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Reflection paper on risk based quality management in clinical trials

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Table of contents

Glossary	3
1. Introduction	4
2. Purpose and content	6
3. Risk based quality management	7
4. Risk assessment	9
4.1. Information gathering for risk identification	9
4.2. Establishing priorities for risk evaluation	10
5. Risk control	11
5.1. Risk mitigation/risk acceptance	11
5.2. Quality tolerance limits	12
6. Risk review and reporting quality	13
6.1. Risk review cycle.....	13
6.2. Reporting quality.....	14
7. Proposed approaches	14
8. References	15

Glossary

1. Central technical facility

Laboratory or other technical facility in which the measurements or assessments of the laboratory, ECG or other tests are centralised.

2. Central monitoring

Document review, data review and analysis performed remotely from the investigator site by the sponsor to examine the data collected in order to check compliance, identify unusual data patterns, deviations from protocol or missing or invalid data. Examples of central monitoring techniques include checks of submitted documents (e.g. checklists for TMF content completed by investigators, training evidence etc.), clinical data checks (e.g. range checks, calendar checks etc., rate of reporting adverse events), compliance data/metrics checks (e.g. number of reported deviations from the protocol, rate of reporting adverse events... etc.).

3. Data safety monitoring board (DSMB)

Also referred as Independent Data-Monitoring Committee (IDMC)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

4. Electronic data capture (EDC)

A system that allows collecting clinical trial data in electronic form and importing them without the use of paper. Electronic data capture systems are varied and can include eCRF: electronic Case Report Form, IVRS/IWRS (Interactive Voice/Web Response System), transfer of laboratory data from one system to another.

5. Failure mode and effects analysis (FMEA)

A FMEA is mainly a qualitative analysis to help to identify potential failure modes.

6. Good clinical practice (GCP)

As defined by the principles of ICH E6 guidelines ¹ (ICH GCP), is a set of internationally recognised ethical and scientific standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.

7. Project

A project may be a single clinical trial or a clinical programme which includes several trials.

8. Quality assurance

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

9. Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks associated with the planning and conduct of clinical trials and clinical development programmes.

10. Quality management system

A management system used to direct and control an organisation with regard to quality. It is the system that an organisation uses to manage the quality of their services or products. It usually consists of formal controlled procedural documents, such as policies, standard operating procedures, work instructions, forms & templates. As part of the quality system there are usually quality control and quality assurance processes.

11. Sponsor

An individual, company, institution, or organisation, which takes responsibility for the initiation, management, and/or financing of a clinical trial.

12. Sponsor-investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

13. Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Event/Reaction.

14. System

The system in a company or an organisational structure that provides the framework under which the work of the company can be managed efficiently and effectively. It relates to people (individuals, groups or organisations), facilities, technology and data (information for decision making).

1. Introduction

Good clinical practice (GCP)¹, is a set of internationally recognised ethical and scientific standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.

ICH GCP requires in Section 5.1, that the sponsor implements and maintains systems for quality assurance and quality control; similarly the Article 2 of the GCP Directive 2005/28/EC requires the implementation of procedures necessary to secure the quality of every aspect of the trial. The aim of these quality management procedures is to provide assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible. The same requirements apply to Contract Research Organisations (CROs), vendors or other service providers to whom the sponsor has delegated any trial related duties and functions of the sponsor.

The key elements of the quality system include:

- documented procedures and validated methods being developed, implemented and kept up-to-date;
- documentation system that preserves and allows for the retrieval of any information/documentation (quality records/essential documents) to show actions taken, decisions made and results;
- appropriate training of sponsor personnel as well as of the personnel in affiliates, at the Contract Research Organisations (CROs), vendors or other service providers and at trial sites;

- validation of computerised systems;
- quality control, for example monitoring of trial sites and central technical facilities on-site and/or by using centralised monitoring techniques;
- quality assurance including internal and external audits performed by independent auditors.

The current manner in which some elements of a quality system are implemented by sponsors and their agents (CROs etc.) is generally acknowledged to be time-consuming and constitutes a major proportion of the cost of development of medicines. In addition, the ICH GCP guideline was finalised in 1996 when clinical research was largely paper based, but the available technology and the approach to the conduct of clinical trials has evolved considerably in the meantime.

Whilst often successful in achieving a good quality clinical trial, the current practice can however be expensive and there are too many trials in which avoidable quality problems arise. This is illustrated by the nature and extent of findings, identified by European GCP inspectors, during inspections. The combination of these findings and the high cost of the oversight of clinical trials strongly suggests that current approach to clinical quality management is in need of review and reorientation.

The general problem can be summarised by stating that current practices in clinical research are not proportionate to risk nor well adapted to achieving the desired goals. The origins of the problem are multifactorial and include:

- cost of clinical development and limitations on the resource that can be made available;
- development deadlines, pressure from investors and other factors determining project deadlines;
- fragmentation of roles into many niche players, often without clear distribution of tasks or coordinated organisation, and each with its own priorities, risks and business environment. This is also reflected in piecemeal implementation of technology, with fragmented, unconnected and poorly standardised solutions;
- globalisation of clinical trials, complicating the regulatory, business and scientific/medical environment and patient population within which they operate;
- risk aversion – society and its institutions (public and private) is increasingly risk averse, often with little appreciation of the actual or relative risk of different activities, leading to imbalanced or disproportionate risk mitigation;
- stifling of innovation by restrictive practices, preconceived ideas, incorrect perceptions, leading to a failure to evolve processes and resistance to the implementation and acceptance of new approaches or technologies e.g. application and adoption of a single model of monitoring to the management of all trials, which is neither appropriate nor effective;
- the regulatory environment may be over-interpreted, or misunderstood, resulting in a failure to achieve its actual intent;
- poor design of studies and study processes, often being much more complicated than necessary to achieve what is required, thus diminishing focus and resource available to achieve the quality necessary for the more important objectives;
- failure to identify priorities. Both study and process design is often cluttered by data collection requirements or quality control activities (e.g. monitoring etc.) of limited importance that distract greatly from the most important issues;
- poor risk identification and poor risk mitigation – a lack of use or understanding of risk-management tools and techniques, is often associated with a reactive, fire-fighting approach to

problem management. This results in processes largely based on corrective rather than preventive action;

- lack of proportionality (one size fits all) in the implementation of quality control activities (e.g. monitoring etc.) often related to a lack of understanding of the impact of variability in trial conduct and measurement or data collection on the study results and their reliability;
- lack of knowledge or more particularly real understanding of the goals of the legal framework and guidelines, and the flexibility that they currently present;
- lack of capabilities of at least one of the parties to operationally fulfil the requirements of the study.

These issues are often deeply embedded in the culture and thinking of the organisations and people involved and are consequently very difficult to change. This paper intends to open up the discussion on approaches to clinical trials to new thinking, in order to facilitate the development of proportionate clinical trial processes.

Areas that are most often raised as causing particular concern are the design and complexity of the study protocols and data to be collected, the extent and nature of the monitoring that is implemented, as well as the related data management and the extent and nature of documentation required to be completed and retained for a given study.

A proportionate approach is required and should be adapted to the risk of the research conducted by any sponsors (academic researchers, small medium sized enterprises (SMEs) and large multi-national pharmaceutical companies). Sponsors are expected to cope with this challenge and to move towards a more systematic and risk based approach. There is a need to find better ways to make sure that limited resources are best targeted to address the most important issues and priorities, especially those associated with predictable or identifiable risks to the wellbeing of trial subjects and the quality of trial data and results.

As part of the EU implementation of the ICH Q9² and Q10³ principles and concepts, amendments to Chapter 1 of the GMP Guide (Pharmaceutical Quality systems) were published. Quality Risk Management has become an accepted standard. This concept can be adapted and described for clinical research with medicinal products.

2. Purpose and content

The purpose of this reflection paper is to encourage and facilitate the development of a more systematic, prioritised, risk-based approach to quality management of clinical trials, to support the principles of Good Clinical Practice and to complement existing quality practices, requirements and standards.

Quality in this context is commonly defined as fitness for purpose. Clinical research is about generating information to support decision making while protecting the safety and rights of participating subjects. The quality of information generated should therefore be sufficient to support good decision making.

Each step of the clinical trial process is setting the stage for decision making by one or more of the parties involved. Quite a number of these decisions are formalised by legislation and by GCP. From protocol design, submission to the ethics committee and competent authority, initiation of a trial, informed consent, protection of the subjects and on-going oversight of the risk benefit of the trial to trial reporting, decisions are made at various levels and documented. The process continues, in the case of the development of new products, through finalisation of the first study report⁴, initiation of new trials, and finally if the continued development of the product has been permitted and the sponsor

decides to progress, the process reaches the marketing authorisation stage. Clinical trial results are also published in peer review journals where they influence other research and may lead to changes in medical practice and treatment strategies.

Every decision is made on the basis of knowledge founded on the data and information accumulated to date. Each of those decisions will only be as good as the processes used to collect, analyse, interpret and report the information to the decision maker, in a format that they can use. Many of these formats in themselves are standardised, such as the protocol, informed consent document, safety reports, clinical study report, marketing authorisation application dossier or journal publications.

Since perfection in every aspect of an activity is rarely achievable or can only be achieved by disproportionate allocation of resource, it is necessary to establish a risk based quality management system for which the ultimate principles are reliability of the trial results and the well being and safety of trial subjects. This system is based on identification of trial priorities and mitigation of the significant and serious risks and establishing tolerance limits within which different processes can operate.

This paper has been developed taking into account the activities of other groups in this field (e.g. ADAMON⁵, ECRIN⁶, OPTIMON⁷ MRC/DH/MHRA joint project: Risk adapted approaches to the management of clinical trials⁸, the Organisation for Economic Co-operation and Development (OECD)⁹), the CTTI (Clinical Trial Transformation Initiative)¹⁰, FDA "Guidance for Industry Oversight of Clinical Investigations — A risk-based approach to monitoring"¹¹, the principles of ICH Q8 Pharmaceutical Development¹², ICH Q9² Quality Risk Management and ICH Q10³ Pharmaceutical Quality System).

The examples given within the text fulfil the purpose of illustration of the topics addressed.

3. Risk based quality management

The basic idea of risk based quality management is the identification of the risks on a continuous basis for risk-bearing activities throughout the design, conduct, evaluation and reporting of clinical trials. The process should start at the time of protocol design so mitigation can be built into the protocol and other trial related documents (e.g. monitoring plan).

In addition to the mitigation of identified risks, opportunities to introduce beneficial and proportionate adaptation of conventional practices regarding the management, monitoring and conduct of the trial should also be identified. Risk based quality management is a systematic process put in place to identify, assess, control, communicate and review the risks associated with the clinical trial during its lifecycle. The principles of risk management and the overview of the process as outlined in ICH Q9² apply as much to clinical trials as to other areas and a simple illustration of the process as applied to clinical trials can be seen in Figure 1. ICH Q9² provides references to various tools that can be used to assist in the risk management process, in particular for risk assessment. Application of risk based quality management approaches to clinical trials can facilitate better and more informed decision making better utilisation of the available resources. Risk management should be appropriately documented and integrated within existing quality systems. It is the responsibility of all involved parties to contribute to the delivery of an effective risk-based quality management system.

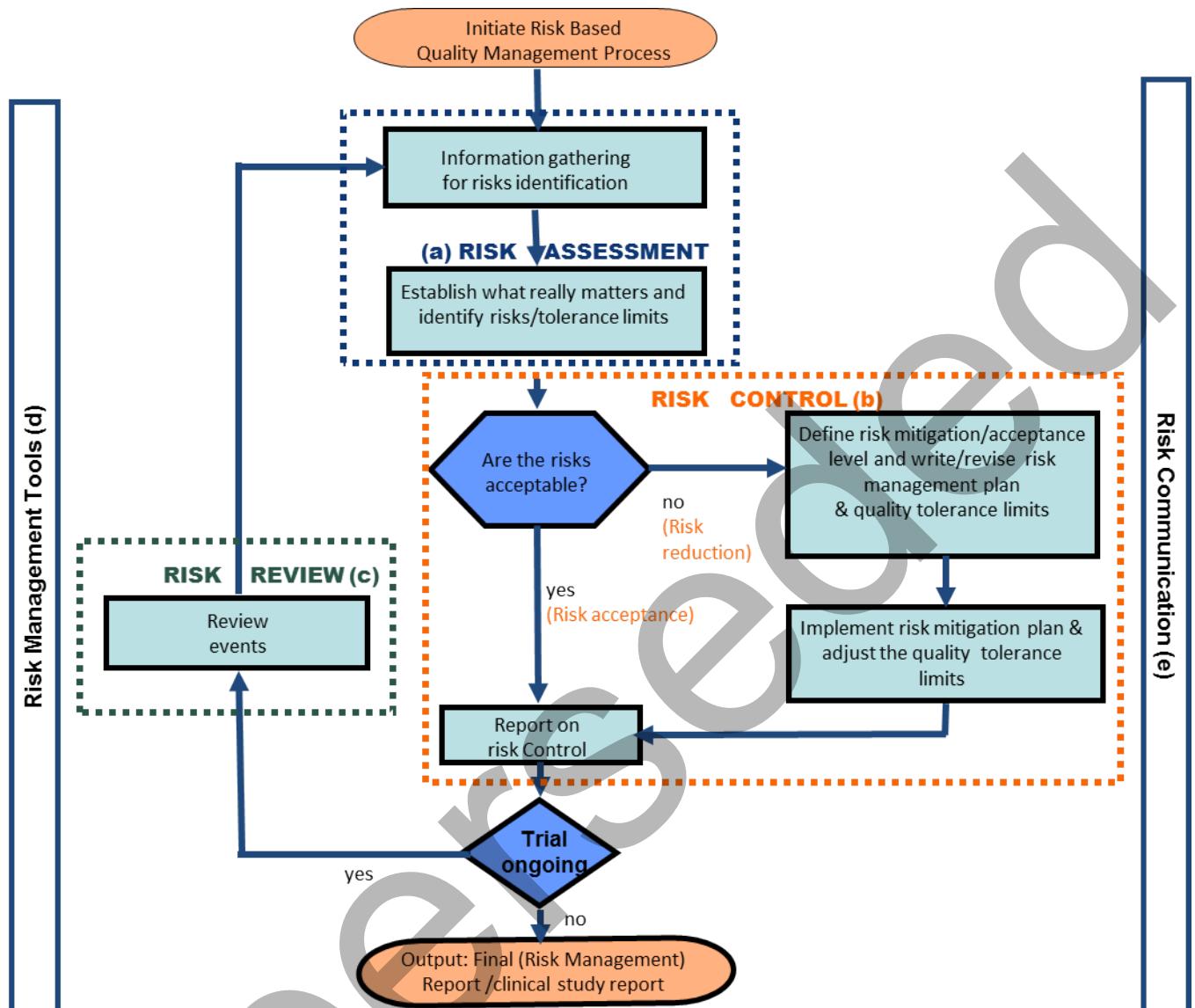


Figure 1: Illustration of a risk based quality management system for clinical trials

(a) Risk assessment requiring knowledge and understanding of what really matters for the establishment of priorities and the identification of risks: what may go wrong? What is the probability (chance/likelihood) of the occurrence of a negative outcome? What, in particular, would be the impact on trial subjects' rights/well-being/safety and/or on the reliability of the trial results? With the priorities in perspective, the assessment of risks consists of the identification of the negative outcomes, their impact and their chance/probability of occurrence.

(b) Risk control: decision making to accept risks or define mitigation measures for identified risks and establish a risk management plan. Areas with no or little risk that have been identified give opportunity to adapt traditional trial oversight and management approaches. Implement the actions identified.

(c) Risk review: on-going reassessment of the risks by review of new information emerging during the conduct of the trial (e.g. new pre-clinical data, new safety data, updated Investigator Brochure, Protocol Amendment) and the outputs of trial management activities (e.g. Monitoring output, Data management, Data Monitoring Committee Meeting Output, Audit Reports), assess impact on risk management plan and tolerance limits.

(d) Risk management tools: can be paper based or built with the use of information technology. The tools can allow detection, identification, prediction, tracking, analysing with the generation of metrics. Broadly the tools support the risk management system and the decision making.

(e) Risk communication: distribution of the documents related to the risk review to all stakeholders and decision makers, communication of risk mitigation/acceptance measures.

All quality management processes are dynamic. Thus, continuous improvement is only ensured, when quality management processes are constantly adapted by collecting and using information on an on-going basis, and when changes are routinely evaluated to make sure they are effective. It is an essential part of the risk based quality management system that review takes place as additional information becomes available.

4. Risk assessment

4.1. Information gathering for risk identification

There are two levels to consider when gathering information for risk identification in clinical trials. At the first level, system risk, the information associated with the environment and its systems should be analysed to identify potential risks that could affect organisations, their technology and their data and products. These risks would indirectly affect a clinical trial. For the second level, project risk, the information directly linked with the trial should be analysed to identify the risks that are trial specific:

1. Information gathered at system level

The globalisation and fragmentation of clinical trial management across and within numerous organisations/departments can produce areas where risks can be envisaged, often at interfaces of quality systems or movements of information/data. Those system related risk factors may have impact across projects and or clinical trials. It is essential that systematic use of information on the quality management system of the sponsor organisation as well as of involved collaborators is obtained and evaluated to identify risks. This would include:

- organisation structures and responsibilities (e.g. organograms, communication plans, contractual partners);
- quality systems and processes (e.g. standardised procedures);
- facilities and computerised systems (e.g. Information technology infrastructure, document management system, data management system, IVRS, eCRF system);
- human resources including training and qualifications of personnel (e.g. job descriptions, training plans, performance management);
- compliance metrics, performance measurements, quality audit and/or inspection outcomes;
- regulatory and ethical framework (e.g. knowledge of national and local approvals and notification required and their timelines).

2. Information gathered at project level

A project may describe a single clinical trial to a full clinical development programme. Information gathering at the project level is to identify potential risks linked with a specific trial/clinical programme. The information to review is specifically related to the trial and would include the following areas: the investigational medicinal product(s), trial design and protocol specific requirements, the project

management, the resources and the training, the equipment and procedures/methods for this specific trial.

- IMP related risk area: any available information about the physico-chemical properties of the active ingredient(s), the manufacturing process of the active ingredient(s) as well as of the investigational medicinal product(s), and the pharmacokinetic, pharmacological and toxicological properties of the investigational medicinal product(s), derived (on-going) from preclinical and clinical trials, including the concerned trial, the requirements for the labelling and packaging of the IMP.
- Trial design related risk area: complexity of trial design, trial population (e.g. vulnerability, morbidity), therapeutic area (e.g. difficult recruitment associated with rare disease), sample size calculation, practicability and adequateness of the eligibility criteria, non-medicinal protocol related activities (e.g. risk associated with biopsies).
- Operational risk area: study budget (e.g. inadequate planning for resourcing monitoring or other trial activities), development deadlines, staff resource level and study specific training (e.g. lack of GCP experience at a trial site), study management team and responsibilities (e.g. lack of revision of documents), clinical trial site selection and management, contract research organisation involvement, clinical trial supply processes and management, clinical site set up and infrastructure, laboratory setup, setup of trial databases (e.g. trial specific IVRS, eCRF with controlled access of the study eCRF and specific site training), site monitoring and central monitoring, management of clinical data including adapted safety monitoring (e.g. lack of SUSARS reporting), reporting and/or communication lines.

4.2. Establishing priorities for risk evaluation

The first step is to clearly understand the processes and outcomes which really matter in order to achieve the objectives of the study protocol and good clinical practice. After the systematic identification of risks and before the definition of mitigation actions, it is first necessary to identify the risks that really matter and to establish priorities. Prioritisation should be oriented to meet the objectives of good clinical practice (assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible) and the scientific objectives of the clinical trial.

The priorities need first to be established at the time of planning and preparation (design) of the clinical trial, including the corresponding documents, trial specific plan, data collection tools and all processes that will be used at the different stages of the trial. They should be carefully set out so that risk analysis is carried out and control measures are designed in a way that is continuously adapted to them.

The priorities should then be reflected in the trial related documents, in the assignment of resources and control procedures, in particular the focus of the data collection and monitoring and data management activities.

The establishment of priorities will guide the analysis and evaluation of risks. Qualitative or quantitative process methodologies based on risk categories can be used. Well established methods, like fishbone diagrams or Failure Mode and Effects Analysis (FMEA), take into account likelihood of occurrence, impact, and detectability of risks and can be useful tools.

The establishment of priorities will contribute to the identification of the risks that need to be mitigated and which should be the object of the risk based quality management process. Their analysis and evaluation can proceed with the knowledge that these risks are the ones that really matter.

Priorities should be continuously reviewed and adapted as deemed necessary during trial conduct.

5. Risk control

Risk control includes the process of decision making to reduce and/or accept risks (see for example ICH Q9² chapter 4.4). The purpose of risk control is to reduce the risk to an acceptable level. During risk control, a mitigation plan should be prepared and implemented. The amount of effort used for risk control should be proportional to the significance of the risk and the importance of the process or outcome exposed to identified risk.

Risk control might focus on the following questions:

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

5.1. Risk mitigation/risk acceptance

Risks might be acceptable if they have limited impact on subject's safety and rights as well as data integrity and reliability.

If a risk is not acceptable, it needs to be reduced by appropriate risk mitigation actions. Those need to be specified in a risk management plan. The latter needs to be reviewed and adapted accordingly.

Mitigation actions should be implemented to address identified risks with respect to the system and could include:

- documented procedures to formally link quality systems of organisation;
- detailed contracts between parties clearly defining roles, responsibilities and tasks to be undertaken;
- measures of oversight of delegated/contracted tasks;
- determination of communication plans, encompassing communication partners, objectives, goals, timetables and tools for all communications;
- tailored training in processes/procedures that may be new and/or unfamiliar;
- use existing data in different databases for risk assessment and risk mitigation, e.g. develop IT-tools and automatic data interfaces;
- quality performance measurement for internal and external service providers, linked to flexibility in plans for oversight and monitoring etc.

Mitigation actions to be implemented to address identified risks with respect to the project and could include:

- protocol design process with collaboration of expert functions including feasibility aspects;
- designing of training material, trial specific plans for monitoring, audit, data management etc. taking into account the identified priorities and risks;

- safety monitoring procedure adapted to each project and stage of the project e.g. post-approval trials where the safety profile for a product is known, such adaptation is most likely to be an efficiency gain of low risk to the patients;
- trial specific adaptation of extent and nature of monitoring, for example, adaptation of on-site monitoring visits, SDV (Source Data Verification) focused on particular data, (complementary) central monitoring processes etc. (subject to appropriate metrics being captured to determine when/if escalation in monitoring would be appropriate), data handling, and evaluation as well as reporting.

5.2. Quality tolerance limits

Having established the priorities and the processes for risk mitigation/acceptance, it is important to define the initial acceptable variation or tolerance limits for the clinical trial data and procedural metrics involved. It is important to recognise that tolerance limits do not need to be established for all variables or procedural metrics. It is envisaged that the limits may be readily deducted or may require an in-depth scrutiny of the objectives and endpoints (e.g. complex, larger and longer trials).

The acceptable variation of clinical trial data, predefined by the tolerance limits, should be established bearing in mind the current state of medical and statistical knowledge about the variables to be analysed as well as the statistical design of the trial. Measurements within the protocol tolerance range would therefore not be "protocol deviations". The introduction of a tolerance range/limit for specific clinical trial data parameters, at an early stage, defined within the protocol, would allow better focus of the data measurement, collection and reporting. Tolerance limits can also be set for procedural metrics from trial management systems (e.g. deliverables for monitoring reports), these could be defined in other appropriate documents (e.g. SOPs, Monitoring plans etc.). The parameters for which a tolerance limit is appropriate should be decided as part of the risk assessment.

One of the benefits of setting tolerance limits early at the time of risk identification or prior to the start of the trial is to allow detection of the deviations from the tolerance range. This would be conducive to rectify or modify the processes to improve the conduct of the study. The other benefit of introducing quality tolerance limits is that it directs the oversight and the monitoring on the parameters that matter to the study objectives and help to design more risk based oversight, management and monitoring strategies. The tolerance limits can be set for a specific trial or some appropriate parameters could be general limits applied to all the sponsor's trials and defined in the sponsor's quality system.

The following are examples of areas for which variation or tolerance limits could be established:

1. Trial data

Consider the precision, the accuracy and the timing of clinical measurements. In particular in relation to the importance of the variable in terms of the trial objectives including safety monitoring (e.g. the occasional omission of some measurements, or early or late performance of some study visits may be in some cases less critical than in others).

With the knowledge of the tolerance limits, attention is only focussed on those situations where these established tolerance limits are exceeded, or exceeded by more than a set frequency or amount. In addition, especially with direct electronic data capture, the measurement and tracking of data within these limits is more easily achieved, reported and where needed acted on.

For example it may be important in some cases to very accurately time a procedure 60 minutes post administration of a dose of medicine for pharmacokinetic purposes and a tolerance of 60 minutes plus

or minus 1-3 minutes may be acceptable, based on the predicted or known PK profile of the drug. In other cases a one hour post dose safety monitoring of blood pressure or heart rate may be equally valid if performed plus or minus 15 minutes from the hour.

Consider the process for data recording/transcription and its accuracy. This would provide information for setting tolerance limits on source data verification requirements.

2. Trial protocol procedures and GCP

Monitor the compliance/deviation from protocols.

Effective mechanisms should be in place to capture protocol and/or GCP deviations and assess their impact on the objectives of the trial and the welfare of trial subjects. Tolerance limits could be set such that detected issues may trigger escalation of monitoring (e.g. additional site visits, additional training).

3. Trial management procedures

Define the metrics that will allow oversight of the trial.

Establish the oversight/management/monitoring strategy.

Define the timing of reporting/retrieval of data.

For example, a monitoring plan could include more emphasis on central monitoring and audit and targeted source data verification on those variables that have been identified as important for meeting the trial objectives, with no or reduced SDV on others. The use of eCRF systems facilitates the use of central monitoring activities and metrics could be developed such that triggers are set for targeted monitoring/audit activities.

An example metric that may trigger targeted activities could identify site with excessive delays in data being entered on to the eCRF system or in serious adverse event (SAE) reporting. The lack of variability in data can also trigger further monitoring, e.g. one digit preference for blood pressure measurements in hypertension trials.

There is potential to develop central monitoring systems using statistical methodology to monitor the quality of the trial conduct and data, with regular metrics reports and records produced that demonstrate the checks/activities that are being undertaken and that they are compliant with the defined monitoring strategy and procedures. This could lead to targeted on-site visits to address the issues that such visits are better placed to detect.

6. Risk review and reporting quality

6.1. Risk review cycle

The concept of risk based quality management in clinical research revolves around the following cycle (as presented in Figure 1):

- risk assessment with information gathering, the establishment of priorities and the identification of risks associated with the study;
- risk control which encompasses setting tolerance limits mitigation and acceptance of risks;
- risk review which necessitates knowledge of the previous steps with the integration of the risk management tools and the communication on the review of the results and data associated to the risk identified and the documentation of the actions needed.

6.2. Reporting quality

The feedback from the risk review cycle should be analysed and summarised. This will include measures of variability of measurements and their timing, assessment of deviations from tolerance limits or protocol requirements, and missing data. Additional information can be achieved by well-designed intra and inter site variance analysis on single or multiple variables. Any analysis of trends should be done in relation to the overall impact on the scientific merits and usability of the generated data as established through priority setting and identification of risks. Such analysis can be supplemented with information on process compliance derived from monitoring/data management reports.

At the end of a trial it should be possible, in a clear qualitative and/or quantitative way, to report on the extent to which a trial has operated within the tolerance limits established and maintained during the trial and whether it has been conducted to acceptable level of quality as assessed by a predetermined methodology. Such a report could be included in the clinical study report⁴ (in section 9.6 Data Quality Assurance) and could describe actions, where possible, that were implemented to correct and prevent deviations from tolerance limits during the trial conduct. Audit outcomes will add to and serve to validate the quality report of a trial.

7. Proposed approaches

Clearly, the implementation of risk management methodology including the design of clinical trial tools requires the coordination and the integration of information from a broad range of sources. The issues giving rise to the problems presented in this paper are multifactorial. Clinical trials themselves cover a large range of objectives and vary enormously from phase 1 to large post authorisation clinical trials. No single tool or approach will address these issues. The references 5-11 provided in section 8 of this paper include a number of tools and discussions of these.

A "stratified approach" concerns categorisation of the trial risk based upon the marketing authorisation status of the investigational products and in relation to its use in the trial as per normal clinical practice. There is increasing consensus that this may not be sufficient on its own and that a "trial specific" or "customised approach" to risk assessment is also required. This would assess risks from the clinical trial protocol, which would be dependent upon, for example, the protocol complexity, subject population, therapeutic indication and nature of endpoints, clinical trial setting, administration of the product and complexity of study procedures and measurement.

It is suggested that there is a separation of prioritisation and risk mitigation approaches according to several dimensions, covering the design, conduct and trial reporting phases of the trial. These should always be aimed at protecting trial subjects' rights, well being, integrity and safety and the assurance of quality of data and the trial results.

The identification of priorities and potential risks should commence at a very early stage in the preparation of a trial, as part of the basic design process. The concerns with trial and protocol design, design of data collection tools/instruments, the design of the monitoring and data management strategies and plans, including the relative role of centralised versus on-site activities and the data quality tolerances, and the design of record keeping for the study should be addressed within the framework of these dimensions, implementing a quality by design approach. Risk assessment and mitigation plans should be appropriately disseminated within the organisation, regularly reviewed and updated when new information becomes available.

In case of a clinical development programme, risk based approaches should ideally be established at the programme level and then protocol by protocol throughout clinical development, building on the

experience achieved with each study and general technical, regulatory and other advances made during the time period involved.

This should allow for periodic interaction and discussion of the approaches taken between the sponsor and the regulators involved in both the clinical trial authorisation and supervision and the marketing authorisation process¹³.

Although approaches including tools have already been proposed and published, this is an evolving area and the concept as presented in this paper will benefit from information sharing and transparency. In building quality into the design and operation of clinical trials, we gain a more efficient and effective management to benefit the data quality and the safety and wellbeing of subjects and the development of medicines. Putting into practice the concept of risk based quality management to clinical trials will benefit the advancement and development of medicines and therapeutics strategies and overall health and well-being of subjects.

8. References

¹ [ICH E6 Good Clinical Practice](#)

² [ICH Q9 Quality Risk Management](#)

³ [ICH Q10 Pharmaceutical Quality System](#)

⁴ [ICH E3 Structure and Content of Clinical Study Reports](#)

⁵ [Clinical Trials 2009; 6: 585–596; O. Brosteanu, P. Houben, K. Ihrig, C. Ohmann, U. Paulus, B. Pfistner, G. Schwarz, A. Strenge-Hesse and U. Zettelmeyer; Risk analysis and risk adapted on-site monitoring in non commercial clinical trials](#)

⁶ [ECRIN Risk-Adapted Monitoring in Clinical Trials](#)

⁷ Contemporary Clinical Trials, Volume 32, Issue 1, January 2011, Pages 16-24; V. Journot, J-P. Pignon, C. Gaultier, V. Daurat, A. Bouxin-Métro, B. Giraudeau, P-M. Preux, J-M. Tréluyer, S. Chevret, V. Plättner, C. Thalamas, S. Clisant, P. Ravaud, G. Chêne and on behalf of the Optimon Collaborative Group; Validation of a risk-assessment scale and a risk-adapted monitoring plan for academic clinical research studies — The Pre-Optimon study

⁸ [MRC/DH/MHRA joint project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products](#)

⁹ [OECD Recommendation on the Governance of Clinical Trials](#)

¹⁰ [CTTI initiatives on developing effective quality systems in clinical trials: Effective and Efficient Monitoring as a Component of Quality in the Conduct of Clinical Trials](#)

¹¹ [FDA Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring](#)

¹² [ICH Q8 Pharmaceutical Development](#)

¹³ Jonathan R. Davis, Vivian P. Nolan, Janet Woodcock, and Ronald W. Estabrook; Roundtable on Research and Development of Drugs, Biologics, and Medical Devices, Institute of Medicine; Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making: Workshop Report; National Academies Press (1 July 1999)