Consultation document

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

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area

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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 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). Many clinical trials, however, pose only a minimal additional risk to subject safety 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 of the research carried out.

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, such as the status and nature of the investigational medicinal product (IMP), the indication, the trial population in which it is to be used, the level 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 and the quality and integrity of the trial outcomes.

The Regulation provides the basis for developing a guideline on risk proportionate approaches in clinical trials. The present recommendations build on 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, and on the ICH E6 GCP R2 addendum.[iv]

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 support and facilitate such adaptations. This guideline applies to all sponsors, commercial as well as 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 both to those clinical trials that are intended to be included in the application for a marketing authorisation for the medicinal product under investigation, clinical trials with novel IMPs and to trials using only IMPs with a marketing authorisation, within or outside the terms of their marketing authorisation.

In this document, more explanations and examples of the areas for potential adaptation are provided, when sponsors follow a risk proportionate approach in the design and conduct of clinical trials.

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

Area	Sections of the Regulation
Content of the application • Investigator's Brochure (IB) • IMP dossier (IMPD) and simplified IMPD (Summary of Product Characteristics (SmPC)) • Insurance	Annex I, Section E. INVESTIGATOR'S BROCHURE (IB) (28), (29) Annex I, Section G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD), 1.2. Simplified IMPD by referring to other documentation 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

The risk to subject safety in a clinical trial mainly stems from two sources: the IMP and the trial procedures.

The Regulation provides for less stringent rules or adaptations with regards to monitoring, traceability of the IMP and content of the TMF, to those clinical trials which pose only a minimal additional risk to subject safety (as defined in Article 2(3) of the Regulation) compared to normal clinical practice.

Some risk adaptations apply in particular to low intervention clinical trials, however, depending on the circumstances, risk adaptations may be applied to any type of clinical trial. In practice all clinical trials determine procedures which are in various respects risk adapted and therefore these considerations are relevant in all cases.

The determination of whether a clinical trial is low intervention or not, is largely based on the marketing authorisation status of the IMP and its intended use in the trial. The IMP risk category has implications for other trial related risks, however it does not determine all of them. 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 be also 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 these trials can be risk adapted.

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 investigational medicinal products, excluding placebos, are authorised;

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

(i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or

(ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products 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 and 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:

- weighing, height measuring, 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 higher 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 introduces a risk-based oversight and management methodology for clinical trials, combining a stratified approach that is based on the marketing authorisation status of the medical 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, trial design, data collection and recording).

Apart from the risks associated with the IMP, there are also risks that can arise from the protocol and study procedures i.e. the intervention. Such risks can have an impact on the clinical trial subjects (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.

A risk based quality management system for clinical trials should include the following steps:

- risk identification
- risk evaluation
- risk control
- risk review
- risk communication
- risk reporting

Risk identification and evaluation

Risk identification and evaluation should be conducted, as this is key to managing and mitigating risks.

The risk evaluation process covers the assessment of: the likelihood of potential hazards associated with the trial, the impact, if they would occur, of these hazards on subjects' safety and data integrity and the extent to which such hazards would be detectable[VI].

For each risk identified, an appropriate mitigation strategy (for e.g. monitoring) should be implemented or a determination made that the risk can be accepted.

Risks should be considered in proportion to its potential impact and the likelihood of its occurrence. 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 investigational medicinal products, clinical sample management and analysis, data processing, analysis (statistics) and reporting [vi].

The risk 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.

Following a risk identification and evaluation in each trial, a risk proportionate approach can be applied. The risk assessment and mitigation should be described and implemented. The

documentation should include the rationale and the responsible functions for any specific actions required (e.g monitor, investigator etc).

For example, as part of the risk identification and risk assessment of the safety reporting process described in the protocol, the sponsor should ensure adequate and tailored training for the investigators and trial staff for those specific adverse events anticipated to occur in the trial subjects due to the nature of the IMP or the disease.

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 on performing risk assessments are available on the websites of some national authorities, academic and non-commercial organisations' initiatives [vii, viii].

Risk control

The purpose of risk control is to reduce the risk to an acceptable level or determine that the risk can be accepted. The main components of risk control are risk mitigation, adaptations and risk acceptance actions.

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.

The risk assessment and risk mitigation would typically involve multiple functions able to consider all the various aspects of the trial, and may include various personnel such as data managers, statisticians, trial managers, monitors and/or auditors and personnel who would have more direct involvement with patients such as clinical experts and investigators with an understanding of the therapeutic area and use of the proposed IMP, as well as pharmacists and research nurses.

Examples of mitigations could involve implementation of risk mitigation steps in procedural documents or manuals (e.g. SOPs, pharmacy manuals, (e)CRF manual, (e)TMF manual,), 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.

Table 1 below highlights the specific areas where the Regulation sets out possibilities to apply risk adaptations ("less stringent rules") in the design and conduct of clinical trials.

Table 1 Areas where risk adaptations can be applied

Risk Adaptations	**Areas impacted**	**Section of the CT Regulation**
1. Safety reporting	Safety profile of IMP Data integrity 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 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 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). The risk review also assesses the impact of the new information on the risk assessment and mitigations. These should be reviewed on an ongoing basis and updated, if necessary. The implementation, effectiveness and need for mitigations should be periodically reviewed.

Risk communication

There should be a process to ensure that the risk assessment and mitigation plan 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.

Risk reporting

In accordance with the ICH guidelines E3- Structure and Content of Clinical Study Reports and E6- Good Clinical Practice, the sponsor should describe the implemented risk adaptations in the clinical study report.

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 recording of adverse events in the CRF (and hence reported to the sponsor) and to the requirements of immediate reporting from the investigator to the sponsor.
As a general rule, any adverse event considered by the investigator as being potentially related to the IMP, and therefore representing an adverse reaction, 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,

and

- adaptations to expedited reporting from the investigator to the sponsor, for certain serious adverse events.

Risk adaptions to adverse event recording, collection and reporting should be detailed in the 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 level of detail and reporting requirements for adverse events may be adapted in the protocol, in line with the scope

and type of a 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 and reported to the sponsor. This applies in particular, but not only, 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 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.

Article 41 of the Regulation gives the possibility for the investigator not to report certain serious adverse events to the sponsor, if provided for in the protocol. 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 expedited reporting. 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, another Committee is also appointed, the sponsor should put procedures in place to ensure that the assessment by this 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

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

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 should be described in detail in the protocol. The risk assessment and mitigation plan may identify adverse events and/or laboratory abnormalities that are critical to safety evaluations and require expedited reporting from the investigator to the sponsor. These requirements should be included in the protocol.

4.3. IMP management

Traceability and accountability

Investigational medicinal products shall be traceable. Drug accountability refers to maintaining documentation that ensures traceability of investigational medicinal products used in a clinical trial.

As set forth in Article 51, paragraph 2 of the Regulation, information on the provisions for traceability should be contained in the application dossier.
The level of accountability needed may vary depending on several factors, such as the authorisation status of the investigational medicinal product(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. The risk assessment and mitigation plan should include justifications for the documentation used to reconstruct drug traceability and the doses administered.

If 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. For these IMPs, the risk assessment and mitigation plan should define the level of accountability of the IMP(s) that is required based on the risk assessment and the requirements in the Member States.

For low-intervention clinical trials, where authorised medicinal products in the concerned Member State are used as IMPs, the sponsor could decide that normal prescribing practice and documentation would apply and if specific documentation of prescribed amounts and doses taken in the patient's medical chart or other source documents other than normal practice is required, e.g. the patient's diary or the case report form (CRF) or the routinely maintained pharmacy documentation on receipt, storage and handling.

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.

Where unlicensed medicinal products are used as IMPs and especially in those clinical trials with high complexity of dosing regimen and used in certain populations, full accountability records of receipt, use and return/destruction is usually required, unless justified in the risk assessment and mitigation plan.

In all cases, 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 and should be documented in the risk assessment and mitigation plan. The level of accountability should correspond to what is necessary for the scientific validity of the trial outcome or the safety to 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 and 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

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 outcome of assessments of sites, staff, facilities, and training needs may also influence monitoring methods utilised. The resulting monitoring strategy should take the identified study-specific risks into account and be proportionate in nature and scope.

There are several risk proportionate approaches that can be applied to monitoring. The type and combination of monitoring activities can be adapted and tailored to suit a particular clinical trial. Examples include on-site monitoring and centralised monitoring. These can be supported by statistical tools, trial steering committees and data monitoring committees.

Centralised monitoring processes provide additional monitoring capabilities that can complement and justify adaptations to the extent and/or frequency of on-site monitoring or may replace them for some types of trial. On-site monitoring remains relevant in certain types of clinical trials, as it is instrumental for the verification of several critical aspects at the trial site, for e.g. the informed consent process, source data verification and IMP handling on site.

In defining the monitoring strategy based on the risk assessment performed, the intensity and focus of the monitoring may vary. The level of on-site monitoring activities may vary from frequent and or detailed monitoring to low levels of visit and activity, or targeted visits to certain sites only or there may be no on-site visits in certain trials.

The risk assessment and mitigation plan should contain the identified risks that are mitigated by monitoring and the type and intensity of monitoring undertaken. A monitoring strategy plan should be put in place based on the risk assessment and mitigation plan.

The trial-specific risks may be such that reduced or no on-site monitoring is justified or that a particular area is not monitored. Centralised and/or on-site monitoring can be used with the flexibility to adapt the requirements throughout the life cycle of a trial. 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. 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. In that case the risk assessment and mitigation as well as the monitoring strategy 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 follow-up and correct identified non-compliance at an early stage. Such escalation procedures will have different processes and actions when using centralised monitoring, in which the data management and/or biostatistician are involved in the identification of issues, and processes other than onsite monitoring may be used for follow-up.

Centralised monitoring enables the review of reported data / information, remote contact, communication and training where relevant and can be used to set certain actions in motion when pre-determined tolerance limits for processes or data have been exceeded.

Monitoring activities (whether they are on-site or done centrally) need to be sufficiently well documented to demonstrate that the monitoring plan has been followed and actions have been taken as a result of the outcome of the monitoring activities. 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 risk assessment and mitigation plan, the monitoring plan should be reviewed and modified as necessary.

A risk adaptive approach to monitoring should include utilisation of one of or a combination of approaches listed below:

- On site monitoring activities;
- Trial oversight structures such as Data Monitoring Committee, Trial Management Group, Trial Steering Committee;
- Monitoring activities that do not require visits to individual sites such as: telephone contact with the site, web-enabled training;
- Centralised monitoring of the trial data.

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 for Good Clinical Practice [iii]

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 the TMF could be affected include the following: 

- Combining of documents: one document serves multiple purposes (job descriptions, curriculum vitae);
- Objectives achieved by other means;
- Absence of documents, as a result of implementation of other risk proportionate measures, for example:
    - Specific on-site monitoring reports, as there may not be on-site visits as a consequence of the implementation of a risk adapted monitoring strategy plan
    - IMP related documentation: investigational medicinal products 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), 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) or where the data values are used in their own right, where accreditation certificates are not applicable (or not available) and other measures such as population statistics in large trials account for divergences;

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. ICH Guideline E6 - Good Clinical Practice

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