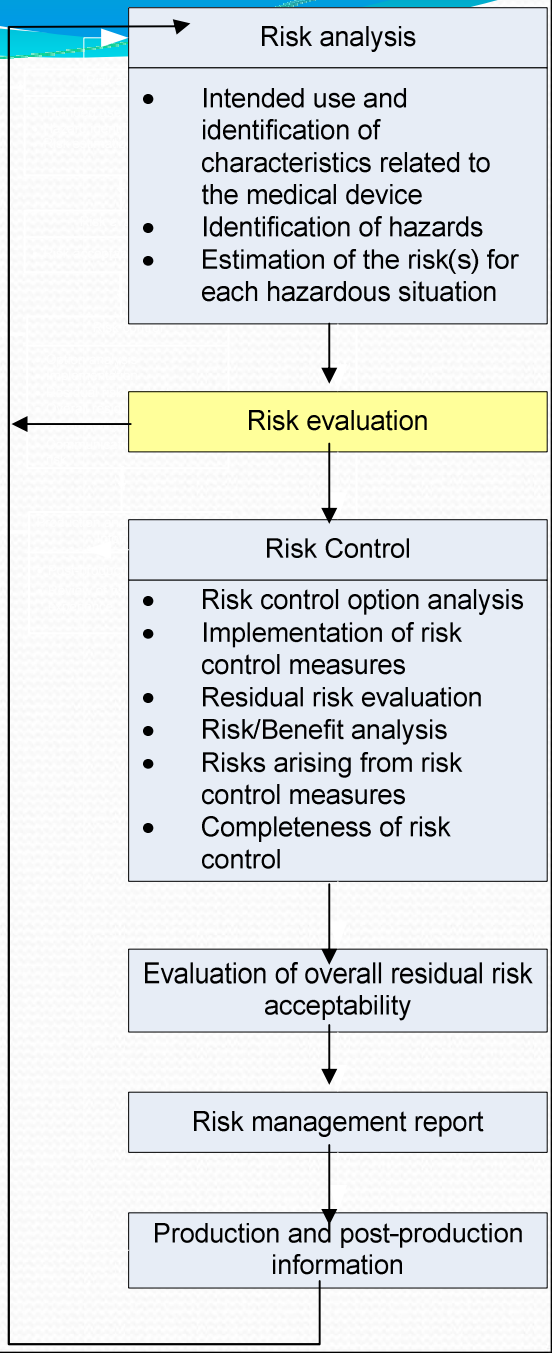
Risk Analysis

- Determine intended use and identify the characteristics related to the safety of the medical device.
- Identify the hazards
- Identify the hazardous situations
- Estimate the risk for each hazardous situation
  - Estimate probability of occurrence and severity of harm.
- To be used in combination with an engineered human tissue



Risk Analysis

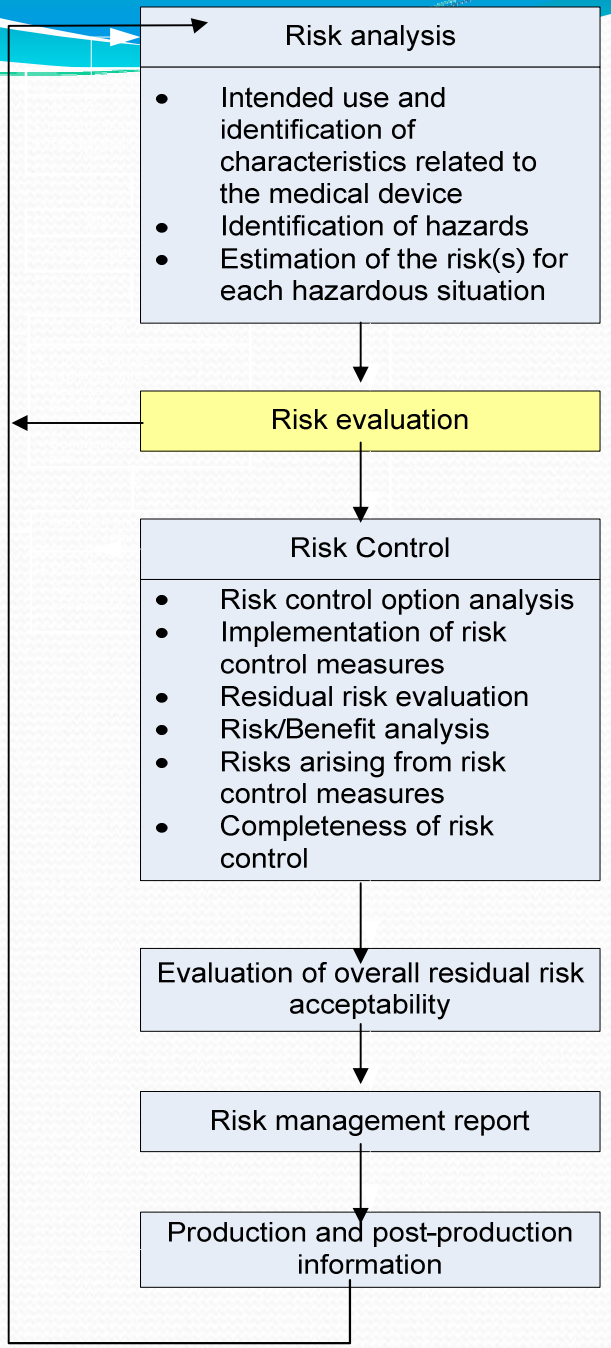
- How is the device to be used?
- Is the device when it is applied in contact with the test subject or other persons?
- What materials and/or components are incorporated in the device or are used with, or are in contact with, the device?
- Is energy delivered to and/or extracted from the test subject?
- Are substances delivered to and/or extracted from the test subject?
- Are biological materials processed by the device for subsequent re-use?
- Is the device supplied sterile or intended to be sterilized by the user, or are other microbiological controls applicable?
- Is the device intended to be routinely cleaned and disinfected by the user?
- Is the device intended to modify the test subject environment?
- Are measurements taken?
- Is the device interpretative?
- Is the device intended for use in conjunction with other devices, medicines or other medical technologies?
- Are there unwanted outputs of energy or substances?
- Is the device susceptible to environmental influences?
- Does the device influence the environment?
- Are there essential consumables or accessories associated with the device?
- Are maintenance and/or calibration necessary?
- Does the device contain software?
- Does the device have a restricted shelf-life?
- What determines the lifetime of the device?
- Are there any delayed and/or long-term use effects?
- To what mechanical forces will the device be subjected?
- Is the device intended for single use?
- Is safe decommissioning or disposal of the device necessary?
- Does installation or use of the device require special training or skills?
- How will information for safe use be provided?
- Can the user interface design contribute to use errors?
- Is the device used in an environment where distractions can cause use errors?
- Does the device use an alarm system?
- Is the device intended to be mobile or portable?
- In what ways might the device be deliberately misused?
- Is the device specifically designed for the subjects enrolled in the trial?
- Is the device to be used after the trial?



Risk Evaluation

Evaluate each identified hazardous situation for risk acceptability.

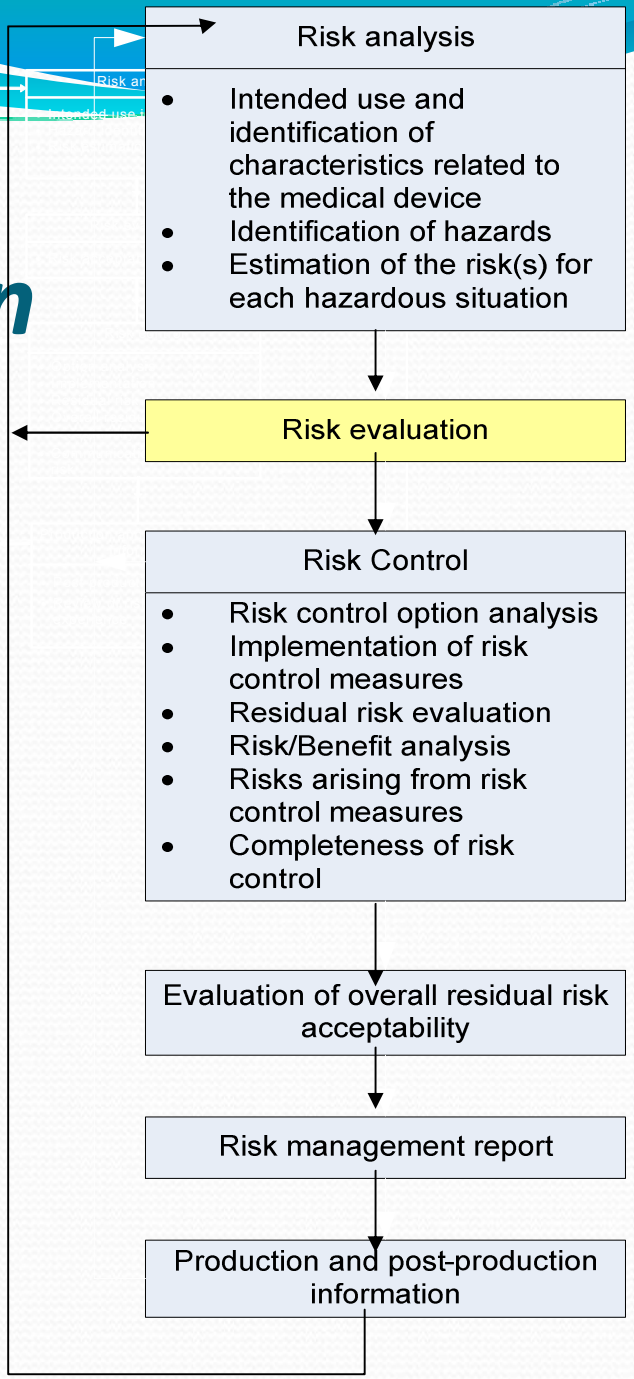
- Use pre-defined criteria from the risk management plan.
- Determine if risk reduction is needed



Risk Control and *Risk Control Implementation*

Pursue risk control if risk evaluation determines risk reduction is needed.

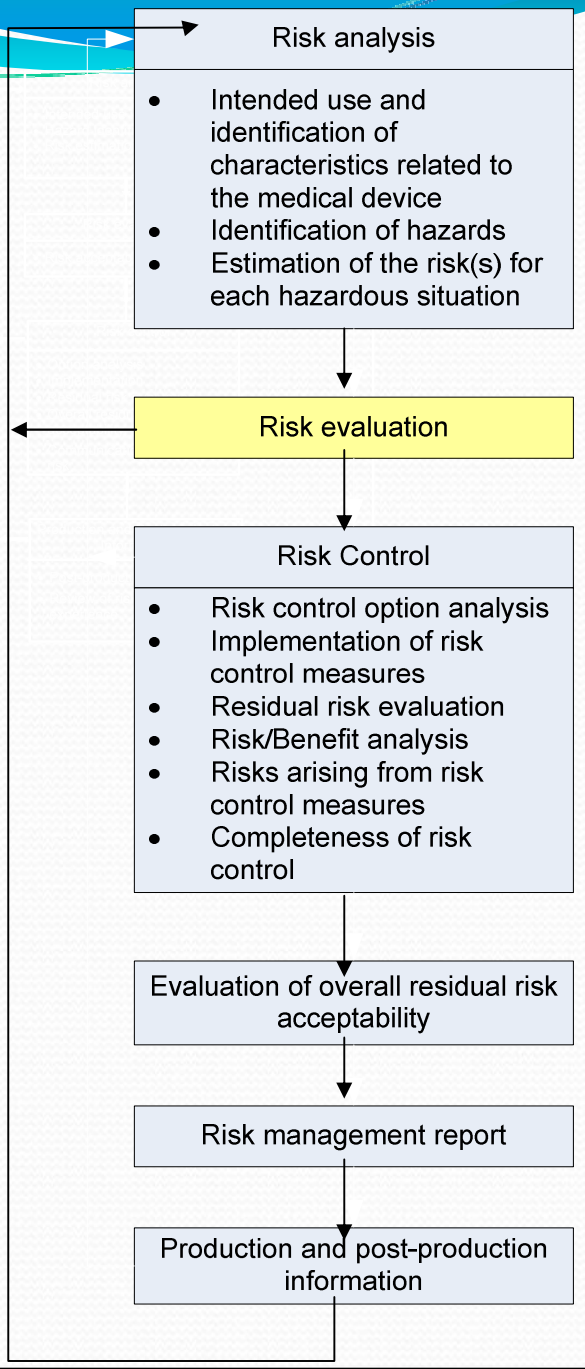
- Choose any combination of the following approaches listed, in the order of preference.
  1) Make it safe by design.
  2) Use protective measures in the device or manufacturing process.
  3) Provide safety information (instructions for safe use, cautions, warnings, etc.).
- *Verify the risk control measures are implemented.*
- *Verify or validate the risk control measures are effective.*



Residual Risk Evaluation

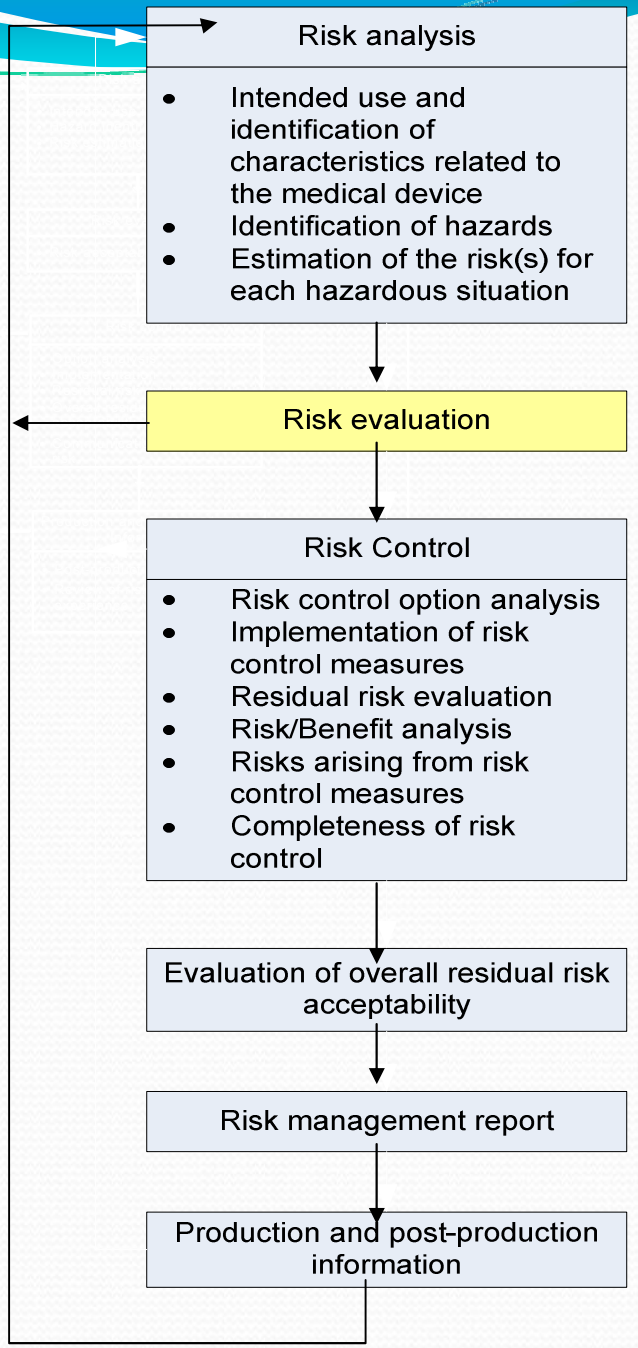
Evaluate the residual risk for each identified hazardous situation after risk control

- If unacceptable, further risk reduction is required.
- If acceptable, the manufacturer shall decided which information to put into the accompanying documents to disclose the residual risk (cautions, warnings, and contraindications.)



Risk/ Benefit Analysis

- Risk/ Benefit Analysis is allowed if the residual risk is judged unacceptable and further risk control is not practical.
- If the medical benefits out weigh the risk, relevant information necessary to explain the residual risk must be placed in the "accompanying documents supplied by the manufacturer".
- If evidence does not support the medical benefits outweigh the risk, the risk remains unacceptable.



Benefit for medical devices

For devices, the benefit for the patient is the combination of:

- Their ability to meet the intended use through a performance which is pre defined by the manufacturer.
- The ability of the HCP to use the device
- The appropriateness of the facility in which the device is used

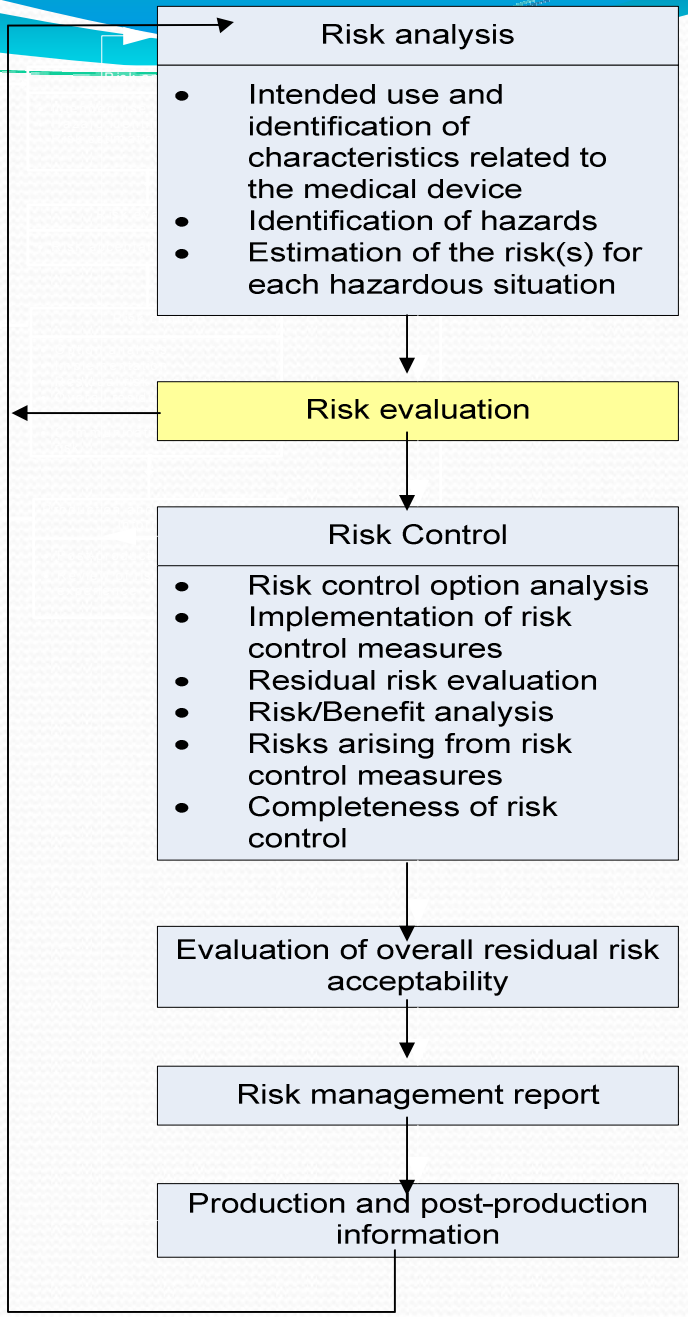
Benefit for medical devices

- It is possible to evaluate the performance of a device objectively during the pre-market phase
- The benefit brought to the patient by such performance depends heavily from the HCP and the facility in which the device is used
- In the pre-market phase the total benefit can be determined only under certain circumstances (clinical evaluation)

Risk Arising from Risk Control

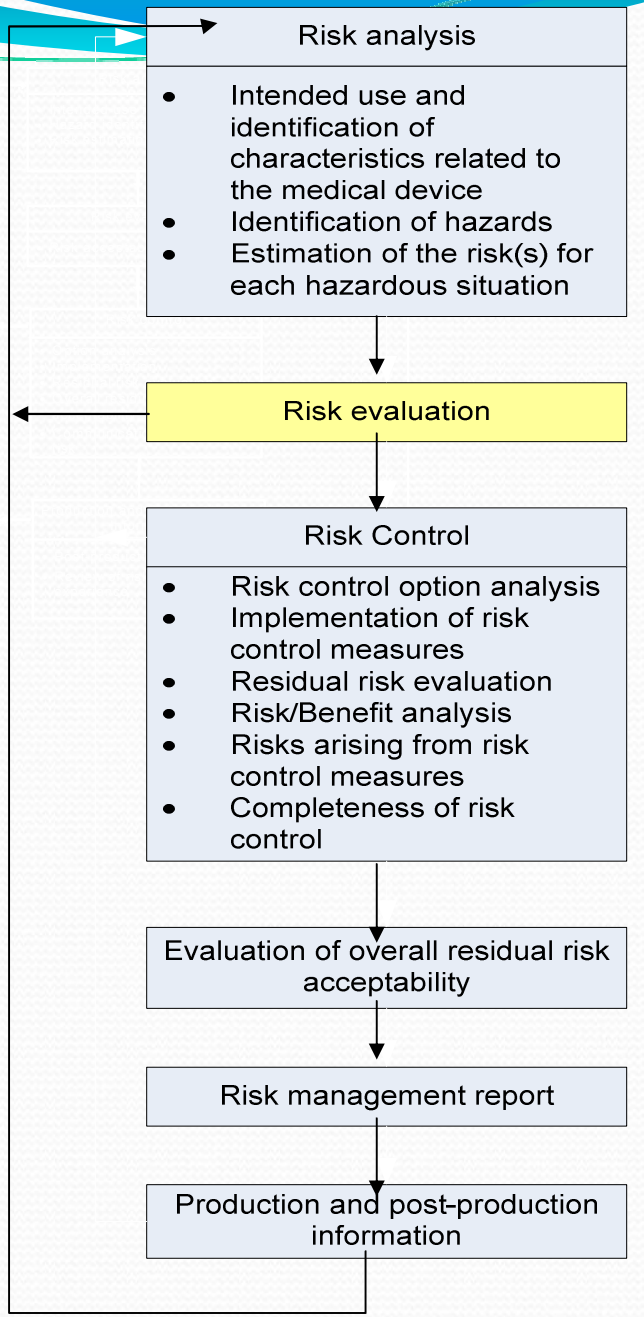
Review the risk control measures to determine if they:

- Introduce any new hazards and hazardous situations.
- Increase the risk of previously identified hazardous situations.



Evaluation of Overall Residual Risk

- Following implementation and verification of all risk control measures, the overall residual risk of the device must be evaluated.
- The result of the overall residual risk evaluation needs to be documented.

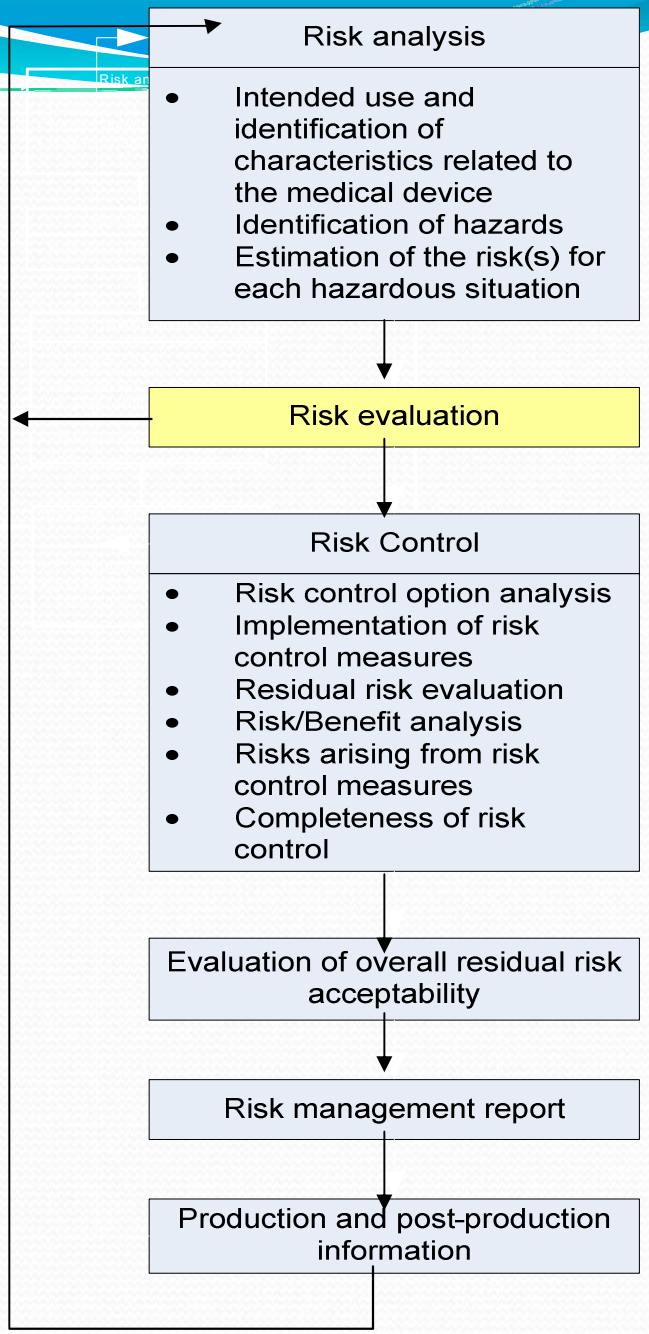


Risk Management Report

Document the results of the risk management process in a report, providing traceability for each hazard to:

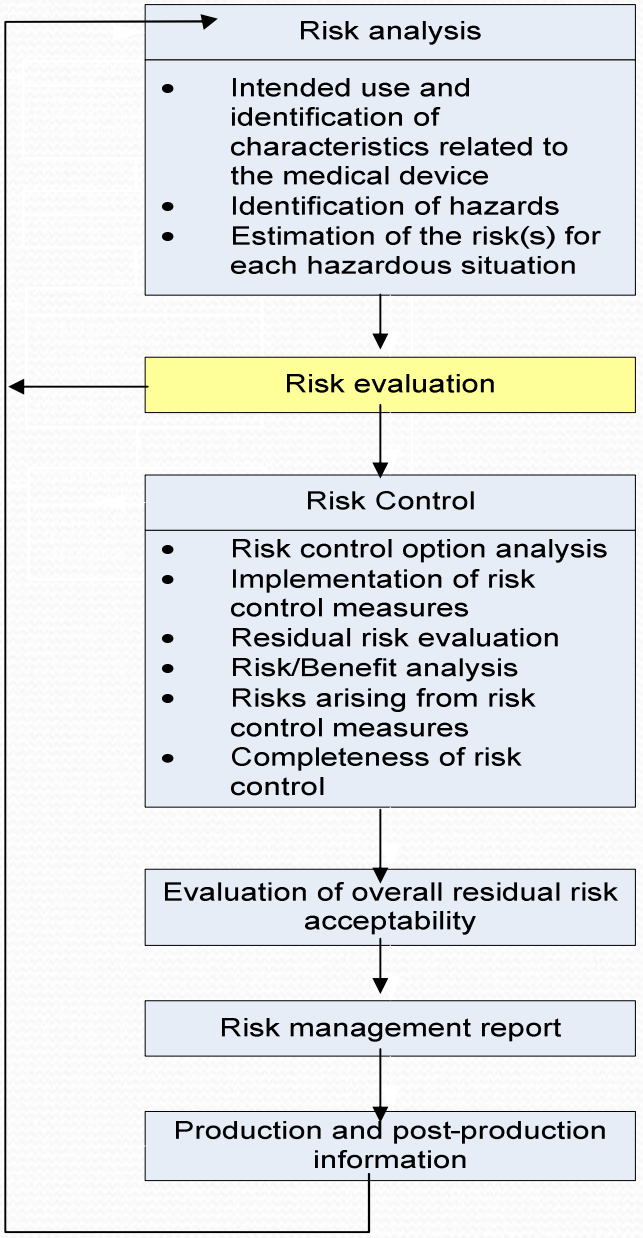
- the risk analysis
- the risk evaluation
- implementation and verification of risk control
- assessment of residual risk

The results of all risk management activities are recorded and maintained in a Risk Management File.



Production and Post- Production Information

- The manufacturer shall establish, document and maintain a feedback system to collect and review information about the device in the production and post-production phase.
- This happens also when the device is part of a combined product
- The information shall be evaluated for relevance to safety to determine if:
  - Previously unrecognized hazards or hazardous situations are present.
  - If the estimated risk from a hazardous situation is no longer acceptable



Production and Post- Production Information

If any of the previous conditions occur,

- The impact on previously implemented risk management activities shall be evaluated and shall be fed back as an input to the risk management process.
- Consider reviewing the applicable risk management file to evaluate changes in the residual risk or its acceptability and impact on previously implemented control actions

Risk Management Activities within a Quality System

- Top management has the responsibility to incorporate risk management into the organization.
- Risk management activities are directed by a controlled process.
- Risk management planning is coordinated with design and development planning.
- Risk analysis begins as early as possible in the device development process.
- Risk identification accomplished by analyzing various aspects of the device life cycle.

Life Cycle Risk Management

Design Input:

Would the device risk be acceptable if the device always operated exactly as specified in the Design Input Specification?

Design Output:

Has the implementation of the design introduced any systemic design errors that adversely affect device safety?

Manufacturing:

Does manufacturing the device introduce any unacceptable safety risks?

Post-Production:

Do design or process changes after market release affect risk?

Have unforeseen risks been identified following market release?

How do we identify risk?

Various analysis techniques can be used to identify the possible hazard situations.

For example

- Fault Tree Analysis (FTA) used to analyze features and therapies.
- Design FMEA approach used to analyze design.
- Process FMEA approach to analyze risk associated with manufacturing assembly.

Risk Estimation and Evaluation

Example of a qualitative risk evaluation method:

	Negligible 1	Marginal 2	Critical 3	Catastrophic 4
Improbable 0	Acceptable	Acceptable	Acceptable	Acceptable
Remote 1	Acceptable	Acceptable	Acceptable	Unacceptable
Occasional 2	Acceptable	Acceptable	Unacceptable	Unacceptable
Probable 3	Acceptable	Unacceptable	Unacceptable	Unacceptable
Frequent 4	Unacceptable	Unacceptable	Unacceptable	Unacceptable

Probability can be reduced, severity never !!

Risk Estimation and Evaluation

Example of a **OUTDATED** qualitative risk evaluation method:

	Negligible 1	Marginal 2	Critical 3	Catastrophic 4
Improbable 0	Acceptable	Acceptable	Acceptable	As Low As Reasonably Practicle
Remote 1	Acceptable	Acceptable	As Low As Reasonably Practicle	Unacceptable
Occasional 2	Acceptable	As Low As Reasonably Practicle	Unacceptable	Unacceptable
Probable 3	As Low As Reasonably Practicle	Unacceptable	Unacceptable	
Frequent 4	Unacceptable	Unacceptable	Unacceptable	

Probability of Occurrence

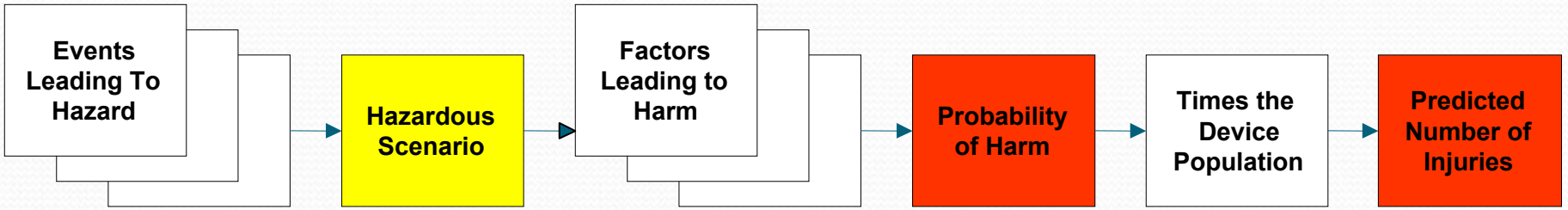
Examples of occurrence:

- **Negligible:** less than one percent chance that one patient may be harmed
- **Marginal:** less than one patient may be harmed
- **Critical:** up to 10 patients may be harmed
- **Catastrophic:** more that 10 patients may be harmed

* Occurrences are over the life of the entire population of devices to be implanted or used.

Risk Evaluation- Input

The probability inputs needed for these prediction models are determined through literature searches, field performance data, and expert opinion.



Risk Acceptance

- Following risk control measures, the overall residual risk posed by the medical device is determined.
- Quantitative results can be summarized to determine the total number of predicted injuries over the entire device population.
- An objective decision of risk acceptance can be made based on this information.

Risk Evaluation - Output

- The output of the risk management process is the Risk Management File.
  - Risk management Procedures
  - Risk Analysis Report
  - Risk Management Plan / Report
  - Risk Forms
  - Risk Meeting Minutes

Production and Post-Production

- RM goes beyond device market release. CAPA driven risk assessments are incorporated into risk management throughout the device life cycle.
- Device safety performance monitoring provides information for continuous improvement on future development projects.
- RM files are updated for incremental residual risk identified following market release.
- Post-production risk management is linked to quality management processes.
  - Validates initial residual risk estimation
  - Provides unforeseen risk identification opportunities

Production and Post-Production Risk Identification

Risk information sources:

a. *complaints/MDR/Vigilance/SADE's ADE's*
b. *field return analysis*
c. *service records*
d. *available competitive, journal, or other published data*
e. *manufacturing process monitoring/controls*
f. *changes or modifications to the design or process*
g. *Pre-post market clinical investigations*

Clinical Risk Management

Relevant Risks

- Risks related to Device(s) used in trial
- Risks related to Objectives of the trial
- Risks related to concomitant treatment

Basically run a risk management process at Clinical Operations level considering the above risk points

- Add + appraise
- identify controls (= instructions per protocol/CRF, training investigational staff etc)

Conclusion

- Risk management shall be performed in compliance with EN ISO 14971.
- Comprehensive risk identification during development is achieved through multiple activities.
- Hazardous situations are identified.
- Risk control is used to eliminate or mitigate risk as low as reasonably practicable.
- Quantitative injury predictions allow us to make residual risk acceptance decisions.
- This process helps us improve the safety of medical products.