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Reflection paper on risk based quality management in clinical trials

Draft

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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 those quality management measures 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. However the sponsor remains responsible for the quality of the trial. The ICH GCP 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.

The key elements of the quality system include:

- Documented procedures being developed, implemented and kept up-to-date
- Training of sponsor personnel as well as of the personnel in affiliates, at partners and at trial sites
- Validation of computerised systems
- Monitoring of trial sites and technical facilities on-site or by using centralised monitoring techniques
- Data management and quality control
- Internal and external audits performed by independent auditors

The current manner in which these quality systems are implemented by sponsors and their agents (CROs etc) are generally acknowledged to be costly and time-consuming, and constitute a major proportion of the cost of development of medicines.

Implementing these processes can be and often is successful in achieving a good quality clinical trial. However it is expensive and there remain too many trials in which avoidable quality problems arise as evidenced for instance by the nature and extent of findings, identified by European GCP inspectors during inspections. The combination of these findings and the very high cost of the processes involved strongly suggest that current approach to clinical quality management is in need of review and reorientation.

A scalable and proportionate approach is required in order to cover the needs of academic researchers, Small and Medium Enterprises (SMEs) and large multinational pharmaceutical organisations.

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.

ICH-GCP, e.g. in respect to auditing, already underlines that the sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial for submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, by the level of risks to the trial subjects, and any identified problem(s). Similarly the GCP requirements for monitoring indicate that the sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on

considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial.

With the implementation of ICH Q9 guideline[2] as GMP Annex 20 in March 2008, Quality Risk Management has become an accepted standard. This concept can be adapted and described for clinical research with medicinal products.

Thus, the purpose of this reflection paper is to 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.

The activities of other groups in this area (e.g. ADAMON[3], ECRIN, OPTIMON[8], MRC/DH/MHRA joint project: Risk Adapted Approaches to the Management of Clinical Trials[4] and the Organisation for Economic Co-operation and Development (OECD)), the FDA CTTI (Clinical Trial Transformation Initiative), CTFG, GCP IWG and the principles of ICH Q8 Pharmaceutical Development[5], Q9 Quality Risk Management[2] and ICH Q10 Pharmaceutical Quality System[6] have been taken into account in developing this paper.

2. Problem statement

The general problem can be summarised by stating that current practices are not proportionate or well adapted to achieving the desired goals and are generally very costly, resulting either in success at an unnecessarily high cost or failure which is also very costly. The origins of the problem are multifactorial. In order to facilitate discussion and identification of solutions, they are presented as simple bullet points below under two groupings .

The environment within which clinical trials are conducted is not without constraints and we understand that there can be issues with the following:

- 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 business 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 to the management of all trials, which is neither appropriate nor effective.
- The regulatory environment may also be over-interpreted, or misunderstood, resulting in a failure to achieve its actual intent.

With the planning and conduct of clinical trials, we understand that there can be issues with the following:

- Poor design of studies, study processes in themselves, often being much more complicated than necessary to achieve what is required, but in so doing 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.

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 and 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.

3. Quality in clinical trials

In order to effectively discuss prioritisation and risk based quality management, it is first necessary to consider how the necessary standard of quality should be defined. Simply advocating the "highest level" of quality has little practical meaning in itself. There is well established evidence in many fields of activity that the cost associated with incremental improvements in quality becomes ever higher as perfection is approached, and becomes disproportionate to any additional benefit achieved.

Quality is commonly defined as fitness for purpose. Clinical research is about generating information to support decision making. The quality of information generated should therefore be sufficient to support good decision making. The adequacy of that quality can also be characterised by stating that it should be such that the decisions made would have been no different had the quality of data and information generated been perfect[9].

Each step of the clinical trial process is preparing for the process of decision making by one 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, consent, ongoing 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 report[7], 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 absolute perfection in every aspect of an activity is rarely achievable or could only be achieved by disproportionate allocation of resource, it is necessary to establish clear priorities, to mitigate the significant and serious risks to those priorities, and to establish tolerance limits within which different processes can operate.

By establishing the priorities, mitigating the most significant risks and operating within sensible tolerance limits, the required quality standard can be described, and its achievement (or failure to achieve it) can be more readily measured, reported and recognised.

This paper seeks to describe the elements needed to achieve this in clinical trials.

4. Information gathering

There are two aspects of the information required for risk based quality management in clinical trials:

A- Systems

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. It is essential that thorough 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,

A.1. Organisation structures and responsibilities

A.2. Quality systems of organisations

A.3. Computerised systems

A.4. Human resources including qualifications of personnel

A.5. Compliance metrics: quality audit and/or inspection outcomes

For example, actions to be implemented to address identified risks could include:

a) Additional documented procedures to formally link quality systems of organisation

b) Detailed contracts between parties clearly identifying roles, responsibilities and tasks to be undertaken, including oversight of delegated/contracted tasks

c) Determination of communication plans, encompassing communication partners, objectives, goals, timetables and tools for all communications

d) Effective training in processes/procedures that may be new and/or unfamiliar

e) Develop IT-tools and automatic data interfaces to be able to use existing data in different databases for risk assessment and risk mitigation

f) Quality performance measurement for internal and external service providers, linked to flexibility in plans for oversight and monitoring etc

B- Project

A project may describe a single clinical trial to a full clinical development programme. This involves gathering and evaluating the available information about the investigational medicinal product(s), the project management and the requirements of the specific clinical trial protocol to identify foreseeable risks. This would include:

B.1. 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 (ongoing) from preclinical and clinical trials, including the concerned trial.

B.2. Study budget, clinical trial sites selection and management, contract research organisation involvement, laboratory setup, setup of trial databases, monitoring and management of clinical data including safety etc.

B.3. Protocol required non IMP interventions, complexity of trial design, subject population etc.

For example, actions to be implemented to address identified risks could include:

a) Protocol design process with collaboration of expert functions

b) Designing of training material, monitoring manual, audit manual, data management plan etc. taking into account the identified risks

c) Safety monitoring procedure adapted to each trial

d) Adaptations to conventional GCP methods, for example, adaptation of on-site monitoring visits, sample/focussed SDV, new central monitoring processes etc., subject to appropriate metrics being captured to determine when/if escalation in monitoring would be appropriate

5. Establishing priorities

Before setting out to identify and mitigate risks it is first necessary to establish the priorities that need to be addressed by a particular process. It is the risks that are a significant threat to those priorities that most merit the allocation of resource in their mitigation.

The objectives of good clinical practice establish the priorities at a very high level as 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 priorities of a trial relate to the protection of trial subjects and to its scientific objectives. They need first to be established at the time of design of the clinical trial, its documents and data collection tools and the 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.

They should be clear, and should not be cluttered with minor issues (e.g. extensive secondary objectives or processes/data collection not linked to the main trial objectives /proper protection of the trial subjects).

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

6. Risk based quality management

The basic idea of risk based quality management is the identification of the risks on a continuous basis for all risk-bearing activities throughout the design, conduct and evaluation of clinical trials based on existing and ongoing generated or emerging information about the investigational medicinal product(s) and the sponsor's and collaborators' systems and organisation. Identification of low risks can also be important as there is potential for adaptation to conventional practice in the management of the trial.

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 Q9 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 Q9 provides references to various tools that could 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 and make the most use of the available resources. It 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.

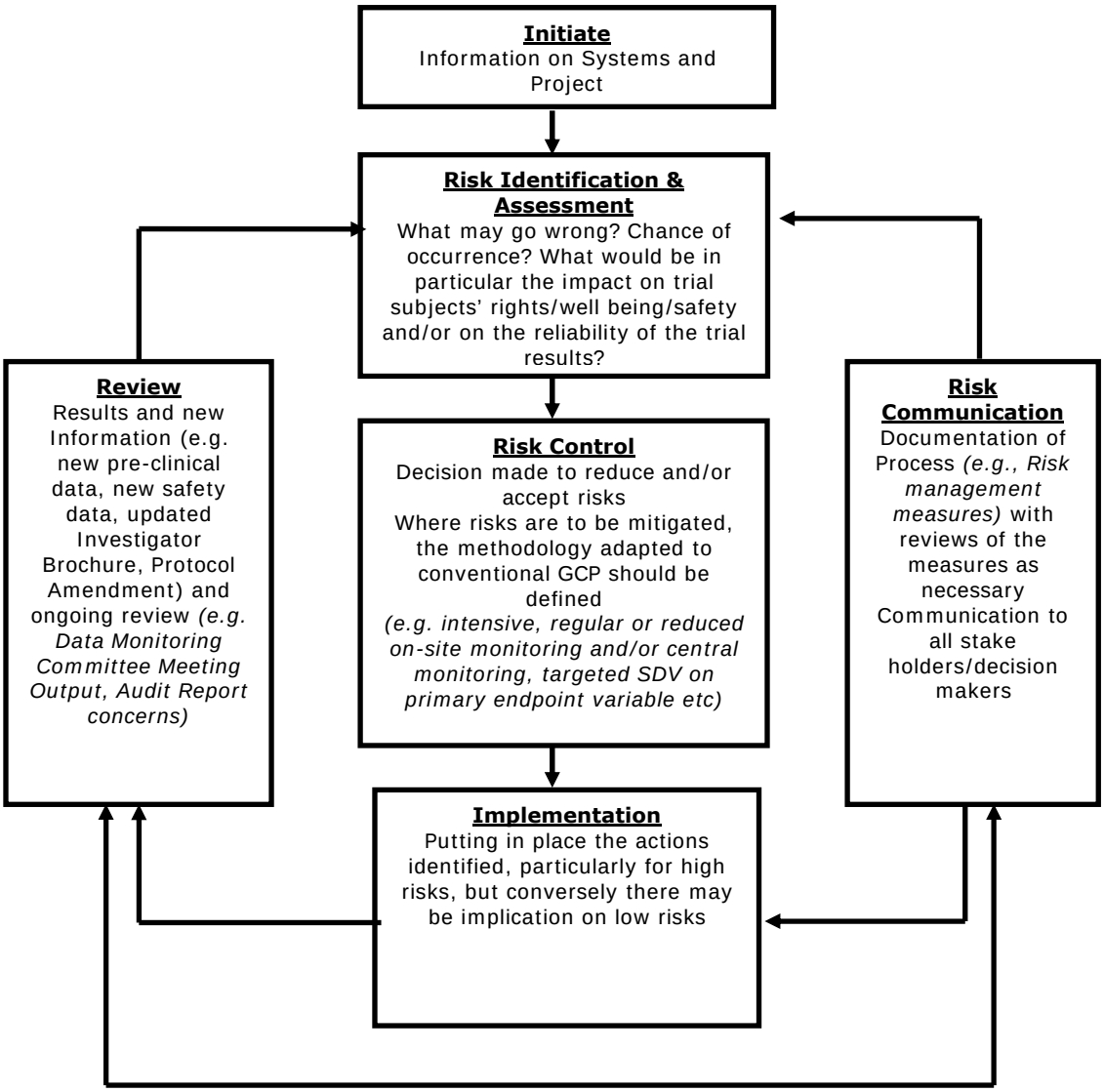

Figure 1: Illustration of a risk based quality management process for clinical trials

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 ongoing 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. Annex 1 provides several points to consider when establishing a risk based quality management approach.

7. Quality tolerance limits

Having established the priorities and the processes for mitigation of risks associated with these, it is then important to establish the acceptable variation or tolerance limits for the clinical trial procedures involved.

The acceptable variation in tolerance limits should be established bearing in mind the statistical design of the trial and the potential impact of the different levels of variability on the power of the trial.

If a deviation is introduced and it is within the tolerance range, the measurement is considered to be "per protocol" and is not classified as a "protocol deviation". The introduction of a tolerance range/limit for clinical trial parameters at an early stage and defined within the protocol would allow better focus on the data measurement, collection and reporting. As illustrated by the examples below, the tolerance limits should be established by allying clinical judgement with the systematic approach for finding the right tolerance limit for clinical data acceptance.

One of the benefits of setting tolerance limits early at the time of risk identification is to allow detection of the deviations from the tolerance range. This would be conducive to rectify or modify the processes to benefit the scope of the study. The other benefit of introducing quality tolerance limits directs the oversight and the monitoring on the parameters that matter to the study endpoints including safety endpoints and help to design more focused management procedures (e.g. data monitoring plan)

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

a) 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 less critical than others).

The accuracy and precision of the measurement itself, the method or instrumentation used, as well as the timing of the measurement should be established. In that way 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. 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 on source data verification requirements.

b) 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. Tolerance limits could be set such that detected issues may trigger more extensive monitoring (e.g. additional site visits).

- Establish the qualification specifications for facilities and equipment

c) Trial management procedures

- Define the metrics that will allow oversight of the trial
- Establish the monitoring frequency and the extent of source data verification
- Define the timing of reporting/retrieval of data

For example, a monitoring plan could include more emphasis on central monitoring and quality assurance and a reduced or targeted source data verification on those variables that have been identified as important for meeting the trial objectives. The use of eCRF systems facilitates the use of

central monitoring activities and metrics could be developed such that triggers are set for additional monitoring/audit activities.

For example, outlying data from sites relating to delays in data being entered on to the eCRF system or in SAE reporting. The lack of variability in data (for example outliers in a parameter with an expected normal distribution) can also trigger further monitoring. The same applies to outlying data from sites due to sense checks or quality checks e.g. on 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 produced to demonstrate the checks/activities being undertaken.

8. Reporting quality

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

- the establishment of the priorities (protection of trial subjects and to its scientific objectives)
- the identification of the risks associated with the study
- the setting of the tolerance limits and the documentation of the processes for mitigation of risks associated with the priorities
- the review of the results and data associated to the risk identified and the documentation of the actions needed

It is then expected that it should be possible, in a clear qualitative and quantitative way to report on the extent to which a trial has operated within the tolerance limits established and been conducted to an acceptable level of quality. The narrative of the clinical study report[7] could be expanded to include such a report.

This will include measures of the variability of parameters and their timing, assessment of deviations from tolerance limits or protocol requirements, and missing data. Additional information can be provided by investigating intra and inter site variability and distribution of single or multiple variables. Such analysis can be supplemented with information on process compliance derived from monitoring/data management reports and audits.

9. Proposed approaches

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 with the collaboration of expert functions. The key issues of trial and protocol design, the design of data collection tools/instruments, the design of monitoring and data management 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. The following approaches could be considered:

Separation of prioritisation and risk mitigation approaches according to several dimensions:

- Protection of trials subjects
  - Rights and integrity
  - Safety

- Credibility of data and results

Addressed at each stage of the trial:

- Design, conduct and reporting phases of the trial

Using a stratified approach depending on the marketing authorization status in relation to the use of the product in the trial and a customised approach depending on:

- Protocol complexity
- Therapeutic indication and nature of endpoints, including population and co-medications
- Administration of the product, dose, formulation
- Complexity of study procedures and measurement, including the nature of the intervention
- Vulnerability of the study population

In case of a clinical development programme, the risk based approach should ideally be planned at the start of the clinical programme, then adapted protocol by protocol throughout clinical development, building on the experience gained 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 authorization and supervision and the marketing authorization process.

The annexes to this paper and its references include a number of models and discussions of these including one proposed by the ADAMON[3] project from Germany, that being piloted by the MHRA[4] UK, the OPTIMON[8] study implemented in France and risk based approach suggested by the OECD. In addition some suggestions made in draft guidance on specific modalities for non-commercial trials are extracted and included for their more general applicability.

Further to this paper, more specific papers on quality design, clinical trial monitoring and documentation, data management and statistical control, safety reporting might be explored as appropriate.

In addition specific considerations regarding the authorisation and supervision of trials should be made using the same dimensions and prioritisation and risk management techniques.

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ANNEX 1- Points to Consider when establishing a risk based quality management approach

NB: The intent is to provide examples and the list is not meant to be an exhaustive list

- To initiate a risk based quality management approach for a trial, it is essential to have a knowledge of the following:
  - status of the systems to be employed and understand the project and its objectives
  - set the priorities that need to be monitored for a particular system
- The impact of these priorities on the protection of trial subjects, the trial scientific objectives and the credibility of the data should be assessed when identifying the risks
- Consider the phase of the trial development: trial design and methodology; trial conduct with subject recruitment and treatment; data evaluation and reporting

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
System/project related topics	Example of risk identification	Examples of mitigation
Sponsor organisation and structure:		
- What are the budgetary arrangements for the trial?	E.g Inadequate planning for resourcing monitoring or other trial activities	E.g. fully forcast the trial cost at the start and regularly review the spending
- What are the processes for qualifying and monitoring the contract research organisations (CRO) or other third parties?	E.g the third party does not have the resources with the necessary experience to carry out the tasks.	At the time of selection, the sponsor to: - document the expectations for the CRO and/or other third party activities/involvement - assign responsibilities to oversee all involved parties with documented processes for selection with pre-selection/pre-qualification

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
		visit(s) with a systematic and logical assessments of key staff, equipment and facilities. On-going monitoring of the activities with regular reviews of the duties and responsibilities and follow up on audits.
- What are the contractual arrangements between all parties?	E.g lack of clear line of responsibilities and duties at the start of the project which could lead to misunderstanding of tasks to be performed and the possibility of key tasks not being completed	Sponsor to establish third party expectation and assign responsibilities to oversee the contract preparation and finalisation Ensure that the contractual agreement describes the responsibilities and duties at the start of the activities and that amendments are implemented if necessary.
- What is the project management structure and what are the processes?	E.g lack of clarity in term of reporting and/or communication lines between the personnel involved with the study design and planning and the operational staff. This could lead to deviations with study procedures that would not be addressed.	E.g All parties involved in the design and planning of the trial should involve the monitors, investigators, study managers, GMP personnel before the initiation of the trial at sites to plan the activities in a pragmatic and timely manner. E.g the sponsor to plan regular reviews of the project in the stages of design and conduct to monitor feasibility and compliance with timelines, study objectives and other priorities.

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
- What is the status of the personnel qualifications, training and experience and how relevant is it to the trial?	E.g lack of medical expertise at the sponsor could lead to the inadequate safety monitoring of a study and the lack of revision of the relevant documents (e.g. Investigator's brochure and the protocol).	The sponsor should ensure the availability of appropriately trained and qualified personnel by addressing within their quality management system the qualifications and training of staff at the start of the contractual agreement but also on an ongoing basis. The evidence of qualifications and training would be assessed on a regular basis within the reporting structure (e.g. by manager) and also by conducting internal audits.
Investigator's site and structure		
Is the investigator's facility adequate for the study?	E.g inadequate facility - the facility does not include a local laboratory that can run all the required biochemistry parameters.	E.g sponsor to assess suitability of facilities against the protocol requirements and document during the site selection process and on an on-going basis. If the parameters required are essential and a priority for the study, sponsor and investigator to organise for the blood analyses to be done as per protocol by selecting a private laboratory.
What is the status of the personnel qualifications, training and experience and how relevant is it to the study?	E.g lack of experience - The personnel other than the investigator and the pharmacist have never been involved in a clinical trial	Sponsor: -to assess suitability of staff qualifications, training and experience prior to the initiation of

Points to consider for the risk identification		Risk Control (Mitigation and/or acceptance)
		the study - to coordinate with the investigator GCP training and awareness sessions before and during the conduct of the trial. - to verify the understanding of personnel's responsibilities in respect to GCP and protocol requirements
How is the medical care organised for the patients?	E.g inadequate medical care with insufficient members of staff to complete the required protocol assessments.	The sponsor should review at the time of site assessment whether the investigator has the capability to provide the medical care as required by the protocol. During the conduct of the study, the medical care of the patients should be monitored by the sponsor by performing review of the monitoring reports, regular reviews of SAEs and SUSARs and outcome of site audits.
How are the medical records organised?	E.g archiving of the medical records is inadequate - the medical records are not kept for more than 2 years after the end of the study.	The sponsor: - to review the capability of the investigator to perform the study as per ICH GCP E6 prior to the start of the study and verify the state of the medical records and their availability - the Sponsor and Investigator should work together to determine the minimum data required in the medical records to ensure 1) the safe, informed medical care of each

Points to consider for the risk identification		Risk Control (Mitigation and/or acceptance)
		participant in an ongoing manner, 2) to verify key study interventions - those records for which the CRF is source and having alternative source records (e.g. laboratory reports, ECGs etc), should be defined in advance of the study - checks should be in place to ensure the records are made consistent with the objectives of the study and intended use of the data - put a plan in place with the investigator to ensure that the records will be kept in accordance with national legislation and are available for at least 5 years after the study has finished - to offer financial help to the investigator for archiving of the records
Sponsor Quality Management System		
- are there standardised process with written instructions?	E.g the sponsor do not have standard operating procedures	The sponsor to establish the process for preparation and approval of Standard Operating Procedures (SOP) and implement SOPs to achieve uniformity of the performance of a specific function.

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
- How are the processes related to quality control documented? What are the activities described for site monitoring, safety and data management monitoring and what are the requirements for computerised system validation?	E.g the quality control steps associated with monitoring activities are poorly described.	The sponsor to: - implement appropriate monitoring measures to ensure the timely collection and action in relation to deviations which may impact upon the subjects' safety (and/or trial data) - design a monitoring and auditing plan customised for the study and based on a risk assessment Quality assurance and quality control measures should be sensitive to detect the relative/comparative extent of non-compliance at a particular site, and respond accordingly to threats to patient safety and data quality. There should be mechanisms in place to verify that issues raised by monitoring and audit procedures have been acted upon in both a corrective and preventative manner.
- What is the process for safety monitoring and the identification of safety concerns?	E.g there is no safety monitoring plan and no regular reviews of the safety data have been planned	Implementation of a safety monitoring plan based on pre-clinical and clinical experience with the IMP. To include: - body system monitoring (consider visit frequency, bloods, ECGs, X-rays, etc) Regular ADR review by trial team (consider frequency) DSMB with the relevant data workflow and

Points to consider for the risk identification		Risk Control (Mitigation and/or acceptance)
		decisions processes For large and/or complex studies the use of an independent safety monitoring board/committee is recommended (see guideline on data monitoring committees Doc. Ref. EMA/CHMP/EWP/5872/03). The absence of such a review committee should be justified, and alternative safety monitoring mechanisms described. The sensitivity of such mechanisms to act promptly on arising safety signals should be considered. Eligibility criteria Withdrawal and stopping criteria Dose modification criteria - where changes are determined necessary (urgent safety measures and/or substantial amendments), documentation should be clear in describing whether the measure relates to current participants, past or prospective participants, and how soon any additional information should be supplied to participants - process for escalation to Regulatory Authority and/or ethical committee should be documented - the sponsor must implement appropriate monitoring measures to ensure the timely collection and action in relation to deviations

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
		which may impact upon the subjects' safety (and/or trial data)
What are the regulatory reporting processes (including submission, notification, expiry date extension etc.)?	E.g lack of regulatory reporting (e.g. failure in the reporting of SAE or SUSAR)	- sponsor to establish before the start which approvals are required (national & local) and what are the timelines
What is the process to remediate to protocol deviations (including eligibility criteria, trial procedure deviations, stopping rule, dose modification rules)?	E.g Failure to remediate to protocol deviations (eligibility criteria, trial procedure deviations, stopping rule, dose modification rules)	The sponsor to: - implement comprehensive and timely collection of any protocol deviations/missing data by sponsor and/ or involved CROs - root cause and remediation plan to be implemented if the deviation has an impact on the subject safety and data integrity - verify the impact of deviations in terms of subject safety and data integrity - escalate activities (re-evaluation of protocol, additional training, closure of sites) - Escalation or moderation of site checks should be made in response to the ongoing assessments; for example sites which are compliant may be monitored in ways which differ from those who are inexperienced/having

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
		compliance difficulties.
What is the process for the review and revision of study documents?	E.g the investigator's brochure was updated 3 years after its initial release	The sponsor to: - put in place timely requirements for the revision and update of the specific documents in line with the regulatory requirements - assign responsibility for review, update and approval of investigator's brochure - ensure that updated information are disseminated to all parties the in a timely manner
Investigational medicinal products:		
What is the product status and what is the level of characterisation (e.g. MAA, new biological or chemical entity, ATIMP)?	E.g inadequate/lack product characterisation (e.g. product specification incomplete)	At the study design, the sponsor to involve the GMP team and Qualified Person and assess the risk linked with the incomplete product specification. Plan to further develop the specification prior to initiation and review results on a regular basis prior to trial initiation. Agree with the regulators on the state of the specifications prior to study initiation and agree to further develop the testing as required.

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
What are potential risks associated with the use?	E.g mild cardio-toxicity was observed in animal species	Sponsor to: - involve GMP and pre-clinical toxicologists at study design and assess the risk of the toxicity observed in non clinical studies - establish the dose/dosage - highlight the risk in the protocol, investigator's brochure and informed consent - plan the relevant markers to allow an assessment of the risk at the start and during the study. Implement safety reviews to detect any concerns at regular time points
What is the manufacture process and is it compliant with GMP (EU/Non UE)?	E.g the IMP is manufactured outside of the EU and the GMP QP or the GMP team has never audited the facility.	Sponsor/GMP QP to: - involve GMP team at study design and assess the need and timing for qualification and auditing of the facility - conduct audit as per the timelines agreed - follow GMP release procedures and issue the GMP release certificate for the IMP to be used in compliance with the protocol
What are the packaging and/or labelling requirements?	E.g the IMP is an existing marketed product being tested for a new indication and the product is being used off the shelves.	Sponsor to: - adhere to legal requirements and label the product in compliance with the requirements of volume 10, Rules Governing Medicinal Products in the European Union Annex 13

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
What are the handling procedures for the IMPs (transport, storage, reconstitution, dispensation and administration)?	E.g the IMP has a short expiry date and needs re-test	Where a product has short stability data and is a sensitive formulation, measures must be adequate to verify the quality of the product during transport, storage, transfer and administration; for example it may be necessary at the time of preparation to add a label, as well as a date. Cold-chain custody may need to be verified prior to further product use etc. The available stability information and robustness of the formulation will determine the necessary sensitivity of measures to check for adequacy of transport and storage conditions. For example temperature sensitive formulations should be closely controlled and checked (to ensure adequacy of control), whereas products without specific storage requirements may need only periodic stock checks against their stated re-test date.
How will the IMP accountability and traceability be performed (e.g. treatment compliance)?	E.g There is no record to document the administration by the patients	The sponsor to: - document with the investigator that the IMP is used in accordance with the approved protocol

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
		- ensure that the investigator explains to each subject the correct use of the IMP and documents the discussion in the medical records - ensure that the investigator checks, at intervals appropriate for the trial, that each subject is following the instructions properly - implement a diary card for the patient to document the administration - to review the data on the diary card and check treatment compliance on an on-going basis
What are the blinding procedures?	E.g while the investigator is away, no other member can unblind the treatment	The sponsor to: -evaluate whether the access to the database and randomisation list is appropriately restricted - review the site back up procedures for unblinding with the investigator and ensure that adequate medical care can be provided at all times - train investigational staff on the blinding procedures
What are (un-)expected adverse reactions?	E.g inadequate information on potential adverse reactions by the IMP used in this setting	- inform about expected adverse reaction and their management in the protocol

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
		- define the expectedness for SUSAR reporting
Study design and methodology		
What is the purpose of the study and are the relevant data collected for the purpose?	E.g the size of the tumour lesion is not recorded at study start.	The sponsor to: - review of the protocol by qualified sponsor personnel - amend the protocol to ensure that the data on the lesion measurement is collected at the start and at the relevant time of evaluation - if the measurement is relevant to the primary endpoint, consider the collection of the MRI scan centrally and establish a independent data review committee
What are the non clinical data and how do they substantiate the clinical research?	E.g the non clinical studies do not substantiate the potential therapeutic effect.	The sponsor to: - review the study hypothesis with qualified sponsor personnel - substantiate the hypothesis of the research with literature research and extrapolation to the IMP structure and characterisation
How complex is the study design (many centres, several trial arms, complex trial related procedures)?	E.g there are several dose levels which could lead to several cohorts.	The Sponsor to: - involve the investigator and product specialists, biostatistician and non clinical specialists in the review of the proposed

Points to consider for the risk identification		Risk Control (Mitigation and/or acceptance)
		protocol and other study supporting materials - identify the starting dose and the proposed dose escalating procedures - document the escalating process in the proposed protocol - check the feasibility of the protocol requirements by involved investigators e.g. the coordinating investigator - on a routine basis, validate the escalation process and assess patient safety on a regular basis
How will the risk benefit evaluation be performed (safety monitoring, collection, reporting and evaluation)?	E.g the safety section in the protocol does not provide any information on how the risk benefit evaluation will be performed	For first in human studies reference to the EMA risk mitigation paper The measures put in place (and defined in the protocol/study records) should be commensurate with the risk of the study. It will be possible for the Sponsor (in discussion with subject matter experts) to define critical criteria such as stopping criteria which are then accordingly given close scrutiny through central and/or site checks. Criteria for moderation/escalation should define the points from which they apply (to ensure consistency of application) e.g. rise/fall from base-line or rise/fall between consecutive measurements.

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
Do the eligibility criteria include a degree of subjectivity/objectivity of assessments?	E.g the eligibility criterion related to the age narrow from 25 years old up to 45 years old.	The sponsor to: - review the need and practicability of the eligibility criteria in relation to the purpose of the study - amend the criteria to fit the purpose of the study
Subject safety, rights and well being		
What are the measures in place for the protection and confidentiality of patient data (including transfer of the patient data; access to the data at site and at the sponsor or third party)	E.g patient hospital number have been recorded on the CRF.	The sponsor to: - review if CRF have been collected from site - ensure that no patient identifier other than the patient number is required - liaise with site and with the staff at the sponsor to ensure that the patient hospital number has not been collected - review if the data have been entered in a database and if they have been disseminated to external parties. If so, the sponsor should delete the data from the database and contact all parties and request for the deletion of the specific data - liaise with the site and provide training on data protection and patient confidentiality
What is the process to ensure adequate	E.g the patients were not adequately informed	The sponsor to:

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
informed consent of the patients?	about the study as they signed the informed consent form after the start of the study procedures	- train investigators and/or study staff in relation to the informed consent procedure and ensure that the dates of the consent discussion and decision are documented in the medical records - review the protocol requirements and the need to consent prior to specific study procedures - ensure that the consent documentation is available at site initiation - monitor the informed consent of all patients in a timely fashion and discuss actions at site to remediate to deviations related to consent
What are the provisions of the insurance cover and indemnity (level of cover)?	E.g some of the patients recruited are 70 and the insurance cover has been set for 18 years old to 65 years old patients	The sponsor to: - review the insurance cover prior to the start of the study and to ensure that there are no conflicts between the insurance cover exclusions and the protocol requirements - the review of the cover should be documented once a year - send the protocol and any amendment to the broker for the insurance to be revised if changes that could affect the cover have taken place

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
Data Management and statistics and reporting		
What are statistical considerations?	E.g the eCRF collection process is not documented in the protocol	The sponsor to: - controlled access of the eCRF with collection process communicated to the site - organise training for the clinical site - support the site and implement a help desk - supervise the collection of the relevant data to match the requirements of the protocol
What is the biometrical and statistical design?	E.g multiple endpoints/data collection unrelated to the primary research questions, sub-studies etc data collection unrelated to the primary research) e.g. Insufficient sample size e.g. Inappropriate design selected e.g. No formal analysis plan in place	Include statisticians and the clinical expert in protocol development Validation of the clinical protocol design by the statistician
Are the patients populations well defined in the protocol/statistical analysis plan?	e.g. failure to have appropriate criteria for per protocol and safety populations in place leads to potential for selection bias	Include statisticians in protocol development. Sponsor to ensure SAP in place at appropriate time (e.g. prior to study unblinding) and reviewed/prepared by Statistician.
What are the provisions for efficacy and safety analyses?	E.g no formal pre-specified analysis or limited/poor detail– potential for accusations of bias	Include statisticians in protocol development. Sponsor to ensure SAP in place at appropriate time (e.g. prior to study unblinding) and reviewed/prepared by statistician.

Points to consider for the risk identification		**Risk Control** **(Mitigation and/or acceptance)**
What is the process for the preparation of the clinical study report?	E.g the report is a compilation of sections prepared by various departments and there are inconsistencies	The sponsor to: - ensure that the data are accurate, reliable and credible by performing quality control and checked between the various sections of the report - to investigate and report on any discrepancy

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