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The F-CRIN collaborative working group

F-CRIN (French Clinical Research Infrastructure Network) is the French counterpart of ECRIN, a pan-European support infrastructure for multinational clinical trials. F-CRIN supports the attractiveness and effectiveness of French investigators and developers within the field of clinical trials.

WP4 – Development of common tools. This F-CRIN working group aimed at proposing sponsors and investigators simple tools and guidelines, as a common base ensuring a minimal standard of quality for large scale national projects intended to scale up to Europe.

WP4d – Risk Management. The initial objective of the Monitoring group of WP4 was to facilitate the implementation of the risk-based approach in monitoring and study conduct activities. However, the group soon perceived the limits of a profession-restricted approach, and redirected its activities towards Global Risk Management. The group developed several activities related to this theme: publication of a newsletter, organisation of workshops, and drafting of a guideline.

The drafting group was composed of French professionals in mainly academic clinical research institutions:

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Format of the guideline

Terms in bold are defined in the glossary.

The different steps are illustrated with the unifying example of a fictive but common trial: a comparative, randomized, phase III, superiority trial, comparing two parallel, open-label, drug arms, in adults with a chronic disease, conducted in several hospital departments in a single country. Methods and tools successively presented are applied to this example.

The related information is presented in a table to which columns are added progressively. So this table expends step by step to end as a comprehensive dashboard. The use of such a dashboard will facilitate the internal and external mastery and communication of the whole process.

ABBREVIATIONS

Acronym	Title
AP-HP	Paris Hospital Network
CE	Communauté Européenne
CTU/CRC/CRO	Clinical Trial Unit / Clinical Research Coordinator / Contract Research Organisation
ECRIN	European Clinical Research Infrastructure Network
EMA	European Medicines Agency
EU	European Union
F-CRIN	French Clinical Research Infrastructure Network
FDA	Food and Drug Administration
GCP	Guideline on Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISO	International Organisation for Standardization
MRC/DH/MHRA	Medical Research Council / Department of Health / Medicines and Healthcare products Regulatory Agency
OECD	Organisation for Economic Cooperation and Development
RACT	Risk Assessment and Categorization Tool
SAE	Serious Adverse Event
WMA	World Medical Association
WP4	Work Package 4 - Development of common tools
WP4d	Work Package 4d - Risk Management

GLOSSARY

Term	Definition according to ISO 31000
Communication and consultation	Continual and iterative processes that an organisation conducts to provide, share or obtain information and to engage in dialogue with stakeholders regarding the management of risk
Consequence	Outcome of an event affecting objectives
Control	Measure that is modifying risk
Establishing the context	Defining the external and internal parameters to be taken into account when managing risk, and setting the scope and risk criteria for the risk management policy
Event	Occurrence or change of a particular set of circumstances
External context	External environment in which the organisation seeks to achieve its objectives
Harm	Damage to health, including the damage that can occur from loss of product quality or availability
Hazard	The potential source of harm
Internal context	Internal environment in which the organisation seeks to achieve its objectives
Level of risk	Magnitude of a risk or combination of risks, expressed in terms of the combination of consequences and their likelihood
Likelihood	Chance of something happening
Monitoring	Continual checking, supervising, critically observing or determining the status in order to identify change from the performance level required or expected
Residual risk	Risk remaining after risk treatment
Review	Activity undertaken to determine the suitability, adequacy and effectiveness of the subject matter to achieve established objectives
Risk	Effect of uncertainty on objectives
Risk analysis	Process to comprehend the nature of risk and to determine the level of risk
Risk assessment	Overall process of risk identification, risk analysis and risk evaluation
Risk attitude	Organisation's approach to assess and eventually pursue, retain, take or turn away from risk
Risk criteria	Terms of reference against which the significance of a risk is evaluated
Risk evaluation	Process of comparing the results of risk analysis with risk criteria to determine whether the risk and/or its magnitude is acceptable or tolerable
Risk identification	Process of finding, recognising and describing risks
Risk management	Coordinated activities to direct and control an organisation with regard to risk
Risk management framework	Set of components that provide the foundations and organizational arrangements for designing, implementing, monitoring, reviewing and continually improving risk management throughout the organisation
Risk management plan	Scheme specifying the approach, the management components and resources to be applied to the management of risk
Risk management policy	Statement of the overall intentions and direction of an organization related policy to risk management
Risk management process	Systematic application of management policies, procedures and practices to the activities of communicating, consulting, establishing the context, and identifying, analyzing, evaluating, treating, monitoring and reviewing risk
Risk source	Element which alone or in combination has the intrinsic potential to give live to risk
Risk treatment	Process to modify risk
Stakeholder	Person or organisation that can affect, be affected by, or perceive themselves to be affected by a decision or activity

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I. INTRODUCTION

1. Scope of the guideline

The standard ISO 31000 and related documents provide principles and general methods to implement risk management (1-3). It is adaptable and flexible to fit with any type of activity, organisation, or risk. It was designed by the International Organisation for Standardisation to propose a common framework for many already existing field-specific guidelines.

However, ISO 31000 non-specificity makes it precisely difficult to comprehend for people not familiar with risk management methods, a frequent situation in clinical research. A document transposing this standard to the clinical research field seemed therefore the best way to disseminate its methods.

This guideline is a transposition of ISO 31000 to clinical research. It presents the principles and general methods of risk management, also mentioning tools already proposed for risk management in clinical research.

This guideline provides clinical research organisations with methods and tools to build their own risk management strategy and gives them the keys for the appropriation of regulatory and guidance documents recently published: new European regulation on Clinical Trials (4,5), OECD recommendation (6), EMA guideline (7), FDA guideline (8).

This guideline deals with the implementation, conduct and valorisation of any clinical study. It is intended for any stakeholder of any profession in a clinical research study. It was drafted by academic professionals, but may be of interest for any clinical research organisation.

2. Risk culture

The term "risk culture" refers to a set of values, beliefs, knowledge and attitudes towards risk, collectivelly shared by a group. Risk culture is fueled by individual education and experience, and collective habits and rules. It is influenced by the intensity of solidarity and sociability within the group. It impacts individual and collective attitudes towards risk, as well as preventive and corrective actions. Risk cultures are often classified as follows:

- Compensation risk culture: Risk is acknowledged and accepted. Choices for financial compensation are made in line with the expected risks.
- Exorcistic risk culture: Risk is denied, sources of danger are neglected. Collective and individual irresponsibility may lead to the transfert of responsibility towards a scapegoat.
- Invulnerability risk culture: Risk is averted by drastic precautions, leading to a dangerous feeling of invulnerability.
- Mastery risk culture: Risk is acknowledged and analysed, uncertainty is accepted. Mitigation measures are chosen in line with stakes .

Mastery risk culture is the one promoted in the present guideline.

3. Risk in clinical research

The ISO 31000 standard defines a **risk** as the “effect of incertitude on objectives”. The effect may be positive or negative. The objectives may have different aspects (finance, health, safety, environment…) and may apply at different levels (strategy of the organisation, logistics, processes, patients, products…) (1-3).

However, other definitions of risk have been proposed:

- Risk is often characterised by the occurrence of an **event**, its **consequences** and the associated **likelihoods**.
- According to ICH Q9 Quality Risk Management, risk is defined as “the combination of the probability of occurrence of harm and the severity of that harm” (9)
- In the MRC/DH/MHRA joint project, risk is defined as “the likelihood of a potential **hazard** occurring and resulting in harm to the participant and/or an organisation, or to the reliability of the results” (10).

This diversity in definitions results from the inherent complexity of the risk notion. Risk is a continuous and multi-dimensional variable.

Clinical research process may be divided into four main steps: study design, study preparation, study conduct, analysis and valorisation. Each of these steps can be associated with a number of more or less significant risks.

- Study design - from formulation of hypothesis to funding establishment - may be associated with risks in design, ethics, funding, and staff qualification.
- Study preparation - from application to competent authorities to first subject enrolment – may be subject to risks in logistics (drugs circuit, data circuit, and randomisation) or organisation (steering board, data and safety monitoring board, adjudication/validation committee).
- Study conduct – from first enrolment to database lock – presents risks related to recruitment, non-compliance with regulatory aspects, data quality, drug dispensation…
- Analysis and exploitation of results is subject to risks related to statistical methodology, impact on target population or public health in general.

Risks also vary depending on the **stakeholder**: subjects, study team, sponsor, competent authorities, target population… A clinical study commonly involves several organisations and stakeholders, and each must consider its specific responsibilities and duties with respect to the study, and the level of risk in relation to these.

4. Legal, regulatory and normative references

Table 1. Legal, regulatory and normative references related to risk management in clinical research.

Short title	Organisation	Reference
Declaration of Helsinki	WMA	16
Directive 2001 on Clinical Trials	EU	17
Directive 2005 on Good Clinical Practice		18
Proposal for a regulation on clinical trials		4
Regulation on Clinical Trials		5
Data Protection Directive		22
Loi Informatique et libertés	France	20
Data Protection Act	UK	21
Common Rule	USA	23
Reflection paper on risk based quality management in clinical trials	EMA	7
Facilitating international cooperation in non-commercial clinical trials	OECD	14
Recommendation on the governance of clinical trials		6
Guidance for Industry - A Risk-Based Approach to Monitoring	FDA	8
MRC/DH/MHRA Joint Project	MRC/DH/MHRA	10
Risk-Adapted Monitoring in clinical Trials	ECRIN	11
ICH Q9 - Quality Risk Management	ICH	9
ICH E6 - Guideline for Good Clinical Practice		19
ISO 9001 - Quality management systems	ISO	24
ISO Guide 73 - Risk management - Vocabulary		1
ISO 31010 - Risk management - Risk assessment techniques		2
ISO 31000 - Risk management - Principles and Guidelines		3

II. RISK MANAGEMENT PROCESS IN CLINICAL RESEARCH

1. The risk management process

The successive steps of the risk management process are described in Figure 1 and developed below. The process applies to all phases of clinical study, from design, preparation, conduct, analysis and exploitation of results.

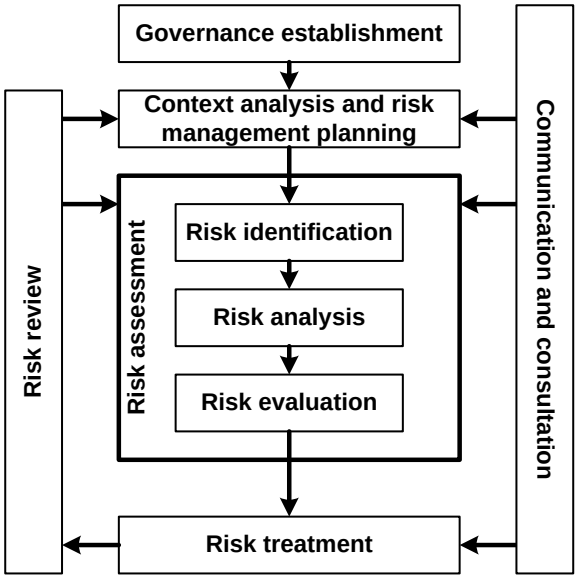

Figure 1. Flowchart of the risk management process.

2. Governance establishment

The risk management process must be integrated in the strategic and operational processes of the study. The sponsor should include all stakeholders in the process. Clear governance rules, responsibilities and accountabilities of the different stakeholders must be defined beforehand, and accepted by all parties. Internal stakeholders may take decisions whereas external stakeholders may simply have an advisory role. However, final decision falls to the sponsor.

The efficiency of a risk management process is difficult to evaluate because it shows itself through the absence of risk-related event. Therefore the adherence of all stakeholders to the process is crucial, and should be promoted through effective communication and consultation. It will help in:

- defining the context appropriately,
- ensuring that the interests of all stakeholders are understood and considered,
- bringing together different areas of expertise for identification and analysis of risks,
- ensuring that risks are adequately identified,
- securing endorsement and support of a risk treatment plan by all stakeholders,
- developing a communication plan,
- enhancing a bottom-up and up-bottom communication,
- reviewing periodically the process.

The central location of the risk management team, either in the study conduct team or at the sponsor's, is also important to enhance its reactivity and its efficiency.

A successful risk management process may be reached by implementing at the governance step:

- training of all persons involved in the clinical study, including the team leaders,
- systematic integration of the risk management process in the socio-organisational system of the sponsor and the study conduct team,
- definition of a well-established decision-making and validation circuit,
- collaboration with existing focus groups and working groups on this topic.

3. Context analysis and risk management planning

3.1. Context analysis

The context analysis requires gathering information for risk identification. This information may result from the experience of the study conduct team or other teams, in the same field or in other fields. It may

consist in figures from surveys or in experts' opinions. It may be study-specific or related to the study background.

The context analysis should include the definition of the external and internal contexts.

Analysing the external context implies the familiarisation with the environment in which the study is developed, including:

- cultural, political, legal, regulatory, financial and economic environment factors, whether international, national, regional or local,
- perceptions and values of external stakeholders: Institutional review board / Independent ethic committee, Regulatory Authorities, Independent Data and Safety Monitoring Committees...

Analysing the internal context implies the understanding of:

- study objectives and strategies in place to achieve them,
- standards and reference models adopted by stakeholders,
- circuits and information flows,
- operational policies and processes,
- decision-making processes,
- perceptions and values of internal stakeholders: sponsor, investigators, Clinical Trials unit / Contract Research Organisation...,
- competences, experience and resources of stakeholders.

See Appendix I – Table A1

3.2. Risk management planning

A risk management plan must be written and validated following the governance rules. It specifies the scope of the risk management process, and the tools and criteria to be used. It includes the definition of:

- the scope (*for example risk management unit = the specific clinical study*) and objectives of the risk management process,
- the responsibilities for and within the risk management process,
- the extent of the risk management activities : who, when, where,
- the relationships between a particular study and other activities of the stakeholders,
- the type of consequences to be analysed during risk analysis,
- the risk assessment methodology and tools: risks areas, risk evaluation scales, rules for risks acceptance or treatment,
- identification of surveys needed to gather information and the resources required for these surveys,
- definition of the methods of evaluation of the performance of the risk management process.

4. Risk assessment

Risk assessment is “the overall process of risk identification, risk analysis and risk evaluation.” It provides an understanding of risks, their causes, consequences and their probabilities.

The purpose of risk assessment is to provide information and analysis to make informed decisions.

4.1. Risk identification

Risk identification is the process of finding, recognising and recording risks. Risk identification addresses the question “What might go wrong?".

Basically, risk identification relies on brainstorming of stakeholders with different functions and perspectives. It is crucial to multiply the sources feeding the brainstorming to ensure identifying all possible risks.

However, the following propositions are not intended to be exhaustive. They aim at guiding the reflection on the risks identification.

4.1.1. Risk areas

Risk identification may start with the identification of risk areas, which are a classification of all study-related aspects from the perspective of risks. For each risk area, the risk management team proposes a score (for example a percentage) expressing the degree of risk perceived within this area by the stakeholders. The risk areas may then be represented as a radar chart (Figure 2).

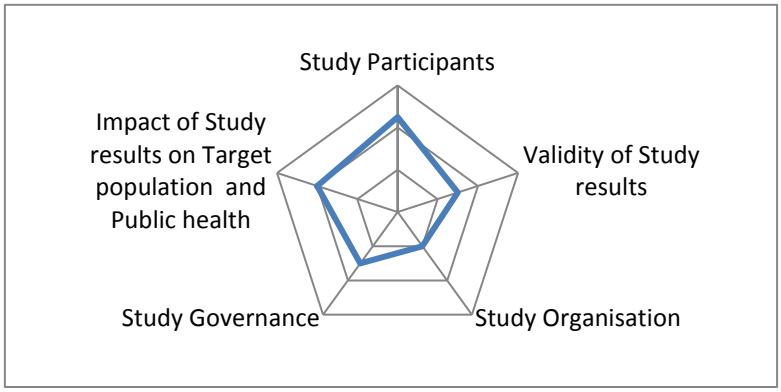

Figure 2. A radar chart presenting a fictive scoring of the risk areas identified by the ECRIN network (11)**.**

4.1.2. Risk identification

Then risk identification is done within each risk area.

Several regulatory documents or academic initiatives suggest leads for risks identification, in particular on safety aspects, subject's rights and data reliability.

4.1.2.1. Identification of risks related to subject's safety

The risk to subject's safety can vary widely and depends on a range of factors, in particular the extent of knowledge and prior experience with the investigational product and the type of intervention.

Moreover, many clinical studies present a minimal additional risk to subject safety in comparison to normal clinical care; in particular when the investigational product is covered by a marketing authorisation. In this case, "low-intervention clinical trials" term is used (4,5). Risk to the subject's safety is therefore considered as the increased risk arising from the research activity as opposed to the baseline level of risk arising from normal clinical practice.

- The Clinical Research & Development Department of Paris Hospital Network (AP-HP) evaluates physical risk related to research procedures, and specifically to intervention and investigation, for all clinical study (12).
- The Adamon risk scale proposes three categories of risk defined according to the potential risk of the intervention: comparable to, higher than or markedly higher than standard medical care (13).
- The MRC/DH/MHRA proposes more or less the same three level-risk scale, with a pragmatic approach using the marketing status of the medicines being investigated (10).
- The OECD recommendation also proposes a three-level stratified approach on subject's safety (6, 14).
- The Optimon risk scale (4-level scale) first identifies the nature of the intervention (drug, surgery, medical device, questionnaire…), then assesses related study characteristics, and deduces a level of risk corresponding to the intensity of harm from the intervention on the subject (15).

4.1.2.2. Identification of risks related to subject's rights

Subjects' rights are under the regulation of different regulations and laws:

- Declaration of Helsinki: this ethical principle protects human subjects involved in medical research (4,5,16-18).

- The ICH E6 guideline for GCP focuses on information and informed consent. Compliance with this standard provides protection means to the rights of trial subjects (19).
- Most countries have a regulation on data protection: Loi informatique et libertés (France), Data Protection Act 1998 (UK), Data Protection Directive (Directive 95/46/EC) (European Union), Common Rule (USA), etc… (20-23)

Some reference texts link design quality and patients' rights but no further information is provided (4,10,13). A poorly constructed study (in scientific and logistics terms) will introduce ethical risks and thus risks to subject rights.

4.1.2.3. Identification based on data reliability

The design of a study has a major impact on the quality of the results. Of critical importance is the identification of areas of potential vulnerability in trial design and planned methodology, which may require mitigation activities to ensure the reliability of the trial results:

- The MRC/DH/MRCA joint project requires considering robustness of the trial design, data collection methods and site issues (10).
- The Adamon initiative offers a structured questionnaire to identify indicators of robustness (13).

4.1.2.4. Identification by tasks

When the organisation already has a quality management system formalised according to the standard ISO 9001, risk identification may be based on processes, sub-processes and tasks which serve as a checklist indicating where to search for specific risks (24).

Table 2. Extraction of the list of processes in a quality management system formalised according to the standard ISO 9001.

Process	Sub-process	Task
Quality Management	Non-compliances management	Follow-up of non-compliances (related or not to the clinical trial)
		Follow-up of spontaneous suggestions for improvement
		Setting-up of corrective and preventive actions
		…
	Audit management	
	Review of quality management system	
	…	
Set-up of the study	Research design	Planning of the research design
		Definition of the study methodology
		Redaction of the protocol
		Redaction of the consent form and notice of information
		Redaction of amendments
		Assessment of the feasibility
		...
…		

Such a quality management system is usually summarised in a process mapping (Figure 3).

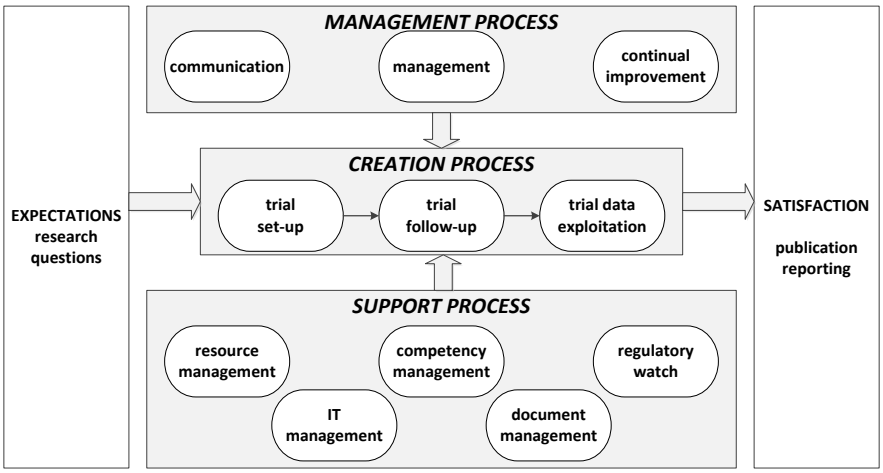

Figure 3. A process mapping in clinical research.

For each task, risks are identified by brainstorming.

When there is no quality management system, tasks may be listed by profession, or according to the chronology of the study.

4.1.2.5. Identification by existing checklist

Three disease-oriented networks are part of ECRIN network: rare diseases, medical devices and nutrition. Each developed a field-specific checklist to facilitate risk identification in their clinical trials, based on trial and sites characteristics : general, regulatory status, population, intervention, design, schedule, data acquisition and integrity, safety vigilance, on-site conduct.

See Appendix II – Table A10

The TransCelerate Biopharma Inc created a tool named Risk Assessment and Categorization Tool (RACT), designed as a checklist allowing an overview of all study aspects: safety, study phase, complexity, technology, patient population, data collection, endpoints, organisational experience, investigational product/study medication, logistics/supply chain, blinding, operational complexity, geography, budget… (25,26).

4.1.3. Risk formulation

There are different ways to formulate a risk. It may be formulated by a nominal group (*ex: no declaration of a death)*, or a subject-verb-complement sentence (ex*: the investigator does not declare a death)*, the latter formulation being more accurate. With the latter formulation, a verb in the active voice should be used, with avoidance of the verb “to be”.

It is important to distinguish a risk, which is an undesirable event (*example: the proportion of missing data on the primary endpoint exceeds the pre-defined threshold*) from the non-realisation of an objective (*example: not to answer the study question*).

See Appendix I – Table A2

4.2. Risk analysis

Risk analysis is "the process to comprehend the nature of risk and to determine the level of risk".

It is about developing an understanding of the risk. It provides an input for risk evaluation and for decision-making on risk treatment and appropriate risk treatment strategies.

Risk analysis consists in determining the causes, the consequences and their probabilities for identified risk events in a specific study, taking into account the presence (or not) and the effectiveness of already existing controls.

4.2.1. Causes analysis

First step of risk analysis is causes and sources of risk analysis. It allows determining nature and type of causes that will produce risks. A risk may have many causes and causes can be in cascade and depend from each other.

Different methods exist to produce causes analysis. An example is a cause and effect diagram (also called an Ishikawa diagram or fish bone diagram). Causes are usually grouped into major categories to identify these sources of variation. The categories typically include people, methods, machines, materials, measurements and environment.

See Appendix I – Table A3

4.2.2. Consequences analysis

Consequences analysis determines the nature and type of impact which could occur assuming that a particular event, situation or circumstance related to the study has occurred. An event may have a range of impacts of different magnitudes, and affect various aspects. Consequence analysis can vary from a simple description of outcomes to detailed quantitative modelling or vulnerability analysis.

Consequences analysis can involve:

- Considering both immediate consequences and those that may arise after a certain time has elapsed, if this is consistent with the scope of the assessment,
- Relating the consequences of the risk to the original objectives of the research,
- Taking into consideration existing controls to treat the consequences, together with all relevant contributory factors that have an effect on the consequences,
- Considering secondary consequences, such as those impacting upon associated systems, activities, equipment or organisations.

See Appendix I – Table A4

4.2.3. Risk quantification

The purpose is to quantify the risk dimension so as to facilitate further decision making.

The output of risk quantification is either a quantitative estimate of risk, such as a risk score expressing the likelihood of a specific event considering specific circumstances, or a qualitative description of risk, such high, medium, or low level, which should be defined in as much detail as possible.

4.2.3.1. Likelihood, detectability and gravity analysis

The **likelihood** of an event is “the probability that this event happens”.

The detectability of an event is the probability of detection of this event. The higher the detectability, the easier it is to anticipate the risks.

The gravity (or severity) of an event quantifies the level of damage and malfunction impacting the study due to this event.

Likelihood and detectability of the causes of a risk must be estimated, as well as the gravity of its consequences. Three general approaches are commonly employed to estimate probability; they may be used individually or jointly:

- Use of relevant historical data to identify events or situations which have occurred in the past, and hence to extrapolate the probability of their occurrence in the future,
- Probability forecasts using predictive techniques,
- Expert opinion collected in a systematic and structured process to estimate probability (example: Delphi process, concensus of opinion or a vote).

Likert scales (5-level or 10-level) are frequently used to rate likelihood, detectability and gravity.

Table 3. Example of 10-level scales for likelihood, detectability and gravity dimensions.

Level	Likelihood	Detectability	Gravity
1	Impossible	Certain	Inconsequential
2	Extremely improbable	Extremely probable	Barely perceptible
3	Very improbable	Very probable	Very limited
4	Improbable	Probable	Limited
5	Unlikely	Possible	Sensitive
6	Possible	Unlikely	Significant
7	Probable	Improbable	Very significant
8	Very probable	Very improbable	Important
9	Extremely probable	Extremely improbable	Very important
10	Certain	Impossible	Disastrous

Note: High score levels are associated with low detectability of the risk, which is somehow counterintuitive but is usefull when combining dimensions.

See Appendix I – Table A5

4.2.3.2. Risk criticality

Criticality combines likelihood, detectability and gravity. Several definitions exist, but the most frequently used are the following:

- Risk criticality = Likelihood x Gravity
- Risk criticality = Likelihood x Detectability x Gravity

The second method is presented in the example.

See Appendix I – Table A6

Note: The choice of the number of levels of the scale is quite arbitrary. Larger scales lead to higher criticality scores, which are more impressive and more likely to make people react.

Example: A criticality score based on three 5-level scales ranges from 1 to 125, while a criticality score based on three 10-level scales ranges from 1 to 1000. Consequently, 94 in the first definition is equivalent to 750 in the second one. However people will probably react more strongly to the second score.

4.2.3.3. Existing controls assessment

The level of risk will depend on the adequacy and effectiveness of existing controls.

Questions to be addressed include:

- What are the existing controls for a particular risk?
- Are those controls capable of adequately treating the risk so that it is controlled to a tolerable level?
- In practice, are the controls operating in the manner intended and can they be demonstrated to be effective when required?

4.3. Risk evaluation

Risk evaluation compares the level of risk found during the analysis process with **risk criteria** established when the context was considered. Risk evaluation is needed to decide which risk need treatment and to prioritise for treatment implementation

The criticality score of a risk found during risk analysis is then compared with decision-making criteria defined in the risk management planning, in order to determine the risk acceptability.

Commonly used rules for acceptability are based on:

- the criticality score (*example: risk is acceptable if criticality is below 500 / 1000*)
- the criticality and gravity scores (*example: risk is acceptable if gravity is below 8 and criticality is below 500*)

Risk acceptance criteria is also commonly summarised into a risk matrix:

Table 4. Example of a risk matrix.

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

However, ethical, legal, or financial considerations, or perceptions of risk may also impact the decision.

5. Risk treatment

Following risk evaluation, decisions may include:

- whether a risk needs treatment,
- priorities for treatments,
- whether an activity should be undertaken,
- which of a number of paths should be followed.

5.1. Generalities

The purpose of **risk treatment** is to reduce the risk to an acceptable level.

Risk treatment involves selecting one or more options for modifying risks, and implementing those options. Risk treatment can include the following options:

- Avoiding the risk by deciding not to start or continue the activity giving rise to the risk,
- Taking or increasing the risk in order to pursue an opportunity (this is frequent in financial trading, not in clinical research),
- Removing the source or causes of risk,
- Lowering the likelihood of risk,
- Lowering the gravity of consequences,
- Sharing the risk with another party or parties (including shared funding, insuring or sub-contracting),
- Retaining the risk by informed decision.

Once a risk treatment is implemented, there may still be residual risks. Therefore, risk treatment must be assessed in order to decide whether residual risk levels are tolerable. If not tolerable, a new risk treatment must be generated and its effectiveness assessed. This is a cyclical process.

However, the amount of efforts used for risk treatment should be proportional to the criticality of the risk.

5.2. Selection of risk treatment options

"Selecting the most appropriate risk treatment option involves balancing the costs and efforts of implementation against the benefits derived." (1-3)

It is important to involve the different stakeholders and experts in the selection of treatment actions because the acceptability of each one may be different.

The feasibility of a risk treatment action and the delay for efficacy are assessed with a Likert scale.

Table 5. Example of 10-level scales for feasibility, efficacy and delay of efficacy dimensions.

Level	Feasibility	Efficacy	Delay of efficacy
1	Impossible	Totally inefficient	Never
2	Extremely difficult	Almost inefficient	Totally out of time
3	Very difficult	Strongly inefficient	Almost out of time
4	Difficult	Moderately inefficient	Somehow too late
5	Manageable	Slightly inefficient	Late
6	Rather manageable	Slightly efficient	Timely
7	Quite manageable	Moderately efficient	Properly
8	Easy	Strongly efficient	Accurately
9	Very easy	Almost efficient	Almost immediately
10	Extremely easy	Totally efficient	Immediately

The over cost for the investigator, in terms of workload, must be evaluated and the propriety of the means must be ensured with the sponsor.

Combining several actions may prove efficient.

Risk treatment itself can introduce secondary risks. A significant risk can be the failure or ineffectiveness of the risk treatment measures. The process of risk occurrence detection needs to be an integral part of the risk treatment plan to give assurance that the measures remain effective.

Secondary risks need to be assessed, treated, monitored and reviewed. These secondary risks should be incorporated into the same treatment plan as the original risk and not treated as a new risk. The link between the two risks should be identified and maintained.

Treatment actions may be:

- curative: to fix the consequence of a risk having occurred
- corrective : to prevent the new occurrence of a risk having occurred
- preventive : to prevent the cause of a potential risk

Example: A patient's intervention allocation is incorrect (the risk) because the randomisation program contains an error (the cause). The typology of actions is:

- *curative: The intervention allocation is corrected for the patient.*
- *corrective: The randomisation program is corrected.*
- *preventive: Each intervention allocation is checked for conformity with the randomisation list before transmission to the site*

Criticality of each risk is re-assessed after treatment. The efficacy of a treatment action is defined as the difference between the criticality before and after treatment.

See Appendix I – Tables A7 and A8

Note: To treat the causes of a risk is usually more efficient than to treat its consequences. Nonetheless, causes are often behavioural concerns, which may prove quite difficult to treat (*example: the principle of uncertainty is not well accepted by the clinicians, which may lead to the occurrence of different risks during study conduct*).

5.3. Preparing and implementing risk treatment plans

A risk treatment plan must document how the chosen treatment options will be implemented. The information provided in treatment plans should include:

- the reasons for the selection of the treatment options, including expected benefits to be gained,
- those who are accountable for approving the plan and those responsible for implementing the plan,

- the proposed actions,
- the related resource requirements, including contingencies,
- the performance measures and constraints,
- the reporting and monitoring requirements,
- the timing and schedule,
- the priority order in which individual risk treatments should be implemented.

The treatment actions must be expressed with an infinitive verb and the characteristics "Who/What/When" must be defined.

The residual risk, after risk treatment, should be documented and subjected to monitoring, review and, where appropriate, further treatment.

6. Monitoring and review

Both monitoring and review should be planned within the risk management process and involve periodic or *ad hoc* surveillance.

Responsibilities for monitoring and review should be clearly defined in the risk management plan.

The monitoring and review processes should encompass all aspects of the risk management process for the purposes of:

- ensuring that treatment are effective and efficient,
- updating risk assessment according to the evolution of the context and progress of the study,
- updating the risk treatment plan.

7. Documentation of the risk management process

All risk management activities should be documented, thus providing the foundation for improvement in methods and tools, as well as in the overall process.

Decision of records creation should take into account:

- the sensitivity of the information,
- the need for continuous learning,
- the legal, regulatory and operational needs for records,
- the benefits of re-using information for management purposes,
- the costs and efforts involved in creating and maintaining records,
- the method of access, retrievability and storage media,
- the retention period.

When the organisation already has a quality management system formalised according to the standard ISO 9001, risk management documentation should be integrated to the quality management process, usually in the process of continuous improvement (24). Each process master record will also have a section integrating metrics for relevant risks. Since a risk – the effect of uncertainty on objectives – is by nature an event, the rate of occurrence of the event will be commonly used as a metric.

Note: The standard ISO 9001-2008 is under revision. The 2015 version will include the implementation of ISO 31000 standard as a requirement.

When no such system exist, risk management documentation will be specifically developped. Specific SOPs may be drafted. A comprehensive dashboard to summarise decisions, master the process, and communicate, is the minimum.

See Appendix I – Tables A9

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APPENDIX I. APPLICATION OF THE RISK MANAGEMENT PROCESS TO A FICTIVE TRIAL

The different steps of the risk management process are illustrated with the example of a fictive but common trial: a comparative, randomized, phase III, superiority trial, comparing two parallel, open-label, drug arms, in adults with a chronic disease, conducted in several hospital departments in a single country. Methods and tools successively presented are applied to this example.

Most of the related information is presented in a table to which columns are added progressively. So this table expends step by step, from Table A2 to Table A9, to end in a comprehensive dashboard. The use of such a dashboard will facilitate the internal and external mastery and communication of the whole process.

Table A1. Context analysis – Study-related stakeholders and their expectations.

Stakeholder	Role	Expectations	Impact
Sponsor	Contracting owner Legal responsibility	Answer to the research question Respect of quality, cost, delay	Reputation Funding
Principal Investigator	Study launching Legal and scientifical responsibility	Answer to the research question Respect of quality, delay	Reputation Career
Subjects	Participant undergoing study procedures	Strengthened follow-up Chance of a better treatment Improve scientific knowledge Oblige the investigator	Modification of health condition (positive or negative)
Investigators	Prescription Data collection	Answer to the research question Respect of quality, delay Chance of a better treatment for their patients Publication Continuing good peer-to-peer relations Financial compensation Wish for simplification or lightening of workload Continuing contact with CTU/CRC/CRO	Increased workload Author in publications Career
CTU/CRC/ CRO	Project management	Collaboration with motivated and efficient partners Satisfaction of partners	Reputation Career Funding Durability
Steering Committee	Validation of inputs, outputs and major decisions	Availability of relevant and reliable data for decision making	Reputation
Competent authority Ethics Committee Authority in charge of data protection Health Ministry …	Study authorisation on ethical, scientific and legal aspects Definition of Health politics based on study results	Availability of relevant and reliable data for decision making on scientific relevance, benefice/risk ratio, rights, target population, safety of participants	Reputation
Target population	Final beneficiaries	Improved care	Modification of health condition (positive or negative)
Medical journals	Publication of study results	Availability of relevant, reliable and original results Respect of Consort Statement	Reputation
Public media	Vulgarisation of study results Controversy	Inform and alert Create emotion	Reputation Increased income

Table A2. Three examples of risk formulation.

Risk area Risk formulation
Validity of Study results The proportion of missing data on the main outcome is higher than the one used for sample size calculation.
Study Participants The investigator does not notify all SAEs.
Study Organisation While configuring the randomisation result page (the randomisation list is stratified by sex), the IT specialist uses the variable Sex instead of the variable Intervention and decodes it with the labels of the variable Intervention.

Table A3. Causes analysis.

Sources and causes	**Risk area** **Risk**
① The trial is open label. ⇒ The subject is disappointed by his/her randomised intervention. ⇒ The subject withdraws his/her consent or is lost of follow-up. ② The investigator forgets to enter some data.	**Validity of Study results** The proportion of missing data on the main outcome is higher than the one used for sample size calculation.
① The investigator does not attend the launching meeting or he/she has received no initial training on clinical research and GCP. ⇒He/she does not master SAE notification procedure. ② The investigator is overloaded.	**Study Participants** The investigator does not notify all SAEs.
① Both variables Intervention and Sex are coded with the same codes. And the IT specialist has psychological troubles and lacks attention to his/her work. ② The configuration of the randomisation application is not double checked.	**Study Organisation** While configuring the randomisation result page (the randomisation list is stratified by sex), the IT specialist uses the variable Sex instead of the variable Intervention and decodes it with the labels of the variable Intervention.

Table A4. Consequences analysis.

Sources and causes	**Risk area** **Risk**	**Consequences**
① The trial is open label. ⇒ The subject is disappointed by his/her randomised intervention. ⇒ The subject withdraws his/her consent or is lost of follow-up. ② The investigator forgets to enter some data.	**Validity of Study results** The proportion of missing data on the main outcome is higher than the one used for sample size calculation.	The conclusion is wrongly retained.
① The investigator does not attend the launching meeting or he/she has received no initial training on clinical research and GCP. ⇒He/she does not master SAE notification procedure. ② The investigator is overloaded.	**Study Participants** The investigator does not notify all SAEs.	Toxicity is underestimated.
① Both variables Intervention and Sex are coded with the same codes. And the IT specialist has psychological troubles and lacks attention to his/her work. ② The configuration of the randomisation application is not double checked.	**Study Organisation** While configuring the randomisation result page (the randomisation list is stratified by sex), the IT specialist uses the variable Sex instead of the variable Intervention and decodes it with the labels of the variable Intervention.	The randomised intervention is systematically confounded with sex. ⇒ The trial results are biased.

Table A5. Assessment of the likelihood and detectability of the causes and the gravity of the consequences.

Sources and causes	Likelihood L (/10)	Detectability D (/10)	Risk area Risk	Consequences	Gravity G (/10)
① The trial is open label. ⇒ The subject is disappointed by his/her randomised intervention. ⇒ The subject withdraws his/her consent or is lost of follow-up. ② The investigator forgets to enter some data.	① **6** ② **8**	**2**	**Validity of Study results** The proportion of missing data on the main outcome is higher than the one used for sample size calculation.	The conclusion is wrongly retained.	**7**
① The investigator does not attend the launching meeting or he/she has received no initial training on clinical research and GCP. ⇒He/she does not master SAE notification procedure. ② The investigator is overloaded.	① **4** ② **9**	**5**	**Study Participants** The investigator does not notify all SAEs.	Toxicity is underestimated.	**9**
① Both variables Intervention and Sex are coded with the same codes. And the IT specialist has psychological troubles and lacks attention to his/her work. ② The configuration of the randomisation application is not double checked.	① **7** ② **7**	**6**	**Study Organisation** While configuring the randomisation result page (the randomisation list is stratified by sex), the IT specialist uses the variable Sex instead of the variable Intervention and decodes it with the labels of the variable Intervention.	The randomised intervention is systematically confounded with sex. ⇒ The trial results are biased.	**10**

Table A6. Calculation of the criticality.

Sources and causes	Likelihood L (/10)	Detectability D (/10)	Risk area Risk	Consequences	Gravity G (/10)	Criticality (LxDxG) (/1.000)
① The trial is open label. ⇒ The subject is disappointed by his/her randomised intervention. ⇒ The subject withdraws his/her consent or is lost of follow-up.	① **6**	**2**	**Validity of Study results** The proportion of missing data on the main outcome is higher than the one used for sample size calculation.	The conclusion is wrongly retained.	**7**	**84**
② The investigator forgets to enter some data.	② **8**					**112**
① The investigator does not attend the launching meeting or he/she has received no initial training on clinical research and GCP. ⇒He/she does not master SAE notification procedure.	① **4**	**5**	**Study Participants** The investigator does not notify all SAEs.	Toxicity is underestimated.	**9**	**180**
② The investigator is overloaded.	② **9**					**405**
① Both variables Intervention and Sex are coded with the same codes. And the IT specialist has psychological troubles and lacks attention to his/her work.	① **7**	**6**	**Study Organisation** While configuring the randomisation result page (the randomisation list is stratified by sex), the IT specialist uses the variable Sex instead of the variable Intervention and decodes it with the labels of the variable Intervention.	The randomised intervention is systematically confounded with sex. ⇒ The trial results are biased.	**10**	**420**
② The configuration of the randomisation application is not double checked.	② **7**					**420**

Table A7. Risk treatment actions and assessment of feasibility, efficacy and delay of efficacy dimensions

Sources and causes	Risk area Risks	Treatment	Feasibility F (/10)	Efficacy E (/10)	Delay of efficacy DE (/10)	Treatment assessment FxExDE (/1.000)
① The trial is open label. ⇒ The subject is disappointed by his/her randomised intervention. ⇒ The subject withdraws his/her consent or is lost of follow-up. ② The investigator forgets to enter some data.	**Validity of Study results** The proportion of missing data on the main outcome is higher than the one used for sample size calculation.	① Move into blinded study	**7**	**8**	**6**	**336**
		② Implement real-time computer checks at data entry (eCRF).	**10**	**8**	**9**	**720**
		② Check CRF pages immediately at reception and send a quick query to the investigator (paper CRF).	**10**	**7**	**7**	**490**
① The investigator does not attend the launching meeting or he/she has received no initial training on clinical research and GCP. ⇒ He/she does not master SAE notification procedure. ② The investigator is overloaded.	**Study Participants** The investigator does not notify all SAEs.	① Identify the investigator likely to notify SAE and train the investigators to GCP and study procedures. Validate the training completion.	**4**	**8**	**6**	**192**
		② Assess the workload of the investigator and demand the consistency with the allocated means (staff and time).	**4**	**4**	**9**	**288**
① Both variables Intervention and Sex are coded with the same codes And the IT specialist has psychological troubles and lacks attention to his/her work. ② The configuration of the randomisation application is not double checked.	**Study Organisation** While configuring the randomisation result page (the randomisation list is stratified by sex), the IT specialist uses the variable Sex instead of the variable Intervention and decodes it with the labels of the variable Intervention.	① Include the label into the code (*ex: 1-male*) in the randomisation application.	**10**	**10**	**10**	**1000**
		① Train the IT specialist to the crucial steps of the implementation of the randomisation procedure.	**9**	**7**	**8**	**504**
		② Systematically double check the crucial steps of implementation of the randomisation procedure.	**8**	**9**	**8**	**576**
		② The statistician systematically compares all subjects' randomisation result with the randomisation list.	**9**	**9**	**8**	**648**

Table A8. Estimation of the likelihood and detectability of the causes before and after risk treatment and the gravity of the consequences

Sources and causes	Risk area Risk	Treatment	L (/10)		D (/10)		G (/10)		C (/1.000)	
			BT	AT	BT	AT	BT	AT	BT	AT
① The trial is open label. ⇒ The subject is disappointed by his/her randomised intervention. ⇒ The subject withdraws his/her consent or is lost of follow-up. ② The investigator forgets to enter some data.	**Validity of Study results** The proportion of missing data on the main outcome is higher than the one used for sample size calculation.	① Move into blinded study	**6**	**4**	**2**	**2**	**7**	**7**	**84**	**56**
		② Implement real-time computer checks at data entry (eCRF).	**8**	**2**					**112**	**28**
		②Check CRF pages immediately at reception and send a quick query to the investigator (paper CRF).		**4**						**56**
①The investigator does not attend the launching meeting or he/she has received no initial training on clinical research and GCP. ⇒ He/she does not master SAE notification procedure. ② The investigator is overloaded.	**Study Participants** The investigator does not notify all SAEs	① Identify the investigator likely to notify SAE and train the investigators to GCP and study procedures. Validate the training completion.	**4**	**2**	**5**	**5**	**9**	**9**	**180**	**90**
		② Assess the workload of the investigator and demand the consistency with the allocated means (staff and time).	**9**	**4**					**405**	**180**
① Both variables Intervention and Sex are coded with the same codes. And the IT specialist has psychological troubles and lacks attention to his/her work. ② The configuration of the randomisation application is not double checked.	**Study Organisation** While configuring the randomisation result page (the randomisation list is stratified by sex), the IT specialist uses the variable Sex instead of the variable Intervention and decodes it with the labels of the variable Intervention.	① Include the label into the code (ex: 1-male) in the randomisation application.	**7**	**3**	**6**	**6**	**10**	**10**	**420**	**180**
		① Train the IT specialist to the crucial steps of the implementation of the randomisation procedure.		**4**						**240**
		② Systematically double check the crucial steps of implementation of the randomisation procedure.	**7**	**2**					**420**	**120**
		② The statistician systematically compares all subjects' randomisation result with the randomisation list.		**2**						**120**

L: Likelihood; D: Detectability; G: Gravity; C: Criticality

BT: Before Treatment; AT: After Treatment

Table A9. Example of a dashboard for the risk management process

STUDY

RISK IDENTIFICATION AND RISK ANALYSIS

Risk identification, causes and consequences analysis

	Risk area	Name		Causes	Consequences
R1	Validity of study results	The proportion of missing data on the main outcome is hugher than the one used for sample size calculation	C1	The trial is open label (The subject is disppointed by his/her randomised intervention so he/she withdraws his/her consent or is lost of follow-up)	The conclusion is wrongly retained
			C2	The investigator forgets to enter some data	The conclusion is wrongly retained
R2	Study participants	The investigator does not notify all SAEs	C3	The investigator does not attend the launching meeting or he/she has received no initial training on clinical research and GCP (he/she does not master SAE notification procedure)	Toxicity is underestimated
			C4	The investigator is overloaded	
R3	Study organisation	While configuring the randomisation result page (the randomisation list is stratified by sex), the IT specialist uses the variable Sex instead of the variable Intervention and decodes it with the labels of the variable Intervention	C5	Both variables Intervention and Sex are coded with the same codes and the IT specialist has phychological troubles and lacks attention to his/her work	The randomised intervention is systematically confounded with sex (The trial results are biased).
			C6	The configuration of the randomisation application is not double checked	

Risk quantification

	Likelihood	Detectability	Gravity	Risk Criticality and Risk Evaluation
R1C1	6	2	7	42
R1C2	8	2	7	112
R2C3	4	5	9	180
R2C4	9	5	9	405
R3C5	7	6	10	420
R3C6	7	6	10	420

RISK TREATMENT

Risk treatment actions

	Actions	Feasibility	Efficacy	Delay of efficacy	Treatment assessment
T1	Change for blinded study	7	8	6	336
T2	Implement real-time computer cheks at data entry (eCRF)	10	8	9	720
T3	To check CRF pages immediately at reception and send a quick query to the investigator	10	7	7	490
T4	Identify the investigator likely to notify SAE and train the investigaor to GCP and study procedures. Validate the training completion	4	8	6	192
T5	To assess the workloaded of the investigator and demand the consistency with the allocated means (staff and time)	4	8	9	288
T6	To include the label into the code (ex:1-male) in the randomisation application	10	10	10	1000
T7	To train the IT specialist to the crucial steps of the implementation of the randomisation procedure	9	7	8	504
T8	Systematically double check the crucial steps of implementation of the randomisation procedure	8	9	8	576
T9	The statistician systematically compares all subject' randomisation with the randomisation list	9	9	8	648

Risk after treatment

Likelihood	Detectability	Gravity	Risk Criticality
4	2	7	56
2	2	7	28
4	2	7	56
2	5	9	90
4	5	9	180
3	6	10	180
4	6	10	240
2	6	10	120
2	6	10	120

APPENDIX II. Risk identification in clinical trials for rare diseases, medical devices and nutrition.

Three disease-oriented networks participated to ECRIN network. Each developed a field-specific checklist to facilitate risk identification in clinical trials. These checklists are large, but probably not exhaustive. Other means of risk identification must be used as well, as described in this guideline.

Table A10. Specific checklists for risk identification in clinical trials for rare diseases, medical devices and nutrition fields.

Trial characteristics	WP4 Rare diseases	WP5 Medical devices	WP6 Nutrition
General			trials in human nutrition
	monocentric trial	monocentric trial	monocentric trial
	multi-centre trial in the same country	multi-centre trial in the same country	multi-centre trial in the same country
	multi-national trial (EU)	multi-national trial (EU)	multi-national trial (EU)
	multi-national trial (including non-EU countries)	multi-national trial (including non-EU countries)	multi-national trial (including non-EU countries)
	manufacturer as sponsor	manufacturer as sponsor	manufacturer as sponsor
	other commercial sponsor	other commercial sponsor	other commercial sponsor
	non-commercial sponsor (investigator driven clinical trial/investigator initiated clinical trial)	non-commercial sponsor (investigator driven clinical trial/investigator initiated clinical trial)	non-commercial sponsor (investigator driven clinical trial/investigator initiated clinical trial)
Regulatory status	orphan designation		
	paediatric investigation plan		
	advanced therapy		
	no special status		
		trial on medical device with CE mark using within label	
		trial on medical device with CE mark using outside label	
		trial on medical device without CE mark	
		trial on medical device with CE mark using within label and containing auxiliary medicinal product	
		trial on medical device with CE mark using outside label and containing auxiliary medicinal product	
		trial on medical device without CE mark containing auxiliary medicinal product	
		observational studies with medical device	
		registries	
			nutrition epidemiology (observational study)
			nutrition intervention (in healthy people)
			nutrition interventions (in patients)
			clinical nutrition in vulnerable groups

Trial characteristics	WP4 Rare diseases	WP5 Medical devices	WP6 Nutrition
			pharmaceutical/Drug trials
Medical device		Medical device category with CE mark without CE mark **Medical device risk class** class I class IIa class IIb class III **Other medical device characteristics** implantable requires a power source sterile contains measuring function combined with medicinal product (pharmaceutical) **Invasiveness of the application** invasive non-invasive **Applying subject** physician health care specialist layman/non-professional trial subject Handling requires assembly requires sterilisation **Period of intended application** transient (less than 60 min) short term (up to 30 days) long term (more than 30 days) **Medical Device Logistics** manufacturing labelling	

Trial characteristics	WP4 Rare diseases	WP5 Medical devices	WP6 Nutrition
		delivery assembly and commissioning storage return or destruction	
Population	**Gender** females males both genders **Age** pregnant women premature infants newborn babies children adults elderly persons **Subjects' status** inpatients day clinic patients outpatients Consent ability Healthy volunteers Patients in normal clinical care emergency patients trial subjects with cognitive or psychological disorders trial subjects with a legal guardian trial subjects under compulsory inpatient care inmates **Critical eligibility criteria** safety-relevant relevant for the effectiveness of the therapy relevant for the validity of the result	**Gender** females males both genders **Age / vulnerable population** pregnant women premature infants newborn babies children adults elderly persons **Subjects' status** inpatients day clinic patients outpatients **Consent ability** Healthy volunteers Patients in normal clinical care emergency patients trial subjects with cognitive or psychological disorders trial subjects with a legal guardian trial subjects under compulsory inpatient care inmates **Critical eligibility criteria** safety-relevant relevant for the effectiveness of the therapy relevant for the validity of the result	**Gender** females males both genders **Age** pregnant women babies children adults elderly persons vulnerable groups **Subjects' status** inpatients day clinic patients outpatients Consent ability Healthy volunteers Patients in normal clinical care trial subjects with cognitive or psychological disorders trial subjects with a legal guardian trial subjects under compulsory inpatient care **Critical eligibility criteria** safety-relevant relevant for the effectiveness of the therapy relevant for the validity of the result

Trial characteristics	WP4 Rare diseases	WP5 Medical devices	WP6 Nutrition
Intervention	new protocol small molecule already registered for another indication new small molecules enzyme-replacement therapy cell therapy gene therapy	surgery combination with pharmacotherapy combination with psychotherapy ionising radiation use of magnetic fields diagnostic	new protocol surgery physiology physiopathology genetics epidemiology behavioural Science nutrition pharmaceuticals/drugs
Design	randomised one arm parallel groups cross over intra-individual cross over open label observer blind single blind double blind sham	randomised one arm parallel groups cross over intra-individual cross over open label observer blind single blind double blind sham	randomised one arm parallel groups cross over intra-individual cross over open label observer blind single blind double blind cohort follow-up
Schedule	overall duration duration for a trial subject	overall duration duration for a trial subject	overall duration duration for a trial subject

Trial characteristics	**WP4 Rare diseases**	**WP5 Medical devices**	**WP6 Nutrition**
	number of visits per trial subjects frequency of the visits contact to trial subjects between visits	number of visits per trial subjects frequency of the visits contact to trial subjects between visits	number of visits per trial subjects frequency of the visits contact to trial subjects between visits
Data acquisition and integrity	prospective retrospective paper based CRF eCRF with paper based source data eCRF with direct data entry by trial personnel eCRF with direct data input from the measuring device procedures of data transfer from the paper-based CRF into the trial database possibility of changes tracking (“audit trail”) in eCRF provisions on the access and entry rights for the eCRF procedures in case of protocol violations procedures in case of misconduct	prospective retrospective paper based CRF eCRF with paper based source data eCRF with direct data entry by trial personnel eCRF with direct data input from the measuring device procedures of data transfer from the paper-based CRF into the trial database possibility of changes tracking (“audit trail”) in eCRF provisions on the access and entry rights for the eCRF procedures in case of protocol violations procedures in case of misconduct	prospective retrospective paper based CRF eCRF with paper based source data eCRF with direct data entry by trial personnel eCRF with direct data input from the measuring device procedures of data transfer from the paper-based CRF into the trial database possibility of changes tracking (“audit trail”) in eCRF provisions on the access and entry rights for the eCRF procedures in case of protocol violations procedures in case of misconduct procedures for data sharing
Safety vigilance	documentation and reporting duties for serious adverse events documentation and reporting duties for device-related adverse events documentation and reporting duties for deaths international reporting duties follow-up period for adverse events	documentation and reporting duties for serious adverse events documentation and reporting duties for device-related adverse events documentation and reporting duties for deaths international reporting duties follow-up period for adverse events	documentation and reporting duties for serious adverse events documentation and reporting duties for product-related adverse events documentation and reporting duties for deaths international reporting duties follow-up period for adverse events
On-site conduct (separate evaluation for each centre)	number of trial subjects to be enrolled at the centre centre/PI experience in clinical trials centre/PI experience in clinical trials with rare diseases centre/PI experience in indication under investigation availability of trial personnel at the centre necessity of a trial-specific training of the trial personnel necessity and availability of specialised trial personnel (e.g. surgery nurse, anaesthesiologist) availability of technical equipment at the centre	number of trial subjects to be enrolled at the centre centre/PI experience in clinical trials centre/PI experience in clinical trials with medical devices centre/PI experience in indication under investigation availability of trial personnel at the centre necessity of a trial- or device-specific training of the trial personnel necessity and availability of specialised trial personnel (e.g. surgery nurse, anaesthesiologist) availability of technical equipment at the centre	number of trial subjects to be enrolled at the centre centre/PI experience in clinical trials centre/PI experience in clinical trials with nutrition treatment centre/PI experience in indication under investigation availability of trial personnel at the centre necessity of a trial-specific training of the trial personnel necessity and availability of specialised trial personnel (e.g. surgery nurse, anaesthesiologist) availability of technical equipment at the centre

Trial characteristics	WP4 Rare diseases	WP5 Medical devices	WP6 Nutrition
	availability of storage/archiving facilities	availability of storage/archiving facilities	availability of storage/archiving facilities
	established data protection procedures	established data protection procedures	established data protection procedures
	established safety reporting procedures	established safety reporting procedures	established safety reporting procedures
	implemented QA system	implemented QA system	implemented QA system
	randomisation and unblinding, possibility of emergency unblinding	randomisation and unblinding, possibility of emergency unblinding	randomisation and unblinding, possibility of emergency unblinding
	possible financial or interest conflicts	possible financial or interest conflict	possible financial or interest conflict