Risk proportionate approaches in clinical trials

Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

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1. Introduction

The legislation for clinical trials has seen significant changes during the last decade, starting with the implementation, in 2004, of the Clinical Trials Directive 2001/20/EC ('Directive'), continuing with the publication of the Good Clinical Practice Directive 2005/28/EC[i] in 2005 and more recently with the Clinical Trials Regulation (EU) No. 536/2014 ('Regulation')[ii].

Despite the relative flexibility of the legislation and guidelines (for e.g. ICH Guideline E6(R2) for Good Clinical Practice[iii]), it has been observed that in general a 'one size fits all' approach to the design and conduct of clinical trials has been followed to comply with the ethical and scientific standards of Good Clinical Practice (GCP). Some clinical trials, however, pose only a minimal additional risk to subject safety and/or trial integrity compared to normal clinical practice. A proportionate approach to the design and conduct of clinical trials is therefore supported by the Regulation. This approach should be adapted to the risk to the subject and/or trial integrity of the research carried out, as well as to the risk related to the reliability of trial results.

Different, proportionate approaches can be taken with regard to the rules to which a clinical trial is designed, conducted, evaluated and reported, depending on a number of factors that may affect the risk posed to a subject and/or trial integrity, such as the status (with or without marketing authorisation) and nature (e.g. properties of the active ingredient, pharmaceutical form, method of administration) of the investigational medicinal product (IMP), the indication, the trial population in which it is to be used, the extent of difference of the trial-related intervention from normal clinical practice, the complexity of the protocol, and the specific operational aspects of the planned clinical trial or the clinical development project.

2. Scope

The goal of the Regulation is to foster innovation whilst ensuring the protection of the participants in clinical trials as well as the quality and integrity of the trial outcomes.

The Regulation provides the basis for developing a guidance document on risk proportionate approaches in clinical trials. The present recommendations should be read in conjunction with the reflection paper prepared in 2013 by the European Medicines Agency (EMA), in collaboration with the Clinical Trial Facilitation Group (CTFG) and the GCP Inspectors Working Group, on risk based quality management in clinical trials [iv], and also the ICH E6 GCP R2 addendum.

This document, based on the requirements of the Regulation, provides further information on how such a risk proportionate approach can be implemented and also highlights the areas identified in the Regulation which allow such adaptations. This document applies to all sponsors, commercial as well as non-commercial/academic and all types of clinical trials, from early development of unauthorised products to clinical research conducted in the post-authorisation phase. Thus it is addressed to all interventional clinical trials of IMPs, including clinical trials with novel IMPs and trials using IMPs with a marketing authorisation, within or outside the terms of their marketing authorisation.

The Regulation however, contains detailed information on (reduced) requirements for the following aspects of a clinical trial, which are not repeated in this document (see table 1):

Table 1

Area	**Sections of the Regulation**
Content of the application	
• Investigator's Brochure (IB)	Annex I, Section E. INVESTIGATOR'S BROCHURE (IB) (28), (29)
• IMP dossier (IMPD) and simplified IMPD (Summary of Product Characteristics (SmPC))	Annex I, Section G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD), 1.2. Simplified IMPD by referring to other documentation
• Insurance	Article 76(3), Annex I, Section O. PROOF OF INSURANCE COVER OR INDEMNIFICATION (INFORMATION PER MEMBER STATE CONCERNED)
Labelling of the IMP	Annex VI. LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS
Informed consent	Article 30

In this document, explanations and examples of the areas for potential adaptation are provided (see table 2) to support sponsors as they implement a risk proportionate approach in the design and conduct of clinical trials.

The Regulation provides for less stringent rules or adaptations with regards to monitoring, safety reporting, traceability of the IMP and content of the TMF in particular, but not limited to low intervention clinical trials; depending on the circumstances, risk adaptations may be applied to any type of clinical trial.

The determination of whether a clinical trial is low intervention or not, is mainly based on the marketing authorisation status of the IMP and its intended use in the trial.. Trials with IMPs which do not have a marketing authorisation cannot be considered low intervention. The IMP risk category has implications for other trial related risks, however it does not determine all of them.

The risk to subject safety in a clinical trial mainly stems from two sources: the IMP and the trial procedures. For example, if a clinical trial is considered low intervention from an IMP perspective, it does not mean that all other risks associated with this trial are low as well. Other risks could be related to the trial design, the clinical procedures specified in the protocol, the patient population, the informed consent process etc. These risks should also be assessed and mitigated where appropriate (see section 4.1.). Equally if a trial is not low intervention, this does not mean that risk proportionate procedures cannot or should not be applied.

3. Low intervention clinical trials

Some clinical trials pose only a minimal additional risk to subject safety compared to normal clinical practice and within this scenario risk proportionate procedures may be applied.

Such clinical trials, defined in Article 2(3) of the Regulation as low intervention clinical trials, are those trials which fulfil all of the following conditions:

(a) the IMPs, excluding placebos, are authorised;

(b) according to the protocol of the clinical trial,

(i) the IMPs are used in accordance with the terms of the marketing authorisation; or

(ii) the use of the IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the Member States concerned; and

(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

The published scientific evidence supporting the safety and efficacy of an IMP which is not used in accordance with the terms of the marketing authorisation could include evidence based treatment guidelines, health technology assessment reports, and clinical trial data published in scientific peer-reviewed journals or other appropriate evidence.

In terms of the level of additional risk or burden to the safety of the subjects posed by additional diagnostic or monitoring procedures as compared to normal clinical practice in the Member State concerned, the following are some examples of what may be accepted as minimal additional burden, thus rendering the clinical trial a low intervention one:

- measuring height and/or weight, questionnaires, analysis of saliva, urine, stool samples, EEG and ECG measurements, blood withdrawal through a pre-existent catheter or with minimal additional venipuncture.

The limit for an acceptable burden could be exceeded when these interventions are conducted in a significantly more frequent manner or on a considerably larger scale than in normal clinical practice. However, it should be noted that additional risk or burden might include non-invasive procedures as well as invasive procedures, as described above, if these are performed with a significantly higher frequency or significantly greater intrusiveness, or a larger number of assessments are undertaken compared to normal clinical practice, during a greater number of visits to the clinic/hospital.

The Regulation specifies that sponsors should indicate in the cover letter of the clinical trial application if they consider a clinical trial to be a low intervention clinical trial and also, a detailed justification thereof should be included.

The Regulation explains the term 'low intervention clinical trial' also in the light of the provisions of the Recommendation of the Organisation for Economic Cooperation and Development (OECD), which introduces different risk categories for clinical trials. Low intervention clinical trials, as defined in the Regulation correspond to the OECD categories A and B(1) [V].

The OECD framework supports the risk-adapted approach by introducing a stratified approach that is based on the marketing authorisation status of the medicinal product being investigated, with a trial-specific approach that considers other issues such as the type of populations concerned by the trial or the informed consent of the patients.

In order to ensure subject safety, low-intervention clinical trials are subject to the same assessment process as any other clinical trial, however with adapted dossier requirements.

4. Risk proportionate approaches in clinical trials

4.1. Risk based quality management

Risks in clinical trials should be considered at the system level (e.g. facilities, standard operating procedures, computerised systems, personnel, vendors), as well as at the trial level (e.g. IMP, auxiliary medicinal products (AxMPs), trial design, data collection and recording).

Risk identification and evaluation should commence prior to the finalisation of the protocol as the risk assessment and mitigation may influence the trial design and procedures, as well as the financing or funding of the clinical trial or development project.

Whenever possible, a knowledge management approach should be applied by sponsors, incorporating available knowledge from previous risk evaluations and issue management for comparable trials or those conducted for the same pathology or compound.

Risk assessment and risk mitigation would typically involve a variety of functions, and therefore may include various personnel such as:

- data managers, statisticians, trial managers, pharmacovigilance personnel, monitors and/or auditors,
- personnel who have more direct involvement with patients such as clinical experts,
- investigators with an understanding of the therapeutic area and use of the proposed IMP, pharmacists, research nurses and laboratory experts.

Apart from the risks associated with the IMP, there are also risks that can arise from the protocol and trial procedures. Such risks can have an impact on the clinical trial subjects safety and well-being (e.g. risks associated with the clinical procedures specified by the protocol, failure to obtain fully informed consent, or failure to protect personal data), on data integrity, on the reliability of the results or their scientific use or validity.

There are also potential risks related to the conduct of the clinical trial, e.g. environmental risks if the IMP is associated with viral vectors or radiation, risks to 3rd parties (e.g. caregivers) etc.

A risk based quality management system for clinical trials should include the following steps[III, iv]:

- critical process and data identification
- risk identification
- risk evaluation
- risk control
- risk communication
- risk review
- risk reporting

Critical process and data identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

Risk identification and evaluation

Risk identification and evaluation should be conducted, as these are key to managing and mitigating risks.

The risk evaluation process covers the assessment of:

- the likelihood of potential hazards (identified risks) associated with the trial,
- the impact of these hazards, if they were to occur, on subjects' safety and rights and data integrity,
- the extent to which such hazards would be detectable[VI].

For each risk identified, an appropriate mitigation strategy (e.g. on-site or centralised monitoring, central medical review of trial data) should be implemented or a determination made that the risk can be accepted or eliminated (e.g. by the trial design). During risk evaluation, the results from inspections and audits from prior comparable clinical trials should be considered.

The risk identification and risk evaluation should take into account the whole spectrum of risk determinants for defining trial management and operations, including, but not limited to: informed consent, insurance coverage, safety reporting, monitoring, trial master file content, data management, computer systems, traceability of IMPs, clinical sample management and analysis, data processing, analysis (statistics) and reporting [vi].

Careful consideration should also be given to the adequacy of the measures to protect the privacy of trial subjects and confidentiality of their personal data, taking into account applicable European laws on data protection and the Declaration of Helsinki.

Examples of risk assessments, and guidance on performing them, are available on the websites of some national authorities and academic and other non-commercial sponsors, as part of these organisations' initiatives [vii, viii].

Risk control

Following risk identification and evaluation in a trial, a risk proportionate approach can be applied. The risk assessment and mitigation should be documented (e.g. in a risk assessment and mitigation plan [vii]) and implemented. The documentation should include the rationale for any specific actions required and identify those responsible for them (e.g. monitor, investigator etc.).

The main components of risk control are risk mitigation, adaptations and risk acceptance actions, including accountability. The aim of risk control is to determine whether the risk is acceptable, and if not to reduce the risk to an acceptable level. For this purpose, predefined quality tolerance limits should be established. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

The resource allocated for risk control should be proportionate to the significance of the risk and the importance of the process or outcome exposed to the identified risk.

Examples of mitigations could involve implementation of risk mitigation steps in procedural documents or manuals (e.g. SOPs, pharmacy manuals, (e)case report form (CRF) manual, (e)TMF manual, laboratory manuals), plans (monitoring plan, data management plan, statistical analysis plan), training material, parameters used for site and vendor selection and planning of performance metrics, contractual quality agreements.

For example, as part of the risk assessment and risk mitigation of the safety reporting process described in the protocol, the sponsor should ensure adequate and tailored training for the

investigators and trial staff to identify, assess, manage and report any specific adverse events anticipated to occur in the trial subjects due to the nature of the IMP or the disease.

Table 2 below highlights the specific areas where the Regulation sets out possibilities to apply risk adaptations in the design and conduct of clinical trials.

Table 2 Areas where risk adaptations can be applied

Risk Adaptations	**Areas impacted**	**Section of the CT Regulation**
1. Safety reporting	Safety profile of IMP Reliability of safety information	Article 41(2) Annex III(2.5, 21)
2. IMP Management	Traceability and accountability	Article 51(1)
3. Trial management	Monitoring	Article 48
4. Trial documentation	Content of the Trial Master File (TMF)	Article 57

Risk communication

There should be a process to ensure that the risk assessment and mitigation activities are documented and any subsequent updates, as well as changes that may impact on trial conduct e.g. protocol amendments, serious breaches, safety reporting, protocol deviations etc. are shared with the relevant personnel (sponsor, vendors and trial sites).

Risk review

An on-going reassessment of the risks should be performed, by review of new information emerging during the conduct of the trial (e.g. new pre-clinical data, new pharmacology and safety data, updated Investigator Brochure, protocol amendments) and the outputs of trial management activities (e.g. monitoring output, data management, DSMB meeting output, audit reports). A reassessment should also be performed prior to the implementation of a substantial modification. After a substantial modification a trial may no longer fit the criteria for low-intervention clinical trials and therefore the risk adaptations previously implemented may no longer apply.

Risk reporting

In accordance with the ICH guidelines E3- Structure and Content of Clinical Study Reports (Section 9.6 Data Quality Assurance) and E6- Good Clinical Practice, the sponsor should describe the implemented risk adaptations and summarise important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report. The risk documentation (i.e. risk identification, evaluation, control, communication, review and reporting) should be retained in the TMF.

4.2. Safety reporting

The Regulation includes provisions for applying a risk proportionate approach for safety reporting. Any such adaptation should be clearly stated and justified in the protocol, which will be submitted to the Member States for clinical trial authorisation.

Risk adaptations to safety reporting according to the Regulation refer to documenting of adverse events in source documents (e.g. medical records), recording of adverse events in the CRF (and hence reported to the sponsor) and to the requirements of immediate (without undue delay, but not later than within 24 hours of obtaining knowledge of the event) reporting from the investigator to the sponsor.

As a general rule, all adverse events should be reported to the sponsor, unless justified in the protocol and supported by the risk assessment outcome.

Article 41 of the Regulation refers to two possible risk adaptations to safety reporting:

- selective recording and reporting of adverse events,
- adaptations to immediate reporting from the investigator to the sponsor, for certain serious adverse events.

Risk adaptations to adverse event recording and reporting should be detailed in the documentation on risk assessment and mitigation activities (e.g. in a risk assessment and mitigation plan) that is produced in conjunction with the protocol development and prior to the start of the trial.

Detailed collection and reporting of adverse events (serious and non-serious) is particularly important where data about the safety profile of an IMP from available pre-clinical and clinical trials is scarce. As the knowledge of a medicine and its use evolve and increasing amounts of data become available in order to determine the benefits and risks of an IMP, the extent (range of events) and level of detail of recording and reporting adverse events may be adapted in the protocol, in line with the scope and type of the clinical trial and the level of knowledge on the safety profile of the IMP tested and the disease profile of the trial subjects. This means in practice that the protocol may select only certain (and not all) adverse events to be recorded in the CRF and reported to the sponsor. This applies in particular to marketed products with a known safety profile, which are tested within the framework of low-intervention clinical trials. In this regard, the following situations apply:

- IMPs are used according to the conditions of the marketing authorisation:
  In this case, a reduced or targeted safety data collection may be appropriate if supported by data from post-marketing use and if the number of subjects exposed during clinical development was sufficient to adequately characterize the medicinal product's safety profile (even in terms of rare adverse drug reactions), and if the occurrence of expected adverse drug reactions was similar across multiple trials in terms of seriousness and severity.

- IMPs are marketed, but used differently to the conditions of the marketing authorisation:
  In such cases, any adaptation to safety reporting should be based on a trial-specific risk assessment. The risk assessment should consider whether the clinical trial under evaluation includes a new population (e.g. in terms of age, gender or other patient characteristics, or using a new combination therapy or a different concomitant medication), a new indication, a different dose or dosage regime or a different route of administration, compared to the conditions of use in the SmPC that may lead to more severe or more frequent adverse drug reactions, new adverse drug reactions or new drug-drug interactions.

In both scenarios described above, expected IMP and anticipated disease or population related adverse events may be waived from recording in the CRF by the investigator and reporting to the sponsor. For example, in oncology indications, where the sufficiently characterised toxic nature of the marketed medicinal products causes -many well-known adverse events, such as nausea, vomiting, headache, or

in COPD patients experiencing disease-related adverse events like breathlessness etc., there might be no added value to record these adverse events and report them to the sponsor. Such a risk adaptation should be described in the protocol, taking into consideration the criteria described above.

Article 41 of the Regulation gives the possibility for the investigator not to report certain serious adverse events immediately to the sponsor, if provided for in the protocol. For example, in cases of blinded clinical trials carried out in high morbidity or high mortality diseases, in which efficacy or safety endpoints meet the criteria of serious adverse events, the sponsor may determine in the protocol that these outcome events are exempted from the rules of immediate reporting to the sponsor. In this case, an independent Data Safety Monitoring Board (DSMB)[1] should be appointed for the evaluation of the safety data from the ongoing trial in an unblinded manner and in regular, adequate intervals. If in such cases, an Adjudication Committee is also appointed, the sponsor should put procedures in place to ensure that the assessment by this Adjudication Committee on whether an event qualifies as a serious adverse event or an efficacy or safety endpoint and the communication of this outcome to the DSMB is performed in a timely manner and delays in serious adverse events reporting are minimised. After each DSMB meeting, the DSMB should advise the sponsor whether to continue, modify or terminate the trial[ix]. The functional roles and operational procedures of the DSMB, as well as its trial-specific tasks (i.e. how frequently the DSMB will meet, what data will be assessed under which viewpoints, description of the decision making process and range of decision) should be described in summary in the protocol and in more detail in the DSMB charter.

The safety reporting rules from the investigator to the sponsor or the DSMB, if applicable should be described in detail in the protocol.

The documentation on risk assessment and mitigation activities (e.g. the risk assessment and mitigation plan) may identify adverse events and/or laboratory abnormalities that are critical to safety evaluations and require immediate reporting from the investigator to the sponsor. These requirements should be included in the protocol.

Annual Safety Reports (ASRs) should describe the risk adapted approach that was undertaken for safety reporting for each trial covered by the respective ASR in case any deviation from regular safety reporting as of the Regulation occurred, e.g. was defined in the protocol as per Article 41(2) of the Regulation. Any serious adverse event (including serious adverse reactions) reported by the investigator to the sponsor (regardless of whether it was required by the protocol to be immediately reported or not) should be included in the ASR.

4.3. IMP management

Traceability and accountability

IMPs shall be traceable. Therefore, documentation should be maintained to ensure full drug accountability and traceability.

Article 51, paragraph 2 of the Regulation requires information on the provisions for traceability should be contained in the application dossier.

The extent of drug accountability documentation needed may vary depending on several factors, such as the authorisation status of the IMP(s), whether its/their use in the clinical trial is within the authorised indication, the trial design (e.g. population, blinding, complexity of the dosing regimen), who is administering the trial product(s) and the toxicity of the IMP(s) and its/their supply chain. If

[1] In line with the provisions of the Regulation, the terms Data Safety Monitoring Board and Data Safety Monitoring Committee are synonymous

allowed in the concerned Member State, in clinical trials where marketed products are used in accordance with the terms of the marketing authorisation, IMPs may be sourced from normal stock of the community or hospital pharmacy. The IMPs could also be provided directly to the sites by the trial sponsor. In this case, the IMPs should be labelled for use in a clinical trial, according to local requirements.

Where unlicensed medicinal products are used as IMPs, full accountability records of receipt, use and return/destruction is usually required, unless justified in the documentation on risk assessment and mitigation activities (e.g. in the risk assessment and mitigation plan).

For low-intervention clinical trials, where medicinal products authorised in the concerned Member State are used as IMPs, routinely maintained pharmacy documentation on receipt, storage and handling may be sufficient, if:

- normal prescribing practice and documentation applies

and

- specific documentation of prescribed amounts and doses taken is available in the patient's medical records or other source documents, e.g. the patient's diary.

In the case of low intervention clinical trials, if a marketed product is re-labelled or repackaged for blinding purposes or distributed outside of normal supply chains, sufficient traceability and documentation should be available to allow for a recall of the IMP or its inclusion in a more general recall of a marketed product, to the extent that recall applies.

In all cases, the documentation on risk assessment and mitigation activities (e.g. the risk assessment and mitigation plan) should include justifications for the level of IMP accountability undertaken.

Risk adaptations performed on drug accountability should take into account the impact of not performing drug accountability, on the reliability of that particular clinical trial results. The extent of drug accountability documentation should correspond to what is necessary for the integrity of the trial data and/or the safety of the trial subjects.

Other risk factors, like the stability of the active ingredient that impact the management of IMP should also be considered in the risk assessment. For example, temperature monitoring or light-protection if applicable should be adapted depending on the outcome of that risk-assessment.

4.4. Trial management

Monitoring

Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data and processes necessary for human subject protection and trial integrity.

The Regulation makes provision for a risk proportionate approach to be applied to monitoring. According to Article 48 of the Regulation, the extent and nature of monitoring should be determined by the sponsor on the basis of an assessment, i.e. the risk assessment, that takes into consideration all characteristics of the clinical trial, such as whether the trial is a low intervention trial, the methodology and objective of the clinical trial, and how the intervention deviates from normal clinical practice and the operational peculiarities of the clinical trial.

The documentation on risk assessment and mitigation activities (e.g. the risk assessment and mitigation plan) should contain the identified risks that are mitigated by monitoring and the type and

intensity of monitoring undertaken. This includes a description of critical data and processes, as well as the quantity and type of source data that needs to be verified against the CRF and corroborated against other records.

Based on the outcome of the risk identification and evaluation, the sponsor should develop a monitoring plan that describes the monitoring methods, responsibilities, and requirements for the trial to be monitored. The monitoring plan should include a brief description of the study, its objectives, and the critical data and study procedures, with particular attention to data and procedures that are unusual in relation to clinical routine and require training of study site staff. The plan should be communicated to relevant parties (e.g. monitors, project managers, data managers, statisticians etc.) and should provide those involved in monitoring with adequate information to effectively carry out their duties.

Sponsors should consider what events would indicate a need for review and revision of the monitoring plan and establish processes to permit timely updates where necessary. For example, a protocol amendment, change in the definition of significant protocol deviations, or identification of new risks to study integrity could result in a change to the monitoring plan.

The type and combination of monitoring activities should be adapted and tailored to suit a particular clinical trial. These include:

- on site monitoring activities,
- monitoring activities that do not require visits to individual sites such as: telephone contact with the site, web-enabled training (remote monitoring),
- centralised monitoring of the trial data (a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians),
- central medical review of trial data,
- centralised monitoring of pre-defined operational metrics critical to quality (e.g. turnaround time of central laboratory results to the investigators).

These activities can be supported by trial oversight structures such as Data Monitoring Committees, Trial Management Groups, and Trial Steering Committees.

On-site monitoring remains relevant in most types of clinical trials, as it is instrumental for the verification of several critical aspects at the trial site, for example adequacy of site facilities, the informed consent process, source data verification and IMP handling on site.

In defining the monitoring strategy based on the trial specific risk assessment performed, the intensity and focus of the monitoring may vary. The level of on-site monitoring activities may range from frequent and or detailed monitoring to lower levels of activity and less frequent on-site visits to targeted visits of certain sites or of a particular activity or in rare circumstances to no on-site visits.

The monitoring strategy may involve central tools to identify the need for targeted monitoring visits based on assessment (statistical or other) of centrally accrued data and information. These processes provide additional monitoring capabilities that can complement and justify adaptations to the extent and/or frequency of on-site monitoring.

The strategy may need to be reviewed during the trial, for example if the protocol is amended, new risks may be identified that require adjusted monitoring methods and strategy. During the conduct of the trial, the intensity of monitoring may be adapted at site/ trial level depending on the outcome of

the monitoring undertaken. In either case the risk assessment and mitigation as well as the monitoring plan should be updated accordingly.

In order to ensure that any monitoring that is carried out is sufficiently focused, escalation procedures should be built in to communicate, follow-up and correct identified non-compliance at an early stage. Management and sponsor staff responsible for trial oversight should receive the output of the on-site or centralised monitoring in a timely manner for review and follow-up. Such follow-up and escalation procedures may include different processes and actions when using centralised monitoring, in which the data management and/or biostatistician also may be involved. When implementing centralised monitoring, the sponsor should avoid the inappropriate use of site resources, e.g. by requesting additional documents required only for monitoring purposes.

Monitoring activities (whether they are on-site or centralised) need to be sufficiently well documented to demonstrate that the monitoring plan has been adhered to and decisions and follow-up actions have been taken. Failure to adhere to the plan can result in ineffective monitoring and potentially compromised data, and also lead to a situation where the sponsor is not in control of the trial. As unanticipated risks may emerge in the course of a trial, resulting in a change to the documentation on risk assessment and mitigation activities (e.g. to the risk assessment and mitigation plan), the monitoring plan should be reviewed and modified as necessary.

4.5. Trial documentation

Content of the Trial Master File (TMF)

According to preamble 52 of the Regulation, in order to be able to demonstrate compliance with the clinical trial protocol and with the Regulation, a clinical trial master file, containing relevant documentation to allow supervision (monitoring and auditing by the sponsor and inspection by Member States) shall be kept by the sponsor and the investigator. Guidance on the content of the TMF is provided in the guideline on GCP compliance in relation to the trial master file (paper and/or electronic) for content, management, archiving, audit, and inspection of clinical trials and the ICH Guideline E6(R2) for Good Clinical Practice [iii] The latter guidance states that the essential documents listed should be supplemented or reduced where justified (in advance of the trial initiation). This justification should be based on the outcome of the risk assessment, which may identify where adaptations can be applied that would result in some of the documents no longer being relevant.

Article 57 of the Regulation states that the essential documentation in the TMF shall take into account all characteristics of the clinical trial including in particular whether the clinical trial is a low-intervention clinical trial.

Risk proportionate approaches applied to a trial therefore may affect the content of the TMF. The extent of these changes would be directly related to the type of clinical trial and the outcome of the trial risk assessment, with more adaptations likely to be possible for low intervention clinical trials.

Examples of how risk-adaptation could affect the TMF include the following:

- combining of documents: one document serves multiple purposes (screening logs and recruitment logs, signature and delegation logs, site assessment and site initiation etc.),
- absence of documents, as a result of implementation of other risk proportionate measures, for example:
    - Investigator Brochure as the Summary of Product Characteristics is being used instead,

- Clinical Study Report may be absent as it is replaced by a medical journal publication,
- IMP related documentation: IMPs with a marketing authorisation and supplied to the patients via a routine medicines supply chain (i.e. from the pharmacy, based on a medical prescription) may not require any additional accountability records or only limited recording of consumption of the IMP e.g. in the CRF or patient diary. Therefore, the following documents may not be needed to be included in the TMF: instructions for handling, shipping records, certificates of analysis of IMPs or trial-related materials, drug accountability documentation (see also Section 4.3), destruction documentation, temperature monitoring records (if the IMP is used as per normal clinical practice and stored in the usual place, for those that do not have temperature monitoring – e.g. ambient storage in hospital theatre), sample of labels as these may just be the normal hospital dispensing label,
- hospital laboratory accreditation certificates and reference ranges (when these laboratories are not providing information that is critical to the reliability of the trial results).

5. References

i Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

ii Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

iii Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, E6(R2), Step 5, adopted by CHMP on 15 December 2016, issued as EMA/CHMP/ICH/135/1995

iv Reflection paper on risk based quality management in clinical trials, EMA/269011/2013, 18 November 2013

v OECD Recommendation on the Governance of Clinical Trials, OECD website, 2013

vi ICH Guideline Q9 – Quality Risk Management

vii http://forums.mhra.gov.uk/showthread.php?1678-Examples-of-risk-assessments

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

ix Guideline on Data Monitoring Committees, EMEA/CHMP/EWP/5872/03, January 2006