ECRIN guidance document on risk assessments

Introduction

One of the principles of GCP as embedded in the EU Clinical Trials Regulations[i] is the need to have procedures in place to assure the quality of every aspect of the trial. Monitoring can be used to verify that the rights and well-being of human subjects are protected, the reported trial data are accurate, complete, and verifiable form source documents and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP and with the applicable regulatory requirement(s). ICH GCP details that it is the Sponsor responsibility to ensure trials are adequately monitored. The extent and nature of monitoring should be determined by the Sponsor, and can be based on considerations such as the objective, purpose, design, complexity, blinding size and endpoint of the trial. It is generally accepted that a risk assessment provides a good basis to decide on appropriate levels of monitoring. [ii]

The ECRIN Working Package 5 on Monitoring (2006-2007) had as an objective to develop a risk assessment tool and to assess its reliability. Conclusions included that the data contained a high inter-assessor variability, which prevented the further development of the risk assessment tool and related monitoring levels to go as far as expected[iii]. This document is set up to summarise those aspects of the risk assessment tool development and other projects [iv v] that were considered useful for any trialist who is setting up the process of risk assessment.

Purpose

The purpose of this document is to provide guidance to Sponsors on how to conduct and follow up on a risk assessment. The risk assessment itself will form the basis the development of a trial specific monitor plan.

Risk assessment questions

In the period 2006-2007 ECRIN Working Package 5 on Monitoring collated a list of key questions that should be addressed during a risk assessment. For this existing risk assessment tools were analysed for risk covered and studies concerned. Possible criteria were identified through the identified tools.

The Delphi method was used to reach a consensus on a list of items:

- A first questionnaire was built and sent to clinical research experts from ECRIN countries. This questionnaire aimed at evaluating the acceptance of the principle of a risk-based approach, and at delimitating the desired fields for risk assessment. Responses were analysed according to their relative frequency. Additional suggestions from the experts were considered and discussed within the ECRIN Working Package 5.
- A second questionnaire was then built, and sent to the experts. This questionnaire aimed at estimating their ability to increase or to reduce the risk. Items were selected on a frequency basis. Additional suggestions from the experts were considered and discussed within the ECRIN Working Package 5.
- The final list was designed after a meeting of the ECRIN Working Package 5; see below:

TOPICS AND ITEMS		**COMMENTS, *EXAMPLES***
Study Participants		
1	Difficulties or incapacity to give informed consent	*from language, emergency condition, age, legal incapacity, cognitive impairment,...*
2	Collection of indirectly identifying or sensitive characteristics	indirectly identifying characteristics: *social insurance number, phone number,...* sensitive characteristics: *ethnic origins, sexual, religious, politic preferences,...*
3	Expected inherent hazards related to study interventions or investigations	study interventions: *drug, procedure,...* study investigations: *outcome assessments,...*
4	Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population	target population: *babies, elderly people, at risk of mortality or severe morbidity,...* risk carrying interventions or investigations: *open-heart surgical intervention on babies,...*
5	Study interventions used outside authorised indication / product licence / state of the art or in early stage / phase of development	outside authorised indication / product licence / state of the art: *new target population, new drug combination, dose or timing, new procedure,...* early stage / phase of development: *first studies on human being, exploratory trial,...*

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Validity of Study Results		
6	Pre feasibility assessment of the study recruitment based on reliable sources	pre feasibility assessment: *estimation based on clinical department activity, documented pre-screening registry,...*
7	Concealment of randomised study interventions, allocated or to be allocated, during allocation, follow-up and investigations	concealment during allocation: *centralised allocation,...* concealment during follow-up: *placebo,...* concealment during investigations: *blinded outcome assessment,...*
8	Objective assessment of primary and the main secondary outcomes	objective assessment: *blinded biological measurement, Adjudication / Validation Committee,...*
9	Complexity of study procedures	study procedures: *recruitment, design, follow-up* complex recruitment: *cluster accrual,...* complex designs: *crossover design, dose escalation, structured therapeutic interruption,...* complex follow-up: *different types of follow-up visit, additional investigations as compared to standard of care,...*
Study Organisation		
10	Education and experience of the sponsor or investigator sites' staff to GCP or study procedures	GCP procedures: *informed consent, anonymisation, SAE reporting, queries management,...* study procedures: *trial interventions, trial investigations,...*
11	Existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the Coordinating Centre in case of documented delegation, and by the investigator sites	
12	Intervention management tracking system run by a qualified organisation	for drugs: *packaging, labelling, distribution, restocking, dispensation, accountability, expiry date, re-labelling, storage conditions,...*
13	Quickness and security of data entry in the database	quick data entry: *e-CRF,...* secure data entry: *FTPS site, passwords,...*
14	Full cleaning of database while study is still in progress	*frequent computer data checking, frequent query reminders, real-time data corrections,....*
15	Availability of the appropriate resources at the start of the study	
Study Governance		
16	Existence of management review organisations	management review organisations: *Coordinating Centre, Adjudication / Validation Committee*
17	Existence of ethic and scientific review organisations	ethic and scientific control organisations: *Steering Committee, Data Safety and Monitoring Board*
18	Influence / interference of a private organisation upon study governance	influence / interference: *drug supply by a pharmaceutical firm, agreement to transfer the database to the organisation, publication policy...*
Impact of Study Results on Target Population and Public Health		
19	Major impact of study results on target population and public health	on target population: *modification of standard of care,...* on public health: *major economic impact on public health management,...*

Performing risk assessment

Key recommendations also from literature [iv] [v] for performing risk assessments include:

- Use assessors who are knowledgeable in the respective medical indication and research field
- Use a combination of assessors (e.g. clinician, methodologist, trial manager)as they will have complementary opinions and allow for discussion amongst the assessors as part of the risk assessment (e.g. in meeting)
- Ensure assessors are trained on performing risk assessments, e.g. via performing mock risk assessments of trials that are on the extreme end of the scale of risks

- As part of the risk assessment, consider trial organisation and/or any quality management measures in a trial that may not be covered by trial protocol
- Where external review has been performed, refer to comments of the external reviewers
- Ensure risk assessments are documented

Follow up on risk assessment

- Ensure it is documented (e.g. in monitor plan) how risks are controlled/reduced/eliminated; methods to do so can include:
  - Site/staff training
  - Review by external committees, such as Data Monitoring Committee and Trial Steering Committee
  - Central monitoring, including statistical review
  - On-site monitoring
  - Site self assessments
- Ensure Sponsor is informed of the risk assessment and any outcomes of the risk assessment

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References

[i] 2005/28/EC; GCP Directive (8 April 2005)

[ii] Baigent C *et al.* Ensuring trial validity by data quality assurance and diversification of monitoring methods. *Clin Trials* 2008; 5; 49-55

[iii] ECRIN=TWG Deliverable 13 & 14, Development of a risk assessment took, assessment of its reliability and definition of a common monitoring strategy and report, preparation date 08-Oct-2008

[iv] Journot V *et al* Proposal and evaluation of a risk- assessment scale and risk-adapted monitoring plan in academic clinical research studies – the Pre-Optimon study

[v] Brosteanu O *et al* Risk analysis and risk adapted on-site monitoring in non-commercial clinical trials *Clin Trials* 2009; Nov 6. [Epub ahead of print] PubMed PMID: 19897532